

Promoting Access to Medical Technologies and Innovation

SECOND EDITION

Intersections between public health, intellectual property and trade



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and trade

2nd Edition



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WTO ISBN 978-92-870-4996-4 (print) / 978-92-870-4997-1 (electronic version)

WIPO ISBN 978-92-805-3174-9 Publication Number: 628E/20

WHO ISBN 978-92-4-000827-4 (print) / ISBN 978-92-4-000826-7 (electronic version)

This publication can be obtained through:

World Health Organization

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Switzerland
Tel: + 41 22 338 91 11
Email: publications.mail@wipo.int
Website: www.wipo.int/publications

World Trade Organization

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CH-1211 Geneva 21
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Fax: + 41 22 739 54 58
Email: publications@wto.org
Website: www.wto.org/Publications
Online WTO bookshop: <https://onlinebookshop.wto.org>

A PDF version of this publication is available on the websites indicated above.

Printed in Switzerland, 2020.

Publication designed by Book Now Ltd, London. Cover photos © Andrew Brookes / via Getty Images, Roxana Wegner / via Getty Images, lam Anupong / Shutterstock.com.

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Acknowledgements

This publication is the product of extensive collaboration between the WHO, WIPO and WTO Secretariats, led by the Department of Public Health, Innovation and Intellectual Property in the WHO, the Global Challenges Division in WIPO and the Intellectual Property, Government Procurement and Competition Division in the WTO.

Research, authoring and substantive review was done by: Hans Georg Bartels, Peter Beyer, Erika Dueñas, Dzintars Gotham, Roger Kampf, Nancy Pignataro, Charles Randolph, Antony Taubman and Jayashree Watal.

The contribution of many others are warmly acknowledged, in particular: Daniel Glenn Adams, Marco Aleman, Lucie Archambeau, Andrea Arce Gallardo, Aditi Bana, Tobias Bednarz, Shakeel Bhatti, Thomas Bombelles, Mathew Bryan, Denis Cohen, Andrew Czajkowski, Cynthia Dapaah, Amy Dieterich, Aida Dolotbaeva, Jicui Dong, Nicole Drews, Edward Elliott, Carsten Fink, Gilles Forte, Martin Howell Friede, Martha Parra de Friedli, Dimitar Gantchev, Minelik Alemu Getahun, Trevor Gunn, Jorge Gutierrez, Anneke Hamilton, Dalila Hamou, Nicole

Homb, Anne Marie Huvos, Fei Jiao, Aegyoung Jung, Mosahid Khan, Irene Kitsara, Arne Klau, Daniel Ismael López Salcedo, Geidy Lung, Wahyu Retno Mahanani, Joscelyn Magdeleine, Allison Mages, Nicola Magrini, Darlan Marti, Christophe Mazenc, Maegan McCann, Devin McDaniels, Tanvi Misra, Tomoko Miyamoto, Ali Akbar Modabber, Anna Caroline Müller, Benoît Müller, Giovanni Napolitano, Sergio Napolitano, Harrison Hunter Ottaway, Josefita Pardo de Leon, Philippe Pelletier, Mansur Raza, Alex Riechel, Andrew Rintoul, Alejandro Roca Campaña, Debbie Roening, Robina Sandhu, Vasee Sathiyamoorthy, Nadezhda Sporysheva, Catherina Maria E. Timmermans, Adriana Velazquez Berumen, Lien Verbauwhede, Thomas Verbeet, Xavier Vermandele, Hannu Wager, Max Wallot, Victoria Weyulu, Michele Woods, Sacha Wunsch-Vincent, Ning Xu, Young-Woo Yun and Qi Zhang.

Special thanks for editorial and administrative support are due to: Charlotte Beauchamp, Stephanie Carmel, Bassam Peter Khazin, Anthony Martin, Veronica Pini Scerbo, Jenny Rouse, and Heather Sapey-Pertin.

Foreword by the Directors-General

International cooperation on public health is inherently multi-dimensional, with a focus on building effective health systems. It is dynamic and responsive to the demands of countries around the globe. Towards this goal, the World Health Organization (WHO), the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO) have been working closely together for almost two decades to support global endeavours to improve health outcomes.

The first edition of this study in 2012 was intended to support international cooperation on health, IP and trade issues in a transparent and holistic manner. For this purpose, it draws together the three agencies' respective areas of expertise. The goal remains to provide a platform for sharing practical experience and understanding of a wide range of policy instruments. This is conceived as a means of supporting and informing ongoing technical cooperation and policy discussions, especially at a time when the world grapples with the multi-dimensional challenges of the response to the COVID-19 pandemic.

We have been encouraged by the strong, positive feedback signalling that the study has contributed to a more informed and inclusive policy debate. It highlights that the study has helped to progress a common resolve to work towards universal access to essential medical technologies and to strengthen and diversify innovation systems to respond to evolving demand.

The second edition of the study captures the insights from our further extensive policy dialogue and joint technical assistance activities. This includes a series of trilateral symposia on topical questions in which we, personally, had the benefit of participating and which reflects our common desire to build policy coherence in the public health area.

The revised study records the numerous significant developments that we have seen since 2013. These include efforts made towards achieving universal health

coverage, challenges posed by antimicrobial resistance, the changing disease burden and new global disease threats. The study reviews public and private sector innovation models, as well as the repercussions of an increasingly diverse medical technologies industry and the rise of innovative and production capacity in developing countries. It draws practical lessons from experiences regarding how public health, IP, trade and competition rules all interact with each other in the broader context of the human rights dimension of health and the United Nations' Sustainable Development Goals (SDGs). And it provides insights on measures to promote innovation and access to medical technologies, noting the growing network of free trade agreements and the importance that trade plays for access to medical technologies.

The study supports informed priority setting, resource allocation and policy decisions through an improved empirical foundation. It integrates more comprehensive and accessible data and information on prices, access, patents and licensing, as well as trade. The insert at the beginning of the study summarizes issues that have come up in the context of COVID-19 and guides the reader to relevant parts of the study where those issues are addressed.

We trust that this updated resource will remain a reliable platform for future policy debate and analysis and will provide helpful guidance for those who seek up-to-date answers to challenging questions. We pledge continuing commitment for further collaboration among our three agencies, together with our partners whose insights have contributed much to the study. This will support our work towards the shared objectives of universal health coverage, better health outcomes for all, fulfilment of the SDGs and, first and foremost, the design of effective and lasting responses to public health crises. The COVID-19 pandemic has brought extraordinary challenges to peoples' health, economies and societies at large. Global collaborative efforts are required now more than ever before.

Tedros Adhanom Ghebreyesus
Director-General, WHO

Francis Gurry
Director General, WIPO

Roberto Azevêdo
Director-General, WTO

An integrated health, trade and IP approach to respond to the COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) pandemic constitutes an extraordinary global public health crisis. It has created a pressing need for intensified global cooperation. The pandemic has from its outset raised issues at the crossroads of public health policy, trade policy and the framework for and the management of innovation, including those relating to intellectual property (IP) rights.

The text of the second edition of this publication had been completed prior to the COVID-19 outbreak. This special insert maps myriad challenges posed by the outbreak in relation to the integrated health, trade and IP policy frameworks set out in this study. It provides cross-references to the relevant sections of the main text.

A dramatic impact on health systems

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – a newly emergent coronavirus first recognized in December 2019 – causes COVID-19. According to evidence available as of 27 May 2020, most people with COVID-19 develop mild (40 per cent) or moderate (40 per cent) disease, approximately 15 per cent develop severe disease that requires oxygen support and 5 per cent have critical disease.¹

Based on the information notified to the World Health Organization (WHO) under the International Health Regulations (IHR) 2005, the WHO Director-General on 30 January 2020 declared a public health emergency of international concern. The WHO subsequently issued temporary recommendations relating to trade, including recommendations pertaining to travel, cargo and goods. The WHO Director-General on 11 March 2020 characterized the COVID-19 outbreak as a pandemic.

UN General Assembly resolutions A/RES/74/270 “Global solidarity to fight the coronavirus disease 2019 (COVID-19)”² and A/RES/74/274 “International cooperation to ensure global access to medicines, vaccines and medical equipment to face COVID-19”,³ as well as World Health Assembly resolution WHA73.1 “COVID-19 response”,⁴ recognized the dramatic impact of the global outbreak on health systems, which has, in some cases, entirely overwhelmed existing capacity and, in others, placed systems under immense strain and underscored the need for cooperation and collaboration in the spirit of unity and solidarity.

Governments around the globe have implemented restrictions to economic and social activities in an effort

to slow the virus's spread, including through policies of confinement, physical distancing and restrictions on travel. These restrictions have sought to reduce pressure on health systems, allow sufficient time to improve health infrastructure and develop diagnostics, vaccines and treatments to effectively respond to the virus.

Policy challenges posed by the pandemic

The COVID-19 pandemic has generated sudden, far-reaching impacts on health systems, and has prompted significant social and economic repercussions around the world. This extraordinary threat to peoples' health and livelihoods has required urgent action:

- to monitor and contain the spread of the virus;
- to understand relevant virology and epidemiology;
- to mobilize and coordinate the requisite resources;
- to deploy the necessary health care system infrastructure;
- to ensure that health care products, technologies and protective equipment are available and can be accessed equitably in sufficient quantities worldwide; and
- to develop, test, manufacture and ensure equitable access to diagnostics, vaccines and therapeutics, medical devices and other relevant technologies.

Meeting the demand for health technologies and medical services

The pandemic triggered a massive global demand for existing health technologies to combat COVID-19, including diagnostics, medicines, ventilators and other medical devices, as well as for consumables used in hospitals, such as personal protective equipment (PPE). This has put pressure on public procurement systems and led to shortages and other supply and access challenges for certain products in developed and developing countries.

➤ Determinants of access: Chapter II, section A and Chapter IV

Government priorities have included ensuring sufficient access to intensive care equipment such as ventilators, ensuring sufficient PPE to minimize infection risk to front-line workers and ensuring access to testing services and

products. Governments in a number of countries have taken steps to enhance and adapt manufacturing capacity to meet a surge in demand for hospital equipment and PPE, including through redirecting production lines to manufacture essential products. To date, generic manufacturers in Bangladesh have begun producing a generic version of remdesivir to treat COVID-19, which is patented in a number of other countries, benefitting from the transition period under the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), which currently exempts least-developed countries (LDCs) from implementing patent protection for pharmaceutical products and from protecting clinical trial data.

➤ **LDC TRIPS transition periods: Chapter II, section B.1(g)(v)**

To ensure adequate access to diagnostics, health systems have, among other things, set up contact tracing systems and “drive-through” testing facilities as well as organized new laboratory networks to utilize capacity in smaller labs. Although vaccines for COVID-19 are still early in their development, a number of governments have invested in ensuring that sufficient manufacturing capacity is available to produce the necessary volumes if and when an effective vaccine is found.

Facilitating the movement of health workers, for example through visas or work permits and recognition-of-qualifications programmes, has been considered by certain governments as instrumental to keeping health systems operational.

➤ **Health services under the WTO General Agreement on Trade in Services (GATS): Chapter II, section B.3(c)**

Telemedicine may be used to overcome geographical limitations and physical distancing requirements.

➤ **Software licensing and eHealth: Chapter II, section B.1(e)(v)**

Authorities in many jurisdictions have expedited procurement of essential products via emergency procedures, such as shortening public procurement timelines and issuing direct contract awards. A number of countries have put in place transparency mechanisms with regard to emergency procurement following best international practices in this regard. Some countries and regional groupings have used pooled procurement for select goods.

➤ **Procurement mechanisms: Chapter II, section B.4 and Chapter IV, section A.8**

A number of competition authorities across the globe have launched investigations relating to COVID-19 health

products, including into price hikes for health products and diagnostic manufacturing information held as a trade secret. In the Netherlands, an investigation was started into Roche’s dominant position regarding COVID-19 test equipment and materials. Roche committed to release all the relevant know-how and to scale up production in order to enhance testing capacities in the Netherlands.⁵ Several competition authorities have issued guidance⁶ on the application of competition policy in times of urgency and limited supply and clarified whether and when coordination between firms in order to respond to crisis needs could be permitted, at least temporarily.

➤ **Competition law and policy: Chapter II, section B.2 and Chapter IV, section D.2**

Preserving effective international trade

While low- and middle-income countries face particular challenges caused by the global scarcity of key health technologies, the vast majority of countries are net importers of all categories of health technologies, including those needed to address COVID-19.

➤ **International trade in health-related products: Chapter IV, section D.1(a)**

Preserving the integrity of global trade is critical to ensure equal access to needed health technologies and will support countries in recovering from the crisis and building health systems that foster greater resilience against future pandemics. While recognizing that governments may take emergency measures to address public health challenges, including shortages of COVID-19 technologies, G20 Trade Ministers⁷ have called upon countries to ensure that any trade-restrictive measure taken to promote public health be “targeted, proportionate, transparent and temporary”.⁸ Ensuing declarations and statements by a wide range of WTO members have underscored the importance of a predictable, transparent, non-discriminatory and open global trading system for pandemic response and recovery. In particular, they have emphasized the importance of well-functioning supply chains and the need to facilitate cross-border flows of vital medical supplies and services.⁹ Countries and international organizations work closely together to facilitate the smooth cross-border flow of vital medical supplies and to avoid unnecessary disruptions to global trade and supply chains.

Governments have concomitantly implemented both trade-restrictive measures (e.g. restrictions on exports of key products) and trade-facilitating ones to reduce costs and delays (e.g. facilitation and simplification of customs procedures).

➤ **WTO Trade Facilitation Agreement: Chapter IV, section D.1(b)**

Some countries have reduced or eliminated tariffs on certain imported health technologies or deferred payment deadlines for the same.

➤ **Tariffs: Chapter IV, section D.1(b)**

Regulatory conformity checks have been streamlined through international cooperation and standards, as well as through mutual or unilateral recognition of third-country approvals.

➤ **WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and WTO Agreement on Technical Barriers to Trade (TBT Agreement): Chapter II, section B.3(b)**

Intellectual property and the pandemic

The global IP system provides an incentive framework in which urgently needed innovation in relation to COVID-19 can be encouraged. It covers the stages from invention to supply of a product or service. Given their particular importance, patents are the focus of this section, while other aspects of IP are discussed further in the main study.

➤ **IP system: Chapter II, section B.1, Chapter III, section D and Chapter IV, section C**

The disclosure requirement and dissemination of patent information ensure access to technical information, which can support research and development (R&D) needs. The World Intellectual Property Organization (WIPO) has established a COVID-19 search facility¹⁰ within its global PATENTSCOPE database. The tool offers predefined search strings that support the searching of COVID-19-related patent information. The European Patent Office (EPO)¹¹ and a number of national patent authorities have developed similar tools, as well as databases of COVID-19-related patents. For example, China launched a freely accessible database for COVID-19-related patents; the Republic of Korea has made available patent information on technology relating to the diagnosis and treatment of COVID-19, including patent analysis and trend reports, and, as part of the PROSUR/PROSUL regional technical cooperation initiative, Argentina, Brazil, Chile, Colombia, Ecuador, Peru and Uruguay have published patent reports on technologies relevant to COVID-19.¹² The United States Patent and Trademark Office (USPTO) has created a COVID-19 Prioritized Examination Pilot Program that fast-tracks examination of COVID-19-related applications filed by small and micro enterprises.¹³ The Brazilian National Institute of Industrial Property prioritizes the examination of patent applications related to innovations that can be used to fight COVID-19 from 7 April 2020 to 30 June 2021.¹⁴

The Medicines Patent Pool provides patent information in its Medicines Patents and Licences database (MedsPaL),

in response to the call for user-friendly databases in the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI).¹⁵ As of writing, the database includes information about a number of medicines in trials to treat COVID-19: remdesivir, lopinavir/ritonavir, favipiravir and ruxolitinib, as well as biotherapeutics tocilizumab, sarilumab and siltuximab.

➤ **Patent information: Chapter II, section B.1(b)(viii)–(xi)**

➤ **Disclosure requirement: Chapter II, section B.1(b)(iii)**

Well-functioning IP systems should consider the interests of a wide range of stakeholders, such as start-ups, R&D institutions, both public and private, universities and corporations, as well as the interests of funders, whether public or private, and of the public at large, including patients, who ultimately benefit from innovation that meets their needs. To achieve this delicate balance, each country can tailor its domestic IP system to its particular needs and circumstances, including through TRIPS flexibilities.

➤ **IP policy options and flexibilities in the IP system: Chapter II, section B.1(g)**

The IP system has a number of features that support and facilitate R&D and access, including certain exclusions from patentable subject matter and limited exceptions to patent rights. Those options are available to support countries' access to medical technology and innovation policies.

➤ **IP exclusions and exceptions: Chapter II, section B.1(b)(vii) and Chapter IV, sections C.1 and C.3**

For example, national IP systems have certain options with respect to patenting material that exists in nature. Patentability may have relevance for biotechnological R&D on the SARS-CoV-2 virus.

➤ **Patentable subject matter: Chapter III, section D.4(a)**

Domestic IP laws frequently provide for research exceptions. Where a research exception is available, R&D on patented COVID-19-related technologies does not constitute patent infringement.

➤ **Research exceptions: Chapter III, section D.5(a)–(b)**

In countries where a regulatory review exception exists, a patented invention can be used without the consent of the patent holder for the purposes of developing information to obtain regulatory marketing approval.

➤ **Regulatory review exception: Chapter IV, section C.3(a)(i)**

A number of national patent systems provide options addressing the further development, and repurposing,

of existing medicines, including incremental innovation, medical indication claims and limiting evergreening.

➤ **Further development and repurposing: Chapter III, section D.4(b)–(c)**

Available policy measures include compulsory licences and government-use licences. Legislation has been passed in some countries to ensure that mechanisms for expedient compulsory licensing and government-use licensing are in place if needed in order to facilitate access to COVID-19 therapies, for example, in Canada and Hungary.¹⁶ In Germany, legislation has authorized the Federal Ministry for Health to order the competent authority to allow the use of patent-protected inventions to ensure the supply of various health technologies, including medicines, diagnostics and personal protection equipment, on the grounds of public interest or national security.¹⁷ In Israel, a government-use licence has been issued for the import of generic lopinavir/ritonavir in COVID-19 treatment.¹⁸

➤ **Compulsory licences and government-use licences: Chapter IV, section C.3(a)(ii)**

As regards the Special Compulsory Licensing System for manufacture and export of pharmaceutical products,¹⁹ questions have been raised regarding the response that the system can provide to the COVID-19 pandemic²⁰ and the fact that developed country WTO members excluded themselves from using the System as importers.²¹

➤ **Special Compulsory Licensing System: Chapter IV, section C.3(a)(iii) and Annex III**

Civil society organizations have submitted oppositions against patents on technologies that could be potentially used in a new COVID-19 medicine; some have requested patent revocation.²² Such measures have traditionally been used more often by commercial competitors.

➤ **Pre-grant and post-grant patent review: Chapter IV, section C.2**

A balanced copyright system that supports the interests of rights holders and allows access to copyright-protected works can support R&D activities and enable the development of digital solutions to support diagnostics and treatment. Text and data mining exceptions have been used in initial research into COVID-19, including for tracking and predicting its spread, and are being used in the search for treatments.

➤ **Exceptions to copyright: Chapter II, section B.1(e)(ii)**

Software licensing schemes can also support the development of eHealth products and digital processes that may allow easier diagnosis and treatment of COVID-19 patients.

➤ **Software licensing and eHealth: Chapter II, section B.1(e)(v)**

Many organizations, corporations and other rights holders have undertaken voluntary actions and initiatives during the COVID-19 crisis. Open licensing models have been used collaboratively to develop and manufacture hardware to resolve supply chain weaknesses. Numerous private sector companies have taken access-oriented actions that include: (i) committing to non-exclusive and royalty-free licensing or issuing non-enforcement declarations of patent rights in some or all jurisdictions;²³ (ii) publishing scientific data on a free-to-use basis; (iii) publishing technical specifications of vital equipment (e.g. ventilators); and (iv) sharing knowledge to enable others to manufacture and use such technologies.²⁴

In addition, among other voluntary actions in support of R&D that have been observed are the permission to use text and data mining and machine-learning technologies and to freely access and reuse COVID-19-related scientific literature protected by copyright,²⁵ and the making available of standards protected by copyright.²⁶ For example, as part of the Open Covid Pledge, a number of private companies and universities are granting free access to patented technologies and protected designs related to diagnosing, preventing, containing and treating COVID-19.²⁷

➤ **Licensing approaches: Chapter III, sections C.5(g), D.1, D.2 and D.5(c) and Chapter IV, section C.3(b), (c) and (e)**

Governments and the private sector have also undertaken initiatives to transfer technology and know-how to make, adapt or use COVID-19-related technologies.

➤ **Manufacturing and technology transfer: Chapter IV, section A.10**

A concrete example of IP management for a new COVID-19 technology is seen in a vaccine candidate developed at Oxford University in the United Kingdom and licensed to an originator pharmaceutical company for manufacture. Development and manufacture are supported by US\$ 750 million in funding from the Coalition for Epidemic Preparedness Innovations (CEPI) (see below) and Gavi, the Vaccine Alliance. While exact contract terms are not public, the originator company has committed to supplying the vaccine globally on a no-profit basis and has signed an agreement with an Indian-based manufacturer allowing the latter to supply low- and middle-income countries.²⁸

➤ **Socially responsible licensing: Chapter IV, section C.3(c)**

International initiatives to support R&D of, and equitable access to, COVID-19 technologies

Since the outbreak of the COVID-19 pandemic, myriad public and private actors have launched collaborative global efforts to develop treatments, vaccines and diagnostics with the aim of guaranteeing equitable access to those technologies. Many such efforts strive to simultaneously address both R&D and access needs. Collaborative efforts include substantial investments in product development partnerships (PDPs) to support non-commercial development of a vaccine and large multi-stakeholder R&D initiatives.

➤ Frameworks for urgent innovation to address pandemics: Chapter III, section C.3 and section E

The WHO Strategic Preparedness and Response Plan for 2019 includes actions to coordinate international R&D efforts. Such actions include use of the R&D Blueprint Global Coordination Mechanism and the convening of expert consultations that have resulted in a Coordinated Global Research Roadmap.²⁹ The WHO's R&D Blueprint for COVID-19 highlights the importance of a collaborative approach, stating that "virus materials, clinical samples and associated data should be rapidly shared for immediate public health purposes and that fair and equitable access to any medical products or innovations that are developed using the materials must be part of such sharing".³⁰ Genetic sequences of viral samples are being shared openly, worldwide. Timely sharing of epidemiological and other data is also crucial.

➤ Sharing of health-related data: Chapter IV, section A.4(f)

➤ Access and benefit-sharing for genetic resources: Chapter II, section D and Chapter III, section E.4

To ensure efficiency in testing potential treatments, WHO launched the "Solidarity" clinical trial, which enrolls patients in one single randomized trial to facilitate the rapid worldwide comparison of unproven treatments. As of 3 June 2020, more than 3,500 patients have been recruited in 35 countries, with over 400 hospitals actively recruiting patients. The WHO is facilitating access to thousands of treatment courses for the trial through donations from a number of manufacturers.³¹

UN General Assembly resolution A/RES/74/274³² underscored that equitable access to health products is a global priority and that the availability, accessibility, acceptability and affordability of health products of assured quality are fundamental to tackling the pandemic. World Health Assembly resolution WHA73.1³³ is concerned, *inter alia*, about the continued functioning of the health system and universal health coverage,

promotion of R&D, including through open innovation, as well as timely, equitable and affordable access to health technologies. It called on "international organizations and other stakeholders [...] to work collaboratively at all levels to develop, test, and scale-up production of safe, effective, quality, affordable diagnostics, therapeutics, medicines and vaccines for the COVID-19 response, including, existing mechanisms for voluntary pooling and licensing of patents in order to facilitate timely, equitable and affordable access to them, consistent with the provisions of relevant international treaties, including the provisions of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) and the flexibilities within the Doha Declaration on the TRIPS Agreement and Public Health".³⁴ It also called for restrictions on the movement of medical equipment and medicines to be temporary and specific; for sharing of knowledge, lessons learned, experiences, best practices, data, materials and commodities; and for collaboration to promote both private sector and government-funded research and development.

The WHO, together with a group of other global health actors, private sector partners and other stakeholders, has launched the Access to COVID-19 Tools (ACT) Accelerator, a collaboration to accelerate the development, production and equitable global access to new COVID-19 essential health technologies.³⁵

In response to an initiative of the Government of Costa Rica, the WHO on 29 May 2020 launched the Solidarity Call to Action and the COVID-19 Technology Access Pool. The Call has been endorsed by 39 other member states as well as other stakeholders.³⁶ It states that "the COVID-19 pandemic has revealed the fallibility of traditional ways of working when it comes to equitable access to essential health technologies" and "sets out an alternative, in line with WHO's efforts to promote global public health goods, based on equity, strong science, open collaboration and global solidarity". Key elements of the Solidarity Call to Action include:

- public disclosure of gene sequences and data;
- timely publication of all clinical trial results;
- encouragement of governments and R&D funders to include clauses in funding agreements with pharmaceutical companies and other innovators concerning equitable distribution, affordability and transparency, including the publication of trial data;
- use of global non-exclusive licensing for relevant health technologies, including through licensing to the Medicines Patent Pool; and
- promotion of open innovation models and technology transfer that increase local manufacturing and supply capacity, including through joining the Open Covid Pledge and the United Nations (UN) Tech Access Partnership.³⁷

To operationalize the Solidarity Call to Action, the COVID-19 Technology Access Pool (C-TAP), working through its implementing partners, will compile in a single compendium of commitments to voluntarily share COVID-19 health technology-related knowledge, IP and data.³⁸

Additionally, with the support of WHO and Unitaid, the Medicines Patent Pool has temporarily expanded its mandate to cover any COVID-19-related health technologies, including vaccines and diagnostics.³⁹

➤ **Patent pools in the area of health: Chapter III, section C.5(g)**

The UN Tech Access Partnership, hosted by the UN Technology Bank, aims to support developing countries scale up local production of critical health technologies. It does so by facilitating connections between experienced manufacturers and local manufacturers in developing countries to share key data, knowledge and other relevant support through a coordinated network.⁴⁰

➤ **Manufacturing and technology transfer: Chapter IV, section A.10**

The need for rapid development of new technologies has spurred unprecedented government investment in R&D. Launched by the European Commission in May 2020, “Coronavirus Global Response” pledging events reached a total of EUR 15.9 billion by the end of June 2020 to fund collaborative development and universal deployment of, and access to, diagnostics, treatments and vaccines against coronavirus.⁴¹ The Commission has also instituted a “temporary framework” to allow state aid to go to COVID-19-related R&D, if beneficiaries commit to grant non-exclusive licences under non-discriminatory market conditions to third parties in the European Economic Area.⁴²

The CEPI, a PDP created in the wake of the 2014 Ebola virus outbreak by philanthropies and a number of governments, has to date received US\$ 1.4 billion from governments for COVID-19-related work, an unprecedentedly large investment in a PDP.⁴³ CEPI requires that producers provide equitable access to any vaccine developed through its funding. It further requires product developers to be willing to undertake technology transfer to enable production by a global network of manufacturers.⁴⁴

➤ **Product development partnerships: Chapter III, section C.6**

To support research on COVID-19 as well as on future threats to health, Medicines for Malaria Venture (MMV) has compiled 80 compounds, including ones in development and marketed drugs that have a known or predicted

activity against SARS-CoV-2, in its “COVID Box”.⁴⁵ The MMV offers free access to the COVID Box for research purposes. Researchers who use it are expected to place any resulting data in the public domain.

Regulatory responses

Regulatory assessment and approval of health technologies are essential in every health system to ensure product quality, safety and efficacy. As an effective COVID-19 treatment has not yet been found, researchers are exploring the repurposing of older medicines, and “compassionate use” of medicines (clinical use before approval) is taking place in specific cases.

➤ **Regulation of health technologies: Chapter II, sections A.6 and D.3 and Chapter IV, section A.11**

The WHO’s Emergency Use Listing (EUL) procedure aims to streamline the process by which new or unlicensed products can be used during public health emergencies. The list assists interested UN procurement agencies and member states in determining the acceptability of specific products, based on an essential set of available quality, safety and efficacy and performance data. The EUL provides a time-limited listing for unlicensed products in an emergency context when limited data are available and products are not yet ready for application for WHO prequalification. The EUL is currently open to candidate in vitro diagnostics (IVDs) to detect SARS-CoV-2.⁴⁶

➤ **WHO prequalification: Chapter IV, section A.11**

Ensuring transparency

Transparency and the availability of up-to-date information on measures taken by governments are of critical importance, and cut across both legal and policy areas of this publication.

The International Health Regulations (2005) include a broad notification requirement, which aims at detecting, early on, all public health events that could have serious and international consequences, and preventing or containing them at source through an adapted response before they spread across borders.⁴⁷ Notifiable events must be reported to the WHO immediately, i.e. within 24 hours after having carried out the assessment of public health information related to the event. Following notification, State Parties shall also:

- continue to communicate to the WHO sufficiently detailed public health information available to it on the notified event, where possible including case definitions, laboratory results, source and type of the risk, number of cases and deaths, conditions affecting the spread of the disease and the health measures employed;

- submit information about health measures taken in addition to those recommended by WHO; and
- report, when necessary, the difficulties faced and support needed in responding to the potential public health emergency of international concern.

Transparency in COVID-19 R&D and access initiatives is also an essential part of the WHO Solidarity Call to Action.

The WIPO COVID-19 IP Policy Tracker⁴⁸ online listing provides information on measures adopted by IP offices in response to the COVID-19 pandemic, such as the extension of deadlines to ensure continued operations. In addition, the Policy Tracker provides information on legislative and regulatory measures taken by governments, as well as on voluntary actions of a broad range of stakeholders, to improve access. It relies on information provided by IP Offices, member states and other entities, hence is not an exhaustive list of all actions taken regarding COVID-19.

To promote transparency, the WTO monitors and reports on trade-related measures pertaining to goods, services and IP rights implemented by its members in response to the pandemic.⁴⁹ It has issued a number of information notes and reports on trade in the context of COVID-19, including on trade in medical goods, transparency, export prohibitions and restrictions, the treatment of medical

products in regional trade agreements, standards and regulations, and trade in services.⁵⁰

The way forward

The COVID-19 pandemic has placed immense pressure on health systems and trade systems around the world. The urgent search for technologies that may help to control the pandemic has mobilized unprecedented research efforts and investments. It has given rise to new models of working. Rapid and efficient innovation is needed more than ever, and equitable access to new technologies is of paramount importance. Adequate management of IP is central to achieving these goals.

National and international responses to the pandemic reflect policymakers' growing experience in tackling pressing health needs, with initiatives considering health, trade and IP elements in a holistic manner. Responses to the pandemic span such a wide range of technical areas that nearly every section of this trilateral study is of relevance to the global response to COVID-19.

The Directors-General of the three organizations emphasized in the foreword to this study: "the COVID-19 pandemic has brought extraordinary challenges to peoples' health, economies and societies at large. Global collaborative efforts are required now more than ever before".

Endnotes

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Executive Summary

Why this study?

Public health is inherently a global challenge and thus assumes high priority for international cooperation. The World Health Organization (WHO) is the directing and coordinating authority for health, but the interaction between health issues and other policy domains – human rights, development policy, intellectual property (IP) and international trade – creates a strong rationale for cooperation and coordination between the WHO and other international organizations, in particular the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO). This study and its updated and reviewed second edition have emerged from an ongoing programme of trilateral cooperation among these agencies. It responds to an increasing demand, particularly in developing countries, for strengthened capacity for informed policy-making in areas of intersection between health, trade and IP, focusing on access to and innovation of medicines and other medical technologies. The need for cooperation and coherence at the international level has intensified over the past decades, as successive multilateral decisions have confirmed.

The study is set in an evolving health policy context. An integrated approach can reinforce a dynamic, positive interplay between the measures that promote innovation and those that ensure access to vital medical technologies. The aim of the technical cooperation activities of the WHO, WIPO and the WTO is to facilitate understanding of the full range of options and their operational context. This study draws together the materials used in technical cooperation and addresses needs for information in an accessible, systematic format to support ongoing collaborative efforts.

Navigating the study

The study has been prepared as a capacity-building resource for policy-makers. The study is structured so as to enable users to grasp the policy essentials, and then to look more deeply into areas of particular interest. After explaining the need for policy coherence and the role of each of the cooperating agencies to address the global disease burden and health risks (see Chapter I), the study lays out a general panorama of the policy landscape (see Chapter II), so that all interrelated elements can be seen in context. It then provides more detailed accounts of issues specifically connected with innovation (see Chapter III) and access (see Chapter IV). The contents reflect the multilateral policy debate over the past two decades, recognizing that innovation and access are inevitably intertwined – both are indispensable ingredients to meeting an evolving global disease burden.

- Chapter I presents the general background to health policy relating to medical technologies and to international cooperation in this field, sets out the distinct roles and mandates of the three cooperating agencies, and outlines the global disease burden that defines the essential challenge for health policy.
- Chapter II outlines the essential elements of the international framework – health policy, IP and trade policy, including regulatory issues, as well as technical barriers to trade, sanitary and phytosanitary measures, health services and procurement rules. It lays the basis for the following, more detailed analysis of the innovation and access dimensions in Chapters III and IV. It outlines the key insights of economics for medical technology innovation and access. A final section reviews the policy issues associated with traditional medical knowledge and access to genetic resources, in view of its significance for national health systems and as an input to medical research.
- Chapter III provides a more detailed overview of policy issues concerning the innovation dimension of medical technologies. The historical pattern of medical research and development (R&D) provides a backdrop for analysing the current R&D landscape. The chapter looks at challenges with overcoming market failures in medical product R&D in areas such as neglected diseases and antimicrobial resistance. It then outlines alternative and complementary instruments to incentivizing and financing R&D. It outlines the role of IP rights in the innovation cycle, including issues relating to IP management in health research and selected pre- and post-grant patent issues. A final section looks at influenza vaccines as a distinct example of innovation management and product development to address a specific global health need.
- Chapter IV deals with key aspects of the access dimension, describing the context for access to health technologies, with more detailed case studies on access in respect of HIV/AIDS, hepatitis C, tuberculosis (TB), non-communicable diseases (NCDs), and vaccines. It sets out the key determinants of access related to health systems, IP and trade, and it analyses access to health products in specific areas. It reviews in particular pricing policies, transparency across the value chain of medicines and health products, taxes and mark-ups, and procurement mechanisms, as well as regulatory aspects and initiatives to transfer technology and boost local production, patent quality and review procedures, compulsory and voluntary licences, free trade agreements and international investment agreements, tariffs and competition policy.

As access and innovation issues are increasingly considered across a broader range of policy areas, a

more diverse set of stakeholders, values, experience, expertise and empirical data now shapes and informs policy debates, through:

- greater diversity of policy voices, creating opportunities for cross-fertilization between traditionally distinct policy domains
- enhanced possibilities for harvesting the practical lessons of a far wider range of innovation and access initiatives
- improved global inclusiveness, quality and availability of empirical data on a range of interconnected factors, including the global health burden, access and pricing of medicines, regulatory and trade policy settings, and national IP systems.

The cross-cutting character of these policy domains means that some themes are introduced in Chapter II, in the course of sketching out the general policy framework, and are later elaborated in Chapter III and/or Chapter IV, which look in more detail at how these elements have bearing on innovation and access, respectively. For example, the general elements and principles of IP policy are set out in Chapter II, while Chapter III elaborates aspects of IP policy, law and practice that bear particularly on innovation of medical technologies, and Chapter IV considers how specific aspects of IP impact access to technologies. Similarly, the broad rationale for regulation of medical technologies is set out in Chapter II, and Chapters III and IV deal with the implications of product regulation, respectively, for the innovation process and for access to medical technologies. Regarding trade policy, Chapter II sets out the main elements, and Chapter IV considers the impact of trade and trade policy settings on access to medicines and other medical technologies.

The global burden of disease necessitates dynamic responses

The global burden of disease is in transition. Populations are ageing due to progress in preventing and treating infectious diseases. But the burden of NCDs in low- and middle-income countries (LMICs) is rising, leading to a double burden of disease (see Chapter I, section C). While preventive measures with respect to lifestyle, physical inactivity, tobacco use and harmful use of alcohol, nutrition and environmental factors are key, the innovation system has to adjust to these changes in the global disease burden. The focus on access to medicines – which, in the past, has been on communicable diseases such as HIV/AIDS, TB and malaria – has broadened. Access to treatments for NCDs, including expensive cancer treatments in middle-income countries, will be the challenge of the future and the focus of the access debate (see Chapter IV, section B.4).

Access to medicines and the right to health

Access to medicines and health services is an element of the fulfilment of the right of everyone to the enjoyment of the highest attainable standard of health. Furthering access to medicines is also part of the United Nations Sustainable Development Goals (SDGs) (see Chapter II, section A.1–3). Lack of access to health technologies is rarely due to a single factor. The “value chain” of medicines and health products (see Figure 4.3) includes R&D, regulation, selection, procurement and supply, distribution, prescribing of medicines and diagnostics, dispensing, and responsible use (see Chapter IV, section A.2). Selection of the medications requires a health system to identify which medicines are most important to address the national burden of disease. This selection can be guided by the WHO Model List of Essential Medicines. Political commitment to adequate and sustainable funding is a basic condition for effective and sustainable access. Universal health coverage (UHC) has crystallized as a key aim of the SDGs (see Chapter IV, section A.1). Affordable prices are a critical determinant of access to medicines, especially in countries where the public health sector is weak and a large part of the population pays for medicines out of pocket. Generic medicine policies are key interventions to control health budgets and make medicines and other health products and services more affordable. Yet even generic medicines can still be unaffordable to health systems. A substantial part of the global population cannot access even the most basic medicines (see Chapter IV, section A.3). The overarching condition for providing access to needed medical technologies and health services is a functioning national health-care system (see Chapter IV, section A.4–12.).

Efforts to scale up treatment coverage for HIV/AIDS have become a major focus for policy-makers since the turn of the millennium. Low prices for generic antiretroviral treatments have helped governments and donor agencies strive to end the AIDS epidemic by 2030, as set out in target 3.3 of the SDGs (see Chapter IV, section B.1). In the area of antimicrobial resistance (AMR), there is a need to simultaneously secure wide availability of core antimicrobials, while also ensuring good stewardship (appropriate antimicrobial use to improve patient outcomes and minimize the development and spread of resistance) and the research in, and development of, new antimicrobials (see Chapter II, section A.5, Chapter III, section C.2 and Chapter IV, section B.2).

While most cases of TB can be successfully treated with medicines that have been available for many decades and are low cost, there has been growing concern about drug-resistant TB. Three new medicines were approved between 2012 and 2019 to treat drug-resistant TB, but access to them has been limited for reasons including

limited clinical data, lack of national registration, high prices and a lag in implementing new treatment guidelines (see Chapter IV, section B.3).

NCDs put an enormous and continuous financial strain on household budgets, and major gaps in access to both originator and generic medicines for NCDs persist. Shortcomings in access have been highlighted, for example, for newer cancer treatments and insulin for diabetes. For all countries, the cost of inaction far outweighs the cost of taking action on NCDs (see Chapter IV, section B.4). Health systems, including in high-income countries, face rising launch prices, in particular for cancer and “orphan” medicines.

Hepatitis C has seen treatment breakthroughs, but these new treatments entered the market at very high prices, leading to treatment being unavailable, rationed or delayed in numerous countries. Thanks to the conclusion of licensing agreements for some of the treatments, generics are available at relatively low prices in most LMICs (see Chapter IV, section B.5). National immunization programmes are a highly effective public health tool for the prevention of illness and the spread of infectious diseases. Distinct market conditions and know-how requirements create a different landscape for the development and dissemination of vaccines (see Chapter III, section B.4(e) and Chapter IV, section B.7; see also Chapter III, section E). Other areas addressed by the study are access to paediatric formulations and medical devices (see Chapter IV, sections B.6 and B.8).

Measures to contain costs and increase access

Governments employ many different means to contain costs for medical technologies. Policies aimed at increasing access concern areas such as procurement, pricing and IP (see Chapter IV, sections A and C), and they increasingly use health technology assessments to control costs (see Chapter IV, section A.4). Import tariffs (see Chapter IV, section D.1), various taxes (see Chapter IV, section A.5) and mark-ups along the supply chain (see Chapter IV, section A.6) can increase consumer prices and constrain access, and can also be targeted by cost-containment policies, which must, however, ensure sustainable margins for commercial suppliers in order to be economically viable.

Differential pricing applied by companies can be a complementary tool to increase access. Price differentials may exist across different geographical areas or according to differences in purchasing power and socio-economic segments (see Chapter IV, section A.4(g)). Another strategy for enhanced access to medicines is

to promote the development of local production capacity and leverage technology transfer. Policy coherence associated with local production is crucial to achieving sustainable public health and industrial development benefits (see Chapter IV, section A.10).

The WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) makes available to WTO members flexibilities in implementing access policies, such as patentability criteria and patent review procedures, and regulatory review exceptions (see *inter alia* Chapter II, section B.1 and Chapter IV, section C.3). With regard to access to patented products, these flexibilities include the use of compulsory or government-use licensing, wherein generic versions of the patented product can be locally manufactured or imported without the authorization of the patent holder.

Regulation of health technologies

Regulation of health technologies addresses essential health policy objectives: products must be safe, efficacious and of adequate quality. It also shapes the landscape for access and innovation. Regulatory review processes affect the time and cost it takes to bring new products to market and may delay market entry of new products (see Chapter II, section A.6).

Clinical trials are research studies in which groups of human participants are enrolled to evaluate the safety and/or effectiveness of new health technologies. The registration and publication of clinical trials are important for public health. The WHO considers registration of clinical trials a scientific and ethical responsibility and maintains the International Clinical Trials Registry Platform. From the perspective of public health policy, clinical trial results should be publicly available, so that researchers and other interested groups can assess the efficacy and potential side effects of new products (see Chapter III, section B.7). The emergence of biotherapeutic medicines has raised challenges for regulatory systems, notably with regard to regulating similar biotherapeutic (also termed biosimilar) products (see Chapter II, section A.6).

Another challenge for regulatory systems is posed by substandard and falsified (SF) medical products, which are found in all parts of the world but are typically a much greater problem in regions where the regulatory and enforcement systems are weak. To effectively combat SF medical products, regulatory intervention may be required, whereas the approach to falsified or counterfeit medical products may involve criminal investigation (see Chapter II, section B.1(f) and Chapter IV, sections A.12 and C.3(h)). WHO prequalification has contributed substantially

to improving access to quality medical products in developing countries through ensuring compliance with quality standards (see Chapter IV, section A.11(a)).

Innovation in medical technologies: the evolving policy landscape

Innovation in medical technologies requires a complex mix of private- and public-sector inputs. It differs from innovation more generally due to the ethical dimension of health research, a rigorous regulatory framework, liability questions and the high cost and high risk of failure. Economic, commercial, technological and regulatory factors have precipitated rapid change in the current landscape for R&D, involving more diverse innovation models and a wider range of active players. Providing adequate incentives to absorb the high cost and associated risks and liabilities is a central policy challenge; this has been the historic role of the patent system, in particular as applied to pharmaceuticals. While estimates vary of the actual cost of medical research and product development, innovation is undoubtedly costly and time consuming. The risk and uncertainty of innovation increases R&D costs in this sector, which include the development costs of the vast majority of inventions that fail before reaching the market (see Chapter III, section B.3). Rising expenditure for medical research has not been matched by a proportionate increase in new products entering the market, sparking a debate about research productivity and a quest for new models of innovation and for financing R&D. Many initiatives are exploring new strategies for product development, thus informing a rich debate about how to improve and diversify innovation structures to address unmet health needs. Current policy discussions have identified possibilities for open innovation structures, and a range of “push and pull” incentives, including schemes such as prize funds that would delink the price of products from the cost of R&D (see Chapter III, section C.5). The WHO Consultative Expert Working Group on Research and Development: Financing and Coordination recommended some of these options, including beginning negotiations on a globally binding convention or treaty on R&D (see Chapter III, sections C.4 and C.5(i)).

New thinking on industry’s role and structure and the public/private divide

The evolving innovation landscape is driving change in the pharmaceutical industry. Driving factors include rising global spending on prescription drugs, increasing payer scrutiny of prescription drug prices in high-income markets, the progress of non-profit initiatives engaged in medical research and product development, new

research tools and platform technologies, increased industry focus on personalized medicines, and the greater share of global demand from large middle-income-country markets. The historic industry model of vertically integrated in-house R&D is opening up to more diverse and collaborative structures, with major industry players developing products by integrating technologies that are licensed in or acquired through mergers and integration of smaller firms. Originator firms have also invested in generic production capacity. An increasing proportion of new medicines are for orphan indications. At the same time, most large pharmaceutical companies have withdrawn from antimicrobial research in light of the poor potential for investment returns.

The role of public research and academic institutions, increasingly, also in developing countries, has come under the spotlight as those institutions seek to reconcile public-interest responsibilities with the capital and product development capacity offered by private-sector partnerships (see Chapter II, section C; Chapter III, sections A and B; and Chapter IV, section D.5(d)).

Research and innovation gaps in neglected diseases and other areas: a policy challenge generating practical initiatives

For diseases that predominantly affect people living in poorer countries, the innovation cycle is not self-sustaining and fails to address their health needs, due to low potential for revenue, underfunded health services and generally weak upstream research capacity. A similar situation arises where sales are likely to be low, for example, in antibiotics and treatments or vaccines for emerging pathogens. In this type of environment, market-based incentives, such as patent protection, cannot by themselves address the health needs of developing countries.

The landscape of health research for these diseases has evolved. Product development partnerships (PDPs) have been a significant development over the past decade, drawing together not-for-profit entities and industry players, with major philanthropic funding, significantly increasing the number of products in development for neglected diseases, and identifying pathways regarding existing research gaps (see Chapter III, section C.6). Originator pharmaceutical companies also engage increasingly in philanthropic research. Several companies have established dedicated research institutes to research diseases disproportionately affecting developing countries or participated in cooperative projects to share assets and knowledge, such as WIPO Re:Search, which has been developed to make better use of IP-protected assets

and improve access (see Chapter III, section C.6–8). However, much more needs to be done by the international community in this area.

AMR has been recognized as a global threat, and is addressed by many countries in national action plans and by a WHO Global Action Plan on Antimicrobial Resistance. Private investments are insufficient to fill current R&D gaps. New non-profit initiatives have been established by a range of actors to reinvigorate the pipeline of drug candidates.

The IP system at the centre of debate on innovation and access

Apart from the patent system and test data protection, other relevant IP rights include trademarks, for example, the relationship with international non-proprietary names (INNs), and copyright, for example, covering the package insert of medicines (see Chapter II, section B.1(d)–(e)). The patent system has been widely used for health technologies, especially by the pharmaceutical sector. Indeed, the pharmaceutical sector stands out in terms of its dependence on patents to capture returns to R&D, but its role in innovation and how to enhance its effectiveness are matters of continuing debate (see Chapter III, section B). The rationale for having patents is to make investment in innovation attractive and to offer a mechanism that ensures that the knowledge contained in the patent documents is accessible. Patents can function to structure, define and build innovation partnerships. The role of intellectual property rights (IPRs) in the innovation cycle is addressed in Chapter III, section D. The impact of patents on access is complex and an area of particular focus. IP policy, the laws that embody the policy, and the administration and enforcement of those laws each aim to balance and accommodate a range of legitimate interests in a way that promotes overall public welfare (see Chapter II, section B.1).

The global IP framework is defined in particular by the treaties administered by WIPO and the TRIPS Agreement, which forms part of the WTO legal system and in turn incorporates the substantive provisions of several WIPO treaties, including the Paris Convention. The TRIPS Agreement sets minimum standards for IP protection and enforcement. For example, patents must be available for any innovation in all fields of technology, provided they are new, involve an inventive step (or are non-obvious) and are capable of industrial application (or are useful). Substantive patent examination leads to a higher degree of legal certainty regarding the validity of granted patents. Where search and examination are of low quality, this can have an adverse effect because it may raise false expectations in respect of the patent's validity. Review procedures allow courts and other review bodies to correct erroneous grant of patents and give relief where

necessary, in order to ensure that the patent system, as a whole, functions as a public-interest policy tool. Strict patentability criteria and strict patent examination supported by patenting examination guidelines contribute to preventing strategies employed to delay the entry of generic competition, such as “evergreening” (see Chapter III, section D.4(b) and Chapter IV, section C.1).

Integral to the patent system is the requirement to disclose the innovation described in patent documents, thus creating an extensive knowledge base. The resultant patent information serves as a tool for charting freedom to operate, potential technology partnerships, and procurement options, as well as giving policy-makers insights into patterns of innovation (see Chapter II, section B.1(b)(viii)–(xi)). While patent information has become more accessible, coverage of data for many LMICs remains a challenge. Recent trends show a growth in patent applications on health technologies from key upper-middle-income economies (see Chapter III, section A.5).

The protection of clinical trial data also illustrates the complex relationship between the IP system and innovation and access. Protecting these data against unfair commercial use is important given the considerable efforts made to generate these data, which are needed to bring new medicines to the market. For this purpose, in some jurisdictions, newly approved medicines are protected by periods of regulatory exclusivity, such as data exclusivity and market exclusivity, during which the medicines regulatory authority may not accept a submission for approval of a generic and/or may not approve a generic for marketing. The TRIPS Agreement requires protection of test data but does not specify the exact form it should take, and national authorities have taken diverse approaches (see Chapter II, section B.1(c)).

How IP is managed can determine its impact on public health

Appropriate licensing of patents can help build partnerships and enable innovation through cooperation to bring new health technologies to fruition. Private-sector licensing strategies typically aim at commercial objectives, but public-sector entities can use patents to leverage public health outcomes. New models of socially responsible licensing protect IP while ensuring that new health technologies are available and affordable. Public–private partnerships have resulted in creative licensing agreements that forgo profit maximization in favour of providing essential technologies to poorer countries at affordable prices. Voluntary licences also form part of corporate social responsibility programmes, especially for HIV/AIDS treatments. The Medicines Patent Pool

has reinforced the trend towards voluntary licensing programmes that increase access to medicines by enabling new formulations and enhancing provision of cheaper generic medicines for developing countries (see Chapter IV, section C.3(b)).

Policy options and IP flexibilities also impact on public health

A wide range of policy options and flexibilities are built into the international IP regime and can be used to pursue public health objectives. Action is needed at the regional and domestic levels to determine how best to implement such flexibilities, so that the IP regime responds to each country's individual needs and policy objectives. Key options include transition periods for least-developed countries (LDCs) (see Chapter II, section B.1), differing IP exhaustion regimes, refining the criteria for grant of a patent, making available pre-grant and post-grant review procedures, exclusions from patentability and exceptions and limitations to patent rights once granted, including regulatory review exception ("Bolar" exception) to facilitate market entry of generics, as well as compulsory licences and government-use licences. Countries have used one or more of these instruments to improve access to medicines for both communicable and noncommunicable diseases (see Chapter IV, section C.1–3). WTO members amended the TRIPS Agreement to permit wider use of compulsory licensing. The additional flexibility enables members that need to import medicines because of insufficient or no local manufacturing capacity to seek supply from generic manufacturers in other countries where the medicines are patent protected. For this purpose, potential exporting members can grant special compulsory licences exclusively for export under what is termed the "Special Compulsory Licensing System" (see Chapter IV, section C.3 and Annex III). While the legal scope for flexibilities is now clearer, thanks also to the Doha Declaration, and some flexibilities are widely implemented (such as "Bolar" exceptions), policy debate continues on the use of measures such as compulsory licensing.

International trade is an essential avenue to access

International trade is vital for access to medicines and other medical technologies, markedly so for smaller and less-resourced countries. Trade stimulates competition, which, in turn, reduces prices and offers a wider range of suppliers, improving security and predictability of supply. Trade policy settings – such as tariffs on medicines, pharmaceutical ingredients and medical technologies – therefore directly affect the accessibility of such products

(see Chapter II, section B.3–5 and Chapter IV, section D). Trade policy and the economics of global production systems are also key factors in strategic plans to build domestic production capacity in medical products. Non-discriminatory domestic regulations founded on sound health policy principles are also important for a stable supply of quality health products. Access to foreign trade opportunities can create economies of scale to support the costs and uncertainties of medical research and product development processes.

Developed countries have dominated trade in health-related products, but India and China have emerged as leading global exporters of pharmaceutical and chemical inputs and, in the case of China, of medical devices, and some other developing countries have shown strong export growth recently. Countries' imports of health-related products differ considerably according to their level of development, illustrating substantial and widening gaps in access: in 2016, a small number of countries (China, European Union member states, Japan and the United States) accounted for the majority of imports. Some new players are emerging from developing countries, while LDC imports have grown least, starting from a low base.

Import tariffs on health-related products can affect access: since they increase cost early in the value chain, their impact on price may be magnified. Developed countries have largely eliminated such tariffs, in line with the WTO Pharmaceutical Agreement of 1994. Other countries have reduced tariffs significantly, but the picture is still mixed: some developing countries structure tariffs to promote local production, while LDCs apply lower tariffs (see Chapter IV, section D.1).

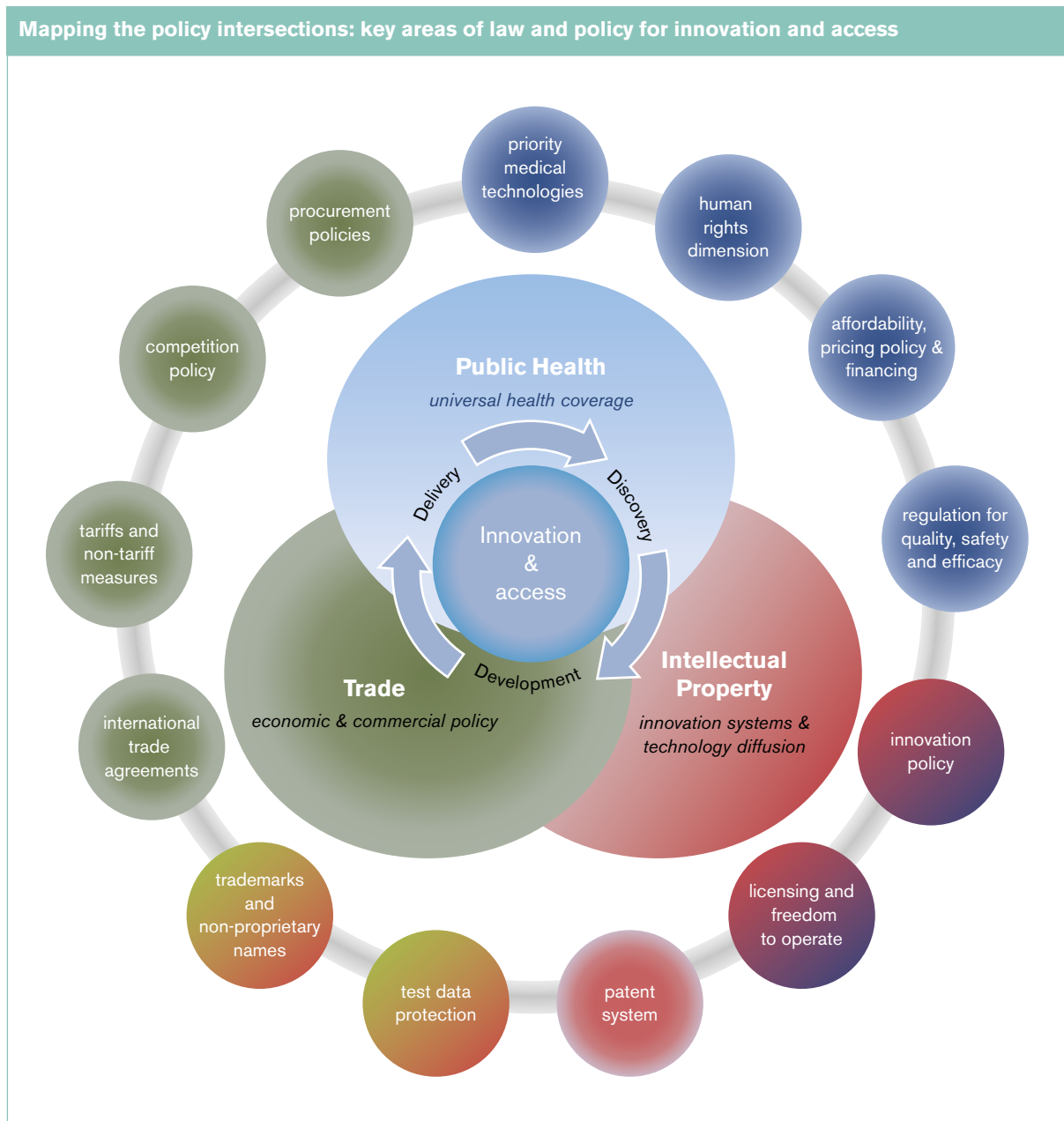
Competition policy promotes effective innovation and supports access

Competition policy is relevant to all stages in the process of supplying health technologies to patients, from their development to their sale and delivery. The creation of sound, competitive market structures through competition law and enforcement thus has an important role to play in both enhancing access to health technologies and fostering innovation in the pharmaceutical sector. It can serve as a corrective tool if IP rights hinder competition and thus constitute a potential barrier to innovation and access. Competition authorities in several jurisdictions have taken action to address anti-competitive practices in the pharmaceutical sector, including some patent settlements, certain licensing practices and pricing policies. Competition policy also has an important role to play in preventing collusion among suppliers of medical technology participating in procurement processes (see Chapter II, section B.2 and Chapter IV, section D.2).

Access to medical technologies through more effective government procurement

In many countries, access to medical technologies largely results from government procurement, with pharmaceuticals made available through public funds or subsidies. Procurement systems aim to obtain medicines and other medical products of good quality, at the right time, in the required quantities and at favourable costs. These principles are particularly important in the health sector, given the large expenditures, health impact of value for money and quality issues, with some programmes reportedly paying considerably more than necessary for medicines (see Chapter IV, section A.8).

Procurement policies favouring open and competitive tendering, coupled with the rational use of medicines, become all the more important in ensuring continued access in a fiscal climate in which national budgets are under pressure and philanthropic programmes face funding constraints. Good governance in procurement is consistent with increasing access to medical technologies through lower prices and uninterrupted supply. The WTO's plurilateral Agreement on Government Procurement provides an international framework of rules to promote efficiency and good governance in public procurement, with particular application to procurement of medicines, promoting transparency, fair competition and improved value for public expenditure (see Chapter II, section B.4).



Free trade agreements have increasing relevance to access

The international policy and legal framework has been made more complex by the growth of free trade agreements (FTAs) and international investment agreements, outside the established multilateral fora (see Chapter II, section B.5 and Chapter IV, section C.5). Policy debate in this context has focused on IP, such as patent term extensions, regulatory exclusivities and other measures, such as patent linkage, as well as pharmaceutical regulation provisions

in these agreements, and their impact on access to medicines. The later generation of FTAs often includes side letters or provisions confirming the Doha Declaration and, in particular, the right of WTO members to take measures to protect public health. These agreements also set standards in other policy areas with implications for access, notably, standards established on government procurement and competition policy, as well as preferential tariffs on pharmaceuticals, inputs and other health products. FTAs usually require implementation in domestic laws, which, in turn, can directly affect access to, and innovation in, medicines and medical technologies.

I. Medical technologies: the fundamentals

Against the background of the global burden of disease (GBD) and global health risks, this chapter outlines the fundamental imperative for collaboration. It demonstrates the need for a coordinated approach, taking into account health, intellectual property (IP) and trade variables, to ensure coherent decision-making in the area of public health at the international, regional and domestic levels.

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A. Public health and medical technologies: the imperative for international cooperation

Key points

- The WHO, WIPO and the WTO each have distinct, but complementary, mandates to work on issues relating to public health, IP and trade.
- Although this study focuses on relevant developments relating to medicines, it also covers other medical technologies, such as vaccines and medical devices, including diagnostics, due to their importance for achieving public health outcomes.
- Public health and IP policy-makers are faced with the challenging task of identifying the right mix of policy options to best advance their national objectives. Governments are therefore seeking more coherent, comprehensive and accessible information for policy debate.
- This study is designed to serve as a background reference for policy-makers in the widest sense – lawmakers, government officials, delegates to international organizations, non-governmental organizations (NGOs) and researchers.

Health is a fundamental and universal human right. The attainment by all peoples of the highest-possible level of health is the foundational objective of the WHO. The Preamble of the WHO Constitution emphasizes that international cooperation is essential for the promotion of health:

“The health of all peoples is fundamental to the attainment of peace and security and is dependent upon the fullest co-operation of individuals and States. The achievement of any State in the promotion and protection of health is of value to all. Unequal development in different countries in the promotion of health and control of disease, especially communicable disease, is a common danger.”

This central objective of the WHO, the essential logic of international cooperation, and the responsibility to take practical action have compelling implications for the international community. Accordingly, public health outcomes are also of importance to both WIPO and the WTO. In this regard, WIPO and the WTO focus on the social and developmental dimensions of innovation and the transfer and dissemination of technology, as well as access to these technologies. WIPO and WTO policy discussions and technical cooperation activities, including a range of programmes conducted in partnership with the WHO, have focused increasingly on public health matters. WTO members have stressed the need for a positive link between public health and the global trading system. In the Doha Declaration on the TRIPS Agreement and Public Health (Doha Declaration),¹ trade

ministers recognized “the gravity of the public health problems afflicting many developing and least-developed countries, especially those resulting from HIV/AIDS, TB, malaria and other epidemics”, and articulated “the need for the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) to be part of wider national and international action to address these problems”.

“Our three organizations, together with other stakeholders, share a responsibility to address these challenges so that innovative technologies come to the market, in affordable, sustainable and accessible form.”²

Roberto Azevêdo, *Director-General, WTO*

1. Policy coherence

The WHO, WIPO and the WTO each have distinct, but complementary, mandates to work on issues relating to public health, IP and trade. The three organizations therefore share a responsibility to strengthen practical dialogue between themselves and other partners in order to fulfil their mandates more effectively, to ensure the efficient use of resources for technical cooperation and to avoid duplication of activities.

Coherence is vital in international action to address public health problems. Such coherence has never been more important for the technical cooperation work of the

three organizations than it is at the present time. The WHO brings vast expertise in all areas of public health, including medicine and vaccine policies, medical devices, regulatory questions, pricing and procurement, in addition to other factors affecting access to medicines. WIPO is uniquely positioned to help work towards creating a truly global view and understanding of the IP system, including the flexibilities in implementation of the patent system at the national level, to provide information on patents, including information on the patent status of key medicines and vaccines in developing countries, and to lend its expertise on patent law and its interplay with public policy. The WTO works on several aspects of trade policy that have direct relevance to public health, including IP rules and flexibilities within the international legal system, as they affect both the access and innovation dimensions.

The Doha Declaration has served as a catalyst for developing coherence at the international level. In conjunction with its role of making public health issues a central focus of work carried out by the WTO on IP and international trade, the Doha Declaration has been taken up in a series of World Health Assembly (WHA) resolutions on ensuring accessibility to essential medicines and public health, innovation and IP. Notably, the Doha Declaration was a point of reference in the negotiations that led to the adoption of the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI)³ in 2008. The 2007 WIPO Development Agenda (WIPO, 2007) deals extensively with flexibilities in international IP law, including the health-related flexibilities specifically identified in the Doha Declaration.

These mandates and competencies have been at the centre of policy debates. The UN 2030 Agenda for Sustainable Development, adopted in 2015, calls for cooperation to support sustainable development (target 17.16) and emphasizes the importance of research and development and access to medicines in accordance with the Doha Declaration (target 3.b).

A number of UN high-level meetings have called for cooperation and policy coherence as being central to tackling urgent health issues. For example, the 2016 Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance⁴ called for enhanced “capacity-building, technology transfer on mutually agreed terms and technical assistance and cooperation for controlling and preventing antimicrobial resistance (AMR), as well as international cooperation and funding to support the development and implementation of national action plans”. Similarly, the 2017 Moscow Declaration to End TB and the 2018 UN High-Level Meeting on Non-Communicable Diseases called for increased collaboration among stakeholders and technical partners.⁵

“[U]niversal health coverage is one of the targets the nations of the world have adopted in the Sustainable Development Goals. And it’s also our top priority at WHO. But we’re aware that achieving universal health coverage is not the job of WHO alone, or of the health sector alone. It will take cooperation between all of us.”⁶

Tedros Adhanom Ghebreyesus, *Director-General, WHO*

2. Scope of the study

This study focuses on issues relating to access to medical technologies and innovation. Besides medicines and vaccines, the study addresses other medical technologies, such as medical devices, including diagnostics, due to their importance for achieving public health outcomes. Some of the lessons learned about access and innovation with respect to medicines may be useful with respect to these other medical technologies. While there are significant differences regarding the role of IP for innovation and access, other important determinants for public health, such as health promotion, lifestyle modification, access to adequate and nutritious food, health infrastructure, human resources, health financing and health systems (except where these directly relate to medicines and medical technologies), do not fall within the scope of this study.

3. The need for this study

Governments have choices to make regarding the appropriate implementation of policy instruments in their domestic systems and practices. Even though international standards apply to most of the main policy instruments – in particular, IP – there is “policy space” within and around those standards. Public health and IP policy-makers are faced with the challenging task of identifying the right mix of policy options to best advance their national objectives. Governments are therefore seeking more coherent, comprehensive and accessible information for policy debate. The aim of the technical cooperation activities of the WHO, WIPO and the WTO is to facilitate understanding of the full range of options and their operational context. This study draws together the materials used in technical cooperation and addresses emerging needs for information in an accessible, systematic format, to support ongoing collaborative efforts.

“[I]nnovation exists to improve the quality of life, the foremost basis of which is health, without which nothing really matters. This recognition opposes a humanitarian imperative to economic rationalism.”⁷

Francis Gurry, *Director General, WIPO*

The Doha Declaration recognized that “intellectual property protection is important for the development of new medicines”. At the same time, it also recognized the concerns about IP effects on prices. The challenge for governments is to use the policy instruments at their disposal to address both aspects in a mutually reinforcing manner. Since the early 2000s, policy-makers have sought effective ways to strengthen the positive linkages between, on the one hand, the private sector’s capacity to finance research and development (R&D) and, on the other hand, the public policy goals of selecting, supplying and using medicines in the most rational way.

“Universal health coverage is not a dream for the future. It is a reality now. Countries at all income levels are proving that universal health coverage is achievable and affordable, with domestic resources.”⁸

Tedros Adhanom Ghebreyesus, *Director-General, WHO*

Rising health-care costs have led to increased national public health budgets and higher public expectations for health care. In difficult economic times, there is even more reason to evaluate the efficiency and fairness of health services, including expenditure on medicine and medical technology. Effective delivery of health care also means adapting technologies to diverse local needs and priorities. The world is facing an increased burden of non-communicable diseases (NCDs). The increased availability of patents for medicines has implications that pose a further challenge in a wider range of countries, notably in key low-cost exporting countries that have traditionally specialized in generic medicine production. The evolving disease burden, the lack of appropriate medicines required for treating neglected diseases and the challenges of AMR and emerging pathogens with pandemic potential all require the development of new treatments, vaccines and diagnostics. Innovation needs to be encouraged – in terms of both inventing new products and providing effective systems to bring them

through very complex product development stages, and to market and deliver them to patients. Policy-makers have recognized the need to look beyond conventional approaches to R&D to address the innovation gap – particularly in the area of neglected diseases, pathogens such as Ebola virus and resistant bacterial infections.

“Trade and the multilateral trading system can help in creating a more favourable global environment for public health policies and the implementation of a balanced and effective intellectual property system.”⁹

Roberto Azevêdo, *Director-General, WTO*

4. Who should read this study?

This study is designed to serve as a background reference for policy-makers in the widest sense – lawmakers, government officials, delegates to international organizations, non-governmental organizations (NGOs) and researchers who seek a comprehensive presentation of the full range of issues, including institutions and legal concepts with which they may be unfamiliar. It is also designed to serve as a factual resource for the three organizations’ technical cooperation activities. Nothing in the study should be taken as a formal position or the interpretation of rights and obligations by any of the three organizations, or by any of their respective members. Actual policy choices and interpretations of member states’ rights and obligations remain exclusively a matter for governments.

“Health, innovation and trade are, in the present configuration of the world, inextricably connected and mutually dependent. We will not be able to enjoy relative health security unless we continue to innovate and bring on new technologies to improve health outcomes.”¹⁰

Francis Gurry, *Director General, WIPO*

B. The cooperating agencies: the WHO, WIPO and the WTO

Key points

- The WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends.
- WIPO is the specialized agency of the United Nations dedicated to developing a balanced and accessible IP system that rewards creativity, stimulates innovation and contributes to economic development in the public interest.
- The core mission of the WTO is to open trade, based on a rules-based, inclusive international trading system. It provides a negotiating forum to its members, monitors the implementation of trade agreements, settles disputes upon request by its members and builds capacity, including as regards the TRIPS Agreement protection and enforcement standards and related policy options.
- Partnership is crucial for an effective international response to the ever-evolving challenges at the interface of public health, IP and trade. For this purpose, the WHO, WIPO and the WTO collaborate with other international and regional organizations, as well as with civil society and the private sector.

This section provides a brief overview of the specific roles, mandates and functions of the WHO, WIPO and the WTO, which cooperate within the general international framework on issues related to the interface between public health, IP and trade concerning innovation in, and access to, medical technologies.

1. World Health Organization

The WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends.

Monitoring the impact of trade and intellectual property rights (IPRs) on public health is one of the strategic areas of the work of the WHO. Following the adoption of the TRIPS Agreement, the Forty-ninth World Health Assembly (WHA), in May 1996, adopted the first mandate of the WHO to work on the interface between public health and IP.¹¹ In subsequent years, many more resolutions were adopted, continually broadening and reinforcing the WHO mandate to work on issues related to public health, IP and trade.

In May 2003, WHO member states decided to establish the Commission on Intellectual Property Rights, Innovation

and Public Health (CIPIH) to examine the interface between IPRs, innovation and public health.¹² Its 2006 report (WHO, 2006a) contained 60 recommendations aimed at fostering innovation and improving access to medicines. It concluded that:

“Intellectual property rights have an important role to play in stimulating innovation in health-care products in countries where financial and technological capacities exist, and in relation to products for which there are profitable markets. In developing countries, the fact that a patent can be obtained may contribute nothing or little to innovation if the market is too small or scientific and technological capability inadequate. [...] Where most consumers of health products are poor, as are the great majority in developing countries, the monopoly costs associated with patents can limit the affordability of patented health-care products required by poor people in the absence of other measures to reduce prices or increase funding.”

Following CIPIH recommendations, WHO member states adopted in 2008 and 2009 the GSPA-PHI, which was a major step forward in the process of achieving global consensus on practical action on public health, innovation and IP. The GSPA-PHI reaffirmed and extended the mandate of the WHO to work at the interface of public health and IP. A comprehensive evaluation and an overall programme review of the GSPA-PHI were published in 2016 and 2017, respectively (Capra International, 2016; WHO, 2017e).

In 2019, the WHO Secretariat developed a new, comprehensive Access Roadmap, which outlines the programming of the WHO's work on access to medicines and vaccines for the period 2019–2023, covering implementation of the GSPA-PHI as well as other relevant strategic documents, such as the WHO Global Strategy on Human Resources for Health: Workforce 2030.¹³

The WHO has produced a large body of material to provide evidence-based guidance to its member states in order to support them during the process of shaping their policies on public health and IP. Examples of such guidance include patent landscape analyses for key hepatitis C medicines (WHO, 2016d), a range of detailed analyses of opportunities and challenges in local production¹⁴ and a technical background document on intersections in trade and health (WHO, 2015d).

The WHO also fulfils technical functions outside the scope of the GSPA-PHI that are of significant relevance to the intersection of medicines, IP and trade. For example, the Model List of Essential Medicines (EML),¹⁵ reviewed every two years, comprises the medicines that satisfy the priority health-care needs of the population,¹⁶ and is used by many countries as a basis for developing national formularies (lists) to guide procurement, among other purposes. As another example, the WHO provides a quality assurance mechanism through its Prequalification platform.¹⁷ Hundreds of medicines and other health products have been quality assured through WHO prequalification, without which, in many cases, quality assurance would have been difficult or impossible (see Chapter IV, section A.11 (a)).

2. World Intellectual Property Organization

WIPO is the specialized agency of the United Nations dedicated to developing a balanced and accessible IP system which rewards creativity, stimulates innovation and contributes to economic development in the public interest.

The core activities of WIPO include:

- administering multilateral treaties and supporting the evolution of the international legal IP frameworks
- providing global IP services for a fast, efficient and more cost-effective route for IP protection across borders, and also to facilitate alternative dispute resolution services
- cooperating with governments, intergovernmental and non-governmental organizations, and with public and private-sector stakeholders to assist in developing and implementing national IP and innovation strategies, developing appropriate regulatory frameworks and

building the infrastructure and human capacity needed to harness the potential of IP for economic development

- developing technical platforms to facilitate cooperation among IP offices
- developing free databases of patents, trademarks and industrial designs to facilitate access to knowledge
- building awareness, understanding and respect for IP
- working in partnership with the United Nations and other organizations to identify IP-based contributions to climate change, food security, public health and other global challenges.

In 2007, the WIPO General Assembly established the WIPO Development Agenda¹⁸ to ensure that development considerations form an integral part of the work of WIPO. Development is considered to be a cross-cutting issue that impacts various sectors of the organization. The 45 Development Agenda recommendations guide the work of WIPO.

Several areas of the work carried out by WIPO have particular relevance for public health.

The WIPO Global Challenges Program addresses innovation and IP as they relate to global and interconnected issues, such as climate change, public health and food security. The Program seeks to raise awareness and understanding of the interplay among innovation, technology transfer and the dissemination of technology, among other things, as they relate to health innovation and access to medicines. WIPO Re:Search, a public–private partnership (PPP), aims at enabling the sharing of IP and expertise to promote the development of medicines to treat neglected diseases (see Chapter III, section C.8).

WIPO facilitates discussion among member states on the identification of issues in patent law that require multilateral attention and actions, with a view to keeping pace with the rapidly evolving technological, economic and social environments.¹⁹ The continuing growth in the number of patent applications worldwide and the constant development of technologies present a challenge for the effective and efficient handling of patent applications, for the achievement of high quality in patents that are granted, and for the role of patents in contributing to innovation and the dissemination of technology. WIPO advises its member states not only on establishing and implementing the requisite legal framework but also on how to assess options and to develop coherent policy strategies. In 1995, WIPO and the WTO established an agreement as a basis for collaboration in the provision of legal and technical assistance relating to the TRIPS Agreement.²⁰ WIPO member states have been engaged in discussions in the Standing Committee on the Law of Patents (SCP)²¹ on issues related to patents and health since 2011 (see Box 2.10).²²

The WIPO Traditional Knowledge Program aims at achieving more effective use of IP principles and systems for the legal protection of traditional knowledge, including traditional medicine.²³

The WIPO Program for Building Respect for IP facilitates international policy dialogue on IP, notably through the work of the Advisory Committee on Enforcement (ACE) (see Chapter II, section B.1(f)(iii)) and provides technical and legislative assistance to member states on IP law enforcement and awareness-raising.

In line with its goal of fostering international policy dialogue on IP and public health, WIPO also engages substantively with other relevant stakeholders – UN and intergovernmental organizations, governments of member states, civil society and NGOs, as well as the private sector and academia.

3. World Trade Organization

The core mission of the WTO is to open trade, based on a rules-based, inclusive international trading system. It provides a negotiating forum for its members, monitors the implementation of trade agreements, provides assistance to build capacity, including as regards the TRIPS Agreement protection and enforcement standards and related policy options, and resolves disputes upon request by its members. International trade and trade rules intersect with public health objectives in various areas and in many different ways. Most directly, integration into the world economy can enhance access to the most basic requirements for good health, such as the safe supply of food or access to health-related products and services. Trade also offers the opportunity for economies to grow and thus contributes to the alleviation of poverty and ill health.

The importance of public health has been recognized in the rules of the multilateral trading system since 1947. The General Agreement on Tariffs and Trade (GATT), adopted in 1947 and subsequently incorporated in the GATT 1994, contains an exception in Article XX(b), which explicitly recognizes the right of governments to enact trade-restricting measures that are necessary to protect human life and health. The right to take measures for the protection of health is recognized in a number of provisions in other WTO agreements, including the TRIPS Agreement.²⁴

The implementation of the rights and obligations established under the covered agreements is overseen by the Ministerial Conference and subsidiary WTO bodies. Ministers have recognized that under WTO rules no country should be prevented from taking measures for the protection of human, animal or plant life or health, or of the environment, at the levels it considers appropriate, subject to certain requirements.²⁵

In the area of IP, the search for a balance between the need to protect IPRs to provide incentives for R&D on the one hand and, on the other hand, to address concerns about the potential impact of such protection on the health sector – in particular its effect on prices – has been an important consideration in the WTO's work. A number of provisions in the TRIPS Agreement are directly relevant to public health. WTO members have the flexibility to interpret and implement these provisions in a manner supportive of their right to protect public health. The importance of creating a positive, mutually reinforcing link between the IP system and access to medicines was recognized in the Doha Declaration in 2001. In 2003, the General Council of the WTO adopted an additional flexibility in the form of a special compulsory licensing system for export of medicines. This system is designed to deal with the difficulties of WTO members lacking sufficient manufacturing capacities to make effective use of compulsory licensing when they have to import the medicines needed from third-country suppliers where patents have been granted.

The WTO serves as a useful and effective forum for discussions regarding the interface between IPRs and public health, for example, through discussions at the TRIPS Council.

The WTO Secretariat aims to enhance the participation and informed decision-making of its members and observer governments through awareness-raising, capacity-building and the provision of factual and technical information. To achieve this objective, the WTO regularly engages in technical assistance activities, which comprehensively cover the relationship between trade, IPRs and public health.²⁶

A core function of the WTO is to resolve disputes among its members concerning their compliance with their commitments under the Marrakesh Agreement Establishing the World Trade Organization (WTO Agreement). The WTO has developed extensive jurisprudence concerning the intersection between public health and trade rules under the GATT 1994, the Agreement on Technical Barriers to Trade (TBT Agreement), the TRIPS Agreement and other agreements.

4. Trilateral cooperation

Since 2001, the principles enshrined in the Doha Declaration have shaped the framework for multilateral cooperation in this area and have guided the WHO, WIPO and the WTO, including for the provision of technical and policy support requested by members, joint publications and mutual participation in training programmes.

WTO Agreements and Public Health: A Joint Study by the WHO and the WTO Secretariat (WHO and WTO, 2002) examined the linkages between trade and health

policies in general, to enable trade officials and health officials to better understand and monitor the effects of their work on each other's areas of responsibility. The study remains a useful resource on many issues, such as health services, infectious disease control, food safety and tobacco.

The 2007 WIPO Development Agenda – specifically, Recommendation 40 – requested the WIPO Secretariat to intensify its cooperation on IP-related issues with relevant international organizations, in particular with the WHO and the WTO, in order to strengthen the coordination for maximum efficiency in undertaking development programmes.²⁷ In the WHO, the GSPA-PHI adopted in 2008 requested the WHO “to coordinate with other relevant international intergovernmental organizations, including WIPO, WTO and UNCTAD, to effectively implement the global strategy and plan of action”.²⁸

Given that partnership is crucial for an effective international response to the ever-evolving challenges facing public health, the WHO, WIPO and WTO Secretariats have intensified interagency collaboration on matters related to public health, IP and trade.²⁹ Within their respective mandates and budgets, common activities are planned and carried out jointly to ensure that data, experiences and other information are exchanged, and to ensure that the best use is made of the available resources (Krattiger et al., 2015).

This collaboration relies on cooperation with other international and regional organizations, as well as with civil society and the private sector. The WHO, WIPO and the WTO have therefore broadened the base of their collaborative and consultative networks dealing with

public health issues. In their capacity-building activities, the three organizations regularly include speakers from relevant international organizations, industry and civil society.

Since 2010, the WHO, WIPO and the WTO have organized a series of joint technical symposia (see Box 1.1).³⁰ These are designed to improve the flow of practical information to guide and support technical cooperation in the future. Similarly, the launch of the initial version of this trilateral study has been a further milestone on the road towards stronger cooperation. The study also laid the groundwork for a distance learning course, Promoting Access to Medical Technologies and Innovation, on the intersections between public health, IP and trade, which commenced in 2016.³¹

5. Other international key stakeholders

The period since 2001 has seen dramatic growth in the number and diversity of participants in international policy debates concerning innovation in, and access to, medical technologies. Consideration of these issues necessarily entails a multidisciplinary and pluralistic approach. A distinctive feature of the debates has been the range of perspectives during discussions, coupled with the depth of expertise and practical experience that has been drawn from international and intergovernmental organizations, procurement and product development initiatives, and NGOs such as public health advocates and industry associations. The study recognizes and values the work of many others, and no suggestion is made about the relative importance of any organization, whether mentioned or not.

Box 1.1: WHO–WIPO–WTO technical symposia

- 2010 Access to Medicines: Pricing and Procurement Practices³²
- 2011 Access to Medicines: Patent Information and Freedom to Operate³³
- 2013 Medical Innovation – Changing Business Models³⁴
- 2014 Innovation and Access to Medical Technologies: Challenges for Middle-Income Countries³⁵
- 2015 Public Health, Intellectual Property and TRIPS at 20: Innovation and Access to Medicines: Learning from the Past, Illuminating the Future³⁶
- 2016 Antimicrobial Resistance – How to Foster Appropriate Use of Antibiotics, Access and Innovation³⁷
- 2018 Sustainable Development Goals: Innovative Technologies to Promote Healthy Lives and Well-Being³⁸
- 2019 Cutting-edge Health Technologies: Opportunities and Challenges³⁹

C. The global burden of disease and global health risks

Key points

- Understanding the patterns and trends of the global burden of disease (GBD) is important in order to develop effective strategies to improve health and identify the range of medical technologies that are needed.
- Longer life expectancies and population ageing have resulted in an increased focus on non-communicable diseases (NCDs) in low- and middle-income countries, in addition to high-income countries. NCDs caused 60 per cent of the burden of disease (measured by DALYs) in 2016.

This section introduces the GBD concept and explains trends related to it.

International efforts to address public health issues need to be grounded in a clear understanding of GBD, and future efforts should be guided, as far as possible, by best estimates on the evolving disease landscape. The GBD measurement methods were developed in order to generate comprehensive and internally consistent estimates of mortality and morbidity by age, sex and region. The burden of disease studies aim to summarize overall loss of health associated with diseases and injuries. The key feature of this concept is a summary measure called the disability-adjusted life year (DALY), which is now widely used to measure the burden of ill health. The DALY concept was introduced as a single measure to quantify the burden of disease, injuries and risk factors (Murray and Lopez, 1996). The DALY is a measure that combines years of life lost due to premature death, and years of life lived in less than full health (see Box 1.2).

1. Current estimates of global and regional burden of disease

Globally, the average burden of ill health in 2016 was 358 DALYs per 1,000 people, a reduction of 22 per cent since 2000.⁴⁰ Global life expectancy at birth has increased from 67 years in 2000 to 72 years in 2016.⁴¹ The WHO

African Region bore the highest burden of ill health per person in 2016, with an average of 587 DALYs per 1,000 population. This is more than twice the burden of disease in the region with the lowest DALY rates (270 per 1,000 population) in 2016, the WHO Western Pacific Region.⁴²

2. Trends: major cause groups contributing to the total disease burden

The proportional contribution of the three major cause groups to the total disease burden has changed substantially since 1990, as part of the so-called “epidemiological transition” (Jamison et al., 2013). Globally in 2000, communicable, maternal, neonatal and nutritional (CMNN) conditions grouped together contributed 43 per cent of the total disease burden in terms of DALYs, and NCDs contributed 47 per cent. By 2016, the share of NCD burden had increased to 60 per cent, more than double the burden caused by CMNN diseases, which represented 29 per cent of burden in DALYs. The share of injury burden has changed little, from 10 per cent of DALYs in 2000 to 11 per cent in 2016.⁴³

The three leading contributors to overall DALYs in 2016 globally were ischaemic heart disease, stroke and lower respiratory infections (see Figure 1.1). The leading causes of death in 2016 were ischaemic heart disease, stroke and chronic obstructive pulmonary disease (see Figure 1.2).

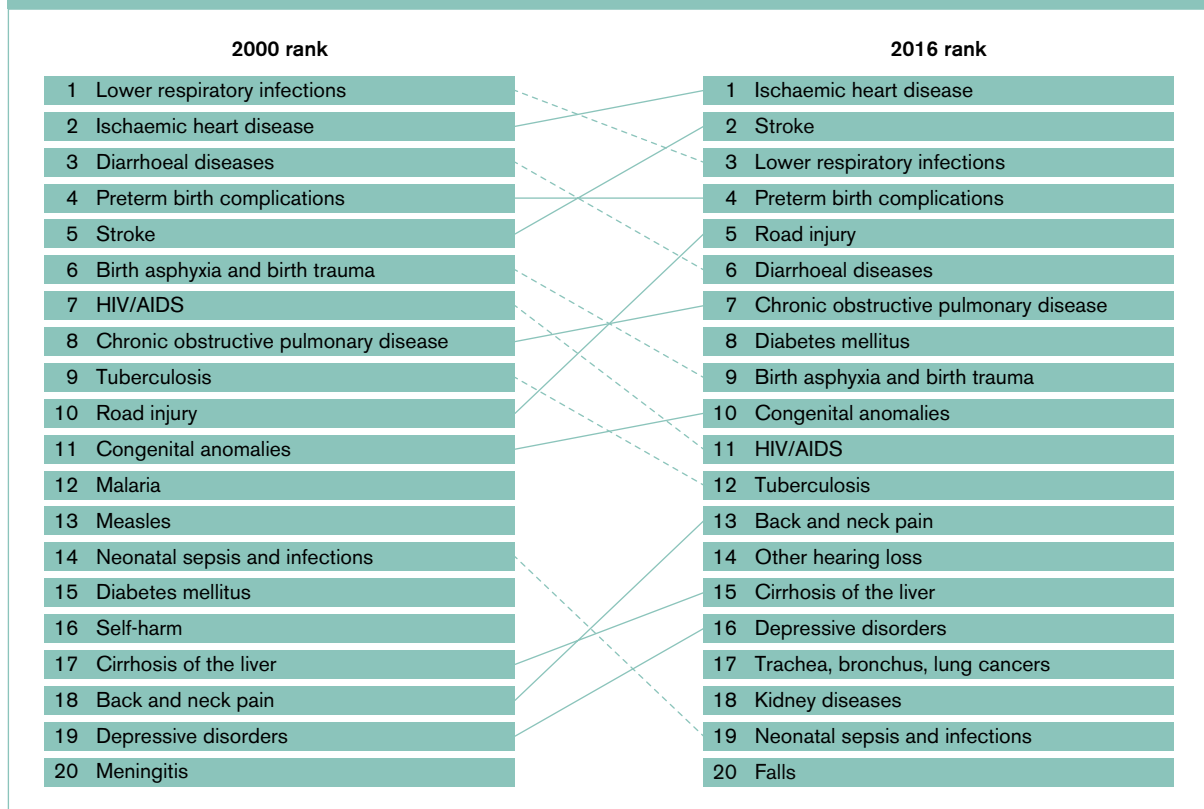
Box 1.2: The disability-adjusted life year (DALY)

The DALY extends the concept of potential years of life lost due to premature death to include equivalent years of “healthy” life lost by virtue of being in states of poor health or disability (Murray and Lopez, 1996). One DALY can be thought of as one lost year of “healthy” life, and the burden of disease can be thought of as a measurement of the gap between the current health status and an ideal situation where everyone lives into old age, free of disease and disability. DALYs for a disease or injury cause are calculated as the sum of the years of life lost (YLL) due to premature mortality in the population and the years lost due to disability (YLD) for prevalent sequelae associated with the disease or injury. YLL is calculated from the number of deaths at each age multiplied by a global standard life expectancy of the age at which death occurs. YLD for a particular cause in a particular time period is estimated as follows:

$$\text{YLD} = \text{prevalence} \times \text{disability weight}$$

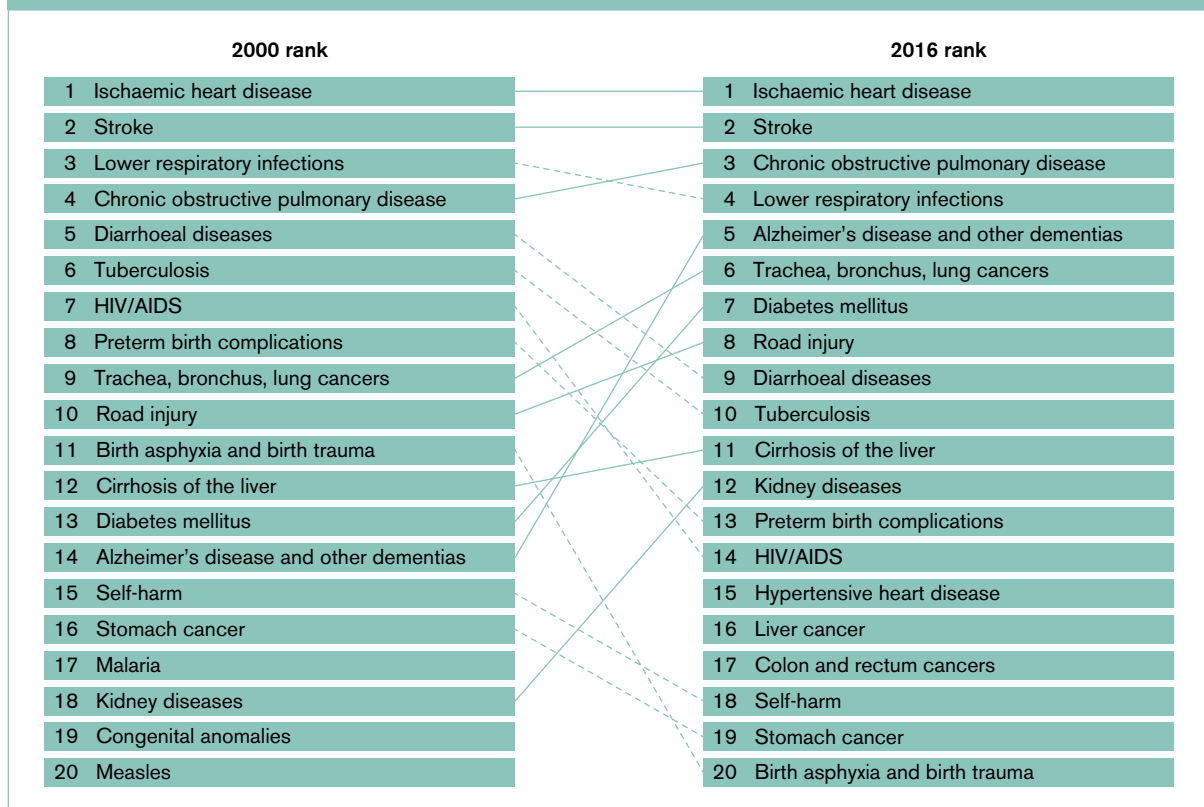
The weight factor reflects the severity of the disease on a scale from 0 (perfect health) to 1 (death).

Figure 1.1: Leading causes of disease burden in DALYs in 2000 and 2016 globally



Source: World Health Organization. Disease burden and mortality estimates, available at: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates>.

Figure 1.2: Leading causes of death in 2000 and 2016 globally



Source: World Health Organization. Disease burden and mortality estimates: Cause-specific mortality, 2000–2016, available at: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates>.

3. Trends in global health risks

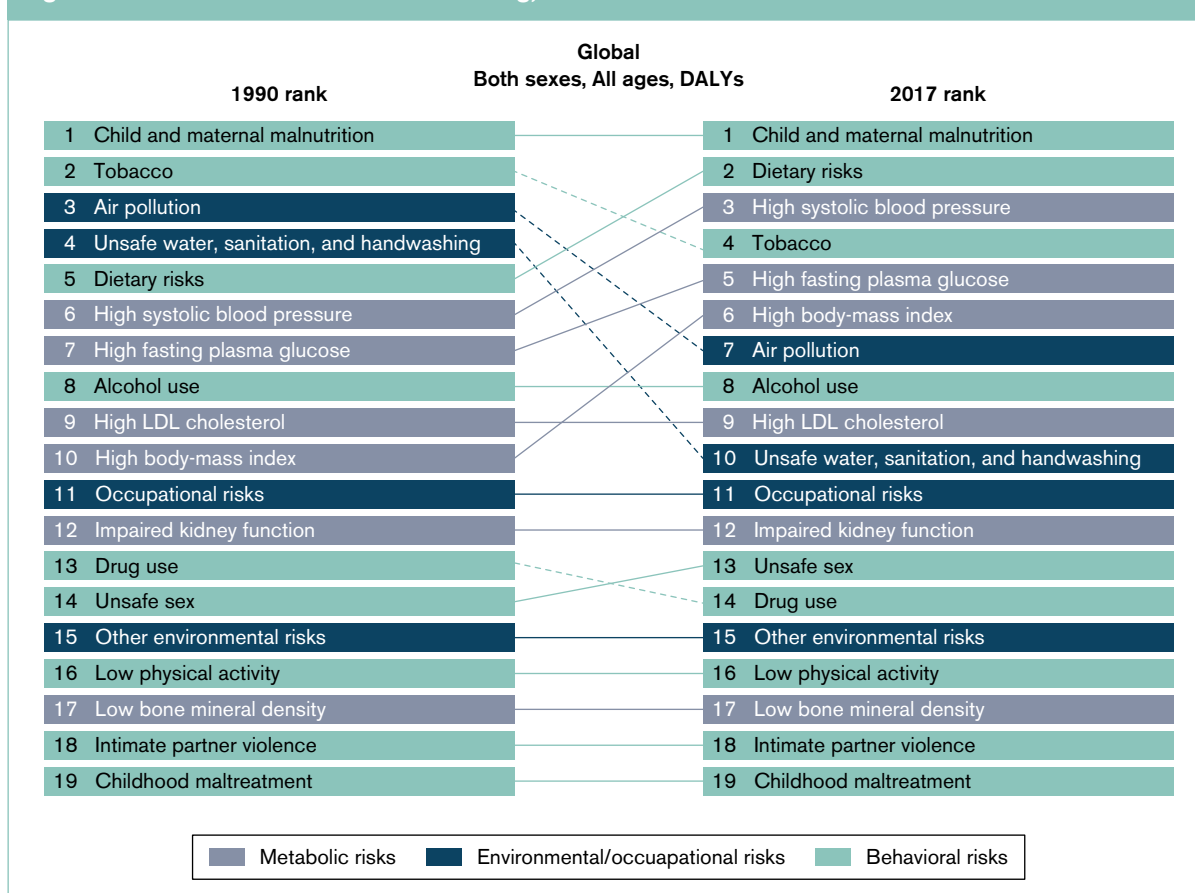
Mortality and burden of disease can be attributed to selected major risks. In this context, the WHO defines “health risk” as “a factor that raises the probability of adverse health outcomes” (WHO, 2009). In 2017, the leading global risks for mortality were dietary risks (responsible for 19 per cent of deaths globally), high systolic blood pressure (19 per cent), tobacco use (14 per cent), high fasting plasma glucose (12 per cent), air pollution (9 per cent), high body-mass index (8 per cent), high LDL cholesterol (8 per cent), child and maternal malnutrition (6 per cent), alcohol use (5 per cent) and impaired kidney function (5 per cent) (Level 2 risk groups).⁴⁴

The leading global risks for burden of disease as measured in DALYs (see Figure 1.3) are child and maternal malnutrition (13 per cent of global DALYs),

dietary risks (10 per cent), high systolic blood pressure (9 per cent), tobacco (9 per cent), high fasting plasma glucose (7 per cent), high body-mass index (6 per cent), air pollution (6 per cent), alcohol use (4 per cent), high LDL cholesterol (4 per cent) and unsafe water, sanitation and handwashing (3 per cent).⁴⁵

Health risks are in transition: populations are ageing due to successes against infectious diseases. At the same time, patterns of physical activity, as well as food, alcohol and tobacco consumption, are changing. Low- and middle-income countries (LMICs) now face a double burden of increasing chronic, non-communicable conditions, as well as the communicable diseases which traditionally affect the poor. Understanding the role of these risk factors is important for developing clear and effective strategies for improving global health (WHO, 2009; Jamison et al., 2013).

Figure 1.3: Global burden of disease ranking, 1990 and 2017



Source: Institute for Health Metrics and Evaluation. Global Burden of Disease study, available at: <http://ihmeuw.org/4sdh>. Data are given as Level 2 risk groups.

D. Factors shaping public health policy

Key points

- Achieving sustainable and more equitable public health outcomes depends on the dynamic interplay of national public health policy, including effective health systems and adequate financing of health systems, a sound regulatory environment, trade and competition settings, procurement policies, innovation strategies and the IP system.
- Innovation cannot take place in isolation from concerns about access, and access has to be seen in the broader context of the need for innovation and effective regulation.
- There is a continuing need for new, adapted and more effective health technologies to meet the challenges presented by the evolving global burden of disease.
- An increasing number of national, regional and international policy processes, including the framing of trade agreements, involving a multiplicity of agencies, are tackling issues that impact access to, and innovation in, medical technologies.

1. Seeking effective outcomes within a complex policy environment

Building a sustainable global response to the demand for both innovations in medical technology and effective and equitable access to needed technologies is a complex and constantly evolving challenge. While it is often expressed in abstract or political terms, the effort fundamentally concerns how to deliver improved health outcomes. Creating new medical technologies, assessing these technologies, providing for their effective distribution and ensuring that they are used rationally are, ultimately, practical processes. These processes range from the work of laboratory research scientists to the care provided by community health workers in a rural clinic.

The policy, economic and legal environment influences and can determine the actions, choices, priorities and allocation of resources that are applied at a practical level. This policy environment is complex: it comprises laws, regulations and policy instruments, at national, regional and international levels, which address diverse fields, including public health, international trade and the IP system. Effective progress and sustained impact on public health cannot be attained by working within the confines of one discrete set of policy measures or legal instruments. Lack of coherence, or the prospect of conflict, between law and policy in different fields can thwart progress and impede practical benefits. It follows that understanding the intersections between these different policy measures is key to ensuring that they work harmoniously for overall public health benefit.

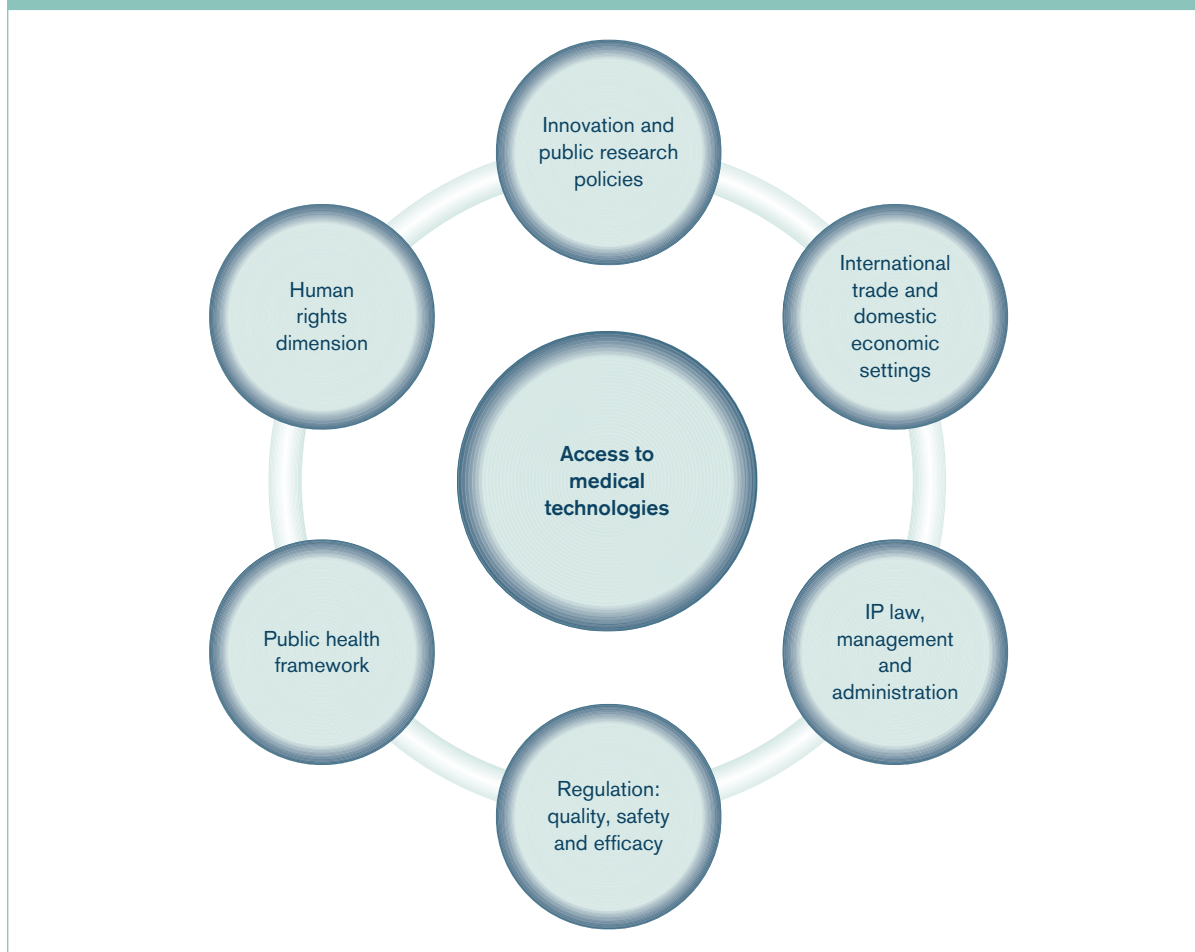
2. Transforming policy intersections

The emphasis on “intersections” – understanding the linkages and interplay between distinct areas of law and policy (see Figure 1.4) – is a consistent theme in recent debate on public health policy. This study identifies two levels of intersection:

- Points of interaction between the legal and policy principles in different domains, so that law and policy instruments can be interpreted and applied in practice to promote public health
- The integration of sets of data drawn from diverse fields, so that policy-makers can work from an improved, integral base of information, combining data on public health, determinants of access to medical technologies, coverage of relevant IP rights and trade settings.

Trade and commercial perspectives are sometimes regarded as being essentially at odds with promoting public health. Yet the commercial environment, the promotion of competition and of private-sector innovation, and the regulation of trade are crucial determinants for access to medicines. International trade is vital for access to medical technologies, and no country is entirely self-sufficient, even those that have strong local production. Economies of scale for industry and a competitive market can improve affordability of medical technologies. Openness to international trade generally promotes competition, improving affordability and access. By enabling a wider range of suppliers to serve the population, it can also enhance security of supply. Trade policy settings, such as tariffs, quotas and other

Figure 1.4: The distinct policy domains of public health



regulations, have a direct effect on prices and availability. Many governments have taken national legal and policy measures to enable or promote generic competition in the supply of medicines in order to reduce prices. WTO rules have been interpreted in dispute settlement to provide for public health objectives, such as enhanced entry of generic medicines, and the Doha Declaration has affirmed that the TRIPS Agreement can and should be interpreted from a public health perspective.

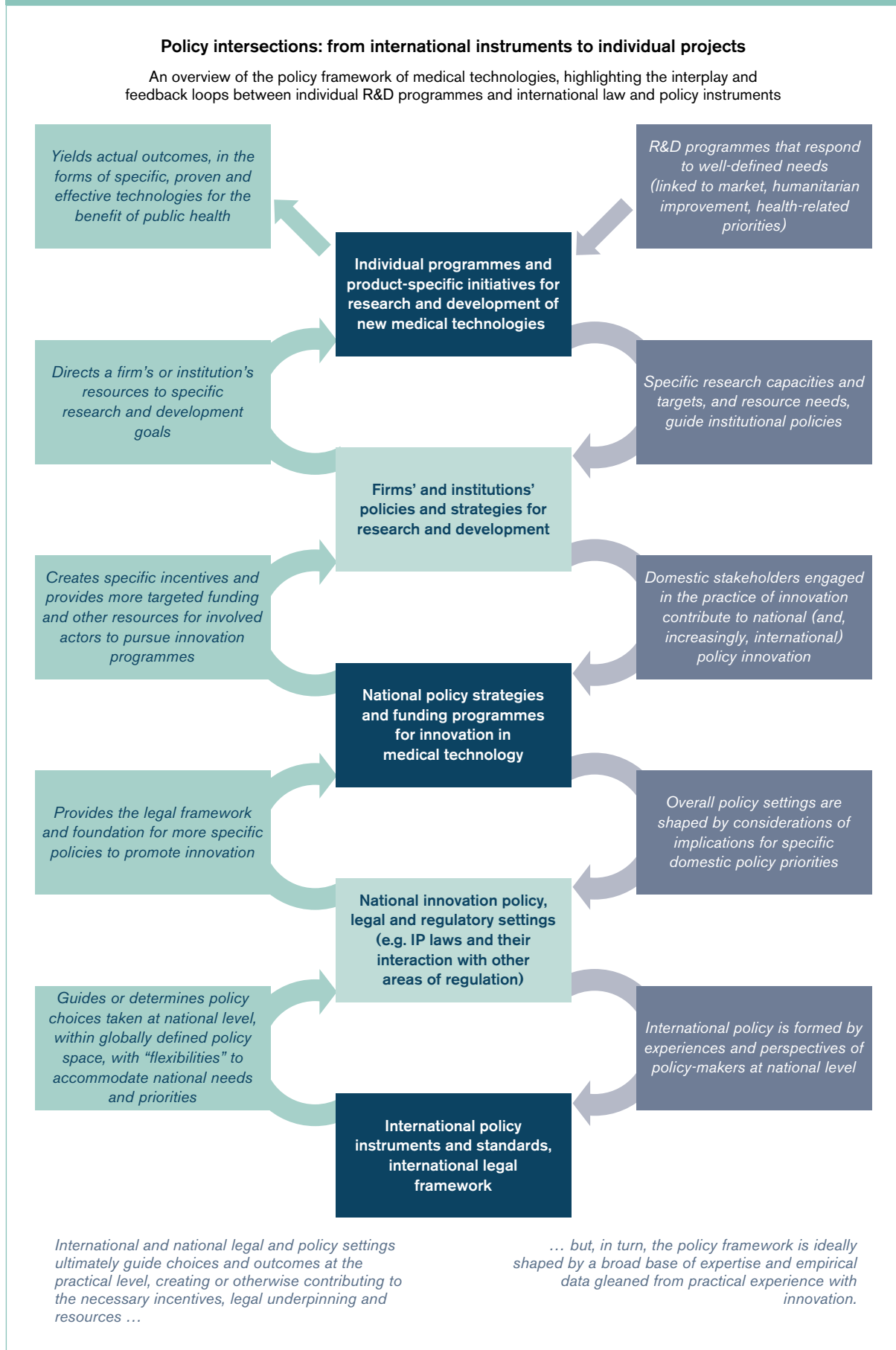
Trade policy and the economics of global production systems are also key factors in strategic plans to build domestic production capacity that aim for better access to medical products. Procurement policies favouring open and competitive tendering, coupled with the rational use of medicines, become all the more important in ensuring continued access in a fiscal climate in which national budgets are under pressure and philanthropic programmes face funding constraints. Programmes for access to medicines also stand to benefit from better, more integrated use of data, including on current and projected disease burdens, efficacy of medicines, the costs of R&D, price and IP coverage of medicines, and trade and regulatory measures.

Policy discussions have increasingly covered the innovation dimension. Indeed, the intersection between innovation and access is fundamental, and forms the fulcrum of the present study. Policy measures aimed at promoting access or innovation need to recognize that these two concepts are intrinsically intertwined. Merely leveraging enhanced access to the stock of existing, proven medicines is insufficient. The current pharmacopeia needs constant expansion to keep pace with the evolving disease burden. The disease burden continues to evolve, with, for example, the growing burden of NCDs in LMICs becoming a priority area of concern. New strains of viruses and AMR challenge the efficacy of existing treatments. And medical innovation has historically failed to address major diseases that are endemic in the LMICs.

3. Building stronger links between local, national and global levels

Countries develop national health policies and strategies for guiding health development, taking into account the international legal and policy framework. Conceptually,

Figure 1.5: Policy intersections between distinct levels



these policies and strategies are based on, and draw their strength from, a national vision for social development and relevant policies. National health policy is aimed at organizing and strengthening the national health systems in such a way that they effectively help in achieving the objectives of the policy. Health policy refers to decisions, plans and actions that are undertaken to achieve specific health-care goals within a society. It may be in the form of a formal document backed up by institutionalized processes and reviewed periodically, or it may be dispersed among a number of different documents, including notices, plans, strategies, decisions and directives. Health laws, rules and technical guidelines are also considered to be components of health policy.

Promoting medical innovation policy is a challenge, as it operates at the intersection of several policy domains. The essential challenge for innovation in medical technologies can be expressed in simple terms:

- First, to secure the requisite resources (including know-how, research and product development capacity, clinical trial expertise, regulatory infrastructure, background and platform technologies and research tools, and financing)
- Second, to apply these innovation resources most effectively towards addressing unmet public health needs.

Yet meeting this challenge entails working on complex intersections between different policy areas, applying a mix of incentives and market interventions, providing funding and other support for R&D, developing infrastructure, and building a public research base and a skilled research workforce. Equally, promoting innovation

can entail making better use of existing resources, leveraging access to existing technologies, drawing on drug development skills and R&D infrastructure, and drawing more effectively on indigenous research and innovation capacity, to expand the medical technology development pipeline. A host of international, regional and national legal and policy instruments influence innovative activity.

International legal instruments need to be understood through the prism of national experience with their implementation. A systematic understanding of the intersection between these different layers of policy and practice (see Figure 1.5) is required to assess how international, national and institutional policies determine actual innovation outcomes, and how, in turn, practical experience influences the policy framework.

4. The empirical challenge: an accessible base for policy

Policy-makers dealing with the challenges of medical technology access and innovation are more numerous and more diverse than at any time previously, and contend with a host of policy, legal and administrative structures at national, regional and international levels. For example, national regulatory authorities who seek to safeguard the public against unsafe or ineffective medicines deal with clinical trial data that may be protected by IP laws, and work within a legal and policy framework shaped by multiple international and regional instruments. Patent offices, which face unprecedented workloads, must use the best possible sources of technological data when searching and examining prior art⁴⁶ to decide whether

Box 1.3: Health and medical technologies: fundamental concepts

While the terms “health technologies” and “medical technologies” are sometimes used interchangeably, “health technologies” is the broader term, encompassing medical technologies. There are no watertight definitions of either term. The WHO defines a health technology as application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives.⁴⁷

Medical technologies are associated with the concept of medical intervention. These interventions can be preventive (e.g. vaccine), diagnostic (e.g. in vitro diagnostic kit, stethoscope, thermometer), therapeutic (e.g. medicine, surgical instrument, surgical procedure, implant) or rehabilitative (e.g. physiotherapy equipment, assistive device such as a crutch). Medical devices are a subgroup of medical technologies, including any article, instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article that does not achieve its primary intended action in or on the human body solely by pharmacological, immunological or metabolic means. Examples include syringes, defibrillators, in vitro tests and hip prostheses. Health technologies include, in addition to medical technologies as outlined above, for example, assistive technologies, such as a white stick which may be used by a person who is blind, or a treadmill and exercise equipment which may be used as a health-promoting device.⁴⁸

As technology evolves, more combination products materialize – such as medicines in medical devices delivery sets. There are also more and more examples of combined medical technologies. Metered-dose inhalers for the treatment of asthma are an example of important essential medicines commonly delivered through proprietary devices.

to grant patents on claimed inventions. Procurement programmes must contend with a host of rapidly evolving factors while assessing evolving disease burdens, clinical needs, the selection of essential medical technologies, efficacy, prices and availability, and regulatory and IP aspects. Common to all these diverse challenges is the requirement for a stronger empirical base so that policy choices are more likely to address practical needs. While there have been significant improvements in the quality and inclusiveness of data, as well as access to the necessary information technology (IT) tools required to convert raw data into accessible knowledge services for stakeholders, more needs to be done to further improve the empirical basis for solid decision-making.

Development of health technologies (see Box 1.3) is, in many cases, a complex, risky and uncertain process, drawing on diverse inputs originating from both the public and private sectors, and often requiring scrupulous testing and regulatory oversight. Innovation in medicines and vaccines is among the most uncertain and expensive forms of technology development, creating the need for distinct innovation structures, close regulatory and ethical attention, appropriately high standards of safety and efficacy, and specific or targeted incentives.

Providing access to medicines, vaccines and other medical technologies – the key focus of this study – is an essential ingredient for an effective response, but it is far from being sufficient in and of itself to achieve broad public health objectives. At the national level, the political commitment of the government is required so that it allocates the requisite financial resources to the health sector to develop strong health systems. Effective access to medical technologies is dependent on access to appropriate clinical infrastructure and medical services. Prevention is another key aspect. For example, the major proportion of the burden of NCDs can be prevented by reducing the exposure of populations to tobacco use, unhealthy diets, physical inactivity and harmful use of alcohol. To this end, effective health prevention and promotion programmes are required to address the main risk factors.

As the disease burden shifts and evolves, there is a continuing need for new, adapted and more effective medicines. Access to necessary medical technologies is not, therefore, a static equation – an integral feature of appropriate access strategies must be recognition of the value of targeted and appropriate innovation, both for major new breakthroughs and for adaptations to, and improvements in, existing technologies.

Innovation does not take place in isolation from concerns about equitable access to medicines and other medical technologies. The social value of medical innovation must be measured in part by the extent to which it is effectively and sustainably available to the people who need it. The widespread and equitable health impact of new technologies cannot be achieved without ensuring appropriate means of access to finished products. Thus, an overall policy on medical innovation needs to consider the access dimension as well – how, in practice, a new technology will be made available to those who need it, so that it does not remain an abstract theory and is not reserved only for a narrow segment of society. Building access considerations into innovation policy has numerous dimensions, ranging from the core aim of research and product development activities, to work on “appropriate” or adaptive forms of existing technologies suitable for resource-poor clinical environments, and to consideration of freedom-to-operate (FTO) strategies and mechanisms for integrating technologies into a finished product so that it can be distributed widely and in the most effective form.

Access also has to be understood in a wider context. For example, regulation of medical products is an integral part of the access equation. “Access” is not simply the capacity to purchase – or to be supplied with – a basic commodity or consumer product. The availability of a technology generally must be backed by sound regulation that is both monitored and enforced, so as to provide reasonable guarantees that the technology is safe and effective. Equally, many medicines and technologies require a certain degree of clinical support and backup, including diagnosis, prescription and dispensation, and appropriate follow-up.

Endnotes

- 1 WTO document WT/MIN(01)/DEC/2.
- 2 Azevêdo, R., introductory remarks, Sustainable Development Goals: Innovative Technologies to Promote Healthy Lives and Well-Being, A Joint Technical Symposium by the WHO, WIPO and WTO, Geneva, 26 February 2018, available at: www.who.int/dg/speeches/detail/who-wipo-wto-technical-symposium-on-sustainable-development-goals-innovative-technologies-to-promote-healthy-lives-and-well-being.
- 3 WHA, Resolution WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property; WHA, Resolution WHA62.16: Global strategy and plan of action on public health, innovation and intellectual property.
- 4 UN document A/RES/71/3.
- 5 See Russian Federation, Ministry of Health and World Health Organization (WHO), 2017; UN document A/RES/73/2.
- 6 Ghebreyesus, T. A., introductory remarks, Sustainable Development Goals: Innovative Technologies to Promote Healthy Lives and Well-Being, A Joint Technical Symposium by the WHO, WIPO and WTO, Geneva, 26 February 2018.
- 7 Gurry, F., introductory remarks, Sustainable Development Goals: Innovative Technologies to Promote Healthy Lives and Well-being, A Joint Technical Symposium by the WHO, WIPO and WTO, Geneva, 26 February 2018.
- 8 Ghebreyesus, T. A., speech at the opening ceremony of the UHC Forum, Tokyo, 14 December 2017, available at: <https://www.who.int/director-general/speeches/detail/opening-ceremony-uhc-forum>.
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- 12 WHA, Resolution WHA56.27: Intellectual property rights, innovation and public health.
- 13 See WHA document A72/17, available at: https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_17-en.pdf.
- 14 For more information, see: www.who.int/phi/publications/local_production/en/.
- 15 See <https://www.who.int/medicines/publications/essentialmedicines/en/>.
- 16 See https://www.who.int/topics/essential_medicines/en/.
- 17 See <https://extranet.who.int/prequal/>.
- 18 See <https://www.wipo.int/ip-development/en/agenda/>.
- 19 See WIPO document A/59/8, available at: https://www.wipo.int/edocs/mdocs/govbody/en/a_59/a_59_8.pdf.
- 20 Agreement Between the World Intellectual Property Organization and the World Trade Organization of 22 December 1995, available at: https://www.wipo.int/treaties/en/text.jsp?file_id=305582.
- 21 See <https://www.wipo.int/policy/en/scp/>.
- 22 See https://www.wipo.int/patents/en/topics/public_health.html.
- 23 See https://www.wipo.int/about-wipo/en/activities_by_unit/index.jsp?id=122.
- 24 For example, see Article 8 of the TRIPS Agreement; the Doha Declaration on the TRIPS Agreement and Public Health; Article 2.1 of the Agreement on the Application of Sanitary and Phytosanitary Measures; Article 2.2 of the Agreement on Technical Barriers to Trade; and Article XIV(b) of the General Agreement on Trade in Services.
- 25 Doha Ministerial Declaration, adopted on 14 November 2001, WTO document WT/MIN(01)/DEC/1, para. 6.
- 26 For more information on the WTO activities, see WTO document IP/C/W/634.
- 27 See <https://www.wipo.int/ip-development/en/agenda/recommendations.html>.
- 28 WHA, Resolution WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property, para. 4(5).
- 29 See https://www.who.int/phi/implementation/trilateral_cooperation/en/; https://www.wipo.int/policy/en/global_health/trilateral_cooperation.html; and https://www.wto.org/english/tratop_e/trips_e/who_wipo_wto_e.htm.
- 30 For more details regarding each symposium see https://www.who.int/phi/implementation/trilateral_cooperation/en/; https://www.wipo.int/policy/en/global_health/events.html; and https://www.wto.org/english/tratop_e/trips_e/who_wipo_wto_e.htm.
- 31 See https://www.wipo.int/academy/en/news/2016/news_0005.html; and <https://welc.wipo.int/acc/index.jsf?lang=en>.
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- 46 For more information on prior art, see Chapter II, section B.1(b)(iv) and WIPO document SCP/12/3 Rev.2, para. 210.
- 47 WHA, Resolution WHA60.29: Health technologies.
- 48 For WHO definitions of health technology and medical devices, see: https://www.who.int/medical_devices/definitions/en/.

II. The policy context for action on innovation and access

This chapter outlines the policy framework for public health, intellectual property (IP), international trade and competition, focusing on how they intersect, with particular emphasis on medical technologies. The framework comprises the human rights dimension of access to medicines; the policy, economic and legal features of IP and innovation systems; regulation of medical products; competition policy; and relevant trade policy measures, including import tariffs, non-tariff measures, rules on trade in services, government procurement, and regional and bilateral free trade agreements (FTAs). In addition, it discusses the economics of innovation and access to medical technologies and outlines the interface between genetic resources, traditional knowledge and traditional medicine, IP and trade.

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A. Public health policy

Key points

- Ensuring access to essential medicines constitutes a core human rights obligation of states.
- Under United Nations Sustainable Development Goal (SDG) 3, target 3.8 specifically aims to achieve universal health coverage, including access to safe, effective, quality and affordable essential medicines and vaccines for all. Other SDGs deal with the need to put in place an environment that fosters innovation, including in low- and middle-income countries (SDG 9), and promote international cooperation to support their implementation (SDG 17).
- The WHO assesses the impact of trade agreements on public health and provides support to its member states on the implementation of TRIPS flexibilities in collaboration with other relevant international organizations.
- The WHO Global Strategy and Plan of Action on Public Health, Innovation, and Intellectual Property (GSPA-PHI) aims to “encourage and support the application and management of intellectual property in a manner that maximizes health-related innovation, especially to meet the R&D needs of developing countries, protects public health and promotes access to medicines for all, as well as explore and implement, where appropriate, possible incentive schemes for R&D”.
- Effective regulation promotes public health by ensuring that products are of the required quality, safety and efficacy and also by ensuring provision of the necessary information to enable the use of such products in a rational manner.
- The emergence of biotherapeutic products raises questions of how to build national capacities to regulate similar biotherapeutic products based on appropriate guidelines from the WHO and leading regulators.
- Antimicrobial resistance (AMR) is a global threat and has attracted increasing focus from health agencies, governments and international organizations. Among other things, a UN Interagency Coordination Group (IACG) on Antimicrobial Resistance has provided practical guidance for approaches needed to ensure sustained, effective action to address antimicrobial resistance at the global and national levels.
- Regulatory exclusivities (data exclusivity and market exclusivity) affect innovation in, and access to, medicines. Countries have adopted different regimes of test data protection, ranging from data exclusivity to keeping the data secret, while allowing the competent authorities to rely on the data.

As the epidemiological data presented in the previous chapter highlight, low- and middle-income countries (LMICs) are facing a double burden of infectious and non-communicable diseases (NCDs). Internationally and nationally, the human rights framework, specifically the right of everyone to the enjoyment of the highest attainable standard of physical and mental health (in short, the right to health),¹ has provided an important mechanism to further the public health policy goals of ensuring and improving access to medicines for those who are most in need. Additionally, building on the Millennium Development Goals (MDGs), the Sustainable Development Goals (SDGs) reinforce and enhance the much-needed international platform for action on key concerns ranging from alleviating poverty to improving access to medicines, and are based on a commitment to global partnership and cooperation.²

The policy context for innovation and access to medical technologies needs to consider the frameworks that currently exist at the intersection of public health, innovation and access. The following section focuses on

the right to health under international human rights law, the health-related SDGs, developments in the WHO on public health, access and innovation, national health policies, and regulation of medical technologies.

1. Health and human rights

The human rights dimension has provided an important legal and policy vantage point for consideration of public health and pharmaceutical issues. International human rights law defined under customary international law and international human rights treaties creates binding obligations on parties. The WHO Constitution was the first international instrument to state that “the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition” (Preamble). The right to health is a central element of the international human rights system. It is part of the Universal Declaration on Human Rights,

adopted in 1948, and the 1966 International Covenant on Economic, Social and Cultural Rights (ICESCR), as well as of regional human rights instruments and many national constitutions. It also constitutes the basis for the overall objective of the WHO – laid out in Article 1 of its Constitution – which is “the attainment by all peoples of the highest possible level of health”. The Declaration of Alma-Ata, adopted in 1978, provided a more global perspective on tackling the inequities in access to health-care systems in general, linking the social dimension of achieving the highest attainable level of health and access to essential medicines. Most countries adhere to one or more international or regional treaties and provide for certain forms of the right to health in their national constitutions (Hogerzeil and Mirza, 2011). In 2016, provisions that require governments to protect and/or fulfil the right to access quality medicines and to ensure their availability could be found in at least 22 national constitutions (Perehudoff et al., 2016).

The scope and content of the right to the highest attainable standard of health under Article 12 of the ICESCR, to which 166 countries are party, has been interpreted by the UN Committee on Economic, Social and Cultural Rights (CESCR) in General Comment No. 14.³ General Comment No. 14 further explains that the four elements of availability, accessibility, acceptability and quality are essential to the enjoyment of the right to health by all. The CESCR lays down the general obligations of states, which are defined in the framework of “respect”, “protect” and “fulfil”:

- The obligation to respect includes, but is not limited to, requiring states to refrain from interfering with the enjoyment of the right to health.
- The obligation to protect, among other things, requires states to adopt measures to prevent other parties from interfering with the enjoyment of the right to health.
- The obligation to fulfil requires that sufficient recognition be given to the right to health through legislative implementation and adoption of positive measures and policies to enable individuals to enjoy the right to health.

Although obligations under the ICESCR are subject to progressive realization, the CESCR has set out minimum core obligations which ought to be implemented by countries without delay. These obligations include ensuring non-discriminatory access to essential medicines.⁴ In this context, the Special Rapporteur on the right to health identified four dimensions of access to medicines: medicines must be accessible in all parts of the country; they must be affordable to all, including those living in poverty; they must be accessible without discrimination on any of the prohibited grounds, such as sex, race, ethnicity and socio-economic status; and reliable information about medicines must be accessible

to patients and health professionals in order to facilitate informed decision-making.⁵ The CESCR also expressed its view on the impact of intellectual property rights (IPRs) on prices of essential medicines in its Comment No. 17 on the right of everyone to benefit from the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he or she is the author.⁶ The CESCR notes in paragraph 35 that this right cannot be isolated from other rights guaranteed in the ICESCR. Parties are therefore obliged to strike an adequate balance, whereby the private interests of authors should not be unduly favoured but adequately balanced with the interest of the public in enjoying broad access to their productions. The CESCR states that, ultimately, IP is a social product and has a social function and parties thus have a duty to prevent unreasonably high costs for access to essential medicines. In Comment No. 24, paragraph 24, the CESCR states that “parties should ensure that intellectual property rights do not lead to denial or restriction of everyone’s access to essential medicines necessary for the enjoyment of the right to health”.⁷

In the context of neglected diseases, where health interventions and research and development have long been inadequate and underfunded (although the picture has started to change), states are obliged to promote the development of new medical technologies through R&D and international cooperation (OHCHR and WHO, 2008).

In April 2002, the UN Human Rights Council (HRC) established a mandate for a Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health.⁸ The Special Rapporteurs⁹ have prepared independent reports,¹⁰ following consultations with many stakeholders, including the WHO. Some of these reports deal with access to essential medicines, the role of the pharmaceutical industry and IP issues (see Annex I).

These intersections and their linkages to human rights have also been the focus of several reports and resolutions of the HRC and its predecessor, the UN Commission on Human Rights (see Annex I). Resolutions of the HRC have called upon member states to promote access to medicines for all, including through using the full provisions in the TRIPS Agreement, which provide flexibilities for this purpose. The importance of IP protection as an incentive for the development of new medicines has been recognized, as have concerns about the effects of IP protection on prices.¹¹

Putting the right to health in the context of the 2030 Agenda for Sustainable Development, Resolution 35/23 urged countries to fully implement the SDGs, including target 3.b, which calls for support of R&D and access to affordable essential medicines and vaccines in accordance with the Doha Declaration on the TRIPS Agreement and Public Health (Doha Declaration). Further, with regard to R&D, the HRC has called upon states

to “continue to collaborate, as appropriate, on models and approaches that support delinking the cost of new research and development from the prices of medicines, vaccines and diagnostics for diseases that predominantly affect developing countries, including emerging and neglected tropical diseases (NTDs), so as to ensure their sustained accessibility, affordability and availability and to ensure access to treatment for all those in need”.¹²

Several UN General Assembly resolutions and political declarations have noted the need to ensure access to affordable medicines. The first such resolution was passed in 2001 and concerned HIV/AIDS.¹³ Several others have followed, including the political declarations on AMR (2016), NCDs (2018), TB (2018), universal health coverage (2019), and further political declarations on HIV/AIDS (2011 and 2016) (see Annex I). With respect to the HIV/AIDS epidemic, the UN General Assembly has passed several resolutions pertaining to protecting the human rights of people living with HIV and improving access to HIV treatment.

A political declaration adopted by the UN General Assembly on 8 June 2016¹⁴ included a commitment to remove obstacles that limit the capacity of LMICs to provide affordable and effective HIV/AIDS prevention and treatment, including by amending national laws and regulations, so as to optimize:

- (i) the use of the flexibilities contained in the TRIPS Agreement specifically geared to promoting access to, and trade in, medicines, and while recognizing the importance of the IPR regime in contributing to a more effective AIDS response, ensure that IPR provisions in trade agreements do not undermine the flexibilities, as confirmed in the Doha Declaration
- (ii) addressing barriers, regulations, policies and practices that prevent access to affordable HIV treatment by promoting generic competition
- (iii) encourage new partnerships to reduce treatment costs and encourage development of new medicines.

2. Access to essential medicines: an indicator for the fulfilment of the right to health

The UN High Commissioner for Human Rights created sets of indicators for 12 aspects of human rights, including the right to health. The indicators for the fulfilment of the right to health refer to five aspects which are often subject to inequity and discrimination:

- sexual and reproductive health
- child mortality and health care
- natural and occupational environment
- prevention, treatment and control of diseases
- access to health facilities and essential medicines.

Access to essential medicines is a vital component of fulfilling the right to health and universal health coverage. A lack of equity in the supply of essential medicines, high prices, informal payments and out-of-pocket payments for the medication required excludes the poor and vulnerable, and does not facilitate the realization of the right to health. Key segments of the population that in many cases face barriers to accessing essential medicines include people living in poverty or other situations of marginalization, children, older people, internally displaced people, persons with disabilities and detainees. It is the obligation of governments, as part of their human rights commitments, to ensure that these vulnerable segments of the population have access to essential medicines. Different approaches exist to promote the fulfilment of governments' constitutional and international obligations with regard to the right to health, including: developing strategies and plans of action as elaborated in paragraph 43(f) of CESCR General Comment No. 14; establishing and/or strengthening participatory accountability mechanisms; and ensuring meaningful stakeholder participation in policy development, implementation and monitoring (Hogerzeil et al., 2006; Toebes et al., 2014). Selected reports on access to medicines are summarized in Box 2.1.

3. Universal access and the UN Sustainable Development Goals

The SDGs consist of a set of 17 goals and 169 targets.¹⁵ The SDGs aim to continue the process initiated by the MDGs,¹⁶ taking a broader and more comprehensive approach, recognizing the complexity of problems affecting humanity and their interdependence on one another. All the SDGs are designed to be cross-cutting, and the interlinkages and networks within the SDGs are as important as the individual goals themselves (WHO, 2015b). This collaborative approach is particularly suitable to the area of medical technologies, where the affordability, availability, quality and appropriateness of products are influenced by of a long chain of policy decisions, market forces and other factors.

SDG 3 aims to “Ensure healthy lives and promote well-being for all at all ages”. Its 13 targets cover a wide range of health issues, from combating infectious diseases and NCDs to improving reproductive, maternal, newborn and child health.

Two of the 13 targets are specifically focused on the topics of this study: target 3.8 – “Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all” – and target 3.b – “Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance

Box 2.1: Selected reports on access to medicines and R&D**Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines (2016)**

In November 2015, the United Nations Secretary-General convened a High-Level Panel on Innovation and Access to Health Technologies (known as the United Nations Secretary-General's High-Level Panel on Access to Medicines, UNHLP). It comprised individuals from diverse stakeholder groups acting in their individual capacities. A background note submitted by the WTO Secretariat to the UNHLP called for building policy coherence in public health, supported by greater transparency and accessibility of data and efforts to enable policy responses to be based on integrated health, trade and IP data.¹⁷ The submission by the WHO summarized its previous work on the topic, highlighted issues concerning patentability standards and the magnitude of therapeutic benefit, and outlined alternative and new approaches to R&D, such as Global Antibiotic Research & Development Partnership (GARDP) (see Box 3.7). WIPO stated in its Information Note for the UNHLP that it remains committed to working within the UN system and with other multilateral organizations on policy issues related to innovation and global health and that it is pleased to share its expertise and specialized data on various forms of IP with the UNHLP and indeed with all interested stakeholders.

The Report of the UNHLP (UNHLP, 2016) recommended, among other things, to work together to facilitate access to medicines through legislation, and test and implement new models of financing and rewarding R&D, and to avoid the inclusion of provisions in FTAs that interfere with the right to health. It recommended that WTO members should respect the Doha Declaration and make full use of TRIPS flexibilities, including by applying “public health-sensitive patentability criteria” and implementing legislation that facilitates the issuance of compulsory licences that are “quick, fair, predictable and implementable” for legitimate public health needs. It recommended that the Secretary-General initiate a process for governments to negotiate global agreements on the coordination, financing and development of health technologies, including a binding R&D convention that delinks R&D costs from end prices. It recommended that governments should require manufacturers and distributors of health technologies to disclose the costs of R&D, manufacture, marketing and distribution, as well as public funding that supported the R&D.

The findings of the UNHLP Report have been discussed at the WTO TRIPS Council, the World Health Assembly and the UN Human Rights Council, among others.¹⁸ Some WTO members brought the UNHLP Report to the attention of the TRIPS Council in order to facilitate an exchange of views on the Panel's recommendations, as well as national experiences regarding the use of TRIPS flexibilities. Some other members questioned the scope of the Panel's mandate and terms of reference, including the statement that there was policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies.¹⁹ In SCP meetings, WIPO member states either requested discussion of the UNHLP Report to guide future work of the SCP on patents and health or stated that the Report could not build a basis for discussions in the SCP since it did not reflect member states' views.²⁰ At the WHO Executive Board and World Health Assembly, a number of member states commended the Report and called for its recommendations to be implemented in the WHO's action plan, while other member states criticized the Report.²¹

The UN General Assembly, in December 2016, took note of the UNHLP Report and requested “the Secretary-General to promote discussion among member states and relevant stakeholders on appropriate policy options to promote access to medicines, innovation and health technologies, as well as other, broader aspects, bearing in mind, as appropriate, all relevant reports, such as the report of the High-level Panel on Access to Medicines” as well as this trilateral study.²²

The Lancet Commission on Essential Medicines Policies (2017)

The Commission identified five “core challenges for essential medicines policies”: adequate financing to pay for an appropriate set of essential medicines, ensuring the affordability of essential medicines, assuring the quality and safety of essential medicines, appropriate use of medicines, and “missing” essential medicines (as noted in SDG target 3.b):

1. To finance universal access to essential medicines, governments should reduce out-of-pocket spending on medicines, track expenditures on medicines and provide adequate financing, with assistance provided by the international community to low-income countries to achieve this, where necessary.
2. To ensure affordability, the Commission recommended the better monitoring of medicines' affordability, price and availability; comprehensive policies for affordability; benefit packages that guide procurement and reimbursement; and better international transparency.

(Continued)

(Continued)

3. To assure medicines' quality and safety, quality assurance mechanisms should be internationally harmonized, duplication among national regulatory agencies should be minimized and these agencies should be transparent and accountable, the WHO Prequalification Team should be involved, and payers and procurement agencies should have transparent quality assurance mechanisms.
4. To strengthen use of quality medicines, independent pharmaceutical analytics units should be established to generate information to promote quality use in collaboration with other stakeholders, and stakeholder groups should implement interventions to tackle local medicines use problems, guided by information from the analytics units.
5. To develop "missing" essential medicines, a global R&D policy framework that includes new financing mechanisms should be created by governments, a general "Essential Medicines Patent Pool" should be created, and the pharmaceutical industry should better align its R&D with global health needs and develop strategies for ensuring access to medicines (Wirtz et al., 2017).

with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all".

Other SDGs also have a close link to achieving public health objectives. In particular, this concerns the SDGs dealing with the need to put in place an environment that enables innovation, including in LMICs, as well as those promoting international cooperation to support the implementation of the SDGs. SDG 9 is to "Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation". Innovation takes place on all levels along the value chain of medicines and health products (Cornell University, INSEAD and WIPO, 2019). Actions under SDG 9 can play an important role for technology transfer and the development and commercialization of medical technologies, by enhancing manufacturing capacities, reducing logistic costs, increasing timeliness by the use of information and communication technologies and decreasing red tape in order to facilitate expeditious trade (WTO, 2018). SDG 17 stresses the need to "Strengthen the means of implementation and revitalize the global partnership for sustainable development" to support and achieve the ambitious targets of the 2030 Agenda, bringing together national governments, the international community, civil society, the private sector and other actors. Targets 17.6, 17.7 and 17.8 stress the importance of international cooperation for enhancing knowledge-sharing and the development, transfer, dissemination and diffusion of technology. In addition, as regards the contribution of trade, target 17.10 calls for the promotion of a "universal rules-based, open, non-discriminatory and equitable multilateral trading system", recognizing the key role trade plays for the overall implementation and achievement of the SDGs. This has implications for providing access to affordable medicines for all (see Chapter II, section B and Chapter IV, section A).

4. Public health, innovation and access in the WHO

The WHO policy framework for public health, innovation and access has been developed over many years and consists of a large number of WHO resolutions that reflect the growing consensus among member states regarding the distinct role of the WHO in this area.

(a) Resolutions dealing with public health, intellectual property and trade

Immediately after the TRIPS Agreement came into effect, member states in the WHO discussed its potential impact on public health and requested the WHO Director-General "to report on the impact of the work of the World Trade Organization (WTO) with respect to national drug policies and essential drugs and make recommendations for collaboration between WTO and WHO, as appropriate".²³ Since then, the interface of public health, IP and trade has been the subject of many debates and resolutions that reflect a growing consensus over the years (see WHO Document EB 144/17 for a list of key WHO resolutions). The 52nd World Health Assembly (WHA), in 1999, provided the WHO Secretariat with a mandate to work with WHO member states on monitoring the impact of the TRIPS Agreement and other trade agreements and to help member states develop adequate health policies to, if necessary, mitigate the negative impact of trade agreements.²⁴ The implementation of the resolution included the establishment of a WHO network for monitoring the implications of the TRIPS Agreement on public health. Over the years, the mandate of the WHO was further expanded to include, where requested by individual member states, technical and policy support on formulating coherent trade and health policies and the implementation of TRIPS flexibilities,²⁵ while noting that this should be done in collaboration with other relevant international organizations. The WHA recognized the importance of IPRs in fostering R&D, but also urged

member states “to consider, whenever necessary, adapting national legislation in order to use to the full the flexibilities contained in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)”.²⁶ Many subsequent resolutions contain similar language. With regard to HIV/AIDS, in the same year member states highlighted “the difficulties faced by developing countries in effective use of compulsory licensing in accordance with the Doha Declaration on the TRIPS Agreement and Public Health (Doha Declaration)”.²⁷

The WHA also mandated the WHO Secretariat to support member states – at their request and in collaboration with the competent international organizations – in their efforts to frame coherent trade and health policies,²⁸ as well as to provide, on request and in collaboration with other competent international organizations, technical and policy support to countries on TRIPS flexibilities²⁹ (see Annex II for a list of the relevant WHA resolutions).

Thus, while, in the beginning, the resolutions focused on monitoring and assessing the impact of trade agreements, they became more specific over the years – specifically mentioning IP and TRIPS flexibilities. The mandate of the WHO was extended to include, on request, technical and policy support on formulating coherent trade and health policies and the implementation of TRIPS flexibilities while, at the same time, making it clear that this should be done in collaboration with other relevant international organizations.

Based on this mandate, the WHO has published a wide range of materials,³⁰ including on: access to hepatitis C treatment (WHO, 2016a, 2018c), the role of IP in local production, as well as patent data on specific medicines (WHO, 2016b, 2016c), the intersection between trade and health policies (WHO, 2015d), access to HIV treatment (WHO, 2014a, 2014d), making use of TRIPS flexibilities for improving public health (e.g. UNAIDS et al., 2011), developing a public health perspective on the examination of pharmaceutical patents (e.g. Correa, 2007), remuneration guidelines for the non-voluntary use of patents on medical technologies (e.g. WHO, 2005) and implementation of the WTO General Council Decision on paragraph 6 of the Doha Declaration (e.g. Correa, 2004).

The establishment of the Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH) (see section 4(b) below) and the subsequent adoption of the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI) (see section 4(c)) were key milestones in implementing this mandate.

(b) The Commission on Intellectual Property Rights, Innovation and Public Health

In 2003, the WHO established the CIPRH “to collect data and proposals from the different actors involved

and produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries”.³¹

In its final report of April 2006, the CIPRH focused on the overarching question of how to promote innovation and improve access to medical technologies in developing countries through the different stages of the development of medicines – discovery, development and delivery (CIPRH, 2006). The report made 60 recommendations addressed to governments of developed and developing countries, the WHO and other intergovernmental organizations and stakeholders. Recommendations covered the whole innovation cycle and included R&D policies, procurement and health delivery systems; the role of patents and protection of clinical test data; management of IP; TRIPS flexibilities; competition policy; and the regulation of quality, safety and efficacy of medicines, as well as the impact of FTAs on access to medicines.

The report led to the GSPA-PHI, which was adopted in 2008 and 2009.³²

(c) The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property

The adoption of the GSPA-PHI was a major step forward towards a global consensus on practical action on public health, innovation and IP. The overarching objectives of the GSPA-PHI are to promote new thinking on innovation and access to medicines, as well as (based on the recommendations of the CIPRH report) to provide a medium-term framework for securing an enhanced and sustainable basis for needs-driven, essential health R&D relevant to diseases which disproportionately affect developing countries, proposing clear objectives and priorities for R&D and estimating funding needs in this area. The GSPA-PHI states that, while IPRs are an important incentive for the development of new health-care products, this incentive alone is not sufficient to trigger the development of the health products needed to fight diseases in a scenario in which the potential paying market is small or uncertain.³³ The lack of financing for R&D into diseases disproportionately affecting developing countries was subsequently addressed by two WHO expert working groups.³⁴

Overall, WHO member states agreed that the GSPA-PHI should “encourage and support the application and management of intellectual property in a manner that maximizes health-related innovation, especially to meet the research and development needs of developing

Box 2.2: The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property

Main aims:

- Promote new thinking on innovation and access to medicines
- Promote and build capacity for innovation and R&D (for Type II and Type III diseases, and for the specific needs of developing countries in relation to Type I diseases)
- Improve access to medical technologies
- Mobilize resources for R&D

GSPA-PHI elements:

- Element 1: Prioritizing R&D needs
- Element 2: Promoting R&D
- Element 3: Building and improving innovative capacity
- Element 4: Transfer of technology
- Element 5: Application and management of IP in order to contribute to innovation and promote public health
- Element 6: Improving delivery and access
- Element 7: Promoting sustainable financing mechanisms
- Element 8: Establishing monitoring and reporting systems

countries, protects public health and promotes access to medicines for all, as well as explore and implement, where appropriate, possible incentive schemes for research and development" (see Box 2.2).³⁵

The GSPA-PHI also reaffirms and broadens the mandate of the WHO to work at the interface of public health and IP. The GSPA-PHI has been summarizing, updating and expanding the various mandates in the area of public health and IP that were given to the WHO through the resolutions adopted since the TRIPS Agreement came into effect. On the other hand, this overall mandate is linked to the clear aspiration of member states to ensure closer collaboration between relevant intergovernmental organizations and their respective work on public health and IP-related issues. Element 5 of the plan of action therefore requests governments and international organizations to "strengthen efforts to effectively coordinate work relating to intellectual property and public health among the secretariats and governing bodies of relevant regional and international organizations in order to facilitate dialogue and dissemination of information to countries".³⁶ This provision, together with the text of the resolution itself, which requests the WHO Director-General "to coordinate with other relevant international intergovernmental organizations, including WIPO, WTO and UNCTAD, to effectively implement the global strategy and plan of action",³⁷ also provides the basis for the trilateral cooperation established by the Secretariats of the WHO, WIPO and the WTO.³⁸

Following a request approved by the WHA in 2015,³⁹ an expert panel reviewed the GSPA-PHI. Its recommendations for the overall programme review of the GSPA-PHI were adopted by the WHA in 2018.⁴⁰

(d) Other developments in the WHO

Other developments in the work of the WHO with bearing on access and innovation include:

- The Pandemic Influenza Preparedness (PIP) Framework for the Sharing of Influenza Viruses and Access to Vaccines and other Benefits, which addresses IP issues and was adopted by the WHA in May 2011⁴¹ (see Chapter III, section E)
- The Political Declaration on the Prevention and Control of Non-communicable Diseases, adopted after the First Global Ministerial Conference on Healthy Lifestyles and Non-communicable Disease Control and the UN High-level Meeting on Prevention and Control of Non-communicable Diseases held in September 2011, as well as the follow-up process⁴² (see Chapter IV, section B.4)
- A range of activities to tackle AMR, including the establishment of a non-profit R&D organization – the Global Antibiotic Research & Development Partnership (GARDP) – initiated by the WHO and Drugs for Neglected Diseases *initiative* (DNDi)⁴³ (see Chapter II, section A.5; Chapter III, section C.2; Chapter IV, section B.2)
- The establishment of the Global Observatory on Health R&D, a centralized and comprehensive source of information and analyses on global health R&D⁴⁴ (see Chapter III, section C.5(a))
- An initiative on the fair pricing of medicines, and associated biennial Fair Pricing Forums, in which WHO member states, non-governmental and patient organizations, and the pharmaceutical industry discuss options for a fairer pricing system that is sustainable

for both health systems and the pharmaceutical industries⁴⁵ (see Chapter IV, section A.4)

- A series of analyses directed at developing a framework that could bring together and guide policy-makers and others from all relevant fields to support the local production of medicines, vaccines and diagnostics in a manner that should improve access, maximizing the potential to improve public health⁴⁶ (see Chapter IV, section A.10).

5. Cross-cutting efforts to tackle antimicrobial resistance

AMR occurs when bacteria, parasites, viruses and fungi become resistant to antimicrobial medicines that are used for treating the infections they cause. Every time an antimicrobial medicine is used, it diminishes the effectiveness for all users, because its usage increases the possibility of the development of resistance.⁴⁷ AMR has been recognized by the United Nations as a global threat and has attracted increasing focus from health agencies, governments and international organizations. The drivers of AMR lie in humans, animals, plants, food and the environment (IACG, 2019).⁴⁸ Since the impact of AMR is global, it goes beyond human health and will have economic and other consequences, and a sustained, comprehensive response needs to involve different actors and sectors, such as human and veterinary medicine, agriculture, finance, environment and consumers.⁴⁹ This approach is called “One Health”, and it endeavours to engage all stakeholders to address the global AMR challenge. The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), the UN Environment Programme (UNEP) and the WHO signed a memorandum of understanding in 2018 and developed a common work plan to address AMR in a holistic manner.⁵⁰

The UN Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance of 16 December 2016⁵¹ suggested a number of actions needed to prevent a “post-antibiotic era,” among which was the establishment of the *ad hoc* UN Interagency Coordination Group (IACG) on Antimicrobial Resistance to provide practical guidance for approaches needed to ensure sustained, effective global action to address antimicrobial resistance.⁵² The IACG brought together a range of multilateral organizations, including the WHO, FAO, UNEP, WIPO, the OIE and the WTO, as well as a number of individual experts.⁵³ The IACG report to the UN Secretary-General for submission to the UN General Assembly in September 2019 made a number of recommendations, which aimed at providing practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance (IACG, 2019). The 14 recommendations were structured into the five following areas: A. Accelerate progress in countries; B. Innovate to secure the future; C. Collaborate

for more effective action; D. Invest for a sustainable response; E. Strengthen accountability and global governance. *Inter alia*, the report aimed at supporting mobilization of action by all stakeholders; highlighted the urgency of the action needed; took a consistent “One Health” approach to AMR, cutting across human, terrestrial and aquatic animal and plant health, as well as food and feed production and the environment; focused on strengthening existing systems; and considered options for further international collaboration.

In his report to the UN General Assembly, the Secretary-General called upon the Tripartite Organizations to establish a joint secretariat and, through the support of the joint secretariat, in close collaboration with UNEP, other UN system entities, member states and other stakeholders, to further define the modalities of implementation of the IACG report in a transparent manner and undertake the required institutional and governance arrangements.⁵⁴

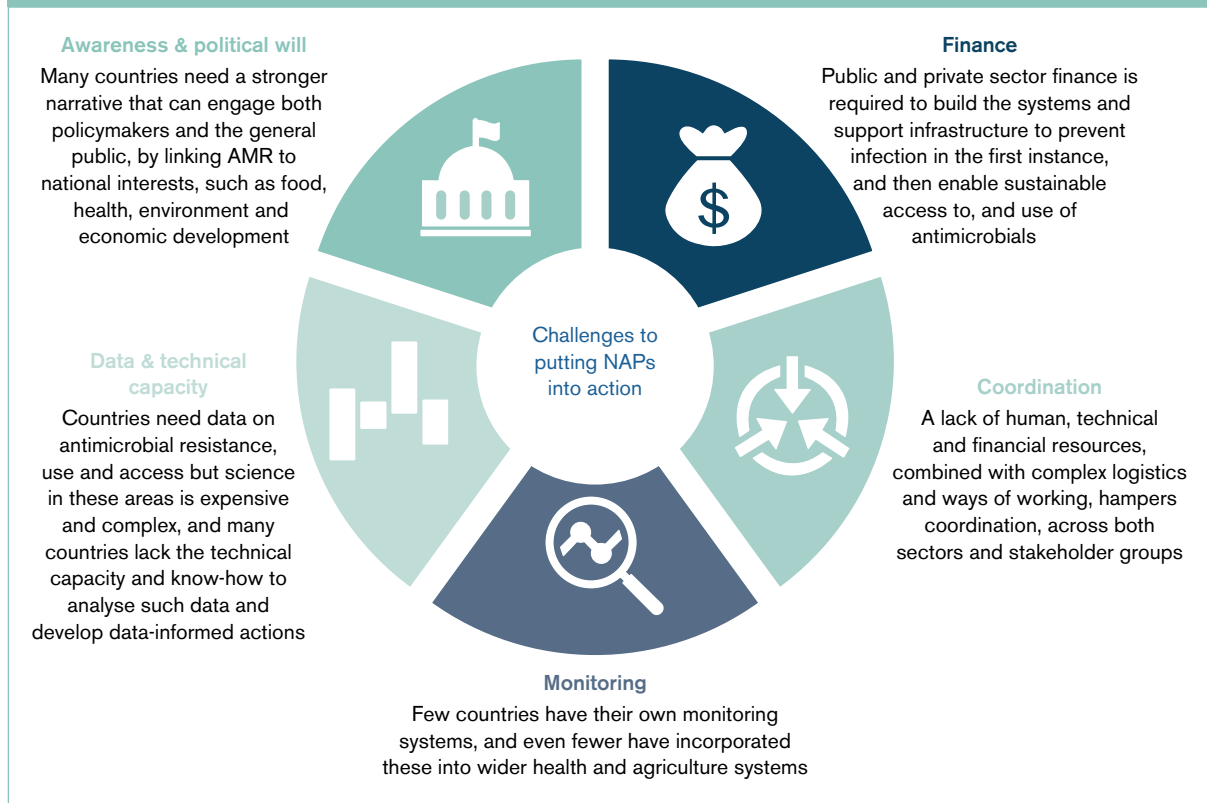
In a resolution adopted by the General Assembly on 10 October 2019, member states agreed to enhance cooperation to address AMR, as it poses a challenge to achieving universal health coverage, noting the work of the UN IACG and its recommendations as contained in the report of the Secretary-General.⁵⁵ AMR was the subject of the sixth WHO–WIPO–WTO Joint Technical Symposium in 2016,⁵⁶ and is covered in trilateral technical assistance activities.⁵⁷

The work of the WHO on AMR is based on the Global Action Plan on Antimicrobial Resistance, adopted by the WHA in 2015,⁵⁸ and spans a range of awareness-raising, policy implementation and technical activities.⁵⁹ The WTO works on AMR concerns by, among other things, administering relevant aspects of the WTO Agreement on Sanitary and Phytosanitary Measures (SPS Agreement) and Agreement on Technical Barriers to Trade (TBT Agreement) (see section B.3(b)). Trade law can potentially support the implementation of international standards for appropriate use of antibiotics, including in animal husbandry and/or good manufacturing practice. While WIPO does not have an official mandate to work on AMR-related issues, WIPO collaborates with the WHO and the WTO on public health, trade and IP issues, including in relation to AMR, and has published research on the interface between antibiotic innovation and IP (Sampat, 2015; WIPO, 2015c; Jenner et al., 2017).

To address the challenge of AMR, many countries have developed national action plans.⁶⁰ However, a number of factors make the implementation of a national action plan difficult for many countries, among them awareness and political will, finance, coordination, monitoring, and data and technical capacity (see Figure 2.1).

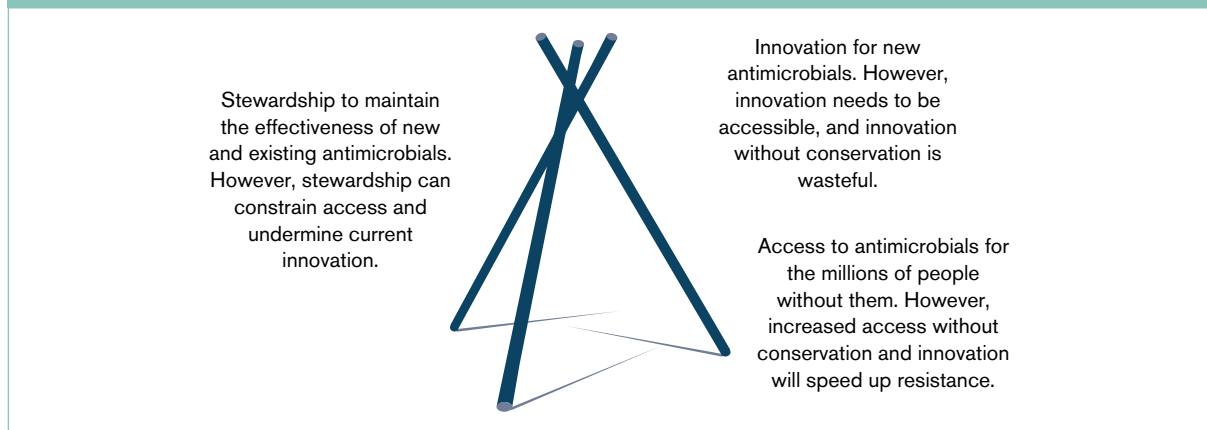
Possible measures against AMR include: improvement of hygiene; infection control to prevent the spread of resistant

Figure 2.1: Key challenges in implementing national action plans



Source: Interagency Coordination Group on Antimicrobial Resistance (IACG) (2018), "Antimicrobial Resistance: National Action Plans", IACG Discussion Paper.

Figure 2.2: Stewardship, innovation and access: a delicate balance of conflicting goals



Source: "Antimicrobial Resistance – A Global Epidemic", Background paper for the Technical Symposium on Antimicrobial Resistance: How to Foster Innovation, Access and Appropriate Use of Antibiotics? Prepared by the Secretariats of WHO, WIPO and WTO (2016).

bacteria; development of new antimicrobials against which bacteria are not resistant; and improved conservation efforts to maintain the effectiveness of new antimicrobials and of existing drugs. Stewardship, innovation and access are three key objectives in addressing AMR (see Figure 2.2). R&D in antimicrobials is further discussed in Chapter III, section C.2. Access to antimicrobial medicines is further discussed in Chapter IV, section B.2.

6. Regulation of health technologies

Regulation of health technologies is intended to ensure the quality, safety and efficacy of medicines (including vaccines and other biological medicines), or, in the case of medical devices, the quality, safety, effectiveness and performance of such devices (WHO, 2003b). Regulation also plays an important role in influencing access to

new products. However, unjustified regulatory measures and/or a lack of transparency in the regulatory process and slow procedures can become obstacles to access. Higher safety standards and other additional regulatory requirements may require manufacturers to provide more data to prove the safety of products or further invest in production facilities in order to reach the necessary quality standards. As a consequence, higher regulatory standards can increase the level of investment needed and can contribute to higher prices for end products.

A functioning regulatory system is a prerequisite for ensuring the quality, safety and efficacy of products on the market. National governments are responsible for establishing national or regional regulatory frameworks and authorities with a clear mission, sound legal basis and realistic objectives. The authorities should have an appropriate organizational structure, an adequate number of qualified staff, sustainable financing, and access to up-to-date evidence-based technical literature, equipment and information, coupled with the capacity to exert effective market control. Regulatory authorities must be accountable to both the government and the public, and their decision-making processes should be transparent. Monitoring and evaluation mechanisms should be built into the regulatory system in order to assess attainment of established objectives.⁶¹

Most countries have a regulatory authority and formal requirements for providing marketing authorization for medicines.

Other medical technologies, such as medical devices, are often subject to lower regulatory requirements. But the regulation of medical devices, which is done in accordance with their risk level, can be more complex and requires expert professionals to review dossiers. The WHO has published guidance in this regard – *WHO Global Model Regulatory Framework for Medical Devices Including in vitro Diagnostic Medical Devices* (2017) – and has prepared country profiles on the regulation of medical devices in order to analyse regulatory gaps and better understand needs (WHO, 2017).⁶²

Another challenge facing regulatory agencies is the growing complexity of supply chains for pharmaceutical manufacture. For example, a company that has received good manufacturing practice (GMP) certification to supply active pharmaceutical ingredients (APIs) from a stringent regulatory authority may also purchase APIs from other manufacturers who have not been certified.

The role of the WHO in strengthening health technology regulation includes the issuance of recommended norms and standards through its expert committees, the assessment of regulatory systems and support to regulatory capacity-building at national or regional levels, and support for post-marketing activities, in addition to

the prequalification of essential medicines, vaccines and certain medical devices, in particular, in vitro diagnostics, so as to facilitate the procurement of adequate quality products internationally (see Chapter IV, section A.8).

It is a complex task to balance the benefits of the early access to new products with uncertainties regarding their quality, efficacy and safety, and to find an acceptable level of risk. Regulators face the complicated challenge of using the best science available to balance the various different interests of the public in general, patients and producers of regulated medical technologies while ensuring that products are safe and efficacious. Optimizing the use of the scarce resources available to regulators will assume ever-increasing importance in the future. In this environment, new products will inevitably create new regulatory challenges.

The following section reviews the concept of regulation of medical technologies, with a specific focus on medicines.

(a) Why regulate medical products?

Governments have to ensure that the manufacture, distribution and use of medical products are regulated effectively to protect and promote public health (Rägo and Santoso, 2008). The objective of medicines regulation is to ensure that:

- products are of the required quality, safety and efficacy
- products are appropriately manufactured, stored, distributed and dispensed by licensed manufacturers, wholesalers and health professionals
- manufacturing and trade of substandard and falsified (SF) products are detected and adequately sanctioned
- health professionals and patients have the necessary information to enable them to use products (particularly medicines) in a rational manner
- promotion and advertising, where legal, is fair, balanced and aimed at rational use
- access is not hindered by unjustified regulatory barriers
- adequate pharmacovigilance is in place (e.g. monitoring at the population level serious adverse events).

While people have been taking remedies of different origins to ease pain, discomfort and disease symptoms for millennia, ideas about how to ensure that medicines are of the requisite quality are relatively more recent. The era of modern medicines and medical technology regulation began after various breakthroughs in chemistry, physiology and pharmacology in the 19th century.

Later, however, governmental responses to various medical catastrophes effectively served to accelerate the development of medicines regulation. For example, the 1938 US Federal Food, Drug, and Cosmetic Act, with its requirement for premarket notification for new drugs, was introduced following the deaths in the United States of more than 100 people as a result of ingesting diethylene glycol, which was used as a solvent in a sulfanilamide elixir, a raspberry-flavoured antibiotic syrup. The second major push for increased governmental oversight was the thalidomide disaster. Thalidomide, originally prescribed as a sedative, was given to expectant mothers experiencing morning sickness. Between 1958 and 1960, thalidomide was introduced in 46 countries worldwide, resulting in an estimated 10,000 babies being born with severe birth defects (Rägo and Santoso, 2008). In the field of medical devices, about 300,000 women in 65 countries were reportedly affected by the production of certain silicone breast implants sold from 2001 to 2010, which had a substantially higher risk of rupture and leakage than other implants.⁶³

These disasters created a concerted push for more oversight, precisely because medical products are not ordinary consumer products. Consumers often lack the knowledge to make informed choices about when to use a particular medicine, which medicines to use and how to use them. They may not have sufficient information to weigh potential benefits against the risk of side effects. In most countries, therefore, professional advice from prescribers or dispensers is required. Medicines that are not effective or are of poor quality can lead to therapeutic failure, worsening of disease or resistance to the medicines and can cause patients to lose confidence in the health-care system.

The quality, safety and efficacy of originator medicines are in large part determined through extensive pre-clinical and clinical research and trials. For a generic medicine or similar biotherapeutic to be approved, the quality standards must be the same as for originator products, and therapeutic equivalence with originator products has to be shown through appropriate studies.

(b) Clinical trials

Clinical trials are research studies in which large groups of human participants are enrolled to evaluate the safety and/or effectiveness of new medicines or new medical devices by monitoring their effects in human subjects (both patients and healthy volunteers can be involved). However, the first use of new medicines by human beings is always carefully carried out on only a very limited number of trial subjects. It is also important to note that clinical trials have a vital role in evaluating the safety of interventions, as many safety parameters can be controlled by quality. The researchers measure how the subjects' health changes

when compared with no treatment (placebo) or standard treatment. Interventions that can be evaluated in clinical trials may also include surgical procedures, radiologic procedures, other treatments, diagnostics or preventive methods (e.g. vaccines).

Most clinical research that involves the testing of new medicines progresses in an orderly series of steps called phases. This allows researchers to ask and answer questions in a way that results in reliable information about the product's safety and efficacy, and it also protects patients. Most clinical trials are classified into one of four phases:

- **Phase I trial:** the first studies in healthy volunteers evaluate: the safety of the medicine, including the appropriate dosage and side effects; how a new medicine should be given (by mouth, or injected into the blood or the muscle); how often it should be given; and what dose is considered safe. A Phase I trial usually involves only a small number of healthy volunteers or patients.
- **Phase II trial:** a Phase II trial continues to test the safety of the medicine and begins to evaluate how well the new medicine works (efficacy). Phase II studies usually focus on a particular condition or disease in a larger group of people (several hundred).
- **Phase III trial:** these trials investigate the efficacy of the medicine in large groups of human subjects (from several hundred to several thousands) by comparing the intervention against the standard of care or placebo, as appropriate. Phase III trials also serve to monitor adverse effects and to collect more information on safety.
- **Phase IV or "post-marketing" trial:** after a medicine is approved for market, the purpose of Phase IV trials is to evaluate further the side effects, risks and benefits of a medicine over a longer period of time and in a larger number of people than in Phase III clinical trials. Phase IV trials involve several thousand people (NIH, 2001).⁶⁴

(c) Research ethics

(i) *Clinical trial ethics*

Clinical trials not only involve issues around safety of the tested products, but they also raise various ethical issues. Among the most important questions to be addressed by research ethics committees before allowing a clinical trial to proceed are:

- the benefit–risk ratio
- protection of the dignity of potential participants, which includes the validity of the informed consent process (quality of information provided and absence

of coercion of participants) and the protection of privacy (confidentiality of personal data)

- equitable access to expected benefits of the research (new knowledge or new products)
- the special attention given to vulnerable groups and the absence of discrimination.

Many international and national bodies have developed guidance for the ethical conduct of research over a period of more than 70 years. Following the publication of the Nuremberg Code in 1947, the World Medical Association (WMA) adopted the Declaration of Helsinki in 1964. It has been reviewed regularly in the interim, with the most recent version adopted in 2013. The *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, first published in 1982 by the Council for International Organizations of Medical Sciences, and most recently revised in 2016 in collaboration with the WHO (CIOMS, 2016), constitutes another globally recognized ethical guidance instrument. One essential ethical condition for comparing two treatments for a disease with a randomized controlled trial (in which participants are allocated at random to receive one of several clinical interventions) is that there must be a good reason for thinking that one treatment is better than the other, yet, at the same time, there is genuine uncertainty among experts in the field over whether a treatment will be beneficial (equipose).

Following a resolution of the WHA adopted in 2006,⁶⁵ an important tool designed to improve clinical trial transparency was developed by the WHO – the International Clinical Trials Registry Platform, which helps to provide public access to information about clinical trials that are under way around the world (see Chapter III, section B.7).

(ii) Health databases and biobanks

Health databases and biobanks (collections of patients' biological material and associated data) are governed by ethical principles. The WMA has adopted the Declaration of Taipei,⁶⁶ which provides additional clinical principles for the application of the Declaration of Helsinki to health databases and biobanks.

Principles outlined in the Declaration of Taipei include:

- The rights to autonomy, privacy and confidentiality, which also entitle individuals to exercise control over the use of their personal data and biological material
- Collection and storage of data and samples must be voluntary, and consent is only valid if the concerned individuals have been adequately informed about certain key aspects of how these data/samples will be used, including information on commercial use

and benefit-sharing, IP issues and the transfer of data or material to other institutions or third countries

- Requirements for consent may be waived to protect the health of the population in the event of a clearly identified, serious and immediate threat where anonymous data will not suffice.

On IP, the Declaration of Taipei finds that "special considerations should be given to the possible exploitation of intellectual property. Protections for ownership of materials, rights and privileges must be considered and contractually defined before collecting and sharing the material. Intellectual property issues should be addressed in a policy which covers the rights of all stakeholders and [is] communicated in a transparent manner".

(iii) Bioethics

UNESCO describes the field of bioethics as follows:

"Stem cell research, genetic testing, cloning: progress in the life sciences is giving human beings new power to improve our health and control the development processes of all living species. Concerns about the social, cultural, legal and ethical implications of such progress have led to one of the most significant debates of the past century. A new word has been coined to encompass these concerns: bioethics."⁶⁷

According to the Universal Declaration on Bioethics and Human Rights, key bioethics principles to be respected include:

- Human dignity and human rights, including that the interests and welfare of the individual should have priority over the sole interest of science or society
- Pluralism, or accommodation of different value systems
- Transparency and access to information
- Benefit–risk ratio, autonomy, prior informed consent, privacy and confidentiality
- Respect for human vulnerability and personal integrity
- Equitable sharing of benefits resulting from scientific research with society as a whole and within the international community, in particular with developing countries
- Protecting future generations: the impact of life sciences on future generations, including on their genetic constitution, should be given due regard
- Protection of the environment, the biosphere and biodiversity.⁶⁸

The diverse issues to be considered are not insulated from one another. Questions in relation to technology

and its legal protection may address a variety of levels, including:

- The ethical aspects of a technology as such (e.g. should research on embryonic stem cells be permitted?)
- The ethical aspects of national authorities granting exclusive IP rights over a technology (e.g. is it contrary to morality to patent a genetically modified mammal?)
- The ethical aspects of an individual, a firm or an institution seeking exclusive IP rights over a technology (e.g. should a publicly funded agency patent its research results? When is it unethical to do so, for instance, in the absence of any necessary consent?)
- The ethical aspects of how an IP right holder should exercise exclusive rights over a technology (e.g. should the holder of a patent over a basic research tool license it in an open or restrictive way? Are public institutions ethically obliged to license medical technology from an explicitly humanitarian perspective?).⁶⁹

In terms of intergovernmental normative work, all three partner organizations of this trilateral study participate in the UN Inter-Agency Committee on Bioethics.⁷⁰ Key UN instruments concerning bioethics include the Universal Declaration on the Human Genome and Human Rights (1997),⁷¹ the International Declaration on Human Genetic Data (2003)⁷² and the Universal Declaration on Bioethics and Human Rights (2005).⁷³ The work of the WHO on bioethics includes, among other things, establishment of the Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing and convening the Global Summit of National Bioethics Committees.⁷⁴

(d) Biotherapeutic products

(i) Background

Biotherapeutic products (also known as biologics, biologicals or biopharmaceutical products) represent one of the fastest-growing pharmaceutical industry sectors. The increasing clinical importance of biologics is reflected in the number of products added to the WHO Model List of Essential Medicines⁷⁵ (e.g. bevacizumab in 2013, trastuzumab and rituximab in 2015, and adalimumab and nivolumab in 2019).

Biotherapeutic products are produced by biotechnological processes using biological material and can include blood-derived products and therapeutic recombinant proteins, among others. Often, the term is used for therapeutic recombinant proteins, therapeutic substances that are manufactured by genetically engineering a cell line (that produces and purifies the desired protein from the cell culture).

Currently, the market is dominated by originator products (reference biotherapeutic products, or RBPs), and prices for such products are often high. Similar biotherapeutic products (SBPs, sometimes called biosimilars, follow-on biologics or subsequent-entry biologics) are products that are similar in terms of quality, safety and efficacy to the originator product (the RBP).⁷⁶

Biotherapeutic products can be further divided into compounds with lower molecular weight (“simple” biologics), which are generally smaller proteins that are not antibody based (e.g. insulins), and compounds with higher molecular weight (“large” biologics), such as monoclonal antibodies (“mabs”). Analytical characterization of “simple” SBPs is often easier than of larger SBPs such as mabs, and this has, in some cases, facilitated abbreviated approval pathways.⁷⁷

(ii) Pathways for the registration of biotherapeutic products

Due to the complexity of the molecules, market authorization for biotherapeutic products in general requires more and larger clinical studies, compared with small-molecule products, to demonstrate that the products are similar from a structural and clinical perspective. For this reason, the WHO has developed specific guidelines for such products⁷⁸ and some regulatory authorities, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), apply specific rules for biotherapeutic products (discussed below).

Similar biotherapeutic products approved by a regulatory authority must have no clinically meaningful differences to the reference product (FDA, 2019b).⁷⁹ The efficacy and safety of SBPs cannot be assured by relying on the in vitro test data and simple bioequivalence tests (a single-dose trial in healthy volunteers). Rather, current regulatory policies require that SBPs undergo large, costly clinical trials to demonstrate their similarity with the originator product. These are normally Phase II or III trials (see section 6(b) above), enrolling hundreds of patients and lasting for months. The US Federal Trade Commission (FTC) noted in 2009 that the development of SBPs is likely to cost between US\$ 100 million and US\$ 200 million and take 8–10 years, compared with US\$ 1 million to US\$ 5 million and 3–5 years for small-molecule generics (FTC, 2009). A 2016 report commissioned by Medicines for Europe stated that it can cost around EUR 150 million to EUR 250 million and take up to nine years to develop SBPs (Simon-Kucher, 2016).

Regulatory systems are tasked with defining when such a product can be considered “similar” to, or “interchangeable” with an RBP, and different regulations for different categories of similar biotherapeutic products may be needed.

While the characteristics of a small-molecule medicine are mainly defined by its chemical structure, making such medicines relatively easy to replicate, biotherapeutics consist of complex proteins that often cannot be fully characterized by chemical or physical methods. Slight variations in the production process, including cell line selection and growth medium, can significantly affect the unique properties of biotherapeutic products and may thereby have an impact on the clinical safety and efficacy of the product. The product characteristics and manufacturing process of SBPs should, therefore, ideally deviate as little as possible from the process used for the reference product.

Some medicines regulatory authorities, such as the FDA, EMA⁸⁰ and Swissmedic,⁸¹ as well as the WHO,⁸² have issued guidelines with respect to the evaluation and/or authorization of SBPs. Guidelines and regulatory pathways are taking shape in many middle-income countries, for example, Colombia, India, Malaysia, Peru and the Russian Federation have all published biosimilar guidelines (Welch, 2016b; GaBI, 2018a). Before the establishment of specific pathways for the registration of SBPs, some countries have approved a number of non-originator biotherapeutic products since the early 2000s (Bosco and Chance, 2013; GaBI, 2018b). These biotherapeutics are different from SBPs approved through demonstrating comparability with the RBP.

(iii) What will be the effect of SBPs on prices?

Due to the complexity of biotherapeutic products and their manufacturing processes, and the need for randomized controlled trials (trials in which patients are randomly allocated to receive either the test substance or a placebo; see also section 6(b) above), developing a biosimilar is much more costly and time consuming than developing generic versions of traditional small-molecule medicines. There is uncertainty as to how much competition can be expected from SBPs and to what extent such competition can lead to price decreases. This uncertainty is due to a number of factors, including the need for sophisticated technical know-how, high development costs, challenging storage and handling issues, laws which grant temporary exclusivity of testing data to the sponsor of the originator product, immunogenicity concerns, and possible additional regulatory requirements (such as post-market surveillance and pharmacovigilance) to ensure safety and efficacy (Roger and Goldsmith, 2008). Experience in the development of small-molecule generics has shown that substantial reductions in prices generally will not take place until such time as there are several manufacturers of the same product in the market. Early estimates predicted price decreases would be limited to

around 10–40 per cent (Mulcahy et al., 2014; Blackstone and Fuhr, 2013). Substantial price reductions of around 70 per cent have been seen in Denmark, Finland and Norway for similar infliximab, translating to large increases in SBP market share (Chopra and Lopes, 2017; Schafer et al., 2016; Welch, 2016a). Many companies that are well known as originators have entered the SBP market.

The use of biotherapeutic products is limited in many LMICs' health systems due to a range of factors, including the generally high prices of biotherapeutic product, the need (in some cases) for health facilities that can support supervised infusions, and the need (in some cases) for complex diagnostic technology. However, the use of biotherapeutic products in resource-limited health systems is increasing. A 2017 WHO pilot project was launched to prequalify selected biotherapeutic products and SBPs (see also Chapter IV, section A.11(a)). The WHO's Prequalification Team has developed a WHO pilot procedure for prequalification of two biotherapeutic products – rituximab and trastuzumab – and is inviting manufacturers to submit an Expression of Interest (EOI) for product evaluation to the WHO Prequalification Team – Biotherapeutic Products.⁸³

The WHO has partnered with the Utrecht Centre for Affordable Biotechnologies (UCAB) in an initiative to develop an SBP, palivizumab, a treatment that prevents respiratory infections in infants born prematurely. It is estimated that the SBP version can be produced for US\$ 250 per patient, equivalent to about 5–15 per cent of originator prices in high-income countries (Crowe, 2017; Sanchez-Luna et al., 2017).

(e) Future of regulation

A range of “advanced therapies” or “advanced therapy medicinal products” is being approved by regulators and entering clinical use,⁸⁴ including gene therapies, cell therapies and tissue engineering (see Boxes 2.3 and 2.4). Nanoparticles that deliver chemotherapy medicines selectively to cancer cells are in development.⁸⁵ These advanced therapies may offer revolutionary treatments for a number of diseases or injuries, such as Alzheimer's disease, sickle cell disease, severe liver conditions, cancer and muscular dystrophy, as well as skin injuries in burn victims. They offer huge potential for research, patients and industry.

The future of medicines regulation and other regulated medical technologies is increasingly reliant on highly sophisticated scientific skills and the capacity of regulators, combined with a greater degree of collaboration and cooperation. The regulatory system, supported by relevant legislation, is an important component of a functioning modern health system and is essential in order to facilitate innovation and access to new, safe and effective medicines.⁸⁶

Box 2.3: CRISPR-Cas9 gene-editing technology

CRISPR (clustered regularly interspaced short palindromic repeats) is a naturally occurring bacterial defence system, which uses an enzyme to identify and cut the DNA of an invading virus to disable the attack. Researchers have adapted this mechanism to cut DNA at a specific location. For example, CRISPR-Cas9 enables researchers to deploy the Cas9 enzyme to a precise portion of DNA. The Cas9 enzyme then acts as “scissors” to cut the targeted segment and then a customized DNA segment can be inserted into the DNA strand. This technology is considered to be a breakthrough discovery. It provides researchers, for the first time, with a highly flexible, precise, easy-to-use and efficient tool for editing the genomes of living cells, among other uses. More recent developments include the use of CRISPR-Cas13 to edit RNA instead of DNA.⁸⁷

Therapies based on CRISPR are in development for a number of diseases, including sickle cell disease and certain cancers (Mullin, 2017). CRISPR is expected to contribute to the development of other therapies, for instance, increasing the efficacy of CAR T-cell therapy (see Box 2.4) (Eyquem et al., 2017). CRISPR is also being used in the development of LMIC-directed technologies. For example, a CRISPR-based diagnostic system has been developed that is able to detect a range of viruses, including Zika and dengue virus, with a very high degree of sensitivity. It is believed that this system, once developed further, will be easily adaptable to different viruses, rugged in “field” conditions and affordable (Cohen, 2017).

However, CRISPR-based technology is still not fully understood, and potential undesired side effects are being researched.⁸⁸ A number of legal, regulatory and ethical questions have been raised, specifically with respect to the application of the technology in clinical germline editing (Lander et al., 2019).

Public discussion of the patent landscape for CRISPR technology has focused on the long-running patent dispute between the Broad Institute of Harvard University and the Massachusetts Institute of Technology on one side and the University of California at Berkeley on the other (Jewell and Balakrishnan, 2017). Studies investigating the patent landscape have found a variety of patent holders, including a hospital, a number of universities, individual researchers and companies, with main patent clusters in China, Europe, Japan, the Republic of Korea and the United States (Ferreira et al., 2018; Martin-Laffon et al., 2019). While the first patents were identified in 2001, increased patent activity has been observed since 2012. By July 2019, 12,000 CRISPR patents had been identified worldwide, falling into 4,600 patent families with more than 740 CRISPR patents granted (Kwon, 2019, referring to data available from www.ipstudies.ch/crispr-patent-analytics/t). Three main application fields for patent commercialization have been found: (1) CRISPR-Cas9 used in medical applications with a focus on human therapeutics and drug discovery; (2) research tool applications, cell line and animal models; and (3) agriculture and food applications (Ferreira et al., 2018). Aspects of licensing approaches by some patent holders are addressed in Chapter III, sections C.5(g) and D.5(c)–(d).

Box 2.4: CAR T-cell therapy

Chimeric antigen receptor T-cell (CAR T-cell) therapy is a novel type of cell therapy for some people living with some types of blood cancer. T-cells are a type of immune cell. By altering the T-cells of the patient, the therapy boosts their ability to recognize and kill specific cancer cells. CAR T-cell therapy involves collecting a sample of the patient's T-cells and then modifying the cells through gene editing to produce chimeric antigen receptors on their surface, which enable the T-cells to recognize tumour cells more effectively. The CAR T-cells are then reinfused into the patient, where they activate the patient's immune system so that it attacks cancer cells targeting the specific antigen on the tumour cells. Success is not just a function of the engineered cells, but of the patient's own immune system.⁸⁹

CAR T-cell therapies first obtained FDA approval in 2017 for the treatment of advanced leukaemia in some children and adults. It is believed that CAR T-cell therapies may eventually offer curative treatment for some cancers. Significant proportions of patients in early clinical trials, for certain cancers, achieved complete remission (the disappearance of all signs of cancer). However, the majority of CAR T-cell clinical trials currently under way are for the treatment of haematological malignancies; while the use of CAR T-cell therapy in solid tumours has thus far had limited success, it is an area of active development (Pettitt et al., 2018; Shum et al., 2018). Due to the potential for CAR T-cell therapies to cause serious side effects, as part of regulatory approval, a company offering such therapy must manage long-term follow-up studies to fulfil post-marketing requirements and must collect patient safety information for 15 years.⁹⁰

A review of patent activity related to CAR T-cell therapy has found early patent publications in the mid-2000s with publications increasing markedly in 2013 (Jürgens and Clarke, 2019). It has found 1,914 patent documents in 399 patent families worldwide, with the biggest group of applications made through the Patent Cooperation Treaty (PCT), followed by applications with the patent offices in China, the European Patent Office (EPO), the United States and a number of other countries. The analysis revealed that the most cited patent was held by the University of Pennsylvania.⁹¹ It found strong partnership between the University of Pennsylvania and Novartis, evidenced by co-authorship in numerous patent applications. It also concluded from patent applications with co-inventors from the same countries that little international cooperation took place. According to Armstrong (2019), the number of published international patent applications related to CAR T-cell technology increased from 60 in 2014 to 450 in 2018, the main applicants being universities in the United Kingdom and the United States and pharmaceutical companies. Possible patent law issues associated with CAR T-cell therapies include questions related to patentable subject matter and industrial applicability/utility (see Chapter II, section B.1(b)(iii)), patenting material that exists in nature (see Chapter III, section D.4(a)), and exclusions from patentability for diagnostic and therapeutic methods (see Chapter IV, section C.1(a) and Box 4.17). Where such exclusions apply, patent claims may seek patent protection using “active treatment step” and “second/further medical use claims” (Black, 2017; Gainey, 2018; see also Chapter III, section D.4(c)).

Besides regulation, many other health policy aspects impact innovation in, and access to, medical technologies. The supply of medicines and medical technologies within health systems, as well as their procurement, price regulation and the funding of health systems, is covered in Chapter IV, section A.

Also, the increasing use of mobile devices in health brings new regulatory issues that need to be addressed, such as accreditation of applications, liability, interoperability, (cross-border) data flows and patient data confidentiality.⁹²

(f) Regulatory exclusivities

Regulatory exclusivities are conferred by national or regional law. The period of protection of regulatory exclusivities may overlap with, and is independent of, the term of patent protection (see Figure 2.3). Regulatory exclusivities is an umbrella term that encompasses data exclusivity, which is one way of implementing test data protection (see section B.1(c)) and market exclusivity:

- Data exclusivity provisions prevent regulatory authorities from relying on the reference product test data for approval of a generic medicine for a given period of time.
- Market exclusivity provisions prevent a regulatory authority from granting market approval for a certain period of time. Market exclusivity is distinct from data exclusivity because it prevents a competing firm from obtaining regulatory approval whether or not it is referring to the originator's data (Thomas, 2014). For example, once the data exclusivity period has lapsed, a competitor can rely on the originator test data to submit an application for approval, whereas market exclusivity provisions will still prevent market authorization being granted until the market exclusivity period has also lapsed.

Countries that grant data exclusivity rights generally provide for a fixed period of between five and eight years, with the possibility of an extension in some cases. The fixed period usually runs from the date of marketing approval of the originator product in the same country as that where the test data protection is sought. Some WTO members, such as the European Union and the United States, allow an additional period of data exclusivity for new indications and formulations.

In the European Union, originator medicines granted approval by the EMA enjoy ten years of marketing protection, and eight years of data protection, both starting at marketing authorization.⁹³ This means that the EMA or a national authority could begin assessing the application of a prospective generic competitor at the end of year 8 (relying on reference product data to support

their application), while marketing authorization could only be granted at the end of year 10. The ten-year marketing protection period can be extended to 11 years if the holder of the marketing authorization obtains an authorization for one or more new therapeutic indications during the first eight years that are found to bring significant clinical benefit over existing therapies. This is known as the “8+2+1” system of exclusivities granted in the European Union.⁹⁴

A separate exclusivity is granted in the European Union for drugs designated as orphan drugs (see Chapter III, section B.6). Orphan exclusivity in the European Union confers ten years of market exclusivity from any *similar*⁹⁵ product for the same indication as the originator product, and can be extended by two years for the completion of a paediatric investigation plan that sets out paediatric use of an orphan drug.⁹⁶ Orphan exclusivity in the European Union runs in parallel to general protection periods granted to all originator medicines (outlined in the paragraph above), and may be shortened from ten to six years, if, at the end of the fifth year, the product no longer meets the criteria for orphan exclusivity.⁹⁷

The US legislature has introduced a range of different types of regulatory exclusivity, including five years' data exclusivity for new chemical entities (Thomas, 2015). As regards biologics, the Biologics Price Competition and Innovation Act provides that similar biotherapeutic products cannot be submitted for approval for four years after the date of first approval of the reference product, nor can they be approved until 12 years after that date if they rely on data submitted by the originator company.⁹⁸ The United States awards one year of exclusivity to the first “interchangeable” SBP to enter the market (see section 6(d) above).⁹⁹ Each of the exclusivities varies in its eligibility criteria, scope of protection and underlying policy objectives (see Box 2.5 for selected examples). The time frame for these exclusivities can have a significant impact on the time it takes for generics or SBPs to reach the market.

Following the 1997 introduction of paediatric marketing exclusivity,¹⁰⁰ there was a reported increase in paediatric research and in products having their labelling changed to account for paediatric use. However, much of the research conducted for paediatric marketing extensions was conducted on products that treat conditions of public health importance for children (e.g. high blood pressure). It has been reported that some manufacturers have delayed paediatric trials until late in the period of their product's marketing exclusivity (Kesselheim, 2010).

In countries where data exclusivity exists, exceptions and limitations to data exclusivity may apply. US law shortens the period of data exclusivity to four years where the applicant for a second product certifies that the patent is invalid or that the second product does not infringe the patent (subject to a possible stay during infringement proceedings). Canada does not provide data exclusivity if the originator product

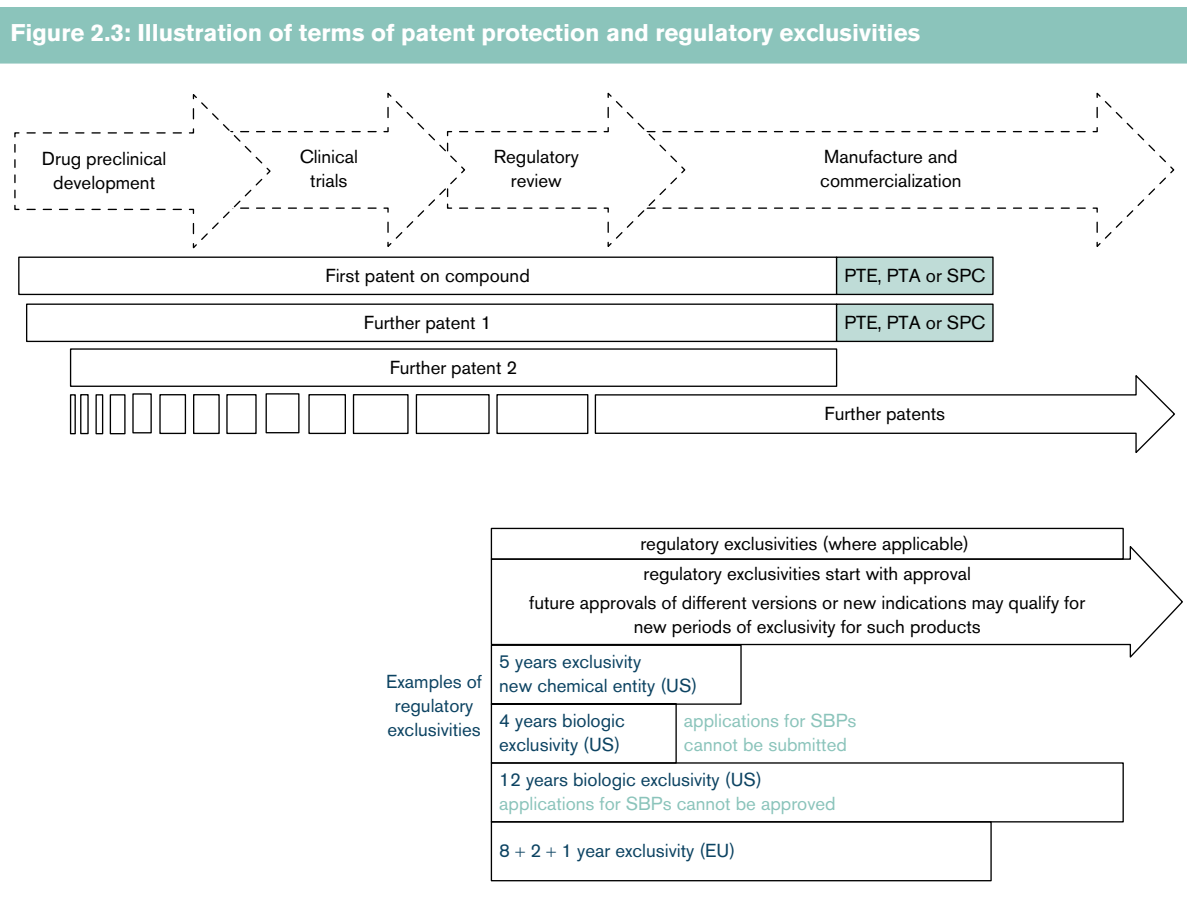
Box 2.5: Selected types of US regulatory exclusivity

Type	Eligibility criteria	Scope of protection	Period	Objective
New Chemical Entity (NCE) Exclusivity	Drugs containing NCEs – i.e. the FDA has not previously approved at least one of its active ingredients	This is a general data exclusivity provision for non-biotherapeutics in the United States No generic application accepted for drugs containing the same active ingredient, unless the sponsor submits a New Drug Application (NDA) and has performed all the required pre-clinical and clinical studies itself	5 years	To encourage development of innovative medicine products that include an entirely new active ingredient
New Clinical Study Exclusivity (for an Original or Supplemental NDA)	NDAs or Supplemental NDAs that contain reports of new clinical studies conducted by the sponsor, which are essential to FDA approval of that application (Supplemental NDAs make changes to product that is already the subject of an NDA)	This is a general data exclusivity provision for non-biotherapeutics in the United States No generic application may be approved for the same drug, for the same indication The FDA may still accept generic applications and may issue tentative approval of a generic drug, which will become effective once the exclusivity period has ended An NDA for the same drug, for the same indication, will still be accepted if the sponsor has performed all the required pre-clinical and clinical studies itself	3 years	To encourage improvements upon drugs that are already known
Orphan Drug Exclusivity	Orphan drugs to treat a rare disease or condition: (1) affecting fewer than 200,000 people in the United States; or (2) for which there is no reasonable expectation that sales of the drug would recover its costs of development	No generic application may be approved for the same drug, for the same indication Applies even where the sponsor of a subsequent application has performed all the required pre-clinical and clinical studies itself The FDA may still grant marketing approval for the same drug, for a different indication	7 years	To encourage firms to develop pharmaceuticals to treat rare diseases and conditions
Qualifying Infectious Disease Product Exclusivity	Antibacterial or antifungal drugs intended to treat serious or life-threatening infections	Extends the period of New Chemical Entity, New Clinical Study or Orphan Drug Exclusivity	5 years (starting from end of previous period of exclusivity)	To provide additional incentives for development of antibiotics
Pediatric Exclusivity	NDA holders or applicants who complete pediatric studies requested by the FDA	Extends the period of existing patent or regulatory exclusivity protection	6 months (starting from end of previous period of exclusivity or patent protection)	To improve availability of appropriate pediatric labelling on drug products
Biologics Exclusivity	Biologics	Applications for follow-on biologics will not be accepted	4 years	To encourage the development of biologic products
		Applications for follow-on biologics may be accepted but will not be approved if the follow-on biologic relies upon data developed by the sponsor of the reference biologic	12 years	

Source: J. R. Thomas, *Pharmaceutical Patent Law*, 3rd edition (2015).

is not being marketed in its territory.¹⁰¹ Colombia does not provide data exclusivity if the originator product is not marketed in its territory within 12 months of the grant of local marketing approval. Chile does not provide data exclusivity if the application for local marketing approval is filed more than 12 months after registration or marketing approval was first granted in a foreign country.

Data exclusivity has the potential to impede the implementation of compulsory licensing of patents. For example, in 2016, the issuing of a compulsory licence was considered by the Government of Romania for the hepatitis C medicine sofosbuvir, but it was reportedly not pursued because EU data exclusivity would expire only in 2024 (Paun, 2016; 't Hoen et al., 2017).



Source: WHO, WIPO, WTO Secretariats.

Notes:

- Timelines are not proportionate, and timing of patent and regulatory elements will vary from case to case. Patent grant and regulatory approval can take a shorter or longer period.
- The word “patent” refers to the patent application filed, the grant of a patent and the maintenance of a patent. The left side of the “patent” bars indicate the date of patent filing. Due to the diversity in time needed for the patent procedure, no indication of patent grant is made in the chart. Granting of a further patent is independent of earlier granted patents and does not extend the patent protection period of any earlier patent.
- The period of patent protection available in national law does not end before 20 years counted from the filing date. Often patents are abandoned, invalidated, not maintained, etc. before the maximum protection period of 20 years is reached.
- The first patent normally covers the compound, and further patents may cover other aspects, such as combinations, uses, etc. as provided in domestic law. The first patent and further patents are not necessarily held by the same entity.
- Some jurisdictions provide for limited patent term extensions (PTEs), limited patent term adjustments (PTAs) or limited additional protection in the form of supplementary protection certificates (SPCs). Not every patent will be extended. PTEs, PTAs and SPCs do not have always have the same duration.

In some countries, exceptions to data exclusivity may cover the protection of the public interest, such as where compulsory licences are issued to protect public health.¹⁰² For example, Chile and Malaysia waive data exclusivity if the product is the subject of a compulsory licence, and Chile, Colombia and Malaysia waive data exclusivity where necessary to protect public health.¹⁰³ Another example concerns where it is necessary for exports under compulsory licence under the Special Compulsory Licensing System: Canada and the European Union waive data exclusivity for products produced under compulsory licence for export.¹⁰⁴ Data exclusivity waivers are also provided within the Medicines Patent Pool licensing agreements, as well as in other licensing agreements aimed at enabling generic competition in LMICs.¹⁰⁵

The awarding of additional exclusivities, such as data exclusivity, generally increases the expectation of revenues for a manufacturer bringing a new product to market and thus, in theory, offers incentives for product development at the expense of delayed generic entry. Some studies are available on the relationship between data exclusivity and other regulatory exclusivities and innovation (Williams, 2017; Goldman et al., 2011; Gaessler and Wagner, 2018; Budish et al., 2015).

(g) Patent linkage

Normally, different agencies are responsible for granting patents (patent offices) and for approving medicine products for entering the market, each of them operating

independently. Nevertheless, some countries link regulatory approval, normally based on quality, safety and efficacy, to the patent status of the medicine. This is referred to as “patent linkage” and can take several forms. In its simplest form, linkage may involve a requirement that a patent owner simply be informed of the identity of any manufacturer seeking regulatory approval for a generic version of the originator’s medicine product. A stronger version of patent linkage prohibits the granting of marketing approval for a medicine product by a third party prior to the expiration (or invalidation) of a patent covering that product. An even stronger form of linkage prohibits not only the granting of marketing approval but also the consideration of a generic medicine application during the patent period.

Some stakeholders argue that patent linkage provisions place regulatory agencies in the role of “patent enforcers”,

that some patent linkage provisions make no exception for generic medicines produced under compulsory licence, and that patent linkage provisions can unjustifiably extend exclusivity of the product in the market, if the regulatory agency is unable to begin a review of the generic medicine application during the patent period. On the other hand, proponents of patent linkage argue that it prevents unnecessary infringement and that it increases transparency and predictability through the identification of patents relevant to each pharmaceutical product as part of the marketing approval process.

For explanation and discussion of patent rights and the patent system, see Chapter II, section B.1(b); Chapter III, section D.3–4; and Chapter IV, section C.1–4.

B. Intellectual property, trade and other policy dimensions

Key points

- Intellectual property (IP) protection is intended to strengthen market-based incentives to invest resources in product development and the marketing of new technologies.
- The global legal IP framework is defined in particular by the treaties administered by WIPO, and the WTO TRIPS Agreement. Multilateral standards for IP are generally minimum standards, thus leaving considerable scope for policy-makers to decide on their implementation in a way that supports public health objectives.
- The patent system is designed to support innovation and, at the same time, offer a mechanism to ensure that such innovations are accessible to society. Published patents and patent applications are an important source of technical and legal information.
- The trademark system serves to distinguish products and to inform the consumer. Trademarks are used to brand both original and generic products. To avoid confusion, trademarks for pharmaceutical products need to be distinct from the international non-proprietary names (INNs) of the products.
- The TRIPS Agreement allows for flexibilities in national implementation. The subsequent Doha Declaration confirmed “the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility” to protect public health.
- Competition law and policies have an important role to play in enhancing access to health technologies and fostering innovation. Unwarranted restrictions on competition, whether resulting from the abuse of a dominant position resulting from intellectual property rights (IPRs) or other factors, or anti-competitive agreements, can be addressed through competition law enforcement. With regard to innovation, a key concern is merger control, where competition authorities must ensure that mergers do not threaten R&D pipelines.
- All countries rely on imports, to varying degrees, to meet the health-care needs of their populations. This reliance is particularly pronounced for the national health systems of smaller developing countries.
- The WTO Agreement on Government Procurement provides an appropriate framework for rules at the international level that are intended to promote efficient trade and best practices in the area of public procurement. These can contribute to improvements in the accessibility and affordability of medicines and thus towards more efficient and cost-effective health systems.
- Free trade agreements (FTAs) have shaped the framework for access and innovation in many countries.

This section provides an overview of legal and policy instruments relating to the IP and international trade system that are relevant to medical innovation and access to medical technologies at the international level.

1. Intellectual property systems

IPRs that are most relevant to innovation in, and access to, medical technologies, as well as cross-cutting issues related to their enforcement are outlined in this section.

(a) Introduction to IP systems

IP systems operate by providing limited rights to exclude certain defined third-party use of protected material. IP protection is generally intended to strengthen market-based incentives to invest resources in product

development and the marketing of new technologies. Such incentives are considered especially valuable for the development of medical technologies due to the considerable financial and technical resources required, coupled with the high risk of failure even at a late stage in product development and issues related to product liability. Many medical technologies are expensive to develop but are relatively cheap to reproduce. In such instances, it would be unsustainable for companies to invest capital in product development and regulatory approval if their competitors were in a position to immediately introduce replica products (see Chapter III, section B.4 for discussion of a range of incentive models for innovation).¹⁰⁶

In as much as IP protection operates through a right to exclude others, it can inhibit forms of competition (such as market entry for generic medicines) and hinder further innovation (e.g. where no research exception)¹⁰⁷

exists). IP policy, the laws that embody the policy, and the administration and enforcement of these laws each aim to balance and accommodate a range of legitimate interests in a positive-sum way that promotes overall public welfare.

The balancing factors are diverse – in the case of patents, they comprise exclusions from patentable subject matter, definition of patentability criteria, exceptions and limitations to patent rights, limits on patent term and maintenance fees to encourage under-utilized patents to lapse, in addition to instruments beyond the scope of patent law, such as competition policy. While the appropriate balance is ultimately set by national policy-makers and legislators, the international legal framework provides the context and general principles for national systems. The global IP framework, which is the focus of this section, is defined in particular by the treaties

administered by WIPO, and the TRIPS Agreement, which forms part of the WTO legal system and in turn incorporates the substantive provisions of several WIPO treaties, including the Paris Convention (see Box 2.6).

The TRIPS Agreement has considerable implications for the application of IP to medical technologies, notably through the implementation of international standards requiring patents to be available for inventions in all areas of technology, including pharmaceutical products, and the requirement to protect undisclosed test data submitted for obtaining marketing approval against unfair commercial use and disclosure. Negotiation of the TRIPS Agreement and its subsequent implementation have seen a continuing focus on IP and health issues (see Box 2.7) and, particularly, the nature and impact of obligations under the TRIPS Agreement on pharmaceutical patents and test data protection.

Box 2.6: The Paris Convention

The Paris Convention for the Protection of Industrial Property (the Paris Convention) was concluded in 1883 and has been revised several times, most recently in 1967. It applies to industrial property in the widest sense, including patents, trademarks, service marks, industrial designs, utility models, trade names and the repression of unfair competition. It provides, *inter alia*, for national treatment, right of priority and common rules.

The principle of national treatment under the Paris Convention means that each contracting state must grant the same advantages to nationals of other contracting states as it grants to its own nationals with respect to the protection of industrial property. Nationals of non-contracting states are entitled to national treatment under certain conditions.

The right of priority means the following: on the basis of an earlier regular application filed in one of the contracting states, the applicant applies for protection of the same industrial property subject matter within a certain period of time (priority period) in any of the other contracting states. Then the later applications will not be affected by any event that may have taken place in the interval between the filing date of the first application (priority date) and the filing date of the later application, such as any publication of the invention claimed in a patent application or the sale of articles bearing the trademark or incorporating an industrial design. The priority period under the Paris Convention lasts 12 months in the case of patents and utility models, and six months in the case of industrial designs and trademarks.

The common rules that must be followed by all contracting states include:

- Patents granted in different contracting states for the same invention are independent of each other.
- The grant of a patent may not be refused, and a patent may not be invalidated, just because the sale of the patented product, or of a product obtained by the patented process, is not allowed, is restricted or is limited under national law.
- Contracting states may take legislative measures providing for the grant of compulsory licences, with certain limitations, to prevent the abuses which might result from the exercise of the exclusive rights conferred.
- The registration of a trademark in a contracting state is independent of its possible registration in any other country, including the country of origin. Consequently, the lapse or annulment of the registration of a mark in one contracting state will not affect the validity of registration in other contracting states.
- A contracting state must accept an application for a trademark which has been previously duly registered in another contracting state (the country of origin), but it is allowed to refuse that application when it does not comply with the requirements under the national law.
- Each contracting state must refuse registration and prohibit the use of marks which constitute a reproduction, imitation or translation, or are liable to create confusion, or are considered by the competent authority of that state to be well known in that state as being already the mark of a person entitled to the benefits of the Paris Convention and used for identical or similar goods.
- Each contracting state must provide for effective protection against unfair competition.

Box 2.7: TRIPS and public health: key milestones

- 1986 Punta del Este launches Uruguay Round negotiations with mandate on IP.
- 1994 Negotiations conclude and the TRIPS Agreement is adopted at the Marrakesh Ministerial Conference.
- 1995 The TRIPS Agreement enters into force, and the WTO is established and is given legal and administrative responsibilities for the TRIPS Agreement.
- 2000 Most TRIPS obligations come into effect for developing-country members, while a transition period is applied in relation to pharmaceutical product patents.
- 2000 WTO panel rules on TRIPS dispute concerning regulatory review (“Bolar”) exceptions to facilitate entry of generic medicines.
- 2001 WHO–WTO Workshop (Høsbjør, Norway) discusses Differential Pricing and Financing of Essential Medicines.
- 2001 Doha Declaration on the TRIPS Agreement and Public Health is adopted, including extension of transition period to 2016 for least-developed country (LDC) members to implement patent and test data protection.
- 2002 WTO General Council adopts waiver of obligation to provide for exclusive marketing rights during transition period for LDCs.
- 2003 “Paragraph 6” mechanism is adopted enabling special compulsory licences for export of medicines, as additional TRIPS flexibility, initially in the form of a legal waiver, followed by the 2005 Protocol on a permanent amendment of the TRIPS Agreement.
- 2005 TRIPS obligations to protect patents for pharmaceutical products apply to developing-country WTO members (but not LDCs).
- 2005 TRIPS Council extends the transition period for LDCs to implement the TRIPS Agreement as a whole until 2013.
- 2013 TRIPS Council extends the transition period for LDCs regarding the implementation of TRIPS until 2021.
- 2015 TRIPS Council extends the transition period for LDCs to implement patent and test data protection in the pharmaceutical sector until 2033. General Council waiver of obligations to provide for mailbox applications and exclusive marketing rights during the transition period.
- 2017 Protocol Amending the TRIPS Agreement (new Article 31 *bis*) enters into force.

Article 7 of the TRIPS Agreement notably describes the objectives of protection and enforcement of IPRs in terms of a balance of rights and obligations. The objectives refer to “the promotion of technological innovation”, “the transfer and dissemination of technology”, the mutual advantage of both “producers and users of technological knowledge”, and also “social and economic welfare”. The principles set out in Article 8 state that WTO members may adopt measures necessary to protect public health and nutrition, provided that such measures are consistent with the provisions of the TRIPS Agreement. The Doha Declaration, a landmark declaration adopted at the WTO Ministerial Conference in 2001, reaffirmed these objectives and principles as guidance for the implementation of TRIPS provisions in line with public health policy. The Doha Declaration referred to a set of flexibilities, or legal options within the framework of the TRIPS Agreement (discussed further below, after a general review of IP issues).

The multilateral standards for each form of IP are generally minimum standards, which often leave considerable scope for implementation. The TRIPS Agreement specifies that

WTO members are free to determine the appropriate method of implementation of TRIPS standards within their own legal practice. When determining the range of options for implementation, policy-makers therefore consider international and, where applicable, regional standards as well as practice in other countries and their own national needs and priorities. Countries may also implement more extensive protection if they wish, provided it is TRIPS consistent. Such protection is sometimes referred to as “TRIPS-plus”. These standards have been established in the IP sections of an increasing number of bilateral and regional agreements (see Chapter IV, section C.5) and are also motivated by a country’s domestic policy considerations (see section B.5 below).

The principle of non-discrimination forms a cornerstone of the international IP system. “National treatment” provides that countries must not discriminate between their own nationals and the nationals of foreign countries with regard to the protection of IP, other than as permitted by some fairly narrow exceptions. The principle was set out as early as 1883 in the original text of Article 2 of the Paris Convention, and was subsequently largely

applied in Article 3 of the TRIPS Agreement. “Most-favoured-nation (MFN) treatment” provides that countries must not discriminate between the nationals of different foreign countries with regard to the protection of IP. The application of MFN treatment is also subject to some exceptions. Long an obligation in international trade law, MFN was applied to IP for the first time through Article 4 of the TRIPS Agreement. Application of the principle means that if two countries agree to give each other’s nationals a higher level of IP protection in a bilateral treaty, they must extend the same benefit to nationals of all other WTO members.¹⁰⁸ In regard to the non-discrimination principles, the TRIPS Agreement is thus significantly different from other main WTO agreements, in that it normally does not permit countries to discriminate against nationals of their trading partners.

Apart from such general principles, each form of IP is subject to specific standards, reflecting its distinct policy purposes, different subject matter and economic effects. These differences are apparent in the scope of protected subject matter, the scope of rights, the duration of protection, and the nature of exceptions and other safeguards for third-party interests, as well as in how these rights are enforced.

(b) Patent law and policy

Since 2000, there has been considerable growth in the use of patents for medical technologies, in terms of the volume of patent filings, the geographical base of activity (with a notable rise in patents from certain emerging economies), and the diversity of private and public entities seeking patents. This same period has also been marked by an intense debate on the role of the patent system regarding innovation in, and access to, medical products.

The dual effect of IP protection – promoting the development of new medicines and impacting prices – was recognized in the Doha Declaration. Since then, debate has focused on the implications of patent rights for access to essential medicines. In addition, it has been discussed whether the patent system provides sufficient and appropriate incentives to ensure the development of new products in certain areas – for example, with respect to neglected diseases or certain countries. In practice, patents are also used as a medium for concluding many technology partnerships and R&D collaborations, with multiple licensing arrangements in order to deliver a new medical technology to the public.

(i) *The rationale of the patent system*

The rationale of the patent system is to make investment in innovation attractive and to offer a mechanism that ensures that the knowledge contained in the patent application is accessible to society. Among other obligations, the

obligation of patent owners to publicly disclose their inventions enables society to know, and eventually use, the knowledge contained in patent documents. If an invention could be freely used by others at no additional cost, “free-riders” would not bear the cost of development. This would reduce the expected returns of the original inventor and would result in, in theory, the under-provision of new inventions. A 2008 WIPO report explains that it is for this reason that the patent system intends to correct the market failure that would result in the under-provision of innovative activities by providing innovators with limited exclusive rights to prevent others from exploiting their invention, thereby enabling the innovators to appropriate returns on their innovation activities.¹⁰⁹

However, the use of the exclusive right can itself contribute to a market distortion and can lead to a situation characterized by inefficiencies, high prices and the under-provision of goods. Empirical studies find evidence of both positive and negative effects of patents on innovation. Inconclusive evidence on the role of the patent system in encouraging R&D and technology transfer makes it difficult to draw any clear-cut conclusions about the effectiveness of the patent system for economic development.¹¹⁰

A number of mechanisms exist in patent systems to prevent and correct undesired effects:

- Patent rights only last for a limited period of time.
- Exclusions from patentable subject matter and exceptions and limitations to patent rights are permitted in order to ensure harmony with broader public policy goals.
- Patent application, examination and grant procedures, as well as opposition, appeal and other review procedures, allow courts and other review bodies to correct erroneous grant of patents, and give relief where necessary, in order to ensure that the patent system, as a whole, functions as a public-interest policy tool.

(ii) *The international framework*

The substantive multilateral standards for patent protection are largely those set out in the Paris Convention and the TRIPS Agreement. The Paris Convention did not regulate what is considered patentable and, until the TRIPS Agreement came into effect in 1995, there was considerable diversity in national law and practice in this respect. In 1988, at an early stage in the negotiations of the TRIPS Agreement, a WIPO report cited 49 countries that either did not grant patent protection for pharmaceutical products at all or only provided a limited form of such protection. Some of these countries also excluded pharmaceutical manufacturing processes.¹¹¹ The duration of patents also varied considerably from country to country.

The TRIPS Agreement is the first multilateral treaty to stipulate the core criteria for patentable subject matter (see also section (iii) below on patentability criteria). The TRIPS Agreement provides that patents must be “available for any inventions, whether products or processes, in all fields of technology” (Article 27 of the TRIPS Agreement). The reference to “all fields of technology” means that patents must be available for pharmaceutical products (such as a new chemical compound with medicinal effect) and processes (such as a method of producing the medicine). It also provides that the available term of protection shall not end before the expiration of a period of 20 years counted from the date of filing the application. The most significant change of relevance to the area of public health was the requirement that pharmaceutical products be patentable in developing countries from 2005. These requirements came into effect progressively, but now apply to all WTO members, except LDCs, for which a transition period was extended until 2033 (see Box 2.7).

Even with these international standards for patent protection, there is no such thing as a worldwide patent. Patents are granted under national law or on a regional basis. Article 4*bis* of the Paris Convention provides the independence of patents obtained for the same invention in different countries. This means that a patent granted in one country conveys no rights in any other country. A patent on a pharmaceutical technology in one country cannot be used to prevent generic competition in other countries where no patent is in force. An invention may be patented in one country and not in another.

There is, however, a global system for filing patent applications, known as the Patent Cooperation Treaty (PCT), administered by WIPO (see Box 2.8). A final decision on whether a patent should be granted is not taken internationally. Rather, it is taken separately by the national or regional authorities responsible for national patent jurisdictions; a number of regional agreements have also harmonized and simplified patent laws within the respective regions.¹¹²

Despite this regional and international cooperation, national patent laws and practices differ, leading to potentially diverging outcomes. Where patent applications are filed for the same invention in different national or regional patent offices, they are processed separately according to the applicable national law or regional law, and such processing may have diverging outcomes. For example, when a PCT application relating to a certain pharmaceutical compound reaches the national phase in the PCT contracting states, different substantive patentability requirements may apply under the patent law of each country or region. Based on the application of these requirements in the national examination processes, the patent claims may be amended in one country and remain unchanged in another (regarding claims, see also section (vi) below). Consequently, the same PCT application may result in a patent grant in one country, a patent grant with restricted claims in another country and a patent refusal in a third country. Moreover, a patent could be invalidated by a court in one country but confirmed by a court in another country. The majority of patents are applied for, and ultimately obtained in, a

Box 2.8: The Patent Cooperation Treaty

The Patent Cooperation Treaty (PCT)¹¹³ makes it possible to seek patent protection for an invention simultaneously in all PCT contracting states by filing an international patent application. Such an application may be filed by anyone who is a national or resident of a PCT contracting state, either with the national patent office of the contracting state of which the applicant is a national or resident, with a competent regional patent office or with the International Bureau of WIPO in Geneva (the “receiving office”). The effect of the international application is the same as if national patent applications had been filed with the national patent office of each contracting state. The PCT regulates in detail the formal requirements with which any international application must comply, but it does not determine the substantive rules that a country applies in deciding whether or not ultimately to grant a patent.

The PCT provides an international phase within which the international application is subjected to an international search, resulting in an international search report (a listing of the citations of published documents that might affect the patentability of the invention) and a preliminary and non-binding written opinion on whether the invention appears to be novel, to involve an inventive step (to be non-obvious) and to be industrially applicable in light of the search report. The international application, if not withdrawn, is published together with the international search report. In addition, an optional non-binding international preliminary examination is carried out if requested by the applicant. If the applicant decides to continue with the international application, with a view to obtaining national or regional patents, the applicant needs to commence separately the national/regional procedure in each PCT contracting state in which the applicant wishes to obtain patent protection (“enter the national phase”). During this “national phase”, a country’s authorities will apply the substantive rules on eligibility for patents that are defined under national law, which may result in different outcomes from country to country.¹¹⁴ If the applicant does not initiate the national phase before a specific office within the required time limit, the application loses effect with the same consequences as a withdrawal of a national application.

relatively small number of countries – typically, those countries where the patent holder intends to concentrate production or marketing efforts, or where there are significant competitors or production capacity.

(iii) *Basic patent issues*

Patents are territorial rights. In addition, patent protection is limited in time. Patent laws generally provide that patent protection shall not end before the expiration of 20 years counted from the filing date. This rule is set out in Article 33 of the TRIPS Agreement and was applied in the WTO case of *Canada – Term of Patent Protection* in 2000.¹¹⁵ Patent owners, on the other hand, may abandon a patent earlier if, for example, the commercialization of the invention does not generate the expected return on investment and fails to cover the costs of maintaining the patent. Patents may be abandoned by a failure to respond to patent office notices on time, a failure to pay maintenance fees or filing a written expression of abandonment. Patents may also be invalidated in court or administrative procedures based on grounds established by the domestic law. In countries where no patent application is filed, or where a patent application has been withdrawn or refused, or where a granted patent is no longer in force, a published invention enters into the public domain, provided there is no other patent or other right covering the same technology. The WIPO Committee on Development and Intellectual Property (CDIP) has examined the relationship between patents and the public domain and produced a Study on Patents and the Public Domain.¹¹⁶

While a published patent application informs the public of the fact that an application is pending, patent protection begins only with patent grant. Domestic law may provide for provisional protection of published patent applications, where available, usually conditional on patent grant and availability of the publication in the national language. Such provisional protection may take the form of payment of royalties, for example, in European Patent Office (EPO) member states or in the United States. Not all countries provide for provisional protection; for example, the laws of Brazil and India do not provide for provisional protection.¹¹⁷

In line with Articles 27 and 29 of the TRIPS Agreement, certain patentability criteria are common to all patent laws: (i) the subject matter claimed in the application must consist of patentable subject matter; (ii) the claimed subject matter must be new; (iii) it must involve an inventive step (or be non-obvious); (iv) it must be industrially applicable (or useful); and (v) the invention must be properly disclosed. These requirements apply cumulatively. Failure to satisfy any one criterion leads to rejection of a patent application.¹¹⁸

Even though the same essential patentability criteria are found in the vast majority of countries, there is no agreed

international understanding about the definition and interpretation of these criteria. This creates some policy space regarding their establishment under the applicable national law. Accordingly, patent offices and courts interpret and apply national patentability requirements on a case-by-case basis within the applicable legal framework. Many patent offices provide patent examination guidelines for consistent and coherent application of patent law with more specific guidance, often basing this guidance on cases previously decided by the responsible courts.¹¹⁹ Such guidelines can also assist patent examiners when new technologies emerge or where patent applications and the application of patentability criteria raise ethical concerns (see Box 2.9). The EPO has issued examination guidance, for example, for biotechnological inventions,¹²⁰ computer-implemented inventions¹²¹ and artificial intelligence and machine learning¹²² as part of the EPO Guidelines for Examination.¹²³

Inventorship, ownership and entitlement to apply

Every invention is created by an inventor or inventors. While international IP law is silent on who should be considered the inventor – leaving this question to be determined by national laws – the general practice is that those who contribute to the conception of at least one of the claims in the patent are joint inventors, irrespective of the proportion that they contributed.

Inventorship does not necessarily imply ownership. Inventions by employees made during the course of their employment, depending on the rules of the national law, may belong to the employer, with or without a specific agreement. Contracts of employment or a consultancy may provide that inventions made outside the course of employment also belong to the employer or the party who engaged the consultant. Inventors frequently assign their economic rights to an invention to the bodies that provide funding for their research.

Policies on ownership of patents on inventions derived from research undertaken within public institutions such as universities can have a significant effect on how medical technologies are developed. In the absence of clear guidelines, uncertainty can ensue.

Patentable subject matter

Patents are only available for patentable subject matter. In the absence of an internationally agreed definition of patentable subject matter, national laws define the requirement either positively or through a negative list of excluded subject matter – or both. Exclusions from patentable subject matter may be general – such as mere discoveries, scientific principles or abstract ideas. Patentable subject matter that does not fall into such categories can be excluded on other grounds. This would

Box 2.9: Societal and moral values in the patent system

What is considered contrary to morality depends on the fundamental values of a society in a given context. Article 27.2 of the TRIPS Agreement¹²⁴ provides a flexible framework for moral assessments to be made, which leaves room for societal and ethical values to be taken into account.¹²⁵

In 2008, the Enlarged Board of Appeal of the EPO ruled that claims were not patentable if directed to products which could only be prepared by a method necessarily involving the destruction of human embryos, even if the said method was not part of the claims.¹²⁶ In 2014, the EPO Board of Appeal confirmed the exclusion from patentability for inventions which make use of publicly available human embryonic stem cell lines originally derived by a process resulting in the destruction of human embryos.¹²⁷ In 2011, the Court of Justice of the European Union, while not touching upon questions of a medical or ethical nature, ruled that any human ovum capable of commencing the process of development of a human being is a “human embryo” and claims concerning the use and destruction of a human embryo are excluded from patentability.¹²⁸ In 2014, the Court of Justice of the European Union (CJEU) held that unfertilized human eggs whose division and development had been stimulated by parthenogenesis but which, in the absence of paternal DNA, were not capable of developing into a human being (“parthenotes”) did not constitute a human embryo and parthenotes were not excluded from patentability.¹²⁹ In Australia, stem cells are patentable so long as the material is removed from its natural state and that there is demonstrable use, except in the case of embryonic stem cells, which are specifically excluded from patentability under section 18(2) of the Patent Act 1990 (Commonwealth). Parthenotes may be patented.¹³⁰

Article 27.3(b) of the TRIPS Agreement allows WTO members to exclude from patentability plants and animals and essentially biological processes for their reproduction. This exclusion does not extend to microorganisms and to non-biological and microbiological processes for the reproduction of plants or animals, which must be patentable. There has been no determination in the WTO of the scope of this provision.¹³¹ Some patent systems exclude parts of plants and animals, such as cells, cell lines, genes and genomes; others consider them a particular type of chemical substance, if isolated and purified from their natural environment, and thus patentable subject matter (this is discussed further in Chapter III, section D.4(a)). A number of countries have expressly elected to exclude patents on any unaltered genetic materials.

include, for example, inventions that would be considered against morality if commercially exploited (see Box 2.9), or certain methods for medical treatment of humans or animals (Article 27.3(a) of the TRIPS Agreement). A number of countries have opted to exclude from patent grant (or not permit the enforcement of) inventions concerning methods of medical treatment (or, with similar effect, to limit the enforcement of such patents). Some national laws articulate very specific exclusions, such as for first and second medical indications, or expressly allow for the patenting of such claims (see Chapter III, section D.4(c)). The WIPO report on the international patent system has collated information from primary national/regional legislation on exclusions from patentable subject matter.¹³²

Novelty

The criterion of novelty is intended to ensure that patents are only granted on technologies that are not already available to the public. In many jurisdictions, this criterion is understood to mean that a claimed invention must not already have been disclosed to the public, anywhere in the world, before the filing or priority date of the patent application – for example, through publication, or as a result of having been publicly made, carried out, orally presented, or used, before filing a patent application or

before the priority date, if any. National laws define which kind and form of documentation, if any, constitutes prior public disclosure relevant to an assessment of novelty.¹³³

For example, consider a case where a patent application claims a new type of cast used to immobilize a patient’s arm. At the time of filing the patent application, this invention was known only to the employees of the company filing the application. These employees were bound by their employment contracts not to disclose their knowledge to the public. In such a case, the invention has not been disclosed to the public and would be considered novel for the purpose of patent examination. However, if, before the patent filing took place, the cast was tested on patients without confidentiality arrangements already agreed and in place, the claimed invention may no longer be considered novel, since access to the relevant knowledge may not have been sufficiently restricted and therefore it may be considered to have been disclosed to the public.

Inventive step/non-obviousness

Patent law, in general, defines only the basic concept of what constitutes an inventive step and leaves interpretation to patent offices and supervising courts. Practice has developed different methodologies to

determine the existence of an inventive step based on a number of indicators checked by a patent examiner. This criterion is understood in many jurisdictions to mean that the invention must represent a sufficient technical advance in relation to the state of the art – a technical advance from what has been used or described before in the relevant area – that could not have been obvious to a person working in the technical area related to the invention with “ordinary skill” or average knowledge (“person skilled in the art”) on the relevant date (being the filing date or priority date of the patent application). While some laws require that this person have “ordinary” or “average” skill, a WIPO study found that no national/regional law explains or defines the term “person skilled in the art”,¹³⁴ although it can be deduced that average or ordinary skill is the skill expected to be possessed by a hypothetical person who is an ordinary, duly qualified practitioner in the relevant field.¹³⁵ In some countries, administrative guidelines or jurisprudence provide guidance on the meaning of the term.¹³⁶

The inventive step (or non-obviousness) may be demonstrated by an “unexpected” or “surprising” effect that would not have been evident, at the time of invention, to the person skilled in the art. For example, a mixture of medicines consists of a painkiller (analgesic) and a tranquilizer (sedative). It was found that, through the addition of the tranquilizer, which intrinsically appeared to have no painkilling effect, the analgesic effect of the painkiller was intensified in a way that could not have been predicted from the known properties of the active substances.¹³⁷

What is obvious, or not obvious, may change over time. For example, considerable effort was needed to isolate a gene at the end of the 20th century. Today, however, this is considered more routine (see Chapter III, section D.4(a)). The 2019 WIPO Study on Inventive Step (Part III) has gathered information about how WIPO member states apply the inventive step criterion in the field of organic and inorganic chemistry, including pharmaceutical application.¹³⁸

Industrial applicability/utility

Industrial applicability (or utility) means that the invention can be made or used in any industry, including agriculture, or that it has a specific, credible and substantial utility. In general, in order to comply with the requirement, an applicant has to indicate the ways by which the claimed invention satisfies the possibility of industrial application in the description unless it is clear to a person skilled in the art from the nature of the claimed invention. This general requirement is given a specific form in many countries. For example, the EPO Board of Appeal has decided that the mere fact that a substance can be produced is not sufficient if the inventor cannot describe a concrete use of that product, for example, to relate that product

to a disease or identified condition.¹³⁹ In general, the application of this requirement does not pose practical problems in patent examination.

The requirement of industrial applicability has gained importance for the determination of the patentability of inventions in the field of biotechnology – more specifically, of inventions concerning, for example, a sequence or partial sequence of a gene. While product patents granted on gene sequences in general cover all known and unknown uses of a claimed gene sequence, that is, even those uses are protected which are not yet known by the patentee, some jurisdictions require that patent applications specify with respect to the industrial applicability (utility) criterion which function the claimed gene or gene sequence fulfils, or even require that the function be included into the claim (see Chapter III, section D.4(a)). In the latter case, the scope of protection of a product claim will be restricted to the claimed use.

The UK Guidelines for Examining Patent Applications for Biotechnological Inventions¹⁴⁰ explain that the industrial application of genes or protein sequences is not apparent from the invention itself. Based on UK Supreme Court and EPO jurisprudence, the Guidelines state that a practical application and profitable use, as well as a concrete benefit, must be derivable directly from the patent and common general knowledge so that a skilled person was enabled to exploit the claimed invention. The Patent Examination Guidelines issued by the Korean Intellectual Property Office (KIPO)¹⁴¹ state that, for inventions involving genes, DNA fragments, antisense, vectors, recombinant vectors, transformants, fused cells, proteins, recombinant proteins, monoclonal antibodies, microorganisms, animals, plants, etc., a specific, substantial and credible utility must be stated in the description of the invention. Where the utility is not described or not inferred based on the specification, the invention does not meet the industrial applicability requirement under Article 29(1) of the Patent Act.

Disclosure

Sufficient disclosure of an invention is required in order to grant a patent. Article 29.1 of the TRIPS Agreement sets out the rule that an applicant for a patent shall disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art. In some countries, the applicant may also be required to indicate the best mode for carrying out the invention known to the inventor at the filing date. The description part of the patent application, in general, allows for the disclosure requirement to be fulfilled. The description should be clear and definite without any ambiguity.¹⁴² In some countries, the applicant may also have to disclose details of patents applied for or granted in other jurisdictions (an option under Article 29.2 of the TRIPS Agreement).

In cases where the application refers to biological material, supplementing a disclosure in writing, the deposit of a sample of this material in an authorized institution can be permitted by patent law. The WIPO Budapest Treaty on the International Recognition of the Deposit for Microorganisms for the Purposes of Patent Procedure¹⁴³ provides for a system under which the deposit of a microorganism with any “international depositary authority” is recognized for the purposes of the patent procedure in the contracting states, irrespective of where the international depositary authority is located.¹⁴⁴ The Treaty does not define what is meant by a microorganism. According to the Guide to the Deposit of Microorganisms under the Budapest Treaty, Section D, cell cultures can be deposited with a number of international depositary authorities.¹⁴⁵

The disclosure requirement is considered one of the important rationales of the patent system as it enables dissemination of information and an increase in the public stocks of knowledge, with an increase in overall social benefits, such as inducing technology transfer.¹⁴⁶ Some argue that disclosure of a patented invention is often not sufficient to “work” the patent, for example, in the field of biotherapeutics (Mandel, 2006; Price and Rai, 2016). One of the fundamental questions raised with respect to the disclosure requirement is the extent to which a patentee must disclose his or her invention within the patent system in order to contribute to the promotion of innovation and to the transfer and dissemination of technology to the mutual advantage of producers and users of technological knowledge. While an invention must be described in the patent in such a manner that a person skilled in the art can carry out the invention without undue experiment or trials, in order to produce the invention to an economically profitable extent, the technical information contained in a patent often needs to be supplemented with further information. The disclosure requirement is designed for the specific legal and technical purposes of the patent system. Technical information disseminated through the patent system cannot replace other sources of information, for example, textbooks and scientific journals.¹⁴⁷

In some cases, a patent might be inadvertently granted even if the requirement concerning the sufficiency of disclosure under the applicable national/regional law has not been complied with. If so, the patent may be defective. Most patent laws provide procedures for the revocation or invalidation of patents where the statutory patentability requirements are not met. Therefore, it would be a risky strategy to intentionally not fully disclose an invention in a manner inconsistent with the disclosure requirement under the applicable national/regional law. For example, the Supreme Court of Canada¹⁴⁸ held that the Canadian patent 2,163,446 granted on an invention for the treatment of impotence was void because the patent application did not satisfy the disclosure

requirements set out in the Canadian Patent Act, R.S.C. 1985, c. P-4. The Court stated that adequate disclosure in the specification was a precondition for the granting of a patent. The specification, which included the claims and the disclosure, had to define the “precise and exact extent” of the right being claimed. The public, from the perspective of a person skilled in the art, had to be enabled only by the specification to make the same use of the invention as the inventor could at the time of the patent application. In this case, the claims were structured as “cascading claims”, with Claim 1 involving more than 260 quintillion compounds, Claims 2 to 5 concerning progressively smaller groups of compounds, and Claims 6 and 7 each relating to an individual compound. The Court stated that the practice of cascading claims was common and did not necessarily interfere with the disclosure requirement. The skilled reader knew that, when a patent contained cascading claims, the relevant claim would usually be the one at the end concerning an individual compound. The compounds that did not work were simply deemed invalid, with any valid claim surviving. However, in this case, the claims ended with two individually claimed compounds, and there was no basis for a skilled person to determine, only from the disclosure in the specification, which of Claim 6 and Claim 7 contained the effective compound. Further testing would have been required to determine which of those two compounds was actually effective. The Court found that the patentee had chosen to withhold information needed to fully disclose the invention.

(iv) Patent procedures

Whether a claimed invention in a patent application meets all patentability criteria is usually established by the patent office that receives the application. Although Article 62 of the TRIPS Agreement states that compliance with reasonable procedures and formalities may be required for the acquisition and maintenance of IP rights, neither the TRIPS Agreement nor the Paris Convention mandates specific patent procedures. As a result, countries have room to manoeuvre in developing an approach to patent procedures that is accommodating of their circumstances (WIPO, 2014a). In general, a patent can be granted following: (i) formality examination only; (ii) formality examination and prior art¹⁴⁹ search; or (iii) formality examination, prior art search and substantive examination.

Under a substantive examination system, a prior art search and substantive examination are carried out by the national/regional patent office. If the office establishes that all applicable requirements have been met, it grants a patent. Such substantive examination leads to a higher degree of legal certainty regarding the validity of granted patents – higher than the degree of certainty provided by a system that simply registers patent applications

without carrying out substantive examination. However, where search and examination are of low quality, this can have an adverse effect because it may raise false expectations in respect of the patent's validity. Where patent offices do not have the necessary resources to maintain up-to-date prior art documentation and employ examiners with the requisite expertise – or where they do not have a sufficient number of applications to justify having qualified examiners across all technical areas – a substantive examination system may not be the most suitable approach. Alternative options include: grant of patents without substantive examination; the registration of patents granted following substantive examination elsewhere; the use of other offices' search and examination results; and cooperation between different patent offices.¹⁵⁰ Patent offices have developed a number of mechanisms and practical arrangements to make use of the search and examination results from other patent offices, aiming at improving the overall quality of patents.¹⁵¹ For example, the Patent Cooperation Treaty (PCT) provides for non-binding international search and international preliminary examination, carried out by a number of patent offices that are specifically appointed for that purpose by the PCT Union Assembly.¹⁵² These search and examination reports can be used by patent offices to decide on a patent grant. Other cooperation mechanisms exist at a regional¹⁵³ and bilateral¹⁵⁴ level. WIPO Centralized Access to Search and Examination (CASE) is an example of a platform for participating patent offices to store, share and retrieve information that is relevant to patent search and examination.

Where patent laws provide for full examination of patent applications, patent offices examine them with regard to the formal and substantive patentability criteria. Applicants must often narrow the scope of the claims during this process in order to avoid rejection of their applications. The applicant may also have to remove claims which the patent examiner considers do not meet the patentability criteria. This may be because they are already known and therefore are not novel, or because they may be obvious and therefore are not inventive. The scope of rights in a granted patent may end up being less than what is originally claimed in the application.¹⁵⁵

Some countries currently employ registration systems as opposed to examination systems. They do not provide for substantive examination and thus do not assess whether a claimed invention fulfils the patentability requirements. The validity of the patents can be challenged before the competent court. Some argue that it is sensible to defer determination of the compliance with the patentability criteria until a patent is actually litigated. The validity of such an argument may depend on the cost, duration and amount of patent litigation, on the one hand, and the cost of setting up and maintaining an examination system, on the other hand. In countries with less-well-functioning judicial systems, correction of erroneously granted patents may be challenging.

The flexibility of the international patent system enables countries to move from one system to another. A WIPO guide outlined various options that countries can choose from when designing search and examination of patent applications in accordance with their policies (WIPO, 2014a). It described, for example, the option of limiting substantive examination to certain strategic fields of technology while applications relating to other fields of technology may be subject to formality examination only or to outsourcing, either within or outside the country. With reference to this guide, the 2018 Intellectual Property Policy of the Republic of South Africa¹⁵⁶ announced the introduction of substantive search and examination of patent applications, initially restricted to pharmaceutical patents due to resource constraints.

(v) Review procedures

Patent systems provide for review procedures to allow third parties to intervene in the patent examination process before the grant of a patent (e.g. before an administrative body, such as an appeal board), or to challenge a patent after its grant (before an administrative body or a court) (see Chapter IV, section C.2). Such procedures complement the office procedures for patent grant and enable the public to contribute to patent quality. The most common mechanisms are opposition systems, re-examination proceedings, administrative revocation and invalidation mechanisms, and third-party submissions.¹⁵⁷

(vi) Rights conferred by a patent

The scope of protection conferred by a patent is defined by the patent claims. The claims must be drafted in a clear and concise manner and must be fully supported by the disclosure of the invention. The rights conferred by a patent, once granted, depend on whether the subject matter is a product patent or a process patent. A product patent confers on its owner the exclusive rights to prevent third parties from making, using, offering for sale, selling or importing the patented invention into the country where the patent rights are granted (Article 28.1(a) of the TRIPS Agreement). A process patent confers on its owner the exclusive rights to prevent third parties from using the process, and from using, offering for sale, selling or importing for these purposes at least the product obtained directly by that process (Article 28.1(b) of the TRIPS Agreement). For example, a process that is patent protected in one country can be used in another country, where the patent is not in force, for production. The products resulting directly from that process, however, must not be imported without the patent owner's consent into the country where the process patent is in force (WTO, 2012).

In addition, Article 34 of the TRIPS Agreement places the burden of proof in civil law infringement cases on the purported patent infringer by determining that a product is deemed to have been produced using a patented process under the following conditions:

- The product obtained by the patented process is new.
- An identical product was produced by the defendant without the consent of the patent holder.
- It is likely that the identical product was made by the patented process.
- The owner of the patent has been unable through reasonable efforts to determine the process actually used.

In practice, patents are used not only to exclude competitors but also to allow a third party to make, use, offer for sale, sell or import the patented invention through licensing. Patent owners can license, sell or transfer ownership of their patents. A licence is a contract in which the patent holder allows another party to use the IP, either in return for a payment of royalties (or some other consideration, such as marketing of the product or access to the other party's assets) or free of charge, for a certain field of use, in a certain territory (which may be for the life of the patent). Licences are frequently used to allow pharmaceutical companies to further develop and/or produce a medical technology where patents are owned by another company or research institution under mutually agreed terms (see also Chapter III, section D.5(c) and Chapter IV, section C.3(b), (c) and (e)).

Patents and marketing approval are separate issues. The grant of a patent on a new medicine in a country does not give the right holder the right to sell the medicine in that country without the approval of the regulatory authority. It is irrelevant for the regulatory approval whether or not a patent is granted. Some countries, however, require applicants for regulatory approval to submit information on whether and which patents are granted, and they do not allow their regulatory authorities to grant marketing

approval when a relevant patent subsists ("marketing approval/patent linkage", see section A.6(g)).¹⁵⁸

(vii) *Exceptions and limitations to patent rights*

Exceptions and limitations to patent rights are tools used to address diverging interests. Such tools are common to all IP systems. Exceptions and limitations may restrict the enforcement of patent rights with respect to certain uses of the patented invention, for example, personal and/or non-commercial use. Articles 5 and 5ter of the Paris Convention contain certain rules on compulsory licences and certain limitations on exclusive rights in the context of safeguarding the public interest. Articles 30, 31 and 31bis of the TRIPS Agreement provide for exceptions and limitations to the rights, and these provisions set out the conditions under which they may be applied. The WIPO Standing Committee on the Law of Patents (SCP, see Box 2.10) has undertaken work in the area of exceptions and limitations.¹⁵⁹

One very common exception is the research exception, which allows others to use the patented invention for research purposes during the life of the patent (see Chapter III, section D.5(a)). Another common exception is the regulatory review exception (also known as the "Bolar" exception), which allows generic competitors to make limited use of a patented invention before the patent expires, to pursue marketing approval of a competitor product (see Chapter IV, section C.3(a)(i)).

National laws may also authorize the grant of "compulsory licences" under certain conditions to third parties for their own use, or for use by or on behalf of governments, without the authorization of the right holder. Under a compulsory licence or government-use authorization, a court or the responsible authority grants specific permission to a person other than the patent owner to produce, import, sell or use the patent-protected product, or use the patent-protected process. Patent owners are, in principle, entitled to receive remuneration. For details on legal requirements regarding the grant of compulsory and government-use licences, see Chapter IV, section C.3(a)(ii).

Box 2.10: WIPO Standing Committee on the Law of Patents

The SCP serves as a forum to discuss issues, facilitate member coordination and provide guidance concerning the progressive international development of patent law. The SCP is composed of all member states of WIPO and the Paris Union and of accredited observers, for example, intergovernmental and non-governmental organizations. Since 2011, the SCP has focused on topics such as exceptions and limitations to patent rights, technology transfer, quality of patents, including opposition systems, and patents and health.¹⁶⁰ The SCP has produced studies and draft reference documents on exceptions and limitations to patent rights, including those that may be relevant to public health, such as the regulatory review exception,¹⁶¹ the research exception¹⁶² and compulsory licensing.¹⁶³ It also produced a study examining constraints faced by developing countries and LDCs in making full use of patent flexibilities such as exceptions and limitations.¹⁶⁴ The SCP collates information on certain aspects of patent law, which is regularly updated by member states and available on the SCP website.¹⁶⁵

(viii) Patent information

The patent system requires disclosure of inventions to the public (see section (iii) above) and makes published patents and patent applications an important source of technical and legal information (Bregonje, 2005). Information in patent documents includes bibliographic data about the inventor, patent applicant or patent holder, a description of the claimed invention and related technology developments and a list of claims (regarding this term, see section (vi) above), indicating the scope of protection which is sought by the applicant. Other information is available on patents apart from the patent documents themselves, for example, search and examination reports related to patent applications, patent legal status information and, where the applicable law provides for access to the file, correspondence between the patent office and the applicant. Patent information is a basis for IP and business strategies and decisions,¹⁶⁶ and input into R&D processes. Improving access to patent information related to health is also a concern of the GSPA-PHI, which addresses the need for access to user-friendly global databases containing public information on the administrative status of health-related patents.

WIPO Standards¹⁶⁷ are recommendations and guidelines that have been adopted by the Committee on WIPO Standards (CWS).¹⁶⁸ They help IP offices establish and administer their IP data and information practice and publication systems. WIPO Standards have led to a fairly uniform structure of patent documents all over the world: they address the transmission, exchange, sharing and dissemination of patent information between IP offices, and facilitate retrieval and access to technical information contained in patent documents.¹⁶⁹ WIPO also collects and publishes examples of IP office practices in the WIPO Handbook on Industrial Property Information and Documentation.¹⁷⁰ This has made patent information search easier and more user friendly.

While Article 29.1 of the TRIPS Agreement mandates disclosure of an invention in the patent application, it does not require publication of patent documents *per se*. However, under Article 12 of the Paris Convention, patent offices, as a minimum, must regularly publish the names of the proprietors of granted patents, with a brief designation of the patented inventions, in an official periodical journal. Patent applications are generally published for public access 18 months after their filing dates (or priority dates, as the case may be). Similarly, Article 21 of the PCT generally requires publication of PCT international applications promptly after expiration of 18 months from the priority date.

The form and content of patent publication varies considerably from country to country. Some patent offices publish only patent applications, not granted patents. Other offices do not publish patent applications but publish only granted patents or just a short notice about the patent grant. In such a case, access to the technical

information and assessment of the scope and legal status of a patent is much more difficult, and only a file inspection at the patent office will yield detailed information about the claimed invention. On the other hand, countries may opt to publish all documents generated during the process of patent prosecution, including additional useful information, such as search and examination reports, corrections, amendments, translations and legal status information. A 2019 WHA resolution emphasized the importance of transparency in patent status in the context of public health (see Chapter IV, section A.4(f)).¹⁷¹

The WIPO Patent Register Portal¹⁷² provides links to online patent registers and gazettes, and to information related to legal status, from more than 200 jurisdictions and patent information collections. It helps identify what information can be retrieved online and how that information can be accessed.

PATENTSCOPE¹⁷³ is the WIPO database for patent information. It provides access to published PCT international applications as well as to a number of national and regional patent collections.¹⁷⁴ Besides using advanced search options and offering full text search within documents, the database uses a range of tools to make the technical information more accessible and to help overcome language barriers. For example, the search interface is available in more than 20 languages and offers a multilingual search tool called Cross Lingual Information Retrieval (CLIR),¹⁷⁵ which performs a search in PATENTSCOPE in different languages simultaneously. WIPO Translate¹⁷⁶ is an instant translation tool, designed specifically to translate patent-related texts. WIPO Pearl¹⁷⁷ provides access to scientific and technical terms derived from patent documents across different languages and helps searches for scientific and technical knowledge.

While publication and digitization of patent information have made knowledge more easily accessible and searchable, no database has complete coverage of all patent documents ever published worldwide (WIPO, 2015b). Besides patent office databases (primary sources), commercial entities provide patent information services and additional services, tailored to specific patent information needs. To support the public in finding patent information related to medicines, special databases have been developed that link medicine data and corresponding patent data. Such databases include the Special Gazette for Medicaments published by the Mexican Industrial Property Institute,¹⁷⁸ the Medicines Patents and Licences database (MedsPaL) maintained by the Medicines Patent Pool, and the Patent Information Initiative for Medicines (Pat-INFORMED), an initiative by WIPO and the International Federation of Pharmaceutical Manufacturers and Associations (see Box 2.11 and Table 2.1).

Another method of identifying relevant patent families (see in this section below) is to search the medicine in question in databases maintained by some countries'

Box 2.11: Selected databases**MedsPaL¹⁷⁹**

The Medicines Patent Pool has established MedsPaL, a publicly available patents and licences database containing information on the patent status of medicines for treatment of HIV, hepatitis C and TB, and other patented essential medicines, in certain LMICs. Patent families are identified for inclusion as those listed in the FDA Orange Book or Health Canada Patent Register, or those identified by WHO/Unitaid patent landscape searches. MedsPaL obtains patent information from different sources, including directly from patent offices and patent databases as well as directly from industry.

Pat-INFORMED¹⁸⁰

The Patent Information Initiative for Medicines (Pat-INFORMED) is a publicly available patent database containing information on the patent status of medicines across a range of disease areas. Pat-INFORMED reproduces information that is voluntarily submitted by patent holders regarding the key patents on specific medicines as approved in a particular market. Pat-INFORMED relies exclusively on patent information provided by the right holders, and the information provided is not verified by WIPO.

Table 2.1: Information available in MedsPaL and Pat-INFORMED

	MedsPaL	Pat-INFORMED
Coverage	Low- and middle-income countries	Global
Types of patent included	Drug product, method of use, intermediates, manufacturing process	Drug product, method of use
Granted patents	Yes	Yes
Pending applications	Yes	No
Expected expiry dates	Yes	No
Oppositions	Yes	No
Licensing information	Yes	No
Data exclusivity	Yes	No
Grant number	Yes	Yes
Priority applications	Yes	No
Ability to directly contact companies with inquiries about patent status	No	Yes
Frequency of updating	Updated every 2 months through an automated process for certain countries; annually for others	At least every 6 months for medicines on the WHO EML, at least annually for others

Sources: Q&A on MedsPaL, available at: <https://medicinespatentpool.org/what-we-do/medspal/>; Pat-INFORMED FAQs, available at: <https://www.wipo.int/pat-informed/en/faqs/>; Pat-INFORMED Terms of Use, available at: https://www.wipo.int/patinformed/documents/pat_informed_terms_of_use.pdf.

medicines regulatory authorities (e.g. FDA Orange Book or Health Canada Patent Register; see section B.1(b)(ix) on patent status and legal status information) or to consult published “patent landscapes” (see section B.1(b)(x) on patent landscapes). No source of information is all-encompassing, nor is there a one-stop shop for patent information or legal information, while the accuracy and validity of the information may change rapidly. It is important that relevant authorities maintain and update frequently the information contained in databases to

ensure that it remains current and accurate. It is important to confirm the correctness of information with the competent patent authority or with the right holder should precise information be needed. Therefore, database terms of use will include a legal disclaimer stipulating that there is no warranty for the information.¹⁸¹

WIPO initiatives to improve access to information and knowledge are founded in the WIPO Development Agenda,¹⁸² Cluster C: Technology Transfer, Information

and Communication Technologies (ICT) and Access to Knowledge. Such initiatives include:

- Access to Research for Development and Innovation (ARDI):¹⁸³ free access to major scientific and technical journals for local, not-for-profit institutions in LDCs, and low-cost access to industrial property offices in developing countries
- Access to Specialized Patent Information (ASPI):¹⁸⁴ free or low-cost access to tools and services for retrieving and analysing patent data for patent offices and academic and research institutions in developing countries
- International Cooperation for Patent Examination (ICE):¹⁸⁵ free expert assistance, training and access to collections of patent documents for developing countries
- Technology and Innovation Support Centers (TISCs):¹⁸⁶ access to technology information and related services to help innovators in developing countries create, protect and manage IP rights
- Digital Access Service (DAS):¹⁸⁷ secure exchange of priority and other similar documents among participating IP offices
- Centralized Access to Search and Examination (CASE):¹⁸⁸ secure sharing of patent search and examination documentation among patent offices.

Such initiatives are particularly important for patent offices in LMICs that are considering patent examination procedures, since they need access to prior art resources as they develop knowledge and practice, for example, on examination of pharmaceutical patent applications, and may want to see results obtained by other patent offices around the world.

A patent family means a number of different patent documents that are either related to each other through one or more common priority documents or are technically equivalent. For instance, a patent applicant may file an initial patent application at one patent office and then subsequent applications in other countries within a specified period of time, claiming the priority (see Box 2.6) of the first application. Members of patent families may therefore be related to each other by such priority claims. Since subsequent filings can claim several priorities of different earlier applications, a variety of different family concepts exists.¹⁸⁹ Databases may use different definitions of what makes up a patent family. For this reason, search results based on patent families may be different for different databases.¹⁹⁰

The retrieval, analysis and exploitation of patent information are complex matters and require specialized skills. Patent searches serve a variety of purposes, and each requires a proper strategy, for example, a patent examiner doing a prior art search, a scientist seeking solutions to a

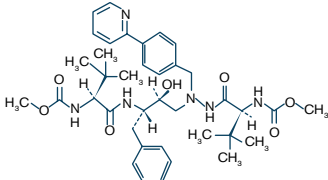
research problem, a procurement officer wanting to identify patent documents related to commercialized medicines, or a generic company assessing business opportunities. Searching patent documents related to pharmaceuticals is further complicated by the fact that a chemical compound can have more than one officially accepted name and can be searched in patent documents by brand name, international non-proprietary name (INN), manufacture name, CAS (Chemical Abstracts Service) Registry Number, International Patent Classification symbol,¹⁹¹ or text representations of chemical structures, such as International Chemical Identifier (InChI). Examples of search parameters for pharmaceutical substances are illustrated in Table 2.2. An applicant may choose any of these indications as long as the invention is sufficiently disclosed.

Patent examiners and IP professionals use a variety of search parameters to conduct searches, often assisted by commercial database services and new software tools.¹⁹² Search algorithms have been developed to allow the translation of one search query variation (e.g. an INN) to other query variations (e.g. a corresponding molecular name, CAS Registry Number and chemical structure). For example, the European Bioinformatics Institute (EMBL-EBI) makes such a search system available on the Internet.¹⁹³ The WIPO Chemical Structure Search¹⁹⁴ in PATENTSCOPE recognizes the names of chemical compounds, including their INN, as well as their structure, from embedded drawings in patent documents. This tool started in 2016 with published PCT applications in English and German (from 1978) and the national collection of the United States (from 1979) and has expanded to other languages and collections since.

(ix) Patent status and legal status information

The term “patent status” is used in this study to refer to all patents related to a specific product, while the term “legal status” refers to various legal and administrative events that occur during the life cycle of a single patent.¹⁹⁵ Patent status and legal status information helps to determine the freedom to operate (FTO) in respect of a project and the extent to which and with whom licences have to be negotiated, but there is in fact no perfect source of information.¹⁹⁶ IP offices provide this information in different formats, inconsistently and in an untimely manner due to differing national and regional patent laws and practices.¹⁹⁷ The WIPO Standard ST.27, adopted in 2017, aims at improving worldwide availability, reliability and comparability of patent legal status data, through promoting an efficient exchange of patent legal status data in a harmonized manner between IP offices, and to facilitate the understanding of end users of patent registers and patent databases about the meaning of certain legal status events across different jurisdictions.

Table 2.2: Examples of search parameters for pharmaceutical substances

Parameters	Examples	Explanation
Manufacturer name	BMS-232632	During the R&D stage, a substance is identified by a code (a combination of alphabets and numbers) in the laboratory or in publications.
INN (generic name)	atazanavir	A unique and universally available designated name to identify each pharmaceutical substance.
Brand name	Reyataz®	Once a drug receives marketing approval, it is sold with a proprietary name registered for trademark protection.
IUPAC chemical name	methyl N-[(1S)-1-[[[(2S,3S)-3-hydroxy-4-[[[2S]-2-[(methoxycarbonyl)amino]-3,3-dimethyl-N'-[[4-(pyridin-2-yl)phenyl]methyl]butanehydrazido]-1-phenylbutan-2-yl]]carbonyl]-2,2-dimethylpropyl]carbamate	The International Union of Pure and Applied Chemistry (IUPAC) sets standards for the naming of the chemical elements and compounds in a structured manner.
CAS Registry Number	198904-31-3	Upon publication of chemical literatures and patents, the Chemical Abstracts Service (CAS) assigns a unique numeric identifier for a newly published compound.
International Patent Classification (IPC) code	A61P 31/18	Although the IPC codes do not pin point a particular substance, it is used with other search parameters to narrow down a search result.
Molecular formula	C ₃₈ H ₅₂ N ₆ O ₇	A chemical formula that shows the number and kinds of atoms in a molecule.
Chemical structure (graphic formula)		Several commercial services offer patent search databases that allow searching compounds by chemical structure in addition to keywords (names) and classification codes. They use various indexing rules so that searchers can also search chemical compounds described in a Markush structure.

Source: WIPO SCP/21/9.

Note: While there are other organizations that assign identifiers to chemical compounds, the CAS Registry Number is one of the most widely used codes by experts in the field of chemistry.

Patent registers record the most important legal events as required by applicable laws and regulations. The most reliable and authoritative information can usually be obtained from these primary sources. Secondary sources, such as commercial patent databases, often compile legal status data from several primary sources, making it easier to obtain an overview of legal status in multiple jurisdictions. However, these secondary sources are not as up to date as primary sources and may lack some of the data contained in primary sources.¹⁹⁸

Assessing the patent status of medical products generally requires specific expertise. A product (including products made of combinations of components, e.g. fixed-dose combinations), its manufacturing process and its use can be covered by several patents protecting various technological aspects.

While information about patent applications and grants is public, resources that directly link patents to medicines already on the market are scarce and limited. For medicines commercialized in the United States, some information can be obtained from the FDA Orange Book,¹⁹⁹ which lists FDA-approved medicines and related patent and exclusivity information. The

Orange Book includes those patents, supplied by the manufacturer, “for which a claim of patent infringement could reasonably be asserted against someone manufacturing or selling an unlicensed version of the drug”.²⁰⁰ Process patents and patents claiming packaging, metabolites and intermediates are not covered by the Orange Book, and information on these patents is not submitted to the FDA.²⁰¹ The Orange Book lists only compound and method-of-treatment patents, and does not include, for example, process patents. In addition, some types of medicines are not listed, for example, most biotherapeutics (see section A.6(d) on biotherapeutic products), for which the FDA maintains a separate list of licensed biotherapeutic products (Purple Book), which provides information on reference product regulatory exclusivity and biosimilarity or interchangeability evaluations, but does not provide information on patents or patent expiry.²⁰²

Health Canada maintains a similar patent register containing an alphabetical listing of medicinal ingredients and their associated patents, patent expiry dates and other related information. Unlike the Orange Book, Health Canada’s Patent Register generally lists patent information for biotherapeutics.²⁰³

The Republic of Korea requires the submission of information about patents that are associated with approved medicines within 30 days from market approval and publishes this information in its Green List.²⁰⁴ The holder of market approval must specify every claim that covers the approved drug product and submit detailed explanation between each claim and the approved medicine.

On the one hand, a patent list for approved medicines is a convenient source of information, making it easy to retrieve patent information. For this reason, many studies start their patent analysis by searching the Orange Book and expanding the search to patent family information.²⁰⁵ On the other hand, linking patent information to information about regulatory processes has been criticized for impacting access to the market by generic products. For further information on patent linkage, see section A.6(g).

(x) Patent landscapes and medical technologies

The term “patent landscape” is used in this study to refer to a report based on patent data (referring to patent documents, either applications or granted patents), search and analysis that provides an overview of the patenting activity in a specific technology field. Usually, it is supported by visualizations, including different perspectives and data analysis, depending on the specific project needs. There is no commonly agreed definition of the term “patent landscape” or a predefined content or structure.

The value of a landscape report is the presentation of a technology area in a manner that is easy to understand for a non-expert. The presentation of the empirical findings is enhanced by visualizations, while a combination of different types of data may lead to interesting insights and conclusions. Patent landscapes can therefore be useful for policy discussions, strategic research planning, investments or technology transfer. However, they only provide a snapshot of the patenting situation at the time the search was carried out.

The first step in landscaping is usually a state-of-the-art search for patent applications/patents in the technological field of interest. The next step is normally to identify the relevant patent family members. The results are then analysed, for example, to answer specific questions, such as those relating to patterns of patenting (Who files applications? What is filed and where?) or certain patterns of innovation (innovation trends, diversity of solutions for a technical problem, collaborations between researchers). Subsequent analysis of the findings may lead to various conclusions or recommendations.

Some landscape reports go further and include legal status information of patent applications/patents, for example, whether applications have resulted in granted

patents and whether such patents are still in force. However, landscape reports rarely cover legal status since this information is generally not easy to obtain, as it is not systematically collected and maintained in a single database (see section (ix) above). Moreover, legal status is always subject to change.

Patent landscape reports are often used as a first step to identify relevant patents, which are further looked into also from a legal status point of view within the framework of a freedom-to-operate (FTO) analysis (see Chapter III, section D.5(f)). An FTO analysis will focus on a limited number of patents and jurisdictions/potential markets of interest, while a patent landscape report will typically include a much broader data set, as its purpose is to provide information about the general landscape rather than questions linked to entry into a market which are FTO specific.

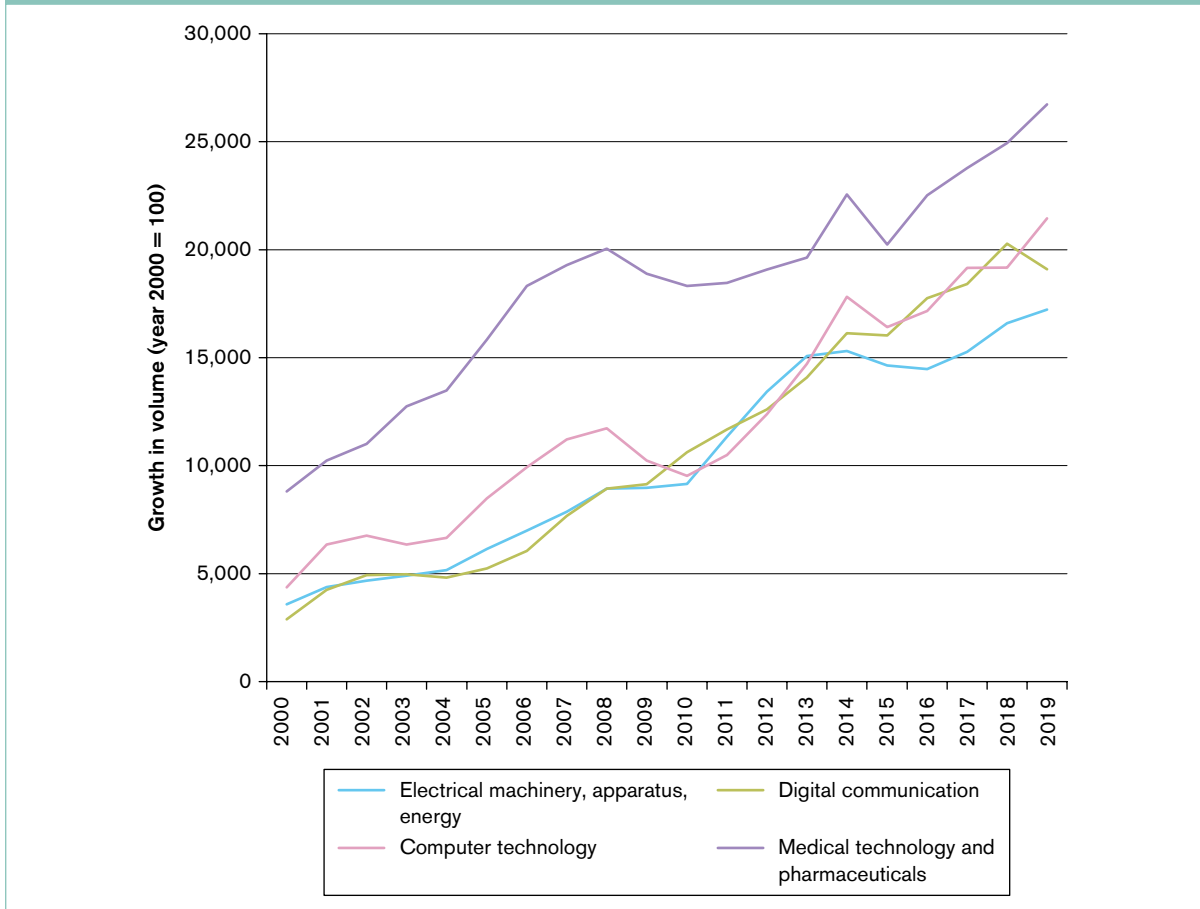
The costs of patent landscape reports can be significant. To enable this information to be shared, WIPO has prepared a list of patent landscape reports in various technical fields,²⁰⁶ including topics related to public health, such as vaccines for selected infectious diseases,²⁰⁷ and assistive devices and technologies for the visually and hearing impaired.²⁰⁸ In addition, WIPO has collected a list of patent landscape reports published by international organizations, national IP offices, NGOs and private-sector entities, which are available in a dedicated, searchable database.²⁰⁹

The WHO, Unitaid and civil society organizations have published numerous patent “landscapes” for medicines of high interest to the global health community. These landscapes are overviews of the key patents on a technology and their status by jurisdiction, and, in some cases, analysis of the coverage of claims, put together by patent experts. These include patent landscapes for HIV medicines, pipeline and approved TB medicines, and pipeline and approved hepatitis C medicines.²¹⁰

(xi) Filing trends under the Patent Cooperation Treaty system

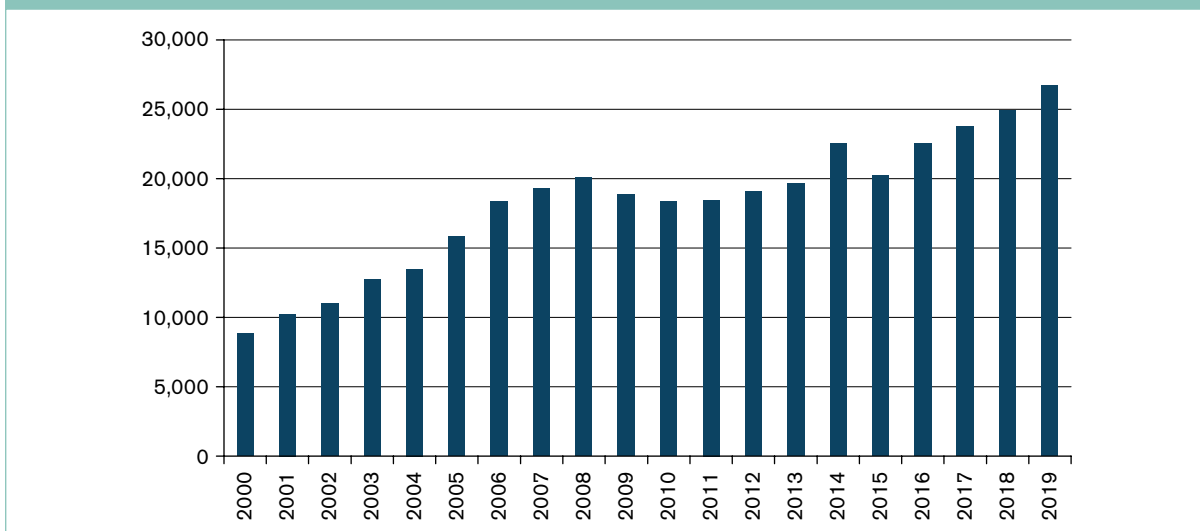
According to WIPO (2019), the area of medical technology accounted for only a relatively small proportion of all applications (6.4 per cent in 2019). However, it should be noted that the term “medical technologies”, as used by WIPO in its annual review of the PCT (WIPO, 2019a), is different from the term used throughout this study. This study also includes data relating to pharmaceuticals (3.7 per cent of all PCT filings in 2019). The PCT filing numbers for both medical technologies and pharmaceuticals accounted for 10.1 per cent of all filings in 2019 and, in this consolidated form, medical technologies and pharmaceuticals represent the field of technology with the highest number of PCT filings between 2000 and 2019 (see Figures 2.4 and 2.5).

Figure 2.4: Growth of the top four technology fields, 2000–2019



Source: WIPO Statistics Database.

Figure 2.5: PCT applications in the field of medical technology, including pharmaceuticals, 2000–2019

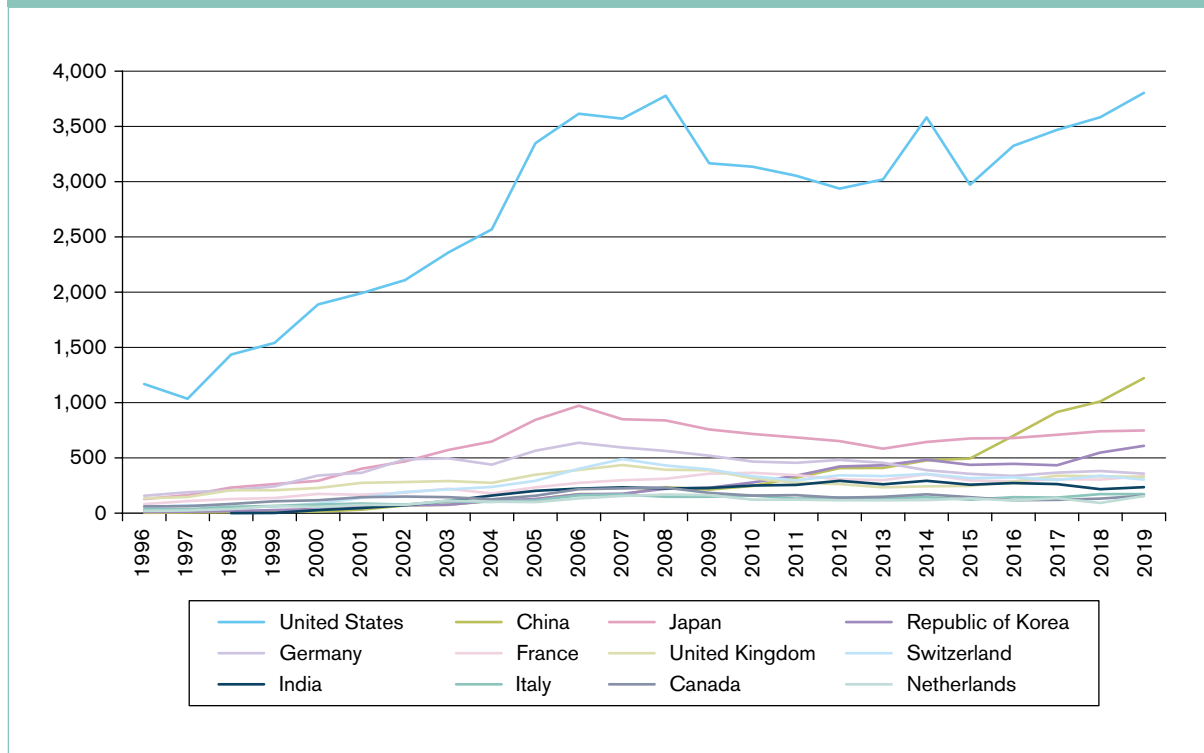


Source: WIPO Statistics Database.

According to the WIPO Statistics Database, the annual total number of published PCT applications in the area of medical technologies between 2000 and 2019 remained in a band between 4,497 and 16,953. In the area of pharmaceuticals, the total number of published PCT applications remained in

a band between 3,808 and 9,772 each year from 2000 to 2019. With respect to medical technologies (as understood in the context of this study, i.e. including pharmaceuticals), the total number of PCT applications filed annually remained in a band between 8,805 and 26,725 each year from 2000

Figure 2.6: Main countries of origin of PCT publications in the field of medical technology, including pharmaceuticals, 2000–2019



Source: WIPO Statistics Database.

to 2019 (see Figure 2.5). The total numbers increased each year until 2008 and then declined in the two following years, then increased again until 2019, with the exception of 2015. Among the top countries of origin are the United States, China, Japan, the Republic of Korea and a number of Western European countries (see Figure 2.6).

(c) Protection of test data

Test data protection is closely related to the regulation of medicines, while also being part of the IP system, since it represents a form of protection against unfair competition. As seen in section A.6 above, in order to obtain marketing authorization for any new pharmaceutical product, submission of test data to regulatory agencies is required in countries that undertake an evaluation of the quality, safety and efficacy of medicines. The generated test data are afforded protection against unfair commercial use and against disclosure under international legal standards that are implemented according to the regulations of the particular jurisdiction.

The rationale for awarding test data protection is that considerable effort, in terms of both time and money, is required to produce data, especially with increasingly stricter regulatory requirements. In producing test data, applicants usually have a strong interest in not allowing free-riding by subsequent applicants on their investment in clinical trials. On the other hand, there

are competing public interests to ensure earlier access to generic products, which can be delayed when generics are unable to rely on originator test data. As a result, the way in which test data are protected is one of the more controversial topics in the debate about public health and IP.

It is important to note that “data protection” in other contexts refers to the safeguarding of personal medical data in the interest of privacy (patient confidentiality). That is not the meaning used here.

(i) How test data are protected

Test data can be protected in different ways, for example, by a regulatory framework of data exclusivity, or reliance on confidentiality or laws on unfair competition. The choice of the protection regime will impact what the regulatory agency can do with data provided by the applicant in the application dossier. The following section sets out the applicable international legal standards, as well as how test data protection is implemented at the domestic level.

International legal standards

Article 10*bis* of the Paris Convention (which requires effective protection against unfair competition in general) and Article 39.3 of the TRIPS Agreement contain multilateral standards relating to the protection of test data.

Article 39.3 of the TRIPS Agreement requires WTO members to protect test data against:

- **Unfair commercial use:** the TRIPS Agreement does not provide a definition of the term “unfair commercial use”, nor does it identify how to achieve this protection. As a result, opinions, as well as national practices, differ on the exact requirements of Article 39.3 of the TRIPS Agreement. Some argue that the most effective way to protect test data is to award a reasonable period of data exclusivity to the originator companies. Others argue that other forms of protection against unfair commercial use are permissible and sufficient. During the Uruguay Round negotiations, the option of making data exclusivity an explicit obligation under the TRIPS Agreement was discussed, but negotiators instead adopted the general wording of the current Article 39.3.
- **Disclosure:** this is an obligation not to ordinarily disclose the data submitted for regulatory approval purposes. Regulatory agencies may, however, disclose the data when disclosure is necessary to protect the public or where steps are taken to ensure that there is no unfair commercial use of the data concerned. For example, the EMA has made clinical trial data available, under certain conditions, to avoid duplication of clinical trials, encourage innovative activities to develop new medicines, and allow academics and researchers to reassess clinical trial data (see Box 3.6).

There is no WTO jurisprudence or authoritative WTO guidance on either of these issues. The matter was raised, but not resolved, in consultations between Argentina and the United States under the WTO dispute settlement mechanism. The mutually agreed solution merely noted that the parties had expressed their points of view and agreed that differences in interpretation are to be solved under the Understanding on Rules and Procedures Governing the Settlement of Disputes (DSU) rules.²¹¹ Nor had these issues been resolved in the TRIPS Council in the lead-up to the Doha Ministerial Conference in 2001, although some views on the interpretation of Article 39.3 of the TRIPS Agreement were put forward by members. What can be stated is that: (i) the flexibilities and pro-public-health interpretation in the Doha Declaration cover the TRIPS Agreement as a whole and therefore apply to test data protection under Article 39.3; (ii) there is no explicit TRIPS requirement to provide data exclusivity, but some form of protection against unfair commercial use is required; and (iii) the fact that two forms of protection are to be provided under Article 39.3 of the TRIPS Agreement highlights that protection against unfair commercial use must involve more than merely not disclosing the data.

That said, there are certain qualifying conditions that apply to the protection of test data:

- **The data are undisclosed:** Article 39.3 only requires the protection of undisclosed data, not previously published information. If the data has been disclosed,

for example, in a scientific journal, patent document or elsewhere, no further protection needs to be granted.

- **The submission of test data is required by countries:** any country that does not require the submission of test data or other data to conduct its own regulatory review of a pharmaceutical product has no obligation under the TRIPS Agreement to provide any test data protection with respect to that product either. The obligation to protect data stems only from the existence of a regulatory requirement to submit those data as a condition of receiving marketing approval.
- **The products for which marketing approval is sought use new chemical entities:** the test data at issue in the TRIPS Agreement only concerns applications for marketing approval of products that utilize “new chemical entities”. This term is not further defined in the TRIPS Agreement, and the WTO has not issued any determination of its scope. There are different views as to whether this condition is applicable to biotherapeutics. Consequently, data protection requirements in this particular industry sector may, or may not, fall within the scope of the TRIPS Agreement.
- **The generation of the data involves considerable efforts:** the TRIPS Agreement does not specify the nature of such efforts, that is, whether they must be technical or economic. Neither does it prescribe that the applicant is required to prove that such efforts have been made.

LDC WTO members are, in any event, not obliged to protect test data with respect to pharmaceutical products due to an extended transition period, which currently runs until 1 January 2033.

National implementation

The possibility to protect test data in different ways under the TRIPS Agreement is reflected in the incorporation of this obligation into national law. In line with their political priorities, countries have adopted different approaches to protection against unfair commercial use. In many cases, the approach chosen has also been guided by provisions that countries have subscribed to in FTAs (Diependaele et al., 2017; see also Chapter II, section B.5 and Chapter IV, section C.5) or, in a few cases, by legally binding commitments providing expressly for data exclusivity in WTO accession protocols (e.g. China, the Russian Federation and Ukraine).²¹² These countries have thus agreed to enter into more detailed obligations than are required under the TRIPS Agreement.

Most high-income countries, and some LMICs, provide for a regime of data exclusivity. Other countries prohibit their respective regulatory authorities from allowing third parties to access and use information submitted to them, in accordance with laws on confidentiality and unfair competition. They do not bar regulatory authorities from relying on test data submitted in an application for a previously approved originator product in order to review and approve an application for second and subsequent market entrants.

Among the other options discussed for test data protection are compensation or cost-sharing models, under which reliance on the originator data would be permitted, provided that the generic supplier participates in the costs of generating the data. The United States, for example, provides both data exclusivity and a mandatory data compensation system of this kind in relation to data submitted in applications for regulatory approval of pesticides (but not pharmaceuticals). The European Free Trade Association (EFTA)–Korea FTA (Article 3, Annex XIII) admits a compensation scheme as an alternative to data exclusivity for pharmaceuticals.²¹³

(ii) Innovation and access dimensions

From the perspective of the originator companies, reliance on their data by competing generic companies may be considered unfair because the second and subsequent market entrants will not have been obliged to invest in costly clinical trials (including failed trials) and thus could compete directly with a major cost advantage. They therefore hold the view that test data protection, especially in the form of data exclusivity, provides an important incentive for the industry to invest in the development of new products and the necessary clinical trials. In addition, originator companies value the relative certainty of data exclusivity when compared with the increased uncertainty that applies in relation to the validity or scope of a patent, which, in turn, increases uncertainty with respect to the ability to temporarily exclude competitors. One such example would be the development of a paediatric version of an existing medicine, which, in certain jurisdictions, would be denied a patent, due to lack of novelty. In such a situation, the protection of the clinical test data would be the only incentive to invest in the development of this formulation, in the absence of other incentive mechanisms, such as grants, market entry awards or advanced market commitments. A similar situation could arise in relation to clinical trials to test the safety and efficacy of known traditional medicines or old medicines that are not patentable, due to lack of novelty (see Box 2.12).

On the other hand, generic pharmaceutical producers will wait for the expiration of any exclusive test data protection period, even though they could, in theory, redo the clinical trials or agree with the originator company on the use of the original data. This does not seem to happen in practice. Applicants for generic medicines want to rely on the originator data so that the generic products can be placed on the market sooner and at lower costs. Reliance on originator data also avoids unethical duplication of clinical trials. Public health advocates therefore highlight that, with regard to developing countries, the additional incentive of data exclusivity for carrying out research and clinical trials is considered marginal, whereas the negative impact on prices, and thus on access to medical technologies, is considerable. The WHO Consultative

Expert Working Group on Research and Development: Financing and Coordination (CEWG) found that “there was no evidence that data exclusivity materially contributes to innovation related to Type II and Type III diseases and the specific R&D needs of developing countries in relation to Type I diseases, and therefore we concluded that its removal where it existed would not adversely affect innovation incentives for these diseases and also would contribute to reduced prices of affected medicines” (WHO, 2012).

(iii) Distinction between the protection of patents and of test data

Patents and test data protection are two distinct categories of IP. The TRIPS Agreement deals with test data protection as a form of protection against unfair competition in the section on protection of undisclosed information and not in the section on patents. While a patent grants legally enforceable rights to the patent owner to protect the invention – for example, a new molecule – irrespective of the effort and investment involved, test data protection covers a different subject matter, specifically the information submitted for regulatory approval (sometimes called the “regulatory dossier”). A patent could be held by one party and the regulatory dossier held by another (e.g. a local licensee under the patent).

Patent protection and test data protection run in parallel for the patented medicines that do make it to market (see the example in Figure 2.3). However, patent protection will typically have begun a number of years earlier. This is because patent applications are usually filed as soon as an invention is made, whereas clinical trials are undertaken only at a later stage in the product development cycle. By the time clinical trials begin, a patent may still be pending or may have been granted. Since test data protection and patent protection are distinct, protecting test data can deliver certain benefits to the company generating the data. Such benefits would manifest, for example, where a product is either not under patent protection (see an example in Box 2.12), where it has only a short remaining period of patent protection or where the validity of the patent is challenged. In such situations, an exclusivity period may delay the early entry of generics into the market because regulators are obliged not to review/approve products until the exclusivity period expires. For example, in Ukraine, after rejection of key sofosbuvir patents, the originator company challenged the registration of a generic product based on data exclusivity provisions in 2016 leading to deregistration of the generic product. It subsequently reached an agreement with the government on providing the originator product at a reduced price. As of August 2017, the originator agreed to include Ukraine on the list of countries to which its Indian licensees can export their generic production.²¹⁴

Box 2.12: The example of colchicine

Colchicine is a remedy for gout, known to the Ancient Greeks and used in the United States since at least the 19th century. While the 1938 Federal Food, Drug, and Cosmetic Act required all medicines to be approved by the FDA, those that had been on the market before the Act was in force were allowed to remain on the market, and colchicine was sold as a generic medicine by a number of pharmaceutical companies. In 2006, under the Unapproved Drug Initiative, the FDA required pharmaceutical companies to conduct clinical trials and other studies if they wanted to keep selling colchicine, with the objective of improving the evidence base for the safety and efficacy of the treatment. One pharmaceutical company conducted the requisite trials, leading to FDA approval of its colchicine product in 2009.²¹⁵ Under the Hatch-Waxman Act, as the approval was technically for a “new indication” (as previous versions had never been specifically approved for these indications), the pharmaceutical company was granted a three-year regulatory exclusivity for acute gout and a seven-year orphan drug exclusivity for another indication, familial Mediterranean fever (a rare genetic disorder) (see Chapter II, section A.6(f)). Other colchicine products previously on the market were required to phase out production. The price of colchicine increased from \$0.09 to \$4.85 per tablet (Brett, 2010; Kesselheim and Solomon, 2010). Additionally, the company was granted method-of-use patents that were expected to expire in the United States around 2028. However, the FDA approved a competitor product in 2014, and several other generic versions have been approved since then.²¹⁶

In addition, test data protection is granted automatically, while obtaining and maintaining patents requires effort and investment. Patents may be revoked. Test data protection does not require maintenance fees to be paid, unlike patents. Compulsory licences under the TRIPS Agreement concern use of patented technology, but not test data. The laws of some countries nevertheless provide for waivers to test data protection for products manufactured under compulsory licences (’t Hoen et al., 2017). While it may be possible to invent around patents, especially patents on formulations, methods of manufacture and chemical intermediaries, it is more difficult for a generic competitor to generate its own clinical trial data. Given these characteristics, some argue that the pharmaceutical industry places more importance on data and other regulatory exclusivities than on patents (Roth, 2012; Diependaele et al., 2017).

(iv) Open access to test data

Open access to test data is desirable from the public health perspective, in particular, to avoid duplication of clinical trials, encourage innovative activities to develop new medicines and allow researchers to evaluate clinical trial data. That said, the question arises how the legitimate public policy objective of open access to test data and the requirement to protect such data against unfair commercial use and disclosure pursuant to Article 39.3 of the TRIPS Agreement can both be met.

For example, as set out in Box 3.6, the European Union has put in place a policy and legal framework regarding public access to clinical trial data.²¹⁷ It provides, among other things, that an EU database be set up and maintained by the EMA with a view to ensuring an appropriate level of transparency in clinical trials. Arguably, in the European Union, the public disclosure of test data does not affect the protection under Article 39.3 of the TRIPS Agreement,

as they are covered by a regime of data exclusivity of up to eight years, during which no competitor can rely on the data in order to obtain marketing authorization. The impact of the European Union’s open access policy on the protection of test data in third countries, however, seems to be unclear.²¹⁸ Once published in the database, the data would no longer have to be considered as “undisclosed” within the meaning of Article 39.3 of the TRIPS Agreement and would therefore not have to be protected by other WTO members. However, the EMA’s Terms of Use specify that the clinical reports may only be used for general information and non-commercial purposes, requesting the user of the data to agree not to refer to the data in support of an application for marketing authorization in third countries. There is no liability provision in the event of non-respect of the Terms of Use.

The EU General Court, in its judgment of 25 September 2018, ruled that Article 39.3 of the TRIPS Agreement does not mean “that protection granted to intellectual property rights must be given absolute precedence over the principle of disclosure of the information submitted in the context of a marketing authorisation application for an orphan medicinal product”.²¹⁹ The Court concluded that “clinical study reports cannot therefore be considered to enjoy a general presumption of confidentiality on the implicit ground that they are, as a matter of principle and in their entirety, clearly covered by the exception relating to the protection of the commercial interests of marketing authorisation applicants”.²²⁰

(d) Trademarks*(i) The trademark system*

Trademarks allow manufacturers and traders to distinguish their goods from those of competitors. They help consumers make informed choices, and they aim

to prevent consumer deception. Trademarks work better in helping consumers assess quality when the goods are not “search” goods, for which the quality is readily discernible before purchase (e.g. red and firm tomatoes), but are “experience” goods, which the consumer has to purchase in order to know its attributes (e.g. cough syrup). Brand advertising expenditures are consequently higher for experience goods than for search goods.²²¹

The registration of trademarks is subject to certain requirements that are reasonably standardized throughout the world and appear in practically all trademark laws. Trademarks must be distinctive, or at least capable of becoming distinctive, of the owner’s goods or services, and they must not be misleading. Trademarks must not infringe rights acquired by third parties, and they must not consist exclusively of signs or indications which may serve, in trade, to designate the kind, quality, quantity, intended purpose, value, or place of origin of the goods, or the time of production, or have become customary in the current language or established practices. Generic terms that use ordinary words to define the category or type of good are not distinctive and should remain available for all competitors to use free of trademark rights.

There is a crucial distinction between the generic name of a product – for example, ampicillin – which must be available to identify any product, and the proprietary trademarks used by both originator and generic companies to distinguish the product they are responsible for manufacturing and distributing. These are sometimes termed “brand names”. The WHO approves generic names, called international non-proprietary names (INNs)

for pharmaceutical substances (see section 1(d)(ii)), which are universally recognized as unique names that identify particular active pharmaceutical ingredients. Trademarks are linked to a product and are used by both originator and, in most cases, generic companies to create trust and brand loyalty between the company, the prescribing practitioner and the patient, potentially allowing the trademark owners to charge higher prices. The often-used term “brand name” medicine to describe an originator product is inaccurate because both originator and generic companies use brand names to market and distinguish their products.

Trademarks are protected under the laws of each country or region, and not globally. International standards for protection of trademarks are set out in the Paris Convention and the TRIPS Agreement. All countries that are party to the Paris Convention have a trademark registry. Trademark applications must be filed separately in each country or region where registration is sought, or using the Madrid System for the International Registration of Marks (Madrid System) (see Box 2.13).²²² It is not unusual for a trademark to be protected in some countries but not in others.

The owner of a trademark has an exclusive right to prevent the unauthorized use of signs that are identical or similar to the registered trademark on related goods or services where such use would result in a likelihood of confusion. The trademark owner, and typically any licensees, may enforce their rights against infringement. However, defences to infringement exist, including trademark fair use. Trademarks have a defined initial

Box 2.13: The Madrid System for the International Registration of Marks

Pharmaceutical companies pursue high numbers of registrations under the Madrid System. International registrations for pharmaceuticals and other medicinal preparations²²³ account for 10 per cent of all international registrations filed yearly. They increased threefold, from 2,810 of 24,414 in 2000 to 6,216 of 61,139 in 2018.²²⁴ The Madrid System offers an option for trademark holders to obtain and maintain trademark protection in export markets. By filing one international application, a trademark holder may obtain protection in the contracting parties,²²⁵ provided that the holder has a “basic mark”, that is, a trademark application or registration with the Trademark Office of a Contracting Party (“Office of origin”). The International Bureau of WIPO carries out a formality examination, with matters of substance being left to each designated contracting party to determine in accordance with their national or regional trademark legislation. If the Trademark Office of a designated contracting party does not refuse protection within a specified period, the protection of the mark is considered to be the same as if it had been registered by the Office concerned.

The Madrid System simplifies the management of the mark by providing for one international registration with one renewal date, and this one registration may contain protection in many designated contracting parties. It is also possible to further extend the trademark protection to additional contracting parties and to manage centrally the renewal and recording of changes of the international registration. During the first five years from the date of the international registration, the international registration depends on the basic mark: if the basic mark is cancelled, the international registration will be cancelled to the same effect. Should this happen, the trademark owner would have the opportunity of transforming the international registration into national and regional rights, to ensure continued protection of the trademark.

term of protection and can be renewed indefinitely,²²⁶ provided they remain in use and maintain their distinctive character and trademark holders see a need to renew them. Rights to a trademark can be lost through cancellation or removed from the registry if the trademark is not renewed or the renewal fees due are not paid. A mark can lose its distinctive character and can become a generic term. This may happen if either the trademark owner or the public, tolerated by the trademark owner, uses a trademark as, or instead of, a product designation or a term in common usage.

(ii) *Trademarks and international non-proprietary names (INNs) for active pharmaceutical ingredients*

In contrast with trademarks, which are proprietary private rights, INNs are generic names for active pharmaceutical ingredients²²⁷ and biotherapeutic products.²²⁸ Lists of proposed and recommended INNs are also available on the WHO INN website and, with searchable capabilities, on the WHO INN MedNet. Moreover, a web service, the INN Global Data Hub, allows authorized users to query the INN database. The WHO has a constitutional mandate to “develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products”. The setting of INNs and their publication are administered by the WHO INN Programme, a core normative programme of the WHO, initiated in 1950. The WHO Secretariat and the WHO INN Expert Group collaborate closely with national nomenclature committees, drug regulatory authorities, pharmacopias and the pharmaceutical industry to select a single name of worldwide acceptability for each active substance that is to be marketed as a pharmaceutical.

The existence of an international nomenclature for pharmaceutical substances, in the form of an INN, is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide. As unique names, INNs have to be distinctive in sound and spelling, and should not be liable to confusion with other names in common use. In order to make INNs universally available, they are formally placed by the WHO in the public domain, hence their designation as “non-proprietary”. An INN can be used by any manufacturer or supplier for their product provided that it is used accurately. For example, “ibuprofen” is an INN and can be used by any manufacturer or supplier for the designation of this product.

Another important feature of the INN system is that the names of chemically and pharmacologically related substances demonstrate their relationship by using a common “stem” as a part of the INN. The use of common stems ensures that a medical practitioner, pharmacist

or anyone dealing with pharmaceutical products can recognize that the substance belongs to a group of substances having similar pharmacological activity. For example, all the monoclonal antibodies are given the suffix/stem “-mab”, while all adrenoreceptor antagonists use the suffix/stem “-olol”.

Ensuring that trademarks are clearly distinguished from INNs is important for the accurate identification of products, and thus for the safety of patients. It is also important to keep INNs in the public domain and to avoid granting private property rights for them. Trademarks must not be derived from INNs and, in particular, they must not include their common stems.²²⁹ The selection of additional names within a series will be seriously hindered by the use of a common stem in a brand name. For the same reasons, INNs should not contain existing trademarks. The INN Expert Group convened by the WHO thus generally rejects a proposed INN that contains a known trademark and there is a procedure for dealing with objections by interested parties. Such objections may be based among other grounds on a similarity between a proposed INN and a trademark. On the other hand, trademarks that include an established INN stem infringe the INN system. The WHA has requested member states to discourage the use of names derived from them, and particularly names including established stems, as trademarks (WHA46.19). It circulates every newly published list of proposed or recommended INNs to all WHO member states. Lists of proposed and recommended INNs are also available on the WHO INN website and WHO INN MedNet.²³⁰ The WHO INN Global Data Hub allows those with appropriate credentials to search for the INNs online.

WIPO and the WHO started cooperating in November 1999, to provide timely and accurate information on INNs to trademark offices of their members. In view of the improvements in communication technology in both organizations, in 2018, the two organizations concluded a cooperation agreement that enables integration of the INN data contained in the WHO INN database into the WIPO Global Brand Database. Trademark examiners in WIPO member states may now search the Global Brand Database for INNs in an accessible format and by using different filters that facilitate the textual comparison between INNs and verbal marks. With the help of this new tool, they will be able to fulfil the public interest in keeping these names free and available for use by pharmacists and medical practitioners around the world, thus preventing medication errors. At the other end of the spectrum, information on existing trademarks that have been properly granted for use on pharmaceutical technologies is key to avoiding counterfeiting in this crucial area. INN experts can also use the trademark data in the Global Brand Database to avoid proposing or recommending new INNs that may cause confusion with existing trademarks, therefore contributing to enhancing pharmacovigilance and more reliable medicines.²³¹

Distinguishing between the INN and the proprietary trademark is important in order to assist the process of selecting specific medicines during a procurement process. This is because procuring a product under its INN opens the process to all manufacturers of the same product designated by the INN. Many countries require distinct labelling with the INN, printed separately from either generic or originator company names, brands or trademarks. Article 20 of the TRIPS Agreement allows members to apply special requirements on the use of a trademark, provided that such requirements do not unjustifiably encumber the use of the trademark in the course of trade.

(iii) Trademarks and unfair competition

Inaccurate or misleading labelling of products can also be considered a form of unfair competition (see section B.2(d)). It is covered by Article 10*bis* of the Paris Convention,²³² which is designed to safeguard against deceptive or misleading labelling.

(iv) Regulatory approval of proprietary names

The names under which new medicines are to be sold in the market (i.e. trademark/brand names) are also reviewed by regulatory authorities and require approval as part of the marketing authorization of a new medicine. Medicine name similarity and medication errors in the 1990s led the FDA and the EMA to introduce assessments of proprietary nomenclature in the interest of public health and safety.²³³ Examination of these names in the context of regulatory approval has become more formalized over the past decade, with the establishment of dedicated bodies in the FDA and the EMA.²³⁴ For example, from January to September 2018, the EMA accepted 182 proposed (invented) names and rejected 150 such names.²³⁵

The criteria for proprietary name evaluation applied by the pharmaceutical regulatory authorities are intended to counter confusion and potential medication errors in the specific context of pharmaceutical distribution and prescription practices. The evaluation thus overlaps to some extent with criteria that are also examined in the context of a trademark application. It aims to exclude names that contain or imply claims regarding drug efficacy and safety which are false, misleading or unsupported by data. In addition, in order to take account of the risks presented by the specific context of pharmaceutical prescription, the regulatory evaluation eliminates names that are verbally or graphologically similar to other drug names or to abbreviations typically used in handwritten prescriptions, such as dosage schedules and forms, or routes of administration. Concerns regarding INNs (see section B.1(d)(ii)), such as similarity with the INN or inclusion of an INN stem, are also taken into account.

The requirement for approval of the proprietary name of a new medicine as part of the overall pharmaceutical regulatory authorization is an important factor in ensuring the safety of a new medicine in the specific context of pharmaceutical distribution and prescription. As the marketing of the medicine is approved by the authorities under a specific name (i.e. it cannot be marketed under another name), the challenge for the pharmaceutical companies is to develop a medicine name that will not only meet the approval of the regulatory authorities but can also be protected as a trademark in the main markets where the medicine will be sold. In order to meet this double objective, and to ensure a successful outcome, companies usually develop a number of possible names for the new medicine and register all of them as trademarks in their main markets, before submitting them as alternatives to the regulatory authorities. This practice partly explains the proliferation of trademark applications in the pharmaceuticals area, which accounted for 4.3 per cent of all trademark applications in 2016 (WIPO, 2017b). Such volumes of applications can lead to a situation where there are many unused trademark registrations in existence (see section (v) below).

(v) Trademark cluttering

The volume of applications for trademark protection can result in trademark registers containing a significant number of unused trademarks. This is sometimes termed trademark cluttering. This can increase the costs of creating and registering new trademarks for other applicants, including producers of generic medicines. Considering the increased demand for trademarks and given the reliance on trademarks, which are not time-limited in the same way as patents, such cluttering of the trademark register can have a serious effect. Some national and regional legislation contains provisions that make the trademark liable for revocation on the basis of non-use. For example, while in the European Union registrations can be renewed indefinitely for consecutive ten-year periods, the European Union also allows for the application for revocation of a trademark on the basis of non-use if the trademark has not been used in the five years since registration. In some jurisdictions, including Cambodia, the Philippines and the United States, the trademark holder has to declare actual use or non-use throughout the life cycle of the trademark.

(vi) Non-traditional marks

Non-traditional marks may consist of signs, such as sound, colour, shape, aspects of packaging and texture. At the international level, these marks were first recognized in Rule 3 of the Regulations to the Singapore Treaty on the Law of Trademarks (2006)²³⁶ and appear in numerous FTAs; however, they are not mentioned specifically in the TRIPS Agreement (although the list of possible signs

that can be registered as trademarks is non-exhaustive). Non-traditional marks are protected in some, but not all, jurisdictions, and they are particularly relevant in the area of pharmaceuticals, where protections have been granted by IP offices and the courts to the colour of drugs, for example, the colour blue, Pantone 284 U, for originator sildenafil, with the name of the company appearing thereon,²³⁷ to the shape of drugs (heart shaped for dextroamphetamine)²³⁸ and to the three-dimensional shape of a medical device (the plastic shell of an inhaler).²³⁹ Pharmaceutical companies rely on non-traditional marks in the same way they rely on trademarks: to make their products unique in the marketplace and to enable patient confidence. Non-traditional marks have been at the centre of litigation, with action being taken against competitors who copy distinctive physical features of a medicine. However, non-traditional marks can have an impact on access to medicine, by increasing transaction costs and by blocking market entry of a generic medicine that would have the same physical characteristics as its reference product (Scaria and Mammen, 2018). Patients may be reluctant to take a generic drug that has different physical attributes (Kesselheim, et al., 2013). The effectiveness of a generic could also, in theory, be undermined by the non-traditional mark, if the physical characteristics of the medicine are important to its efficacy. A study has shown that patients react best when the colour corresponds with the intended results of the medication – for example, a pink colour for antacids (Srivastava and More, 2010). A particular flavour, for example, can be necessary to make a medicine palatable to children.

(vii) *Standardized packaging*

Standardized packaging or “plain packaging” involves regulators requiring features of packaging to comply with certain parameters. A well-known example of standardized packaging is tobacco plain packaging, with Australian legislation, the first of its kind in relation to tobacco products, setting out the physical features, colour and brand display requirements of tobacco products.²⁴⁰ The WTO panel in *Australia – Tobacco Plain Packaging* (see section B.6 below) did not find that this legislation unjustifiably encumbers the use of trademarks in the course of trade within the meaning of Article 20 of the TRIPS Agreement.²⁴¹ In the pharmaceutical sector, standardized packaging mandates identifiers that do not enable consumer preference for particular medicines. In the European Union, regulatory frameworks provide guidelines on the labelling and packaging of medicines relating to the colour and size of packaging.²⁴² Following a review that found 2–3 per cent of hospital admissions in Australia are related to medication errors,²⁴³ the Australian Therapeutic Goods Administration has proposed giving the brand and active ingredient the same prominence on pharmaceutical packaging.²⁴⁴ In Chile, law requires that the INN be printed on the package directly under the

brand name, using the same font and colour in capital letters, and that the text size for the INN must be at least 50 per cent of the brand name size.²⁴⁵

(e) Copyright

Copyright protects every original expression in the literary, scientific or artistic domains, as provided by the Berne Convention for the Protection of Literary and Artistic Works, and as incorporated by reference into the TRIPS Agreement. The list of works protected by copyright in the treaties is not exhaustive and can include literary works, computer programs, databases, films and musical compositions. Copyright protection does not extend to ideas, procedures, methods of operation or mathematical concepts as such. Copyright grants economic rights, which can be licensed or assigned, to derive financial reward to the owner of the work and to encourage the creation of additional works for the benefit of society and the general public. Copyright is an automatic right and, in most cases, it can be obtained without registration or formalities. The Berne Convention minimum standard for the duration of copyright is generally the life of the author of the copyright work plus 50 years; however, longer periods of protection can be provided at the national level.

Copyright, like other forms of IP, has to consider the balance between the rights of authors and owners and the larger public interest. Copyright provides exceptions and limitations that allow access to those works under certain special cases. Both copyright, on the one hand, and exceptions and limitations to copyright, on the other hand, are of particular importance when considering the question of access to medical technology and innovation.

(i) *Copyright and pharmaceutical package inserts*

For pharmaceutical products, a key issue in relation to copyright is whether protection covers the accompanying package inserts or information leaflets. Copyright protection extends to expressions and not to ideas, procedures, methods of operation or mathematical concepts as such. Generic producers are free to use the factual information provided in an insert, because copyright does not extend to the information as such, only to the way it is expressed as an original work; courts have sometimes found that generic pharmaceutical producers cannot reproduce for their own products direct copies of the original expressions contained in package inserts of the first producer of the product. This was the finding in 2002 in South Africa concerning a package insert for the antibacterial medicine amoxicillin/clavulanate potassium.²⁴⁶ A similar finding was initially made in Australia in 2011 in relation to the rheumatoid arthritis medicine leflunomide. The Federal Court found that

copyright subsisted in product information documents. However, later in 2011, the Australian Parliament approved an amendment to Australia's Copyright Act establishing that use of already approved product information in other pharmaceutical product text, in any manner, including a direct reproduction, is not an infringement of copyright. A subsequent Federal Court decision confirmed that generic pharmaceutical companies are able to reproduce product information that has been approved by the Therapeutic Goods Administration in a range of circumstances, without infringing copyright.²⁴⁷

(ii) *Exceptions and limitations – text and data mining*

Text and data mining (TDM) has been defined as “automated analytical techniques” that work by “copying existing electronic information, for instance articles in scientific journals and other works, and analysing the data they contain for patterns, trends and other useful information”.²⁴⁸ TDM can be an invaluable technique for researchers to develop new technologies in health care. For example, a drug discovery company may apply technology to analyse thousands of molecules that might serve as drug candidates and predict their suitability for blocking the mechanism of a pathogen, or to mine large data sets of genetic information and medical records to identify linkages between genetic mutations and disease. New research techniques and diagnostic methods that involve TDM can be developed, thanks to the application of balanced copyright flexibilities for the development of medical innovations.

Flexibilities can be based on fair use clauses, in particular, non-expressive use (Sag, 2009), or on specific statutory TDM exceptions. In 2009, Japan was the first country in the world to permit TDM as a specific exception to copyright. In 2018, Japan extended this exception to the use of raw data, specifically permitting electronic and incidental copies of works and allowing for use of copyright works for data verification. TDM exceptions appear, for example, in the copyright legislation of the European Union,²⁴⁹ United Kingdom,²⁵⁰ France²⁵¹ and Germany.²⁵²

(iii) *Licensing schemes*

Waivers or licences may be available to obtain access to information such as research data that may be copyright protected. Increasingly, research funders, including national governments, require that data produced in the course of research they fund be made available to other researchers. However, acquiring these licences can be time consuming and costly for researchers and their institutions and, as a result, the process can inhibit the speed at which new medical technologies are developed and subsequently reach the market. Licensing schemes,

such as creative commons and open data commons licensing, can ensure that medical research data, for example, can be shared more readily. The WHO Hinari Access to Research for Health Programme is a voluntary licensing initiative that provides free access to copyright works, such as biomedical and health literature, by health workers and researchers in LMICs.²⁵³

(iv) *Orphan works access licensing schemes*

Orphan works are works for which the copyright holders are unknown or cannot be located. The process of identifying and locating the owner of the right can be extremely costly and time consuming for the prospective user of the work, and might eventually yield no results. For example, the Mahidol-Oxford Tropical Medicine Research Unit wanted to make available to its researchers research papers from an early-20th-century malaria therapy experiment in which patients were intentionally infected with malaria. As the research papers were considered orphan works, published in long-defunct journals, it could not. The articles (and the pictures and diagrams within them) could not be copied to make them available online, nor could they be data mined to find patterns and associations which could assist researchers. To enable access to this information, and other information like this, an orphan works licensing scheme was developed in the United Kingdom to grant licences for the use of orphan works for both commercial and non-commercial purposes, subject to certain conditions.²⁵⁴ According to section 77 of the Copyright Act of Canada, if a copyright owner is not located after a reasonable search, a user may apply to the Copyright Board of Canada for a licence to use the work. An EU Orphan Works Directive permits certain uses of orphan works²⁵⁵ and the European Union Intellectual Property Office (EUIPO) has established an online database that provides information about orphan works contained in the collections of EU members.²⁵⁶ The Committee on WIPO Standards (CWS) approved the inclusion of data dictionary and XML components for copyright orphan works in WIPO Standard ST.96.

(v) *Software licensing and eHealth*

Increasingly, electronic and digital processes are used in health-care practice (eHealth or health informatics). eHealth can include electronic health records, e-prescribing, diagnostic tools and health applications on mobile phones to collect health data, provide health-care information or for the real-time monitoring of patient vital statistics. In 2005, the WHO recognized the importance of eHealth and its ability to rapidly transform the delivery of health services and systems around the world, especially in LMICs.²⁵⁷ The WHO Global Observatory for eHealth provides member states with strategic information and guidance on effective practices and standards in eHealth. Copyright law (and, to a lesser

extent, patent law) can protect the specific graphic user interface and functionality that make mobile apps easy to use, supporting access to health care by a broad cross-section of users.²⁵⁸ As a result, while the IP system can support the investment in eHealth initiatives, licensing models are also integral to the widespread use of eHealth services, for example, health information platforms whose effectiveness depends on uptake. Product development can also be enhanced by flexible licensing, reducing costs and shortening development periods. Licensing practice will need to develop approaches to issues of ownership and privacy of electronic health records used as training data for machine learning, or artificial intelligence (e.g. databases of radiological images) (see Box 2.14).²⁵⁹ Open source models, such as those widely used in software development, may be an effective option.

(f) Enforcement

The value of the IP rules detailed above depends on the availability of an effective system of enforcement. As IPRs are private rights, their enforcement is generally the responsibility of the right holders themselves (see Chapter IV, section C.3(h)). Infringements are thus normally pursued by the right holders in civil actions. However, where public interests are at stake, IP infringements can be remedied through criminal measures, for example, when a trader, without permission, knowingly and on a commercial scale, manufactures, distributes or sells goods marked with another company's trademark, particularly in the areas of pharmaceuticals and foods. That said, the enforcement of IPRs is clearly distinct from the regulation of

Box 2.14: Artificial intelligence and health

Artificial intelligence (AI)²⁶⁰ emerged in the middle of the 20th century and, while definitions vary, it can be broadly categorized as computer algorithms simulating human cognitive functions and capabilities, such as perceiving the environment, gaining information to take action and then improving these actions based on machine learning. Artificial neural networks, for example, have been used in drug discovery for screening compounds in the automated design of new classes of medicines and in finding novel uses for known medicines. One area in which AI has shown high effectiveness is the interpretation of imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI) scans (Topol, 2019). AI is already being used in the design and analysis of clinical trials. Some expect that computer modelling and AI may enable reductions in the costs and time needed to carry out clinical trials (Harrer et al., 2019).

Twelve per cent of all AI patent applications refer to the field of life and medical sciences,²⁶¹ and AI is already having a significant impact on the medical landscape, with the potential to improve the future quality of health care. At present, AI is, among other things, being used to enable patient data management and personalized medicine. In particular, AI can improve the working methods of doctors and help complement traditional medical tools and techniques, improving the accuracy and speed of diagnosis.²⁶² For example, a deep learning model based on mammogram images created by a team of US researchers was able to predict whether a woman will develop breast cancer within five years, reducing false positives and unnecessary surgeries (Conner-Simons, 2017). Software applications may help doctors and patients manage conditions through customized monitoring and follow-up care. Guidelines are being developed to assist policy-makers in this area. For example, the International Telecommunication Union (ITU) is working in partnership with the WHO to establish a standardized assessment framework for the evaluation of AI-based methods for health, diagnosis, triage or treatment decisions.²⁶³ The assessment framework will help identify key issues related to ethical, business, legal, technical, or other constraints that arise when using AI in the health field and develop a pragmatic method to solve them.²⁶⁴

Researchers are also making use of AI for data mining and machine learning, to make the development of new medicines quicker as data can be synthesized and analysed more easily (see section B.1(e)(ii) on text and data mining). There are, for example, initiatives that use AI to predict chemical reactions, in which AI is simulating different combinations and their expected effect and properties.²⁶⁵

Software applications use AI and blockchain technology in order to support the maintenance of traceable supply chain security (Lock, 2019; Mok, 2018). AI uses machine-learning processes and compares unique product identifiers, such as a chemical signature or image patterns, with corresponding reference data, with the goal to recognize and authenticate substandard and falsified (SF) products in an automated manner. At the same time, AI uses the data recognized to maintain and improve the database and hence to train and improve the system itself.²⁶⁶

Investment at the national and regional levels in AI technology is increasing.²⁶⁷ However, ethical issues, including accountability and liability for AI decisions and actions, as well as ownership and data privacy concerns, will remain of interest for policy-making. From the perspective of IP, discussions are looking at issues such as how AI-related IP rights are managed, access and ownership of data, and how patentability criteria will be interpreted and applied to AI in different jurisdictions.²⁶⁸ This places a focus on the way that health-care providers that hold “big data” manage data-sharing with AI developers (Geis et al., 2019; UNESCO and IBC, 2017).

medicines for safety, quality and efficacy purposes, including any remedies against substandard and falsified (SF) products (see Chapter IV, section A.12).

(i) The link between intellectual property right enforcement and public health

The motivation to combat SF products differs in the public health context and the IP context. From the perspective of public health, the fight against SF products is exclusively motivated by the threat to public health and related concerns about consumer protection. From an IP perspective, commercially using a sign that is identical to, or cannot be distinguished in its essential aspects from, a registered trademark without the authorization of its owner is the key condition to consider a product as counterfeit. In this context, the primary objectives are to preserve the interest of the trademark owner in enforcing their rights and to prevent consumers from being misled about the origin of the goods that bear the trademark, but also to protect the public interest by fighting infringements that take place on a criminal level.

While the motivation may be different, the methods used to prohibit production, trade and distribution of all kinds of trademark-infringing products and SF products have some similarities, with customs controls and criminal law figuring among the most frequently used means to combat these products. The enforcement of IPRs can thus have implications for the broader public health considerations. In international trade, a trademark plays an important role as a trade identifier and is an indication of trade source, which can and does help to identify fake products. Counterfeiters use trademarks without authorization by the right holder to give the impression that a product is a genuine product, thus falsely representing its identity and source. Therefore, IP enforcement measures to combat trademark counterfeiting can have positive side effects, potentially supporting efforts to keep dangerous products out of the market. This is illustrated by the fact that pharmaceuticals are regularly reported to figure among the top commodities suspended by customs authorities for IPR infringement.²⁶⁹

(ii) Enforcement provisions of the TRIPS Agreement

The TRIPS Agreement is the only comprehensive multilateral legal framework for the enforcement of IPRs. It contains a set of minimum standards that safeguard the rights of IP owners (see Chapter IV, section C.3(h)). These standards include civil court procedures and remedies that should be made available, such as injunctions, damages and orders for the disposal of IP-infringing goods. These remedies must be available for all the IPRs covered by the TRIPS Agreement, including patents, undisclosed information (such as test data), trademarks

and copyright. Administrative procedures, such as actions before administrative authorities, are optional and must conform to the principles applicable to civil procedures. A wider range of procedures, including customs measures and criminal procedures, must be available for counterfeit trademark goods, as defined in the TRIPS Agreement, which may include medical products, and for pirated copyright goods. The TRIPS Agreement also includes certain general obligations or performance standards which provide that WTO members must ensure that these specific enforcement procedures permit effective action, including expeditious remedies to prevent and deter infringement. The application of these procedures must avoid the creation of barriers to legitimate trade and must provide for safeguards against their abuse. The TRIPS Agreement clarifies that WTO members are not under any obligation with respect to the distribution of resources between the enforcement of IPRs and law enforcement in general.²⁷⁰

(iii) The WIPO Advisory Committee on Enforcement

The WIPO Advisory Committee on Enforcement (ACE) is a forum for policy dialogue on questions of IP enforcement and building respect for IP, with a mandate for technical assistance and coordination while specifically excluding norm setting. Since 2016, the Committee has discussed topical issues relating to awareness-raising, IP enforcement policies and regimes, capacity-building activities and legislative assistance on the basis of written contributions of experts.²⁷¹ Issues have included the role of intermediaries in preventing counterfeiting and piracy, online infringements and new technologies in IP enforcement, IP enforcement coordination, effective IP dispute resolution mechanisms and the environmentally safe disposal and destruction of IP-infringing goods.

(g) Flexibilities under the TRIPS Agreement and the Doha Declaration

Determining a nation's optimal choices from within the available range of options is a central consideration in the design of a national IP regime. However, many of these policy options, often referred to as "TRIPS flexibilities", have long formed part of the mechanisms used in patent systems to maintain a balance of public and private interests – well before the TRIPS Agreement was negotiated, and before the Doha Declaration was framed.

(i) Flexibilities in the IP system

The adoption of the TRIPS Agreement standards created diverse options for WTO members to implement their TRIPS obligations while taking into account different considerations, such as the country's stage of development

and specific national interests (e.g. public health). However, despite repeated references to “flexibilities” in the policy debate, neither the TRIPS Agreement nor any of the later instruments have formally defined the exact meaning of this term. The TRIPS Agreement makes only limited use of the term. In fact, although flexibilities are available on a much broader scale, including for developing countries and developed countries, explicit reference to “flexibility” is made exclusively in relation to the special requirements of LDC members to create a sound and viable technological base, thus explaining the motivation for the additional transition period accorded to LDCs (see the Preamble and Article 66.1 of the TRIPS Agreement). The expression “flexibilities” only became part of the wider IP community’s glossary in the lead-up to the Doha Declaration and especially following the conclusion of these negotiations.²⁷²

In articulating the role of “flexibilities”, the Doha Declaration clarified the importance of specific national choices in the implementation of the TRIPS Agreement. It referred to flexibilities in a much more prominent way. This can be explained by the central importance that the debate about policy options to promote public health assumed from the time preparatory work for the Doha negotiations got under way, culminating in the adoption of the Doha Declaration in 2001. The TRIPS Agreement highlights the existence of flexibilities and their importance for the pharmaceutical sector, and the Doha Declaration confirms “the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility” to protect public health. The Declaration lists a number of such flexibilities relating to compulsory licensing and exhaustion. The subsequent decision of 30 August 2003 on the implementation of paragraph 6 of the Doha Declaration (2003 Decision) once more confirms “the rights, obligations and flexibilities that members have under the provisions of the TRIPS Agreement”.²⁷³

Based on the Agreement between the World Intellectual Property Organization and the World Trade Organization of 22 December 1995,²⁷⁴ WIPO provides legal and technical assistance relating to the TRIPS Agreement. Government offices in charge of drafting laws frequently request advice from WIPO regarding how to use the TRIPS flexibilities in their countries. Advice is provided after careful consideration of the flexibilities, consistency in relation to the TRIPS Agreement and their legal, technical and economic implications. However, the ultimate decision regarding the choice of legislative options lies exclusively with each individual member state. Four clusters of flexibilities have been identified in WIPO’s work (see Box 2.15):²⁷⁵

- The method of implementing TRIPS obligations
- Substantive standards of protection
- Mechanisms of enforcement
- Areas not covered by the TRIPS Agreement.

The use of flexibilities is also addressed in the WHO GSPA-PHI and the Roadmap for Access to Medicines, Vaccines and Other Health Products 2019–2023 (see Box 2.16) and in a number of recommendations contained in the WIPO Development Agenda (Chapter I, section B.2). Following the request of the Committee on Development and Intellectual Property (CDIP), WIPO prepared studies on patent-related flexibilities in the multilateral legal framework and their legislative implementation at the national and regional levels. These studies present a non-exhaustive number of flexibilities, with annexes and tables reflecting corresponding legal provisions and practices in a number of countries. The studies show a diverse approach to the implementation of TRIPS flexibilities in national laws.²⁷⁶

Since 2011, the WIPO Standing Committee on the Law of Patents (SCP) has reviewed legislation by member states and has identified that many countries provide for exceptions and limitations to patent rights relating to: (i) private and/or non-commercial use; (ii) experimental use and/or scientific research; (iii) extemporaneous preparation of medicines; (iv) prior use; (v) use of articles on foreign vessels, aircraft and land vehicles; (vi) acts for obtaining regulatory approval from authorities; (vii) exhaustion of patent rights; (viii) compulsory licensing and/or government use; and (ix) certain use of patented inventions by farmers and breeders.²⁷⁷ A WIPO study has examined the constraints faced by developing countries and LDCs in making full use of patent flexibilities and their impacts on access to affordable, especially essential, medicines for public health purposes in those countries. Countries continue to report that they face constraints in making full use of flexibilities such as compulsory licensing, including political and economic pressure from some industrialized countries, the complexity of practical implementation, insufficient institutional capacity and lack of coordination between patent offices, ministries of health and trade, and drug regulatory authorities.²⁷⁸

(ii) *Background to the Doha Declaration*

The negotiators of the TRIPS Agreement aimed to ensure that countries would make patents available for pharmaceutical products while, at the same time, retaining certain options on patentability and scope of rights for public health purposes. However, the extent to which the Agreement was supportive of public health became highly controversial, particularly around the time when most of the substantive obligations of the Agreement for developing countries came into force, in 2000. In a landmark legal action, a pharmaceutical industry association and 39 of its affiliate companies filed complaints at the Pretoria High Court, alleging, among other things, that South Africa’s law on medicines allowed for parallel importation of (HIV/AIDS) medicines and was inconsistent with the TRIPS Agreement. The lawsuit triggered an active campaign led by NGOs and AIDS activists. During the court process, it was revealed that the South African law was based on a WIPO model law and, in the end, the companies withdrew

their complaints unconditionally, in 2001. By that time, many governments and others were convinced that the relationship between the TRIPS Agreement and public health needed to be clarified.

In April 2001, the WHO and WTO Secretariats convened a workshop in Høsbjør, Norway, on differential pricing and financing of essential drugs. Following the publication of the report on that workshop,²⁷⁹ the African Group

proposed that the WTO convene a special session of the Council for TRIPS to initiate discussions on the interpretation and application of the relevant provisions of the TRIPS Agreement, with a view to clarifying the flexibilities to which members are entitled and, in particular, to establish the relationship between IPRs and access to medicines. The proposal to hold the special session was supported by all members.²⁸⁰ This was followed in June 2001 by a detailed written proposal prepared by a

Box 2.15: Definition of flexibilities according to WIPO

According to the WIPO CDIP report,²⁸¹ the term “flexibilities” means that there are different options through which TRIPS obligations can be transposed into national law, so that national interests are accommodated and TRIPS provisions and principles are also complied with. This definition would effectively delimit the scope of the concept, as it:

- Highlights the idea of using various options as a means of implementation
- Refers to the legislative process of implementation, reflecting the view that the first step needed in order to take advantage of a given flexibility consists of incorporating that flexibility into national law
- Refers to the reason for flexibilities, which is to accommodate national interest
- Reflects that a given flexibility needs to be compatible with the provisions and principles of the TRIPS Agreement.

These flexibilities can be categorized in different ways, including by grouping them according to the lifetime of the respective IPR. Flexibilities can thus be exercised:

- Regarding the process of acquisition of the right
- Regarding the scope of the right
- By enforcing and using the right.

WIPO established a database of flexibilities in the IP system. This database allows searches for implementation of flexibilities in national IP laws in selected jurisdictions.²⁸²

Box 2.16: TRIPS flexibilities highlighted in the GSPA-PHI and Road Map for Access to Medicines, Vaccines and Other Health Products, 2019–2023

The GSPA-PHI (see section A.4(c) and Box 2.2) includes explicitly actions relating to the flexibilities reaffirmed by the Doha Declaration. It urges member states to consider implementing TRIPS flexibilities, including those recognized in the Doha Declaration, by incorporating them into their national laws (Element 5.2a). Regarding more extensive IP protection than that required under the TRIPS Agreement, member states are urged to take the impact on public health into account when considering the adoption or implementation of such obligations (Element 5.2b). Member states should also take flexibilities into account when negotiating other (bilateral or regional) trade agreements (Element 5.2c). In addition, the GSPA-PHI highlights a number of flexibilities and public policy options available to member states, which are designed to facilitate research and access to medical technologies:

- Research exception (Element 2.4e)²⁸³
- Voluntary patent pools of upstream and downstream technologies (Element 4.3a)
- For countries with manufacturing capacities, consider taking measures to implement the WTO Paragraph 6 System (Element 5.2d)²⁸⁴
- Develop effective and sustainable mechanisms in LDCs in order to improve access to existing needs, acknowledging the transitional period until 2016 (Element 6.1b)²⁸⁵
- Regulatory review exception, also known as “Bolar”-type exception (Element 6.3a).²⁸⁶

The WHO Road Map for Access to Medicines, Vaccines and Other Health Products, 2019–2023, lists the following deliverables with regard to TRIPS flexibilities:²⁸⁷

- Provide information on country experiences promoting public health approaches in the implementation of health-related provisions of the TRIPS Agreement, including relevant TRIPS flexibilities and intellectual property management
- Provide technical support (as appropriate, upon request, in collaboration with other competent international organizations), in order to promote access to pharmaceutical products.

group of developing countries calling for the WTO to take action to ensure that the TRIPS Agreement did not in any way undermine the legitimate right of WTO members to formulate their own public health policies and implement them by adopting measures to protect public health. At the Fourth WTO Ministerial Conference in Doha, Qatar, on 14 November 2001, ministers adopted by consensus the Doha Declaration, addressing the concerns that had been expressed.

(iii) Content of the Doha Declaration

In articulating the general role of the TRIPS Agreement in promoting access to medicines, and in clarifying specific flexibilities to that end, the Doha Declaration has provided a clearer context for specific operational choices for the use of policy options under the TRIPS Agreement.

The Doha Declaration recognizes the gravity of the public health problems afflicting many developing countries and LDCs, and, in particular, the public health problems resulting from HIV/AIDS, TB, malaria and other epidemics. This defining statement was followed by a number of important statements signalling to all members that they are free to use the provisions of the TRIPS Agreement in a manner that is supportive of public health. Paragraph 4 confirmed that “the TRIPS Agreement does not and should not prevent members from taking measures to protect public health”, that it “can and should be interpreted and implemented in a manner supportive of WTO members’ right to protect public health and, in particular, to promote access to medicines for all”, and, in addition, that WTO members have the right “to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose”.

Paragraph 5 of the Doha Declaration specifically confirms four aspects in which the provisions in the TRIPS Agreement provide flexibility for this purpose:

- The first clarification concerns the way in which the TRIPS Agreement is interpreted. Each provision of the TRIPS Agreement shall be read in the light of the object and purpose of the Agreement as expressed, in particular, in its “objectives” and “principles”. These terms are not otherwise defined in the Doha Declaration, but there is a parallel with the respective titles of Articles 7 and 8 of the TRIPS Agreement – although objectives and principles can also be found elsewhere in the Agreement.²⁸⁸
- The second and third clarifications concern compulsory licensing. Each WTO member has “the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted”. These clarifications dispelled a misconception that compulsory licences were only available in national emergencies. Each WTO member also has the right to determine what constitutes a

national emergency or other circumstance of extreme urgency. These clarifications have practical relevance because, in such situations, countries are exempted from first attempting to negotiate a voluntary licence with the patent holder. In terms of examples of these types of emergency, the Doha Declaration cites “public health crises, including those relating to HIV/AIDS, TB, malaria and other epidemics”.

- Finally, the Doha Declaration also confirms the freedom of each WTO member “to establish its own regime for such exhaustion without challenge”, subject to the rules against discrimination according to nationality. This allows a WTO member to choose between national, regional or international exhaustion.²⁸⁹ Exhaustion governs the extent to which an IPR holder can prevent the resale and importation of genuine goods placed on the market with its consent in the same or another country. Countries are thus free to determine whether or not they want to allow parallel importation of patented goods, including medical products.

The panel in *Australia – Tobacco Plain Packaging* considered that paragraph 5 constitutes a “subsequent agreement” of WTO members within the meaning of Article 31(3)(a) of the Vienna Convention on the Law of Treaties, and thus expresses an agreement among members on the approach to be followed in interpreting the provisions of the TRIPS Agreement.²⁹⁰

Paragraph 6 of the Doha Declaration prompted the commencement of work that subsequently culminated in the adoption of an additional flexibility designed to help countries with insufficient or no manufacturing capacities in the pharmaceutical sector to make effective use of compulsory licensing.²⁹¹ Article 31*bis* of the TRIPS Agreement implemented that decision, and it entered into force on 23 January 2017.

Paragraph 7 of the Doha Declaration reaffirmed the commitment of developed-country WTO members to provide incentives to their enterprises and institutions in order to promote and encourage technology transfer to LDC members, as set out under Article 66.2 of the TRIPS Agreement, thus confirming that technology transfer to LDCs is also a public health issue. In addition, paragraph 7 contained an instruction to the TRIPS Council to extend the transition period for LDCs, with respect to their obligations regarding patents and test data protection for pharmaceutical products (including enforcement procedures and remedies). The initial agreed transition period deadline of 1 January 2016 was extended to 1 January 2033.²⁹²

(iv) Implementation of the Doha Declaration

Unlike the TRIPS Agreement itself, the Doha Declaration does not oblige any specific legislative enactment. The

Doha Declaration has been referenced in the work of other international organizations, notably in many WHO resolutions, the WIPO Development Agenda and UN General Assembly resolutions.

(v) *Least-developed country transition periods*

The TRIPS Agreement provides for a number of transition periods so that countries can engage in a phased implementation of their TRIPS obligations. Some of these transition periods specifically target the patenting of pharmaceutical products. Transition periods have expired for developed and developing-country WTO members. Based on the Doha Declaration and subsequent TRIPS Council Decisions, LDCs continue to benefit from an extended transition period until 1 January 2033 with regard to pharmaceutical patents and test data protection for pharmaceutical products (including enforcement procedures and remedies).²⁹³

The WTO General Council also approved a waiver for LDCs from the transitional obligations under Article 70.8 and Article 70.9 of the TRIPS Agreement until 1 January 2033.²⁹⁴ As a result of the waiver for Article 70.8, LDCs are not obliged to allow for the filing of patent applications for pharmaceutical inventions during the transition period. Nor are they under an obligation to grant exclusive marketing rights for pharmaceutical products while patent applications are pending – even for products that otherwise fall within the very specific circumstances set out in Article 70.9. These decisions are separate from the general extension of the LDC transition period, which covers all TRIPS obligations except the non-discrimination principles until 1 July 2021.²⁹⁵ Further extensions of the LDC transition periods are possible upon duly motivated request by LDC members.

At the national level, therefore, LDCs may, for the moment, maintain their existing legal standards of protection and enforcement without having to comply with the patent and test data protection obligations specified in the TRIPS Agreement, with respect to pharmaceutical products. However, if LDCs wished to lower their standards of patent protection for pharmaceutical products, which would be permitted under the above extension decisions, they normally would still need to take action to incorporate these changes into their national laws. This is what happened in Rwanda in 2009, when a new law on the protection of IP was adopted. It excludes from patentability “pharmaceutical products, for the purposes of international conventions to which Rwanda is party”.²⁹⁶ Under Rwanda’s previous patent legislation, pharmaceutical products were patentable subject matter. The 2018 Revised Policy on Intellectual Property in Rwanda²⁹⁷ expressed the desire to create an environment that enabled more local manufacturing of pharmaceuticals, including an enabling IP environment for investments in pharmaceuticals in Rwanda. That

notwithstanding, the policy proposed that Rwanda, as an LDC that wanted to ensure access to affordable medicines for the most vulnerable, continued “the exceptions in the patenting regime for, among others: a) pharmaceutical patents, b) new medical uses of known substances, c) research exception, d) marketing approval (“Bolar” exception), e) clinical test data exception”. Alternatively, LDCs may leave their laws unchanged and simply declare that, until the end of the transition period, they will not enforce legal provisions relating to test data protection or patents in the area of pharmaceuticals. For any of these measures, the LDCs concerned would, in any event, also need to check the conformity of the intended action with their own legal system and with the legal obligations that result from their membership of regional organizations or from bilateral trade agreements or other treaties to which they are a party.

The transition period potentially offers opportunities for these countries to attract investment for the local production of pharmaceutical products.²⁹⁸ While some LDCs exclude pharmaceutical products from patent protection during the transition period, others, such as LDCs that are members of the Organisation africaine de la propriété intellectuelle (African Intellectual Property Organization) (OAPI), have until now foregone this option because the Bangui Agreement provides for the granting of pharmaceutical patents.²⁹⁹ However, a revision of the Bangui Agreement adopted in Bamako, Mali, in December 2015 will exempt LDC members of OAPI from the obligation to provide for the protection and enforcement of patents and undisclosed information until 2033.³⁰⁰ For the Bamako Act to enter into force, 12 ratifications by OAPI members are required; in October 2019, nine ratifications had been deposited.

(h) *Terms of accession to the WTO*

Terms of accession to the WTO are another potential source of IP commitments in the WTO system. New WTO members have to negotiate their accession to the WTO under Article XII of the Marrakesh Agreement Establishing the World Trade Organization (WTO Agreement).³⁰¹ The terms of accession are thus a matter of negotiation. These negotiations take place between the acceding member and existing members that choose to participate in the Working Party on the accession. At a minimum, terms of accession always provide for compliance with all multilateral WTO agreements, including the TRIPS Agreement, subject to possible transitional periods. In a number of cases in the past, existing members also requested additional commitments. If accepted by the acceding member, such additional commitments are noted in the Working Party report and referenced in the Protocol of Accession, which forms part of the WTO Agreement for that member. Newly acceding members may accept terms of accession that require higher levels of IP protection than those provided by the TRIPS Agreement. However,

not all elements in the Working Party report are of equal legal status. While some amount to legally binding commitments, which are detailed in the report and in the Protocol of Accession, other elements are of a descriptive nature, merely reflecting the information provided to the Working Party by the acceding country. In such cases, no commitment is noted by the Working Party.

Issues relating to IP and pharmaceutical products have featured in a number of accession negotiations (see Abbott and Correa (2007) for an overview of IP elements in WTO accession agreements). For example, when Ukraine acceded to the WTO in 2008, it recorded a commitment to notify the first applicants for marketing approval of originator pharmaceutical products about subsequent applications, in order to give the first applicants an opportunity to submit information regarding whether these later applications had permission to use the original test data and to grant exclusive rights to test data for at least five years (see section A.6(f)).³⁰²

With regard to LDCs, it was agreed in the 2001 Ministerial Declaration launching the Doha Development Agenda that WTO members would work to facilitate and accelerate negotiations with acceding LDCs. In 2002, the WTO General Council adopted guidelines for the accession of LDCs.³⁰³ The guidelines provide, among other things, that transitional periods foreseen under specific WTO agreements must be granted – taking into account individual development, financial and trade needs – and that these transitional periods are to be accompanied by action plans for compliance with the trade rules. In addition, a decision taken at the Eighth WTO Ministerial Conference, in December 2011, stipulated that “requests for additional transition periods will be considered, taking into account individual development needs of acceding LDCs”.³⁰⁴ Subsequently, the WTO General

Council decision of 25 July 2012 further streamlined and operationalized the LDC accession guidelines, among others, through enhanced transparency and the undertaking that additional transition periods be favourably considered on a case-by-case basis.³⁰⁵ LDCs that acceded to the WTO since its establishment in 1995 include Cambodia and Nepal (2004), Cape Verde (2008), Samoa and Vanuatu (2012), Lao People's Democratic Republic (2013), Yemen (2014), and Afghanistan and Liberia (2016) (see Box 2.17). Typically, acceding LDCs undertook a commitment to fully implement the TRIPS Agreement as of the date determined in their respective accession protocols. However, at the time of writing, the TRIPS Council, while preparing for the review of Samoa's implementing legislation, has not yet initiated the review of any of these countries' implementing legislation.

2. Competition law and policy

Among the policy instruments available to governments in addressing public health concerns, competition policy has an important role to play in ensuring access to medical technology and fostering innovation in the pharmaceutical sector. Competition is conducive to freedom of choice, low prices and good value for money, while serving as an important driver of innovation and productivity improvement.

(a) The dual function of competition law and policy

When examining policies which are designed to foster innovation and ensure access to medical technologies, competition policy can be considered as having two interrelated functions, which complement each other (Hawkins, 2011).

Box 2.17: The example of Cambodia: an LDC's terms of accession to the WTO

Cambodia was the first LDC to conclude WTO accession negotiations (many LDCs were original WTO members on its formation in 1995). Its Working Party was established in 1994 and met from 2001 until 2003, and Cambodia acceded to the WTO in 2004. In its terms of accession, Cambodia made a commitment to implement the TRIPS Agreement no later than 1 January 2007 – although an extension had been agreed for LDC members in the Doha Declaration until 1 January 2016 for patents and test data protection with respect to pharmaceutical products, and a general extension was later agreed for LDC members until 1 July 2013.

Cambodia's commitment to implement the TRIPS Agreement as of 2007 was made on the understanding that, during the transition period, it would, among other things, grant exclusive rights to test data for five years and provide for patent linkage to marketing approvals³⁰⁶. Cambodia thus accepted demands from existing members that went beyond the express obligations set out in the TRIPS Agreement. By doing so, Cambodia, in its accession agreement, appeared to have given away a number of the flexibilities under the Agreement that it would otherwise have benefited from under current transition periods.

However, immediately prior to adoption of the decision on Cambodia's accession, the then WTO Deputy Director-General, speaking on behalf of the Chairman of the Working Party on the Accession of Cambodia, clarified that: “The results achieved in the case of Cambodia speak for themselves, and in this context I should also add that the terms of this accession do not preclude access to the benefits under the Doha Declaration on the TRIPS Agreement and Public Health to Cambodia as a (least developed country)”.³⁰⁷

First, competition policy is important in terms of informing regulatory measures and other relevant policy choices relating to innovation in, and access to, medical technologies. Competition bodies can be given the mandate to undertake broad policy reviews of competition and regulation, pharmaceutical price regulation regimes, pharmacy regulation and wholesale/distribution arrangements. They can make policy recommendations for a range of policies affecting competition – not only the operation of competition and consumer protection laws, but also in areas directly affecting public health. Institutions such as the Organisation for Economic Co-operation and Development (OECD) and the World Bank have published studies on the interplay between competition policy and health regulation. Such interplay fosters coordination between competition authorities and agencies that regulate the prices of medical products and the health sector generally.³⁰⁸

Second, the enforcement of competition law also helps to correct anti-competitive behaviour that may take place in the different business sectors involved in developing and supplying medical technology to patients who need them. It aims to discipline anti-competitive practices that can, for example, restrict R&D, limit the availability of resources needed for the production of medical technology, create unnecessary barriers to the entry of generic or inter-brand competition, and restrict available distribution channels and consumer choices generally. Practices that have been identified as detrimental in this regard include (but are not limited to): (i) abuses of IPRs through refusal to deal by companies with market power with, or imposition of, overly restrictive conditions in medical technology licensing; (ii) preventing generic competition through patent settlement agreements that were considered anti-competitive; (iii) mergers between pharmaceutical companies that lead to undesirable concentration of R&D and IPRs; (iv) cartel agreements between pharmaceutical companies, including between manufacturers of generics; (v) anti-competitive behaviour in the medical retail and other related sectors; and (vi) bid rigging in public procurement. Recently, excessive pricing in the pharmaceutical sector has also been identified as behaviour that may merit competition authority scrutiny.³⁰⁹ These practices can be addressed on a case-by-case basis through competition law enforcement (see Chapter IV, section D.2).

(b) The interface between competition law and policy, and IP protection

In the area of innovation, the aims and effects of IP protection and competition policy are complementary: both are aimed at fostering innovation by creating incentives to develop new products and services.³¹⁰ IP protection for novel medical technologies is generally considered to be an important means of promoting investment in R&D of new medical technology. This leads

to competition between different originator companies with regard to the development of valuable new medical technologies, and therefore with regard to their earlier production and availability. This form of competition is generally enhanced by IPRs. Competition policy also helps to maintain the innovative potential of the industry by keeping the market structure open and providing countermeasures to anti-competitive behaviour.

As competitors are excluded from using the patented or otherwise protected medical technology, IPRs provide an incentive for them to come up with alternative or superior products. IPRs, when used to exclude competitors, may provide a commercial advantage to an innovator who can be the first on the market (this is called the “first mover” advantage) (Bond and Lean, 1977), and initial profits can encourage competing originators to enter those markets by developing competing products. Ideally, this leads to so-called between-patent competition in pharmaceutical markets: alternative products of the same therapeutic class may be available, and producers of medical technologies then compete in the same market.

(i) Addressing competition policy concerns in the legal framework for IP protection

Competition policy has informed the legal framework for IP protection in that international agreements as well as national IP laws recognize the role competition policy has to play in providing “checks and balances” to IPRs.³¹¹ Legal provisions on competition can be considered an integral part of rules on IP protection.

At the international level, the relevance of competition policy in designing rules on IP protection has long been recognized by the Paris Convention as grounds for granting compulsory licences to prevent the abuse of IPRs. It is also reflected in several provisions of the TRIPS Agreement.³¹²

Article 8.2 of the TRIPS Agreement stipulates that appropriate measures (consistent with the provisions of the Agreement) may be needed to prevent the abuse of IPRs by right holders, or the resort to practices that unreasonably restrain trade or adversely affect the international transfer of technology. On the face of it, this provision is not necessarily concerned only with competition law violations, but also with the arguably more general concept of “abuse” of IPRs.

In a related area, but focusing on the specific issue of licensing practices that restrain competition, Article 40.1 of the TRIPS Agreement records the agreement among WTO members that some licensing practices or conditions pertaining to IPRs, which restrain competition, may have adverse effects on trade and may impede the transfer and dissemination of new technology. To address

this concern, Article 40.2 of the TRIPS Agreement recognizes the right of WTO member governments to take measures to prevent anti-competitive abuses of IPRs. Article 40.2 of the TRIPS Agreement also contains a short illustrative list of practices which may be treated as abuses. These are exclusive grant-back conditions, conditions preventing challenges to validity, and coercive package licensing.³¹³

Under Article 31 of the TRIPS Agreement, setting out certain conditions on the use of a patent without the authorization of the right holder, subparagraph (k) makes it clear that members are not obliged to apply certain of these conditions in circumstances where the compulsory licence is granted “to remedy a practice determined after judicial or administrative process to be anticompetitive” – namely, requirements to show that a proposed user has made efforts to obtain voluntary authorization from the right holder on reasonable commercial terms and conditions, and that such efforts have not been successful within a reasonable period of time, as well as the requirement that authorization for use of a patent under a compulsory licence be predominantly for the supply of the domestic market of the member authorizing such use. Moreover, authorities may consider the need to correct anti-competitive practices while determining the amount of remuneration due.

In many countries, national IP legislation implementing the TRIPS Agreement also recognizes the role of competition policy with regard to IPRs. For example, the Indian Patents Act provides for the grant of compulsory licences without prior attempt to obtain a licence from the patentee on reasonable terms and conditions in case of anti-competitive practices adopted by the patentee (Section 84.6(iv)), as well as the right to export any products produced under such licences, if necessary.

(ii) *Enforcing competition law in the IP context*

Competition law enforcement provides a useful tool for correcting abuses of IPRs on a case-by-case basis.³¹⁴ Generally speaking, no special principles of competition

law apply to IP, but the anti-competitive use of IP rights is subject to the application of competition law disciplines. Nor is IP protection presumed to confer market power or to indicate anti-competitive behaviour. Indeed, IPRs are considered useful in creating functioning markets and fostering innovation. Competition law does not, as a general rule, prevent IPR holders from exercising their exclusive rights. This general respect for IPRs under competition law is based on the assumption that IPRs were acquired legitimately through a system that does not confer overly broad IPRs. For example, a January 2012 decision by the Competition Authority, which had fined a pharmaceutical company for exclusionary abuse of dominant position, was confirmed by the State Council of Italy. The State Council highlighted that the simple enforcement of IPRs was not sufficient to constitute an abuse of a dominant position, but the strategy employed by the company did so.³¹⁵

The role of competition law enforcement therefore is to provide “corrective” measures only where needed. Enforcement action under competition laws may be warranted where the IP protection system itself is unable to prevent unlawful restrictions of competition. There has been growing interest in ensuring an appropriate balance between IP and competition law and policy across a range of jurisdictions.

(c) Preserving innovation: merger control in the pharmaceutical sector

There has been an increasing number of mergers in the pharmaceutical sector, including between originator and generic companies with potential new medicine pipelines (UNCTAD, 2015b). To ensure that consolidation does not significantly impede effective competition, competition agencies in various jurisdictions conduct merger control activities. They may make mergers subject to divestiture of certain branches of research in order to prevent the abandonment of research for potentially competing future medical technology (see Box 2.18 for European Commission merger control activities).³¹⁶

Box 2.18: Merger control in the European Union³¹⁷

In recent years, the European Commission has prevented transactions that could compromise R&D efforts to launch new medicines or to extend the therapeutic use of existing medicines. The Commission intervened to protect innovation competition in a number of cases that, for example, threatened to thwart advanced R&D projects for life-saving cancer medicines or for pipeline insomnia medicines at an early stage of development. The potential competition concerns identified related mainly to the risk of: (i) depriving patients and national health-care systems of some medicinal products; and (ii) diminishing innovation in relation to certain treatments developed at a European or even global level, with the potential to result in price increases for some medicines in one or several member countries. In most cases, the Commission cleared all these transactions only after the companies offered remedies to ensure that pipeline projects were not dropped and found a new operator to drive them forward.

(d) Unfair competition

Unfair competition is covered by Article 10*bis* of the Paris Convention.³¹⁸ It requires countries of the Paris Union to assure to nationals of such countries effective protection against unfair competition, that is, against acts of competition that are contrary to honest practices in commercial matters. The TRIPS Agreement extends this obligation to all WTO members (Article 2.1 of the TRIPS Agreement). In particular, they shall prohibit certain acts that create confusion, discredit competitors through false allegations and mislead the public as to the nature, the manufacturing process, the characteristics, the suitability for their purpose, or the quantity, of the goods.

Protection against unfair competition serves to protect competitors as well as consumers, together with the public interest. When determining honesty in business dealings, all these factors have to be taken into account. This approach is consistent with Article 7 of the TRIPS Agreement, which reflects the intention of establishing and maintaining a balance between the societal objectives mentioned therein.³¹⁹ Consequently, a determination of what amounts to an act that is contrary to honest practices in commercial matters may, depending on the circumstances, reflect a balancing of these interests.³²⁰

The rules on the prevention of unfair competition and those on the control of anti-competitive practices are interrelated in that both aim at ensuring the efficient operation of markets but do so in different ways. The first set of rules is aimed at protecting competitors and consumers against acts of competition that are contrary to what would be regarded as truthful and fair within a certain market. The latter set of rules is aimed at ensuring competition in the marketplace that is free from private restraints and abuses of market power.

Countries have implemented protection against unfair competition in their domestic laws in diverse ways. Some have passed special legislation on the topic, while others rely on general consumer protection and similar laws.

3. Trade policy settings

All countries rely to varying degrees on imported goods to provide for the health-care needs of their populations. In most countries, especially in smaller developing countries with little or no local production capacity in medical technologies, such imported goods make a unique contribution to the country's national health system. Countries are also increasingly engaging in trade in health-care services. Trade policy thus affects the way in which markets for medical technologies are opened to competition from imported goods and services.

Rules for international trade are established at the multilateral level within the framework of the WTO. One

of the cornerstones of the WTO is non-discrimination in international trade relations. This is implemented through the principles of national treatment and most-favoured-nation (MFN) treatment. These principles are enshrined in all WTO agreements, including the GATT in relation to trade in goods, the General Agreement on Trade in Services (GATS) in relation to trade in services, and the TRIPS Agreement in relation to IP. In the case of the GATT and GATS, important exceptions apply, notably as regards special and differential treatment in favour of developing countries, and with respect to regional integration agreements.

The WTO also guarantees its members the right to protect public health. Since its inception in 1947, the GATT has given countries the right to take trade-restricting measures necessary to protect human, animal or plant life or health under certain conditions set out in Article XX(b). The GATS contains a similar exception with regard to trade in services in its Article XIV(b). These general exceptions can justify a measure that would be otherwise inconsistent with WTO obligations and commitments, provided that the health measures, and the ways in which they are applied, satisfy certain conditions, such as that they are not applied in a manner that constitutes an unjustifiable discrimination or a disguised restriction to international trade. Furthermore, Article 8 of the TRIPS Agreement recognizes the right of members to take measures to protect public health, as long as these measures are consistent with the TRIPS Agreement.

(a) Tariffs

Tariffs or customs duties on imported goods are a traditional trade policy instrument and are preferred under WTO rules to quantitative restrictions, such as quotas, which are generally prohibited. Tariffs are relatively transparent and, unlike quotas, do not impose rigid restrictions on volumes of imports.

WTO members have agreed to certain maximum levels for their respective tariffs on all or most imported products, including pharmaceuticals (for tariffs on health-related products see Chapter IV, section D.1 (b)). These maximum levels are called "tariff bindings" and vary according to each country and product. They are the result of decades of tariff negotiations that have gradually led to tariff bindings on more products, which create a more predictable and stable trading environment. Successive rounds of negotiations have also led to lower bound tariff rates and, in fact, WTO members frequently apply tariffs below the bound rate. For example, developing countries have bound their tariffs on formulations on average at 21.3 per cent *ad valorem* (calculated on the value of the imports), but they actually applied tariffs on average at 2.5 per cent *ad valorem* in the year 2016.³²¹

Tariffs make imported goods, including medicines, more expensive for consumers. Nevertheless, many countries

apply tariffs to bolster the competitive position of locally based companies in the domestic market, in an attempt to preserve employment or promote the development of the industry (e.g. the local production capacities of the pharmaceutical sector), or to maintain a certain level of independence from international markets. For consumers, tariff protection can result in costly outcomes. Tariffs also raise revenue for governments, although, in the case of medicines, the revenue amounts raised are generally not significant.

In developed countries, the tariffs applied on medicines are very low, if not zero. A number of WTO members, mainly developed countries, concluded the WTO Pharmaceutical Agreement in 1994 (see Chapter IV, section D.1(b) and Box 4.29). Under this Agreement, they eliminated tariffs on all finished pharmaceutical products as well as on designated active ingredients and manufacturing inputs. Since 1994, the parties have periodically updated the agreement's coverage. Developed countries have applied tariffs on medicines of less than 0.1 per cent *ad valorem* in 2016. Developing countries have lowered their applied tariffs rates on medicines from 6.7 per cent to 2.5 per cent on average. Included in these developing countries are a few countries with local manufacturing industries that apply relatively high tariffs on finished products. In the case of LDCs, the applied rates range from 4.4 per cent to 2.2 per cent, on average.

Tariff exemptions can often be granted for certain medicines or certain purchasers. Public-sector and private non-profit buyers often benefit from waivers from tariffs. Health Action International (HAI), in collaboration with the WHO, has identified the various costs associated with the prices of medicines in different countries. For some countries, the data include information on tariffs and exemptions.³²²

(b) Non-tariff measures

The steady decrease of tariff rates through successive rounds of negotiations over the past 60 years has led to a shift in focus to other types of trade measures. Some experts argue that these other trade measures are increasingly used in place of tariffs to protect domestic industries. Non-tariff measures (NTMs) include, among others, sanitary measures, technical regulations, pre-shipment inspections, import licensing, price control measures, charges and taxes, restrictions on distribution and after-sales services. Several WTO agreements, including the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and Agreement on Technical Barriers to Trade (TBT Agreement), are dedicated to these types of NTMs. A basic objective of such agreements is to establish rules for the use of these measures so that they do not become discriminatory or unnecessary trade barriers. While all

these measures can affect trade in pharmaceuticals, the following two have a direct link to public health outcomes.

(i) *Sanitary and phytosanitary measures*

The SPS Agreement contains specific rules for countries that aim to ensure food safety and prevent the transmission of plant- or animal-carried diseases to humans via trade. This Agreement aims to strike a balance between recognizing the sovereign right of members to determine the level of health protection they deem appropriate, and preventing SPS regulations that represent unnecessary, arbitrary, scientifically unjustifiable or disguised restrictions to international trade. The SPS Agreement requires that SPS measures are not more trade restrictive than required to achieve the appropriate level of sanitary and phytosanitary protection, taking into account technical and economic feasibility. It therefore encourages members to follow international standards, guidelines and recommendations. Members are permitted to adopt SPS measures that result in higher levels of health protection, or measures for which international standards do not exist, provided that those measures are scientifically justified.

The SPS Committee oversees the implementation of the SPS Agreement and facilitates the exchange of information among members regarding regulatory procedures and the use of risk assessments in the development of SPS measures, among other things. In addition, the Committee provides a forum for members to discuss specific trade concerns in relation to the SPS measures of another member (see Box 2.19).

(ii) *Technical barriers to trade*

The TBT Agreement applies to technical product requirements that are not covered by the SPS Agreement. The TBT Agreement helps support the alignment of divergent national regulations to international standards, which, in turn, promotes regulatory cooperation and convergence among national systems. The TBT Agreement strongly encourages such regulatory alignment by requiring that members should normally use relevant international standards as the basis for their regulatory measures (i.e. technical regulations, conformity assessment procedures and domestic standards). When trade frictions arise due to differences in regulatory systems or approaches, the TBT Committee of the WTO provides a forum for members to discuss and solve problems. The TBT Committee also serves as an incubator for best practices on how to regulate, that is, a place where members can share experiences, including on good regulatory practices (such as internal coordination, analysis of regulatory and non-regulatory alternatives, and transparency and public consultation).

Box 2.19: Antimicrobial resistance in the SPS Committee

Since 2018, the issue of antimicrobial resistance (AMR) has been raised in the SPS Committee meetings, within the context of the sharing of information on SPS-related legislation, and also as a specific trade concern.

In July 2018,³²³ the European Union informed the Committee of its new Regulation on Veterinary Medicinal Products, which takes effect by the end of 2021. One of the key objectives of the Regulation is to address the public health risk of AMR, following a “One Health” approach. The Regulation provides for actions against AMR, including through prudent use of antibiotics, and reserving certain antimicrobials for treatment of infections in humans only and banning their use in animals for growth promotion. It was part of a package that also included a new regulation on medicated feed, which contained measures aimed at fighting the misuse of antimicrobials, including a ban on their use in medicated feed for prophylaxis, and limits on treatment duration. Regarding the EU Regulation on Veterinary Medicinal Products, certain WTO members raised concerns that foreign producers had to abide by EU production methodology requirements related to antibiotic use restrictions in livestock, despite the differences in the prevailing sanitary conditions, as well as different regional conditions and disease prevalence in third countries.³²⁴ Members queried the scientific basis of the measures and were concerned about the unnecessary restrictive impact on international trade. They cautioned against any unilateral approach, expressing a preference for multilateral efforts taken to collaboratively set standards to address AMR by FAO, the OIE and the WHO, including through the Codex Task Force on Antimicrobial Resistance. The European Union replied that the ban on using antibiotics as feed additives had been in force in the European Union since 2006 and was based on a scientific opinion. It was in line with the growing international recognition of the need to phase out the use of antimicrobials as growth promoters, some of which were critically important for human medicine. The new Regulation imposed stricter requirements on operators in the European Union than on operators in non-EU countries. The new import requirements should be considered as part of the overall fight against the global spread of AMR, and not as trade barriers.³²⁵

The Agreement covers both instruments that are mandatory (“technical regulations”) and those that are voluntary (“standards”), as well as procedures to assess conformity with them, such as inspections. Technical regulations and standards include, for example, quality requirements for pharmaceuticals, labelling and packaging requirements for foods and medicines, as well as, for example, safety standards for X-ray machines. The TBT Agreement incorporates the principle of non-discrimination, in terms of both national and MFN treatment. It also requires that technical regulations shall not be more trade restrictive than necessary to fulfil a legitimate objective, taking account of the risks that non-fulfilment would create. The Agreement also contains similar obligations to conformity assessment procedures and standards. The protection of human health or safety is listed in the Agreement as a legitimate objective. In other words, the TBT Agreement allows countries to regulate trade to protect health but requires that such measures do not discriminate or unnecessarily restrict trade. Under the TBT Agreement, only unnecessarily trade-restrictive regulations are thus prohibited, while regulations that are, for example, necessary to protect human health are allowed, even if they strongly restrict trade. Regulatory harmonization, that is, the alignment of national regulations with international standards, is another fundamental pillar of the TBT Agreement. The Agreement strongly encourages such regulatory alignment by requiring members to use relevant international standards (i.e. technical regulations, conformity assessment procedures and domestic standards) as the basis for their regulatory measures. The Agreement also provides for flexibility by

relieving members of such obligation when they consider that an international standard would be ineffective or inappropriate for the fulfilment of legitimate objectives pursued by the measure in question. Finally, the Agreement expressly refers to an additional important benefit of harmonization through international standards by recognizing in its Preamble “the contribution which international standardization can make to the transfer of technology from developed to developing countries”.

(c) Trade in services

Trade in health services has been growing, thanks to the increased mobility of individuals (whether patients or health services providers) and the growing role of the private sector in the provision of health services (i.e. establishment of transnational corporations), as well as the communications revolution, which has brought an explosion in the number of mobile applications and health-related connected devices. Also, health services contribute significantly to the effective availability and proper use of many pharmaceuticals and other medical technologies, notably services concerned with prevention, diagnosis and treatment, but also ancillary and technical support. For many sophisticated diagnostic services or treatment regimes, there is no clear distinction between effective and appropriate access to a technology as such, and the supply of related services. Choices made in opening health services to foreign services and services providers may therefore affect access to medical technologies.

(i) The multilateral legal framework

The GATS is the main multilateral legal instrument governing trade in services, including health services. It defines trade in services as the supply of a service through four different “modes of supply”, each bearing on the health sector:

- Mode 1: cross-border supply (e.g. telemedicine-health)
- Mode 2: consumption abroad (e.g. a patient seeking medical treatment in a foreign country)
- Mode 3: establishment of commercial presence (e.g. a clinic opening an overseas subsidiary or investing in an existing facility abroad)
- Mode 4: presence of natural persons (e.g. a physician moving abroad to work in a foreign-owned clinic).

(ii) The scope of GATS commitments in health-related sectors

The GATS grants WTO members full flexibility when it comes to deciding whether to include binding commitments for the opening of health-related sectors and which modes of supply to open to foreign competition, as well as the level of obligations that they are prepared to undertake. Health services fall into several categories: (i) hospital services; (ii) other human health services; (iii) social services; (iv) medical and dental services; and (v) services provided by midwives, nurses, physiotherapists and paramedical personnel.³²⁶ Other services complement and facilitate access to health services and medical technologies, such as: insurance services; R&D on medical sciences; the pharmacy, wholesale and retail sale of various pharmaceuticals, medical and surgical goods and devices; maintenance and repair services for medical equipment; and technical testing and analysis services. However, many public-sector health services lie outside the scope of the GATS, since its disciplines do not cover services “supplied in the exercise of governmental authority” (i.e. those supplied neither “on a commercial basis” nor “in competition with one or more service suppliers”).

Many countries have gradually liberalized their health services, thus creating more opportunities for private operators. However, such countries remain reluctant to make this opening binding under the terms of the GATS. Apart from health insurance services, there are, therefore, fewer legally binding commitments under the GATS to liberalize health services *per se* than there are for any other sector (see Table 2.3). This may be due to the major role played by public entities in providing public health services, coupled with political sensitivities. Health services have not been the object of active bilateral negotiations, and commitments in this sector are mostly made as a result of a particular country’s own initiative (Adlung, 2010). It is important to note, in any

Table 2.3: Number of GATS commitments (as of 2020)

Medical and dental services	52
Nurses, midwives, etc.	22
Hospital services	49
Other human health services (ambulances, etc.)	25
Social services	15
Other health-related and social services	6

Source: WTO Secretariat

Note: The schedule of commitments of the European Union (25) is counted as one, but includes commitments of its 25 member states as of 2004. Bulgaria, Romania and Croatia have separate schedules of commitments.

event, that committing to open a service sector to foreign competition does not affect a government’s capacity to regulate the sector.

Across the health sectors under consideration, there is generally reluctance to enter commitments on cross-border supply of health services. This is probably due to uncertainties on how to design and enforce appropriate regulation of service suppliers located abroad (a pattern also observed across other service sectors).

Bindings with respect to health services consumed abroad account for the highest number of full commitments, perhaps reflecting governments’ reluctance – and inability – to prevent their nationals from leaving the jurisdiction in order to consume services abroad (a practice that also occurs in all service sectors). Some members restrict the portability of insurance coverage for treatment abroad, possibly deterring patients from seeking treatment outside their jurisdiction.

Nearly half the commitments relating to the supply of health services through commercial presence appear to be bound without limitations at the sectoral level, a result that seems to be above average for all sectors.³²⁷ Most commitments under this mode, however, are subject to limitations, for example, limits on foreign equity and requirements for joint venture or residency. Some members apply economic needs tests – criteria such as population density, existing medical facilities, degree of specialization, type of medical equipment, and distance from a facility or availability of transport infrastructure are considered before new hospitals or clinics are authorized.

Unlike the other modes of supply, commitments on health services supplied through health professionals working abroad have been undertaken on a “horizontal” basis by the vast majority of members. This means that they equally apply to all services sectors for which a member has undertaken binding commitments. Most WTO members have closely restricted commitments on this mode, focusing on highly skilled persons or on individuals linked to a commercial presence, as opposed

to the self-employed (Adlung, 2009). Some add further restrictions to their commitments, referring to language, residency or nationality requirements, recognition of diplomas, strict time limits, economic needs tests or quotas, thus restricting further the already limited level of bindings. Evidence suggests, however, that health professionals benefit from better access conditions in practice than they would if they were exclusively limited to GATS bindings. Health services commitments are also limited as to the breadth of covered activities, such as exclusions of public suppliers, restrictions of commitments on hospital services to privately supplied or privately funded services, or types of medical specializations covered. However, it is important to note that there has been an increase in the number of commitments in health services with the accession of new members to the WTO.

(iii) The growing economic importance of trade in health services and the impact of GATS commitments

According to Global Health Observatory (GHO) data, health expenditure represented US\$ 7.5 trillion or 10 per cent of global gross domestic product (GDP) in 2016. It is expected that an additional 40 million jobs will be created in the health sector by 2030 (WHO, 2016e). Available statistics show that, in the OECD area, the health-sector workforce increased by 48 per cent between 2000 and 2014, which is 3.5 times more than the increase in total employment. However, this increasing demand is challenging, and trade in services clearly has a role to play to respond to some foreseen shortages in certain jurisdictions. Empirical evidence regarding the share of health services in international trade is limited, due to the lack of reporting of detailed official statistics by many countries. However, estimates derived from an experimental data set produced by the WTO Secretariat show that health services account for US\$ 50 billion. The establishment of foreign-controlled medical institutions is the predominant method of providing such services (71 per cent), followed by health treatment received abroad (23 per cent), cross-border supply, such as telemedicine (5 per cent) and temporary presence of health professionals/workers (1 per cent).

Health services are globalizing, through increased cross-border movement of health-care workers and patients, as well as technological developments and decreasing telecommunications costs, which are contributing to the development of eHealth across a range of activities (e.g. teleradiology, telediagnosis, telepathology, teleconsultation and telesurgery).

However, it is almost impossible to measure the impact of GATS commitments on health services – and any other sector – because of limited data and the difficulty of distinguishing the effects of bindings under trade

agreements from those of other policy and regulatory measures. However, studies suggest that the effects of GATS commitments – where these exist – on trade patterns have most likely been insignificant. GATS commitments do not entail additional liberalization, but (at best) bind existing levels of market access. Consequently, the commercialization of health services has occurred irrespective of GATS obligations, and the main effect of the GATS seems to have been to make national policies more predictable (Adlung, 2010). The coverage of health services in FTAs is discussed in Chapter IV.

(iv) Challenges linked to the opening of trade in health services

An increasing challenge in the context of health services is linked to demographic changes (i.e. ageing population), which is driving the growth in demand for medical and care-related services. Opening of trade in health services should not be seen as an end in itself, but, rather, as a tool to generate distinct benefits if properly used in a broader policy context. From a public health perspective, increasing trade in health services bears both opportunities for improving health service delivery (e.g. accessibility in remote areas, alleviating human resource constraints, additional resources) and risks for equity (e.g. serving only certain segments of the population, large initial investments for telecommunications networks, attracting investment). The concern is often expressed that opening (trade in) health services may create a two-tier system – good services for the rich, bad services for the poor – thus jeopardizing equitable access for all. For example, exporting health services via the Internet from delocalized centres may boost employment opportunities in developing countries, and contain costs in developed countries. By attracting health-care workers to financially more attractive opportunities, this may leave gaps in the local health sector.

Publicly owned and operated health facilities thus require an appropriate regulatory framework in order to ensure that more open trade in health services benefits all sections of the population. An impact assessment on the supply of health services should precede binding commitments under the GATS or any other trade agreement. The mobility of health workers is a key issue, with workers tending to move from the poorest regions to richer cities within a country, and from there to high-income countries. Demand for foreign health workers has increased in high-income countries because of insufficient numbers of health professionals being trained locally, and due to ageing populations in these countries. When considering the mobility of health professionals, recognition of qualifications is also a requisite for the supply of services in foreign markets. Governments wishing to contain “brain drain” remain free to do so, as such measures are not subject to GATS disciplines, particularly those that relate to the temporary mobility of foreign health workers.

The limited scope of this commitment, both its definition and specific commitments, means that the GATS has probably traditionally played an insignificant role in the international migration of health personnel, but could help to fill an increasing resources gap in the future.

4. Government procurement

Government procurement refers generally to the purchasing of goods, services and construction services, or any combination thereof, by, or on behalf of, government bodies in fulfilment of their public service responsibilities, including in areas of socially vital importance, such as health care. This section addresses the positive impact a well-designed framework for government procurement can be expected to have on the health sector. It sets out the rules established for that purpose by the plurilateral Agreement on Government Procurement (GPA) under the WTO (as amended in 2012), and the size of procurement markets in health-related sectors covered by that Agreement.

(a) The importance of a transparent and competitive procurement process for the health sector

The possibility of achieving significant savings through the introduction of better government procurement tools is especially relevant for the health sector, where, according to the World Bank, the procurement of medicines has been particularly prone to weak governance, contributing to stock-outs, wastage, poor quality and price inflation (Savedoff, 2011). Available surveys show that, in many LMICs, availability remains far from adequate and prices remain many times higher than international reference prices (IRPs) (see Chapter IV, section A.3). The introduction of more efficient, transparent and competitive procurement procedures in the context of public health systems has the potential to contribute substantially to improvement in the accessibility and affordability of medicines, thus helping to establish more efficient and cost-effective health delivery systems that minimize waste and prevent fraudulent and corrupt practices. A range of evidence relating to cost reductions that have been achieved through the application of transparent and competitive procurement processes in the health-care sector is summarized in Chapter IV, section A.8.

(b) Procurement of medical technologies and health services under the GPA

The GPA provides an appropriate framework for rules at the international level that are intended to promote efficient trade and best practices in the area of public procurement.

The GPA is a plurilateral agreement, meaning that only those WTO members that have acceded to it (48 as at 5 May 2019) are bound by its rules.

In addition to its role as a binding international agreement, the GPA has served as a model in several bilateral and regional trade agreements that embody government procurement commitments. It is also broadly consistent with the United Nations Commission on International Trade Law (UNCITRAL) Model Law on Procurement of Goods, Construction and Services, including the 2011 revision, which has inspired the national legislation of many countries, and it reinforces other international instruments such as World Bank guidelines and the work of the OECD on prevention of corruption. As a consequence, the basic disciplines of the GPA are relevant to substantially more procurement and potentially more countries than its current membership would suggest.³²⁸

(i) GPA coverage

The GPA has important application vis-à-vis the public health sector, specifically with regard to the areas it covers – the procurement of medicines, pharmaceutical products and health services. In principle, the GPA promotes transparency and fair competition and helps to deliver improved value for money for governments and their agencies. Unless otherwise explicitly excluded, the GPA covers all goods procured by covered entities in values above the relevant thresholds,³²⁹ including medicines and pharmaceutical products (see Table 2.4).

The GPA applies only to such goods and services and government agencies or entities that have been specifically committed by the parties and included in their respective schedules of commitments in Appendix I of the GPA. To determine the specific market access commitments undertaken by GPA parties in the health-care sector, the following factors must be taken into consideration: (i) whether, and if so which, health-related entities are covered in a GPA party schedule of commitments; and (ii) whether, and if so which, health-related products and services are covered by the GPA.

In relation to the first aspect, health-related entities are covered by GPA parties at various levels of government (see Table 2.4). More precisely:

- Almost all parties expressly cover such entities at the central government level (e.g. federal entities and ministries)
- The majority of parties that have a sub-central level of government (e.g. states, provinces, cantons and municipalities) cover them at this level or do not expressly exclude them
- Three parties cover other types of health-related government entities (e.g. hospitals).

Table 2.4: Coverage in the health sector by parties to the WTO GPA

Party to the WTO GPA as of 5 May 2019	Coverage of health-related entities at the central government level	Coverage of health-related entities at the sub-central government level	Coverage of goods (pharmaceutical products are generally considered to be goods)	Coverage of health-related services
Armenia ^a	✓		✓	✓
Australia ^d	✓	✓	✓	X
Canada	✓	✓	✓	X
European Union, including its member states ³³⁰	✓	✓	✓	X
Hong Kong, China	✓	N/A	✓	X
Iceland ^b			✓	X
Israel ^c	✓	X	✓	X
Japan	✓	X	✓	X
Korea, Republic of	✓	X	✓	X
Liechtenstein ^b			✓	X
Moldova, Republic of ^a	✓		✓	X
Montenegro ^a	✓		✓	X
Netherlands, with respect to Aruba	✓	N/A	✓	X
New Zealand ^e	✓	✓	✓	X
Norway ^a	✓		✓	X
Singapore	✓	N/A	✓	X
Switzerland	✓	✓	✓	X
Chinese Taipei	✓	✓	✓	X
Ukraine ^b			✓	✓
United States	✓	✓	✓	✓

Notes: Names of parties to the WTO GPA are those used in the WTO. The symbols “✓” and “X” have been used respectively to indicate whether a party’s coverage is expressly stated to include health-related entities or not. Where a party’s coverage has been presented in generic or descriptive terms and no additional details have been provided – for instance, by way of an illustrative list – the specific entry has been left blank. In addition, a footnote is provided indicating that the item is neither expressly covered nor expressly excluded. It should also be noted that the following do not have sub-central levels of government and accordingly have scheduled no commitments in this regard: Hong Kong, China; Netherlands with respect to Aruba; and Singapore.

^a In Annex 2 of Armenia, Republic of Moldova, Montenegro and Norway, health-related entities are neither expressly covered nor excluded.

^b Health-related entities (Annex 1 and Annex 2) are neither expressly covered nor excluded.

^c Israel has expressly excluded the following goods procured by its Ministry of Health: insulin and infusion pumps, audiometers, medical dressings (bandages, adhesive tapes excluding gauze bandages and gauze pads), intravenous solution, administration sets for transfusions, scalp vein sets, hemodialysis and blood lines, blood packs and syringe needles. It should be noted that a number of these exclusions have been deleted as a result of the conclusion of the GPA negotiations.

^d In its GPA coverage, Australia expressly excluded health services (Annex 5) and procurement of blood and blood-related products, including plasma derived products (Annex 4).

^e In addition to explicitly covering sub-central health-related entities, Annex 2 of New Zealand also clarifies that procurement undertaken by the listed district health boards through their agent Health Alliance Limited is covered. Procurement of public health services is expressly excluded from New Zealand’s coverage (Annex 5).

As is made clear in the revised GPA text, the GPA does not apply to goods or services procured with a view to commercial sale or resale.

In addition, the European Union has undertaken binding commitments under the GPA for health-related entities at

the central government level for all its member states and for a significant number of such entities at the sub-central government level. For its part, the United States is covered by the federal Department of Health and Human Services, and health-related entities in a number of its states. New Zealand expressly covers its district health boards.³³¹

Another key point is that, under the GPA, pharmaceutical products are generally considered to be goods, and accordingly, unless otherwise specified, are normally considered to be covered by the GPA when purchased by entities listed in the parties' schedules, in values above the relevant thresholds. Furthermore, none of the GPA parties currently incorporates a general exclusion of such products in its schedules. One smaller party has excluded a number of goods procured by its Ministry of Health. With regard to the coverage of health-related services under the GPA, Ukraine and the United States are the only GPA parties currently covering them. New Zealand expressly excludes procurement of public health services. Overall, the GPA thus provides relatively broad coverage for entities in the health-care sector, particularly with respect to goods (including medicines); on the other hand, its coverage of health services is limited.

(ii) *The magnitude of GPA parties' health-related procurement*

The GPA is the pre-eminent international instrument regulating trade in government procurement markets. As a result of several rounds of negotiations and the addition of new members, the GPA parties have opened procurement activities worth an estimated US\$ 1.8 trillion annually to international competition (i.e. to suppliers from GPA parties offering goods, services or construction services). In order to appreciate the importance of the government procurement markets covered by the GPA in health-related fields, it is necessary to quantify the potential value of these market access commitments. An important source of statistical information on the size of covered procurement markets is now available from recent statistical reports that have been submitted by the GPA parties to the Committee on Government Procurement. Although these statistical reports are not necessarily consistent in all respects (efforts are under way to ensure greater consistency in methodological approaches), they nevertheless represent a useful source of information regarding the magnitude of the market access commitments under the GPA.³³²

These official sources make clear that the size of government procurement markets in health-related sectors covered by the GPA is substantial.³³³ For example, the United States notes in its statistical reports that the total general expenditure, by function, of the 37 states covered under the GPA in 2010 was US\$ 49 billion for hospitals and US\$ 47 billion for health.³³⁴ In addition, the United States reports that the value of goods and services covered by the GPA and procured by the Department of Health and Human Services in 2010 was estimated to be around US\$ 10 billion. The European Union also notes in its statistical report for 2013 that its covered entities had procured an estimated EUR 28 billion of medical and laboratory devices, pharmaceuticals and related medical consumables covered by the GPA.³³⁵ Japan reports that

the value of contracts covered by the GPA awarded by the Ministry of Health, Labour and Welfare in 2010 was estimated at US\$ 1.8 billion.³³⁶

5. Free trade agreements

The terms "regional trade agreement" (RTA), "free trade agreement" (FTA), "bilateral trade agreement" (BTA) and "preferential trade agreement" often overlap. The WTO defines any reciprocal trade agreement between or among two or more partners, not necessarily belonging to the same region, as a regional trade agreement. This study uses the term "free trade agreement" as a synonym.

FTAs are discussed here in general terms; they are covered with more specific reference to access to medicines aspects in Chapter IV, section C.5.

(a) Trends in trade negotiations beyond the multilateral arena

There is a worldwide trend for countries to enter into economic integration arrangements in various bilateral and regional configurations (see Figure 4.9), in parallel with multilateral agreements – a development that is presenting significant systemic challenges for the multilateral system outlined in this chapter (and analysed in WTO, 2011).

Early agreements focused on trade in goods and the elimination of tariff duties and other restrictions between parties to an agreement that were applied at the border. As border measures were reduced or even eliminated, FTAs evolved to cover a wide range of domestic regulatory policy areas, such as services and IP. Modern FTAs include parties, or regions, with different levels of development. Negotiations covering a wide range of trade-related disciplines started with the Uruguay Round, where broader coverage was a deliberate strategy to allow all negotiating parties to benefit in terms of trade, in order to compensate for real or perceived trade losses. The resultant trade openness from the FTAs has fostered harmonization of national practices, international governance and the rule of law, which transcend national borders. In the area of IP law and policy, this trend might entail changes in national laws, which, in turn, can directly affect access to, and innovation in, medicines and medical technologies.

Motivations to negotiate and implement FTAs may include:

- Neutralizing "beggar-thy-neighbour" trade policies that seek benefits for one country at the expense of others
- Increasing market size

- Enhancing policy predictability
- Signalling openness to investors
- Fostering the expansion of international production networks (WTO, 2011).

The *World Trade Report 2011* concludes that, for LMICs, having policies in common with high-income countries may create benefits by allowing them to import regulatory systems that are “pre-tested” and represent “best practices”. On the other hand, developing countries may also be pressured to adopt common rules that are inappropriate for their national context, or which could be used by high-income countries to protect vested interests.

Increasing market size can be one goal of establishing an FTA, as it enables companies to exploit economies of scale and gain a relative advantage over competitors in third countries. In addition, preferential access to a larger market may increase a country’s attractiveness as a destination for foreign direct investment (FDI). Both aims are potentially of particular value for small economies, which may help to explain why these countries agree to make concessions on other more controversial issues, such as IPRs or environmental standards, when negotiating FTAs with large economies (WTO, 2011).

(b) The non-discrimination principles and FTAs

The key feature of FTAs is the preferential treatment for its parties, which is not automatically extended to third parties. Article XXIV of the GATT 1994 and Article V of the GATS provide for broad exceptions to the principles of non-discrimination and allow WTO members to negotiate and implement FTAs. However, the TRIPS Agreement does not provide for such an exception. In concrete terms, if two WTO members agree on higher standards of IP protection than those provided in the TRIPS Agreement, they cannot, in principle, deny the same higher level of protection to nationals of any other WTO member. In other words, the agreed higher level of protection would not be limited to nationals of the FTA parties but would have to be extended to the nationals of all other WTO members as well. This can have important implications for access to medicines and medical technologies, as well as for the innovation of new products.

For example, if two countries agreed to provide patent term extensions for one another’s patent holders, the MFN treatment principle under the TRIPS Agreement would require them to provide the same patent term extensions to patent holders from all other WTO members. In contrast, if they agreed to reduce or eliminate tariffs on pharmaceuticals or chemical ingredients imported from one another as part of an FTA or customs union, they would not need to reduce or eliminate tariffs on imports from other countries.

(c) Intellectual property standards

As discussed in Chapter II, section B.1 (a) and Chapter IV, section C.5(a), WTO members are free to incorporate into their national laws more extensive IP protection than the minimum standards required by the TRIPS Agreement, provided that this protection does not contravene TRIPS requirements. A number of FTAs provide for more extensive protection for patents and test data, as well as higher enforcement standards, which can affect trade in pharmaceuticals and can have an impact on prices for medical technologies (see Chapter IV, section C.5).

Moreover, in areas that usually operate through the use of national regulations, such as IP, services and competition policy (WTO, 2011), in any event, it would be costly in practice to tailor regulations in order to favour nationals originating from preferential partner economies, and this becomes even more difficult as the number of FTAs to which a country is a signatory increases. Thus, reasons of principle and practicality lead to a “ratcheting-up” effect on IP standards, in that they can lock in higher levels of protection, with potential effects on innovation and access to medical technologies.

(d) Investor–state dispute settlement

Another important element of a number of FTAs is investor–state dispute settlement (ISDS) mechanisms, which allow private entities to sue national governments for alleged violation of FTA provisions in a tribunal established to resolve the dispute (see Chapter IV, section C.5(b)).

(e) Commitments in other areas

A thorough analysis of the potential effects of FTAs on innovation in, and access to, medical technologies must take into account the commitments and standards agreed in all key policy areas that directly relate to the pharmaceutical sector, such as tariffs for inputs and finished products for wholesale or retail, government procurement and competition law.

Due to the low average applied tariff across products and countries (see Chapter IV, section D.1(a)), there is not usually much room left for exchanging preferential tariff concessions in trade agreements. Therefore, matters including investment, competition policy and government procurement have increasingly made their way into the more recent generation of FTAs, complementing the reduction of trade barriers and reflecting the trend towards the convergence of regulatory regimes. Modern FTAs contain specific, stand-alone FTA chapters on regulatory issues. For example, around 64 per cent of FTAs include a dedicated competition chapter (Anderson et al., 2018).

Alternatively, as is often the case for the competition sector, they can become an integral part of chapters, for example, on IPRs or government procurement (WTO, 2011).

6. Resolving trade disputes at the WTO

Health has been touched upon in numerous WTO disputes.³³⁷ The WTO Appellate Body in *EC – Asbestos* considered that the preservation of human life and health through the elimination, or reduction, of the well-known, and life-threatening, health risks posed by asbestos fibres was a “value [that] is both vital and important in the highest degree”.³³⁸ Similarly, in *Brazil – Retreaded Tyres*, the Appellate Body agreed with the panel that “few interests are more ‘vital’ and ‘important’ than protecting human beings from health risks”.³³⁹ At issue in that dispute were Brazil’s measures aimed at reducing exposure to risks, including dengue fever and malaria, arising from the accumulation of waste tyres.

In the area of the TRIPS Agreement, the panel report in *Canada – Pharmaceutical Patents* illustrates the policy space available to members to use permissible exceptions to seek appropriate balance between the interests of patent holders and users. The panel found that Canada’s regulatory review provision was permissible under the so-called “three-step test” under Article 30 of the TRIPS Agreement,³⁴⁰ but that its stockpiling provision was not justified under Article 30, especially because there were no limitations on the quantity of production for stockpiling or market destination of the products manufactured under this provision.³⁴¹

In 2018, the intersection between public health, IP and trade was addressed in comprehensive panel reports in *Australia – Tobacco Plain Packaging*.³⁴² At issue were Australia’s tobacco plain packaging (TPP) measures requiring that tobacco products and their retail packaging appear in a uniform manner.³⁴³ The Panel Reports discuss, *inter alia*, certain aspects of coherence in domestic and international law and policy.

In these disputes, the complainants challenged the TPP measures as being *unnecessary* within the meaning of Article 2.2 of the TBT Agreement and *unjustifiable* within the meaning of Article 20 of the TRIPS Agreement. The complainants did not dispute the harmful consequences of tobacco consumption and acknowledged the importance of effective tobacco-control measures to reduce the public health burden resulting from tobacco use. Their key argument was, however, that the TPP measures were not capable of contributing to their public health objective. Having examined an extensive amount

of evidence provided by the parties, the panel concluded that the TPP measures, as applied in combination with other tobacco-control measures maintained by Australia, *are capable* of contributing, and *do in fact contribute*, to their objective of improving public health by reducing the use of, and exposure to, tobacco products.

The panel recognized the importance of use of trademarks to distinguish products in the marketplace, on the one hand, and the exceptional gravity of the domestic and global health problems at issue, involving a high level of preventable morbidity and mortality, on the other hand, and considered these factors in the light of the TPP measures’ contribution to improving public health. The panel found that the complainants had not demonstrated that the trademark-related requirements of the TPP measures *unjustifiably* encumber the use of trademarks in the course of trade within the meaning of Article 20 of the TRIPS Agreement. In its analysis, the panel noted that Australia, while having been the first country to implement TPP, had pursued its relevant domestic public health objective in line with the emerging multilateral public health policies in the area of tobacco control as reflected in the WHO Framework Convention on Tobacco Control (FCTC) and the work under its auspices, including the Article 11 and Article 13 FCTC Guidelines.³⁴⁴

The panel similarly found that the complainants had not demonstrated that the TPP measures are more trade restrictive than necessary to fulfil a legitimate objective, within the meaning of Article 2.2 of the TBT Agreement.³⁴⁵ In that context, the panel noted that, while Australia had not demonstrated that the Guidelines constituted a “standard” under Annex 1.2 of the TBT Agreement with respect to TPP, they provided important guidance to FCTC parties in addressing packaging, and, as relevant, implementing plain packaging as an element of a comprehensive scheme of effective tobacco-control policies.³⁴⁶

The panel rejected the complainants’ claims that the TPP restrictions on the use of figurative elements of trademarks, geographical indications and marks of origin were contrary to certain other provisions of the TRIPS Agreement, including those incorporated by reference from the Paris Convention (1967).³⁴⁷ In discussing the interpretation of the provisions of the pre-existing treaties incorporated by reference into the TRIPS Agreement, the panel recalled that it is a general principle of interpretation to adopt the meaning that reconciles the texts of different treaties and avoids a conflict between them. Accordingly, one should avoid interpreting a provision of the Paris Convention (1967) as incorporated by reference into the TRIPS Agreement to mean something different than that within the context of the Paris Convention (1967) except where this was explicitly provided for.³⁴⁸

C. Economics of innovation and access to medical technologies

Key points

- Knowledge or new, useful information possesses the characteristics of what is commonly called “a public good”.
- Special challenges in the area of health technologies include the long product development times, the necessarily stringent regulatory burden, the relatively high risk of failure and the comparatively low marginal costs of production.
- The pharmaceutical sector stands out in terms of its dependence on patents to capture returns on research and development (R&D).
- Several policy options exist within and outside the patent system to attenuate the negative price and welfare effects of patents, especially on pharmaceuticals.

The past decades have seen more systematic efforts to use the tools of economic analysis to support discussions on health policy. The WHO Commission on Macroeconomics and Health (WHO, 2001a) was a major milestone along this road. This study does not attempt to advance economic analysis and the theoretical understanding of the economics of technology innovation and access issues. Rather, it recognizes the growing importance of economic concepts in policy debate, and it briefly reviews the main economic concepts and the current body of literature dealing with the IP aspects of these issues.

In the economics of innovation and IP, knowledge or new, useful information has been considered to have, to some extent, the classical characteristics of a public good: non-excludability and non-rivalry. Non-excludability means that it is not possible to exclude others from using the knowledge once it is made public. Non-rivalry means that one person's use of the knowledge does not restrict or diminish the amount of it available or its value for use by others. Its non-rivalrous character means that knowledge can be easily shared and replicated. In the absence of some kind of protection against unauthorized sharing or replication, private entities may not invest in the creation of knowledge, since others could benefit for free from their efforts once the knowledge is public. Therefore, for the original private investors, generating a reasonable level of return on their investments might prove difficult. Consequently, where investments can be recouped only through sales, no protection at all would lead to chronic underinvestment in the creation of knowledge, or, in other words, markets would fail to produce knowledge in socially optimal quantities.

Economists wrestle with the question of how best to finance the creation of new knowledge, particularly when private investment is involved. Special challenges arise in

the area of medical technologies in general and medicines in particular, given the long product development times, the necessarily stringent regulatory burden, the relatively high risk of failure (such as when pharmaceuticals fail tests on safety and efficacy at a late stage in their development) and the comparatively low marginal costs of production.

The patent system can result in a net social benefit. While patents may increase costs to society in the short term by restricting competition, it is hoped that they generate greater and more dynamic benefits as a result of encouraging more innovation in the long term. The requirement to disclose the invention in patent applications helps to disseminate scientific and technical information that could otherwise be kept secret. In these circumstances, society benefits from research conducted by those “standing on the shoulders of giants” to create additional new and useful inventions. Patents can also be useful instruments for obtaining finance (venture capital).

Costs associated with research in the pharmaceutical sector are high, but once introduced into the market, it has been relatively easy for other companies to reverse engineer new pharmaceutical compounds and market generic versions at much lower prices. Several studies have shown that when an array of different choices is examined – patents, trade secrets, lead times and other business strategies – the pharmaceutical sector stands out as the one that depends most on patents as a means of capturing returns on R&D investments. This finding has also been borne out by large-scale, multi-sector industry surveys conducted in the United Kingdom (Taylor and Silberston, 1973), the United States (Mansfield, 1986; Levin et al., 1987; Cohen et al., 2000) and many other countries (WIPO, 2009). However, the advent of biologics is changing the industrial organization of the industry, as biotherapeutics are not as easy to reverse

engineer as traditional small-molecule innovations. As a result, trade secrecy surrounding the production process has turned into an important protection mechanism for biotherapeutics (Price and Rai, 2015, 2016). While biologic innovator companies regularly seek product patent protection, details of the manufacturing processes that are not covered by those patents may be kept as trade secrets. It has been observed that this combination of protection by patents and trade secrets can complicate achieving sufficiently similar production processes for similar biotherapeutic products (SBPs). In addition, it has been argued that, due to the 12-year regulatory exclusivity period for biotherapeutic products in the United States, companies might rely rather on trade secrets than patent protection, which would lead to a lack of disclosure (Price and Rai, 2016). On the other hand, the view has been held that, in the future, technological advances may further enable reverse engineering even for biological therapeutic products and would reduce the value of trade secrets for manufacturing processes (Weires, 2019).

The period of commercialization of a medicine under patent protection is typically much shorter than the patent term (period between grant and expiry). It has been estimated that the effective patent term of a new medicine, which is the balance remaining in the patent term after obtaining the relevant regulatory approvals, is an average of 8 to 13.5 years in the US market, depending on the source (US Congress, Office of Technology Assessment, 1993; Grabowski and Kyle, 2007; Aitken and Kleinrock, 2017).

The pharmaceutical sector has a higher accounting rate of profit compared with most other industries, which, according to the US Government Accountability Office, was just over two times the average profit margins for the 500 largest companies in industries other than pharmaceuticals and software in 2015.³⁴⁹ The majority of spending on biomedical R&D is undertaken in only a few countries, while medical innovation benefits patients around the world, when and where it is accessible and affordable (Viergever and Hendriks, 2016). This raises the question of how the R&D expenditures should be equitably shared among countries.

According to the National Science Foundation, US pharmaceutical companies invested three times as much in R&D, relative to their sales, than the average US manufacturing firm in 2015.³⁵⁰ Moreover, most of the investments made in R&D performed by pharmaceutical companies in the United States come from the relevant companies themselves, rather than from outside funding sources, including the US federal government.³⁵¹

In order to understand the effect of pharmaceutical product patents, several attempts have been made by economists to simulate the effect on prices and welfare of the introduction of pharmaceutical patents. One study found that the extent of price reduction after patent expiry varied greatly between products and countries

and concluded that future research should gather more country-specific data (Vondeling et al., 2018). One such study concludes that the introduction of product patents on pharmaceuticals in just one therapeutic subsegment in India would lead to significantly higher prices and welfare losses, which are estimated to range from US\$ 145 million to US\$ 450 million per year (Chaudhuri et al., 2006). On the other hand, a study using Indian pharmaceutical market data on central nervous system medicines, from 2003 to 2008, showed little evidence of substantial increases in average pharmaceutical prices in this market, but statistically significant price increases of about 12 per cent in one segment of this market, namely, products protected by a compound patent (as opposed to secondary patents) (Duggan and Goyal, 2012). However, these findings are limited by narrow inclusion criteria and failure to account for “mailbox” patents,³⁵² wherein the Indian post-TRIPS amendments to the Patents Act included a clause that allowed Indian generic companies to continue to manufacture medicines for which patents were granted in India with applications filed since 1995, upon payment of a royalty to the patent holder. Further studies done with data after 2015 will shed light on more systematic effects on prices, as the mailbox patents will have expired.

Price regulation, whether in terms of direct cost-plus or indirect price reimbursement models, including those based on reference pricing, can be efficient means to lower prices, but they have to be worked out carefully in order not to result in medicine shortages in the market.³⁵³

Compulsory licences have also been reported as having resulted in substantially reduced prices of patented medicines during the patent term (see Chapter IV, section C.3(a)(ii)). However, compulsory licences may have limited effectiveness for more complex technologies such as biotherapeutics, as they do not oblige the patent owners to cooperate in divulging trade secrets about production processes, transferring the additional know-how and/or transferring materials that might be required.

Permitting parallel imports does not automatically result in lower prices. The reason is that parallel importing is not determined solely by the IP regime chosen by a country. Rather, it also depends on the conditions in the individual contract between the manufacturer and the wholesaler, as well as on the differences in the marketing authorization granted, including, for example, the trade name of the product, which may vary from one jurisdiction to another.

Another potential solution is differential or tiered pricing, under which lower prices are applied in poorer countries (see Chapter IV, section A.4(g)). In order to maximize profits, a monopolist selling under different market conditions could use a form of price discrimination based on differing willingness and ability to pay for the product. One alternative to differential pricing is uniform pricing, whereby the seller sets one price, adjusted for transport,

distribution and other costs, for all consumers in all countries. It should be noted that parallel importation by design limits the ability to segment markets and employ price differentiation, among countries in which parallel importation is possible and practised.

A medicine protected by patents should, in principle, lend itself to differential pricing. In such circumstances, both consumers in poorer countries and patent-owning companies would be better off. It would also seem that, in these circumstances, the market itself could move closer to solving the problem of equitable sharing of R&D costs. In order for price discrimination to occur, three conditions would need to be fulfilled:

- The seller must have some control over price, such as some degree of market power
- The seller must be able to identify and segregate consumers according to varying price sensitivities
- The seller must be able to limit resale from low-priced markets to high-priced markets or, in other words, must be able to segment the market (Watal, 2001; see also Chapter IV, section A.4(g)).

However, in practice, there is little evidence that pharmaceutical companies engage in differential pricing based on per capita income (Scherer and Watal, 2002; Watal and Dai, 2019 – see Box 2.20). Flynn et al. (2009) showed that, in the case that income distribution in the local economy is unequal, the firm will maximize its revenue by selling a restricted quantity to the wealthy at a high price, resulting in relatively similar prices between countries of different per capita income levels. Danzon et al. (2015) found evidence that income inequality does contribute to relatively high drug prices. Besides, they

found that, in such markets, prices of originator products are only slightly reduced, even after generic entry.

In addition to concerns about the price or affordability of patented medicines, concerns have been raised about delays in the availability of these medicines in other countries from the date of first approval in the first country. One study (Lanjouw, 2005) found that, while for high-income countries, patents unambiguously encourage the introduction of new drugs, companies tend to launch products later where there is price regulation. The picture is mixed for the other countries. Lanjouw concluded that, for LMICs with a high capacity to manufacture generic versions of new drugs, introducing strong IP protection may mean having fewer new drugs on the market, as patent owners may delay entry due to expectations of low ability to pay, and generic producers cannot enter due to patent protection. On the other hand, while price regulation makes it less likely that new drugs will be available quickly in LMICs, such regulation does not appear to prevent new products from being launched eventually.

This research has been taken further by others, including Kyle and Qian (2014), who examined the effects of patent protection on availability of new medicines and found that patents do encourage launches of these molecules in local markets. Cockburn et al. (2016) also conclude that, while originator companies tend to launch later where there is price regulation, longer and more extensive patent rights accelerate product launch across all countries. Following these studies, a WTO working paper (Watal and Dai, 2019) studies both the question of availability and affordability with respect to innovative medicines in a post-TRIPS era (see Box 2.20).

Box 2.20: Product patents and access to innovative medicines in a post-TRIPS era

Watal and Dai (2019)³⁵⁴ investigated two questions: (1) How does the introduction of product patents for pharmaceuticals affect the likelihood of pharmaceutical firms launching new and innovative medicines in those markets? (2) For innovative medicines,³⁵⁵ how much do patent owners or generic pharmaceutical firms adjust their prices to local income levels?

Using launch data from 1980 to 2017 covering 70 markets, the study finds that introduction of product patent for pharmaceuticals in the patent law has a positive effect on the likelihood of earlier launch, especially for innovative pharmaceuticals. However, this effect is quite limited in low-income markets. Also, innovative pharmaceuticals are launched sooner than non-innovative ones, irrespective of the patent regime in the local market.

Using a panel data set of originator and generic prices from 2007 to 2017, the study finds evidence of some differential pricing for both originator and generic products. Overall, originators differentiate by about 11 per cent and generics by about 26 per cent. Differential pricing is larger for pharmaceuticals to treat infectious diseases, particularly for HIV/AIDS medicines, than for those to treat NCDs. However, pharmaceutical prices are far from being fully adjusted to local income levels in either case. It is clear that competition, especially that within a particular medicine market as opposed to the market of medicines that treat similar medical conditions, can effectively drive down prices in both originator and generic markets.

Some countries provide incentives to originator companies to introduce their products soon after first marketing anywhere in the world, by counting the term of test data exclusivity from the date of first approval globally, as opposed to the date of first approval in that country. For example, Chile has implemented such a system following the US–Chile FTA (Fink, 2011).³⁵⁶ For countries with a weak regulatory framework, somewhat delayed introductions, on the other hand, have the advantage of avoiding adverse events associated with withdrawals for safety reasons.

Finally, it is important to note that patents and other IPRs are meant to be market-based instruments. They play a limited role in providing incentives to develop new medicines for “neglected diseases” or “diseases of the poor” in regions where there are small markets. Thus, the ongoing debate on access to medicines has generated a debate on alternative non-price-linked mechanisms for incentivizing innovations, such as prizes or advance market commitments (AMCs), and it has spawned new business models such as product development partnerships (PDPs).³⁵⁷

D. Genetic resources, traditional knowledge and traditional medicine

Key points

- Traditional medicine is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses.
- As with other medicines for human use, traditional medicines should be covered by regulatory frameworks to ensure that they conform to required standards of safety, quality and efficacy.
- The commercial exploitation of genetic resources (GRs) and traditional knowledge (TK) by other than the TK holders raises questions of legal protection of TK against unauthorized use.
- Documentation of traditional medical knowledge, such as databases and national inventories, can be used as evidence of prior art in patent procedures.
- The essential effect of the Convention on Biological Diversity (CBD) and the Nagoya Protocol is to confirm national sovereignty over GRs and to establish a right of prior informed consent (PIC) over access to, and use of, GRs and associated TK. The three main objectives of the CBD are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of GRs.
- The WHO Pandemic Influenza Preparedness (PIP) Framework governs the sharing of influenza viruses (and related materials) between research centres and commercial entities.

Traditional medicine has long been used as a mainstay of health care for many populations. This section reviews a number of issues concerning traditional medical systems with respect to IP, regulatory systems and trade.

1. Traditional medicine knowledge systems

Traditional medicine is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses.³⁵⁸ It is used as a comprehensive term to refer to both traditional medicine systems, such as traditional Chinese medicine (TCM), Ayurvedic medicine and Unani medicine, and various forms of indigenous medicine being practised traditionally. It is thus best understood as a set of distinct systems of knowledge that include different therapeutic philosophies, products and practices. Traditional medicine that has been adopted by other populations (outside its indigenous culture) is often termed “complementary and alternative medicine” (CAM).³⁵⁹

Traditional medicines can be of different composition, including herbs, herbal materials and preparations, and finished herbal products (herbal medicines). They may also use animal materials or mineral materials. Their

active ingredients are therefore substances derived from plants, animals or minerals.³⁶⁰ Traditional medicine is used widely throughout the world, but especially in developing countries. As of 2018, 88 per cent of WHO member states acknowledged use of traditional and complementary medicine (T&CM) (WHO, 2019f).

Herbal treatments stand out as the most popular form of traditional medicine. International trade in traditional medicines is growing, with the China Chamber of Commerce for Import and Export of Medicines and Health Products, reporting that the total value of exports of Chinese *Materia Medica* is more than US\$ 39 billion, and the annual growth rate is about 0.5 per cent from 2014 to 2018.³⁶¹

The goals for the WHO Traditional Medicine Strategy 2014–2023 are to support member states in:

- harnessing the potential contribution of T&CM to health, wellness, people-centred health care and universal health coverage
- promoting safe and effective use of T&CM through the regulation, research and integration of T&CM products, practices and practitioners into the health system, as appropriate.³⁶²

In the GSPA-PHI, the WHO identified traditional medicine as one of the areas to be addressed in its Quick Start programme. The programme aimed “to support research

and development and to promote standard-setting for Traditional Medicine products in developing countries”.³⁶³ The relevance of integrating T&CM into health systems to strengthen global efforts targeting health challenges has been acknowledged by the World Health Assembly Resolution on Global Action on Patient Safety and the UN Political Declaration on UHC, both adopted in 2019.

2. Traditional medical knowledge in health and IP policy

In international debates, the term “traditional knowledge” (TK) has been used in a broad sense in many contexts, notably, in policy discussions on the environment and biodiversity, health, human rights and the IP system. The term itself has no agreed international legal definition (WIPO, 2015a).³⁶⁴ In this study, “traditional medical knowledge” is used in a specific context, referring to the content or substance of TK, skills and learning, with specific application to human health, wellness and healing. It may apply to traditional medicines as such, or to knowledge systems relating to medical treatment (such as healing massage or yoga postures).

In general, traditional medicine systems may be categorized as follows:

- Codified systems, which have been disclosed in writing in ancient scriptures; these include the systems of Ayurveda, Mongolian traditional medicine, Siddha medicine, traditional Chinese medicine, Thai traditional medicine, Tibetan medicine and Unani medicine
- Non-codified traditional medical knowledge, which has not been fixed in writing, often remains undisclosed by TK holders and is passed on in oral traditions from generation to generation.

The past decade has seen greater attention paid to traditional medical knowledge in several international policy contexts. For example, the United Nations Declaration on the Rights of Indigenous Peoples,³⁶⁵ which was adopted in 2007, states: “Indigenous peoples have the right to their traditional medicines and to maintain their health practices, including the conservation of their vital medicinal plants, animals and minerals”. It also cites medicines within the context of the “right to maintain, control, protect and develop their cultural heritage, traditional knowledge and traditional cultural expressions, as well as the manifestations of their sciences, technologies and cultures”.

3. Traditional medicines regulation

As with other medicines for human use, traditional medicines should be covered by regulatory frameworks

to ensure that they conform to required standards of safety, quality and efficacy. The regulation of traditional medicines takes many different forms around the world. Depending on the national legislative and regulatory framework, they can be sold as prescription or non-prescription medicines, dietary supplements, natural health products, health foods or functional foods. As of 2018, 124 member states (64 per cent) reported that they have laws and/or regulations on herbal medicines (WHO, 2019f).

As part of implementing the WHO Traditional Medicine Strategy 2014–2023, a comprehensive regulatory package is promoted and supported by the WHO, which includes the regulation of products, practices and practitioners of traditional, complementary and integrative medicine. As of 2018, 109 member states reported the presence of a legal framework for T&CMs, and 78 member states reported regulation of T&CM providers (WHO, 2019f). In this regard, the WHO is developing several categories of standards, norms and technical documents, such as a series of benchmarks for training in T&CM, a series of benchmarks for the practice of T&CM, a series on terminology in T&CM, and a traditional medicine chapter in the international classification of diseases.³⁶⁶

Growth in international trade in traditional medical products has sparked discussions on the trade impact of regulations. WTO members have notified and discussed regulations dealing with such products in the WTO TBT Committee (see section B.3(b)(ii) above). Since 1995, more than 80 measures regulating traditional medical products were notified to the TBT Committee.³⁶⁷ The growth that could be observed in such notifications reflects an increasing prevalence of regulation of these products.³⁶⁸ The main objectives of these measures cited by members are the need to protect human health or safety, and the prevention of deceptive practices and consumer protection.

WTO members have raised a small number of specific trade concerns in the TBT Committee dealing with measures on traditional medical products. The purpose is to discuss concerns pertaining to specific laws, regulations or procedures that affect their trade, usually in response to notifications.

For example, in 2010, China, Ecuador and India argued that EU Directives 2001/83/EC and 2004/24/EC on Traditional Herbal Medicinal Products³⁶⁹ introduced unnecessary barriers to trade in traditional medical products.³⁷⁰ The European Union explained that the 2004 Directive provided a simplified registration procedure for traditional herbal medicines, for example, by exempting the manufacturer from providing a number of tests and clinical trials that were otherwise required under the normal authorization procedure.³⁷¹

4. Concerns about misappropriation of traditional knowledge and genetic resources

One problem confronting TK holders is the commercial exploitation of their knowledge by others. This raises questions of legal protection of TK against unauthorized use. Research is continuing on traditional medicines and traditional medical knowledge in various areas, each generating a multitude of policy issues:

- Traditional health practitioners develop their expertise through observation, building on empirical understanding about the use of traditional formulations. Many countries increasingly seek to preserve and promote traditional medicine systems.
- Research efforts are being made to scientifically and clinically validate traditional medicines, to integrate them into countries' health systems.
- Traditional medicine and medical knowledge provide leads for the development of new treatments. Many existing modern medicines are originally based on herbal products. For example, oseltamivir, used to treat various influenza infections, is based on shikimic acid, which is isolated from Chinese star anise, a cooking spice used in TCM.³⁷² Current malaria treatments contain synthetic derivatives of artemisinin, which is derived from a plant, sweet wormwood, *Artemisia annua*. This is an ancient Chinese medicine still used in modern practice, which was used to treat malaria-stricken soldiers during the Viet Nam War and was developed through international partnership into a widely used pharmaceutical product for malaria treatment (Rietveld, 2008).

Reflecting the clinical significance of traditional medicine, some programmes undertake an “integrative” approach, looking for synergies between “traditional” and “conventional” medical research. One such example is a research programme on good practice in TCM Research in the post-genomic era (Uzuner et al., 2012) and initiatives to integrate traditional and contemporary cancer care in the Middle East (Ben-Ayre et al., 2012). Many of the issues highlighted in this debate concern genetic materials used as the basis for medical research, and traditional medical knowledge that is used either directly to produce new products or as a lead in researching new treatments. The principal shift in focus has been to recognize that: (i) the custodians and practitioners of traditional medical knowledge may have legitimate rights; (ii) their knowledge cannot be assumed to be in the public domain, free for anyone to use; and (iii) as financial and non-financial benefits from R&D are shared along the product development pipeline, an equitable portion should also be provided to the origin or source of the material used in research. The Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH) has stated that it sees a need to guard against misappropriation of genetic resources (GRs)

and TK to ensure that the benefits derived from TK are fairly shared with the communities that discovered those resources and their possible medical uses, and to promote the use of such knowledge for the benefit of public health (WHO, 2006a).

Access to GRs and associated TK is primarily regulated by the Convention on Biological Diversity (CBD), which came into force in 1993, and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (Nagoya Protocol), which came into force in 2014.³⁷³ National biodiversity policies frequently reference traditional medicines and medical research. Many other national policies seek to create medical R&D programmes on the basis of their heritage of GRs and associated TK.

The essential effect of the CBD and Nagoya Protocol is to confirm national sovereignty over GRs and to establish a right of prior informed consent (PIC), approval and involvement over access to, and use of, GRs and associated TK. The three main objectives of the CBD are the conservation of biological diversity, the sustainable use of its components, and the fair and equitable sharing of the benefits arising out of the utilization of GRs (see Box 2.21).

How to apply PIC and access and benefit-sharing (ABS) has sparked a wide-ranging debate. For the area of vaccines development, the WHO Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and other Benefits (PIP Framework) has established Standard Material Transfer Agreements to implement ABS considerations for the exchange of viruses in that Framework (for the political debate on ABS aspects regarding the sharing of viruses, see Chapter III, section E).³⁷⁴ With regard to IP, however, the policy issues can be distilled into two broad themes:

- Whether patents and other IPRs can and should be obtained over inventions derived from GRs and associated TK. In particular, what mechanisms, if any, should be put in place to ensure that patents are not erroneously granted over TK and GRs and that patent holders comply with the principles of PIC and ABS. Strategies to ensure that third parties do not gain illegitimate or unfounded IPRs over TK subject matter and related GRs are known as “defensive protection”, such as measures to pre-empt or invalidate patents that claim pre-existing TK as inventions.
- How to recognize and give legal and practical effect to positive IPRs that owners or custodians of GRs and associated TK may have, whether through the existing IP system or through *sui generis* rights. This is referred to as “positive protection”. Positive protection involves preventing unauthorized use of TK by third parties, as well as active exploitation of TK by the originating community itself.

Concerns about taking due account of TK in patent examination have led to initiatives at international and national levels to avoid grant of erroneous patents, on traditional medicines in particular. A leading example is the Traditional Knowledge Digital Library (TKDL), a collaborative project in India between the Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology and Ministry of Health and Family Welfare. An interdisciplinary team of Indian medicine experts, patent examiners, IT experts, scientists and technical officers has created a digitized system enabling consultation of existing literature in the public domain relating to Ayurveda, Unani, Siddha and yoga. Such literature is generally available in traditional languages and formats. Thus, the TKDL provides information on traditional medical knowledge in five international languages and formats that are understandable by patent examiners at international patent offices. The aim is to prevent the grant of erroneous patents,³⁷⁵ while, at the same

time, not publishing TK in a way that would facilitate its misappropriation. The GSPA-PHI urges governments and concerned communities to facilitate access to traditional medicinal knowledge information for use as prior art³⁷⁶ in the patent examination procedures, where appropriate, through the inclusion of such information in digital libraries (Element 5.1f). The WTO TRIPS Council³⁷⁷ and the WIPO Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore (IGC) have discussed how to preclude erroneous patents using GRs and associated TK through the use of databases.³⁷⁸

5. New approaches to IP protection of traditional medical knowledge

Parties to the CBD, members of WIPO and of the WTO have considered the concept of a disclosure requirement

Box 2.21: The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (Nagoya Protocol)

The Convention on Biological Diversity (CBD) and Nagoya Protocol cover both GRs and TK associated with them. While the Convention confirms the sovereign rights of states over their natural resources, the Nagoya Protocol has established a transparent legal framework that aims to ensure that the benefits of utilization and/or commercialization of GRs and associated TK are shared in a fair and equitable way with their country of origin.

Access to GRs under the Nagoya Protocol is subject to two basic requirements: PIC and mutually agreed terms (MAT). Those who wish to access GRs need the PIC of the competent authority in the country of origin or source according to Article 6.1 of the Nagoya Protocol and MAT have to be reached. For instance, a research institute wishing to access a GR that is from another jurisdiction must meet the obligations set by that jurisdiction's ABS legislation. In practice, this could mean establishing contact with the relevant National Focal Point on ABS or other competent authority responsible for granting access to the specific GR, and applying for the necessary permits and entering into a bilateral agreement on MAT that specify the terms and conditions for, in particular, the equitable sharing of benefits. Parties to the agreed utilization of a GR must make sure that due diligence is exercised, ensuring that anyone using GRs in their jurisdiction follows proper PIC and MAT procedures.³⁷⁹

Different approaches have been formulated to managing IPR in accordance with the ABS principles of the Nagoya Protocol. Argentina's model MAT for the CBD generally stipulate that the Government exclusively retains all IPRs related to the material used and its derivatives. At the other end of the spectrum is the Australian model MAT for the CBD, which grants to the user IPRs arising from R&D activity using the material. Under the Swiss model agreement, if commercialization is sought of the fruits of R&D, new PIC and MAT have to be negotiated, and the user has the opportunity to file an application for an IPR within an agreed period of time, after which the provider exercises his or her right to publish the research, thereby placing it in the public domain. Annex 1(j) to the Nagoya Protocol contemplates the possibility of joint ownership of relevant IPRs. Within the PIP Framework, the Standard Material Transfer Agreement (SMTA) 1, which governs the sharing of PIP biological materials within the WHO Global Influenza Surveillance and Response System (GISRS), prohibits the user from obtaining IPR on the material, while SMTA 2, which governs sharing of PIP biological materials outside the GISRS, does not (see Chapter III, section E.3).

The use of digital sequence information on GRs with respect to the objectives of the CBD is being discussed by the parties to the CBD and Nagoya Protocol.³⁸⁰ The term "digital sequence information" has not been defined in the context of the CBD. A similar discussion is taking place in the context of the PIP Framework (see Chapter III, section E.3–4). That debate uses the term "genetic sequence data" and understands both terms as meaning information related to genetic sequencing.³⁸¹ The WHO considers that digital sequence information from pathogens is a global public health good that should be widely available to all and that benefits derived from using such sequence information should be shared equitably with all, without impeding the rapid, timely and broad sharing of sequences for disease control, prevention and preparedness.³⁸²

in the patent system, put forward by its proponents as a means of ensuring that patents on inventions derived from TK and GRs are consonant with the principles of PIC and ABS. The proposals and the debate are diverse and cover areas other than medicine, although patents in the medical area have been the major focus of the debate. The essential thrust of the proposal to implement a disclosure requirement in the patent system would be to require the patent applicant to notify the source or origin of TK and GRs used in claimed inventions and to document compliance with PIC and ABS requirements. A number of countries have implemented such provisions in their national laws, but there is no agreed international standard. An alliance of WTO members has proposed a revision to the TRIPS Agreement to make such provisions mandatory,³⁸³ but other countries continue to question the usefulness and effectiveness of this kind of disclosure mechanism.³⁸⁴ *Key Questions on Patent Disclosure Requirements for Genetic Resources and Traditional Knowledge* (WIPO, 2017b) offers a comprehensive overview of key legal and operational questions on disclosure requirements.

The cultural, scientific, environmental and economic importance of TK has led to calls for it to be preserved (safeguarded against loss or dissipation) and protected (safeguarded against inappropriate or unauthorized use by others), and there are many programmes under way at national, regional and international levels to preserve, promote and protect different aspects of TK. Such measures include: (i) preserving the living cultural and social context of TK, and maintaining the customary framework for developing, passing on and governing access to TK; and (ii) preserving TK in a fixed form, such as when it is documented or recorded.

WIPO is primarily concerned with “protection” in the IP sense (i.e. the protection against copying, adaptation and use by unauthorized parties). The objective, in short, is to ensure that the materials are not used wrongly. Two forms of protection – positive protection and defensive protection – have been developed and applied, as outlined above.

In the WIPO IGC, member states are working on the development of an international legal instrument for the effective protection of TK and on ways to address IP aspects of access to, and benefit-sharing of, GRs, including patent disclosure requirements. Two draft texts are available for member states to discuss.³⁸⁵ The work of the IGC on TK³⁸⁶ is concentrating on positive protection and the IP aspect of protection – the recognition and exercise of rights to preclude others from illegitimate or unauthorized use of TK. As WIPO member states are continuing efforts to negotiate on these issues, no final agreement has been reached. The text of an international legal instrument for the effective protection of TK is, therefore, in flux, and new drafts continue to become available on a regular basis. The

information set out below seeks to provide a broad and informal description of the nature of the discussions under way in the WIPO negotiations.

At the WTO TRIPS Council, members have continuously discussed the protection of TK, including measures taken at the national level and the need to put an international framework for the protection of TK in place. Previously, the African Group had proposed a formal decision to establish a system of TK protection, but this discussion has not led to any conclusions.³⁸⁷

(a) Why protect traditional knowledge?

The IGC has considered the policy objectives for international protection,³⁸⁸ including to:

- Prevent unauthorized use of TK
- Repress unfair and inequitable uses and preclude unauthorized IPRs
- Promote innovation and creativity, community development and legitimate trading activities
- Ensure that PIC and exchanges are based on MAT and promote equitable benefit-sharing (EBS).

(b) What is to be protected, and for whose benefit?

There is, as yet, no accepted definition of TK at the international level. In principle, TK refers to knowledge as such, in particular, knowledge resulting from intellectual activity in a traditional context, and includes know-how, practices, skills and innovations. It is generally accepted that protection should principally benefit TK holders themselves, including indigenous peoples and local communities. However, there is no agreement on whether families, nations, individuals and others (such as the state itself) could be beneficiaries. While TK is generally regarded as collectively generated, preserved and transmitted, so that any rights and interests should vest in indigenous peoples and local communities, in some instances, beneficiaries may also include recognized individuals within communities, such as certain traditional health practitioners (with a specific reference to traditional medical knowledge). Some countries do not use the terms “indigenous peoples” or “local communities” and consider that individuals or families maintain TK.

(c) What is it to be protected from?

TK holders report lack of respect and appreciation for such knowledge. For example, when a traditional healer provides a mixture of herbs to cure a sickness, the healer may not isolate and describe certain chemical compounds and describe their effect on the body in

the terms of modern biochemistry, but the healer has, in effect, based this medical treatment on generations of clinical experiments undertaken by healers in the past, and on a solid understanding of the interaction between the mixture and human physiology, such as in the *Pelargonium* case (Wendland and Jiao, 2018).

(d) How can traditional knowledge be protected?

The diversity of TK means that no “one-size-fits-all” solution could suit all countries and communities. It is also a significant challenge to establish how protection under a national system could be enforced regionally and internationally.

Existing IPRs have been used successfully to protect against some forms of misuse and misappropriation of aspects of TK. *Protect and Promote Your Culture: A Practical Guide to Intellectual Property for Indigenous Peoples and Local Communities* (WIPO, 2017c) explains how to use IP tools to protect and promote TK. Several countries have adapted existing IP systems to the needs of TK holders, including through specific rules or procedures to protect TK. For example, the Chinese State Intellectual Property Office has a team of

patent examiners specializing in TCM. Other countries have developed new, stand-alone *sui generis* systems to protect TK. The international legal instrument for the effective protection of TK, which is being negotiated in the IGC, is a *sui generis* system. Other options are also available, such as contract laws, biodiversity-related laws, and customary and indigenous laws and protocols.

(e) Documentation

Documentation is especially important because it is often the means by which people beyond the traditional circle obtain access to TK. It does not ensure legal protection for TK, which means that it does not prevent third parties from using TK. Depending on how the documentation process is carried out, it can either promote or damage a community’s interests. IPRs may be lost or strengthened when TK is documented. WIPO has developed *Documenting Traditional Knowledge – A Toolkit* (WIPO, 2017a) to help holders of TK, in particular, indigenous peoples and local communities, protect their interests should they decide to document their TK. This toolkit focuses on management of IP concerns during the documentation process, and also takes the documentation process as a starting point for more beneficial management of TK as a community’s intellectual and cultural asset.

Endnotes

- 1 The right to health is recognized in international instruments, such as the WHO Constitution, the Universal Declaration of Human Rights (Article 25) and the International Covenant on Economic, Social and Cultural Rights (Article 12).
- 2 See Sustainable Development Knowledge Platform at <https://sustainabledevelopment.un.org/sdgs>, in particular SDGs 1, 3 and 17.
- 3 UN document E/C.12/2000/4.
- 4 Ibid.
- 5 Report of the Special Rapporteur on the right to health (2006), A/61/338, para. 49.
- 6 UN document E/C.12/GC/17.
- 7 UN document E/C.12/GC/24.
- 8 Commission on Human Rights resolution 2002/31, see <https://www.ohchr.org/EN/Issues/Health/Pages/SRRRightHealthIndex.aspx>.
- 9 See <https://www.ohchr.org/EN/Issues/Health/Pages/SRRRightHealthIndex.aspx>.
- 10 See <https://www.ohchr.org/EN/Issues/Health/Pages/AnnualReports.aspx>.
- 11 UN documents A/HRC/RES/32/15, A/HRC/RES/23/14 and A/HRC/41/L.13.
- 12 UN documents A/HRC/RES/32/15 and A/HRC/41/L.13.
- 13 UN document A/RES/S-26/2.
- 14 UN document A/RES/70/266.
- 15 See Sustainable Development Knowledge Platform at <https://sustainabledevelopment.un.org/sdgs>.
- 16 See <https://www.un.org/millenniumgoals/>.
- 17 All submissions to the UNHLP are available at: <http://www.unsgaccessmeds.org/reports-documents>.
- 18 WTO document IP/C/75. Council for Trade-Related Aspects of Intellectual Property Rights – Annual report (2016) of the Council for TRIPS; WHO document A70/20. Addressing the global shortage of, and access to, medicines and vaccines; UN Human Rights Council. 34th session of the Human Rights Council (27 February to 24 March 2017). Panel discussion on good practices and key challenges relevant to access to medicines as one of the fundamental elements of the right of everyone to the enjoyment of the highest attainable standard of physical and mental health.
- 19 See, in particular, TRIPS Council meetings of 8–9 November 2016, WTO documents IP/C/M/83 and Add.1, and TRIPS Council meetings of 1–2 March 2017, WTO documents IP/C/M/85 and Add.1.
- 20 See WIPO documents SCP/25/6, SCP/26/8, SCP/27/10, SCP/28/12 and SCP/29/8, available at: https://www.wipo.int/meetings/en/topic.jsp?group_id=61.
- 21 UN documents WHA70/2017/REC/3, WHA71/2018/REC/3, EB140/2017/REC/2 and EB144/2019/REC/2.
- 22 General Assembly resolution A/RES/71/159.
- 23 WHA, Resolution WHA49.14: Revised drug strategy.
- 24 WHA, Resolution WHA52.19: Revised drug strategy.
- 25 WHA, Resolution WHA60.30: Public health, innovation and intellectual property.
- 26 WHA, Resolution WHA56.27: Intellectual property rights, innovation and public health.
- 27 WHA, Resolution WHA56.30: Global health-sector strategy for HIV/AIDS.
- 28 WHA, Resolution WHA59.26: International trade and health.
- 29 WHA, Resolution WHA60.30: Public health, innovation and intellectual property.
- 30 For a list of relevant publications from the WHO and other intergovernmental organizations, see <https://www.who.int/phi/publications/en/>.
- 31 WHA, Resolution WHA56.27: Intellectual property rights, innovation and public health.
- 32 WHA, Resolution WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property; WHA, Resolution WHA62.16: Global strategy and plan of action on public health, innovation and intellectual property.
- 33 WHA, Resolution WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property, Annex, para. 7.
- 34 See Chapter III, section C.4.
- 35 WHA, Resolution WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property, Annex, para. 14(e).
- 36 Ibid., Annex Element 5.1(h).
- 37 WHA, Resolution WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property, para. 4(5).
- 38 See Chapter I, section B.4.
- 39 See WHA Resolutions WHA62.16, EB136(17), and WHA68.18.
- 40 WHA, Decision: WHA71(9): Global strategy and plan of action on public health, innovation and intellectual property: overall programme review.
- 41 WHA, Resolution WHA64.5: Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits. See also Chapter III, section E.
- 42 UN document A/RES/66/2. See also WHA, Decision WHA65(8): Prevention and control of non-communicable diseases: follow-up to the High-level Meeting of the United Nations General Assembly on the Prevention and Control of Non-communicable Diseases.
- 43 See <https://www.gardp.org/>.
- 44 See <https://www.who.int/research-observatory/en/>.
- 45 See https://www.who.int/medicines/access/fair_pricing/en/.
- 46 See https://www.who.int/phi/implementation/tech_transfer/en/.

- 47 “Antimicrobial resistance – a global epidemic, Background paper for the Technical Symposium on Antimicrobial Resistance: How to Foster Innovation, Access and Appropriate Use of Antibiotics? Prepared by the Secretariats of WHO, WIPO and WTO”, available at: https://www.wipo.int/edocs/mdocs/mdocs/en/wipo_who_wto_ip_ge_16/wipo_who_wto_ip_ge_16_inf_2.pdf.
- 48 See <https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/>.
- 49 WHA, Resolution WHA68.7: Global action plan on antimicrobial resistance.
- 50 See WHO Document A72/18 at paras. 37–41, available at: http://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_18-en.pdf; see also <http://www.fao.org/antimicrobial-resistance/en/>, <https://www.oie.int/en/our-scientific-expertise/veterinary-products/antimicrobials/> and https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/tripartite/en/.
- 51 UN document A/RES/71/3.
- 52 *Ibid.*, para. 15.
- 53 The IACG developed six discussion papers, which cover the topics: (i) Antimicrobial resistance: Invest in innovation and research, and boost R&D and access; (ii) Antimicrobial resistance: national action plans; (iii) Surveillance and monitoring for antimicrobial use and resistance; (iv) Future global governance for antimicrobial resistance; (v) Optimize use of antimicrobials; and (vi) Meeting the challenge of antimicrobial resistance: from communication to collective action. The discussion papers are available at: <https://www.who.int/antimicrobial-resistance/interagency-coordination-group/public-consultation-discussion-papers/en/>.
- 54 UN document A/73/869.
- 55 UN document A/RES/74/2.
- 56 See https://www.wipo.int/meetings/en/2016/wipo_wto_who_technical_symposium.html; “Antimicrobial resistance – a global epidemic, Background paper for the Technical Symposium on Antimicrobial Resistance: How to Foster Innovation, Access and Appropriate Use of Antibiotics? Prepared by the Secretariats of WHO, WIPO and WTO”, available at: https://www.wipo.int/edocs/mdocs/mdocs/en/wipo_who_wto_ip_ge_16/wipo_who_wto_ip_ge_16_inf_2.pdf.
- 57 See, for example, WTO Workshop on Trade and Public Health, organized in close collaboration with WHO and WIPO, 8 to 12 October 2018, https://www.wto.org/english/news_e/news18_e/tra_15oct18_e.htm.
- 58 See https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1.
- 59 See <https://www.who.int/antimicrobial-resistance/en/>.
- 60 See WHO Library of national action plans, available at: <https://www.who.int/antimicrobial-resistance/national-action-plans/library/en/>.
- 61 See, for example, WHO. Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for National Medicines Regulatory Authorities (NMRAs) – 2nd edition, available at: https://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf?sequence=1; WHO Global Benchmarking Tool, available at: https://www.who.int/medicines/regulation/benchmarking_tool/en/; WHO Global Benchmarking Tool (GBT) for Evaluation of National Regulatory System of Medicinal Products. National Regulatory System (RS): Indicators and Fact Sheets, available at: https://www.who.int/medicines/areas/regulation/01_GBT_RS_RevVI.pdf?ua=1.
- 62 See also http://www.who.int/medical_devices/safety/en/.
- 63 See Regulation (EU) 2017/745 and Regulation (EU) 2017/746; BBC News, “Q&A: PIP breast implants health scare”, 10 December 2013, available at: <https://www.bbc.com/news/health-16391522>.
- 64 See also <https://www.who.int/clinical-trials-registry-platform/about/glossary>. For information on the role of clinical trials in the drug development process, see Chapter III, section B.7.
- 65 WHA, Resolution WHA58.34: Ministerial Summit on Health Research.
- 66 World Medical Association, WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks, available at: <https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/>.
- 67 UNESCO, About the Bioethics Programme, available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/about-bioethics/>.
- 68 UNESCO, Universal Declaration on Bioethics and Human Rights. 19 October 2005, available at: http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html.
- 69 WIPO, *Intellectual Property and Bioethics – An Overview: Consultation Draft*, available at: https://www.wipo.int/edocs/pubdocs/en/intproperty/932/wipo_pub_b932ipb.pdf; see also WIPO Life Sciences Symposium, 4 September 2007, available at: https://www.wipo.int/meetings/en/details.jsp?meeting_id=14142.
- 70 See <https://www.who.int/ethics/about/unintercomm/en/>.
- 71 Available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/>.
- 72 Available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genetic-data/>.
- 73 Available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights/>.
- 74 WHO expert advisory committee on Developing global standards for governance and oversight of Human Genome editing, see <https://www.who.int/ethics/topics/human-genome-editing/committee-members/en/>; The Global Summit of National Bioethics Committees, see <https://www.who.int/ethics/partnerships/globalsummit/en/>.
- 75 The WHO Model Lists of Essential Medicines are available at: <https://www.who.int/medicines/publications/essentialmedicines/en/>.
- 76 World Health Organization, Expert Committee on Biological Standardization, Geneva, 19 to 23 October 2009, “Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)”, available at: https://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1.

- 77 See, for example, Berkowitz, S. A., Engen, J. R., Mazzeo J. R. and Jones, G. B. (2012), “Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars”, *Nature Reviews. Drug Discovery* 11(7): 527–540.
- 78 See <https://www.who.int/biologicals/biotherapeutics/biotherapeutic-products/en/>.
- 79 See also European Medicines Agency, Biosimilar medicines: Overview, available at: <https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview>.
- 80 See European Medicines Agency, Multidisciplinary: biosimilar, available at: <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar>.
- 81 See https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/anpassung_wlbiosimilar.html.
- 82 See https://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/.
- 83 See WHO Pilot procedure for prequalification of biotherapeutic products and similar biotherapeutic products, available at: https://www.who.int/medicines/regulation/biotherapeutic_products/en/.
- 84 The range of products included in the advanced therapy medicinal products category varies slightly between regulators, see <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1560343808209&uri=CELEX:32007R1394> and <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm>.
- 85 See National Cancer Institute, Treatment and Therapy, available at: <https://www.cancer.gov/nano/cancer-nanotechnology/treatment>.
- 86 The supply of medicines and medical technologies within health systems, as well as procurement, price regulation and the funding of health systems, are covered in Chapter IV, section A.4–9.
- 87 UNEP, 2019, p. 12.
- 88 See, for example, Heidi Ledford (2018), “CRISPR gene editing produces unwanted DNA deletions”, *Nature*, online version, 16 July 2018, available at: <https://www.nature.com/articles/d41586-018-05736-3>; Wellcome Trust Sanger Institute (2018), “Genome damage from CRISPR/Cas9 gene editing higher than thought”, 16 July 2018, available at: <https://phys.org/news/2018-07-genome-crisprcas9-gene-higher-thought.html>.
- 89 Manuel Juan Otero (Head of Section, Hospital Clinic of Barcelona), presentation to Cutting-Edge Health Technologies: Opportunities and Challenges, Joint Technical Symposium by the WHO, WIPO, WTO, Geneva, 31 October 2019, available at: https://www.wto.org/english/tratop_e/trips_e/who_wipo_wto_e.htm; WIPO, 2019b, p. 143; WIPO document SCP/30/5.
- 90 US FDA, BLA Approval Letter, 30 August 2017, available at: <https://www.fda.gov/media/106989/download>.
- 91 WO/2012/079000; Jürgens and Clarke, 2019.
- 92 See discussion on “Supporting new data infrastructure and regulatory processes” in Cornell University, INSEAD and WIPO (2019).
- 93 Directive 2001/83/EC of the European Parliament and of the Council on the Community Code Relating to Medicinal Products for Human Use, Articles 10(1) and (5); Regulation (EC) No 726/2004, Article 14(11), see also WT/TPR/S/284/Rev.2, para. 3.295.
- 94 See Frias, Z. (2013), “Data Exclusivity, Market Protection and Paediatric Rewards”, presentation to European Medicines Agency Workshop for Micro, Small and Medium Sized Enterprises, 26 April 2013, available at: https://www.ema.europa.eu/en/documents/presentation/presentation-data-exclusivity-market-protection-paediatric-rewards-zaide-frias_en.pdf.
- 95 The concept of “similarity” in this context is different from the concept of “similarity” in biotherapeutic products (see Chapter II, section A.6(d)). A system of tests is provided in guidelines to determine what constitute “similar” orphan products, see 19.9.2008 C(2008) 4077 final. European Commission, *Communication from the Commission: Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity*, available at: https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/c_2008_4077_en.pdf.
- 96 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1) provides in its Article 37 that for medicinal products designated as orphan medicinal products, if specified criteria in the paediatric Regulation are met, the ten-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 shall be extended to twelve years (two-year extension as reward for compliance with paediatric investigation plan).
- 97 See Guideline on review of the period of market exclusivity of orphan medicinal products, available at: <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:242:0008:0011:EN:PDF>.
- 98 US FDA, Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act, August 2014, available at: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf>.
- 99 42 U.S.C. §262(k)(6).
- 100 21 U.S.C. §355A(b) (1997).
- 101 See C.08.004.1(5) of the Food and Drug Regulations; Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations, available at: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html#a25>.
- 102 't Hoen et al., 2017. This is explained in Chapter IV, section C.3(a)(ii).
- 103 See: s. 5 of Malaysia 2011 Directive of Data Exclusivity; Article 91 of Chilean Law 19.996 as amended in 2012; and Article 4 of Colombian Decree 2085 of 2002; 't Hoen et al., 2017.
- 104 This is explained in Chapter IV, section C.3(a)(iii).
- 105 See Medicines Patent Pool, Frequently Asked Questions (FAQs), 1 June 2018, “6. Why do companies work with the MPP?” (“Licenses include data exclusivity waivers [...]”), available at: <https://medicinespatentpool.org/uploads/2018/04/MPP-FAQ-EN.2018.06.06.pdf>.

- 106 For a review the economics of IP in the field of medical technologies, see Chapter II, section C.
- 107 For an explanation of the research exception, see Chapter III, section D.5(a).
- 108 This effect of “multilateralizing” the scope of bilateral deals on IP is discussed in Chapter II, section B.5(b).
- 109 WIPO document SCP/12/3 Rev. 2.
- 110 Ibid.
- 111 WIPO document MTN.GNG/NG11/W/24/Rev.1.
- 112 Notable regional agreements include: the European Patent Convention (EPC), the Eurasian Patent Convention, the Harare Protocol of the African Regional Intellectual Property Organization (ARIPO), the Bangui Agreement of the African Intellectual Property Organization, the Patent Regulation of the Gulf Cooperation Council (GCC) and Decision 486 on the Common Intellectual Property Regime of the Andean Community (CAN).
- 113 See <https://www.wipo.int/treaties/en/registration/pct>.
- 114 Article 27 of the PCT.
- 115 WTO document WT/DS170.
- 116 See WIPO documents CDIP/8/INF/3, CDIP/12/INF/2REV, and member states’ comments to the study in document CDIP/12/INF/2 REV. ADD.
- 117 Information on provisional protection of published international patent applications in PCT Contracting States is available at the PCT Applicants Guide (in the table, under International Phase, General Information), at <https://www.wipo.int/pct/en/guide/index.html>.
- 118 The WHO, WIPO, WTO joint technical workshop on patentability criteria of 27 October 2015 provided participants with practical insights into how the main substantive patentability criteria are applied in practice at country level and how different definitions and interpretations can impact public health. The presentations given are available from the website of the workshop at https://www.wto.org/english/tratop_e/trips_e/trilat_workshop15_e.htm.
- 119 See Chapter IV, section C.1(b).
- 120 See https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_ii_5.htm.
- 121 See <https://www.epo.org/law-practice/legal-texts/html/guidelines/e/j.htm>.
- 122 See https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_ii_3_3_1.htm.
- 123 See <https://www.epo.org/law-practice/legal-texts/html/guidelines/e/index.htm>.
- 124 Article 27.2 reads “Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.”
- 125 For example, under Article 53 of the European Patent Convention (EPC), patents shall not be granted on inventions whose publication or exploitation would be contrary to *ordre public* or morality (paragraph (a)). Rule 29 of the Implementing Regulations to the EPC, provides further clarifications regarding the patentability of inventions relating to the human body, the use of human embryos for industrial or commercial purposes and a number of other cases where the grant of European patents is excluded.
- 126 See G.0002/06 (Use of embryos/WARF) of 25 November 2008, OJ 2009, 306, available at: <https://www.epo.org/law-practice/case-law-appeals/pdf/g060002ep1.pdf>. See also T 1374/04 (Stem cells/WARF) of 7 April 2006, OJ 2007, 313, available at: <https://www.epo.org/law-practice/case-law-appeals/recent/t041374ex1.html>.
- 127 See T 2221/10 (Culturing Stem Cells/TECHNION) of 4 February 2014, available at: <https://www.epo.org/law-practice/case-law-appeals/recent/t102221eu1.html>.
- 128 See C-34/10 (*Oliver Brüstle v. Greenpeace eV*) of 18 October 2011, available at: <http://curia.europa.eu/juris/liste.jsf?language=en&num=C-34/10>.
- 129 See C-364/13 (*International Stem Cell Corporation v. Comptroller General of Patents, Designs and Trade Marks*) of 18 December 2014, available at: <http://curia.europa.eu/juris/document/document.jsf?text=&docid=160936&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=344078>.
- 130 International Stem Cell Corporation [2016] APO 52.
- 131 The WTO TRIPS Council has reviewed the Scope of Article 27.3(b) since 1999, see WTO document IP/C/W/369/Rev.1. A 2010 WIPO Study (WIPO document SCP/15/3, Annex 3: Denis Borges Barbosa and Karin Grau-Kuntz, Exclusions from Patentable Subject Matter and Exceptions and Limitations to the Rights, Biotechnology) has looked in detail at how countries have implemented biotechnology-related provisions in patent law. Updated information on the exclusion from the patentable subject matter is available at: https://www.wipo.int/scp/en/annex_ii.html.
- 132 Certain Aspects of National/Regional Patent Laws: Revised Annex II of document SCP/12/3 Rev.2: Report on the International Patent System, available at: https://www.wipo.int/scp/en/annex_ii.html.
- 133 Information on how national and regional law defines novelty is published in WIPO document SCP/12/3 Rev.2, Report on the International Patent System, Annex II, Certain Aspects of National/Regional Patent Laws Revised, which is regularly updated and available at: https://www.wipo.int/scp/en/annex_ii.html.
- 134 WIPO SCP/22/3, paras. 13–14.
- 135 WIPO SCP/22/3, para. 23.
- 136 WIPO SCP/22/3, para. 14.
- 137 Example quoted from the PCT International Search and Preliminary Examination Guidelines, para. 13.4(d), available at: <https://www.wipo.int/export/sites/www/pct/en/texts/pdf/ispe.pdf>.
- 138 WIPO document SCP/30/4, available at: https://www.wipo.int/meetings/en/doc_details.jsp?doc_id=435831.
- 139 EPO Board of Appeal, BDP1 Phosphatase/MAX-PLANCK, T 0870/04, of 11 May 2005, available at: <https://www.epo.org/law-practice/case-law-appeals/recent/t040870eu1.html>.
- 140 See <https://www.gov.uk/government/publications/examining-patent-applications-for-biotechnological-inventions>.
- 141 KIPO, Patent Examination Guidelines, Part IX, Examination Criteria by Technology, Chapter 1, Biotechnological Inventions, 2017, available at: https://www.kipo.go.kr/en/HtmIApp?c=92006&catmenu=ek03_06_01.

- 142 WIPO document SCP/22/4, para. 11.
- 143 See <https://www.wipo.int/treaties/en/registration/budapest/>.
- 144 Information on how national and regional law defines sufficiency of disclosure is published in WIPO document SCP/12/3 Rev.2, Report on the International Patent System, Annex II, Certain Aspects of National/Regional Patent Laws, which is regularly updated and available at: https://www.wipo.int/export/sites/www/scp/en/national_laws/disclosure.pdf.
- 145 For example, according to the Guide to the Deposit of Microorganisms under the Budapest Treaty, Section D, available at: <https://www.wipo.int/treaties/en/registration/budapest/guide/index.html>, human cell cultures can be deposited with international depositary authorities in Australia, Belgium, China, France, Germany, Italy, Japan, Mexico, the Republic of Korea, the Russian Federation, Switzerland, the United Kingdom, and the United States.
- 146 WIPO document SCP/22/4, para. 8.
- 147 WIPO document SCP/13/5.
- 148 Supreme Court of Canada Decision of 8 November 2012, 2012 SCC, 60, *Teva Canada Ltd. V. Pfizer Canada Inc.*, available at: <https://scc-csc.lexum.com/scc-csc/scc-csc/en/item/12679/index.do>.
- 149 “Prior art” is, in general, all knowledge that has been made available to the public prior to the filing or priority date of a patent application under examination. Prior art is used to determine the scope of novelty and inventive step, two patentability requirements (WIPO document SCP/12/3 Rev.2, para. 210).
- 150 WIPO documents SCP/12/3 and CDIP/7/3.
- 151 See International Worksharing and Collaborative Activities for Search and Examination of Patent Applications, available at: <https://www.wipo.int/patents/en/topics/worksharing>.
- 152 By 1 July 2020, 23 International Searching and International Preliminary Examining Authorities have been appointed, see https://www.wipo.int/pct/en/access/isa_ipea_agreements.html.
- 153 ASEAN Patent Examination Co-operation Program (ASPEC); PROSUR, a system for technical co-operation between participating countries of Latin America; and the Vancouver Group, a collaboration between the IP Offices of Australia, Canada and the United Kingdom; The five IP offices (IP5: i.e. the European Patent Office (EPO), Japan Patent Office (JPO), Korean Intellectual Property Office (KIPO), National Intellectual Property Administration of the People’s Republic of China (CNIPA) and United States Patent and Trademark Office (USPTO)) have established a mechanism to improve the efficiency of the examination process for patents worldwide, see: <http://www.fiveipoffices.org/index.html>. The IP5 offices handle about 80 per cent of the world’s patent applications and 95 per cent of all work carried out under the PCT.
- 154 Examples include the SHARE pilot work-sharing initiative project between the Korean Intellectual Property Office and the United States Patent and Trademark Office and bilateral Patent Prosecution Highway agreements.
- 155 Patent grant and review procedures from an access-to-medicines perspective are addressed further in Chapter IV, section C.1–2.
- 156 See https://www.gov.za/sites/default/files/gcis_document/201808/ippolicy2018-phasei.pdf, p. 5.
- 157 For further information on opposition systems and other administrative revocation and invalidation mechanisms, see Opposition and Administrative Revocation Mechanisms, available at: https://www.wipo.int/scp/en/revocation_mechanisms/, and WIPO document SCP/18/4. Review procedures from an access-to-medicines perspective are addressed in Chapter IV, section C.2.
- 158 For further information, see Chapter IV, section C.5(a)(vi).
- 159 See WIPO documents SCP/13/3, SCP/15/3, SCP/16/3, SCP/17/3, SCP/18/3, SCP/20/3, SCP/20/4, SCP/20/5, SCP/20/6, SCP/20/7, SCP/21/3, SCP/21/4 Rev., SCP/21/5 Rev., SCP/21/6, SCP/21/7, SCP/23/3, SCP/25/3, SCP/25/3 Add., SCP/27/3, SCP/28/3, SCP/28/3 Add., available at: https://www.wipo.int/patents/en/topics/exceptions_limitations.html. Exceptions and limitations and flexibilities in the patent system from an innovation and access-to-medicines perspective are addressed in Chapter II, section B.1(b)(vii); Chapter III, section D.5(a)–(b); and Chapter IV, section C.3(a), respectively.
- 160 For detailed information, see Topics and issues: patents and health, available at: https://www.wipo.int/patents/en/topics/public_health.html.
- 161 Draft Reference Document on Exception Regarding Acts for Obtaining Regulatory Approval from Authorities (Second Draft), WIPO document SCP/28/3, available at: https://www.wipo.int/meetings/en/doc_details.jsp?doc_id=406783.
- 162 Draft Reference Document on Research Exception, Document SCP/29/3, available at: https://www.wipo.int/meetings/en/doc_details.jsp?doc_id=420102.
- 163 Draft Reference Document on the Exception Regarding Compulsory Licensing, Document SCP/30/3, available at: https://www.wipo.int/meetings/en/doc_details.jsp?doc_id=437425.
- 164 WIPO documents SCP/26/5, SCP/27/5.
- 165 See https://www.wipo.int/scp/en/annex_ii.html.
- 166 An overview of freedom-to-operate issues is provided in Chapter III, Section D.5(f).
- 167 See <https://www.wipo.int/standards/en/>.
- 168 See <https://www.wipo.int/cws/en/index.html>.
- 169 For a list of WIPO Standards, Recommendations and Guidelines, see https://www.wipo.int/standards/en/part_03_standards.html.
- 170 See https://www.wipo.int/standards/en/part_07.html.
- 171 WHA document A72.8. Improving the transparency of markets for medicines, vaccines, and other health products, available at: https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R8-en.pdf.
- 172 See https://www.wipo.int/patent_register_portal/en/index.html.
- 173 See <http://www.wipo.int/patentscope/en/>.
- 174 As at May 2020, more than 60 collections of national and regional offices, see: https://patentscope.wipo.int/search/en/help/data_coverage.jsf.
- 175 See <https://patentscope.wipo.int/search/en/clir/clir.jsf?new=true>.
- 176 See <https://patentscope.wipo.int/translate/translate.jsf?interfaceLanguage=en>.

- 177 See <https://www.wipo.int/reference/en/wipopearl>.
- 178 Gaceta de medicamentos, available at: <https://www.gob.mx/impdi/documentos/gaceta-de-medicamentos?state=published>.
- 179 See <https://www.medspal.org/>.
- 180 See <https://www.wipo.int/pat-informed/en/>.
- 181 See Pat-INFORMED Terms of Use/Disclaimer, available at: <https://www.wipo.int/patinformed/>.
- 182 See <https://www.wipo.int/ip-development/en/agenda/recommendations.html>.
- 183 See <https://www.wipo.int/ardi>.
- 184 See <https://www.wipo.int/aspi>.
- 185 See https://www.wipo.int/patentscope/en/data/developing_countries.html.
- 186 See <https://www.wipo.int/tisc>.
- 187 See <https://www.wipo.int/das>.
- 188 See <https://www.wipo.int/case>.
- 189 For more information, see WIPO Handbook on Industrial Property Information and Documentation, Glossary of Terms (available at: <https://www.wipo.int/export/sites/www/standards/en/pdf/08-01-01.pdf>); and, for example, the EPO patent family definitions (available at: <https://www.epo.org/searching-for-patents/helpful-resources/first-time-here/patent-families.html>).
- 190 See Trippe (2015); WIPO Handbook on Industrial Property Information and Documentation, available at: <https://www.wipo.int/standards/en/#handbook>; Martinez (2010).
- 191 The IPC, established by the Strasbourg Agreement Concerning the International Patent Classification, provides for a hierarchical system of language-independent symbols for the classification of patents and utility models according to the different areas of technology to which they pertain. The standardized application of IPC symbols to patent documents by experts enables language-independent patent searches and makes the IPC an indispensable search tool. For further information, see <https://www.wipo.int/classifications/ipc/en/>.
- 192 WIPO document SCP/28/5.
- 193 SureChEMBL can be accessed free of charge at <https://www.surechembl.org/search/>.
- 194 See https://www.wipo.int/patentscope/en/news/pctdb/2016/news_0008.html.
- 195 An overview of freedom-to-operate issues is provided in Chapter III, section D.5(f).
- 196 Ibid.
- 197 See WIPO Standard ST.27, available at: <https://www.wipo.int/export/sites/www/standards/en/pdf/03-27-01.pdf>.
- 198 One WIPO technical study (WIPO document CDIP/4/3 REV./ STUDY/INF/3) examined the availability of legal status data from primary sources and secondary sources, and described the challenges associated with the availability, reliability and comparability of such data. In total, 87 patent authorities contributed information to the study, which confirmed the sometimes deficient situation regarding availability of reliable legal status data and their comparability. The study includes recommendations for improvement, which would require considerable commitment from national authorities. For further information on the WIPO Project on Patent Legal Status Data, see https://www.wipo.int/patentscope/en/programs/legal_status/index.html.
- 199 The book's full title is the *Approved Drug Products with Therapeutic Equivalence Evaluations*; it is available at: <https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book>.
- 200 See <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm> and 21 U.S.C. §355. New drugs. (b)(1), available at: <https://www.law.cornell.edu/uscode/text/21/355>.
- 201 See <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.53>.
- 202 See <https://www.fda.gov/drugs/biosimilars/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or>.
- 203 See <http://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp>.
- 204 See <https://nedrug.mfds.go.kr/pbp/CCBAK01> (in Korean); "Searching in databases – Korea" at <https://www.epo.org/searching-for-patents/helpful-resources/asian/korea/search.html>; <http://koreaniplaw.blogspot.com/search/label/Green%20List>.
- 205 See, for example, the WIPO Patent Landscape reports on ritonavir, available at: <https://www.wipo.int/publications/en/details.jsp?id=230&plang=EN>, and on atazanavir, available at: <https://www.wipo.int/publications/en/details.jsp?id=265&plang=EN>.
- 206 See https://www.wipo.int/patentscope/en/programs/patent_landscapes/.
- 207 See https://www.wipo.int/edocs/pubdocs/en/patents/946/wipo_pub_946_3.pdf.
- 208 See https://www.wipo.int/edocs/pubdocs/en/wipo_pub_949_1.pdf.
- 209 See https://www.wipo.int/patentscope/en/programs/patent_landscapes/plrdb.html.
- 210 See, for example, Unitaid (2014a); Unitaid and Medicines Patent Pool (2015).
- 211 The Uruguay Round Understanding on Rules and Procedures Governing the Settlement of Disputes; see WTO documents WT/DS171/3 and WT/DS196/4.
- 212 See WTO documents WT/MIN(01)/3, para. 284 (China); WT/ACC/RUS/70, WT/MIN(11)/2, para. 1295 (the Russian Federation); WT/ACC/UKR/152, para. 433 (Ukraine).
- 213 For the text of the Agreement, see <https://www.efta.int/free-trade/free-trade-agreements/korea>.
- 214 WHO, 2018e, p. 11.
- 215 See Drugs@FDA: FDA-Approved Drugs. Colcrys, available at: <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varAppNo=022352>.
- 216 See Wasserman (2016); Drugs@FDA: FDA-Approved Drug Products. Colchicine, available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.
- 217 Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Beings, OJEU L 158/1, 27 May 2014. For more details on the EU's regime, see also the WTO Secretariat Report on the EU's Trade Policy, WTO document WT/TPR/S/357/Rev.1, paras. 3.330–3.334.

- 218 WTO Secretariat Report on the EU's Trade Policy, WTO document WT/TPR/S/317, paras.3.302–3.303. See also the discussion of the impact of open access to data on their use by competitors in third countries, in Judgment of the General Court (Second Chamber), 25 September 2018, in *Amicus Therapeutics UK Ltd and Amicus Therapeutics, Inc. v. European Medicines Agency (EMA)*, para. 84, available at: <http://curia.europa.eu/juris/document/document.jsf?text=&docid=206064&pageIndex=0&doclang=en&mode=lst&dir=&occ=first&part=1&cid=4729437>.
- 219 *Ibid.*, para. 55.
- 220 *Ibid.*, paras. 77 and 85. This decision was appealed and the Advocate General's opinion was delivered on 11 September 2019; see: <http://curia.europa.eu/juris/document/document.jsf?docid=217636&doclang=EN>.
- 221 The economics of TRIPS, A series of primers on economic questions concerning Trade Related Aspects of Intellectual Property Rights, available at: https://www.wto.org/english/tratop_e/trips_e/trips_econprimer1_e.pdf.
- 222 See www.wipo.int/madrid/en/.
- 223 The Nice Classification (NCL), established by the Nice Agreement (1957), is an international classification of goods and services applied for the registration of marks. Class 5 of the Nice Classification includes mainly pharmaceuticals and other preparations for medical or veterinary purposes. For further information, see <https://www.wipo.int/classifications/nice/en/>.
- 224 WIPO IP Statistics Database: <https://www3.wipo.int/ipstats/pmindex.htm?tab=madrid>. These figures relate to goods and services specified in Madrid System registrations by office of origin under Class 5 of the Nice Classification, see <https://www.wipo.int/classifications/nice/en/index.html>.
- 225 As at 27 December 2019, protection is possible in 122 countries, see https://www.wipo.int/madrid/en/news/2019/news_0027.html.
- 226 The term of protection is not less than seven years under Article 18 of the TRIPS Agreement and, under Articles 13(7) of the Trademark Law Treaty and 13(5) of the Singapore Treaty on the Law of Trademarks, ten years with renewal periods of ten years.
- 227 See <https://www.who.int/medicines/services/inn/en/>.
- 228 See https://www.who.int/medicines/services/inn/inn_bio/en/.
- 229 In 1993, the World Health Assembly endorsed Resolution WHA46.19, which states that trademarks should not be derived from INNs and INN stems should not be used as trademarks.
- 230 See <https://www.who.int/medicines/publications/druginformation/innlists/en/>. In addition, the INN Extranet, MedNet, grants members free access to the INN searchable database: <https://mednet-communities.net/inn>.
- 231 WIPO document SCT/40/10 Prov., para. 33.
- 232 Article 10*bis* is also incorporated by reference into the TRIPS Agreement. See Panel Reports, *Australia – Tobacco Plain Packaging*, para. 7.2631.
- 233 Other countries, such as Australia, Canada, Japan, Mexico and South Africa, have established their own reviews of proprietary names under their ministries of health.
- 234 The FDA Division of Medication Error Prevention and Analysis (DMEPA) and the EMA (Invented) Name Review Group (NRG).
- 235 See EMA, “Overview of (invented) names reviewed in September 2018 by the Name Review Group (NRG)”, available at: https://www.ema.europa.eu/en/documents/chmp-annex/overview-invented-names-reviewed-september-2018-name-review-group-nrg_en.pdf.
- 236 Some types of non-traditional marks, such as sound, colour, shape and aspects of packaging, existed and were recognized internationally as early as the 1950s. The Singapore Treaty on the Law of Trademarks and Rule 3 of its implementing Regulations, in force as of 1 November 2011, provide the technical requirements applied to those marks on the international level. For further information, see <https://www.wipo.int/treaties/en/ip/singapore/>.
- 237 EUIPO Registration No: 001909472.
- 238 *Ross Whitney Corp. v. SKF*, 207 F.2d 190 (9th Cir. 1953).
- 239 CTM Registration 002179562 by Glaxo Group Ltd.
- 240 See ss. 18–25 of the Australian Tobacco Plain Packaging Act 2011 No. 148, 2011.
- 241 Article 20 of the TRIPS Agreement reads: “The use of a trademark in the course of trade shall not be unjustifiably encumbered by special requirements, such as use with another trademark, use in a special form or use in a manner detrimental to its capability to distinguish the goods or services of one undertaking from those of other undertakings. This will not preclude a requirement prescribing the use of the trademark identifying the undertaking producing the goods or services along with, but without linking it to, the trademark distinguishing the specific goods or services in question of that undertaking.”
- 242 Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use amended by Directive 2004/27/EC Guideline on the Readability of the labelling and package leaflet of medicinal products for human use (January 2009), Guideline on the packaging information of medicinal products for human use authorised by the Community (Revision 13, February 22008), QRD recommendations on pack design and labelling for centrally authorised non-prescription human medicinal products EMA/275297/2010.
- 243 Roughead et al., 2013, p. 6.
- 244 Therapeutic Goods Administration, Australian Department of Health, Draft Therapeutic Goods Order (TGO 79).
- 245 Decreto Supremo 3 de 2010, Artículo 82, available at: http://www.ispch.cl/anamed/_normativa/decretos_supremos; see also ¿Qué es el DCI?, available at: https://www.minsal.cl/DCL_INN/.
- 246 Case No. 594/2000: Delivered 25 March 2002, by Pretoria's High Court in favour of Beecham Group plc and SmithKline Beecham Pharmaceuticals (Pty) Ltd acting as Plaintiffs, against Biotech Laboratories (Pty) Ltd acting as Respondent. The Court considered the Plaintiffs had demonstrated that the package insert qualified as a literary work according to the definition of the South African Copyright Act, and interdicted Biotech from infringing the copyright. Biotech Laboratories (Pty) Ltd appealed the Court's decision, which was dismissed with costs.
- 247 Case No. FCA 1307: Delivered 18 November 2011 by the Federal Court of Australia, not entitling to any relief in respect of copyright infringement to the Plaintiffs: Sanofi-Aventis Australia Pty Ltd, Sanofi-Aventis Deutschland GmbH and Aventisub II Incorporated, against the Respondent Apotex Pty Ltd.

- 248 United Kingdom, Intellectual Property Office, *Consultation on Copyright* (2011), p. 80, cited in Australian Law Reform Commission (2013), *Copyright and the Digital Economy*, Discussion Paper 79, Sydney; see www.alrc.gov.au/publication/copyright-and-the-digital-economy-dp-79/8-non-consumptive-use/text-and-data-mining/.
- 249 Directive (EU) 2019/790 of the European Parliament and of the Council of 17 April 2019 on copyright and related rights in the Digital Single Market and amending Directives 96/9/EC and 2001/29/EC, OJ L 130 of 17 May 2019, p. 92.
- 250 Copyright, Designs and Patents Act 1988, Section 29A.
- 251 Article 38 of the Law No. 2016-1231 of October 7, 2016, for a Digital Republic added paragraph 10 to Article L122-5 and para. 5 to Article L342-3 of the Intellectual Property Code (*Code de la propriété intellectuelle*).
- 252 Law on Copyright and Related Rights (Urheberrechtsgesetz), Section 60d.
- 253 See <https://www.who.int/hinari/en/>.
- 254 See <https://www.gov.uk/guidance/copyright-orphan-works>.
- 255 Directive 2012/28/EU of the European Parliament and of the Council of 25 October 2012 on certain permitted uses of orphan works.
- 256 EUIPO Orphan Works Database, available at: <https://euipo.europa.eu/ohimportal/en/web/observatory/orphan-works-db>.
- 257 WHA, Resolution WHA 58.28.
- 258 WIPO, *Intellectual Property and Mobile Applications* (2019) provides a comprehensive overview of the legal ecosystem and IP law considerations that are relevant for designers of mobile applications and provides an overview of relevant business issues.
- 259 See, for example, Topol (2019); Kohli and Geis (2018); Kahn and Lauerman (2018).
- 260 A glossary of Selected AI categories and terms is available at: https://www.wipo.int/export/sites/www/tech_trends/en/artificial_intelligence/docs/techtrends_ai_glossary.pdf.
- 261 WIPO, 2019b, p. 31.
- 262 *Ibid.*, p. 34.
- 263 Focus Group for “Artificial Intelligence and Health”, see <https://www.itu.int/en/ITU-T/focusgroups/ai4h/Pages/default.aspx>.
- 264 See Terms of Reference, available at: <https://www.itu.int/en/ITU-T/focusgroups/ai4h/Documents/FG-AI4H-ToR.pdf>.
- 265 See, for example, Society for Laboratory Automation and Screening (2018), “Artificial intelligence to improve drug combination design and personalized medicine”, *PhysOrg*, 25 September; National University of Singapore (2018), “Researchers develop AI platform to rapidly identify optimal personalised drug combinations for myeloma patients”, *Medical Xpress*, 13 August; Masturah Bte Mohd Abdul Rashid and Edward Kai-Hua Chow (2018), “Artificial Intelligence-driven designer drug combinations: From drug development to personalized medicine”, *SLAS Technology* 24(1): 124–125; *IMB RXN for Chemistry*, available at: <https://rxn.res.ibm.com/>.
- 266 US Patent 10,193,695 B1, granted on January 19, 2019.
- 267 WIPO, 2019b, p. 126–130.
- 268 Cutting-Edge Health Technologies: Opportunities and Challenges, Joint Technical Symposium by the WHO, WIPO and WTO, Geneva, 31 October 2019; WIPO, 2019b, p. 143; WIPO document SCP/30/5.
- 269 See OECD and EUIPO (2019); European Commission (2019b).
- 270 Article 41.5 of the TRIPS Agreement.
- 271 All documents of the WIPO Advisory Committee on Enforcement are publicly available at: <https://www.wipo.int/enforcement/en/ace/>.
- 272 WIPO document CDIP/5/4 Rev.
- 273 WTO document WT/L/540, see Chapter IV, section C.3(iii) and Annex II.
- 274 See https://www.wipo.int/treaties/en/text.jsp?file_id=305582.
- 275 WIPO, Advice on flexibilities under the TRIPS Agreement, https://www.wipo.int/ip-development/en/policy_legislative_assistance/advice_trips.html.
- 276 WIPO documents CDIP/5/4 Rev., CDIP/6/10, CDIP/7/3, CDIP/7/3 add., CDIP/8/5, CDIP/9/11, CDIP/13/10, CDIP/15/6.
- 277 See WIPO, Exceptions and limitations to patent rights, https://www.wipo.int/patents/en/topics/exceptions_limitations.html.
- 278 WIPO documents SCP/26/5 and SCP/27/5.
- 279 The report is available at: <https://apps.who.int/iris/bitstream/handle/10665/66919/a73725.pdf>.
- 280 For records of the special session, see WTO document IP/C/M/31.
- 281 WIPO document CDIP/5/4 rev., para.34.
- 282 See <http://www.wipo.int/ip-development/en/agenda/flexibilities/database.html>.
- 283 See Chapter III, section D.5(a).
- 284 See Chapter IV, section C.3(a)(iii).
- 285 See Chapter II, section B.1(g)(v).
- 286 See Chapter IV, section C.3(a)(i).
- 287 See <https://apps.who.int/iris/bitstream/handle/10665/330145/9789241517034-eng.pdf?ua=1>.
- 288 The panel in *Australia – Tobacco Plain Packaging* considered that para. 5 of the Doha Declaration confirmed its view that Articles 7 and 8 of the TRIPS Agreement provided important context for the interpretation of Article 20 of that Agreement. Panel Reports, *Australia – Tobacco Plain Packaging*, para. 7.2411.
- 289 For an explanation, see Chapter IV, section C.3(f).
- 290 Panel Reports, *Australia – Tobacco Plain Packaging*, paras. 7.2409–7.2411 (WT/DS435/R, WT/DS441/R, WT/DS458/R, WT/DS467/R). In their respective appeals, Honduras (WT/DS435/23) and the Dominican Republic (WT/DS/441/23) claimed that the panel erred in finding that para. 5 of the Doha Declaration on the TRIPS Agreement and Public Health constitutes a subsequent agreement within the meaning of Article 31(3)(a) of the Vienna Convention. At the time of writing this report, the Appellate Body has not yet issued its reports.
- 291 See Chapter IV, section C.3(a)(iii).

- 292 WTO document IP/C/73.
- 293 Ibid. For the earlier Extension Decision that was adopted by the TRIPS Council in 2002, see WTO document IP/C/25.
- 294 WTO document WT/L/971.
- 295 WTO document IP/C/64. For the earlier TRIPS Council Decision to extend the transition period in general, see WTO document IP/C/40.
- 296 Article 18(8), Law No. 31/2009 of 26/10/2009 on the Protection of Intellectual Property.
- 297 Republic of Rwanda, Ministry of Trade and Industry, Revised Policy on Intellectual Property in Rwanda, adopted in November 2018, available at: https://www.aripo.org/wp-content/uploads/2020/04/Rwanda_Revised_Policy_on_Intellectual_Property_2018.pdf.
- 298 See Chapter II, section B.1(g)(v).
- 299 See <https://wipolex.wipo.int/en/text/458363>.
- 300 The provision in the revised Bangui Agreement reads as follows: "Jusqu'à la date du 1^{er} janvier 2033 ou à la date à laquelle ils cessent d'être PMA, les Etats membres ayant le statut de PMA ne sont pas tenus d'appliquer les dispositions de l'annexe I en ce qui concerne les brevets consistant en ou se rapportant à un produit pharmaceutique et les dispositions de l'annexe VIII en ce qui concerne les informations confidentielles".
- 301 WTO document LT/UR/A/2.
- 302 WTO document WT/ACC/UKR/152, paras. 425, 433 and 512.
- 303 WTO document WT/L/508.
- 304 WTO document WT/L/846.
- 305 WTO document WT/L/508/Add.1.
- 306 WTO document WT/ACC/KHM/21, paras. 204–206 and 224.
- 307 WTO document WT/MIN(03)/SR/4.
- 308 See World Bank (2005, 2009). For the OECD publications series, Best Practice Roundtables on Competition Policy, see <http://www.oecd.org/daf/competition/roundtables.htm>. In particular, see: Designing Publicly Funded Healthcare Markets (2018); Excessive Pricing in Pharmaceuticals (2018); Generic Pharmaceuticals and Competition (2014); Competition Issues in the Distribution of Pharmaceuticals (2014); Competition in Hospital Services (2012); Generic Pharmaceuticals (2009); Competition, Patents and Innovation II (2009); Competition, Patents and Innovation (2006); Competition in the Provision of Hospital Services (2005); Enhancing Beneficial Competition in the Health Professions (2004); Competition in the Pharmaceutical Industry (2000); and, more generally, Relations Between Regulators and Competition Authorities (1998). See also UNCTAD (2015b).
- 309 See, for example, OECD (2018), Excessive prices in pharmaceutical markets, DAF/COMP(2018)12, in which the OECD Secretariat notes: "The application of competition law against high prices in the pharmaceutical sector requires a deep understanding of market dynamics and sectoral regulation, and of the various regulatory responses that may be deployed to address high prices. As such, it may be appropriate to explore various avenues for intervention, if possible in cooperation with the applicable sector regulator." See also WTO document IP/C/W/651 of 1 February 2019, a submission of South Africa to the TRIPS Council inviting WTO members to share, *inter alia*, experiences relating to excessive pricing in the pharmaceutical and medical technology sector.
- 310 See also Robert D. Anderson and William E. Kovacic, "The application of competition policy vis-à-vis intellectual property rights: the evolution of thought underlying policy change," in Anderson, Pires de Carvalho and Taubman (eds.), 2020.
- 311 See, for example, contributions prepared by Brazil and Peru to the WIPO Advisory Committee on Enforcement, WIPO/ACE/13/5 of 21 August 2018, and discussions on Promoting Public Health through Competition Law and Policy, held at TRIPS Council meetings on 19 November 2018 and 13 February 2019, WTO documents IP/C/M/90 and Add.1, and IP/C/M/91 and Add.1.
- 312 See Robert D. Anderson, Anna Caroline Müller and Antony Taubman, "The WTO TRIPS Agreement as a platform for application of competition policy to the contemporary knowledge economy," in Anderson, Pires de Carvalho and Taubman (eds.), 2020.
- 313 "Exclusive grant-back conditions" refer to any obligation on a licensee to grant an exclusive licence to the licensor in respect of its own improvements to, or its own new applications of, the licensed technology. "Conditions preventing challenges to validity" are those that impose an obligation on a licensee not to challenge the validity of IPRs held by the licensor. "Coercive package licensing" refers to an obligation on a licensee to accept a licence on several different technologies when the licensee's interest is limited to only part of these technologies.
- 314 In that regard, several national or regional competition agencies have published guidelines providing solid foundation for their analysis of IP and antitrust cases: US Department of Justice/Federal Trade Commission, Antitrust Guidelines for the Licensing of Intellectual Property (2017); European Commission, Guidelines on the application of Article 81 of the EC Treaty to technology transfer agreements, EC document 2004/C 101/02; for Canada, see Enforcement Guidelines (2016), <http://www.competitionbureau.gc.ca/eic/site/cb-bc.nsf/eng/04031.html>; an unofficial translation of Japanese Fair Trade Commission, Use of Intellectual Property under the Antimonopoly Act (2007, 2016) is available at: <https://www.jftc.go.jp/en/pressreleases/yearly-2016/January/160121.html>. For a comparative analysis including a wide range of economies, see Robert D. Anderson, Jianning Chen, Anna Caroline Müller, Daria Novozhilkina, Philippe Pelletier, Antonella Salgueiro, et al., "Competition agency guidelines and policy initiatives regarding intellectual property: a cross-jurisdictional analysis of developed and emerging economies," in Anderson, Pires de Carvalho and Taubman (eds.), 2020.
- 315 Judgment of the State Council of 12 February 2014, No. 693, available from the webpage of the Administrative Justice (https://www.giustizia-amministrativa.it/portale/pages/istituzionale/visualizza/?nodeRef=&schema=cds&nrg=201209181&nomeFile=201400693_11.html&subDir=Provvedimenti); Hadrian Simonetti, Appeal, Non-application, Judicial Review on the Acts of the Public Administration for Antitrust Purposes (Notes to the Consiglio di Stato – Italian Supreme Administrative Court – Judgment, sec. vi, no. 693/2014, 2014, available at: <http://iar.agcm.it/article/view/11060>; Giovanni Galimberti and Evelina Marchesoni, "Italy: the abuse of a dominant position by Pfizer in Xalatan case", *Bird&Bird*, May 2014, <https://www.twobirds.com/en/news/articles/2014/global/life-sciences-may/italy-the-abuse-of-a-dominant-position-by-pfizer-in-xalatan-case>.

- 316 Recent mergers between pharmaceutical companies have been reported as resulting in reduced R&D activity in the sector. For a recent overview of EU case law, see Catherine Derenne and Bertold Bar-Bouyssi re (2019), “Pharma and mergers: an overview of EU and national case law”, *e-Competitions Bulletin Pharma & Mergers*, 14 February: 89174; and, for example, LaMattina, 2011. Derenne and Bouyssi re report on “close to 100 pharmaceutical mergers from all over the world since [...] 2004”.
- 317 European Commission, 2019a.
- 318 Article 10*bis* is also incorporated by reference into the TRIPS Agreement, see Panel Reports, *Australia – Tobacco Plain Packaging*, para. 7.2631.
- 319 See Anderson, M ller and Taubman, “The WTO TRIPS Agreement as a platform for application of competition policy to the contemporary knowledge economy,” in Anderson, Pires de Carvalho and Taubman (eds.), 2020.
- 320 Panel Reports, *Australia – Tobacco Plain Packaging*, para. 7.2680. The panel found that Australia’s tobacco plain packaging (TPP) measures themselves did not constitute an act of unfair competition. It further found that the complainants had not demonstrated that the TPP measures compel market actors to engage in acts of unfair competition of such a nature as to create confusion, or amounting to misleading indications or allegations, or otherwise to engage in such acts of unfair competition against which Australia was bound to assure effective protection, see section 7.3.6 of the reports.
- 321 For more details on tariff data, see Chapter IV, section D.1.
- 322 See www.haiweb.org/medicineprices.
- 323 See the report of the July 2018 SPS Committee meeting in WTO document G/SPS/R/92/Rev.1.
- 324 See the report of the November 2018 SPS Committee meeting in WTO document G/SPS/R/93, paras. 3.38–3.44.
- 325 *Ibid.*, paras. 3.45–3.47.
- 326 These sectoral descriptions are found in the Services Sectoral Classification List (WTO document MTN.GNS/W/120), which WTO members have generally used for scheduling their GATS commitments. Sectors (i) to (iii) above are found in the section on “Health-Related and Social Services” sector, and sectors (iv) and (v) under “Professional Services”.
- 327 If one takes into account horizontal limitations listed in some schedules (i.e. limitations applying across all scheduled sectors), partial commitments dominate.
- 328 Robert D. Anderson, Anna Caroline M ller and Philippe Pelletier (2016), “Regional Trade Agreements and Procurement Rules: Facilitators or Hindrances?” A version was published as Robert Schuman Centre for Advanced Studies (RSCAS) Research Paper No. RSCAS 2015/81, December 2015.
- 329 For the full content of GPA parties’ schedules (Appendix 1), including the relevant thresholds, see https://www.wto.org/english/tratop_e/gproc_e/gp_gpa_e.htm.
- 330 Before leaving the EU, the UK participated in the GPA as an EU member. On 27 February 2019, parties to the GPA adopted a decision inviting the United Kingdom to become party to the GPA, in its own right, after leaving the EU.
- 331 Including through their agent HealthAlliance Limited, see Note 1 to Annex 2 of New Zealand.
- 332 Additional statistical information is available at: https://www.wto.org/english/tratop_e/gproc_e/gp_gpa_e.htm.
- 333 It should be noted that the following analysis focuses only on the market access opportunities available under the GPA. It does not consider barriers to market access that could arise outside the scope of the GPA (e.g. IPRs).
- 334 WTO document GPA/108/Add.9. It is recalled that the GPA applies to the entities, goods and services that are specified in each individual party’s schedules.
- 335 WTO document GPA/123/Add.7.
- 336 WTO document GPA/108/Add.4. The reported value was expressed as Special Drawing Rights (SDRs) and has been converted to US dollars. The estimate may be affected by variations in exchange rates and related problems of conversion.
- 337 The following WTO disputes have addressed, among others, health-related measures: *EC – Hormones* (DS26 and DS48); *Canada – Pharmaceutical Patents* (DS114); *EC – Asbestos* (DS135); *EC – Approval and Marketing of Biotech Products* (DS291, DS292 and DS293); *Brazil – Retreaded Tyres* (DS332); *US – Continued Suspension* (DS320); *Canada – Continued Suspension* (DS321); *US – Clove Cigarettes* (DS406); and *Australia – Tobacco Plain Packaging* (DS435, DS441, DS458 and DS467).
- 338 See Appellate Body Report, *EC – Asbestos*, para. 172.
- 339 See Appellate Body Report, *Brazil – Retreaded Tyres*, para. 144. See also Panel Report, *US – Clove Cigarettes*, para. 7.347.
- 340 Panel Report, *Canada – Pharmaceutical Patents*, WTO document WT/DS114/R, para. 7.50.
- 341 *Ibid.*, para. 7.38.
- 342 Panel Reports, *Australia – Tobacco Plain Packaging* (DS435, 441, 458 and 467). At its meeting on 27 August 2018, the DSB adopted the Panel Reports in WT/DS458/R and WT/DS467/R, complaints by Cuba and Indonesia, respectively. Honduras appealed certain findings by the same Panel in its report WT/DS435/R on 19 July 2018, and the Dominican Republic appealed certain findings in report WT/DS441/R on 23 August 2018 (see documents WT/DS435/23 and WT/DS441/23, respectively). At the time of writing this report, the Appellate Body has not yet issued its reports.
- 343 The TPP measures consist of two sets of requirements, namely, format requirements that standardize the presentation of tobacco products and their retail packaging, and trademark requirements that, *inter alia*, permit the use of word marks in standard lettering on retail packaging, but prohibit the use of stylized word marks, composite marks and figurative marks. The TPP measures operate in conjunction with other legislative requirements that were not challenged in these disputes, including graphic health warnings.
- 344 Panel Reports, *Australia – Tobacco Plain Packaging*, paras. 7.2604–7.2605. The WHO Framework Convention on Tobacco Control (FCTC) is available at: [https://apps.who.int/iris/bitstream/handle/10665/42811/9241591013.pdf;jsessionid=D04BBF65D9B0131FE2E7D2B7465326BD?sequence=](https://apps.who.int/iris/bitstream/handle/10665/42811/9241591013.pdf;jsessionid=D04BBF65D9B0131FE2E7D2B7465326BD?sequence=;); the Guidelines for implementation of Article 11 of the FCTC are available at: https://www.who.int/fctc/guidelines/article_11.pdf?ua=1; and the Guidelines for implementation of Article 13 of the FCTC are available at: https://www.who.int/fctc/guidelines/article_13.pdf?ua=1.

- 345 Panel Reports, *Australia – Tobacco Plain Packaging*, para. 7.1732.
- 346 *Ibid.*, para. 7.397.
- 347 Article 6quinquies of the Paris Convention (1967), Articles 15.4, 16.1 and 16.3 of the TRIPS Agreement, Article 10bis(1), 10bis(3)(1) and 10bis(3)(3) of the Paris Convention (1967), Articles 22.2(b) and 24.3 of the TRIPS Agreement. Cuba also invoked Article IX:4 of the GATT 1994.
- 348 Panel Reports, *Australia – Tobacco Plain Packaging*, para. 7.1773, referring to Panel Report, *US – Section 110(5) Copyright Act*, para. 6.66.
- 349 See Figures 4 and 5 in United States Government Accountability Office (2017).
- 350 National Science Board, “Science and Engineering Indicators 2018”, Chapter 4, Table 4-10: Sales and R&D intensity for companies that performed or funded R&D, by selected industry: 2015, available at: <https://www.nsf.gov/statistics/2018/nsb20181/report/sections/research-and-development-u-s-trends-and-international-comparisons/u-s-business-r-d>.
- 351 *Ibid.*, Table 4-9: Funds spent for business R&D performed in the United States, by source of funds and selected industry: 2015.
- 352 The “mailbox” obligation is a transitional one that applies to WTO members which do not yet provide product patent protection for pharmaceuticals and for agricultural chemicals. Since 1 January 1995, when the WTO agreements entered into force, these countries have to establish a means by which applications of patents for these products can be filed. (An additional requirement is that they must also put in place a system for granting “exclusive marketing rights” for the products whose patent applications have been filed.) See “Mailbox” at https://www.wto.org/english/thewto_e/glossary_e/glossary_e.htm.
- 353 For examples of these kinds of measures, see Chapter IV, section A.4(b).
- 354 See https://www.wto.org/english/res_e/reser_e/ersd201905_e.htm.
- 355 Innovative pharmaceuticals are defined in this staff working paper as those that are first-in-class because each presents a new pathway for treating a disease and those that are advance-in-class, i.e. that are not first-in-class but receive a priority review designation from USFDA, which is reserved for medicines that potentially offer major advances in treatment.
- 356 For other examples on the national implementation of test data, see Chapter II, section B.1(c)(i).
- 357 See Chapter III, section C.6.
- 358 WHO, “Traditional, complementary and integrative medicine: About us”, <https://www.who.int/traditional-complementary-integrative-medicine/about/en/>.
- 359 *Ibid.*
- 360 For a definition of herbal medicines, see WHO (1996), *WHO Expert Committee on Specifications for Pharmaceutical Preparations: Thirty-fourth Report*, WHO Technical Report Series, No. 863, Annex 11: Guidelines for the Assessment of Herbal Medicines, available at: <http://digicollection.org/hss/en/d/Js5516e/21.html>.
- 361 Data from the Chinese Chamber of Commerce for Import & Export of Medicines & Health Products, available at: <http://en.cccmhpie.org.cn/>.
- 362 WHO (2013), *WHO Traditional Medicine Strategy 2014–2023*, Geneva: WHO, p. 11.
- 363 WHA, Resolution WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property.
- 364 See also WIPO Glossary, Key terms related to intellectual property and genetic resources, traditional knowledge and traditional cultural expressions, Traditional Knowledge, available at: <https://www.wipo.int/tk/en/resources/glossary.html#49>.
- 365 UN document A/RES/61/295.
- 366 WHO Traditional, complementary and integrative medicine: Activities, <https://www.who.int/traditional-complementary-integrative-medicine/activities/en/>.
- 367 Notifications containing the words “traditional medicine”, “herbal medicine”, “traditional herbal medicinal products” and “traditional medicinal products” are included, see TBT Information Management System: <http://tbtims.wto.org/en/Notifications/Search>.
- 368 From 1 January 2009 until 31 December 2013, WTO members notified 12 measures; from 1 January 2014 until 31 December 2018, WTO members notified 29 measures.
- 369 Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.
- 370 G/TBT/M/51, at paras. 3–9. This STC was subsequently raised in the TBT Committee in 2010 in G/TBT/M/52, 2 at paras. 285–302, in 2011 in G/TBT/M/53, paras. 251–265, G/TBT/M/54, paras. 211–217, G/TBT/M/55, paras. 104–105, in 2012 in G/TBT/M/56, paras. 89–92, G/TBT/M/57, paras. 115–118, G/TBT/M/58, paras. 2.79–2.80 and in 2019 in G/TBT/M/59, paras. 2.109–2.110.
- 371 G/TBT/M/51, at para. 8.
- 372 See Tripathi et al. (2015).
- 373 Convention on Biological Diversity. History of the Convention, <https://www.cbd.int/history/>; Convention on Biological Diversity. The Nagoya Protocol on Access and Benefit-sharing, <https://www.cbd.int/abs/>.
- 374 For the political debate on ABS aspects regarding the sharing of viruses, see Chapter III, section E.
- 375 See <http://www.tkdil.res.in/tkdil/langdefault/common/Home.asp?GL=Eng>.
- 376 For more information on prior art, see Chapter II, section B.1(b)(iv) and WIPO document SCP/12/3 Rev.2, para. 210.
- 377 See WTO document IP/C/W/370/Rev.1 for the latest discussion in the TRIPS Council; see also WTO document WTO/IP/C/M/90/Add.1.
- 378 Information about databases and registries of traditional knowledge and genetic resources that are maintained and managed by WIPO member states and other organizations, as well as about other repositories of traditional knowledge and genetic resources, is available at: https://www.wipo.int/tk/en/resources/db_registry.html.

- 379 WHO (n.d.), “Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications: Study by the Secretariat”, available at: https://www.who.int/influenza/Nagoya_Full_Study_English.pdf.
- 380 See documents CBD/COP/DEC/XIII/16 of 16 December 2016, available at: <https://www.cbd.int/doc/decisions/cop-13/cop-13-dec-16-en.pdf>, and CBD/NP/MOP/DEC/2/14 of 16 December 2016, available at: <https://www.cbd.int/doc/decisions/np-mop-02/np-mop-02-dec-14-en.pdf>.
- 381 See footnote 71 in WHO, 2018a; see also WHO, 2018c.
- 382 See “Comments by the World Health Organization on the draft Fact-Finding and Scoping Study ‘The Emergence and Growth of Digital Sequence Information in Research and Development: Implications for the Conservation and Sustainable Use of Biodiversity, and Fair and Equitable Benefit Sharing’, dated 9 November 2017”, Geneva: WHO, available at: <https://www.who.int/influenza/whocommentscbdds.pdf>.
- 383 See WTO documents IP/C/W/474 and addenda, TN/C/W/52 and addenda, IP/C/M/92/Add.1, and IP/C/M/88/Add.1.
- 384 See WTO documents IP/C/W/368/Rev.1 and Corr.1, IP/C/W/370/Rev.1. Discussions are ongoing in the TRIPS Council. They are regularly reported in the minutes of the meetings. For the latest reports, see WTO document IP/C/M/92/Add.1.
- 385 See <https://www.wipo.int/tk/en/igc/>.
- 386 Ibid.
- 387 WTO documents TN/C/W/59, IP/C/M/92/Add.1, IP/C/M/88/Add.1.
- 388 The latest version of the negotiating text is available at: <https://www.wipo.int/tk/en/igc/index.html>.

III. Medical technologies: the innovation dimension

Chapter II has described the main elements of the policy framework for innovation and access. This chapter considers how this policy framework applies to innovation in medical technologies. It reviews the factors that have spurred innovation in medical technologies in the past, identifies how current models of R&D are evolving, and charts the role of established and new participants in the innovation process, including in the context of neglected diseases, emerging pathogens with pandemic potential and antibacterial treatments. It also covers the role of IP, particularly patents, in the R&D system.

The chapter reflects the fact that, over the past decade, health policy-makers have paid greater attention to the innovation dimension, considering in particular:

- The kinds of collaborative structures, incentive mechanisms, sources of funding and informatics tools that are required in order to build more effective and more broadly based and inclusive innovation processes, and recognizing the changing innovation and development models in the private sector
- How to ensure that medical research activities focus increasingly on areas neglected so far.

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A. Historical pattern of medical R&D

Key points

- R&D in the pharmaceutical sector evolved in typically large, privately owned companies where both R&D and marketing were carried out in-house. Initially, production was widely licensed out by originator companies. Later, however, marketing and the distribution of new medicines were exclusively taken care of by the originator companies.
- Global R&D expenditures by pharmaceutical companies and the number of patent applications have increased substantially between 2004 and 2019.
- Concerns have been raised that the development of new drugs is lagging behind, and about the limited improvement in the therapeutic benefit offered by new medicines over existing treatments.
- While a decline in R&D pharmaceutical productivity has been observed, there are indicators signalling a possible reversal.

1. Innovation for medical technologies in context

Innovation in medical technologies is distinct from innovation in general. It is characterized by several distinguishing features:

- The high costs of R&D and the concomitant high risk of failure
- The important role of public-sector input, such as in basic research funding and making infrastructure available, and in terms of influencing the market for finished products
- The inherent ethical component of medical research, and the potential negative impact on public health of closely held or overly restrictive management of technology and IP
- The need for a rigorous regulatory framework to assess medical technologies in terms of their quality, safety and efficacy.

It is important to understand historical trends in medical R&D and the development of the modern pharmaceutical industry, which provide the context for the dynamics of current developments and the challenges facing the existing innovation system and overall R&D landscape.

2. From early discoveries to “wonder drugs”

The modern pharmaceutical industry grew out of the European chemical industry in Germany and Switzerland, based on a growing understanding of organic chemistry and dyestuffs. France, the United Kingdom and the United States had joined this industry by the beginning of the 20th century, at which point there were still few

medicines available to treat basic infectious diseases. In the early 20th century, there was widespread opposition in academic circles to the patenting of innovation.¹ While there are cases in which scientific discoveries and production methods have been patented, there are many other cases in which they have not.² Prior to the 1930s, the pharmaceutical industry did not invest in R&D to any great extent. However, the discoveries that certain chemicals and microorganisms could be used to treat infections led to the development of a range of products that served as antibacterial agents. Manufacture at industrial scale proved to be another challenge. For example, it was only in 1939, ten years after Alexander Fleming discovered penicillin, that mass manufacture of penicillin got under way in facilities of the US Department of Agriculture. Subsequently, private pharmaceutical companies were enlisted to develop and market the medicine. Penicillin and sulphanilamide formed the basis of a generation of new “wonder drugs”. They were developed in collaboration with teams of researchers from both not-for-profit organizations and private enterprise. IP has played varying roles in the history of different antibiotics.

By the 1960s, more than 50 new patents had been filed in relation to sulfa drugs. These patents were primarily process patents as many countries at the time did not allow product patents on pharmaceuticals. Numerous process patents were taken out on penicillin. It is argued that these patents were not key to the development of improved processes. No one company was able to gain market control, as most fundamental process patents were owned by the US Department of Agriculture, which had a policy of licensing the patents to any company seeking to manufacture penicillin (Quinn, 2013). In the absence of patents, companies developing improved manufacturing processes entered arrangements to mutually share information and samples (Quinn, 2013). The incentivizing role of IP is more obvious in the development of later antibiotics, which involved the search for new exclusive

molecules.³ Synthetic penicillin reflects the changed role of patents in the antibiotics industry, with patents for synthetic penicillin being filed in the United Kingdom by the Beecham Group in 1960. The Beecham Group has stated that the original decision to expand drug research into semi-synthetic penicillin would not have taken place without the incentives of patent protection (Taylor and Silberston, 1973). While patenting by pharmaceutical companies increased soon after the flourishing of antibiotic manufacture, it is difficult to say whether there was a causal link between antibiotics innovation and IP.⁴

3. Growth and evolution of the pharmaceutical industry

The turmoil of war and migration, among other factors, led to the shift of leadership in the pharmaceutical industry from Europe, particularly Germany, to the United States, although trans-Atlantic rivalries continued to be sharp. The mid-1940s saw the rise of the United States-based pharmaceutical industry, and several factors influenced this, including the introduction of regulation on prescription drugs and changes in how patent law was applied.⁵ The interplay between these two specific factors helped develop the modern, vertically integrated pharmaceutical firm that undertakes both in-house R&D and marketing. From 1950 to 1970, the ratio of R&D investments to sales revenues in the US pharmaceutical industry more than doubled, while the ratio of advertising expenses to sales revenues was even higher. Most of the marketing expenditure comprised the cost of informing and influencing doctors on prescription medicines. The period from the late 1940s onwards saw an increase in the grant of both product and process patents for pharmaceuticals.⁶ During the period 1950–1970, the pharmaceutical industry returned consistently higher levels of profit than most manufacturing companies at that time. The period from the mid-1940s to 1970 saw a boom in innovations based on organic and natural products chemistry, which, in turn, led to the isolation and synthesis of vitamins, corticosteroids, hormones and antibacterial agents. The following years were marked by the industry moving from chemistry-based R&D and manufacturing to pharmacology and life-sciences-based activities. Also during this period, most countries increased the stringency of their new drug approval processes, following the 1962 Kefauver–Harris Amendments to the US Federal Food, Drug, and Cosmetic Act, and a phased system for developing new medicines was established – the so-called “Phase I–IV” system for clinical trials (see Chapter II, section A.6(b)). Prescription drugs came to dominate pharmaceutical sales and profits – for example, in the United States, prescription drugs comprised only 32 per cent of consumer expenditures in 1929, but by 1969, this share had increased to 83 per cent (Malerba and Orsenigo, 2015).

Tight control of R&D and marketing was necessary because these companies derived most of their revenues

from a very small number of successful products (Comanor, 1986; Malerba and Orsenigo, 2015). The basis for competition among these companies changed from price factors to non-price factors, such as research and advertising outlays and outputs. This model helped to incentivize innovation – the US R&D-based pharmaceutical industry moved from an average of 20 new products per year in the 1940s to an average of 50 new products per year in the 1950s.

4. From non-exclusive licensing to restricted production

An early example of non-exclusive licensing can be seen in the story of insulin (see Box 3.1).

In the early years of the US pharmaceutical industry – until around 1950 – there was widespread licensing of patented medicines for production by other pharmaceutical companies, which had a salubrious effect on price over time, even during the patent term. For example, streptomycin, for which a patent was granted in the United States in 1948 to scientists at Rutgers University, was licensed on an unrestricted basis at a royalty rate of 2.5 per cent. In the specific case of penicillin, the United States price fell from US\$ 4,000 per pound in 1945 to just US\$ 282 per pound in 1950 (Temin, 1979).

However, in the period up to 1960, a key development in the United States was that innovative companies began to exclusively manufacture products themselves, without licensing them to others. This enabled them to restrict output and generate larger profits. A practice of licensing with high royalty payments could potentially have delivered the same profits to these innovator companies, but such royalty payment rates would have had to be very high in the face of inelastic demand (i.e. where consumer demand for a product does not change appreciably in response to a small increase in price). By one estimate, when demand is inelastic, the royalty rate required to yield a return equivalent to an exclusive, single-supply model would be 80 per cent (Temin, 1979). As an early example of exclusive production, the wholesale price of tetracycline in 1948, before the introduction of generic versions of this medicine in the United States, was US\$ 30.60 per 100 capsules, whereas the production cost for the same quantity was just US \$ 3.00, thus generating a profit rate of 920 per cent. Such high royalty rates were commercially unprecedented, as royalty rates at that time were typically just 2.5 per cent. The 2.5 per cent rate – the royalty rate at which streptomycin was licensed – would have applied in a US Federal Trade Commission (FTC) decision relating to a compulsory licence for tetracycline. This FTC decision did not subsequently enter into force for other reasons (Scherer and Watal, 2002), while in the United Kingdom, a “Crown use” licence – which nowadays would be classed as a type of government-use licence – was granted to the National Health Service to import generic tetracycline.⁷

Box 3.1: IP and licensing in the discovery of insulin

In 1922, researchers at the University of Toronto developed insulin as the substance that is life saving in patients with type 1 diabetes. At the time, the code of ethics of the University required health goods to be free from gain. After extensive deliberation and consideration of precedents, such as a patent on adrenaline (see section D.4(a)), the University decided to apply for patent protection on insulin and to commercialize the medicine in the interests of the medical profession. To that effect, the University set up an Insulin Committee to develop appropriate licensing terms and to manage relations with industry in conformity with the ethical code of doctors and in patients' interests. This choice was motivated by the intention to prevent a commercial monopoly, regulate the conditions of marketing and control the quality of industrial production. An exclusive licence was agreed with a manufacturer for a limited period of one year. The manufacturer improved the production processes and filed its own patent application on the improvement. This led to discussions between the manufacturer and the University about patent dependency and ownership. While the licence contained a grant-back clause for this situation, that clause did not concern the United States. The discussions were resolved through an agreement. The manufacturer ceded its patent to the University and gained legal certainty for continued production using the improved process without costly litigation. The University kept control over the insulin patents in the United States. In addition, the parties agreed on a patent pool. Any further licensees of the University's insulin patents were required to place any further patents on insulin into a common patent pool administered by the University. The University's (non-exclusive) licence agreements enabled the University to implement the principles of its insulin licensing policy and to establish control over the pricing and advertising of the end product. The manufacturer was able to maintain a strong advantage over competitors due to its early investments in process development and manufacture (Cassier and Sinding, 2008).

These conditions of exclusivity and product differentiation extended beyond antibiotics to all medicines obtained through R&D. For instance, the first generation of steroids was widely licensed, while the second generation of synthetic steroids was exclusively produced by patent-owning companies (Temin, 1979).

As early as 1959, the report of the US Senate Subcommittee on Antitrust and Monopoly (Kefauver Committee) accused the industry of price gouging through duplicative research and insignificant molecular modifications to create newly patentable but therapeutically equivalent products. Sceptical views expressed in the current global debate about the benefits of competition, and the appropriate level of returns for innovation in the context of biomedical R&D, echo some of these early criticisms. Senator Kefauver pointed to the huge mark-ups between raw material costs and the final price of a drug; his congressional hearings also exposed a variety of unsavoury marketing practices. Senator Kefauver proposed mandatory cross-licensing of drug patents, pricing limits and marketing restrictions, in order to lower drug prices. These proposals did not ultimately make it into the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act of 1962, which gave the FDA the authority to postpone or reject new drug applications. A number of European countries followed with similar legislation conceived to ensure the quality and safety of medicines.⁸

5. Trends in R&D

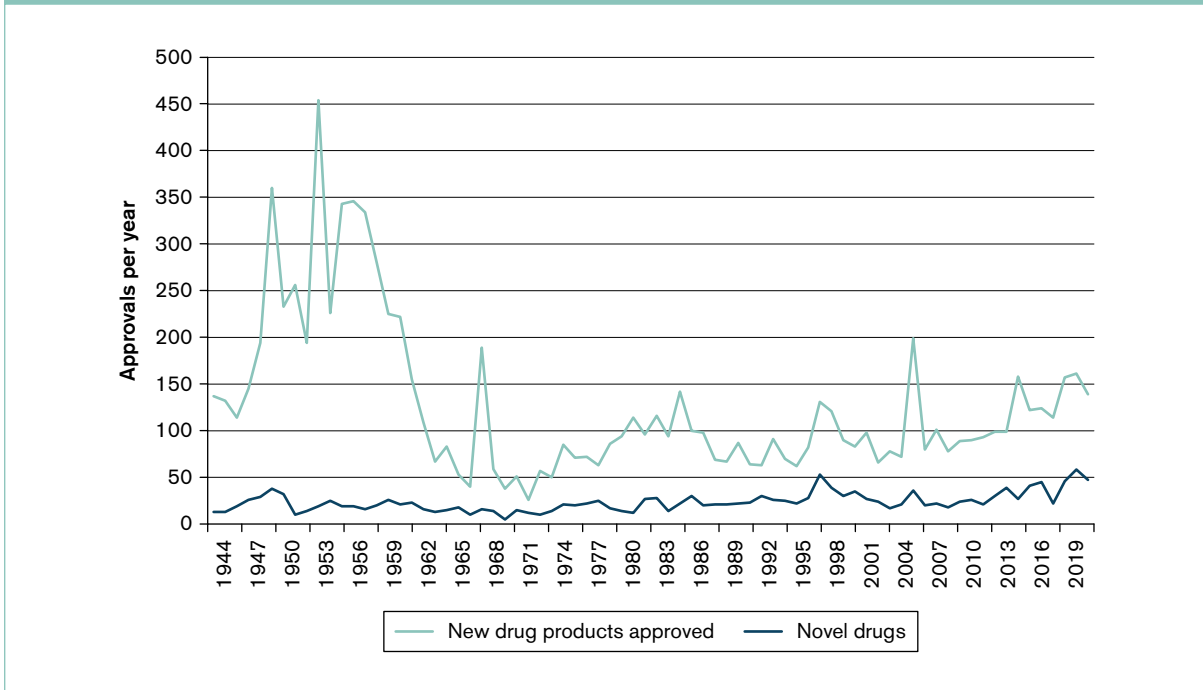
This section describes trends in R&D by looking at a number of indicators, namely, patent activity, R&D

investments and the number of medicines approved each year, as well as the characteristics of these medicines.

Trends in approvals of medicines by the FDA from 1943 to 2019 are shown in Figure 3.1. It displays trends in both approvals of new drug products, which include all approved medicines, including new dosage forms and new indications for medicines that have previously been approved, and approvals of novel drugs, that is, medicines that had never previously been approved in any form. Levels of approvals of new drug products were very high until around 1960, which likely reflects the fact that a wide range of products that did not need approval prior to the establishment of the Federal Food, Drug, and Cosmetic Act in 1938 now needed approval to remain on the market. From around 1960, the number of new products approved per year has varied substantially from year to year but has shown an overall upward trend to 2019. Compared with new product approvals, a far smaller number of approvals concern novel drugs. The number of novel drug approvals has risen slowly but steadily, from lows of 5–23 in the 1960s to a record 59 in 2018.

Figure 3.2 illustrates the parallel trends in R&D expenditures by originator pharmaceutical companies, PCT publication numbers and novel drug approvals. Global R&D expenditures by originator pharmaceutical companies have increased substantially, from an estimated US\$ 118 billion in 2004 to US\$ 182 billion in 2019. When compared with sales, this increase is less pronounced, with R&D expenditures as a proportion of sales rising from 17 per cent in 1995 to 20 per cent in 2018 for a group of large pharmaceutical companies in the United States (see Figure 3.2). Over the same period, yearly PCT patent publications for pharmaceuticals rose

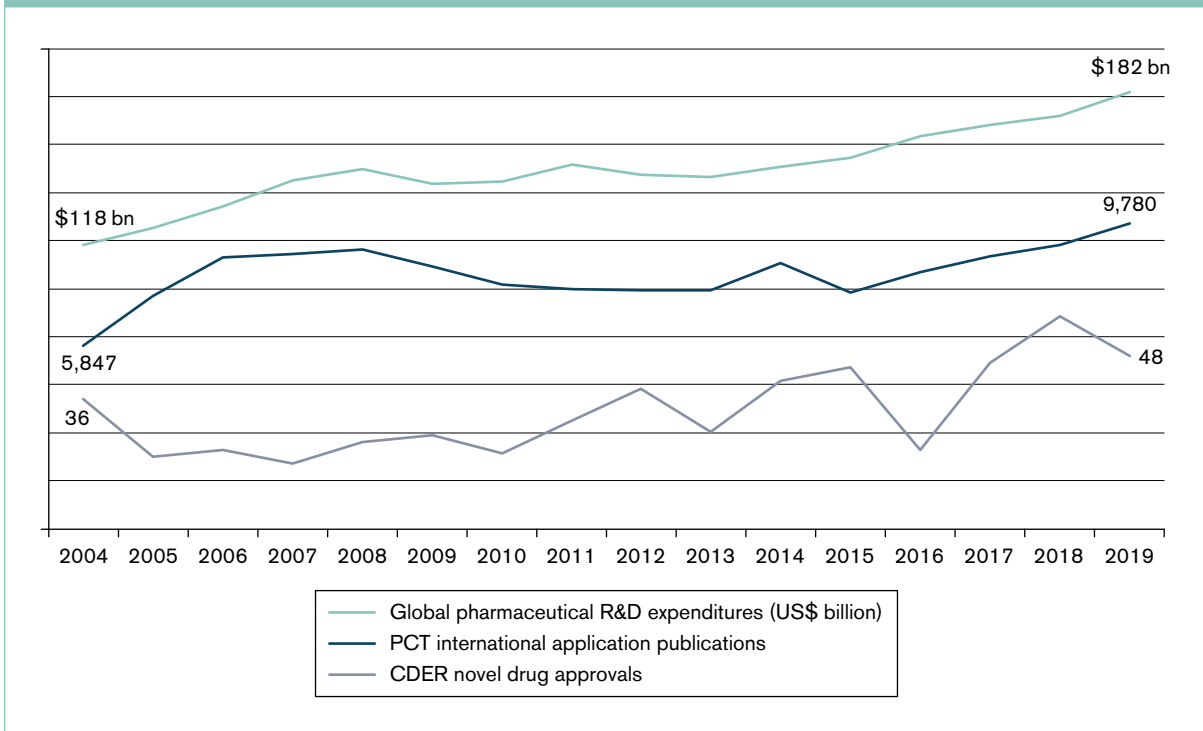
Figure 3.1: Approvals of medicines by the US Food & Drug Administration, 1944–2019



Sources: United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER).

Note: “New drug products” means all products approved under new drug applications and biologics licence applications. “Novel drugs” means new molecular entities approved under new drug applications and new therapeutic biologics approved under biologics licence applications. Data are from the US Food and Drug Administration.⁹ Local maxima at years 1996 and 2004 are in part due to changes in the FDA approval process, rather than true increases.¹⁰

Figure 3.2: Global R&D expenditures, PCT international application publications on pharmaceuticals and novel drug approvals in the United States, 2004–2019¹¹



Sources: EvaluatePharma estimates, in *World Preview* (2013, 2015, 2017, 2019); United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER); WIPO Statistics Database.

from 65,000 to 95,000, and the number of novel drugs approved by the FDA CDER rose from 36 in 2004 to 48 in 2019. A rising number of novel drugs are orphan drugs (i.e. medicines that treat rare diseases (see section B.6)), increasing from 20 per cent in 1999 to 44 per cent in 2019 (see Figure 3.3).

At the same time, concerns have been raised that the development of new drugs is lagging behind, along with concerns about the level of additional therapeutic benefit offered by new medicines over existing treatments.¹² Particular concern has been drawn to antimicrobials, where no new classes of antibiotics have been approved in the last three decades (see section C.2).

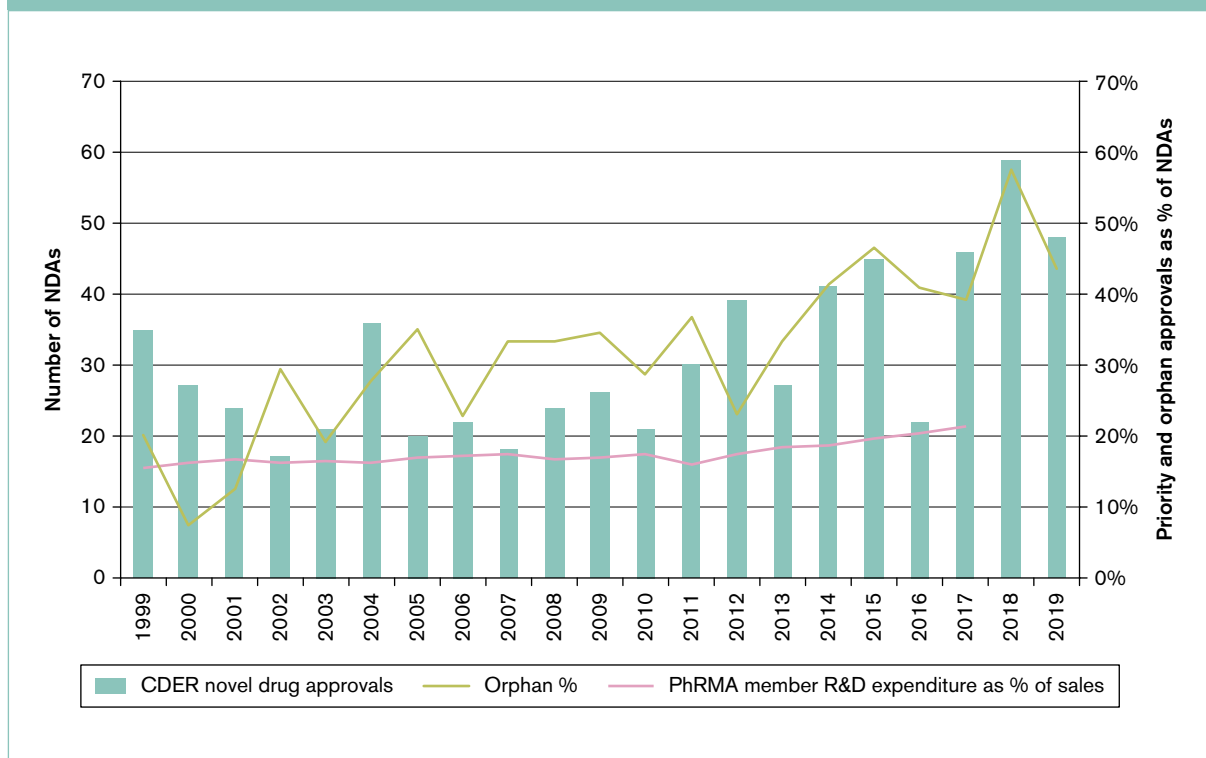
In the same vein, concerns have been expressed that the rate of innovation may be declining, though there is no consensus explanation for these trends. One explanation may be that “the low-hanging fruit have been picked”, while another may be that it is due to problems with the incentive structure in the biomedical innovation system (Bloom et al., 2017). It has also been observed that the adoption of new health technologies has become an increasingly complex exercise, due to the different environments involved, such as regulatory approval processes and multiple interactions among various stakeholders, including governments and regulatory authorities and private and public research actors, such as companies and universities (Cornell University, INSEAD and WIPO, 2019).

The economic literature indeed confirms a decline in R&D pharmaceutical productivity – defined in the literature as the ratio of R&D outputs measured by the rate of introduction of new molecular entities (NMEs) to actual R&D inputs, and thus pharmaceutical R&D expenditures (Griliches, 1994; Pammolli et al., 2011). One explanation could be that pharmaceutical R&D inputs and outputs are hard to measure (Pammolli et al., 2011); other authors wonder whether the costs of R&D expenditures are overstated, for example, by failing to account for inflation in R&D input costs (Cockburn, 2006; Griliches, 1994; Pammolli et al., 2011). Beyond some measurement issues, the concern is that diminishing returns on pharmaceutical R&D may be decreasing incentives to invest in new breakthrough drugs in important future fields (Gordon, 2018; Deloitte, 2018).

However, there are indicators signalling a possible reversal of the productivity in medical R&D (Cornell University, INSEAD and WIPO, 2019). For example, there has been a substantial increase in the number of Phase I and Phase II clinical trials since 2015. It remains to be seen whether that increase results in a corresponding increase in novel drug approvals.¹³

Patent filings in pharmaceuticals, biotechnology and medical technology have been growing over the last four decades (see Figure 3.4). Patents on medical technology grew faster than patents on pharmaceuticals or biotechnology.

Figure 3.3: Novel drug approvals, percentage with orphan designation and R&D expenditure as percentage of sales, 1999–2019¹⁴



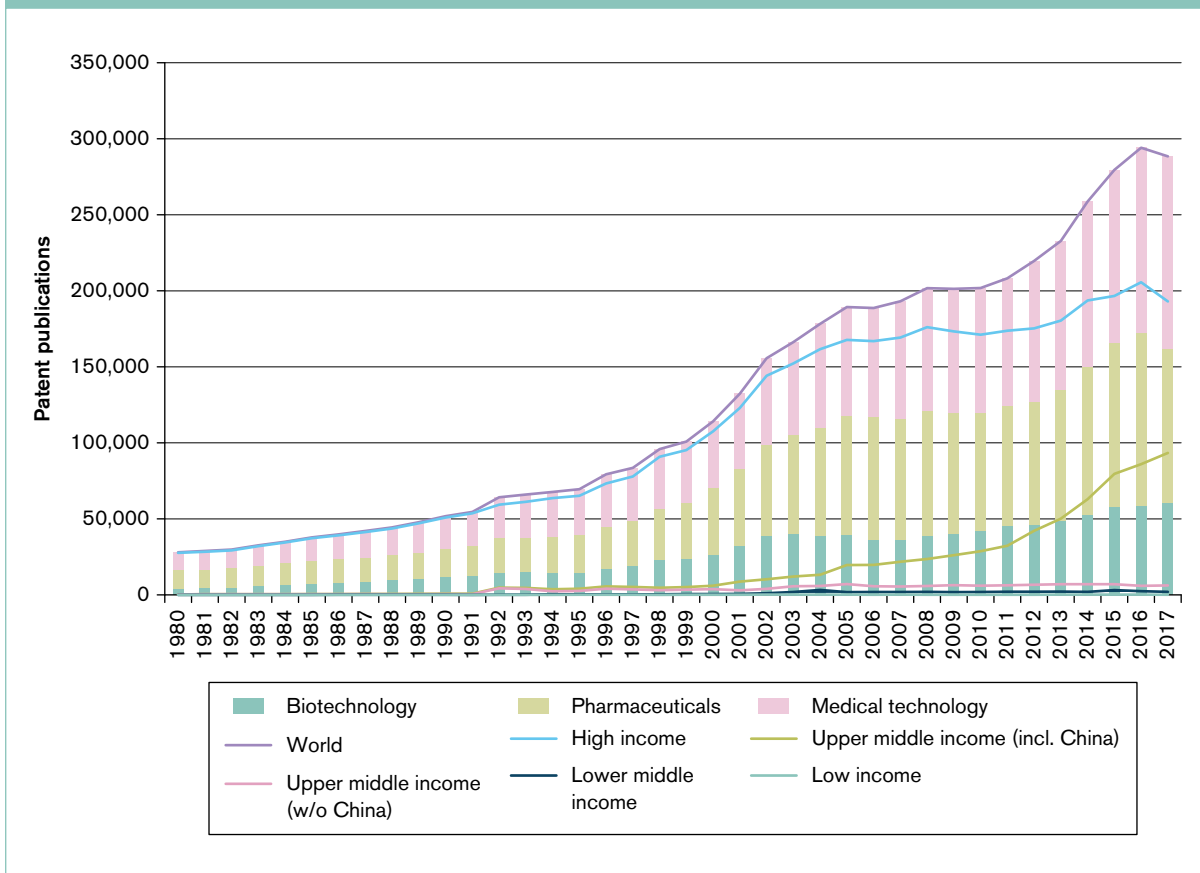
Sources: EvaluatePharma estimates, in *World Preview* (2013, 2015, 2017, 2019); United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2019 PhRMA Annual Membership Survey; WIPO Statistics Database.

This puts medical technologies among the top five fastest-growing technology fields since 2016, the other four being IT-related fields. After strong catch-up, medical technology patents are now as numerous, with about 100,000 worldwide. Upper-middle-income countries have significantly increased patenting activity in health technologies from 2005 to 2017.

in biotechnology, such as single-cell analysis and genetic engineering, raise hopes of acquiring a better understanding of biological processes that may eventually help to find cures for diseases such as Alzheimer's disease, cancer and HIV/AIDS. Modern IT based on the power of big data is widely expected to enable major advances in pharmaceutical and biomedical research, medical technology and health care. The realization of these hopes will depend on a policy, innovation and development environment that supports these efforts, as well as equitable access to any new technologies.¹⁵

The future of biomedical innovation is expected to involve and combine a number of emerging and disruptive technologies, such as biotechnology and IT. Developments

Figure 3.4: Patent publications by technology: performance by sector, income group and world, 1980–2017



Source: Cornell University, INSEAD and WIPO (2019).

B. The current R&D landscape

Key points

- The conventional innovation model of the pharmaceutical industry is leading to structural changes. These changes include an increasing number of mergers and acquisitions, outsourcing of R&D activity and more R&D collaborations, as well as greater focus on R&D in cancer and orphan medicines.
- There is an increasing debate about medicine pricing that has been triggered by prices of new medicines, including in high-income countries.
- The public sector has a significant impact on the innovation cycle at various stages, through financing and undertaking R&D, helping to shape private companies' R&D priorities, and the way in which health products are regulated, procured and disseminated.
- Developing pharmaceutical products and bringing them to market is usually costly and time consuming. However, limited data make it difficult to produce a reliable, independent assessment of the true costs of medical research.
- There are many different mechanisms for promoting innovation. Intellectual property rights (IPRs) are a useful incentive mechanism, but the IP system cannot incentivize inventions in areas where there is no market. The innovation cycle is not self-sustaining in disease areas where markets are small and health services are underfunded, such as in neglected diseases or antimicrobials.
- Vaccines are different from medicines in many respects. The process of proving the safety and efficacy of a vaccine always requires a full regulatory dossier. There has been a significant increase in the development of new vaccines, and new models of innovation, coupled with a growing number of vaccine manufacturers in low- and middle-income countries (LMICs), which are also increasingly engaged in research.
- Access to results from clinical trials is in the interest of science and public health and is necessary for evidence-based decision-making. The WHO has established a global network of clinical trials registries that facilitates access to information on clinical trials. Open access policies for sharing data are important and need to comply with requirements regarding personal data and ethics.

This section reviews the environment in which companies and other public and private entities carry out research, against the background of the evolution outlined in the preceding section.

1. A time of challenges and opportunities for pharmaceutical R&D

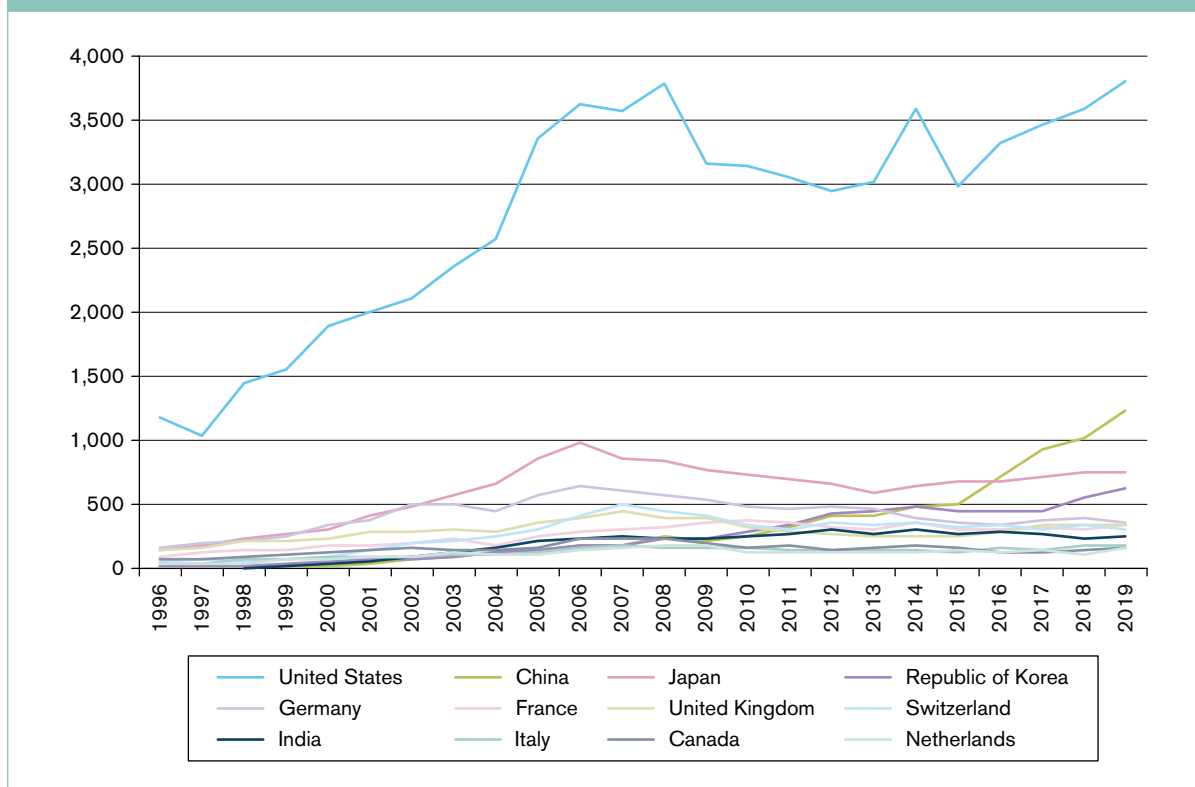
The market for pharmaceuticals is rapidly growing and changing, and the market for prescription pharmaceuticals is projected to reach US\$1.2 trillion globally by 2024 (EvaluatePharma, 2018). The global market is undergoing numerous transformations:

- In OECD countries, retail pharmaceutical expenditure per capita rose 2.3 per cent annually, on average, in the period 2003–2009, but decreased by an average 0.5 per cent annually in the period 2009–2015.¹⁶ At the same time, global spending on prescription drugs increased from to US\$ 455 billion in 2004 to US\$ 789 billion in 2017, and is projected to rise to US\$ 1,204 billion in 2024.¹⁷

- The share of worldwide prescription drug sales represented by biotherapeutic products increased from 17 per cent to 25 per cent between 2010 and 2017 (EvaluatePharma, 2018) and is projected to reach 31 per cent by 2024 (see also Chapter II, section A.6(d)).
- There is increasing political, regulatory and payer scrutiny of prescription drug prices in high-income markets.
- An increasing share of global sales will come from LMIC markets.¹⁸
- Smaller companies are becoming more important in biomedical R&D. Large pharmaceutical R&D companies no longer have the sole advantage of an important tool in drug discovery, namely, high-throughput screening, which is being combined with artificial intelligence (AI), machine learning and DNA-encoding to increase R&D productivity by small companies (Brazil, 2018).

The worldwide sales for originator medicines have increased in absolute terms since 2011 (EvaluatePharma, 2018), and the originator pharmaceutical industry continues to have stable and high profit margins compared with other industries.¹⁹

Figure 3.5: Top countries of origin of PCT publications in the field of pharmaceuticals, 1996–2019



Source: WIPO Statistics Database.

The biopharmaceuticals sector remains one of the most R&D-intensive industry sectors globally (European Commission, 2018b). In absolute terms, the United States continues to lead in R&D expenditures in the life sciences sector, far outstripping, for example, the European Union, Japan and Switzerland.²⁰ The United States is also the top country of origin of international applications filed under the PCT in the field of pharmaceuticals from 1996 to 2019 (see Figure 3.5).

Low R&D efficiencies (i.e. high R&D costs and low new drug approval rates), predominantly until 2015, have led major pharmaceutical companies to implement various changes to their business models (Schuhmacher, Gassman and Hinder, 2016). These include:

- Increased R&D collaborations. R&D is increasingly collaborative, involving partnerships between life sciences companies, academia, non-profit organizations and government entities.²¹ These enable R&D partners to share financial risk, widen their competencies and access enlarged skill sets and technologies.²²
- An increasing share of the R&D pipeline being commanded by cancer treatments. At the same time, prices of cancer medicines at launch are rising, while, among recently approved medicines, only a few offer meaningful clinical benefits (see Box 4.13) (Kim and Prasad, 2015; Davis et al., 2017; Vivot et al. 2017; Grössmann et al., 2017).
- A higher share of products for rare diseases (orphan drugs). Orphan drugs, which constituted 10 per cent of global prescription drug sales in 2010, accounted for 16 per cent in 2017 and are projected to represent 22 per cent by 2024 (EvaluatePharma, 2018). Orphan drugs are developed for small patient populations but benefit from a number of regulatory and financial incentives and often achieve high revenues (see section B.6).
- Strategic mergers and acquisitions (M&A) activity. Pharmaceutical companies increasingly use M&A to compensate for revenue losses caused by price drops following patent expiry, access strategically important technology and acquire promising R&D pipeline products (EvaluatePharma 2018).²³ In 2019, it was estimated that 69 per cent of the portfolios of high-growth pharmaceutical companies (i.e. companies that have consistently outgrown the market for more than 12 years) came from acquisitions or licensing in 2015 (Albrecht et al., 2016). M&A strategies are increasingly diverse, with pharmaceutical companies pursuing acquisitions of non-traditional, technology-oriented businesses (Deloitte, 2018). M&A also forms an important part of the growth strategy of small and medium-sized enterprises (SMEs), with many relying on investment or acquisition by larger pharmaceutical companies to progress through the costly clinical trial process (Herbert, 2018). Acquisitions of generic companies by R&D-based companies and vice versa

have blurred the traditional boundary between R&D-based companies and generic drugs companies. Horizontal integration through M&A among the big companies has led to a concentration of market shares. In addition, mergers most often lead to reduced R&D activity as companies will merge or close R&D centres that were acquired (Gilbert, 2019; Comanor and Scherer, 2013) (see also Chapter II, section B.2(c)).

- R&D cuts and outsourcing. A number of major pharmaceutical companies have cut the size of their R&D units to reduce costs and increase efficiencies (Herbert, 2018). Internal R&D cuts have been accompanied by an increased focus on outsourcing of R&D activities,²⁴ for example, capital-intensive activities such as high-throughput screening (HTS), saving pharmaceutical companies the expense of investing in in-house infrastructure (Brazil, 2018).
- Reduced antimicrobial research. Most large pharmaceutical companies have withdrawn their antimicrobial research programmes in light of poor potential for investment returns.²⁵

The structure of the industry has also evolved:

- The wider technology sector is presenting both challenges and opportunities for the pharmaceutical industry. “Big Tech” companies are entering the pharmaceutical market, disrupting traditional business models.²⁶ On the other hand, pharmaceutical companies are increasingly partnering with or acquiring technology companies, with a view to increasing their digital capabilities (Deloitte, 2018). Effective utilization of data is a key industry focus, with R&D stakeholders focusing on developing their internal technical and data capabilities and identifying potential external data sources (Deloitte, 2018).
- Start-ups are more prominent, particularly in the development of next-generation therapies. One 2019 report notes that, while only a few big pharmaceutical companies are developing next-generation therapies, more than 250 start-ups are focused on gene-based therapeutic solutions.²⁷ The rise of collaborative R&D models (between pharmaceutical companies), the outsourcing of key R&D services and the growth of digital networks has provided start-up companies with access to technologies and technological infrastructure that might have been inaccessible in the past (Brazil, 2018).
- Middle-income markets are increasingly important. The market for pharmaceuticals and medical devices in some middle-income economies is growing rapidly, driven by increased prosperity, health-care reform, local government incentives and overall rising demand for health care.²⁸ While multinationals already have a firm foothold in these markets, local companies are experiencing strong growth, attributed to lower production costs, the success of locally

adapted products and government support.²⁹ Some pharmaceutical companies from certain middle-income economies increased their share of global revenues by a factor of 26 (from US\$ 4.5 billion to US\$ 119 billion) from 2005 to 2015.³⁰

- Medical device companies are also showing signs of a similar trajectory. For example, Chinese medical device companies are already growing much faster than their American counterparts.³¹ While many companies in these contexts specialize in “frugal engineering” – making low-cost, simplified versions of existing technologies suitable for LMICs – they are increasingly investing in the development of new products.³²

The latest wave of innovation in pharmaceuticals, gathering pace from around 1980, is based on advances in the discovery and application of biotechnology. The growing use of bioinformatics in virtual R&D to create computer models of organs and cells offers significant potential for tailored drug discovery and development (PwC, 2008). The decoding of the human genome in the late 1990s spurred hopes of a new wave of innovation in personalized medicine. The first gene- and cell-based therapies were approved in the 2010s, including, for example, sipuleucel-T for prostate cancer in 2010, tisagenlecleucel for leukaemia in 2017 and voretigene neparvovec-rzyl for a genetic cause of blindness in 2017 (approval dates given are for the FDA), with more in development (see Boxes 2.3 and 2.4).³³ Despite scepticism towards genomics being able to deliver more precise diagnostics and medicines (Pray, 2008), sometimes termed “precision medicine” (see Box 4.17), benefits are beginning to be seen for some diseases, but these are mostly limited to a small number of countries, due to high prices and, in some cases, high infrastructure requirements.

There has been an increasingly intense focus on prices of new, innovative medicines, not just in poorer countries but, increasingly, in high-income country markets such as Europe and the United States. This has led to a debate on medicine pricing as well as on the social value of “me-too”-type medicines. The 2006 Congressional Budget Office report summed up the situation as follows:

“The more accurately a drug’s price reflects its value to consumers, the more effective the market system will be at directing R&D investment towards socially valuable new drugs. However, prices can only serve that directing role to the extent that good information exists about the comparative qualities of different drugs and that consumers and health-care providers use that information.” (USCBO, 2006, p. 5)

Certain criticisms of the industry notwithstanding, there is little doubt that modern medicines and technologies have contributed to longevity, especially in countries that have access to newer medicines (Lichtenberg, 2012).

Box 3.2: Adaptation of medical devices to developing-country needs – the example of portable electrocardiographs

Electrocardiography (ECG) records the electrical activity of the heart, assisting in diagnosis of heart conditions. Traditional ECG machines are a widely used diagnostic tool and are commonplace in hospitals. However, they are bulky (about the size of a briefcase), often show readings by printing on custom-format paper and are relatively expensive.

Handheld ECGs were invented in 2007. They were designed to extend the capability of a traditional ECG to a rural populations in LMICs, to help combat the rising number of deaths caused by cardiovascular diseases (GE Healthcare, 2011; Immelt et al., 2009). Rural populations in LMICs are particularly vulnerable, due to their very limited access to qualified health professionals, medical devices and essential medicines to combat cardiovascular diseases.

The first handheld ECG machine, developed in 2007, cost around US\$ 800, compared with traditional units that ranged from US\$ 2,000 to US\$ 10,000. The next generation of portable ECG machines was developed with a built-in screen to allow instant viewing of ECGs, eliminating the need to print them, thereby saving costs and paper (GE Healthcare, 2011; Immelt et al., 2009). They also included wireless technology, which enables health-care workers to perform ECGs in remote areas and immediately transfer the test results to physicians who can interpret them. Due to its efficacy, the portable ECG is now also being used in rural areas in high-income countries.

Changes are also occurring in the way innovation is taking place in medical devices (see Box 3.2). Increasingly, private-sector medical devices companies are seeking to specifically design new devices and health-care delivery models that can be adapted to the needs of LMICs. These actions reflect a growing level of commitment among companies to serve long-neglected markets; they also reflect companies' increased interest in the commercial opportunities arising from addressing the health needs of people who inhabit the middle and bottom levels of the socio-economic pyramid. As a result, companies are committing greater resources towards evaluating local and regional barriers, and they are creating tailored products and services to meet specific cultural or geographic needs. One of the outcomes of this development is devices that are more adapted to the needs of LMICs. Such devices are also less costly than those designed for markets in high-income countries and are thus more affordable. The design of the devices may also serve to enhance accessibility (Cornell University, INSEAD and WIPO, 2019).

2. The key role of public-sector research in medical R&D

The ecosystem of pharmaceutical R&D has evolved such that, in a broad sense, there is a “division of labour” between the public sector and the private sector, in which the public sector concentrates more on upstream research that provides basic scientific knowledge on the mechanisms of disease, while the private sector undertakes downstream research, translating basic research into medical products. The public sector thus significantly influences the innovation cycle by shaping research priorities, at least

with regard to basic research (WHO, 2006a; USCBO, 2006; Cornell University, INSEAD and WIPO, 2019).

The public sector also plays an important role in the innovation cycle at subsequent stages. For example, governments control the quality of health products through their regulatory frameworks, which determine whether a product gets to the market and, if so, how quickly. Additionally, the public sector plays a critical role in the delivery phase of health products because governments are usually the main purchasers of health products and they often organize the distribution and delivery of such products.

The story of the development and commercialization of monoclonal antibody-based therapies provides an example of how public and private enterprise can cooperate in the development of new drugs (see Box 3.3).

It is estimated that government agencies worldwide provided around US\$ 42 billion in health research funding annually (2011–2014), of which about 60 per cent was from the US National Institutes of Health (NIH) (Viergever and Hendriks, 2016). Non-profit entities play an important role in the funding of biomedical research, mainly in high-income countries – the Howard Hughes Medical Institute in the United States and the Wellcome Trust in the United Kingdom are good examples. Public investments can also have a “multiplier” effect; in the United Kingdom, it has been demonstrated that every 1 per cent increase in investments in public medical research is associated with a 0.8 per cent increase in private pharmaceutical R&D investments (Sussex et al., 2016).

Numerous analyses have identified the large contributions of public-sector research to biomedical R&D (Kneller, 2010).

Box 3.3: Monoclonal antibodies

Monoclonal antibodies are a type of immunotherapy drug used widely in oncology, autoimmune diseases and other areas. They are of high importance in both clinical and economic terms, and are now key treatments for numerous cancers and autoimmune conditions.

The techniques underlying the development and manufacture of monoclonal antibodies were developed at the UK Medical Research Council Laboratory of Molecular Biology (LMB), a public research institute. The pioneering researchers at LMB received a Nobel Prize for their work in developing these techniques.³⁴

LMB researchers developed one of the first therapeutic monoclonal antibodies, adalimumab, for rheumatoid arthritis, working in a spinoff company called Cambridge Antibody Technology, on commission from a German chemical manufacturer (Marks, 2015).

After adalimumab, a large number of monoclonal antibody medicines have been brought to market by pharmaceutical companies, using LMB technology. Medicines developed using LMB technology include, for example, the breast cancer treatment trastuzumab, leukaemia/lymphoma treatment rituximab, and bevacizumab, used in treating both colorectal cancer and wet age-related macular degeneration, a common cause of blindness. All three medicines are on the WHO Model List of Essential Medicines. Monoclonal antibodies are also used in many important diagnostics (Marks, 2015).

The LMB has received substantial royalties for the use of the monoclonal-antibody-related technologies in developing immunotherapies, which have, in certain years, comprised a significant part of the LMB's budget.³⁵

A 2011 study suggested medicines developed in the public sector have had, on average, a greater effect on improving public health than other medicines (Stevens et al., 2011). The methodologies of these analyses do not capture basic research, which underlies drug discoveries, for example, by identifying the molecular mechanisms of diseases that new drugs could target. A more recent analysis that included basic research found that public funding contributed to all new drugs approved in the United States over the period 2010–2016, and more than 90 per cent of this funding represented basic research related to the biological targets for drug action rather than the drugs themselves (Cleary et al., 2018).

The pharmaceutical industry spent an estimated US\$ 177 billion on R&D in 2017.³⁶ In many cases, the public and private sectors can work in synergy, with the private sector building upon basic research done in the public sector. The public and private sectors can also come together as PPPs. One example is the European Union's Innovative Medicines Initiative (IMI and IMI2), under which a large number of public–private consortia undertake joint research projects, with private entities matching public investments with in-kind contributions (such as staff time).³⁷ In some cases, public research funders attach conditions to funding to ensure that the public benefits from products developed from public research (see also Chapter IV, section C.3(c)). For example, in the United States, the NIH has developed provisions that would require licensees of IP generated through NIH-funded research to submit a plan of how public health needs for the product will be met (Stevens and Effort, 2008). Similar provisions are used by, for example, the Wellcome Trust³⁸ and CARB-X (see Chapter IV, section C.3(c)).

3. Medical R&D costs

One of the main arguments put forward by industry with respect to the need for strict protection of IPRs is the high cost of R&D for new medical products, with IP protection affording firms confidence that R&D costs can be recouped once the product is approved. There are, however, few sources of data publicly available that enable the true costs of medical research to be assessed. A number of estimates have been published, quantifying the average cost of bringing a new medicine to market. Costs greatly depend on the type of medicine in question. There is a huge difference in costs between a medicine based on a new chemical entity (NCE) not previously used in any pharmaceutical product, and an incremental modification of an existing medicine.

Costs of pharmaceutical R&D can be viewed in various ways. “Out-of-pocket” costs describe actual cash expenditures by the developer. These costs can be further risk adjusted to account for the cost of a failed drug candidate. The costs can also be “capitalized”; capitalized costs include the theoretical losses incurred from investing in pharmaceutical R&D instead of an alternative investment that would have earned returns at a certain percentage over the years before the R&D yields a successful product. One series of studies has estimated the risk-adjusted out-of-pocket cost of bringing an NCE to market at US\$ 114 million (US\$ 231 million capitalized) in 1987, US\$ 403 million (US\$ 802 million capitalized) in 2000, and US\$ 1.4 billion (US\$ 2.6 billion capitalized) in 2013 (DiMasi et al., 1991; DiMasi et al., 2003; DiMasi et al., 2016). Both lower and higher estimates are available,

ranging from US\$ 100 million to US\$ 5 billion (DNDi, 2014; Morgan et al., 2011; Herper, 2012; Prasad and Mailankody, 2017). In some disease areas, returns on R&D investments can be very large; for example, in oncology, for drugs approved during the period 1989–2017, sales of final products brought in US\$ 14.50 for every US\$ 1.00 invested in R&D (Tay-Teo et al., 2019).

The long timelines for pharmaceutical development also contribute to high costs and risk. Bringing a pharmaceutical product from the laboratory stage to marketing stage takes a long time and entails the additional burden of complying with stringent regulatory approval processes, thus resulting in a small number of successful products. An analysis of novel medicines (new active substances) found that mean time from filing of the first patent application to launch of the medicine in the United States was 12.8 years, whereas the mean time from launch to expiry of patent or other forms of exclusivity was 13.5 years (Aitken and Kleinrock, 2017).

The estimates of pharmaceutical R&D costs noted in the preceding paragraphs concern the investments, practices and performance of multinational pharmaceutical companies, reflecting, for example, their choices of disease areas to invest in, drug candidates to take forward in development, and so on. They may not necessarily apply, therefore, to drug development in other models of R&D, such as within a product development partnership. For example, Drugs for Neglected Diseases *initiative* (DNDi), which has developed one NCE and seven improved treatments for neglected diseases (see Box 3.12), estimates that, based on its experience, developing an improved treatment costs EUR 4 million–32 million, and developing an NCE costs EUR 60 million–190 million, including the cost of failures (DNDi, 2019).³⁹

All of these estimations rely on many variables, such as the estimated average length of development, the average size and costs of clinical trials and the probability of success, in that products will finally make it to market. In addition, it is difficult to verify the underlying data, as this is not disclosed for the most widely cited studies. Some of the estimates of pharmaceutical R&D costs, such as the figures in the studies by DiMasi et al. (see in this section above), have been widely discussed (e.g. Love, 2003; Avorn, 2015). There are doubts about the usefulness of such estimations, as costs vary widely between companies and also between the private sector and the public sector (see Chapter IV, section A.4(f)).

Orphan drugs, which, in 2018, were the most common type of novel drug approved in the United States (see Figure 3.3), may have lower R&D costs than non-orphan medicines, for example, due to the smaller size of the clinical trials needed to gain approval. A recent analysis of medicines approved by the FDA in the period 2000–2015 estimated that capitalized clinical trial costs for new molecular entities with orphan designation were

50 per cent lower than costs for non-orphan medicines (Jayasundara et al., 2019).

Originator pharmaceutical companies in Europe and the United States invest about 15–20 per cent of revenues in R&D, depending on the source and year. This proportion has been on a slight upwards trend over the past two decades but is projected to decline over coming years (EvaluatePharma, 2018). According to industry reports, about one fifth of this (3–4 per cent of revenues) is spent on basic (preclinical) research, such as identifying new pharmacological targets and candidate compounds.⁴⁰ Spending on marketing and promotional activities by the industry generally exceeds R&D costs.⁴¹

While precise costs are unknown, medical R&D is very costly and highly risky. Also, many investments do not result in a return, due to product failures in the clinical trials phase. Efforts to develop a treatment for Alzheimer’s disease – the most common form of dementia – illustrate the riskiness of drug development. A large number of drug candidates have failed in Phase III, despite an apparently well-described mechanistic target (beta-amyloid) (Mullard, 2019; Makin, 2018; Langreth, 2019). Failures in Phase III are especially costly for drug developers, as investments have already been made to take the drug candidate through preclinical development and Phase I and Phase II trials (see Chapter II, section A.6(b)). Drugs developers have nevertheless persisted working in this area, as the potential market is expected to be very large.⁴²

Details on R&D costs could be important in setting up novel mechanisms for financing R&D, for example, projecting costs for a product development partnership (see Box 3.12) or evaluating how large milestone prizes need to be designed to cover R&D costs (see section C.5(c)).

4. Incentive models in the innovation cycle

The *2011 World Intellectual Property Report* (WIPO, 2011b) observes that:

“IP rights are a useful incentive mechanism when private motivation to innovate aligns with society’s preferences with regard to new technologies. But such an alignment does not always exist. In addition, it is unclear whether the IP system can incentivize invention that is far from market application, for example, basic science research.”

In reviewing the IP system in the context of the broad sweep of innovation policies, the report distinguishes three mechanisms for promoting innovation:

- Publicly funded innovation carried out by academic institutions and public research organizations

- Publicly funded research undertaken by private firms – notably, through public procurement, research subsidies, soft loans, R&D tax credits and innovation prizes
- Privately financed and executed R&D, financed through the marketplace rather than government revenues and incentivized through the IP system, which is one mechanism of government policy that promotes innovation.

(a) The innovation cycle

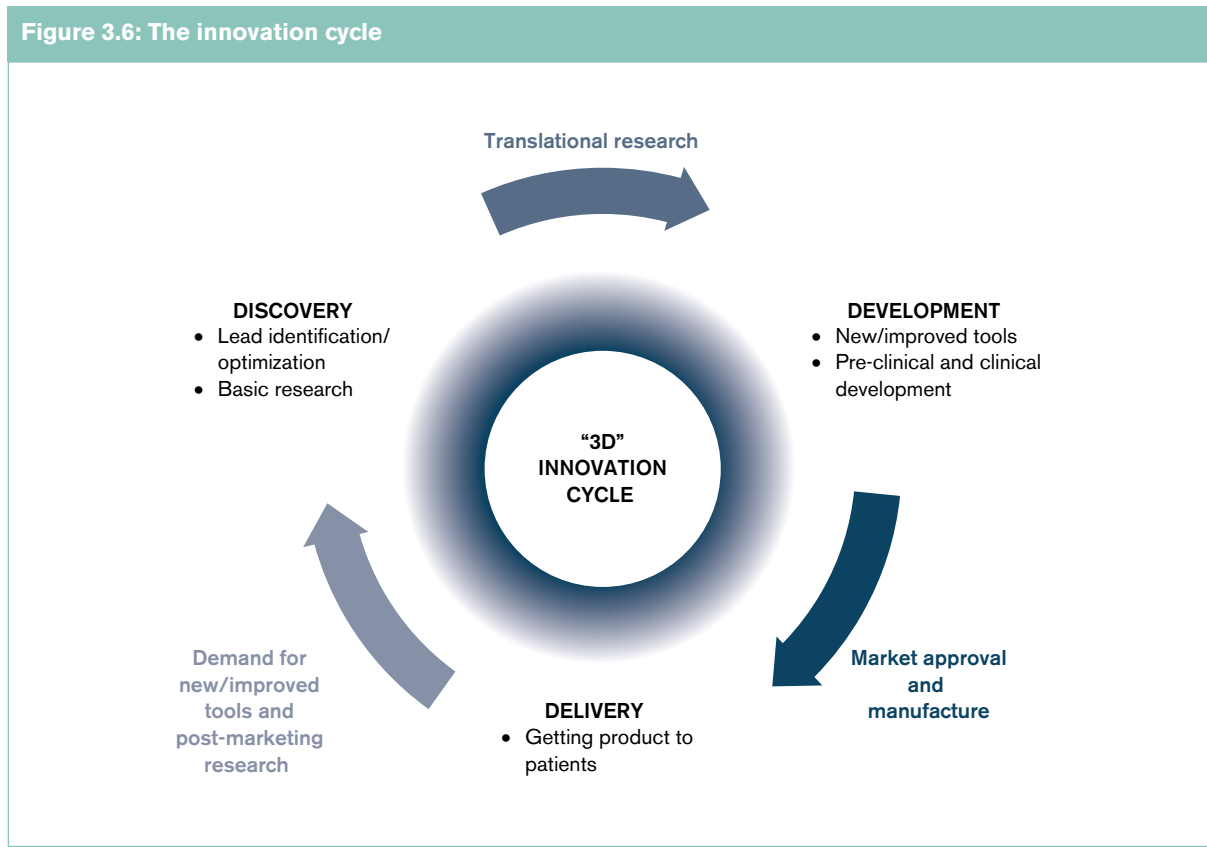
Innovation is often presented as a linear process that culminates in the launch of a product, but innovation in health can also be seen as a cycle (see Figure 3.6). This cycle goes from the discovery of candidate compounds to the testing and development of new products, through to the delivery of these products, and then returns to the R&D of new products (or to the optimization of existing products) through systematic post-marketing surveillance and the development of an increasingly effective demand model based on health needs.

The circular model of health innovations illustrates a critical reality: the current market-driven innovation cycle works better for high-income countries where effective demand for health products is matched by the ability to pay for

them. In contrast, for diseases that predominantly affect patients in LMICs, there is a critical gap in the availability of incentives that fuel the conventional innovation cycle. While there is an urgent need for new medications for diseases that predominantly affect LMICs, that market is characterized by limited purchasing power, coupled with the lack of health insurance systems in many countries. In a similar vein, the classical innovation cycle also may not work for the development of new antibiotics, because the originator company typically cannot count on high sales volumes to recoup its investment in R&D (see section C.2 on AMR). It is also important to note that a large amount of basic research, for example, identifying drug targets, support the cycle.

(b) Absence of self-sustaining innovation cycle in the case of small markets, low incomes or low sales volumes

The CIPIH observed in this context that the IP system needs a certain type of environment in order to deliver expected results. For diseases that predominantly affect people living in poorer countries, the innovation cycle is not self-sustaining, due to low potential for revenue, underfunded health services and generally weak upstream research capacity. A similar market failure arises where sales are



Source: WHO (2006a), p. 23.

likely to be low, for example, in antibiotics and treatments or vaccines for emerging pathogens (see Chapter III, sections B.4(e), C.2 and C.3). In this type of environment, the market alone and market-based incentives, such as patent protection, cannot by themselves address the health needs of developing countries (WHO, 2006a).⁴³

This gap – between health needs and medical R&D efforts – has sparked policy debate on the effectiveness of current medical innovation structures for health needs, in particular for the specific health needs of LMICs. Equally, the compelling need to address this gap has, over the past decade, prompted an array of initiatives to find new ways of combining the diverse inputs, infrastructure and resources needed for product development. These initiatives have explored new ways of integrating these different inputs and steering candidate products through the innovation process, culminating in the delivery of safe and effective new technologies. This approach has typically made use of more collaborative structures, a wider range of non-exclusive and segmented technology licensing models and the development of pre-competitive technology platforms, as well as product development partnerships (PDPs) that harness private-sector capacities and deploy them towards the attainment of not-for-profit public health objectives. Such practical initiatives both respond to, and help to influence, the dynamics of medical innovation today, in terms of both making new technologies available and illustrating in practice the possibilities for a wider range of innovation models.⁴⁴

While it is important to trigger the requisite innovation for neglected diseases, it is also important to ensure that any new medical technologies emerging from such initiatives are affordable for the people who need them. In the existing patent-driven innovation ecosystem, the returns for investment in innovation are generally factored into the price of new-generation products. In contrast, new and innovative finance mechanisms and initiatives aim not to finance the cost of R&D through the price of the end product, thus delinking the cost of research from the price of the product.⁴⁵ These are explored further in section C, “Overcoming market failures in medical product R&D”.

There have been a few successful cases of tailoring innovation to meet identified medical needs. An example is the development of a meningitis vaccine for Africa (see Box 3.4).

(c) Building innovation networks

The CIPIH stressed that the formation of “effective networks, nationally and internationally, between institutions in developing countries and developed countries, both formal and informal” is an “important

element in building innovative capacity” (WHO, 2006a). One example of initiatives to build such collaborative networks for innovation is the European & Developing Countries Clinical Trials Partnership.⁴⁶ It funds research for the prevention and treatment of infective diseases in sub-Saharan Africa.

(d) Overview of innovation structures

A broad range of diverse innovation structures is used in the development of medical technologies. These structures can be characterized according to two factors – the degree of market-based incentives involved, and the extent to which some leverage or exclusivity is exercised over the technology. Often, innovation processes are neither situated in an entirely non-commercial context with no leverage at all maintained over technologies, nor are they a rigid, highly exclusive and entirely private model of technology development. Legal instruments alone, particularly at the international level, do not generally determine where a practical innovation strategy for a specific new technology is, or should be, located on this spectrum, and other factors typically guide choices about the mix of public and private inputs, and the management of technology.

One key feature of the innovation landscape, however, is the dividing line between “pre-competitive” and competitive inputs to innovation. Landmark research projects, such as the Human Genome Project⁴⁷ and the International HapMap Project,⁴⁸ have sought to define a pre-competitive body of data that is openly shared for wide use in research and in the development of inputs at an early stage in the product development pipeline, so as to provide a common platform for companies to compete in the development of finished products. At a later stage in the R&D pipeline, a degree of competition and differentiation between companies can promote a greater diversity of available technologies (Olson and Berger, 2011).

(e) Vaccines: a distinct challenge for innovation

Vaccine development differs from the development of small-molecule, chemically synthesized pharmaceuticals. Vaccines are complex biological entities, and there is no such thing as a “generic” vaccine. Proving the safety and efficacy of a vaccine, even if it is a “copy” of an existing vaccine, requires a full regulatory dossier containing data on pre-clinical and clinical trials. This adds years, and complexity, to the process of making and copying even existing vaccines. Vaccines are typically given to healthy individuals and, in particular, to healthy infants as a prophylaxis against a subsequent infection. Safety is

Box 3.4: New innovation models in practice: tailoring a meningitis vaccine for Africa

The successful 2010 launch of MenAfriVac highlights the role of new approaches to innovation and product development in order to address the health needs of developing countries. Prior to this, vaccines were available for various strains of meningitis, but they were too expensive for those living at risk of the disease in the so-called African meningitis belt. Moreover, they did not offer an appropriate solution for resource-poor settings. Against a background of recurrent epidemics and increasing death rates, stakeholders faced a significant innovation challenge in ensuring the production of a vaccine that would be suitable from a clinical point of view and also sustainable and affordable. The Meningitis Vaccine Project, a consortium led by the WHO and the Programme for Appropriate Technology in Health (PATH), a not-for-profit health technology organization, set about producing a vaccine for the A strain of meningitis that would cost no more than US\$ 0.50 per dose. A review of options led to a decision to develop a production process and to transfer the relevant technology to a low-cost producer in the developing world, rather than subsidizing a vaccine manufacturer in the industrialized world to undertake development and production. An innovative model for vaccine development was established, with key raw materials sourced in India and the Netherlands. The technology developed by the FDA Center for Biologics Evaluation and Research, and the technology and know-how, was transferred to Serum Institute of India Ltd to produce vaccines for clinical trials and, ultimately, full-scale production. This development model reportedly cost one tenth of the conventional estimate for producing a new vaccine. The development and introduction of this new vaccine marks a huge step towards the elimination of epidemic meningitis in sub-Saharan Africa.⁴⁹

therefore paramount, and any remote suggestion of risk to the recipient can result in withdrawal or non-authorization of the vaccine.

The cost of establishing and gaining regulatory approval for a manufacturing facility partly explains the limited number of manufacturers entering the field of vaccines and the relatively small number of qualified products and producers. Other reasons include the lack of production know-how, which can constitute an effective barrier to the viable reproduction of vaccine technologies. Vaccines also often require costly cold-chain infrastructure and only a relatively small number of doses is required to achieve immunization. Thus, profit margins can be relatively low in comparison with the manufacture of other pharmaceuticals.

These challenges mean that private manufacturers have long lacked the necessary incentives to invest in vaccines, particularly those that focus on the specific needs of developing countries. Almost all the important, innovative vaccines introduced since the 1980s have resulted from initial discoveries made by public-sector research institutions (Stevens et al., 2011).

(i) New vaccine innovation in the 21st century

The first decade of the 21st century brought a record number of new vaccines, including vaccines for meningococcal meningitis, rotavirus, pneumococcal disease and cervical cancer caused by human papillomavirus. At the same time, the market for vaccines has grown dramatically. It has multiplied more

than fivefold since 2000 and was worth more than US\$ 31 billion globally in 2016.⁵⁰

This increase in the development of vaccines is due to a number of key factors: more innovative technologies; improved understanding of immunity; investment by PDPs such as Gavi, the Vaccine Alliance;⁵¹ and, more recently, new funding sources and mechanisms such as advance market commitments (AMCs) that contribute to public funding for vaccine development (see Box 3.5). These changes continue to shape the current landscape of vaccine manufacture.

(ii) The role of developing-country manufacturers

The vaccine industry has undergone major changes.

In 2017, LMICs represented 20 per cent of the global vaccine market by value, but 79 per cent by volume (Pagliusi et al., 2018).

There is a small number of high-income-country manufacturers in the vaccine market. About 80 per cent of global vaccine sales by value comes from five large high-income-country multinational corporations that were the product of various M&A of pharmaceutical companies over the past few decades.⁵² However, in terms of volume rather than value, developing-country vaccine manufacturers claim the majority share, at more than 65 per cent in each WHO region except the European Region (WHO, MI4A and V3P, 2018).

Box 3.5: Advance market commitments in vaccines

Although vaccines are among the most effective public health interventions, few of the vaccines that have been developed address diseases that primarily affect the developing world. In the past, new vaccines typically reached low-income countries only decades after they had been rolled out in developed countries. A pilot project on an advance market commitment (AMC) for pneumococcal vaccines was launched in 2007. It was funded by Canada, Italy, Norway, the Russian Federation, the United Kingdom and the Bill & Melinda Gates Foundation. Pneumococcal disease was selected for this project, as it claims 1.5 million lives each year, mostly children in Asia and Africa.

The AMC guarantees a market to manufacturers of a novel and suitable pneumococcal vaccine, with a high introductory price of US\$ 7.00 for each dose. This price is guaranteed for about 20 per cent of the doses that manufacturers commit to sell through the AMC and is designed to help them recover the costs of establishing production capacity. In return, manufacturers have accepted to provide additional doses at a “tail price” of US\$ 3.50 for at least a decade.

Under the oversight of the World Bank and Gavi, the Vaccine Alliance, and in conjunction with UNICEF, the first AMC tender was issued in September 2009. In 2018, 149 million doses of pneumococcal conjugate vaccine (PCV) were procured through the AMC.

In December 2010, Nicaragua became the first country to immunize its children with the new vaccine. As of December 2019, 59 countries have added the AMC-purchased vaccine to their national vaccination schedules (Gavi, 2018).

Developing-country vaccine manufacturers are also increasingly engaged in research. For example, the Serum Institute of India, in collaboration with WHO and PATH, developed a meningitis A vaccine for use in sub-Saharan Africa. The Institute also developed a measles vaccine delivered by aerosol, which ultimately showed insufficient efficacy in trials.⁵³ Cuba has a vibrant research-based biotechnology industry that has developed a number of innovative vaccines, including a meningitis B vaccine, a synthetic haemophilus influenza B vaccine and a therapeutic vaccine to treat types of lung cancer.⁵⁴ It also has numerous innovative products in the pipeline. Chinese companies were, in 2019, developing hepatitis E and human papillomavirus vaccines.⁵⁵ In Brazil, the Oswaldo Cruz Foundation (Fiocruz), through its Immunobiological Technology Institute (Bio-Manguinhos), has 27 projects under development in 2019, 15 of which involve bacterial or viral vaccines.⁵⁶ Also in Brazil, the Butantan Institute has developed a novel adjuvant derived from a by-product of pertussis vaccine production.⁵⁷

5. Challenges in cancer medicines R&D

Oncology represents a large proportion of the global R&D pipeline. In 2017, 43 per cent of registered clinical trials were in the area of cancer, with more trials on cancer treatments than for the next four disease categories combined (Long, 2017). However, progress in finding cures has been slow for many types of cancer (WHO,

2018g). Data show that there is a high level of duplication in cancer R&D, with many similar clinical trials done for similar experimental compounds, but with trial results left unshared (Workman et al., 2017). At the same time, the market for oncology medicines is highly concentrated, with three companies accounting for about 50 per cent, by sales value, of the global market.⁵⁸

A large proportion of cancer medicines offer limited clinical benefits. New medicines for which evidence shows unclear or marginal therapeutic advantages pose challenges for policy-makers, regulators and clinicians, for example, in selecting which medicines to reimburse, approve or prescribe. These challenges have prompted the WHO and others to seek clearer definitions of what constitutes significant improvements over previous therapy in new cancer medicines (WHO, 2018i). One study that analysed cancer medicines approved by the EMA from 2009 to 2013 found that most drugs enter the market without evidence of benefits in survival or quality of life. Later, at a median 3.3 years after approval, 51 per cent were found to have evidence for improvements in overall survival or quality of life and 48 per cent were judged to offer a clinically meaningful benefit (Davis et al., 2017). Another study, analysing medicines for solid tumours approved by the FDA from 2002 to 2014, found an average overall survival gain of 2.1 months (Fojo et al., 2014). At the same time, one study found that solid tumour cancer medicines approved by the FDA from 2000 to 2010 caused higher rates of deaths due to toxicity than the standard of care with which they were compared in trials (Niraula et al., 2012). However, average returns on R&D investment in

cancer are high; for example, one study found that the return on investment was US\$ 14.50 for every US\$ 1.0 of investment in cancer medicine R&D, and that risk-adjusted R&D costs were recouped within a median of three years following drug launch (Tay-Teo et al., 2019).

6. Orphan drugs and orphan indications

“Orphan drugs” is a term given to medicines that treat rare diseases, including rare subtypes of common diseases (Gammie et al., 2015). The threshold for what is considered “rare” differs between countries and is generally based on the incidence of a disease in the relevant regulatory jurisdiction.⁵⁹

In response to concerns that the commercial market for these medicines may be too small to attract R&D investments, legislation has been passed in some countries to compensate for limited market size and to stimulate the development of medicines for rare diseases. Orphan drug legislation was introduced in 1983 in the United States (the Orphan Drug Act), in 1993 in Japan and in 2000 in the European Union (EvaluatePharma, 2018). Incentives include tax credits to partially compensate for clinical trial expenses, waiving of regulatory fees, accelerated approval and additional market exclusivity (details depend on the jurisdiction). For example, orphan drugs are eligible for seven years of market exclusivity in the United States (see Box 2.5) and ten years in the European Union, extended a further two years if a paediatric investigation plan is agreed (see also Chapter II, section A.6(f) for regulatory exclusivities generally).⁶⁰

In response to this legislation, the number of medicines receiving orphan designation in the United States and the European Union has increased rapidly since the turn of the century, from fewer than ten orphan drugs approved by the FDA in the decade before the introduction of the Orphan Drug Act (Giannuzzi et al., 2017) to 34 orphan drugs approved by the FDA CDER in 2018, representing 58 per cent of all novel drug approvals (see Figure 3.2).⁶¹ Orphan drugs are projected to represent nearly one quarter of prescription drug sales globally by 2024, and growth in sales of orphan drugs is expected to be double that of the pharmaceutical market overall (EvaluatePharma, 2018). In some disease areas, a majority of newly approved medicines are orphan medicines; for example, about two thirds of cancer medicines approved by the FDA in the period 2011–2015 qualified as orphan medicines (Amanam et al., 2016). This represents a significant shift in the focus of the pharmaceutical industry’s R&D efforts and is a relevant factor to consider in discussions of global health research prioritization (WHO, 2012).

At the same time, orphan drugs are priced at far higher levels than other originator medicines, and prices of orphan drugs are rising. The mean annual price of an orphan drug in the United States was US\$ 147,000 in 2017 (EvaluatePharma, 2018), and a number of orphan drugs have broken drug pricing records. For example, an orphan drug gene therapy approved to treat an inherited cause of blindness was reported to be priced at US\$ 425,000 per eye (Scutti, 2018; Miller, 2018).

It has been argued that, in some cases, companies have divided larger (non-orphan) diseases into multiple newly defined subtypes with smaller patient populations in order to benefit, in each individual indication, from orphan drug legislation incentives and bolstered ability to demand high prices (Daniel et al., 2016). Legislation attempting to curb such business practices has been enacted in Japan and was proposed, though not enacted, in the United States (Daniel et al., 2016; European Commission, 2018a). In addition, a substantial proportion of new orphan drug approvals are for new indications (new therapeutic uses) of previously approved medicines, constituting 39 per cent of orphan approvals by the FDA in the period 1983–2017 (Miller and Lanthier, 2018).

As the threshold for what regulators consider to be an orphan drug is, in general, based on the disease incidence in the particular country, in some cases, treatments that receive orphan drug designation in a country may be common diseases at the global level.

Some medicines with orphan designation are of significance in the global health context; numerous medicines added in recent years to the WHO Model List of Essential Medicines were originally approved by regulatory agencies in high-income countries as orphan drugs, such as imatinib for chronic myeloid leukaemia, and bedaquiline and delamanid (both added to the WHO EML in 2015), which are treatments for TB, the leading infectious killer globally. They nevertheless received orphan designation with the FDA and EMA, based on the relatively low prevalence of TB in the European Union and the United States.

7. Registration of clinical trials in pharmaceutical product development

Registration of clinical trials means making accessible to the public, by means of a registry, an agreed set of information about the design, conduct and administration of clinical trials.⁶² A clinical trials registry is a publicly accessible database containing entries with information about the design, conduct and

administration of clinical trials. Besides the registration of clinical trials, the publication of the results of clinical trials is equally important for public health. Patients take part in clinical trials in the hope that they will contribute to advances in medical science and they do this altruistically. Participants expect that results will be used to further scientific research. Sponsors of clinical trials will often not provide details of clinical trials that have failed, although this is valuable knowledge and could be used to help prevent a repetition of such trials, and thus help to avoid exposing patients to unnecessary risks. It would be in the interest of public health if the details of all clinical trials were to become publicly available, allowing interested parties to verify the data.

In 2017, research funders signed the “Joint statement on public disclosure of results from clinical trials”; signatories included the European Commission (for the Horizon 2020 Societal Challenge: Health, Demographic Change and Wellbeing), UK Medical Research Council, Indian Council of Medical Research, Research Council of Norway, Bill & Melinda Gates Foundation and Wellcome Trust. In the statement, the signatories pledged to develop and implement a policy with mandated timeframes for prospective registration and public disclosure of the results of clinical trials that they fund, co-fund, sponsor or support. In addition, they agreed to monitor adherence to the policies and share publicly the outputs of these monitoring processes.⁶³

The WHO maintains the International Clinical Trials Registry Platform (ICTRP).⁶⁴ The ICTRP Search Portal had 560,000 records as of the third quarter of 2019, and provides a searchable database containing the trial registration data sets. These data sets constitute international standards for clinical trials registration. The platform also has the unique ability to link together (bridging) records registered in different countries (or multi-country trials). As of 2019, the ICTRP database received more than 4,500 new clinical trial registry entries each month; the number of new clinical trials globally continues to increase.

The WHO considers the registration of all interventional trials a scientific and ethical responsibility. The rationale for the ICTRP includes the following considerations:

- Decisions about health care should be informed by all the available evidence.
- Publication bias and selective reporting make informed decisions difficult.
- Improving awareness of similar or identical trials enables researchers and funding agencies to avoid unnecessary duplication.

- Describing clinical trials in progress can make it easier to identify gaps in clinical trials research and to define research priorities.
- Making researchers and potential participants aware of trials may facilitate recruitment and increase patients’ active involvement in the clinical trial process.
- Enabling researchers and health-care practitioners to identify trials in which they may have an interest could result in more effective collaboration among researchers, including prospective meta-analysis.
- Registries checking data as part of the registration process may lead to improvements in the quality of clinical trials by making it possible to identify potential problems early in the research process.

The World Medical Association Declaration of Helsinki states that “Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject” and that “[r]esearchers have a duty to make publicly available the results of their research. [...] Negative and inconclusive as well as positive results must be published or otherwise made publicly available” (WMA, 2013). In addition to the ethical imperative, poor allocation of resources for product development and financing of available interventions, and suboptimal regulatory and public health recommendations may occur where decisions are based on only a subset of all completed clinical trials.

However, 30–50 per cent of clinical trials remain unreported across trials of different sizes and product classes (Schmucker et al., 2014; Goldacre et al., 2018). The WHO considers that the prospective registration and timely public disclosure of results from all clinical trials is of critical scientific and ethical importance. Timely results disclosure reduces waste in research, increases value and efficiency in the use of funds and reduces reporting bias, which should lead to better decision-making in health (WHO, 2015f).

Open access policies⁶⁵ are important for effective sharing of clinical trial results and individual participant data from trials, for example, for the purpose of meta-analysis (see Chapter II, section B.1(c)(iv)). As trials are registered, this sets a basis for development of individual participants’ data (IPD)-sharing. Legal frameworks are required to govern the personal and ethical aspects of data collection and use, including PIC of the persons concerned, and enable development of international norms and standards for the sharing of IPD from clinical trials.

Since 2010, the EMA has begun providing access to clinical trial data, allowing interested parties to verify the data (see Box 3.6).⁶⁶

Box 3.6: European Medicines Agency makes available clinical trials data

Following the adoption of the new EMA policy on the publication of clinical data for medicinal products for human use in October 2014,⁶⁷ the EMA started providing open access to data submitted by pharmaceutical companies in support of their regulatory applications (dossiers) in October 2016,⁶⁸ the first regulatory authority worldwide to do so. The objective of the policy is to avoid duplication of clinical trials and to encourage innovative activities to develop new medicines, and also to allow academics and researchers to reassess clinical trial data.

In addition, the European Union adopted a regulation in 2014 that requires an EU Clinical Trials Portal and Database to be established.⁶⁹ The portal will be a “single entry port” for regulatory submissions, streamlining and harmonizing regulatory review, and for accessing clinical trial data, and is expected to be opened in 2020.⁷⁰ Clinical trial information will be accessible to the public, unless the confidentiality of the information can be justified on certain grounds. A summary of the results of a clinical trial and a summary for laypersons shall be submitted in the database within one year of the end of the clinical trial in all EU member states, irrespective of its outcome. Additionally, the clinical study report shall be submitted 30 days after a marketing authorization for a medicinal product has been granted, the procedure is completed or the marketing authorization application is withdrawn.

The terms of use for the EMA clinical data publication website clarify that the clinical reports are protected by copyright or other IPRs (see Chapter II, section B.1(e)) and can be considered commercially valuable when used for commercial and regulatory purposes. Therefore, they may only be viewed on the screen using the interface provided by the EMA and not be used for the purpose of submitting an application to obtain a marketing authorization or any extension or variation thereof anywhere in the world, nor may the user make any unfair commercial use of the reports (see Chapter II, section B.1(c)).⁷¹

C. Overcoming market failures in medical product R&D

Key points

- Market mechanisms, such as intellectual property rights (IPRs), do not work for incentivizing medical R&D for diseases that disproportionately affect people in developing countries. For neglected diseases, a key factor is the limited purchasing power of both governments and patients in the countries where such diseases predominate and a chronic lack of investment in R&D.
- While a huge research gap for neglected diseases remains, the health R&D landscape and the share of the global disease burden have been changing since 1990 and funding of R&D for neglected diseases has increased, predominantly from the public sector.
- Stewardship, innovation and access are three key objectives in addressing antimicrobial resistance (AMR). The current antimicrobial development pipeline is insufficient to address the increasing resistance seen in priority pathogens. The lack of investment in R&D to address AMR has been discussed in numerous political fora, and a number of reports have analysed the problem and suggested solutions.
- The WHO R&D Blueprint is a global strategy and preparedness plan to ensure that targeted R&D strengthens emergency responses by bringing medical technologies to populations and patients during epidemics.
- In 2012, the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) made recommendations for new and innovative models of financing R&D, including establishing a binding global instrument for R&D and innovation for health.
- New innovation mechanisms and models aimed at increasing R&D to find effective treatments for neglected diseases have been discussed and implemented at international and national levels. Examples include the Drugs for Neglected Diseases *initiative*. An innovative model set up in cooperation among multiple stakeholders is WIPO Re:Search Sharing Innovation in the Fight Against Neglected Tropical Diseases.
- Product development partnerships have significantly increased the number of products in development for diseases that predominantly affect developing countries.

In the traditional, dominant model of financing pharmaceutical R&D, private investments in R&D are incentivized by the promise of potential profits once a product reaches the market. The promise of potential profits is supported by the expectation that relatively high prices can be charged to payers during the protection period of the IPRs and/or regulatory exclusivity schemes. Market failures arise, for example, in cases in which the target patient population and/or relevant payers will not be able to pay, or where there is a small market for other reasons. Examples of such market failures, and current initiatives seeking solutions to the failures, are outlined in this section. Much of the debate over market failures in biomedical R&D has centred around neglected diseases, and, since the early 2010s, AMR and pathogens of epidemic potential, such as Ebola virus disease. Many proposals for incentivizing R&D, including incentive mechanisms alternative and supplementary to IPRs, as well as novel models of funding R&D, have been made.⁷²

1. Diseases disproportionately affecting people in developing countries

There is a particular problem in incentivizing medical R&D for diseases that disproportionately affect people in

developing countries, as the market mechanisms, such as IPRs, do not work in this case. A key factor is the limited purchasing power of both governments and patients in the countries where such diseases predominate; unlike for other diseases, there is no positive spill-over from drug development targeted at more affluent markets. This section deals with the challenges of medical innovation in diseases that affect disproportionately people in developing countries.

Both the CIPIH (WHO, 2006a) and the GSPA-PHI refer to diseases that disproportionately affect people in developing countries. This concept is based on the three types of diseases distinguished by the Commission on Macroeconomics and Health (WHO, 2001a):

- Type I diseases are found in both rich and poor countries and affect large numbers of vulnerable populations in both. Examples of communicable diseases include measles, hepatitis B and haemophilus influenzae type B. Examples of NCDs include diabetes, cardiovascular diseases and tobacco-related illnesses.
- Type II diseases are incident in both rich and poor countries, but with a substantial proportion of cases in poor countries. Examples of such diseases include HIV/AIDS and TB. While both diseases are present

in rich and poor countries, more than 90 per cent of cases occur in poor countries.

- Type III diseases are those that are overwhelmingly or exclusively incident in developing countries. Examples of such diseases include African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis).

Type II and Type III diseases are often referred to as neglected diseases. These also include the neglected tropical diseases (NTDs) that are a specific focus of the work of WHO and affect more than one billion people, as well as neglected aspects of diseases that affect high-income countries, for example, HIV vaccine research and certain genotypes of hepatitis C.⁷³

The distribution of NTDs is restricted by climate, in particular by its effect on the distribution of vectors and reservoir hosts. In most cases, there appears to be a low risk of transmission beyond the tropics. Unlike influenza, HIV/AIDS and malaria and, to a lesser extent, TB, most NTDs present little threat to the inhabitants of high-income countries, thus triggering less attention. They are relatively neglected by the pharmaceutical research that is needed to develop new diagnostics and medicines and to make accessible interventions to prevent, cure and manage the complications of these diseases.

The situation has been characterized by a chronic lack of investment in R&D to find effective treatments for neglected diseases. The innovation effort is starkly disproportionate to the public health challenge posed by such diseases.

In 1990, the Commission on Health Research for Development found that of the US\$ 30 billion global investment in health research in 1986, only 5 per cent, or US\$ 1.6 billion, was devoted specifically to health problems of developing countries, although an estimated 93 per cent of the world's burden of preventable mortality occurred in the developing world.⁷⁴ Later, based on this data, the Global Forum for Health Research coined the term “10/90 gap” to highlight the gap between the share of the global disease burden and the resources devoted to addressing it. In a 2015 analysis, it was found that poverty-related and neglected diseases represent 14 per cent of the global burden of disease but attract only 1.3 per cent of global R&D expenditure (von Philipsborn et al., 2015).

While a huge research gap for neglected diseases still exists, both the health research landscape and the share of the global disease burden have been changing positively since 1990. The G-FINDER survey reported that the funding of R&D for neglected diseases was more than US\$ 3 billion in 2017, representing the first (small) year-on-year increase since 2012. The three “top tier” diseases – HIV/AIDS, TB and malaria, received 70 per cent of funding, leaving only 30 per cent of funding in the neglected diseases area available for carrying out

research on all other neglected diseases (Chapman et al., 2017). Significantly more money is spent on development of new medicines than on vaccines. Only a small proportion of neglected disease R&D spending – less than 10 per cent for most disease categories – goes to diagnostics. Funding comes predominantly from the public sector. In 2016, the public sector provided almost two thirds (US\$ 2.0 billion, 64 per cent) of global funding, with high-income countries contributing 96 per cent of this. The philanthropic sector contributes US\$ 671 million (21 per cent) and the private sector invested US\$ 497 million (16 per cent) (Chapman et al., 2017). A 2017 survey found 685 product candidates for neglected diseases, of which 57 per cent targeted HIV, TB or malaria. The most common type of treatment in the pipeline was vaccines (Young et al., 2018).

WHO strategies in this area include the 2021–2030 road map for neglected tropical diseases, the End TB Strategy, and the Global Technical Strategy for Malaria 2016–2030.

2. Antimicrobials and antimicrobial resistance

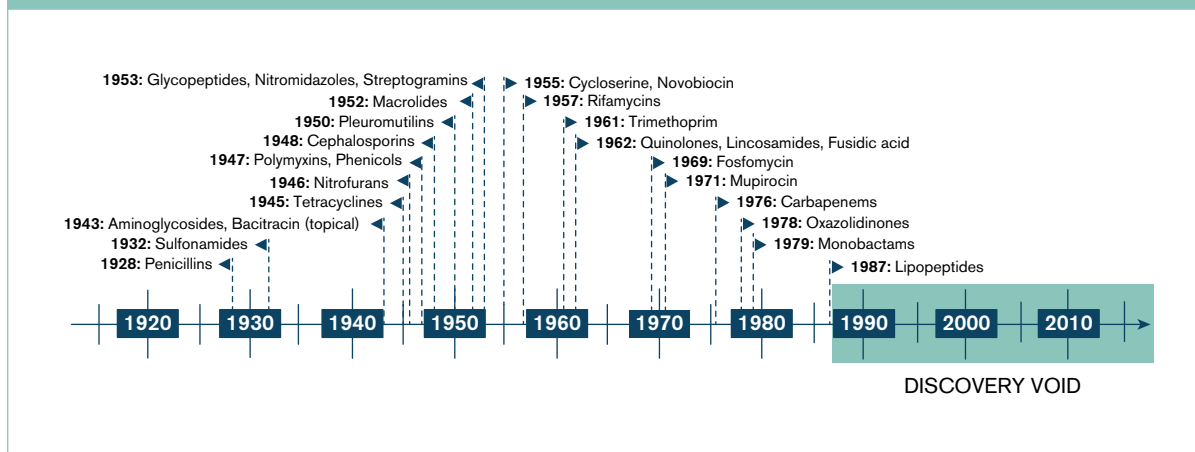
While it is challenging to come up with concrete numbers,⁷⁵ it is increasingly obvious that the disease burden caused by AMR is high and increasing steadily in both high-income countries and LMICs:

- The European Centre for Disease Prevention and Control (ECDC) estimates that infections with resistant bacteria in the European Union and European Economic Area accounted for 33,110 attributable deaths and 874,541 DALYs in 2016, which is comparable to the combined disease burden of influenza, TB and HIV/AIDS.⁷⁶
- The US Centers for Disease Control estimate that in the United States each year, at least 2 million people get an antibiotic-resistant infection, causing more than 35,000 deaths.⁷⁷

While infections with antibiotic-resistant bacteria affect all age groups, the elderly and infants are disproportionately affected and suffer from a significantly higher burden of disease. One study estimated that, globally, 214,000 neonatal sepsis deaths are attributable to resistant pathogens each year, a vast majority of them in LMICs (Laxminarayan et al., 2016). In Europe, health-care-associated infections dominate, representing about 63.5 per cent of the total burden of AMR infections (Cassini et al., 2019).

Many of these infections could be prevented through strengthened infection prevention and control, using available tools and ensuring access to clean water, sanitation and hygiene in health facilities (WASH (water, sanitation and hygiene) practices).

Figure 3.7: Timeline of the discovery of different antibiotic classes in clinical use



Source: ReAct, available at: <https://www.reactgroup.org/antibiotic-resistance/course-antibiotic-resistance-the-silent-tsunami/part-3/nearly-empty-pipeline/>.

The current antimicrobial development pipeline is insufficient to address increasing resistance of priority pathogens. Following the period of high discovery rates of new antibiotics in the mid-20th century, scientific challenges and a lack of investment resulted in very few new classes of antibiotics being developed. Of the approved classes of antibiotics, none were discovered in the last three decades (see Figure 3.7). For Gram-negative bacteria, which are, overall, the more dangerous category, all of the approved classes of antibiotics were discovered before 1965 (Deak et al., 2016).

Private-sector pharmaceutical companies have steadily divested from antimicrobial R&D; in 2019, only three large pharmaceutical companies were still active in this field, while 23 have abandoned it since 1980.⁷⁸ Less than 5 per cent of venture capital investments in pharmaceutical R&D between 2003 and 2013 was invested in antimicrobials research, and investments decreased over this period.⁷⁹ As of September 2019, 32 new antibiotics that target therapeutics and 4 combinations that target WHO priority pathogens were in the pipeline (WHO, 2019a). However, most of the private-sector development remains focused on existing classes of antibiotics, where the risk of failure is significantly lower (Jenner et al., 2017). In addition, an expert group identified 36 older, “forgotten” antibiotics – that is, antibiotics that are no longer manufactured – that may be useful if brought back to the market (Pulcini et al., 2016).

Private investments are insufficient to fill the current R&D gap, although the market potential varies widely among new, superior and “me-too” antibiotics. The fact that new antibiotics must compete with existing generic treatments and should be used sparingly to slow the development of resistance limits their market potential.⁸⁰ In addition, the market-driven R&D model does not direct investment to the most urgent public health needs, such as fighting multidrug-resistant pathogens,

where the patient population is still relatively small. Besides new antimicrobials, new and affordable point-of-care diagnostics are also urgently needed to support responsible and prudent use of antimicrobials.

The lack of investment in R&D to address AMR has been discussed in numerous political fora, and a number of reports have analysed the problem and suggested solutions. Examples include the UK Review on Antimicrobial Resistance and the DRIVE-AB report.⁸¹ The IACG suggested that one way of optimizing and increasing the impact of funding for R&D in this area would be through “delinking” mechanisms (see section C.5).⁸²

A combination of push strategies (e.g. direct funding, research grants, government laboratories or tax credits) that support research inputs and pull strategies (e.g. milestone prizes, new reimbursement models or market entry rewards) that reward research output would stimulate investment and the development of new products. The importance of delinkage was underlined in the Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance in 2016. While countries have not reached consensus on how to sustainably finance new pull and existing push mechanisms, in recent years, a number of regional and global initiatives have been established (see Box 3.7).

In addition to product development, critical needs include applied and interventional research on preventing AMR development and transmission, promoting appropriate and prudent use, improving animal husbandry, preventing hospital-acquired infections and gathering further evidence on antimicrobial residues in the environment and their impact. In many cases, improved infection prevention and control measures offer better value for money and a quicker solution than developing new health technology solutions.

Box 3.7: Initiatives to revitalize the antimicrobial pipeline**The WHO priority pathogens list and antibacterial pipeline analysis**

As part of implementation of the Global Action Plan on Antimicrobial Resistance, the WHO has produced a list of priority antibiotic-resistant pathogens (priority pathogens list, or PPL).⁸³ The WHO also produces analyses of the current clinical development pipeline for antibacterial agents, to assess the extent to which the pipeline addresses priority pathogens.

These analyses are intended to guide R&D efforts, by identifying where R&D efforts should be directed and where there are research gaps.

The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)

CARB-X is a global partnership based at Boston University, launched in 2016.

CARB-X provides financial, scientific and business support to accelerate R&D on new agents to combat pathogens identified as priorities by the WHO and US Centers for Disease Control. The aim of CARB-X is to support R&D projects through the pre-clinical and Phase I stages, so that they are able to attract further private or public investments from other sources for later development.⁸⁴

The Global Antibiotic Research and Development Partnership (GARDP)

GARDP is a not-for-profit drug developer that addresses global public health needs by developing affordable new or improved antibiotic treatments. GARDP was established in 2016 by the WHO and Drugs for Neglected Disease *initiative* (DNDi; see Box 3.12). GARDP is an important element of the Global Action Plan on Antimicrobial Resistance, which calls for new PPPs to encourage R&D of new antimicrobial agents and diagnostics.

GARDP's R&D strategy is based on global health priorities, target product profiles and R&D roadmaps. GARDP aims to deliver four new treatments by 2023, and currently has four R&D programmes, focusing on sexually transmitted infections, neonatal sepsis, paediatric antibiotics and antimicrobial memory recovery (revisiting previously abandoned research projects). GARDP plans to implement the principle of delinking the costs of R&D from product revenues, to ensure affordability as well as sustainable quality production.⁸⁵

The Global Antimicrobial Resistance Research and Development Hub (Global AMR R&D Hub)

The Global AMR R&D Hub,⁸⁶ established in May 2018 under the lead of the German Federal Government, is open to countries and observers and aims at improving coordination of, and increasing investment in, R&D for AMR. By December 2019, the Global AMR R&D Hub plans to launch an online Dynamic Dashboard that will present all AMR R&D investments globally, including data from the human, animal, plant and environment health sectors.

The International Centre for AMR Solutions (ICARS)

Established by the Government of Denmark in 2018, ICARS is an international One Health knowledge and applied research partnership, committing to working closely with low- and middle-income countries to support intervention and implementation research to tackle AMR.⁸⁷ It aims at translating aspects of national action plans and policies into evidence-based practices on the ground, while building capacity and capability within countries.

3. The WHO R&D Blueprint for Action to Prevent Epidemics

In 2014 and 2015, the world experienced the largest and longest Ebola outbreak in history. The outbreak showed that new models were needed for coordinating and financing R&D for preventing and treating pathogens of epidemic potential such as Ebola virus and others (see Box 3.12). As a direct response, the WHO developed the R&D Blueprint.

The R&D Blueprint is a global strategy and preparedness plan to ensure that targeted R&D will strengthen the

emergency response by bringing medical technologies to populations and patients during epidemics.⁸⁸ Under the R&D Blueprint, the WHO follows a systematic approach to ensure that missing vaccines, treatments and diagnostics for each blueprint pathogen are developed at least to clinical Phase II to ensure better preparedness in case of a major outbreak. The basis is a list of priority blueprint pathogens with pandemic potential that the WHO considers the greatest threats (see Box 3.8), which is regularly updated. For each pathogen, the WHO systematically reviews all the treatments that are on the market (if any) and in development and identifies gaps. Based on the specific virus and the research landscape, the WHO,

in collaboration with all stakeholders, defines research priorities to fill remaining gaps, which could be a vaccine, treatment or diagnostics, depending on the medical needs. Based on this, the WHO develops target product profiles for missing products, defining the characteristics of each. The target product profiles are guiding researchers and funders such as the Coalition for Epidemic Preparedness Innovation (CEPI) and the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) to invest in and develop the missing tools.⁸⁹

Box 3.8: WHO R&D Blueprint for Action to Prevent Epidemics: priority list as at February 2018⁹⁰

- Crimean-Congo haemorrhagic fever (CCHF)
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever (RVF)
- Zika virus disease
- Disease X

Note: Disease X represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease, and so the R&D Blueprint explicitly seeks to enable cross-cutting R&D preparedness that is also relevant for an unknown “Disease X” as far as possible.

4. WHO Expert Working Groups on R&D financing

The WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) examined the financing and coordination of R&D, and reviewed proposals for new and innovative models of financing R&D. The CEWG report was published in 2012.

The criteria for assessing the proposals included: public health impact; efficiency/cost-effectiveness; technical, financial and implementation feasibility; role of IP; delinking; access, governance and accountability aspects; and capacity-strengthening potential.⁹¹ A detailed presentation and analysis of each of these proposals is set out in Annex 3 of the 2012 CEWG report (WHO, 2012) (see Box 3.9).

The CEWG also developed principles that should guide health R&D funding allocation more generally, in particular, that health research and development should be needs driven and evidence based and be guided by the following core principles: affordability, effectiveness, efficiency and equity.⁹²

5. Novel approaches to biomedical R&D

This section presents examples of initiatives that explore novel models of biomedical R&D. It includes information on various WHO developments. This section also reviews

Box 3.9: 2012 CEWG report: key recommendations

Approaches to R&D:

- Open knowledge innovation, pre-competitive R&D platforms, open source and open access schemes, and the utilization of prizes, in particular, milestone prizes
- Equitable licensing and patent pools

Funding mechanisms:

- All countries should commit to spend at least 0.01 per cent of GDP on government-funded R&D aimed at addressing the health needs of developing countries in relation to product development.

Pooling resources:

- Between 20 per cent and 50 per cent of funds raised for health-related R&D aimed at addressing the needs of developing countries should be channelled through a pooled mechanism.

Strengthening R&D capacity and technology transfer:

- Address the capacity needs of academic and public research organizations in developing countries.
- Utilize direct grants to companies in developing countries.

Coordination:

- Establish a global health R&D observatory and relevant advisory mechanisms under the auspices of the WHO.

Implementation through a binding global instrument for R&D and innovation for health:

- Formal negotiations on an international convention on global health R&D should be initiated.⁹³

the role of PDPs and the efforts of research-based pharmaceutical companies in addressing neglected health areas.

There is a drive to find alternative and innovative ways to undertake needs-based research. New initiatives aimed at increasing R&D to find effective treatments for neglected diseases are under way, involving a diverse group of actors and a large number of collaborative partnerships. An example of an innovative model set up in cooperation among multiple stakeholders is WIPO Re:Search (see section C.8).

One important concept that evolved from this discussion is that of delinking the price of the final product from the costs of R&D. This concept is based on the fact that patents allow developers to recoup the costs and make profits by charging a price in excess of the costs of production. This way of financing R&D is considered to constitute a barrier to access to medicines where it results in product prices that the health system, or patients paying out of pocket, cannot afford. The principle of delinkage is based on the premise that the costs and risks associated with R&D should be rewarded, and incentives for R&D provided, other than through the price of the product. This type of delinkage is particularly advocated in the case of financing R&D for neglected diseases and new antibiotics.⁹⁴

Delinkage can be facilitated by both push mechanisms and pull mechanisms. Push mechanisms are incentives that provide funding to begin an R&D project, such as grant funding or tax credits for investments in R&D. Pull mechanisms are incentives that offer rewards for certain achievements in the R&D process, such as milestone prizes (e.g. awarded upon entry into Phase I, II, or III trials) or end prizes. The following section, while not exhaustive, describes some of these approaches. Assessments of many related proposals can be found in the reports of the WHO Expert Working Group on Research and Development: Financing and Coordination and the CEWG.

(a) Monitoring health R&D

Improving the availability of information on financial flows in health R&D and the state of the R&D pipeline can support policy responses to fill research gaps. Following the recommendation of the CEWG (see Box 3.9), the Global Observatory on Health R&D has been established within the WHO Secretariat to monitor and analyse relevant information on health R&D for neglected diseases. The Global Observatory on Health R&D is a global initiative that aims to help identify health R&D priorities based on public health needs, by consolidating, monitoring and analysing relevant information on the health R&D needs of developing countries, building on

existing data collection mechanisms and supporting coordinated actions on health R&D.⁹⁵

A number of other initiatives also contribute to understanding the financial flows and pipeline of health R&D, for example, G-FINDER, which publishes data on neglected disease R&D funding,⁹⁶ WHO analyses of the pipeline for antibacterial medicines⁹⁷ and the reports of Treatment Action Group on the pipeline for medicines for HIV, TB and hepatitis C virus.⁹⁸

(b) Grants

Grants are a common method for financing public-sector research. A grant may enable an SME to, for example, undertake initial research for a medicine on a neglected disease and bring a potential new medicine through Phase I trials, at which stage it may be possible to attract commercial funding.

While grants can be useful for stimulating R&D, they provide no guarantee that a viable drug will ultimately be delivered. This is because grants are paid irrespective of the results achieved.

Innovative financing mechanisms that utilize “push” funding include Unitaid (see Box 3.10) and CARB-X (see Box 3.7).

(c) Prizes

Prizes work as a pull mechanism in R&D by offering rewards for success, thereby making investment more attractive and the delivery of a specific product more likely (see Box 3.11). There are two categories of innovation inducement prizes: the first is awarded for reaching a specified milestone in the R&D process; the second rewards the attainment of a specified endpoint (such as a new diagnostic, vaccine or medicine with a particular profile in terms of performance, cost, efficacy or other important characteristics). Such prizes pre-specify certain characteristics of the product (i.e. target product profiles) that the winner, it is hoped, will ultimately develop. Other prizes can recognize innovations that bring substantial benefits to society without seeking a pre-specified product.

While inducement prizes would provide incentives for drug development, they would also aim to delink R&D costs from the prices of medicines. The effect that such prizes could have on innovation and access would largely depend on the size of the prize fund, the application and design of the medicines developed and the manner in which they align research efforts with health priorities, while aiming to leverage access by keeping prices of finished products low.

Box 3.10: Unitaid⁹⁹

Created in 2006, Unitaid is an international organization, hosted by the WHO, that invests in innovations for global health. Unitaid's work supports access to products that prevent, diagnose and treat diseases more quickly, affordably and effectively.

Unitaid researches and identifies new health solutions with potential to alleviate the burden of HIV/AIDS, TB and malaria, as well as HIV co-infections such as hepatitis C and human papillomavirus. Through calls for proposals, Unitaid finds partners best qualified to put key innovations into practice. These partners receive grants from Unitaid to fast track access and reduce the costs of more effective medicines, technologies and systems. In this way, Unitaid's investments establish the viability of health innovations, allowing partner organizations to make them widely available.

With regard to IPRs, Unitaid's flagship project is the Medicines Patent Pool, which negotiates voluntary licences with originator companies (see Box 4.24).

Since its establishment, Unitaid has received approximately US\$ 3 billion in contributions from donors, the main donors being France, the United Kingdom, Brazil, the Bill & Melinda Gates Foundation, Norway, the Republic of Korea, Chile and Spain. Innovation is at the core of Unitaid, and a key source of income is innovative financing, particularly the airline tickets levy implemented by Chile, France and the Republic of Korea. To date, Unitaid has received nearly US\$ 2 billion from such innovative financing mechanisms, accounting for two thirds of total contributions.

Box 3.11: Examples of prize schemes**The Longitude Prize**

The Longitude Prize is for an affordable, accurate, fast and easy-to-use test for bacterial infections that allows health professionals worldwide to administer the right antibiotics at the right time.¹⁰⁰

The Life Prize

The Life Prize (previously the "3P Project"), launched by Médecins Sans Frontières and run by the International Union Against Tuberculosis and Lung Disease, is a proposed initiative that, among other things, would incentivize the development of new TB treatments by offering milestone prizes for a product that fits a target product profile (Brigden et al., 2017).

The EU prize for innovative vaccine technology

The European Commission offered a EUR 2 million "inducement prize" to a research team offering novel solutions to improving temperature stability of vaccines, as refrigerating vaccines presents a major challenge in many LMICs. Submissions were received from 49 competitors; the prize was awarded to a German company (European Commission, 2014a).

The Horizon 2020 prize to reduce misuse of antibiotics

The European Commission offered a EUR 1 million prize for a rapid point-of-care test to identify which upper respiratory tract infections can be treated without antibiotics. Such a test could support a reduction in unnecessary use of antibiotics, a driver of antimicrobial resistance.¹⁰¹

US Patent and Trademark Office Patents for Humanity programme

The US Patent and Trademark Office (USPTO) Patents for Humanity programme awards prizes to applicants who develop innovations to address pressing global needs.¹⁰² Awardees receive a certificate to accelerate the examination of their patent applications before the USPTO, as well as certain re-examination or appeal proceedings. The programme has rewarded innovation in medical devices adapted for difficult environments: one of its 2018 winners developed a portable, low-water kidney dialysis machine for use in areas that lack infrastructure required for traditional dialysis. Unlike the other examples above, the Patents for Humanity programme does not issue specific target product profiles.

Prizes can have a favourable impact on the development of, and access to, health products. For example, certain requirements relating to IP management may be imposed on a prize winner, including allowing free use of the technology by the public sector or developing countries, in order to promote competition for supply. Some prize schemes include such IP requirements (e.g. the Life Prize), while others do not (e.g. the Patents for Humanity programme) (see Box 3.11). Where IP management is not integrated into the prize mechanism, access to the resulting technology will not be influenced by the awarding body and will depend on the patent holder's business strategy.

(d) Advance market commitments and advance purchase commitments

AMC agreements aim to create greater incentives for the R&D of a specific product, through either market creation or risk reduction. AMC agreements operate as contracts between a purchaser (normally a government or an international financing agency) and suppliers. They usually contain some form of agreed guarantee with regard to price or volume. By effectively guaranteeing a market, pharmaceutical companies are incentivized to undertake R&D.¹⁰³ Box 3.5 provides an example of how AMCs can be implemented.

(e) Priority review vouchers

A priority review voucher (PRV) is a scheme that aims to reward companies that develop health products that address small markets or limited patient groups, as is the case also with neglected diseases. The PRV entitles a company to receive priority review (i.e. quicker review by the responsible regulatory authority) for any additional health products that would not otherwise qualify for priority review. A company can use this scheme to advance the marketing date of a potential "blockbuster" product, thus generating increased and earlier revenues from that product.

A PRV scheme was introduced in the United States in 2007. Under this scheme, companies that obtain marketing approval from the FDA for a product to treat or prevent one of 16 NTDs are entitled to receive a PRV. In 2012, the scope of eligibility was extended to include rare paediatric diseases,¹⁰⁴ and, in 2016, was extended to include "medical countermeasures" (health products that could be used for public health emergencies stemming from a terrorist attack or a naturally occurring "emerging" disease).¹⁰⁵ PRVs have now more often been issued for rare paediatric diseases than for neglected diseases (see Table 3.1).¹⁰⁶ A PRV can be used by the recipient for any future product filing, or it can be sold to another

company at a rate determined by the market: PRVs have been sold numerous times, for amounts ranging from US\$ 67.5 million to US\$ 350 million (see Figure 3.8; Ridley and Régnier, 2016).

Since this scheme was introduced in the United States, a number of PRVs have been issued (see Table 3.1). The first PRV was issued in April 2009 for the development of an antimalarial drug, and the second, in December 2012, for bedaquiline, the first anti-TB drug in 40 years (see Chapter IV, section B.3).

Some argue that the value of the voucher is too small to have meaningful impact on the allocation of R&D resources by large pharmaceutical companies. A voucher might be attractive for smaller companies, but these companies are less likely to progress a health product through to development phase in view of the large costs of that phase. The value of a voucher is uncertain since it does not guarantee that an additional company product will, in fact, ultimately be approved by the regulatory authority, nor does it guarantee that the time saved by a priority review will actually exceed one year. It has been argued that the value of PRVs has decreased because they were granted too often (Ridley and Régnier, 2016).

The PRV mechanism can also be used to finance non-profit drug development initiatives. The WHO Special Programme for Research and Training in Tropical Diseases (TDR) partnered with a non-profit pharmaceutical company to develop moxidectin for the treatment of onchocerciasis, an NTD. The prospect of obtaining a PRV enabled the non-profit pharmaceutical company to raise US\$ 13 million from a social impact investment fund to develop moxidectin, as the revenue from selling the PRV is expected to be significant (see Figure 3.8) and would be reinvested in the NTD sector, offering the funder a "multiplier" effect. In 2018, the FDA approved moxidectin and awarded a PRV (Olliaro et al., 2018).

(f) Tax breaks for companies

Many countries provide tax credits for R&D expenditures, enabling companies to account for expenditure on R&D against their tax liabilities. In the United Kingdom, tax credits were introduced with the express goal of incentivizing research on vaccines for HIV/AIDS, TB and malaria, though this tax credit was discontinued in 2017 due to low uptake (Rao, 2011; HM Revenue & Customs, 2016). Tax credits are also provided for orphan (rare disease) products in some countries (see section B.6).

Tax credits cannot by themselves remedy the absence of market incentives for neglected diseases. As long

Table 3.1: PRVs issued, 2009–2019

Year awarded	Disease	Category	Product
2009	Malaria	ND	artemether/lumefantrine
2012	Tuberculosis	ND	bedaquiline
2014	Morquio A syndrome	RPD	elosulfase alfa
2014	Leishmaniasis	ND	miltefosine
2015	High-risk neuroblastoma	RPD	dinutuximab
2015	Rare bile acid synthesis disorders	RPD	cholic acid
2015	Hereditary orotic aciduria	RPD	uridine triacetate
2015	Hypophosphatasia	RPD	asfotase alfa
2015	Lysosomal acid lipase (LAL) deficiency	RPD	sebelipase alfa
2016	Cholera	ND	single-dose live oral cholera vaccine
2016	Duchenne muscular dystrophy	RPD	eteplirsen
2016	Spinal muscular atrophy (SMA)	RPD	nusinersen
2017	Duchenne muscular dystrophy	RPD	deflazacort
2017	Batten disease	RPD	cerliponase alfa
2017	Chagas	ND	benznidazole
2017	B-cell acute lymphoblastic leukaemia	RPD	tisagenlecleucel
2017	Mucopolysaccharidosis (MPS) VII	RPD	vestronidase alfa
2017	Biallelic RPE65 mutation-associated retinal dystrophy	RPD	voretigene neparovec-rzyl
2018	X-linked hypophosphatemia (XLH)	RPD	burosumab-twza
2018	Onchocerciasis (river blindness)	ND	moxidectin
2018	Lennox-Gastaut or Dravet syndrome	RPD	cannabidiol
2018	Smallpox	MTMC	tecovirimat
2018	Malaria	ND	tafenoquine
2018	Adenosine deaminase-severe combined immunodeficiency (ADA-SCID)	RPD	elapegamase-lvlr
2018	Primary haemophagocytic lymphohistiocytosis	RPD	emapalumab-lzsg
2019	Fascioliasis	ND	triclabendazole
2019	Cystic fibrosis	RPD	tezacaftor/ivacaftor
2019	Dengue	ND	dengue tetravalent vaccine
2019	Spinal muscular atrophy	RPD	onasemnogene abeparovec-xioi

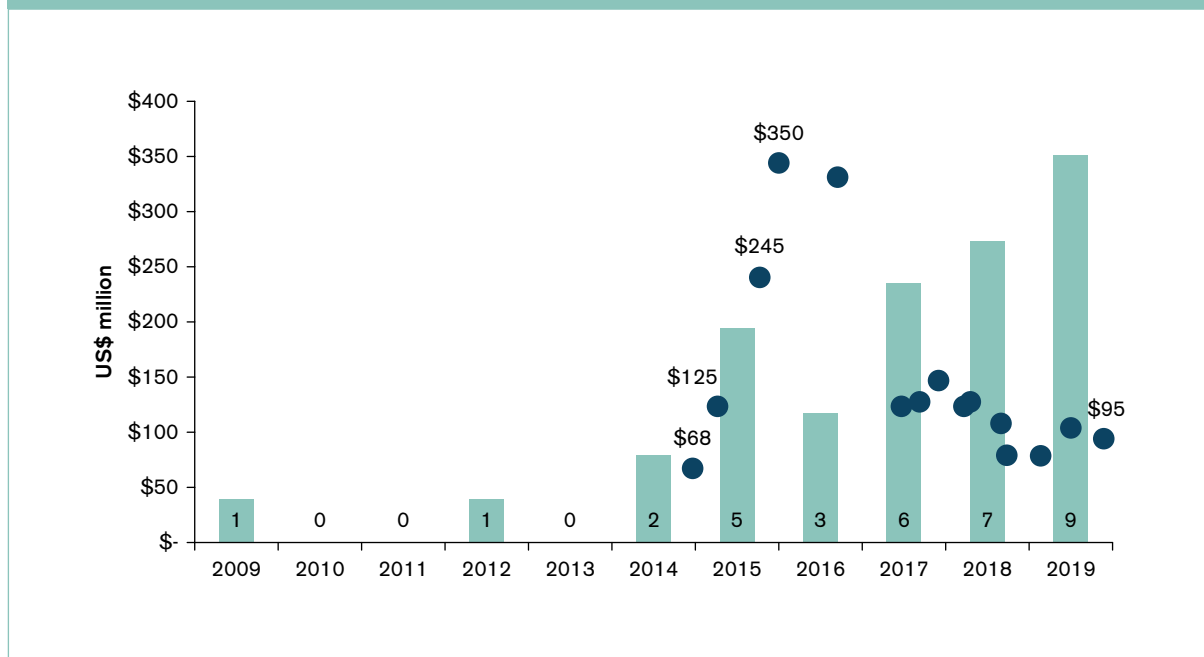
Source: Adapted from www.priorityreviewvoucher.org, a website maintained by David Ridley, one of the authors of the PRV.

Notes: ND = neglected disease; RPD = rare paediatric disease; MTMC = material threat medical countermeasure.¹⁰⁷

as a company has to recover a substantial amount of its investment in R&D for a drug through revenues, tax credits cannot effectively drive innovation for products for which there is no demand. Some commentators have questioned the application of tax credits for profitable products (Bagley, 2018; Hughes and Poletti-Hughes, 2016).

Tax credits cannot help where companies are operating at a loss – as is the case with some biotechnology companies in their start-up phase, before they have launched any approved product onto the market. Another disadvantage of the introduction of tax breaks is that they may simply subsidize R&D that a company would have undertaken anyway.

Figure 3.8: Number and sales values of PRVs



Source: <http://priorityreviewvoucher.org>.

(g) Patent pools

A patent pool is an agreement between at least two patent owners to group their patent rights relating to a specific technology and to license the rights to use these patents to each other and to third parties, subject to certain conditions, such as the payment of royalties. Pooling the relevant patents necessary to use a technology, or to produce downstream products, allows licensees to enter into only one licence agreement with one legal entity and has been advocated as a tool to be used in R&D for neglected diseases. Patent pools have been used since the 19th century in different industry sectors. Early patent pools were aimed at fixing prices and keeping competitors out of the market, and thus came into conflict with competition law. Today, most patent pools aim to enable access to new technologies and to foster downstream competition. By reducing transaction costs for licensees, patent pools provide easy access to all patented technologies needed to produce standardized products. The audio-visual industry, for example, has adopted pooling as an instrument to facilitate licensing of standard technology and has established a number of successful patent pools.¹⁰⁸ The success of patent pools depends on two key factors: (i) the participation of key patent holders, as, without their participation, the patent pool can be held hostage by patent holders outside the pool; and (ii) ensuring that administrative costs for the patent pool are kept low (Merges and Mattioli, 2017). Competition concerns can also arise from patent pools, as they may provide an opportunity for possible anti-competitive behaviour. It is thus important to ensure that licensing terms are worldwide and non-exclusive and any analysis should

examine whether the patent pool encourages collusive behaviour (WIPO, 2014b). An illustration of potential competition concerns for patent pools is the European Commission's investigation of a patent pool agreement for non-invasive prenatal testing in 2014, based on its block exemption for technology transfer agreements¹⁰⁹ and its guidelines on technology transfer agreements.¹¹⁰

In the field of pharmaceutical inventions, with funding from Unitaid, the Medicines Patent Pool (MPP) was established to pool patents for ARVs and has since expanded its scope of work (see Chapter IV, section C.3(b)). The MPP voluntary licences provide the freedom to develop new treatments, such as fixed-dose combinations – single pills composed of several medicines – and special formulations for children.

The Broad Institute of MIT and Harvard University entered into discussions about a potential patent pool to make CRISPR gene-editing technology (see Box 2.3) more widely available by streamlining the non-exclusive licensing procedure and limiting the duration of a licence for commercial research developing human therapeutics.¹¹¹ However, uncertainty around patent status related to questions of ownership,¹¹² and uncertainty around the scope of patents involved (Jewell and Balakrishnan, 2017), have made patent pooling difficult. This underlines the need for patent information, including through patent landscape reports, to support patent pool initiatives (see Chapter II, section B.1(viii)).

Patent pooling was also discussed as a possible solution to clear patent thickets to facilitate a response to SARS.¹¹³

(h) Open source drug discovery and development

Open source drug discovery and development builds on two principles borrowed from open source software development. First, open source drug discovery is based on the idea of collaboration, that is, organizing and motivating groups of independent researchers to contribute to research projects. Second, it is based on an open approach to IP that makes the outcome of that research generally available, through either the public domain or the use of customized licences (Maurer, 2007; Masum and Harris, 2011).

The success of open source models in the IT sector (e.g. web technology and the Linux operating system) and biotechnology sector (e.g. human genome sequencing) highlights both the need and the potential to initiate a similar model in health care, such as an open source model for drug discovery. Several open source drug discovery projects are currently under way.¹¹⁴ Most have secured financing either in the form of government grants or from philanthropic sources. These funds are used to cover administrative expenses and may also be used to fund access to laboratories and computer facilities and payment to researchers. Similarly, examples of open source data platforms are emerging, including the TB-Platform for Aggregation of Clinical TB Studies,¹¹⁵ Worldwide Antimalarial Resistance Network¹¹⁶ and Infectious Disease Data Observatory for Ebola.¹¹⁷ These platforms can be particularly useful in drug repurposing, where an existing drug can be used to treat another disease and where a significant amount of pre-clinical and clinical data already exists (Balasegaram et al., 2017).

However, the results of open source initiatives have been limited to date. Initiatives thus far have been on a relatively small scale, including in terms of funding. While they seem ideally suited to promoting pre-competitive research, the model would likely have to be combined with financing models to cover the costly development phases. Biopharmaceutical firms have used different organizational modes (i.e. licensing agreements, non-equity alliances, purchase and supply of technical and scientific services) to enter into relationships with different types of partners, with the aim of acquiring or commercially exploiting technologies and knowledge. These relationships can include large pharmaceutical companies, biotechnology product firms, biotechnology platform firms and universities.

(i) *A global binding framework for R&D and a pooled fund for R&D*

In adopting the GSPA-PHI, the World Health Assembly (WHA) called for “further exploratory discussions on the utility of possible instruments or mechanisms for essential health and biomedical R&D, including, inter alia, an essential health and biomedical R&D treaty”.¹¹⁸

The CEWG recommended that WHO member states negotiate a global convention or a treaty under the auspices of Article 19 of the WHO Constitution, aimed at providing effective financing and coordination mechanisms to promote R&D. Countries would, among other things, invest 0.01 per cent of their GDP in R&D for Type II and Type III diseases and in R&D for the specific needs of developing countries in relation to Type I diseases. Part of these contributions would be collected in a pooled fund at the global level (WHO, 2012).

WHO member states agreed to explore, evaluate and independently monitor existing mechanisms for contributions to health R&D for such diseases and, if needed, develop a proposal for effective mechanisms, including pooling resources and voluntary contributions.¹¹⁹ The WHO TDR explored implementation of a pooled fund, and published concrete proposals to set up a voluntary fund to finance neglected disease research.¹²⁰ Six “demonstration projects” were selected as precursors to such a fund, but WHO member states have not, ultimately, pursued the concept. Sufficient funding to finance the demonstration projects did not materialize (WHO, 2017d).

6. Product development partnerships

The term “public–private partnership” (PPP) is usually used to describe an initiative that consists of a partnership between government and at least one private-sector company. Today, such partnerships manage a large proportion of all neglected diseases drug development projects worldwide. PPPs have common characteristics:

- They integrate public- and private-sector approaches, and generally use industry practices in their R&D activities.
- They manage neglected diseases R&D portfolios, and they target one or more neglected disease.
- They are created in order to pursue public health objectives rather than commercial gains, and also to provide funding to cover existing research gaps.
- They ensure that the developed products are affordable (WHO, 2006a).

It is difficult, however, to clearly identify the common denominator in all initiatives that are identified as PPPs. Some may not be true “public–private” partnerships, in the sense that they may not have partners from both the public and private sectors (Moran et al., 2005). The broader category of product development partnerships (PDPs) embraces such initiatives that do not necessarily have a public- or private-sector partner, and thus do not qualify as PPPs in the strict sense. It therefore encompasses equally public-health-driven,

Box 3.12: Examples of successful product development partnerships**DNDi**

DNDi is a collaborative, patient-needs-driven, non-profit R&D organization that aims to bridge gaps in existing R&D in essential drugs for neglected diseases. Since its establishment in 2003, DNDi has developed a number of new treatments for neglected diseases, including one NCE, two new fixed-dose combinations, three improved treatment regimens and two new paediatric formulations.¹²¹ DNDi currently has more than 30 projects in its pipeline.¹²² Together with the WHO, DNDi has initiated GARDP, a not-for-profit research and development organization developing and delivering new or improved antibiotic treatments (see Box 3.7).

To ensure access to the end product, DNDi utilizes non-exclusive licences and contractual commitments from industrial partners to sell the products on a cost-plus basis. By negotiating access commitments at a very early stage in the R&D process, DNDi delinks the costs of R&D (financed with DNDi funding) from the final price of the product (maintained at the lowest-possible sustainable level by the manufacturing partner).

This approach is illustrated in the example of artesunate and amodiaquine (ASAO), a new fixed-dose combination for malaria, which DNDi developed with various public- and private-sector partners, while retaining ownership of the related IP. DNDi then licensed IP to a pharmaceutical company for the industrial production, registration and distribution of ASAO in Africa and other developing countries, under a “no-profit-no-loss” price. In addition, ASAO can be freely produced and distributed by any other pharmaceutical company in the world. A more recent example is fexinidazole, the first NCE to be developed by DNDi, in collaboration with Sanofi. Fexinidazole was rediscovered by DNDi when searching for compounds with anti-parasitic activity among those for which development was abandoned for strategic reasons in the 1980s. As part of the collaboration, DNDi was responsible for pre-clinical, clinical and pharmaceutical development, and Sanofi for industrial development, registration, production and distribution of the drug. In December 2017, Sanofi submitted fexinidazole to the EMA, which issued a positive opinion in early 2019. The Democratic Republic of Congo approved the medicine in late 2018.

Vaccine R&D efforts to tackle the threat of Ebola

Over the period 2013–2016, an unprecedented outbreak of Ebola virus disease took place in West Africa, prompting a wave of interest and funding for R&D in Ebola vaccines. Initiatives created partially in response to the outbreak include the WHO R&D Blueprint for Action to Prevent Epidemics and the Coalition for Epidemic Preparedness Innovations (see section C.3).

At the time of the outbreak, a number of vaccine candidates were in the pipeline but had stalled at various stages of development due to a lack of funding (Reardon, 2014). The most mature candidate, rVSV-ZEBOV, was originally developed by the Public Health Agency of Canada, licensed to NewLink Genetics, which then sold exclusive rights to MSD (the name under which Merck and Co. Inc. operates outside the United States and Canada).¹²³ Phase I clinical trials were undertaken in 2014 by a broad coalition of public and private partners, in order to allow Phase II trials during the Ebola outbreak. In 2016, Gavi, the Vaccine Alliance signed an agreement with Merck to use the vaccine for future outbreaks of Ebola. Having shown a high level of efficacy in a Phase III trial (Henaou-Restrepo et al., 2017; Cross et al., 2018), rVSV-ZEBOV was submitted for review by the FDA in 2018.¹²⁴

Other vaccine candidates are also in development and similarly involve multiple public and private-sector partners.¹²⁵

TB Alliance

TB Alliance is a not-for-profit product development partnership dedicated to the discovery, development and delivery of better, faster acting and affordable TB drugs. TB Alliance was established in 2000, at a time when there were no TB drugs in clinical development.¹²⁶

TB Alliance manages the largest pipeline of TB drugs in history, which comprises candidates in all phases of clinical development and is directed to different parts of the TB epidemic, including treatments for drug-sensitive TB, drug-resistant TB and improved paediatric formulations for first-line TB treatments.¹²⁷

Under a collaboration agreement with Janssen, TB Alliance managed key parts of the later-stage clinical development of bedaquiline, a novel treatment for drug-resistant TB (see Chapter IV, section B.3).¹²⁸ TB Alliance has also recently received FDA approval for pretomanid, another treatment for drug-resistant TB.¹²⁹

not-for-profit organizations that use private-sector approaches to develop new products in conjunction with external partners. This study uses the term PDP, not PPP, as it is more descriptive of new structures for medical innovation.

The emergence of PDPs since the late 1990s, drawing together actors from the public and private sectors, has been a major development in efforts to focus R&D towards diseases that disproportionately affect LMICs. These new partnerships have been constituted in a number of ways, but usually with the involvement of non-profit organizations, foundations and industry. Previously, the majority of funds for PDPs were provided by the philanthropic sector, but, in 2017, government funding overtook philanthropic funding.¹³⁰ These partnerships have significantly increased the number of products in development for diseases and conditions that predominantly affect developing countries, and they play an important role in identifying pathways and overcoming bottlenecks in research for neglected diseases.

In 2017, funding to PDPs involved in research into neglected diseases amounted to US\$ 508 million. This represented 14 per cent of global funding for research on neglected diseases. Four PDPs – the Programme for Appropriate Technology in Health (PATH), Medicines for Malaria Venture (MMV), the International AIDS Vaccine Initiative (IAVI) and Drugs for Neglected Diseases *initiative* (DNDi) – accounted for over half of all PDP funding.¹³¹

PDPs form alliances with stakeholders drawn from the public and private sectors because PDPs and these entities have the potential to capitalize on the opportunities that each may offer the other. PDPs are performing the service of integrating inputs from different branches of a very diverse industry. PDPs also seem to have lower research costs than research-based pharmaceutical companies, for a number of reasons. PDPs benefit from lower capital costs as a result of their capacity to leverage in-kind inputs. They also benefit from the fact that they do not have to fund a fully loaded development pipeline. Instead, they select their projects from a pool of existing projects in the public and private domains. On the other hand, their costs could be expected to increase substantially as more projects enter large-scale Phase III trials. In this case, the PDP cost-efficiency profile would probably change, since late-stage failures are more expensive than early-stage failures (Moran et al., 2005). DNDi and the initiatives that emerged in response to the 2014–2016 Ebola epidemic are examples of public–private collaboration and PDPs. PDPs have a pressing imperative during public health crises, such as the Ebola epidemic, that calls for strong and efficient

collaboration globally and locally – while urgency is often defined and experienced locally, readiness and response requires global cooperation.¹³² Examples of needs-driven partnerships can be found in Box 3.12.

7. Research for neglected diseases: the role of pharmaceutical companies

Research-based pharmaceutical companies are increasingly engaged in philanthropic research. Aggregated contributions make the industry the second largest sponsor of research for neglected diseases in 2017, after the US NIH and ahead of the Bill & Melinda Gates Foundation.¹³³ A number of companies have established dedicated research institutes to develop new products targeting diseases that disproportionately affect developing countries, or participate in cooperative projects and PDPs, thus sharing assets and knowledge. Table 3.2 gives details of some industry-supported R&D centres that are dedicated to research in neglected diseases. In total, research-based pharmaceutical companies were reported in 2017 to be engaged in 109 projects aimed at developing new medicines and vaccines for diseases that have been prioritized by the WHO TDR. Of these projects, 90 per cent are collaborative, involving over 50 universities, NGOs and other public- and private-sector institutes.¹³⁴

Treatment coverage for NTDs increased by 76 per cent from 2008 to 2015. Global NTD treatment is highly reliant on treatment donations by a few pharmaceutical companies; the number of tablets donated has quadrupled, from 353 million in 2009 to more than 1.5 billion in 2015.¹³⁵ There was a decrease in reported private-sector R&D projects, from 132 in 2012 to 109 in 2017 (IFPMA, 2013, 2017), but, overall, private-sector investments in NTD R&D have increased notably, from US\$ 345 million in 2008 to US\$ 554 million in 2017 (though this increase represents, in part, a greater number of companies providing data).¹³⁶

8. WIPO Re:Search – Mobilizing intellectual property for global health

The WIPO Re:Search public–private consortium,¹³⁷ led by WIPO in partnership with the Seattle-based NGO BIO Ventures for Global Health (BVGH), accelerates the discovery and development of medicines, vaccines and diagnostics for NTDs, malaria and TB by catalyzing the sharing on concessionary terms of IP assets, compounds, data, clinical samples, technology and expertise among

Table 3.2: Pharmaceutical industry centres dedicated to NTDs R&D			
Company	R&D centre	Location	Active since
AbbVie	AbbVie	North Chicago, IL, US	2009
AstraZeneca	Cambridge Biomedical Campus (CBC)	Cambridge, UK	2015
Celgene	Celgene Global Health	Summit, NJ, US	2009
GSK	Diseases of the Developing World Center	Tres Cantos, Spain	2002
Merck	R&D Translational Innovation Platform "Global Health"	Geneva, Switzerland	2014
Merck & Co. Inc. (operates as MSD outside the United States and Canada)	MSD Wellcome Trust Hilleman Laboratories	New Delhi, India	2009
Novartis	Novartis Institute for Tropical Diseases (NITD)	Emeryville, CA, US	2002
	Novartis Institutes for BioMedical Research (NIBR)	Emeryville, CA, US	2016
	Genomics Institute of the Novartis Research Foundation (GNF)	La Jolla, CA, US	2010
Eisai	Eisai Inc. Andover Research Institute	Andover, MA, US	1987
	Eisai Pharmaceuticals India Pvt. Ltd.	Visakhapatnam, India	2007
	Tsukuba Research Laboratories	Tsukuba, Ibaraki Prefecture, Japan	1982
Sanofi	Marcy l'Etoile Research and Development Campus	Lyon, France	Vaccines (Dengue) since the 90s; Medicines since 2015

Source: Information provided by the International Federation of Pharmaceutical Manufacturers and Associations.

members. The WHO supports WIPO Re:Search through the provision of technical advice.

WIPO Re:Search unites the scientific expertise and creative thinking of academic, non-profit and government investigators, the first-hand disease knowledge of researchers in endemic countries and the material assets and R&D experience of global pharmaceutical companies, to drive innovation and product development for the world's poorest populations. As at January 2020, WIPO Re:Search had 146 members in 42 countries (including 35 African organizations), and had facilitated 156 research collaborations. Ten ongoing collaborations have achieved key product development milestones (e.g. positive "hits" or activity against pathogens or drug targets of interest).

Sharing of assets and participation in collaborations is optional. The terms and conditions of each collaboration are governed by licence agreements and other agreements individually negotiated by the participating entities. Such agreements must be consistent with the WIPO Re:Search Guiding Principles,¹³⁸ which

organizations agree to abide by as a condition of consortium membership. The Guiding Principles include the following provisions:

- All licences granted for R&D and manufacture anywhere in the world are to be royalty free.
- For any products developed under a WIPO Re:Search collaboration agreement, providers of the relevant IP are to provide royalty-free licences for product use and sale in all LDCs. Providers are also to consider in good faith the issue of product access for all developing countries, including those that do not qualify as LDCs.

The Consortium Structure

- The WIPO Re:Search Resource Platform,¹³⁹ operated by WIPO, is an interactive online tool designed to facilitate information sharing and spur collaborations. It enables users to view and retrieve information on WIPO Re:Search members, collaborations and IP assets, such as compounds available for licensing

through WIPO Re:Search. All the information is publicly available.

- The WIPO Re:Search Partnership Hub – operated by BVGH – leads collaboration development and management activities. It identifies investigators and companies with complementary capabilities and needs, and then introduces those parties to determine if there is reciprocal interest in collaborating. If so, the Partnership Hub facilitates communications between partners to align on milestones and agree on timelines and responsibilities. Once legal agreements are in place between the participating entities, the Partnership Hub provides alliance management support to help ensure successful outcomes. Depending on the specific needs of the collaboration, such support includes coordination of regular update calls,

recruitment of additional partners with needed expertise, and assistance in identifying relevant and high-value award opportunities.

The WIPO Re:Search Fellowship Programme

Between 2013 and 2019, the Government of Australia provided funds in trust to WIPO Re:Search to support, *inter alia*, research and training of scientists from Africa and the Indo-Pacific region. These funds were employed to create targeted research and training fellowships focused on NTDs, malaria and TB. This programme arranged 20 fellowships for scientists from LMICs at advanced laboratories in North America, Europe and Australia. The fellowships enabled the sharing of IP, knowledge and experience among hosts and fellows, and engendered long-lasting professional relationships and networks.

D. Intellectual property rights in the innovation cycle

Key points

- International legal standards can have a major impact on innovation systems. The choices made at the regional and national levels within the international legal frameworks are key. Similarly, the management of IP – often shaped by overall innovation structures – can have a direct impact on R&D outcomes and access.
- Patent law is only one element of the innovation process. The role of patent law in developing new medical technologies depends on its legal and administrative design and on specific decisions by individual parties during the development process. Patents do not have the same importance for all industries.
- Pre-grant patent issues of particular relevance to innovation include the patenting of material that exists in nature, patenting of incremental innovation and certain patent filing strategies referred to as “evergreening”, and granting of patent protection on a known product for which a new medical indication has been identified.
- Incremental innovation can improve the safety, therapeutic effect or method of delivery of an existing medicine or vaccine. Whether such inventions merit the granting of a patent is judged on a case-by-case basis.
- Post-grant issues affecting health technology R&D discussed in the study include the patenting of research tools in the field of biopharmaceuticals, the existence of a research exception in national patent laws, licences as tools for partnership building, cooperation and technology transfer, and freedom to operate (FTO) analysis as a basis for a risk-management decision in relation to R&D, product launch and commercialization.

Following the introduction to IPRs in Chapter II, section B.1, this section looks at the impact of IPRs on innovation in the pharmaceutical sector, with a particular focus on patent-related issues. It first examines the interdependence of the international, regional and national framework, and the importance of choices made with respect to the management of IPRs, then proceeds to analyse questions related to patentability in the pre-grant phase, as well as issues related to the use of patents in the post-grant phase. It concludes with an overview of issues regarding freedom to operate.

1. IP management within the broader legal and policy framework at national and international levels

While the international legal dimension of IPRs is critically important to the medical innovation ecosystem – and has garnered much attention in policy debate – it is essential to consider the various layers of IP law and policy, which ultimately influence the directions that research takes. Provisions of the TRIPS Agreement, for instance, can be understood as part of the interplay between international and domestic law and policy frameworks. Policy measures with bearing on medical technologies range from the strategies of individual projects to the standards of international law:

- General policies and strategies for management of IP at the institutional or project level, whether within the private, public or philanthropic sector, and including

practical choices, such as whether or not to file for a patent, and, if so, where; and how to exercise the ensuing rights

- National innovation policy settings, including targeted incentive initiatives, and policies for the management of publicly funded medical research
- National legislative settings, including IP laws and their interaction with other aspects of the regulatory system, such as competition policy and regulation of medicines
- International cooperation on public health and specific international initiatives, including on neglected diseases research
- The international legal framework, comprising a complex of so-called “hard law” and “soft law” instruments and standards spanning trade and investment, IP, public health, human rights, bioethics and related areas.

Consequently, while international legal standards can have a major impact on innovation systems (e.g. in requiring pharmaceutical inventions to be patentable), the choices made at the regional and national levels within the international legal framework are key (e.g. in determining and applying specific patentability criteria under national law). Similarly, the choices made by a public-sector research programme or a private-sector company regarding the management of IP can have a direct impact on R&D outcomes and access. These choices for IP management are often shaped by overall innovation structures, such as those discussed in section B.4 above.

Table 3.3: IP issues that may arise at each stage of the product development pipeline

Innovation planning for health outcomes	Initiating research on unmet public health needs	Initial choices on presence and absence of IP protection	Beyond the initial research: proof of concept and scaling-up	Clinical trials and regulatory approval	Manufacture and distribution	Distribution and marketing phase
<ul style="list-style-type: none"> Setting IP policies and management strategies, including clarifying questions of ownership, access and control over research outcomes. Surveys of existing technology as research inputs and patterns of ownership (according to patent holder, and territorial effect of patents in force), to identify potential partners and possible barriers, as well as avenues for productive new research. Assessment of freedom to operate, status of existing technology, in addition to prospects for technology partnering, access and pooling options. 	<ul style="list-style-type: none"> IP or non-IP incentives for private investment in research and other contributions (including financial and other resources, background technology, infrastructure, scientific and technology management expertise, management of regulatory processes, risk exposure and opportunity cost). Negotiation of terms and conditions covering R&D, including using IP when negotiating guarantees of development and access to finished product; negotiation or implementation of public-interest safeguards to ensure adequate access to research outcomes. Establishing and implementing publication and IP management policies for researchers. 	<ul style="list-style-type: none"> Following initial research outcomes and their subsequent elaboration, the decision at an institution or company level whether or not to seek IP protection on particular innovations and in which jurisdictions, guided by an overall product development, commercialization and diffusion strategy. Decisions at national and regional levels concerning the patentability of the research outcome according to patent grant criteria. Management of know-how, confidential information and other forms of IP. 	<ul style="list-style-type: none"> IP arrangements in negotiations on financing and conducting clinical trials, and in attracting further investment, philanthropic support or allocation of public resources. Other incentives trigger innovation in certain fields, e.g. through "orphan disease" schemes. Assessment of the IP implications of moving beyond a pure research phase into the preliminary stages of full drug development. 	<ul style="list-style-type: none"> Arrangements for generating, protecting and accessing clinical trial data; incentives for investing in this process, and the laws and policy settings that govern this; mechanisms for facilitating or reducing the cost of regulatory approval, such as push and pull incentives, e.g. AMCs. IP aspects of issues, such as mutual recognition of regulatory approvals, sharing of data, negotiating or otherwise ensuring access to, and use of, clinical trial data. 	<ul style="list-style-type: none"> Access to necessary manufacturing, excipient and adjuvant drug delivery and platform technologies. IP management strategies for effective global outcomes (including different ownership in different markets or jurisdictions; different approaches to control or licensing of IPRs in rich and poor countries; role of IP in tiered pricing; "march in" rights and other forms of guarantees of access to public- or philanthropic-funded research). Requirements of national competition policies. 	<ul style="list-style-type: none"> Monitoring and enforcing access guarantees, such as licensing provisions providing for effective access for particular patient groups and requirements for timely introduction of medicines to specified markets. Managing IP that may be relevant to improvements and new indications, and regulatory approval; fulfilling access commitments. Assessing the implications of regulations governing the use of IP in the marketplace, e.g. measures against anti-competitive practices.

2. Intellectual property and the product development process

An overview of relevant IP issues that arise at each stage of the product development pipeline can help to clarify the linkages between specific issues and choices within a narrower operational context, and the overarching policy objective of improved public health outcomes (see Table 3.3). Each of these issues is not a narrow “technical” question that can be considered entirely in isolation. Rather, the successful development and diffusion of a new technology is a consequence of the combined impact of choices taken at each of these steps.

The debate on the value and practical impact of the patent system, in particular, in delivering needed medical technologies has highlighted two key points:

- Patent law is not a stand-alone innovation system. It is only one element of the innovation process, and one which can be deployed differently in diverse innovation scenarios. Patent law has little bearing on many other factors that lead to the successful development of technologies, for example, the nature and extent of demand, commercial advantages gained by marketing and ancillary services and support, commercial and technical viability of production processes, and compliance with regulatory requirements, including through effective management of clinical trials data.
- The role of the patent system in developing a new medical technology depends not only on legislative and regulatory settings but also on a variety of choices made by individuals at different stages of the development process as to whether and when to obtain patent rights and how to exercise them. They may rely on exclusive commercial positions or draw from a range of non-exclusive and open licensing structures, waivers of rights and specific non-assertion undertakings (see Chapter IV, section C.3(c)). Notably, in the case of not-for-profit initiatives in public health, these approaches are not necessarily aimed at securing financial advantages. Instead, they are aimed at leveraging access to technologies.

Patents do not have the same importance for all industries. In addition, they have quite different impacts on markets, as is illustrated by the comparison between the medical devices industry and the pharmaceutical industry (see Table 3.4).

3. Patent filing strategies in the public and private sectors and the exercise of patent rights

Apart from the provisions of the national or international law and their interpretation by the courts, the patent filing strategies of applicants could determine the innovation

and imitation landscape for medical technologies. Filing a patent application involves a series of decisions regarding the specific invention(s) for which patents are to be sought, including the practical purpose for which they are sought, in which jurisdictions, in whose name, with whose funds and when.

Factors determining whether or not a patent application is filed may range from whether the technology is a better solution than any currently available options, to the size of the potential market for the technology or the likelihood of competition. For public-sector researchers, notably in the field of public health, considerations tend to be focused on concerns about how the decision to patent or not patent the technology would advance the institutional or policy goals of their particular research establishment, and whether a patent would help secure suitable partners for downstream product development. When determining patent strategies, the capital requirements needed to further develop the technology into a medical product must be considered, including the need to license any other proprietary technology, the cost of satisfying any regulatory requirements, and the prospects of attracting investment or partners to finance or co-develop these requirements if they cannot be met in-house.

From the inventor’s perspective, patent protection may not be the best strategy if, without it, secrecy can be maintained and the technology cannot be reverse engineered. Similarly, patenting would not be the best strategy if competitors were able to easily develop alternatives that are not covered by the patented claims (i.e. they could design around them) or it was likely to be difficult to ascertain whether competitors were using them without authorization.

Patent application filing strategies determine the countries or territories in which protection is to be sought. Fees must be paid for the grant and maintenance of each patent in each separate country or territory, which can be expensive, and may not be justified in markets where the patent is unlikely to be used. The Patent Cooperation Treaty (PCT) enables a single patent application to be filed with effect in all PCT contracting states (see Chapter II, section B.1(b)(ii) and Box 2.8). Since national processing of an application only takes place in the subsequent national phase, patent applicants can use the international phase to decide in which PCT contracting states they will eventually seek patent protection.

Patent filing strategies can be offensive or defensive. An offensive strategy aims to leverage exclusive rights over a technology in order to extract economic returns from either exclusive use of the patented technology or licensing arrangements. A defensive patent strategy is aimed solely at protecting the inventor’s or patent owner’s freedom to operate (FTO) using its own technology, by avoiding a situation in which a competitor obtains exclusive rights

to it. Equally, patent holders may waive patent rights, or grant a royalty-free licence, or declare that they will not assert certain patents once acquired in certain territories, for certain uses, or in general.

There are differences between private and public patenting strategies. Private-sector entities – mostly publicly traded or privately held companies – aim to generate a return on their shareholders’ investment. In contrast, public-sector and public-interest entities generally conduct research with the aim of serving a general or specific public interest and do not produce commercial products. They focus on smaller portfolios of fewer patents, which typically contain broader claims over key results of upstream research. These patents can be licensed to private-sector entities that have capacity to carry out additional R&D. This, in turn, may lead to delivery of products to the public, and, at the same time, may generate revenue for public-sector entities.

Some countries have adopted policies to encourage research institutions and universities to obtain patents based on inventions arising from publicly funded research. The best-known example of such a policy is the US Bayh-Dole Act of 1980.¹⁴⁰ Similar measures have been adopted in other countries, such as South Africa’s Intellectual Property Rights from Publicly Financed Research and Development Act of 2008 and the Philippine Technology Transfer Act of 2009. Such policies, and a general trend towards more active management of technologies created through publicly funded research, are leading to the steady accumulation of publicly held patent portfolios, including on key upstream technologies that provide platforms for a range of new medical technologies.

PDPs that focus on R&D for new products aimed at addressing neglected health needs may also have

distinct patent filing and IP management strategies (see section C.6).

4. Pre-grant issues: questions of patentability

This section considers selective aspects of patent law that are especially relevant to the innovation dimension of medical technologies.¹⁴¹

(a) Patenting material that exists in nature

While modern biotechnology plays an increasing role in pharmaceutical R&D and production, patents have been granted on biotechnological inventions since the 19th century.¹⁴² For instance, German patent DE 336051 was granted in 1911 to Friedrich Franz Friedmann on the production of a therapeutic against TB involving the continued vaccination of tubercle bacilli obtained from turtles.

The maturing of genetic engineering, including the rise of genome editing techniques such as CRISPR, has been accompanied by an intense public debate about the desirability and appropriateness of applying patent law to modern biotechnology. Important legislative and administrative steps have been taken to clarify some of these issues, such as Directive 98/44/EC of the European Parliament and of the Council on the legal protection of biotechnological inventions¹⁴³ and the USPTO revised Guidelines for Determining Utility of Gene-Related Inventions of 5 January 2001 (USPTO, 2001). Some jurisdictions require that the function of a gene needs to be clearly identified and to be related to the claimed part of the gene sequence.¹⁴⁴

Table 3.4: The different roles of patents in the medical devices industry and the pharmaceutical industry¹⁴⁵

Medical devices industry	Pharmaceutical industry
<i>Characteristics:</i> Medical devices are mainly based on mechanical/electrical technology, IT and systems engineering. The trigger for innovation typically arises from a clinician’s practice.	<i>Characteristics:</i> Pharmaceutical products are based on chemistry, biotechnology and genetics. Fundamental research and applied research, including that based on traditional knowledge, are the basis for innovation.
<i>Patents:</i> Given the interplay among many fields of art, technically complex devices may be protected by hundreds of patents covering the structure, function and/or methods of using the device.	<i>Patents:</i> Active ingredients/chemical compounds are usually covered by a small number of patents, with additional patents addressing variations of such ingredients/compounds, e.g. salts and esters, polymorphs, ways of delivery or formulations.
<i>Design and invent around:</i> In the field of medical devices, to opt for an unprotected design and thus invent around patents is relatively common because alternative technical solutions can be found. This, in turn, enables the creation of greater competition in the market through alternative types of devices, with variations and continuous iterative improvements produced by other companies within the patent term. Competition, coupled with the continuous need and pressure for innovation, lead to relatively short commercial life cycles of about 18–24 months, which is much shorter than the potential patent term of 20 years. However, while the product may change frequently, the technology may be continuously used in successor products.	<i>Design and invent around:</i> In the pharmaceutical area, to invent around patents is often more difficult. Patents covering chemical compounds can exclude competitors from producing comparable products for the entire patent term. In general, pharmaceuticals, if proven efficacious and safe, can enjoy a long commercial life cycle of about 10–20 years or more without undergoing significant changes. Patents will thus be exploited until the end of the patent term.

Box 3.13: Patenting products of nature – the *Myriad* case

BRCA-1 and BRCA-2 are two genes linked to susceptibility to breast and ovarian cancer. The risk of getting cancer increases if these genes show certain mutations. Identifying the mutations is therefore important for diagnosis and for monitoring women at higher risk. Myriad Genetics Inc., in collaboration with others, obtained product patents on the isolated DNA coding for two genes, BRCA-1 and BRCA-2, on a related screening method, and on methods of comparing or analysing BRCA sequences. As a product patent protects not only the functions disclosed in the patent but also all other possible future therapeutic uses of the gene, concerns were raised that the patents held by Myriad Genetics could serve as a disincentive to carrying out further research on possible functions of this gene and the development of diagnostic methods, and impact on access to such tests. Opposition proceedings before the European Patent Office (EPO) led to revocation and restriction of respective European patents in 2004 (Von Der Ropp and Taubman, 2006). Where the patents were in force, Myriad Genetics adopted a restrictive licensing policy that, in practice, only allowed Myriad to perform the complete sequence analysis in their laboratories in the United States (Matthijs and van Ommen, 2009). Public health concerns were raised about the issue of having only one source for diagnostic testing.

In 2013, the Supreme Court of the United States decided that Myriad did not create or alter any of the genetic information encoded in the BRCA-1 and BRCA-2 genes or in their DNA.¹⁴⁶ The Court held that a naturally occurring DNA segment is a product of nature and is not patent eligible merely because it has been isolated.¹⁴⁷ Accordingly, it rejected Myriad's patent claims on the BRCA-1 and BRCA-2 genes. On the other hand, the Court found that claims relating to "complementary DNA" (cDNA), being synthesized in a laboratory from naturally occurring messenger RNA (mRNA) were patent eligible. Notably, the Supreme Court did not consider the patent eligibility of any of Myriad's method claims.

Since the 2013 decision, the number of BRCA tests offered by laboratories in the United States has grown substantially, although the tests vary in how extensively BRCA genes are assessed for mutations (Toland et al., 2018).

In 2015, the patentability of BRCA-1 was also considered by the High Court of Australia.¹⁴⁸ Like the Supreme Court of the United States, the High Court of Australia found that the BRCA-1 was a naturally occurring phenomenon, and that the isolation of nucleic acid comprising the gene lacked the inventiveness necessary to qualify for patent eligibility.¹⁴⁹ The Court also noted the "chilling effect" that the relevant claims, if granted, would have on the use of any isolation process in relation to the BRCA-1 gene.¹⁵⁰

In 2018, the USPTO issued guidance on subject matter eligibility to support patent examiners considering claims relating to naturally occurring products in the wake of the *Myriad* decision. Research found that the *Myriad* decision has also been used to reject patent claims for non-DNA products (Aboy et al., 2018). Some have argued that the *Myriad* decision has led to more time and money being spent on patent applications, as, for example, many applications require a second round of patent examination (Aboy et al., 2018). One study argued that companies may keep information about natural phenomena and correlations as trade secrets rather than relying on patent protection to secure a return on investment, with a potential negative impact on research and patient care (Dreyfuss et al., 2018). For example, an administrative complaint has been filed against Myriad for not supplying genomic data that had been compiled on individuals,¹⁵¹ with Myriad maintaining its database as a trade secret (Conley et al., 2014). Ultimately, however, the new generation of genetic research and diagnostic practice does not always require the isolation of genes, and thus does not generally infringe claims to isolated sequences (Holman, 2014).

A 2001 WIPO survey¹⁵² provides information about national legislation of WIPO member states related to the protection of biotechnological inventions under patent and/or plant variety protection systems, including information as to which countries might admit the patenting of genes, cells or plant varieties. A WIPO study in 2010 looked at how countries have implemented exclusions from patentable subject matter, and exceptions and limitations to patent rights related to biotechnological inventions.¹⁵³ WIPO collates information about exclusions from patentable subject

matter in national/regional patent laws in a database hosted by the SCP.¹⁵⁴

One specific biotechnology patent law issue that is relevant to pharmaceutical production relates to the patentability of material existing in nature, or synthesized or extracted chemical compounds that already exist in nature. A distinction is made between a naturally occurring compound and an artificially extracted and isolated compound. The latter is considered to be a new entity and patentable subject matter in some jurisdictions.¹⁵⁵

In 1911, Japan granted a patent (No. 20785) for an isolated, naturally occurring substance, aberic acid (now termed thiamine, or vitamin B1) from rice bran, which had been identified for the prevention of beriberi, a disease caused by a lack of vitamin B1. The same year, a US court upheld a patent granted to an inventor who had isolated adrenalin from the human suprarenal gland, purified it and identified that it could be used in the treatment of heart disease.¹⁵⁶

Biotechnology invention has entered into the realm of genetics. Patents have been filed, and granted in some cases, for technologies that genetically modify the gene code. For example, a spin-out company holds the patent for gene expression systems using alternative splicing in insects, a technique that has been used to create genetically modified strains of dengue-fever-transmitting mosquitos. While, in many cases, existing patentability criteria are applied by patent law practice and by the courts to determine the patentability of biotechnology inventions, patenting material that exists in nature is not without controversy, as is the application of technology as such. Concerns have been raised about biosafety and unpredictable consequences.¹⁵⁷ A case in the US courts illustrates how controversy also extends to the patenting of human genes (see Box 3.13). As technology develops, for example, DNA editing tools that could rewrite the DNA of sperm, eggs or embryos destined for live births, there may be an increased role for policy-makers. Calls have already been made for the adoption of a moratorium on heritable genome editing.¹⁵⁸ In 2018, the WHO established an expert panel to examine the challenges associated with genome editing. The panel is tasked with making recommendations on appropriate governance mechanisms for human genome editing.¹⁵⁹

(b) Incremental innovation and evergreening

Incremental innovation can improve the safety, therapeutic effect or method of delivery of an existing medicine or vaccine, or improve the efficiency with which it can be manufactured, with positive outcomes for public health. Patents can be granted on incremental innovations if they meet the patentability criteria. Thus, the application of the inventive step/non-obviousness criterion¹⁶⁰ also has implications for incremental innovation.¹⁶¹ The SCP has published a study assessing the application of inventive step in the chemical sector, including pharmaceuticals.¹⁶²

(i) Examples of incremental innovation

Frequently, the first approved formulations of a drug are followed by changes in the formulation or route of administration that improve the effectiveness of the

treatment. These incremental innovations include, for example:

- New dosage forms that increase adherence: Controlled-release formulations, which permit less frequent administration (e.g. once daily rather than twice daily), potentially increasing adherence; more stable drug levels; decreased side effects; formulations for sustained delivery, or sublingual or rapid-dispersion tablets, which are easier to take than capsules and give a more rapid effect.
- New dosage forms with improved efficacy: Frequently, the addition of an excipient or a second active ingredient (a fixed-dose combination) can improve the efficacy of a drug and/or convenience of use. There are numerous examples of new dosage forms with improved efficacy, such as the inclusion of corticosteroids with antivirals, and the coformulation of antiretroviral drugs.
- New formulations with improved storage characteristics: Reliance on the cold chain is a barrier to access for many drugs that lose their activity when stored out of the cold chain. Products with improved heat stability (or simply decreased storage volume) are easier to ship and to store, enabling access in resource-poor settings. Examples include vaccines (oral polio vaccine, nasal influenza) that can be stored in a fridge rather than a freezer and oral drugs that can be stored at room temperature.
- New routes of delivery: Many drugs are first approved for administration by injection, a route which limits ease of access. Formulations allowing alternative routes of administration (e.g. oral, nasal, topical patch) can simplify administration and/or effectiveness. Examples include oral forms of antibiotics and nasal vaccines.
- Improved drug delivery devices: Products such as an inhaler or an injector pen combine a medicine with a delivery device. Combination drug product devices can be updated and patented incrementally if the patentability criteria are met for each incremental innovation (see Box 3.14) (Beall and Kesselheim, 2018). Such improvements to the device do not extend patent protection for the medicine. It may be, however, that the improved device offers the most efficient way to administer the medicine. Patents can be perceived as a barrier to access the medicine to be delivered by the device in cases where the device cannot be easily invented around. Protection of such incremental innovation through patent or regulatory regimes could be linked to increased prices and prolonged lack of generic competition.

Other incremental innovations related to a known, approved drug can have a significant impact on effectiveness. For example, improved processes for production can decrease the cost of manufacture. Improved processes for purification can decrease the contamination of the drug with residual potentially toxic substances.

Box 3.14: Examples of drug-device combinations

The EpiPen is an example of the complexities posed by the protection of the drug delivery device. Epinephrine (adrenaline) by auto-injector is the first-line treatment for anaphylaxis, a severe allergic reaction that can result in death. The EpiPen auto-injector device allows a patient to self-administer epinephrine, a drug first synthesized more than 100 years ago (Bennett, 1999). The EpiPen provides a dose of adrenaline through a spring-loaded needle that can penetrate the skin through clothing, allowing rapid administration in anaphylaxis. A hypodermic auto-injector was first patented in 1977. Although the EpiPen in its current form was first approved in 1987, it is covered by five patents on the drug delivery device that incrementally cover the auto-injector and the needle cover. Rights to commercialize EpiPen were acquired by a company in 2007. Prices were increased; in the United States, the price for a pack of two EpiPens was listed at US\$ 608 in 2017, a 500 per cent increase on the price in 2009.¹⁶³ There has been little competition in the field of auto-injectors. EpiPens are made of multiple parts, and it is difficult to achieve a reliable and sufficiently different design that does not infringe on the existing patents, especially when FDA rules standardized the way these devices work to mitigate the potential that the redesigned device will not meet clinical and safety needs. However, in 2018, the FDA issued draft guidance intended to streamline the approval of devices when the differences in design do not affect the clinical effect or safety profile.¹⁶⁴ The first generic alternative of the EpiPen was approved by the FDA in 2018.¹⁶⁵

Another example is asthma metered-dose inhalers (MDIs). In 2008, new US regulations required MDIs containing chlorofluorocarbon (CFC) propellants to be banned due to the effect of CFCs on the ozone layer. Leading up to the ban, new devices using hydrofluoroalkane (HFA) propellants were developed, approved and protected by patents. New HFA MDIs entered the US market at substantially higher prices than the older CFC MDIs, and mean costs increased (Gross, 2007; Jena et al., 2015).

An analysis of the effect of device patents found that, for device/medicine combination products in which the device is inseparable from the administration of the medicine, the additional protection provided for the medicine by the device patent, beyond patents on the medicine, was a median 4.7 years for products that had both device and medicine patents listed in the FDA Orange Book, and a median nine years for products that had only device patents listed (Beall et al., 2016).

As a final example, the devices used to administer naloxone, an emergency treatment for opioid overdose, are under increased demand due to the epidemic of opioid abuse. Two devices are available – an auto-injector (similar to the EpiPen) and a nasal spray. Both devices are originator products that are protected by numerous patents and do not have alternatives available in the US market.¹⁶⁶ In view of access concerns, in 2018, a municipal health department, together with a civil society group, requested that the US Government authorize production of generic versions of these products without authorization from the right holder under 28 U.S.C. §1498(a).¹⁶⁷

(ii) Evergreening

Concerns have been raised that patenting of new forms, or other minor variations, of existing products that have no additional therapeutic value and display limited inventiveness can be used to prolong patent protection in an inappropriate manner, thus creating a negative effect on access to medicines, as well as on further innovation – a strategy referred to as “evergreening”. The CIPIH defined evergreening as a term popularly used to describe patenting strategies “when, in the absence of any apparent additional therapeutic benefits, patent holders use various strategies to extend the length of their exclusivity beyond the 20-year patent term” (WHO, 2006a).

In reviewing the evergreening debate, the CIPIH commented that “demarcating the line between incremental innovations that confer real clinical improvements, therapeutic advantages or manufacturing improvements, and those that offer no therapeutic benefits is not an easy

task. But it is crucial to avoid patents being used as barriers to legitimate competition”. The CIPIH recommended that governments “take action to avoid barriers to legitimate competition by considering developing guidelines for patent examiners on how properly to implement patentability criteria and, if appropriate, consider changes to national patent legislation”.¹⁶⁸

The central issue is: when does an adaptation or modification of a first patented invention itself become separately eligible for a patent? In this respect, it is important to judge every individual invention claimed in a patent on its merits. The mere fact that an innovation is incremental is not a ground for refusing the granting of a patent. In fact, most innovation is incremental by nature, since technology normally progresses in incremental steps. In order to distinguish inventions that meet the inventive step/non-obviousness criterion from others that do not meet the criterion, patent law and practice have developed and established patentability criteria that need to be met before a patent can be granted.

Some health policy-makers argue that therapeutic efficacy should be used as an additional criterion to prevent evergreening and that patent protection for incremental innovations should be granted only if the invention provides sufficient additional therapeutic benefits. While the therapeutic value of a product as such is not a patentability criterion in most jurisdictions, therapeutic advantages over what exists in the prior art¹⁶⁹ may be considered when determining inventive step. Furthermore, any intention behind patent grant – for example, to build a defensive layer of additional patents to be used against competitors – is not a relevant criterion in the granting procedure. Post-grant measures such as exceptions and limitations to patent rights, and the regulation of licensing practices, can be applied to deal with undesirable effects of validly granted patents. Thus, a patent must be available if the patentability criteria of novelty, inventive step and industrial applicability, among others, are met.

In the context of a patent system, and to the extent that the evergreening debate concerns the grant of patents (rather than how patent rights are exercised by patent holders), the debate can be considered from two angles:

- How are the patentability criteria defined by the relevant national law and interpreted by case law and practice? Many countries have revised their legislation to adopt different types of measures. Section 3(d) of India's Patents Act 1970 (see Box 3.15) and Section 26.2 of the Philippines' Intellectual Property Code are two examples of a narrow definition of patentability criteria. Countries apply different approaches, however, and various definitions and practices exist in the granting of patents to pharmaceutical inventions (e.g. for claimed inventions relating to second medical use, dosage regimes, etc.). In 2001, Brazil introduced a "prior consent" system, meaning that the Instituto Nacional da Propriedade Industrial (National Institute of Industrial Property, Brazil) (INPI) could only grant patents for pharmaceutical products and processes when consent was given by the Ministry of Health's Agência Nacional de Vigilância Sanitária (National Agency for Sanitary Vigilance, Brazil) (ANVISA).¹⁷⁰ ANVISA developed guidelines limiting secondary patents. However, a 2017 resolution (following judicial decisions that ANVISA does not have authority to examine patentability requirements) now limits the assessment to be undertaken by ANVISA to the analysis of public health risk, such as a prohibited substance.¹⁷¹ In some cases, domestic patentability criteria may reflect a party's international obligations under FTAs. For example, under the Australia–United States FTA (AUSFTA), the parties confirm that patents shall be available in their respective jurisdictions for any "new uses or methods of using a known product".¹⁷²
- How are the patentability criteria applied by examiners? Some patent offices have set up search and examination guidelines as instruments to support the examiners' work, with a view to ensuring high quality of granted patents. Such guidelines need to be regularly revised and maintained. WIPO has published a collection of links to a range of patent offices' guidelines for easy access to this information.¹⁷³ Many patent offices, for example in Brazil, China, Germany, the United Kingdom and the United States, and EPO, have established examination guidelines for pharmaceutical inventions.¹⁷⁴ Guidelines for patent examiners along similar lines as Section 3(d) of India's Patents Act 1970 were adopted by Argentina in May 2012¹⁷⁵ and the Andean Community in 2004.¹⁷⁶ In addition, patent offices need to regularly train examiners and maintain a supportive infrastructure (e.g. prior art databases).

The impact of policies targeting secondary patents has been assessed in two separate studies, with one report concluding that there had been a rise in rejections of patent application in India based on Section 3(d) following the Supreme Court decision in 2017 (Ali et al., 2017). Another study found that India, as an example of a country with more restrictive criteria for granting secondary patents, does not show a significant difference in primary and secondary patent grant rates when compared with countries such as the United States and Japan, and the EPO, where secondary patents were found to be granted at a significantly lower rate than primary patents. According to the author of this study, the restrictions on secondary patents have therefore had little direct effect on patent examination outcomes.¹⁷⁷

One question that has been raised is whether this task of ascertaining whether incremental innovation that otherwise meets the criteria for patentability offers therapeutic benefits or deters competition should be assigned to patent offices or would better be determined by competition or health authorities (Yamane, 2011).

Leaving aside the question of patentability, it must be noted that the granting of a patent on an incremental improvement of a pharmaceutical is independent from the granted patent of the original product. Specifically, it does not extend the patent term of the earlier patent. While the improved form of the medicine will be covered by the new patent, the patent protection of the original version will end with the expiration of the first patent.

However, even if the patent on the original version has expired, and a generic version could be commercialized from the mere patent point of view, it still may not be possible to bring a generic to the market for regulatory reasons, including where regulatory exclusivities apply (see Chapter II, section A.6(f)).

Box 3.15: How India defines and applies patentability criteria

When revising its patent law to comply with the TRIPS Agreement requirement that pharmaceutical products be patentable, India adopted specific patentability criteria for chemical products by introducing Section 3(d) to its Patents Act (Patents Amendment Act 2005). Section 3(d) states: “the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant” is not an invention. Section 3(d) provides the following explanation: “For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy”.

In 2007, the Indian Patent Office, following an opposition filed by a patient organization, refused to grant a pharmaceutical company a patent for the cancer drug imatinib mesylate, based on Section 3(d). In 2013, the Indian Supreme Court rejected an appeal against this decision.¹⁷⁸ It held that, while Section 3(d) did not bar patent protection for all incremental inventions, the invention, in order to be patentable, had to pass the test of enhanced efficacy as provided in Section 3(d) read with its explanation. The beta crystalline form of imatinib mesylate was a new form of a known substance, imatinib, and lacked the enhancement in efficacy required under Section 3(d). The Supreme Court decided that “efficacy” under Section 3(d) of the Indian patent law was “therapeutic efficacy”, and stated that the term must be interpreted “strictly and narrowly.” As there was no evidence offered to indicate that imatinib mesylate would produce enhanced therapeutic efficacy as compared with imatinib, the appeal against the rejection of the patent application was unsuccessful.¹⁷⁹

In 2015, the High Court of Delhi noted that the purpose of Section 3(d) is to encourage incremental innovation in pharmaceuticals. Section 3(d) determined a threshold for what subject matter qualified as the same and what qualified as a new invention under Section 2(j) of the Patents Act. Where such derivatives are considered “the same” as a known substance under Section 3(d), they will, as a matter of course, be covered by any existing patent protection for that known substance.¹⁸⁰

Finally, research in Australia on who owns follow-on innovation patents found that substantial patenting activity is undertaken by companies other than the originator, including generic manufacturers, and that such third parties hold up to three quarters of secondary patents (Christie et al., 2013; Lloyd, 2013).

(c) Medical indication claims

Article 27.3(a) of the TRIPS Agreement allows countries to exclude from patentability diagnostic, therapeutic and surgical methods for the treatment of humans or animals. In some countries that have implemented this exclusion in their law, so-called medical indication claims have emerged in practice. Such claims must not cover the method of treatment but can claim an already known product for a new medical use.

When a previously known substance, used for a certain non-medical purpose, is later found effective in the treatment of a disease, a patent application may be filed claiming the known substance specifically for the use relating to the “first medical indication” (also called “second use” or “new use”) of the known product.¹⁸¹ If the first indication or earlier use of the known substance was already medical in nature, newly filed product claims

on that substance for another medical use are labelled “second medical indication”. Such claims, if granted because all patentability criteria under the applicable law have been met, protect an already known product for the specified medical use. The TRIPS Agreement does not expressly address this question. Patent laws differ on this point.

Some patent laws specifically rule out the patenting of first or second medical indication inventions. For example, the Andean Community Decision 486, the common IP law for the member states of the Andean Community, stipulates in Article 21: “Products or processes already patented and included in the state of the art [...] may not be the subject of new patents on the sole ground of having been put to a use different from that originally contemplated by the initial patent”.¹⁸² Section 3(d) of the Indian Patents Act (2005) provides that the “new use for a known substance” is not an invention, unless there is enhanced therapeutic efficacy.¹⁸³ The 2012 Patenting Guidelines in Argentina say that therapeutic treatment methods were not considered as industrially applicable; medical indication claims were not considered as fulfilling the novelty requirement; and Swiss-type medical claims (see in this section below) would be equivalent to a medical treatment method. Therefore, such inventions were not patentable.¹⁸⁴ The Patenting Guidelines of the

Philippines,¹⁸⁵ providing guidance on Sections 22 and 26 of the Intellectual Property Code, accept first, second and further medical use claims, stating that “this new technical effect of a known substance must lead to a truly new therapeutic application, which is the treatment of a different pathology”. The Guidelines require that second and further medical uses claims must be drafted in a Swiss-type claim format. The Guidelines note that the EPO has abandoned this type of claim format. The Intellectual Property Office of the Philippines has nevertheless decided to continue to accept Swiss-type claims for subsequent medical use claims, also to help the examiners distinguish subsequent medical use claims over first medical uses.

Some jurisdictions allow first, second and further medical indication claims. This is the case, for example, under Article 54(4) and (5) of the European Patent Convention (EPC) as revised in 2000 (referred to as EPC 2000).¹⁸⁶ In essence, these provisions state that the novelty requirement does not exclude the patentability of a known substance used for a new method for treatment or diagnostic.¹⁸⁷ The European Patent Office Enlarged Board of Appeal clarified that “where it is already known to use a medicament to treat an illness, Article 54(5) EPC does not exclude that this medicament be patented for use in a different treatment by therapy of the same illness”.¹⁸⁸ It should be noted that all other patentability criteria under the EPC must be met before a patent on a known substance for a new medical use can be granted. Such a patent, however, does not extend the patent protection covering the already known medical use.

Prior to the revision in 2000, the EPC allowed patent claims on a first medical indication, but not on further medical indications. In 1984,¹⁸⁹ the EPO Enlarged Board of Appeal accepted for the EPO the practice in Switzerland to grant claims in the following form: “the use of compound X in the manufacture of a medicament for the treatment of indication Y”. Such claims were called Swiss-type medical claims. They were process claims, covering the manufacturing process of a known medicine for a novel medical indication. These claims did not cover a method of treatment for the human or animal body, which is excluded from patentability under Article 53(c) of the EPC. With adoption of the EPC 2000, which allowed claims on further medical indications under the new Article 54(5), the Swiss-type claims became obsolete in Europe, and the Enlarged Board of Appeal decided that such claims would be no longer accepted for applications with a filing or priority date as of 29 January 2011.¹⁹⁰

As illustrated in the case of fluoxetine (see Box 3.16), prices can differ widely for the same active ingredient when it is sold as a different product to treat a different condition.

A 2018 UK Supreme Court decision may illustrate implications of medical indication patents for the generics industry.¹⁹¹ The case relates to the manufacture by generics of the so-called “skinny label” products, which are for the treatment of an off-patent indication, but prescribed by doctors, sold by pharmacists and used by patients for the indication that is still patent protected, and whether the generics manufacturers infringe the patent. The decision suggests that patent infringement requires that the manufacturer could reasonably foresee the use of the medicine for the protected purpose and wants this use. As a consequence, the “skinny label” products would not infringe the patent when there is no subjective intention of the manufacturer to infringe. In this particular case, no infringement was found, also because the defendant had made it clear that it did not intend to infringe the patent by applying for a market approval explicitly excluding the patented indications and by sending warnings to pharmacies and related institutions not to prescribe and sell the medicine for the patent-protected indications.

The patentability of first, second and further medical indications is a matter of debate, and therefore exemplifies the continuing challenge in patent law of balancing access against innovation. On the one hand, opponents of medical indication patents argue that such patents impede access to medicines, reward uninventive activities and unnecessarily prolong effective patent protection for a certain medical substance. On the other hand, proponents express the view that an additional medical use can itself be inventive, and that the development and clinical testing of a second use is no less in need of incentives than the first use, and, in some cases, may be more therapeutically valuable than the first use.

Box 3.16: Second use patents: the case of fluoxetine

Fluoxetine (better known as “Prozac”) was first marketed in the United States in 1987 for the treatment of depression, and its US base patent expired about 14 years later, in 2001. However, fluoxetine was discovered to also be useful in the treatment of a second indication, premenstrual dysphoric disorder. A pharmaceutical company obtained a patent on this second use in 1990 (United States Patent No. 4,971,998) and secured regulatory approval for this indication in 2000 under the trade name Sarafem. Although both medicines contain the identical active ingredient (fluoxetine hydrochloride), at an identical dosage level (20 mg), the prices differ widely in the United States; in one pharmacy, it was found that Prozac was US\$ 0.83 per pill, while Sarafem was US\$ 9.26 per pill.

5. Post-grant issues: questions related to the use of patents

Once a patent has been granted, certain legal and practical considerations determine how it influences and impacts on the development and dissemination of the patented technology. These include options for defining the legal scope of patent rights, and approaches to their licensing. This section outlines several of these considerations that are most relevant to product development.

(a) Research exception

A research exception or experimental use exception is one of the most commonly used types of “limited exceptions” to national patent laws pursuant to Article 30 of the TRIPS Agreement. A WTO dispute settlement panel has defined the term as “the exception under which use of the patented product for scientific experimentation, during the term of the patent and without consent, is not an infringement”.¹⁹² This exception enables researchers to examine the patented inventions and to research improvements without having to fear that they are infringing the patent.

Many countries provide varying levels of exceptions for acts carried out for experimental purposes or scientific research. In general, the scope of the exception can be defined through the purpose of the research or experiment, whether it allows an experiment or research with a commercial intent, and/or how the experimental act related to the patented invention (i.e. whether it allows for research *with* or *on* a patented invention).¹⁹³

Some countries limit the exception to acts carried out without commercial or gainful intent. For example, in the United States, the US Court of Appeals for the Federal Circuit held in *Madey v. Duke University*¹⁹⁴ that using a patent without the consent of the patent holder in order to further the “infringer’s legitimate business interests” was to be considered patent infringement.

Some countries apply the research exception only to acts that explore how the invention works or seek to further improve the invention, and this is often referred to as “research on the invention”.¹⁹⁵ In these countries, using the patented invention to perform research on a different subject matter, also called “research with the invention” is not covered by the research exception. This distinction is particularly relevant for the discussion on research tools (see subsection (b) below).

Some countries define that acts, such as studies, undertaken to obtain market approval for medical technologies fall under the research exception (see Chapter IV, section C.3(a)(i)).¹⁹⁶

Where a research exception is not wide enough in a particular jurisdiction to allow research for a follow-on product, such as use of a patented research tool (see subsection (b) below), the researcher needs to obtain a licence on terms to be mutually agreed. Alternatively, compulsory licensing may allow such downstream research, subject to compliance with the requirements under the applicable national law.¹⁹⁷

The SCP identified 113 countries that provide for research exceptions.¹⁹⁸ Replies to a questionnaire from WIPO member states and regional offices provide information on various national practices regarding the experimental use and scientific research exception.¹⁹⁹

(b) Research tools

Historically, the discussion of research exceptions has largely concerned biotechnology research tools. Patentable biotechnological inventions are not necessarily end products such as new drugs, but can be “upstream” research tools that are essential for the development of “downstream” pharmaceutical products. Research tools are resources used by scientists to facilitate an experiment or produce a result. Research tools can be research techniques (e.g. gene-editing tools such as CRISPR-Cas and DNA amplification techniques), research consumables (e.g. enzymes or reagents) or research targets (e.g. genetic material used for new drugs or vaccines). Where technologies comprise DNA sequences, genetic researchers often have no way to invent around them. For example, expressed sequence tags are tiny portions of an entire gene that can be used to help identify unknown genes and to map their positions within a genome. Polymerase chain reaction is a well-known research tool or technique used to amplify small segments of DNA. Broad patenting of these types of inventions may disadvantage those wishing to use them to develop other products, while narrower claims may allow their downstream use.

Where a research exception exists (see subsection (a) above), it does not necessarily apply to use of patented research tools in all circumstances. In a number of countries, the research exception is restricted to experimental acts that are related to the subject matter of the patented invention or experimental acts *on*²⁰⁰ the patented invention, and they do not except research with the protected tool.²⁰¹ In Belgium, the text of the research exception provision states that the exception applies to “[...] acts accomplished for scientific purposes on and/or with the subject matter of the patented invention”.²⁰² Switzerland has introduced a right to a non-exclusive licence with regard to the use of research tools, for example, for cell proliferation in the field of biotechnology.²⁰³ The Appendix of WIPO document SCP/29/3 compiles various legal provisions on the research exception.²⁰⁴

Without the freedom to use research tools through exceptions to patent rights, licensing is key to enabling access to relevant technologies. While patent holders are entitled to set the terms of the licence, the scope of these terms can sometimes be restrictive.

In the United States, the NIH wants to ensure both broad access to research tools that have been developed using public funds and the preservation of opportunities for product development. To this end, the NIH promotes licensing policies that realize both product development and availability of new research tools to the scientific community.²⁰⁵ In addition, US law requires that a federal agency may only grant an exclusive or partially exclusive licence on a federally owned invention if “the public will be served by the granting of the license, as indicated by the applicant’s intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention’s utilization by the public, and that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention’s utilization by the public”.²⁰⁶

In the case of CRISPR, each of the key patent holders (some being publicly funded) have out-licensed their rights to spinoff companies that can then licence the technology exclusively in specific areas, including human therapeutics and CAR T-cell therapy, to commercial partners. As a result, while CRISPR is freely available as a research tool for academic research, broad exclusive licences are granted by the spinoff companies to other licensees, such as biopharmaceutical companies. However, these companies do not always have the capacity to work on the full range of gene targets that are included in these broad exclusive licences. This can have a negative impact on competition and create innovation bottlenecks for drug discovery and development (Contreras and Sherkow, 2017).

(c) Licensing and assignment with respect to innovation

A patent owner may lack the resources to exploit an invention and to scale up from the laboratory research stage to bring a product to market. The resources required to develop a product include the skills, facilities and capital to conduct further research; carry out tests, trials and production engineering; obtain regulatory approval; and then manufacture, market and distribute the final product. The ingenuity and competitive edge of an invention alone are not sufficient to ensure its successful implementation. In this situation, a public- or private-sector patent owner must consider whether it is in its best interests to assign the technology or to license it to another party who can develop it. Each choice offers

different degrees of control over the technology and may yield different levels of return and health benefits.

A patent assignment may include sale, or transfer free of compensation, to a PDP, for example. An assignment entails a loss of control over the technology. In general, an assignment at an earlier stage of R&D offers a lower return to the assignor than at a later stage, as the assignee is typically assuming greater uncertainty and risk. The assignor may assume obligations to provide technical advice for a certain period.

Patent licences vary in scope. An exclusive licence guarantees that the licensee will have no competition in the production and distribution of the given product, not even from the licensor. Licences can be restricted to a particular territory, and can allow or prohibit sublicences. A non-exclusive licence allows the licensor to grant other licences to other parties in the contractual territory. Licences can also be restricted to particular fields of use. This allows a licensor to grant a licence to the same patent or related patents to different parties in different fields. Patents for medical technologies are often suitable for field-of-use licences because such technologies often have multiple uses. For example, the same technology can be applied to diagnostic and therapeutic uses with respect to the same disease or different diseases. Field-of-use licensing grants the licensor greater freedom to deal with the patent with other parties in other fields of use and extract greater returns. Licences can also include options to commercialize additional compounds or fields of use that could allow the licensee to integrate additional products into its pipeline. The return from a licensee to the licensor depends on the objective of the licensor and the licensee, the degree of exclusivity, size of contractual territory, restrictions on use, options included and the duration of the licence, as well as the value of the technology itself. Alternatively, technology can be voluntarily shared, even without a formal licensing arrangement.

A licensing strategy covers an entity’s inputs as well as its outputs in the product development process. The strategy determines, in line with the entity’s overall objectives, what licensing models are to be pursued, and to what end. Public-interest IP management can promote innovation by granting licences on non-exclusive terms or, where exclusive licensing is necessary to promote further development, it can restrict the licensed field of use to reserve other areas of research that may use the same technology.²⁰⁷

(d) Patents in R&D agreements and other forms of collaboration

Medical technologies are developed through a diverse spectrum of forms of collaboration that have implications

for access post patent grant. At one end of the spectrum, traditional public-sector research places all results in the public domain, where they are freely available for use by others involved in product development. At the other end of the spectrum is the conventional vertically integrated private-sector business model, which involves conducting R&D in-house within a single company group, exercising exclusive rights to prevent its use by others, thus furthering the company's own commercial interests. Increasingly, few pharmaceutical companies have the capacity to operate in a fully integrated and entirely exclusive manner.

Between these two extremes, new forms of commercial collaboration can be found. They combine different inputs in order to deliver a complex product such as a new drug or vaccine. In the field of biotechnology, there are frequently several different licensors and other right holders by the time the final product is ready for market. Patent rights can also be leveraged in other, non-conventional ways, such as to enable access to improvements and developments of licensed technologies through open source or public health patent pools and also through commercial patent pools that enable competitors to develop products based on shared pre-competitive technology platforms (see the discussion of innovation structures in section B.4).

Collaborative research partnerships often broach the divide between the public and private sectors with research being undertaken through collaborative PPPs involving industry and universities. Increasingly, these research collaborations take place across borders and the management of IP can become more complex when dealing with multiple jurisdictions. In the United Kingdom, model agreements have been developed to support these forms of collaboration.²⁰⁸ A Fast Track Model Agreement was also produced by Public Health England to evaluate potential treatment options for Ebola and Zika virus diseases and to share the results with stakeholders for a coordinated global response.²⁰⁹

(e) Patent clusters and patent thickets

There is no generally agreed definition of the term "patent thicket". One author describes a patent thicket as a "dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology" (Shapiro, 2001). In such a situation, multiple patent rights owned by different parties have to be considered by competitors as well as new entrants into a market within that field of technology. Eventually, they must negotiate multiple licence agreements, and this may present difficulties and impede the implementation of a project. The European Commission has identified the creation of "patent clusters" by filing numerous additional patents for the

same medicine as a common strategy employed by pharmaceutical companies (European Commission, 2009). Companies reportedly file a significant number of these additional patents on variations of the same product, especially for blockbuster medicines, very late in the life cycle of a medicine, when the main patent is about to expire.²¹⁰ The Commission found that these patent clusters make it more difficult for generic competitors to evaluate whether they can develop a generic version of the original medicine without infringing one of the numerous patents filed around one medicine. The number of patents also increases the risk of potentially costly litigation for generic companies.

Patent thickets have been observed for complex technologies, such as information and communications technology (ICT) and pharmaceuticals. They can arise in technical fields where a number of companies compete at the same level and where patent ownership is fragmented. Key issues that have been highlighted with respect to patent thickets include: the high density of patents potentially impeding R&D; high, possibly excessive, licensing costs; refusal of the patent holder to grant a licence; and difficulties associated with inventing around a patent (IPO, 2011).²¹¹

Cross-licensing agreements have been proposed as a solution. However, some have argued that this measure could aggravate the issue, as it could induce competing companies to obtain larger numbers of patents in order to improve their bargaining capacity. Patent pools have also been suggested as a way to address transaction costs.²¹²

Empirical studies of patent thickets show varied results. One study found that, among academic researchers in the biomedical field, 3 per cent had abandoned a project during the preceding three years due to too many patents covering their particular research field. The study found that access to tangible research input was more problematic, as 20 per cent of academic-to-academic requests were refused.²¹³ Another study found that 40 per cent – including 76 per cent of those in the biosciences industry who responded to the survey – considered that their research was affected by difficulties in accessing patented technologies. Of these respondents, 58 per cent reported delays, 50 per cent reported changes in their research plans and 28 per cent had abandoned their research. The most common reason for changing or abandoning the research was overly complex licensing negotiations (58 per cent), followed by high individual royalties (49 per cent).²¹⁴

(f) Freedom-to-operate issues

This subsection briefly sketches the issues involved in a freedom to operate (FTO) analysis.²¹⁵

(i) Defining freedom to operate

FTO assessments are important in deciding whether to initiate or continue with R&D projects, or use or market new products. An FTO assessment is based on a legal opinion on whether the making, using, selling or importing of a specified product is free from potential infringement of third-party IP or tangible property rights. Managers use FTO analysis when making risk-management decisions in relation to R&D, product launch and commercialization. However, FTO does not mean an absolute freedom from any risk of infringing another party's IP. It is a relative assessment based on analysis and knowledge of IP landscapes for a given product, in a given jurisdiction, at a given point in time.

(ii) Freedom-to-operate strategies

The decision to undertake an FTO analysis, and to commission an FTO opinion from legal counsel or a patent attorney, is based on a preliminary risk assessment. FTO considerations are relevant at all stages of the product development cycle. In practice, however, carrying out a detailed FTO analysis and legal opinion on every product or process early in the pipeline would be impractical. This is because the detailed specifications of the product could not be known to a sufficient degree of detail and certitude. On the other hand, obtaining any needed licences at a late stage in the development process runs the risk that either no licence would be obtained or the conditions would be unfavourable and thus the bargaining flexibilities would be reduced. In addition, there could be a risk of becoming involved in a lawsuit for IP infringement.

Negotiating a licence is a straightforward way to obtain the consent of the right holder for the intended commercial activity. This approach may have the advantage of focusing on mutual interests in a deal in a way that proves beneficial for all parties. Licences may include additional information, such as know-how, regulatory data, trade secrets and trademarks. Agreements may include up-front payments, milestone payments or royalty rates, or a combination of all three, or they may be in the form of a cross-licence, whereby the licensees and the licensor grant each other certain rights. Licences may also include – and indeed frequently do – grant-backs for improvements, options on new inventions and the mutual sharing of new data. These options may be particularly relevant if long-term collaboration is sought and if further research has the potential to lead to improvements in the licensed/protected technology.

However, licence negotiations may not always lead to the desired agreement, even if a potential licensee has made reasonable efforts to obtain a licence. In such situations, a compulsory licence is a route that could possibly be explored.²¹⁶

Instead of seeking a licensing agreement or a compulsory licence, another viable strategy could be to aim to have the “blocking” patent invalidated. The blocking patent may have been granted erroneously and could therefore be challenged and invalidated. However, going into litigation can be costly and lengthy, and the outcome is often uncertain.

An additional option would be to seek a non-assertion covenant, in which a right holder confirms in a public statement that the rights will not be enforced under certain circumstances or in certain defined fields or geographies. Such agreements may be particularly relevant for “humanitarian” licensing aimed at responding to socio-economic needs. In addition, these agreements deliver the added benefit of ensuring that product liability issues are simplified (Krattiger, 2007b).

Instead of pursuing available legal options, the company may adapt the project to the IP situation. One such option could be to modify the product in such a way that no licence would be required. Such a strategy works if available alternatives exist and if the different options are analysed at an early R&D stage (i.e. when it may be easier to modify the product). The lack of alternative options may serve to incentivize further research to find a new solution for the project. Inventing around may delay product development but can lead to new inventions – and perhaps even better products – thus resulting in new IP for cross-licensing. On the other hand, inventing around may increase costs.

A review of available legal, research and financial options may lead to a decision to abandon the project. The alternative, electing to overlook existing patents and awaiting a choice by the patent holder whether or not to enforce their rights, could result in additional financial loss – particularly if there is a successful claim for damages based on knowing infringement.

Finally, FTO issues can also be resolved through M&A of competing companies.

The process of developing a sound strategy for securing FTO should consider all options, and decisions should be based on the assessment of the risks of each option in relation to the institutional context, product type and market dynamics. In practice, several options are typically pursued concurrently.

An FTO opinion provides only a snapshot of the IP related to a product at a given point in time. The patent landscape changes as patent applications are filed, and as patents are granted, expire or are invalidated. Therefore, strategies need to be regularly revised, and tactics need to be adapted in response to changing circumstances.

E. Sharing of influenza viruses and access to vaccines and other benefits

Key points

- The WHO Pandemic Influenza Preparedness (PIP) Framework for the Sharing of Influenza Viruses and Access to Vaccines and other Benefits provides a global approach to the sharing of influenza viruses with pandemic potential. It also enables the sharing of benefits derived from such viruses, including the management of related intellectual property (IP).
- The Standard Material Transfer Agreements (SMTAs) agreed under the PIP Framework stipulate that participating laboratories should not seek to obtain intellectual property rights (IPRs) on PIP biological material. In addition, these agreements provide for a range of options for biological material recipients, such as influenza vaccine manufacturers, to enter into benefit-sharing agreements.

A highly significant development in itself, given its central role in preparing for a potential pandemic, the PIP Framework serves to illustrate many of the points made in earlier sections of this chapter relating to the role of public-sector institutions and networks, capacity-building in medical innovation, sharing of benefits of the fruits of innovation, and dealing with IP in a public health context.

1. WHO Global Influenza Surveillance and Response System

The WHO Global Influenza Surveillance and Response System (GISRS) (formerly known as the Global Influenza Surveillance Network) was created in 1952 to advise WHO member states on influenza control measures. This system monitors the evolution of seasonal influenza viruses and other subtypes of influenza viruses that infect humans sporadically. Among its many responsibilities, the GISRS selects and develops candidate influenza viruses for development and production of seasonal and other influenza vaccines, including pandemic vaccines. The GISRS also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential (IVPP). Its activities have contributed greatly to the understanding of influenza epidemiology, and have facilitated effective, internationally coordinated responses to outbreaks of seasonal, H5N1, H7N9 and other influenza virus subtypes with pandemic potential.

The GISRS comprises different categories of laboratories with national influenza centres (NICs)²¹⁷ forming its backbone. Under their WHO terms of reference, NICs are requested to regularly ship representative clinical specimens/virus isolates to WHO collaborating centres²¹⁸ for in-depth antigenic and genetic analyses. To fulfil its role as a global alert mechanism for the emergence of IVPP, the GISRS relies on its members to share IVPP in a timely manner.

The re-emergence of highly pathogenic avian influenza A(H5N1) in 2003 highlighted the risk of an influenza pandemic. The inability of developing countries to secure safe and affordable access to pandemic vaccines was underscored by the global limitation of influenza vaccine production capacity. In early 2007, this situation prompted one country to announce that it would stop sharing its A(H5N1) viruses with the GISRS until it:

- Provided greater transparency of its activities
- Enabled increased access by developing countries to the benefits derived from the use of such viruses, notably vaccines.

This led to the adoption by the May 2007 World Health Assembly (WHA) of a resolution (WHA60.28) that became the basis for negotiations on a framework for the sharing of influenza viruses and other benefits.²¹⁹ Two issues were central to the discussions:

- Improving the transparency of the activities of the GISRS
- Improving fairness and equity of access to influenza vaccines and other benefits derived from the work of the laboratories in the WHO system.

2. Intellectual property rights in the context of PIP negotiations

The role of patents and, more specifically, the rules regarding what the GISRS laboratories should, or should not, do with respect to seeking patent protection on inventions developed with viruses contributed to the GISRS were core issues throughout the negotiation process. Technical papers prepared by the WHO in response to a request by member states found that: "There are no significant patent barriers to the manufacture of any of the marketed types of influenza vaccines. Some patents protect specific processes or products, but for each of the types of

Box 3.17: WIPO Patent Search Report on PIP-Related Patents and Patent Applications

The patent search report highlights several critical points:

- In the pool of patent information assembled and analysed in this report, no patent documents were identified that included claims having, as a sole and/or single element, either a complete native virion, a native viral strain, a native viral genome in its entirety, or a complete assembled complement of native viral proteins from a specific virus.
- The report discusses in detail certain patent families, represented by patent applications, where the scope of the claims is broad and could potentially be construed as covering known viral sequences, processes and compositions of matter. It is well established that issued patents frequently have narrower claims than the corresponding patent applications. Therefore, the scope of the claims in the patent applications identified and analysed in this search may very well be restricted during the patent application prosecution and grant process.
- While some patent applications from members of the WHO Global Influenza Surveillance Network are identified as falling within the scope of the search, the report does not analyse the extent to which collaborations, licences and technology transfer are taking place between these and other entities, including between and among developed and developing countries.
- A number of patent applications were identified from companies based in industrialized countries that are now co-owned by companies in developing countries. This is arguably one form of technology transfer and should be seen in the light of emerging models that facilitate broad access to new technologies, including in health, by developing countries.²²⁰

marketed vaccines, there is sufficient freedom to operate to permit manufacturers in developing and emerging economies to make the vaccine of their choice. For future vaccines based on new technologies, there are potential intellectual property barriers; however, it is not known which, if any, of those technologies could make marketable vaccines that could be sustainably produced".²²¹

In order to provide further information on patenting activity related to IVPP, the WHO, based on Resolution WHA60.28, requested WIPO to prepare a working paper on Patent Issues Related to Influenza Viruses and Their Genes, in 2007.²²² In 2011, upon request from WHO member states, WIPO presented a patent search report on PIP-related patents to the WHO Open-Ended Working Group of Member States on Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and other Benefits (see Box 3.17).

3. The PIP Framework

The PIP Framework was established in 2011²²³ to provide a global approach to the sharing of IVPP for risk assessment and response, including vaccine development, and the sharing of benefits derived from such viruses. The scope of the Framework is limited to IVPP and does not cover seasonal influenza, though discussions are ongoing as to whether its scope should be expanded to include it (WHO, 2018a). The Framework defines the materials covered under it as "PIP biological materials", meaning, in summary, IVPP samples, IVPP modified by GISRS laboratories, human clinical specimens and certain IVPP genetic material.²²⁴

The PIP Framework operates with two Standard Material Transfer Agreements (SMTAs):

- SMTA 1 governs sharing of PIP biological materials within the GISRS, that is, between NICs and WHO collaborating centres. SMTA 1 specifies terms and conditions for transferring viruses within the GISRS and allows onward transfers of the PIP biological materials only if the prospective recipient outside the GISRS has concluded an SMTA 2 with the WHO. Article 6.1 of SMTA 1 requires that neither the provider nor the recipient should seek to obtain any IPRs on PIP biological materials.
- SMTA 2 governs transfer of materials to recipients outside the GISRS. An SMTA 2 is concluded between the WHO and the prospective recipient and defines rights and obligations of the SMTA 2 parties. For example, it allows recipients of PIP biological material any further transfer of that material to a third party only if that third party has also concluded an SMTA 2 with the WHO.²²⁵ Article 4.1 of SMTA 2 sets out a list of options for benefit-sharing and requires the recipient to commit to at least two of them (see Table 3.5).²²⁶ In this manner, the Framework provides opportunities for IP holders to share IP related to pandemic influenza preparedness or response. It does not, however, compel them to do so.

In accordance with Section 6.14.3 of the PIP Framework, manufacturers using the GISRS pay annual cash partnership contributions to the WHO. The PIP Secretariat uses a set of standard operating procedures to identify manufacturers using the GISRS and divide payment of the partnership contributions among companies.²²⁷

Table 3.5: Summary of benefit-sharing options under SMTA 2

	CATEGORY A (Select 2/6)	CATEGORY B (Select 1/6)	CATEGORY C (Consider)
1	Donate % of real-time vaccine production to WHO	Donate diagnostic kits to WHO	Consider contributing to the measures listed below, as appropriate: <ul style="list-style-type: none"> • Donations of vaccines • Donations of pre-pandemic vaccines • Donations of antivirals • Donations of medical devices • Donations of diagnostic kits • Affordable pricing of pandemic products • Transfer of technology and processes • Granting of sublicences to WHO • Laboratory and surveillance capacity-building.
2	Reserve % of real-time vaccine production at affordable pricing to WHO	Reserve diagnostic kits at affordable pricing to WHO	
3	Donate antivirals to WHO	Support laboratory and surveillance capacity-strengthening	
4	Reserve antivirals at affordable pricing to WHO	Support transfer of technology, know-how and/or processes	
5	Licence on technology, know-how, processes or products needed for the production of influenza vaccines, antivirals or adjuvants to developing-country manufacturers, on mutually agreed fair terms	Licence on technology, know-how, processes or products needed for the production of influenza vaccines, antivirals or adjuvants to developing-country manufacturers, on mutually agreed fair terms	
6	Royalty-free licence to developing-country manufacturers or WHO for production of influenza vaccines, antivirals or adjuvants	Royalty-free licence to developing-country manufacturers or WHO for production of influenza vaccines, antivirals or adjuvants	

Source: WHO, available at: www.who.int/influenza/PIP/benefit_sharing/SMTA2BenefitSharingOptions.pdf?ua=1.

As of December 2019, implementation of the Framework has enabled the WHO to secure more than 400 million doses of pandemic vaccine under the SMTA 2 benefit-sharing mechanism, and to collect more than US\$ 198 million through partnership contributions,²²⁸ which has been used to strengthen pandemic response capacities, including laboratory, surveillance, regulatory and risk communications.²²⁹

WHA Decision 70(10) has reaffirmed the importance of the PIP Framework in addressing present or imminent threats to human health from influenza viruses with pandemic potential, and emphasized its critical function as a specialized international instrument that facilitates expeditious access to influenza viruses of human pandemic potential, risk analysis and the expeditious, fair and equitable sharing of vaccines and other benefits.²³⁰ A “specialized international instrument” is addressed in Article 4.4 of the Nagoya Protocol²³¹ (see Chapter II, section D.4 and Box 2.21). The provision stipulates that, where a specialized international access and benefit-sharing (ABS) instrument applies that is consistent with, and does not run counter to, the objectives of the CBD and the Nagoya Protocol, the Protocol does not apply for the party or parties to the specialized instrument in respect of the specific genetic resource covered by and for the purpose of the specialized instrument. In November 2019, parties to the Nagoya Protocol were still considering potential criteria for the identification of a specialized international ABS instrument and any process for recognition of such an instrument.²³² The European Union Regulation on compliance measures for users from the Nagoya Protocol considers that the PIP Framework “constitutes a specialised international access and benefit-sharing instrument

that is consistent with the Nagoya Protocol and that should not be affected by the rules implementing the Nagoya Protocol”.²³³

4. The PIP Framework and genetic sequence data

The role of genetic sequence data (GSD) in the PIP Framework is a matter of ongoing debate among WHO member states.²³⁴ GSD can be used to analyse or synthesize physical material to develop influenza products. With the development of technology in vaccine manufacture, it is expected that, in the future, it will increasingly become possible to develop and manufacture vaccines based on GSD alone, that is, without needing access to biological materials (WHO, 2018a).

GSD are not included in the definition of PIP biological material.²³⁵ Hence, manufacturers using GSD that were developed by, or provided through, the GISRS are not required to sign an SMTA 2. However, payment of the partnership contribution is required by the PIP Framework itself for any use of information, including GSD, provided through the GISRS. Therefore, manufacturers who have received GSD, but not PIP biological material, from the GISRS must pay the partnership contribution, but would not be obliged to share benefits, for example, to share a new product with the WHO in the event of a pandemic (WHO, 2018a). The development of technology that allows development and manufacture of vaccines based on GSD alone may thus present a loophole in the PIP Framework. Discussions are under way on whether and how to make changes to the Framework in respect of these considerations (WHO, 2018a).

Endnotes

- 1 Gaudillière, 2008; Bud, 2008; Cassier and Sinding, 2008; Mowery and Sampat, 2001a; Mowery and Sampat, 2001b.
- 2 WIPO, 2015c, p. 69.
- 3 Ibid., p. 70.
- 4 Sampat, 2015, p. 19.
- 5 This section is largely based on Temin, 1979.
- 6 Streptomycin was introduced commercially in 1946 under a patent granted in 1948. However, scientists at Rutgers University who were involved in the discovery of streptomycin convinced the originator company to license it on an unrestricted basis at a royalty rate of 2.5 per cent and to assign the patents to the Rutgers Research Foundation. In the United States, competition drove down the price of streptomycin from US\$ 4,000 per pound to US\$ 282 per pound by 1950.
- 7 See *Pfizer Corporation v. Ministry of Health, Reports of Patent, Design and Trade Mark Cases* 1965, 82(8), 12 August: 261–321.
- 8 See <https://pubs.acs.org/cen/coverstory/83/8325/8325social.html>.
- 9 Figures in the graph are drawn from: US Food & Drug Administration, Summary of NDA Approvals & Receipts, 1938 to the present, available at: <https://www.fda.gov/about-fda/histories-product-regulation/summary-nda-approvals-receipts-1938-present>; US Food & Drug Administration, Center for Drug Evaluation and Research (2019), *Advancing Health Through Innovation: 2018 New Drug Therapy Approvals*, available at: <https://www.fda.gov/media/121483/download>; author's calculation based on monthly data published by US Food & Drug Administration, Original New Drug Application (NDA and BLA) Approvals, available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=reportsSearch.process&rptName=2&reportSelectMonth=12&reportSelectYear=2017&nav#navigation>.
- 10 See LaMattina (2015); Schwieterman (2006); Relias Media (2005).
- 11 EvaluatePharma reports generally give estimates of historical (and future) global pharmaceutical R&D expenditures for a time period 10 years preceding the report. In some cases, the historical estimates are revised in later reports. For all years shown, the most recently published estimate was used (the 2013 report for 2004–2005, 2015 report for 2006–2007, 2017 report for 2008–2009, 2019 report for 2010–2019). The reports are available at: https://info.evaluategroup.com/worldpreview2018_fp_lp.html; <https://info.evaluategroup.com/rs/607-YGS-364/images/wp15.pdf>; <https://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf>; https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma_World_Preview_2019.pdf. FDA approval data are from US Food & Drug Administration, Center for Drug Evaluation and Research (2020), *Advancing Health Through Innovation 2019 New Drug Therapy Approvals*, available at: <https://www.fda.gov/media/134493/download>. These numbers are for CDER only and do not capture the small number of therapies approvals done by CBER each year that could be considered “medicines”, such as gene therapies. The WIPO Statistics Database is available at: <https://www3.wipo.int/ipstats/>.
- 12 See, for example, Cornell University, INSEAD and WIPO (2019); Wieseler, McGauran and Kaiser (2019); van Luijn et al. (2010); Lexchin (2012); Vitry et al. (2013).
- 13 Cornell University, INSEAD and WIPO, 2019; Pharmaprojects (2019), *Pharmaceutical R&D Annual Review 2019*, London: Pharma Intelligence.
- 14 EvaluatePharma reports generally give estimates of historical (and future) global pharmaceutical R&D expenditures for a time period 10 years preceding the report. In some cases, the historical estimates are revised in later reports. For all years shown, the most recently published estimate was used (the 2013 report for 2004–2005, 2015 report for 2006–2007, 2017 report for 2008–2009, 2019 report for 2010–2019). The reports are available at: https://info.evaluategroup.com/worldpreview2018_fp_lp.html; <https://info.evaluategroup.com/rs/607-YGS-364/images/wp15.pdf>; <https://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf>; https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma_World_Preview_2019.pdf; US Food & Drug Administration, Center for Drug Evaluation and Research (2020), *Advancing Health Through Innovation 2019 New Drug Therapy Approvals*, available at: <https://www.fda.gov/media/134493/download>; US Food & Drug Administration, Summary of NDA Approvals & Receipts, 1938 to the present, available at: <https://www.fda.gov/about-fda/histories-product-regulation/summary-nda-approvals-receipts-1938-present>. Note that these numbers are for FDA CDER only and prior to 2009 include only new molecular entities; 2019 PhRMA Annual Membership Survey, available at: https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMA_2019_membership_survey_Final.pdf.
- 15 Cornell University, INSEAD and WIPO, 2019, Chapter 4, Ten Opportunities for biomedical innovation over the next ten years. See also Cutting-Edge Health Technologies: Opportunities and Challenges, Joint Technical Symposium by the WHO, WIPO and WTO, Geneva, 31 October 2019.
- 16 OECD, 2017a, Figure 10.3, p. 187.
- 17 EvaluatePharma, *World Preview 2013, Outlook to 2018: Returning to Growth*, available at: https://info.evaluategroup.com/worldpreview2018_fp_lp.html; EvaluatePharma, *World Preview 2018, Outlook to 2024*, available at: <https://www.evaluate.com/thought-leadership/pharma/evaluatepharma-world-preview-2018-outlook-2024#download>.
- 18 IQVIA Institute. 2018 and Beyond: Outlook and Turning Points, available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/2018-and-beyond-outlook-and-turning-points>.
- 19 See Figures 4 and 5 in United States Government Accountability Office (2017).
- 20 See <https://www.abpi.org.uk/facts-and-figures/science-and-innovation/worldwide-pharmaceutical-company-rd-expenditure-by-country/>.
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- 34 See de Chadarevian (2011); MRC Laboratory of Molecular Biology (1984); Marks (2015).
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- 41 See Anderson (2014); European Commission (2009a), p. 8.
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- 50 See <https://www.alliedmarketresearch.com/vaccines-market>
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- 54 See European Commission et al. (2015); Rodríguez et al. (2010).
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- 56 See Bio-Manguinhos. Inovação (2019), available at: <https://www.bio.fiocruz.br/index.php/br/home/inovacao-bio>.
- 57 See Quintilio et al. (2009).
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- 59 Thresholds for qualifying for orphan designation: a prevalence of less than 200,000 in the US, a prevalence of less than 5 in 10,000 people in the EU, and a prevalence of less than 50,000 in Japan, see Electronic Code of Federal Regulations. Subpart C—Designation of an Orphan Drug, available at: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=718f6fbc20f2755bd1f5a980eb5eedc&mc=true&n=sp21.5.316.c&r=SUBPART&ty=HTML#se21.5.316_120; European Medicines Agency. Orphan designation: Overview, available at: <https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation>; Nitta, A. Current Status and Challenges of Development for Orphan Drugs in Japan, available at: <https://www.pmda.go.jp/files/000205954.pdf>.
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- 69 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Beings, OJEU L 158/1, 27 May 2014.
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- 71 See <https://clinicaldata.ema.europa.eu/web/cdp/termsofuse>.
- 72 See, for example, CEWG; World Intellectual Property Organization. Committee on Development and Intellectual Property (CDIP). Fourteenth Session. Alternatives to the Patent System that Are Used to Support R&D Efforts, Including Both Push and Pull Mechanisms, with a Special Focus on Innovation-Inducement Prizes and Open Source Development Models. CDIP/14/INF/12, available at: https://www.wipo.int/edocs/mdocs/mdocs/en/cdip_14/cdip_14_inf_12.pdf.
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- 84 See <https://carb-x.org/>.
- 85 See <https://www.gardp.org/>.
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- 91 A detailed presentation and analysis on each of these proposals is set out in Annex 3 of the 2012 CEWG report (WHO, 2012).
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- 105 US Congress, H.R.34 – 21st Century Cures Act, Section 565A(b), available at: <https://www.congress.gov/bill/114th-congress/house-bill/34/text#toc-HD3FD-BC6ABEB6480085141F7C11463C3B>.
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- 116 See <https://www.wwarn.org/about-us>.
- 117 See <https://www.iddo.org/data-sharing>.
- 118 WHA, Resolution WHA62.16: Global strategy and plan of action on public health, innovation and intellectual property, Annex 4, pp. 67–68, available at: https://apps.who.int/gb/ebwha/pdf_files/WHA62-REC1/WHA62_REC1-en.pdf; GSPA-PHI Element 2.3(c).
- 119 WHA, Resolution WHA66.22. Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, available at: http://apps.who.int/gb/ebwha/pdf_files/WHA66-REC1/A66_REC1-en.pdf#page=25, <https://www.who.int/phi/progress-report.pdf>.
- 120 See <https://www.who.int/phi/progress-report.pdf>.
- 121 See <https://dndi.org/research-and-development/treatments-delivered/>.
- 122 See <https://www.dndi.org/diseases-projects/portfolio/>.
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- 142 The issue of patentable subject matter is addressed in Chapter II, section B.1(b)(iii).
- 143 *Official Journal of the European Communities* L 213/13 of 30 July 1998. The directive has been reviewed by an Expert Group set up by the European Commission in 2012, which issued its final report on the development and implications of patent law in the field of biotechnology and genetic engineering in May 2016, available at: <http://ec.europa.eu/DocsRoom/documents/18604/attachments/1/translations/>. Certain Articles of Directive 98/44/EC have been clarified by CJEU jurisprudence and a Commission Notice of 3 November 2016; see OJEU C411/3, 8 November 2016, and WTO document WT/TPR/S/357/Rev.1, paras. 3.275–3.278.
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- 145 See http://www.globalmedicaltechnologyalliance.org/papers/GMTA_Patents_for_Medical_Devices_and_Pharmaceuticals_Rev_FINAL_19_Mar_2012.pdf.
- 146 *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, para. 2116.
- 147 Ibid, para. 2111.
- 148 See *D'Arcy v Myriad Genetics Inc.* [2015] HCA 35.
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- 153 WIPO document SCP/15/3, Annex III, available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_15/scp_15_3-annex3.pdf.
- 154 WIPO, Revised Annex II of document SCP/12/3 Rev.2: Report on the International Patent System, available at: https://www.wipo.int/export/sites/www/scp/en/national_laws/exclusions.pdf.
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- 156 *Parke, Davis & Co. v. H. K. Mulford Co.* 189 F. 95 (S.D.N.Y. 1911).
- 157 UNEP, 2019, p. 18.
- 158 See <https://www.nature.com/articles/d41586-019-00726-5>.
- 159 See <https://www.who.int/ethics/topics/human-genome-editing/GenomeEditing-FirstMeetingReport-FINAL.pdf?ua=1>.
- 160 The issue of inventive step/non-obviousness is addressed in Chapter II, section B.1(b)(iii).
- 161 Further information on incremental innovation and intellectual property, including specific examples, can be obtained from Follow-on Innovation and Intellectual Property, a WIPO Submission to the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH), 20 May 2005, available at: https://www.wipo.int/export/sites/www/policy/en/global_health/pdf/who_wipo.pdf.
- 162 WIPO document SCP/30/4.
- 163 See <https://baltimore.cbslocal.com/2016/08/18/cost-jumps-nearly-500-percent-for-life-saving-epipens/>.
- 164 See <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-combination-products>.
- 165 See FDA (2018).
- 166 Gupta et al. 2016; “Narcan” and “Evzio” in FDA Orange Book, available at: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm.
- 167 Letter from the Baltimore City Health Department and Public Citizen to the Counsellor to the President of the United States. 3 May 2018, available at: <https://www.citizen.org/wp-content/uploads/naloxone-product-government-use-request.pdf>.
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- 169 For more information on prior art, see Chapter II, section B.1(b)(iv) and WIPO document SCP/12/3 Rev.2, para. 210.
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- 173 See <https://www.wipo.int/patents/en/guidelines.html>.
- 174 See WIPO document SCP/30/4, Further Study on Inventive Step (Part III), available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_30/scp_30_4.pdf.
- 175 Joint Resolution 118/2012, 546/2012 and 107/2012 (Ministry of Industry, Ministry of Health and National Industrial Property Institute) of 5 May 2012, published in Official Gazette of 8 May 2012.
- 176 Manual para el examen de solicitudes de patentes de invención en las oficinas de propiedad industrial de los países de la Comunidad Andina, developed by the Andean Community, EPO and WIPO, 2004, available at: http://www.comunidadandina.org/StaticFiles/201166165925libro_patentes.pdf and from the industrial property offices of Bolivia, Colombia, Ecuador, Peru and Venezuela, see https://www.wipo.int/wipo_magazine/en/2005/02/article_0008.html.
- 177 Sampat and Shadlen, 2016; see also Shedlen (2018).
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- 181 The issue of novelty is addressed in Chapter II, section B.1(b)(iii).
- 182 See <https://wipolex.wipo.int/en/legislation/details/9451>.
- 183 Section 3(d) of the Patents Act (2005) as amended excludes from the definition of “invention” the “mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant”.
- 184 New guidelines for examining chemical-pharmaceutical patent applications, effective as of 9 May 2012 and applicable to all pending and new patent applications, were issued in Argentina (Joint Regulation Nos. 118/2012, 546/2012 and 107/2012 issued on 2 May 2012 by the Argentine Patent Office together with the Ministries of Industry and of Health, published in the Official Gazette on 8 May 2012), available at <https://www.boletinoficial.gob.ar/detalleAviso/primera/69099/20120508>. See Anexo 4) - Considerando características farmacotécnicas (xii) - Segunda indicación médica (Nuevos usos médicos).
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- 186 See <https://www.epo.org/law-practice/legal-texts/epc.html>.
- 187 Some guidance about granting of patents by the EPO for first or further medical use of known products can be obtained from the guidelines for patent examination of the EPO, available at: https://www.epo.org/law-practice/legal-texts/html/guidelines/eg_vi_7.htm.
- 188 G 0002/08 (Dosage regime/ABBOTT RESPIRATORY) of 19 February 2010.
- 189 EPO Enlarged Board of Appeal of 5 December 1984, G 0005/83 (Second medical indication), available at: <https://www.epo.org/law-practice/case-law-appeals/recent/g830005ep1.html>.

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- 191 *Warner-Lambert Company LLC v Generics (UK) Ltd t/a Mylan and another* (2018) UKSC 56, available at: <https://www.supremecourt.uk/cases/uksc-2016-0197.html>.
- 192 See *Canada – Pharmaceutical Patents* (DS114).
- 193 WIPO SCP/29/3: https://www.wipo.int/edocs/mdocs/scp/en/scp_29/scp_29_3.pdf, Annex II, p. 10.
- 194 *Madey v. Duke University*, 307 F.3d 1351 (Fed.Cir. 2002).
- 195 See WIPO document SCP/20/4, paras. 36–40, available at: https://www.wipo.int/edocs/mdocs/patent_policy/en/scp_20/scp_20_4.pdf.
- 196 WIPO document CDIP/5/4, Annex II.
- 197 See Chapter IV, section C.3(a)(ii)–(iii).
- 198 WIPO document SCP/29/3, para. 17.
- 199 See www.wipo.int/scp/en/exceptions.
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- 201 The following countries outline that research exceptions only apply to research “on” or relating to the patented invention: Albania; Dominican Republic; Germany; Hong Kong, China; Kyrgyz Republic; the Netherlands; Norway; Russian Federation; Switzerland and Tajikistan. See WIPO SCP/29/3, available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_29/scp_29_3.pdf.
- 202 Article XI.34. §1 er. of the Law of 19 April 2014 of Belgium.
- 203 Article 40b, Swiss Patent Law, <https://www.admin.ch/opc/en/classified-compilation/19540108/index.html>.
- 204 Appendix, WIPO SCP/29/3, available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_29/scp_29_3.pdf.
- 205 See Department of Health and Human Services, National Institutes of Health, Principles and Guidelines for Recipients of NIH Research Grants and Contracts and Obtaining and Disseminating Biomedical Research Resources: Final Note (1999), p. 72093, available at: https://grants.nih.gov/grants/intell-property_64FR72090.pdf.
- 206 35 U.S.C. §209. Licensing federally owned inventions, available at: <https://www.law.cornell.edu/uscode/text/35/209>.
- 207 The WIPO SCP has organized sharing sessions on licensing issues. In SCP 30, the WIPO Secretariat and a number of relevant institutions shared their experiences on capacity-building activities relating to negotiating licensing agreements. The Report of the Sharing Session on 24 June 2019 is available at: https://www.wipo.int/meetings/en/doc_details.jsp?doc_id=455117; all presentations are available at: https://www.wipo.int/meetings/en/details.jsp?meeting_id=50419. In SCP 32, a sharing session discussed challenges and opportunities in relation to types of patent licensing provisions in health-care technologies. Information about the WIPO SCP is available at: <https://www.wipo.int/policy/en/scp/>.
- 208 See <https://www.gov.uk/guidance/model-agreements-for-collaborative-research>.
- 209 See <https://www.gov.uk/guidance/university-and-business-collaboration-agreements-lambert-toolkit#fast-track-model-agreement>.
- 210 See <http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/>.
- 211 WIPO document SCP/12/3 Rev.2.
- 212 Ibid.
- 213 See Reaping the Benefits of Genomic and Proteomic Research, National Academy of Science, quoted after WIPO document SCP/12/3 Rev.2, available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_12/scp_12_3_rev_2.pdf.
- 214 Ibid.
- 215 This section is a summary of Krattiger (2007a).
- 216 For further explanations on compulsory licences, see Chapter IV, section C.3(a)(ii)–(iii).
- 217 Section 4.3 of the PIP Framework defines NICs as meaning influenza laboratories authorized and designated by the member state and subsequently recognized by WHO to perform a number of functions.
- 218 Section 4.3 of the PIP Framework defines WHO Collaborating Centres on Influenza as influenza laboratories designated by WHO and supported by national authorities to perform certain roles within the WHO GISRS.
- 219 WHA, Resolution WHA60.28: Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits.
- 220 Source: WIPO (2011a).
- 221 See https://www.who.int/influenza/resources/technical_studies_under_resolution_wha63_1_en.pdf. See also www.who.int/vaccine_research/diseases/influenza/Mapping_Intellectual_Property_Pandemic_Influenza_Vaccines.pdf.
- 222 See https://www.who.int/influenza/resources/documents/wipo_ipdoc/en/.
- 223 WHA, Resolution WHA64.5: Pandemic influenza preparedness: Framework for the sharing of influenza viruses and access to vaccines and other benefits, available at: https://apps.who.int/gh/pip/pdf_files/pandemic-influenza-preparedness-en.pdf.
- 224 The PIP Framework, in Section 4.1, defines PIP biological materials as including: “human clinical specimens, virus isolates of wild type human H5N1 and other influenza viruses with human pandemic potential; and modified viruses prepared from H5N1 and/or other influenza viruses with human pandemic potential developed by WHO GISRS laboratories, these being candidate vaccine viruses generated by reverse genetics and/or high growth re-assortment. Also included in ‘PIP biological materials’ are RNA extracted from wild-type H5N1 and other human influenza viruses with human pandemic potential and cDNA that encompass the entire coding region of one or more viral genes”.
- 225 See WHO, Standard Material Transfer Agreement 2, Article 4.4, available at: https://www.who.int/influenza/pip/smta2_eng.pdf?ua=1.
- 226 See WHO, Standard Material Transfer Agreements 2 (SMTA2), available at: <https://www.who.int/influenza/pip/smta2/en/>.
- 227 See WHO, Partnership Contribution Collection, available at: https://www.who.int/influenza/pip/benefit_sharing/pc_collection/en/.

- 228 See WHO, PIP Partnership Contributions, as of 30 December 2019, available at: https://www.who.int/influenza/pip/benefit_sharing/pc_total_contributions.pdf?ua=1.
- 229 See, for example, WHO, 2019d.
- 230 Document WHA70/2017/REC/1, available at: http://apps.who.int/gb/ebwha/pdf_files/WHA70-REC1/A70_2017_REC1-en.pdf#page=61.
- 231 The Text of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity is available at: <https://www.cbd.int/abs/text/>.
- 232 See decision adopted by the parties to the Nagoya Protocol on Access and Benefit-Sharing, document CBD/NP/MOP/DEC/3/14, available at: <https://www.cbd.int/conferences/2018/np-mop-03/documents>; WHO 2018a.
- 233 Recital 16 of Regulation (EU) No 511/2014 of the European Parliament and of the Council of 16 April 2014 on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union, available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0511>; WHO, 2018a.
- 234 The PIP Framework uses the term “genetic sequence data”, while the discussions held under the Nagoya Protocol so far refer to “digital sequence information”. Parties to the CBD and Nagoya Protocol have not yet agreed on a definition of “digital sequence information”. However, it generally refers to information associated to genetic sequencing. “Genetic Sequence Data” and “Digital Sequence Information” are sometimes used interchangeably. WHO, 2018a. The Analysis explains that parties to the CBD and the Nagoya Protocol also use the term “digital sequence information” for information associated to genetic sequencing; see footnote 71 in that Analysis.
- 235 WHO, 2011c, Article 4.1.

IV. Medical technologies: the access dimension

Chapter III explained the role of intellectual property (IP) and other policy measures in health innovation; this chapter provides a detailed description of the access dimension and the concepts, laws and policies underlying it, as well as data on availability and access to health technologies and methodological approaches to their measurement. It also offers an overview of the main determinants of access related to health systems, IP and trade policy.

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A. The context: health-systems-related determinants of access

Key points

- Access to health technologies is part of a broader challenge of ensuring access to health care, which requires a functioning health-care system. This includes: the delivery of quality health services; a well-performing health workforce; access to reliable and timely information on health determinants, health system performance and health status; health financing; and good leadership and governance.
- Universal health coverage (UHC) to ensure access to quality health services without financial hardship by all patients has become a leading goal for health in the context of the Sustainable Development Goals (SDGs) but can require trade-offs between the various dimensions of coverage.
- Inadequate financing, high prices and ineffective policy interventions to manage expenditure represent challenges in achieving UHC.
- The WHO Essential Medicines List provides helpful guidance on the selection of medicines for procurement and use in health systems. The WHO also publishes similar lists for other types of health technology.
- Price is a critical determinant of access to health technologies, especially in countries where the public health sector is weak and where treatment is often purchased on the private market and paid for by people out of their own pockets.
- In general, generic products are cheaper than originator products, but even low-priced generic medicines are often still unaffordable for large sections of the population in many low- and middle-income countries (LMICs).
- Countries use a variety of measures to increase the market share of affordable generics in order to control health budgets.
- A range of policy tools is available to governments for controlling pharmaceutical expenditures, including: supply-side and demand-side measures that aim to increase and/or accelerate the use of generics; price controls and reference pricing; health technology assessments; volume limitations and health outcome-based agreements; improved transparency of price and costs across the pharmaceutical value chain; reducing or eliminating taxes and tariffs on medicines; regulating mark-ups; and effective procurement mechanisms.
- Differential pricing can make medicines more affordable to larger segments of the population.
- Procurement systems should be designed to obtain needed health technologies of good quality, at the right time, in the required quantities and at favourable costs. Tendering and pooled procurement can contribute to cost savings in the procurement process.
- Local production is supported in a number of LMICs through national efforts and numerous regional and international initiatives. Policy coherence is crucial to achieving public health and industrial development benefits.
- Regulation should promote access to medical technologies of proven quality, safety and efficacy and should not unnecessarily delay the market entry of products.
- Challenges for regulatory systems that impact access include lack of political support and adequate resources, a focus on regulating products without effective oversight of the whole supply chain, poorly developed systems for post-marketing surveillance, and different standards for locally produced versus imported products.
- The WHO Prequalification Programme has greatly facilitated access to quality essential medicines in LMICs.
- Regulatory convergence of different national systems can remove many of the costs associated with multiple regulatory submissions and multiple testing.
- Substandard and falsified (SF) medical products pose serious public health problems, especially in regions where the regulatory and enforcement systems are weak. Both regulatory and IP tools can be used in a complementary way to combat SF products.

Access to medicines and other medical technologies rarely depends entirely on a single factor. This section describes the main health-systems-related determinants of access to medicines and medical technologies at the interface of health, intellectual property (IP) and trade. The section first explains the importance of a well-functioning health system as an overarching determinant of access. It then presents the concept of universal health coverage and, as one way of conceptualizing the determinants of access to medicines, the model of a pharmaceutical value chain. It then explains how the WHO measures access and affordability, and describes generic medicines policies. It explains pricing issues with respect to access to medical technologies and outlines how taxes, duties and high mark-ups can impact affordability and access to medical technologies. It then describes the importance of effective and efficient procurement mechanisms and of sustainable health financing, considers access issues related to local manufacturing and associated technology transfer, presents regulatory mechanisms and access to medical technologies and concludes with a summary of access issues linked to substandard and falsified medical products.

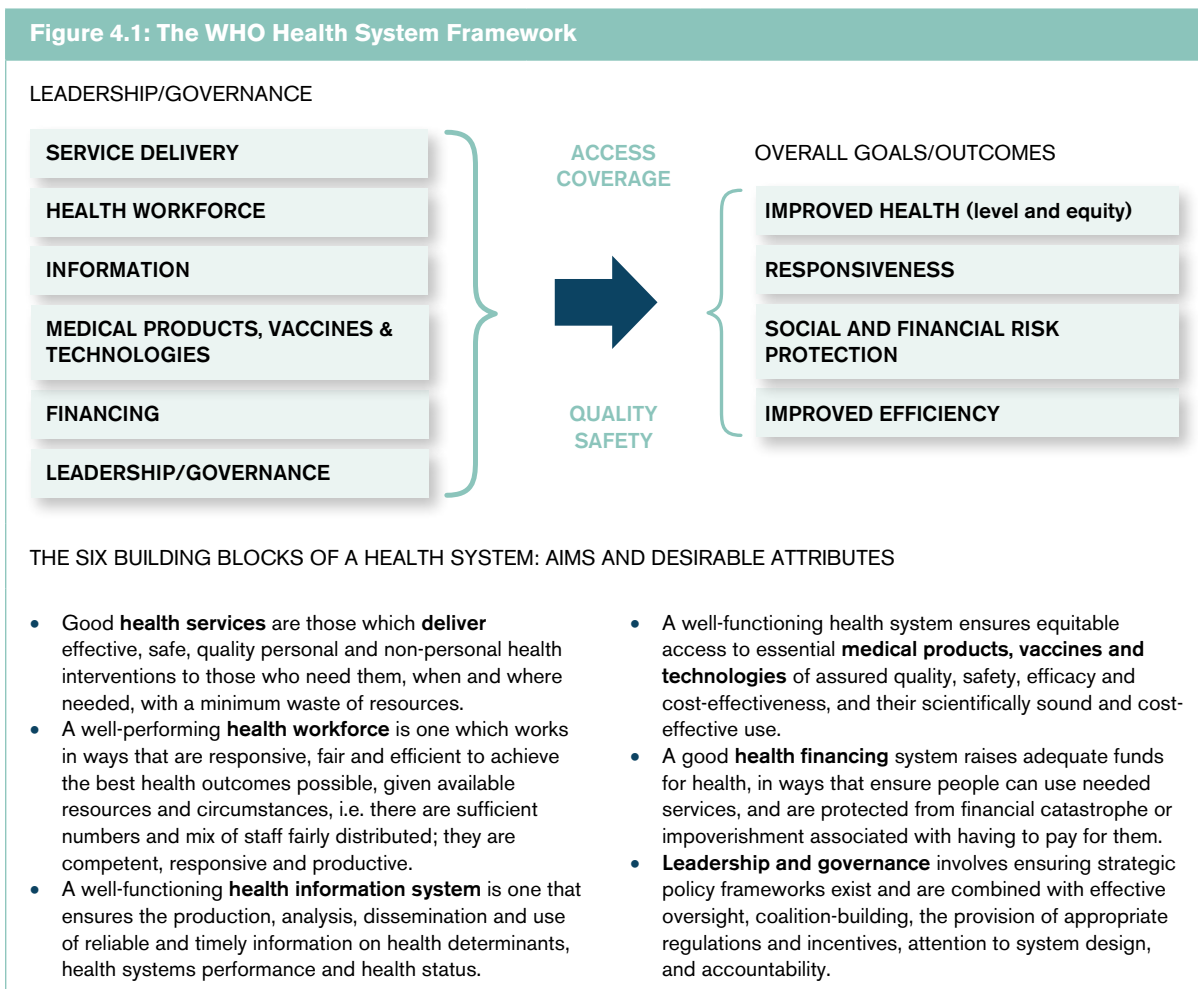
A health system consists of all organizations, people and actions whose primary intent is to promote, restore or

maintain health (WHO, 2000). The WHO conceptualizes health systems in terms of six building blocks, the interplay among which helps in achieving desired health outcomes through ensuring universal coverage and equitable access to quality-assured and safe health care (see Figure 4.1). One important building block of any health system is equitable access to essential medical products of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use (WHO, 2007a). All six building blocks of the health system are interdependent (see Figure 4.1). The issue of access to medicines is one aspect of a broader problem of access to health care. Delivering access requires a functioning national health-care system, as recognized in the WHO Road Map for Access to Medicines, Vaccines and Other Health Products, 2019–2023, which takes a health systems approach to improving access to health products.¹

1. Universal health coverage

The concept of universal health coverage (UHC) has been increasingly recognized in international fora since WHO published the *World Health Report: Health Systems Financing: The Path to Universal Coverage*² in 2010,

Figure 4.1: The WHO Health System Framework



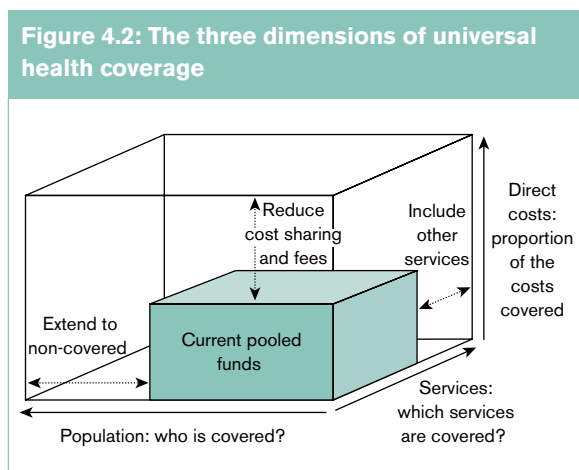
Source: WHO.

and has become a leading, unifying goal for health in the context of sustainable development. UHC means that all individuals and communities have access to quality health services without financial hardship (WHO, 2017h). It includes the full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation and palliative care. Protecting people from the financial consequences of paying for health services out of their own pockets reduces the risk that people will be pushed into poverty because unexpected illness requires them to use up their life savings, sell assets or borrow – destroying their futures and often those of their children (WHO, 2019e).

Achieving UHC is one of the targets the nations of the world set when adopting the Sustainable Development Goals (SDGs) in 2015. It is captured directly in target 3.8 – “Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all” – where it explicitly notes the key role of access to health products. Many of the other health-related SDG targets contribute to UHC.³

The path to universal coverage thus involves important policy choices. Universal coverage involves trade-offs between different dimensions of coverage: the proportion of health costs covered by the government and/or insurance, the proportion of services covered and the proportion of the population covered (see Figure 4.2). These dimensions of coverage reflect a set of policy choices about benefits and their rationing that are among the critical decisions facing countries in their reform of health financing systems towards universal coverage.

WHO projections found that most middle-income countries should be able to mobilize the necessary funding to advance systems towards UHC by 2030 from domestic resources, while many low-income countries would face a funding gap (Stenberg et al., 2017).



Source: WHO. Universal coverage – three dimensions, available at: https://www.who.int/health_financing/strategy/dimensions/en/.

2. International access frameworks: the value chain of medicines and health products

Medical technologies are complex products that can only be effective in conjunction with expert advice and other health services. Thus, ensuring access to health products, and medicines in particular, is not an isolated event, but requires a fully functioning health system.

Over time, a number of access frameworks for access to medicines have been formulated:

- The WHO access framework comprised the following components: rational selection and use of medicines; affordable prices; sustainable financing; and reliable health and supply systems (WHO, 2004).
- Health policy experts have proposed a framework revolving around availability, accessibility, affordability, adequacy and acceptability (Obrist et al., 2007).
- Another proposed framework pays more attention to the international aspects of partnerships for access to medicines (Frost and Reich, 2010).

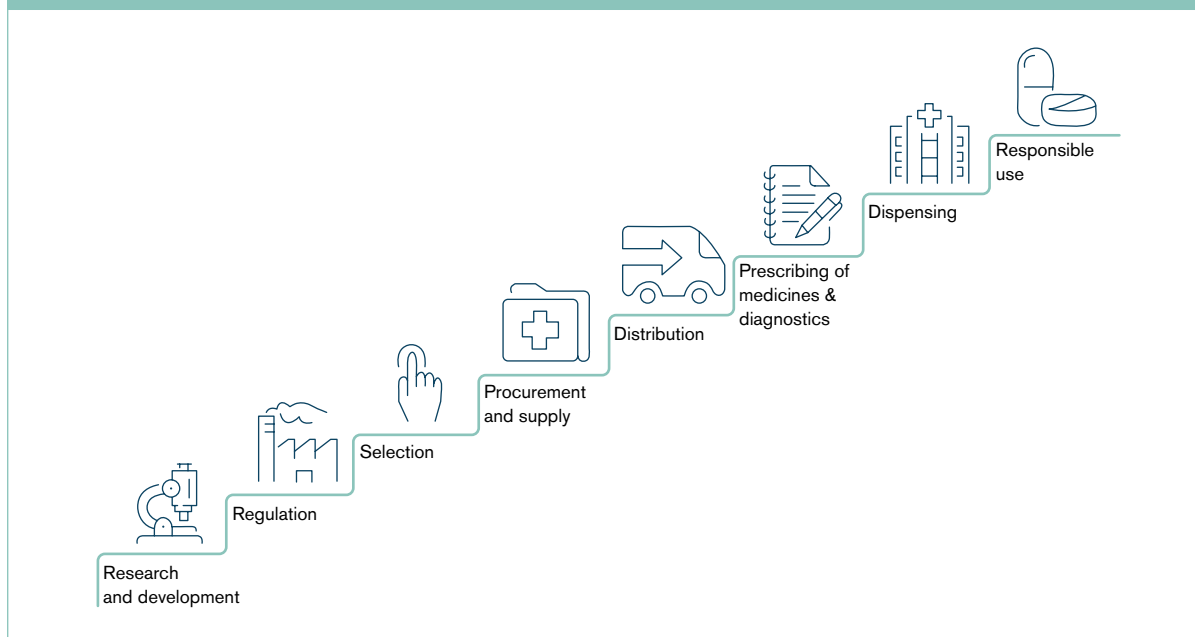
WHO conceptualizes the range of steps and factors that contribute to ensuring access to medical technologies as using the pharmaceutical life cycle, shown in Figure 4.3, which follows a medicine from discovery to use by patients.

Access starts with focusing R&D efforts on public health needs. For example, the WHO target product profiles that define the ideal characteristics of a missing medicine or vaccine for pathogens with pandemic potential such as Rift Valley fever, Ebola, and others are tools to ensure a public health focus (see Chapter III, section C.3). Specific needs of low- and middle-income countries (LMICs) and vulnerable populations and, in particular, children, should be taken into account – for example, by prioritizing oral over intravenous administration.

The manufacturing process, which is linked with market authorization requirements, is key to ensuring that health products are of good quality. National regulatory authorities are responsible for the quality, safety and efficacy of health products. A weak regulatory system can have an impact on patient outcomes and has the potential to impair initiatives for improving access, for example, by taking too long to approve products for use in a country (see Chapter II, section A.6 and Chapter IV, section A.11).

The rational selection of medicines is key to avoiding wasting precious financial resources on less-efficient interventions. The WHO EML and treatment guidelines are key tools that help countries to make rational procurement decisions (see section A.7).

Figure 4.3: Ensuring access along the value chain of medicines and health products



Source: WHO Secretariat.

High expenditures for pharmaceuticals, and high prices for new pharmaceuticals in particular, place increasing pressure on all health systems in terms of their ability to provide full and affordable access to quality health care. The high percentage of health spending on medicines (20–60 per cent, as demonstrated in a series of studies in selected LMICs) impedes progress for the many countries that have committed to the attainment of UHC (Reich et al., 2016).

With respect to procurement, the need for good governance is increasingly recognized as a major hurdle on the road to achieving UHC. Weak governance complicates access to health products by fuelling inefficiencies, distorting competition and leaving the system vulnerable to undue influence, corruption, waste, fraud and abuse. In addition, good access to information is essential for decision-making, monitoring policy implementation and establishing accountability. Appropriate prescribing, dispensing and use of health products is essential for ensuring health impact and effective use of resources. An estimated half of all medicines in the world are inappropriately prescribed, dispensed or sold. This is compounded by the fact that a similar proportion of people use their medicines incorrectly. Factors that contribute to inappropriate prescribing, dispensing and use include an inadequately trained workforce, incorrect diagnoses, the prohibitive costs or simple unavailability of medicines, and activities related to product marketing and promotion. One example of the impact of inappropriate prescribing, dispensing, and sales is seen in the area of AMR, where good stewardship of medicines is key to preserving the efficacy

of available antimicrobials (see Chapter II, section A.5; Chapter III, section C.2; and Chapter IV, section B.2).

Overall, inadequate financing of health products, high prices of new health products and ineffective policy interventions and processes to manage expenditure contribute to the challenges facing the health system in achieving UHC. The OECD estimates that up to one fifth of health spending could be channelled towards better use by avoiding waste that occurs: (a) when health products are priced higher than is necessary; (b) when less expensive but equally effective alternatives are not used; and (c) when purchased products are not used at all (OECD, 2017b).

3. The meaning and measurement of “access”

The WHO has defined “access” to medicines as the equitable availability and affordability of essential medicines during the process of medicine acquisition (WHO, 2003a, 2004). Lack of access is generally understood to mean the absence of available and affordable treatment options for the patient. In the case of medical devices, it not only implies the absence of diagnostic equipment or treatment devices but may also reflect an inability to utilize available devices, for example, due to the lack of maintenance, infrastructure or skilled operators. Appropriate treatment has to be physically available and needs to be affordable for the patient. While there is a lack of systematic data collection on access to affordable essential medicines across countries,⁴ an outline of available data is given below.

Affordability

Prices are a critical determinant of affordability of medicines, especially in countries where the public health sector is weak and a large part of the population has to purchase their treatment on the private market and pay for it out of their meagre resources. “Affordability” of a medicine’s price is calculated by the WHO as the number of days’ wages of the lowest-paid, unskilled government worker required to purchase selected courses of treatment for common acute and chronic conditions (WHO and HAI, 2008). One challenge in measuring affordability of prices is that data are lacking or are of poor quality in most LMICs. Across 26 surveys in LMICs between 2007 and 2014, patient prices for lowest-priced generics were, on average, 2.9 times higher than international reference prices (IRPs) in public-sector facilities and 4.6 times higher in private-sector facilities.⁵ For example, a 2017 study on availability, prices and affordability of medicines for common chronic diseases in the Asia Pacific region found that countries paid 1.4 times the IRP to procure lowest-priced generics and 9.1 times for innovator brands (Wang et al., 2017).

Household out-of-pocket health-care expenditures can be considered “catastrophic” if they exceed 10 or 25 per cent of a household’s total consumption expenditure or income. They are considered impoverishing when they leave household’s non-medical consumption below poverty lines. A 2019 WHO and World Bank report estimated that 927 million people spend more than 10 per cent of their household budget on health care, and nearly 90 million people are pushed into extreme poverty each year because of out-of-pocket health expenses (WHO and the World Bank, 2020). Evidence from WHO regions of South-East Asia and Europe suggest that medicines are the main drivers of household’s out-of-pocket health spending (WHO regional office for Europe, 2019; Wang et al., 2018).

Another approach to measuring access compares the average cost of a basket of medicines, per person, to reported pharmaceutical expenditures per capita. In 2016, the Lancet Commission on Essential Medicines Policies modelled the financial requirements to enable universal access to a basic package of essential medicines in LMICs, estimating that this would require US\$ 13–US\$ 25 per person per year.⁶ Based on the finding that, in 2010, most low-income countries and 13 of the 47 middle-income countries spent less than US\$ 13 per person on medicines, the Commission concluded that a substantial proportion of the global population cannot access even the most basic medicines (Wirtz et al., 2017).

Availability

The WHO analysed availability and affordability of essential medicines in the public and private sectors in 26 surveys in low- and lower-middle-income countries between 2007 and 2014. “Availability” was defined as

the percentage of outlets where an individual medicine product could be physically located on the day of the survey (WHO and HAI, 2008). These surveys of selected generic medicines found that average (median) availability of such medicines was 58 per cent in the public sector and 67 per cent in the private sector, with a wide range of variation between countries.⁷ For example, the median availability of any medicine in the public sector was found to be 35.5 per cent, compared with 56.7 per cent in the private sector in the Asia Pacific region.⁸

It is estimated that costs to patients could be 60 per cent lower in the private sector if generics were stocked preferentially over originator products, due to generally lower prices for generic treatments (Cameron and Laing, 2010). However, as noted earlier, the poorest populations may not be able to afford even the lowest-priced generic products, especially when they are only available through the higher priced private system (Niëns et al., 2010). Ensuring availability of medicines at little or no cost to the patient at the point of use through the public health system is thus critical for universal access and is a primary responsibility of governments.

4. Generic medicines policies, price controls and reference pricing

Generic medicines policies (including policies on similar biotherapeutic products) that aim to increase the market share of cheaper generic medicines, control prices of medicines and regulate the level of medical expenses reimbursement are key policy interventions to control health budgets and make medicines and other health products and services more affordable.

(a) Generic medicines policies

The use of generic medicines has been steadily rising, not only in developing countries but also in developed countries, as a result of economic pressure on health budgets. Many countries are using different measures to increase the market share of cheaper generics to control health budgets. When patents on “blockbuster” medicines have ended or are nearing the end of their patent term, it can be expected that the market share of generics and similar biotherapeutic products will continue to rise further.

Generic medicines policies can be divided into so-called supply-side and demand-side policies (King and Kanavos, 2002).

(i) Supply-side measures

Supply-side measures are primarily directed towards the specific health-care system stakeholders that are responsible for medicine regulation, registration, competition

(antitrust) policy, intellectual property rights (IPRs), pricing and reimbursement. Through such measures, policy-makers can have an impact on the:

- speed with which a generic product is reviewed by the regulatory authority
- decision whether or not to grant a patent according to the applicable patentability criteria
- relationship between market authorization of medicines and patent protection, if any (“Bolar” exception and patent linkage)
- way clinical test data are protected from unfair competition
- ability of the originator to extend IP protection, for example, through patent term extensions
- level of competition among manufacturers, and monitoring of agreements between originators and generic companies
- price(s) of generic product(s)
- reimbursement to the purchasers of medicine(s).

One example of a supply-side measure is the Hatch-Waxman Act in the United States (see Box 4.1).

(ii) Demand-side measures

Generally, demand-side measures are directed at stakeholders such as health-care professionals who prescribe medicines (usually physicians), people who dispense and/or sell medicines and patients/consumers who ask for generic medicines. These measures usually relate to activities that occur after an originator loses market exclusivity and generic medicines have entered the market.

Through the use of appropriate demand-side measures, policy-makers can:

- increase prescribing of generic version(s) by physicians, using the international non-proprietary name (INN)/generic name instead of the brand name

- increase dispensing of the generic version(s) by people who dispense and/or sell medicines (e.g. by generic substitution policies)
- improve the confidence of prescribers, dispensers and consumers in the quality of generic medicines
- influence the overall consumption pattern of the generic medicine(s) in the health-care system
- increase the demand by consumers for generic medicines through lower co-payments as compared with originator products
- improve the perception of generic medicines, in that there is no difference in treatment effect.

Most of the policies in high-income countries work through health insurance systems, which have reimbursement and/or co-payments procedures that do not exist in certain LMICs. The differences in contextual factors between high-income countries and LMICs that influence pro-generic medicines policies make it difficult to predict which policies can be successfully translated from high-income countries to LMICs.

Two enabling conditions may be needed before an LMIC can effectively implement pro-generic medicines policies:

- A mechanism to provide certainty that the generic medicines are of assured quality; this involves having an effective regulatory system
- A robust supply of generic medicines to ensure the availability of assured quality, low-cost medicines.

The characteristics of the health-care systems in many LMICs suggest that demand-side policies driven by consumers may be more important, as medicines are largely financed out of pocket and the selection of products purchased is made directly by consumers or patients without prescribers acting as intermediaries.

Box 4.1: The US Hatch-Waxman Act as a supply-side measure to encourage generic competition

The US Hatch-Waxman Act grants a 180-day regulatory exclusivity period (for regulatory exclusivities, see Chapter II, section A.6(f)) to the first generic applicant to file a certification that a patent associated with an approved medicine is invalid, unenforceable or will not be infringed by the generic product. The purpose of this so-called “generic exclusivity” provision is to encourage generic applicants to challenge, or work around, patents for approved medicines. The Hatch-Waxman Act had a profound effect on generic competition in the United States, with the market share of generic prescriptions growing from 18.6 per cent in 1984 (when the Act was introduced) to 88 per cent in 2015 (Berndt and Aitken, 2011; Wouters et al., 2017). However, the effect of generic exclusivity on the price of generic medicines has been controversial. Applicants who are granted generic exclusivity enjoy an effective “duopoly”⁹ with the originator firm during the exclusivity period and tend to set their prices close to the price of the originator medicine.¹⁰ According to the US Federal Trade Commission (FTC), the price of generic medicines during generic exclusivity periods are, on average, 74 per cent of the originator price, and generics that enter the market with exclusivities are, on average, around 30 per cent more expensive than those that enter the market without them (Tenn and Wendling, 2014; Olson and Wendling, 2013). Similar exclusivity provisions apply to the first applicant with a similar biotherapeutic medicine to establish that its product is interchangeable with a previously approved biotherapeutic medicine.¹¹ For a description of regulatory exclusivities, see Chapter II, section A.6(f).

(iii) *A comparison of selected generic medicines policies*

The price and market share of generic medicines vary widely from country to country.¹² This may be attributed to differences in pricing and reimbursement policies, generic prescription and substitution laws, as well as other political and cultural factors.¹³ One 2014 study observed that the prices paid by the government for a selection of generic medicines were, on average, 7.32 times higher in Australia than in England. The study cites a number of possible explanations for this price differential, including: (1) differences in the price-disclosure regime and the methodology used to set reimbursement prices in each country; (2) the overall market conditions being more supportive of generic competition in England; and (3) higher rates of generic prescription in England (which, in turn, were attributable to greater incentives for generic prescription, better practitioner knowledge regarding the safety, quality and bioequivalence of generic medicines, and less resistance from key stakeholders to generic prescription).¹⁴ Since the date of the study, Australia has reformed its price-disclosure regime and methodology, which now more closely resemble the English system.¹⁵

In New Zealand, publicly funded medicines are subject to a competitive tendering process, which is open to all therapeutically interchangeable medicines. Public subsidization is often limited to one or two products per therapeutic class, with consumers still free to purchase alternative brands on the open market. A 2018 study found that, using this tendering regime, New Zealand was able to negotiate low prices for atorvastatin with the originator company prior to patent expiry, and was able to maintain lower prices following expiry than other countries in the Asia Pacific region, which employed, variously, free pricing in the private market and competitive tendering in the public sector (Singapore), mandatory price cuts upon generic entry (Republic of Korea) and mandatory price cuts combined with subsequent price-disclosure reviews (Australia) (Roughead et al., 2018).

(b) Price control

There is potential for manufacturers to exploit market exclusivity when facing demand for medicines that remains relatively constant irrespective of changes in price (so-called “inelastic demand”). This has led many countries to regulate prices for at least some portion of the pharmaceutical market, most often patented products.¹⁶

Various price control strategies have been used. These include controlling profits of manufacturers, direct price controls, comparing prices to references that are internal or external to the country, constraining spending by physicians, enforcing prescription guidelines, tying

marketing approval to prices and placing limits on the promotion of medicines.

Price controls can be applied at either the manufacturer, wholesaler or retailer level (see Box 4.2 for reference prices and price controls in Colombia). The most direct control method is when a government sets the sale price and prevents sales at any other price. Where governments hold a total or near-total monopsony in (certain types of) health products, this may strengthen their position in price negotiations. Canada's Patented Medicines Prices Review Board aims to ensure that the prices of patented medicines are not excessive, and monitors the prices that companies charge for patented medicines in Canada as compared with a number of other jurisdictions. If the Board considers a price excessive, it can order price reductions and/or the offset of excess revenues.¹⁷ Mexico has a similar system (Gómez-Dantés et al., 2012).

(c) Reference pricing

Reference pricing can determine, or be used for negotiating, the nationally regulated price or reimbursement level of a product based on the price(s) of a pharmaceutical product in other countries (“external”) or relative to existing therapies in the same country (“internal”). Reference pricing typically controls the reimbursement level and thus is mainly useful in countries with insurance-based systems. This is seen as less restrictive than direct price controls.

(i) *External reference pricing*

International or external reference pricing is the practice of comparing the price(s) of a pharmaceutical product with the prices in a set of reference countries (Espin et al., 2011). Various methods can be used for selecting reference countries in the “basket” and for calculating external reference prices. There are also many ways to apply external reference pricing in practice. Box 4.2 describes how external reference pricing and prices controls work in Colombia.

(ii) *Internal reference pricing*

By contrast, internal reference pricing compares the same or similar medicines in the same country. Medicines to be compared are classified according to the Anatomical Therapeutic Chemical classification system (ATC), which compares medicines at five levels, from the organ or system on which the medicine works through to the chemical structure (ATC 5 level).¹⁸ Internal reference pricing is “the practice of using the price(s) of identical medicines (ATC 5 level) or similar products (ATC 4 level) or even with therapeutic equivalent treatment

Box 4.2: Price control and reference prices to reduce prices of medicines in Colombia

The National Commission for the Price of Medicines and Medical Devices of Colombia (CNPMDM) fixes reference prices for all medicines commercialized in the country's public sector at least once a year. To do so, it takes into account the average price in the domestic market for a group of homogenous pharmaceutical products, i.e. products with identical composition, doses and formulas. If the price applied for such a medicine is above the average price for homogenous products, direct price controls are applied and a maximum retail price is fixed by the Commission.

Direct price controls are also applied if there are fewer than three homogenous products on the market or if a medicine is considered of public interest for public health reasons. In such cases, the Commission establishes an international reference price (IRP) by comparing the price applied for the same product in at least three of eight selected countries from the region (Argentina, Brazil, Chile, Ecuador, Mexico, Panama, Peru and Uruguay) and in selected OECD countries. If the price in Colombia is higher than the 25th percentile of prices across a set of 17 countries, the 25th-percentile price is fixed as the maximum retail price for Colombia.¹⁹

Price controls have been used by Colombia in the case of imatinib,²⁰ the first-line treatment for chronic myeloid leukaemia that has been patent protected in the country. In 2014, NGOs²¹ requested the Ministry of Health to declare the public interest, stating that, according to their research, generic prices of the medicine could be up to 77 per cent lower. Under Colombian law, a declaration of the public interest is a condition for the grant of a compulsory licence,²² which would be considered in a subsequent step by the Superintendency of Industry and Commerce (SIC). The decision declaring the public interest has to determine the means needed to address that situation, which can be a compulsory licence or another effective measure.²³ The Ministry of Health initiated the administrative procedure and informed the patent holder in February 2015.²⁴

In February 2016, the Technical Committee for the Declaration of Public Interest, composed of experts from the Ministry of Health, recommended that the Ministry declare the public interest on imatinib as the basis for the grant of a compulsory licence; it also encouraged prior negotiation of the price with the right holder. Following unsuccessful negotiations with the patent holder, the Ministry of Health issued Resolution 2475 of 14 June 2016,²⁵ which declared the public interest for imatinib.²⁶ The Resolution determined that the need to retain expenditure efficiencies in the social security system would be satisfied by price control measures as an alternative to the grant of a compulsory license. Hence, it requested the CNPMDM to include the product in the direct price control scheme, using an updated price control methodology. Resolution 2475 was upheld upon appeal, following which the CNPMDM defined that the medicine price should be determined by the lowest international reference price in a number of defined countries, and not the average price in these countries.²⁷ Based on this methodology, the Commission established a maximum price for imatinib²⁸ at about 44 per cent of its former price.²⁹

(not necessarily a medicine) in a country" to determine a price.³⁰ Internal reference pricing is particularly effective when considering the pricing of originator products, which contain the same active pharmaceutical ingredient (API) as generic versions, but are typically more expensive. India, in its National Medicine Policy 2012, switched to this method of market-based price control from the previous system of price controls based on cost of manufacture. The maximum price allowed for the controlled medicines is based on a simple average wholesale price of all brands in a particular molecule market that have more than 1 per cent market share in that market, plus a 16 per cent retail margin. Patented medicines are exempt from price control for a period of five years from the date of commercialization in India.³¹

(d) Health technology assessments

In recent years, an increasing number of countries have started to introduce schemes in which pricing

negotiations are based on "health technology assessment" (HTA). The International Network of Agencies for Health Technology Assessment defines HTA as "[t]he systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods".³²

An HTA examines a product's safety and efficacy, and undertakes a cost-effectiveness analysis of it relative to other comparable products. Assessing health technologies is a multidisciplinary process: information about the medical, social, economic and ethical issues relating to the use of a health technology is gathered in a systematic, transparent and unbiased manner, so as to inform the formulation of safe, effective health policies that are patient focused and that seek to

achieve best value. Cost-effectiveness analysis in the context of health technology assessment considers the comparative costs and health impacts of a new intervention compared to the existing standard of care to identify if the new intervention represents good value for money. This comparison enables a determination as to whether the costs are proportionate to the health outcomes, and thus whether the medical product should be provided to the patient.³³

In the context of health technology assessments and pricing practices, the concept of “value-based pricing” (VBP) has become increasingly discussed. While there is no precise and widely agreed definition of the concept (Paris and Belloni, 2013; Kaltenboeck and Bach, 2018; Garner et al., 2018; WHO, 2015e), one definition provided is: “value based pricing consists of negotiating prices for new pharmaceuticals based on the value the new medicine offers society, as assessed through HTA” (Husereau and Cameron, 2011). More specifically, the “value-based” component is considered to reflect the incremental cost-effectiveness ratio (ICER) of the new pharmaceutical, that is, the additional benefit per unit of additional cost, compared to the standard of care, within thresholds set by procurers (where procurers have set thresholds). ICER is generally expressed in monetary terms per quality-adjusted life year (QALY) gained, where QALY is the widely used measure of the health benefits of a medicine that combines the survival and quality-of-life effects benefits in one metric.

Methodologies to calculate the applicable additional benefits and additional costs compared to the standard of care can differ substantially (Bertram et al., 2016). To the extent that procurers’ thresholds for maximum acceptable ICER are set according to budgetary constraints, VBP can manifest as pricing at the maximum level that the health system will bear. However, prices that may, in theory, be cost-effective compared with the standard of care may still be unaffordable to health systems. Cost-effectiveness thresholds are often set higher than what would be affordable for a health system if a large volume of products were procured at costs close to the threshold (Garner et al., 2018; Bertram et al., 2016). For example, economic modelling found a new breast cancer medicine to be cost-effective in Peru, although procuring it would have cost Peru’s entire budget for breast cancer treatment (Bertram et al., 2016).

The European Commission’s Expert Panel on Effective Ways of Investing in Health (EXPH) summarized the debate as follows: “The notion of VBP for new pharmaceutical products rests on the attractive and intuitively simple principle of paying more for products that deliver more value.” However, the Expert Panel notes that “[t]here is difference between value-based pricing

as a way to pay more for more benefits from innovation and prices approaching total value. Value-based pricing in the sense of the first part is a way to provide incentives for better innovation, while value-based pricing in the sense of the latter element is a tool for exercise of market power”,³⁴ where “value-based pricing of medicines can be misused as profit-maximisation economic strategy, leading to the setting of prices that are disproportionate to the cost structure.”³⁵ The OECD notes that the objective of “value-based” activities in the health sector is to maximize health benefits for patients and the society as a whole. VBP could improve health innovation as it provides an incentive for the pharmaceutical industry to place a focus on valuable innovation instead of on “me-too”-type products. However, where some form of VBP is practised, there seems to be a long way to go in achieving such a result in practice (Paris and Belloni, 2013).

(e) Market entry agreements (MEAs)

The aim of MEAs (also called risk-sharing agreements, although only a subset of MEAs includes a true risk-sharing component) is to reduce uncertainty around the clinical effectiveness and/or cost-effectiveness, and/or to limit the budget impact, of a technology in real life.³⁶ Different types of MEAs exist; we briefly outline two types below.

(i) Volume limitations

Governments may impose volume limitations to control the quantity of a new medicine that may be sold at a certain per-unit cost. For example, France imposes “price–volume” agreements on manufacturers of new medicines (OECD, 2008). A price–volume agreement links the reimbursement price of a new medicine to a volume sales threshold. If the threshold is exceeded, the manufacturer must provide compensation through price reduction or cash payments to the government (depending on the country and the agreement). Through such volume limitations the payer can control the maximum cost implications of the introduction of new, expensive treatments and limit the incentive for companies to promote the widespread use of new expensive treatments. For example, in England, the National Health Service (NHS) is required by statute to fund procurement of medicines evaluated as cost-effective by the National Institute for Health and Care Excellence (NICE). However, if total expenditures for a given medicine exceed GBP 20 million in any one of the first three years of use, the NHS may request an exception to the statutory funding requirement and may renegotiate pricing with the originator with the option of de-funding the medicine in question.³⁷

(ii) Health-outcome-based agreements

Health-outcome-based agreements represent new approaches to negotiating pricing, such as companies charging for a medicine only for those patients for whom a successful clinical outcome has been achieved. This type of agreement establishes a threshold – defined by either a surrogate marker correlating with the final endpoint of interest or the endpoint of interest itself – demarking whether treatment was either successful or not. If treatment was unsuccessful, the manufacturer has to reimburse either the full or part of the cost of treatment, depending on the agreement between payer and manufacturer.³⁸

(f) Transparency across the value chain of medicines and health products

Having access to information on economic data across the pharmaceutical value chain (see Figure 4.3) is important for stakeholders working to ensure access to health products. For example, knowledge of prices paid in other countries can be useful for negotiations in medical procurement, and information on the costs of pharmaceutical R&D can be important in informing policy discussions on incentivizing and compensating R&D (see Chapter III, section B.3).

At present, information on net prices paid for health products is generally not publicly and systematically made available, with the exception of a few specific areas (Vogler and Schneider, 2019). Some countries host publicly accessible databases of medicine prices, but, in many cases, these reflect pharmaceutical “list prices” and do not account for discounts or rebates that are confidentially agreed during negotiations (Vogler et al., 2012; Vogler and Schneider, 2019). In respect of HIV/AIDS, TB and malaria, and for vaccines for which large international donor-funded procurement programmes are in place – such as through The Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund – a number of price-reporting mechanisms are in place, including the WHO Global Price Reporting Mechanism database, the WHO Market Information for Access to Vaccines (MI4A/V3P) and the Global Fund’s Price and Quality Reporting database (see Box 4.3).³⁹ Beyond HIV, TB and malaria, and vaccines, the International Medical Products Price Guide provides pricing information for many of the medicines on the WHO EML, aggregating information from a range of pharmaceutical suppliers, international development organizations and government agencies; however, for most medicines, a limited number of datapoints are available.⁴⁰

Besides prices paid, there is interest in manufacturing costs. In general, manufacturing costs are not publicly available. In the absence of published information, a

range of studies have estimated the cost of manufacture for medicines and vaccines.⁴¹ A WHO-commissioned study published in 2018 analysed the cost of production for medicines on the EML, finding that the lowest available prices were greater than cost-based estimates of expected generic prices for 77 per cent of comparable items in the United Kingdom, 67 per cent in South Africa and 40 per cent in India (Hill et al., 2018). Manufacturing costs can be a factor in national pharmaceutical price control policies, as can reasonable allowances for other costs (e.g. transportation) and for profit margins; in some countries, governments set maximum prices based (in part) on manufacturing cost information submitted by manufacturers, for example, in China, Iran and Pakistan (WHO, 2015e).

In 2019, the World Health Assembly (WHA) adopted Resolution WHA72.8 urging member states to take measures to publicly share information on net prices (i.e. the amount received by manufacturers after all rebates, discounts and other incentives);⁴² support increased availability of data on clinical trial costs, patent status and marketing approval status; and improve the reporting of information on sales revenues, prices, units sold, marketing costs, and subsidies and incentives.

(g) Differential pricing strategies

Differential pricing (also known as “tiered pricing” or “price discrimination”) occurs when companies charge different prices for the same product depending on the class of purchaser. Price differentials may exist across different geographical areas or according to differences in purchasing power and socio-economic segments. Because differential pricing involves the division of markets into different tiers or groups, the practice is also known as tiered pricing. Such price discrimination is only feasible to the extent that markets can be effectively segmented in order to prevent arbitrage (the purchase of products in the lower-price market and subsequent sale in the higher-price market).

Tiered pricing can be practised in different ways. Sellers can unilaterally set different prices according to different income levels in a way that would maximize their revenues in each market segment. They can also negotiate price discounts with governments or through regional or global bulk purchasing arrangements or license production for specified markets.

Creating market segmentation can be achieved through various marketing strategies (e.g. using different trademarks, licence agreements, dosage forms or presentation of products), by having more stringent supply chain management by purchasers and by having import controls in high-income countries and export controls in poorer countries. Differential pricing

Box 4.3: Examples of databases of medicines prices**Global Price Reporting Mechanism (GPRM)**

The WHO GPRM database provides data on procurement of HIV, TB, malaria and hepatitis medicines, as well as diagnostics. The public database provides information on sales prices and volumes for originator and generic medicines. The main data providers are the Global Fund, the US President's Emergency Plan for AIDS Relief (PEPFAR), Unitaid and the procurement organizations working with them.⁴³

Market Information for Access to Vaccines (MI4A)

The WHO MI4A project provides data on global vaccine markets, including on vaccine purchase data (prices and procurement modalities) and vaccine-specific market analyses. In particular, MI4A aims to identify and address affordability and shortage issues for self-funding and self-procuring countries that are mostly excluded from international support. MI4A leverages the success of the WHO Vaccine Product, Price and Procurement (V3P) project.⁴⁴

WHO Western Pacific Regional Office (WPRO) Price Information Exchange for Essential Medicines (PIEMEDS) system

PIEMEDS is a regional platform to promote price transparency for improved medicine access. It mainly contains procurement prices, along with other publicly available prices shared voluntarily by participating countries. Prices are available for essential medicines and some other high-price medicines.⁴⁵

Price surveys published by civil society

Civil society has also played an important role in enabling price transparency – for example, by surveying generic manufacturers and publishing summaries of prices in tenders. Examples in the area of HIV include Médecins Sans Frontières (MSF)'s *Untangling the Web* reports, first published in 2001, which track the prices of generic antiretrovirals (ARVs),⁴⁶ and monitoring of government procurement prices for ARVs in Russia by the International Treatment Preparedness Coalition (ITPCru).⁴⁷

Price and Quality Reporting

This Global Fund database provides data on procurement transactions made by Global Fund-supported programmes. It includes data on volumes, price, manufacturer, packaging and shipping costs.⁴⁸

Proprietary databases

Certain proprietary databases provide extensive data on health product pricing and procurement. However, these databases are commercial products and are not freely accessible.

can, in principle, make medicines more affordable to larger segments of the population and could also lead to increased sales, thus benefiting pharmaceutical manufacturers (Yadav, 2010).

However, a “floor” is reached for differential pricing where the affordable price for patients would be less than the marginal cost of manufacturing. No commercially operated entity can be expected to sell its medicines at a loss.

Companies often do not use tiered pricing that is proportionate to differences in average income between countries (Watal and Dai, 2019). A possible reason is fear of price erosion in high-income markets as a result of direct or indirect influence of prices in lower income markets. Direct influence can be through the importation of the lower-priced product from other countries, for

example, through parallel importation (see section C.3(f) below). Some have expressed concerns that indirect price influence could occur through the use of reference pricing policies, if reference prices are set based on prices in markets with substantially lower income levels. Companies may also be reluctant to provide tiered prices, as it may be difficult for them to preserve higher prices elsewhere.

Where market segmentation according to socio-economic segments of the population and also differentiation between the public and private sectors is possible, it might support differential pricing within countries. Preventing lower-priced products from flowing back to high-income private markets will remain a challenge, but the trend may be changing. Box 4.4 presents an example on how differential packaging can be used to separate markets and Box 4.5 outlines the concept of

“authorized generics”, where differential branding and registration is used to enable multiple pricing tiers within a market. A number of originator companies have run pilot programmes extending differential pricing, including intra-country differential pricing, to emerging economies. They have also expanded these programmes to encompass a broader range of medicines, including cancer medicines and biotherapeutics.⁴⁹

Differential pricing is well established in the vaccine market. A three-tiered pricing structure is used for most vaccines sold in both developed and developing countries. Companies charge the highest prices in high-income countries, lower prices in countries prioritized by Gavi, the Vaccine Alliance, and intermediate prices in middle-income countries.

5. Taxes

While medicines are often subject to indirect taxes, such as a purchase tax, sales tax or VAT, entities producing and selling medicines may also be subject to direct taxes on the revenue generated (e.g. corporate income tax). Taxes add to the final price paid by the consumer and are, therefore, a factor that affects access to medicines.

One study found that, in 2010, the VAT rate on medicines in high-income countries was between zero and 25 per cent, with Australia, Japan and the Republic of Korea having a tax exemption policy. Similarly, countries such as Colombia, Ethiopia, the State of Kuwait, Malaysia,

Nicaragua, Oman, Pakistan, Uganda and Ukraine reported zero VAT and sales tax on medicines. In LMICs that charged taxes on medicines, the tax rate ranged from 5 per cent to about 34 per cent. In some LMICs, the situation in relation to taxation of medicines is even more complex and variable, sometimes with multiple federal and state taxes being applied. Furthermore, imported and locally made medicines are sometimes taxed differently. The study concludes that domestic taxes such as VAT or sales tax are often the third largest component in the final price of a medicine (Creese, 2011).

Certain practical tax measures can be used to reduce the price of medicines. WHO Guidelines on Country Pharmaceutical Pricing Policies recommend that countries should consider exempting essential medicines from taxation, and countries should ensure any reductions or exemptions from taxes on medicines have the effect of reducing costs to the patient/purchaser (WHO, 2015e). For example, Mongolia removed taxes on imported omeprazole sold in private pharmacies, a move that led to a price fall of between US\$ 5.91 and US\$ 4.85 for a 30-capsule pack, while the Philippines removed 12 per cent VAT, thus reducing the price of a pack of ten generic co-trimoxazole tablets (480 mg) from 14.90 pesos to 13.30 pesos (Creese, 2011).

Another measure that may improve access to medicines is alterations in tax rates. It should be possible to evaluate the consequences of defined changes in tax rates that either improve or reduce access to medicines, and then propose tax policy changes accordingly. In

Box 4.4: Differential packaging

In 2001, as part of the Memorandum of Understanding between the WHO and Novartis to make available artemether-lumefantrine at cost price for use in the public sector of malaria-endemic countries, Novartis developed differential packaging for artemether-lumefantrine destined for the public sector. This differed from the existing packaging for products destined for the private sector. The WHO collaborated with the company to develop four different course-of-therapy packs (for four separate age groups), each containing pictorial diagrams on how to take the medicines and all aimed at improving adherence to treatment among illiterate population groups. Initially, packs were made available to WHO procurement services. They were subsequently made available to UNICEF and, progressively, to additional procurement services supplying the public sector only. The leakage of such packs from the public sector into the private sector is not significant. The use of a distinctive “Green Leaf” logo on the packs facilitates the process of tracking and monitoring of availability and market share at point of sale.

Box 4.5: Authorized generics

“Authorized generics” are lower-priced versions of an originator medicine that are sold by the originator as a generic following expiry of patent and other market protections for the originator medicine. In this way, the originator captures part of the generic market share following patent expiry, and decreases revenues for independent generics manufacturers (Shcherbakova et al., 2011; Gupta et al., 2019). In some cases, the originator’s authorized generic product can benefit from incentives designed to encourage generic market entry – for example, in the United States, authorized generics can benefit from the Hatch-Waxman 180-day exclusivity period granted to the first generic market entrant (see Box 4.1). Recent examples of authorized generic products include lower-priced originator versions of insulin glargine for diabetes and albuterol (salbutamol) for asthma (GlaxoSmithKline, 2019a).

2004, Kyrgyzstan reduced VAT and regional sales tax on medicines, while, in Pakistan, following a successful consumer advocacy challenge, the 15 per cent sales tax on medicines was removed altogether. Although alterations in tax rates may not occur until there is a change in national tax regimes, the impact of this measure may be substantial (Creese, 2011). Removing customs duties (as discussed in section D.1(b) below) is a similar measure that can have a direct bearing on prices and access. In both cases, however, it is important to ensure that savings due to reduced taxes or custom duties are passed on to the consumer, since this is not always the case.

The reduction or elimination of taxes on medicines may also be coupled with the increase in, or introduction of, taxes on public health “bads” (i.e. tobacco, alcohol and unhealthy food). Advocates of this approach often argue that the funds raised from taxes on unhealthy consumption patterns and behaviours can easily balance out, or sometimes surpass, revenue losses due to the reduction or elimination of taxes on medicines, leaving both government and individuals better off (Creese, 2011). In their view, this approach would therefore offer the potential of linking significant revenue gains with improved access to medicines.

6. Mark-ups

A mark-up represents the add-on charges and costs applied by different stakeholders in the supply chain in order to recover overhead costs and distribution charges and make a profit. The price of a medicine includes mark-ups that have been added along its supply chain distribution. Medicine mark-ups can be added by manufacturers, wholesalers, retailers, pharmacists and many others who play a role in the supply chain distribution (WHO, 2015e; Ball, 2011). Like taxes, mark-ups also contribute to the price of medicines and thus have a direct bearing on access to medicines.

Mark-ups, including those charged by wholesalers and retailers, are common in medicine supply chain distributions in both the public and private sectors. For example, a secondary analysis of WHO/Health Action International (HAI) surveys of developing countries indicates that wholesale mark-ups ranged from 2 per cent in one country to a combined mark-up by importers, distributors and wholesalers of 380 per cent in another country (Cameron et al., 2009). In addition, that analysis indicates that there is huge variability in the cumulative percentage mark-ups (i.e. all mark-ups added, from a manufacturer’s selling price to final patient price) between the public and private sectors (Cameron et al., 2009). Mark-ups on medicines can also vary depending on the type of medicine (i.e. originator versus generic). Without appropriate regulation of

mark-ups, there can be significant elevation of the consumer price, and, consequently, a substantial impact on access to medicines.

In high-income countries, mark-up regulation in medicine supply chain distributions is usually part of a comprehensive pricing strategy that also addresses medicine reimbursement (Ball, 2011). There is little data on mark-up regulation in the pharmaceutical supply chain in LMICs. WHO pharmaceutical indicator survey data show that around 60 per cent of low-income countries report regulating wholesale or retail mark-ups. In middle-income countries, regulation in the public sector is at a comparable level (Ball, 2011).

Mark-up regulation can have a positive impact on access to medicines, but may also have some adverse effects (Ball, 2011). Because mark-up regulation reduces margins for businesses, some medicines may no longer be offered, or may be offered in reduced quantities, thus adversely affecting product availability and price competition.

7. Rational selection and use of medicines

Rational selection of medicines requires a country to decide, according to well-defined criteria, which medicines are most important in order to address the national burden of disease. Through its work on the EML, the WHO has provided guidance to countries on the development of their own national essential medicine lists (see Box 4.6).

A list of essential medicines can help countries prioritize the purchasing and distribution of medicines, thereby reducing costs to the health system by focusing on the essential products needed. The addition of a medicine to the WHO EML directly encourages individual countries to add the medicine to their national EML and to internal medicine registries. Some countries restrict medicine importations to medicines based on their national EML. Similarly, several foundations and major charities base their medicine supply on the WHO EML. As at 2019, the WHO repository of national EMLs has lists from 137 countries.⁵⁰

A WHO survey found that, in 2014, 65 per cent of 158 countries where data were available have priority/essential/reference national lists of medical devices. Some of these lists are for procurement and reimbursement processes, while others are lists of priority devices for specific diseases or emergencies.⁵¹ In 2018, the WHO published the first WHO Model List of In Vitro Diagnostics, to mirror the EML.⁵² The WHO has developed multiple other device lists, for example, for maternal, newborn and child health and for Ebola management, as well as a Priority Assistive Products List.⁵³

Equally important as rational selection of medicines is their rational use. Irrational use – the inappropriate, improper or incorrect use of medicines – is a major problem worldwide. Irrational use can cause harm through adverse reactions and increase antimicrobial resistance (Holloway and van Dijk, 2011) and can waste scarce resources (see Chapter II, section A.5). One example is the use of antibiotics in Europe, where some countries use three times as many antibiotics per capita as do other countries with similar disease profiles (Holloway and van Dijk, 2011). Examples of irrational use include:

- the use of too many medicines per patient (“poly-pharmacy”)
- inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections
- over-use of injections when oral formulations would be more appropriate
- failure to prescribe in accordance with clinical guidelines
- inappropriate self-medication, often of prescription-only medicines
- non-adherence to dosing regimes.

In addition, problems with irrational use arise over issues of formulation (such as oral or paediatric formulations), inappropriate self-medication, and non-adherence to dosing regimens by both prescribers and patients. Worldwide patient adherence to treatment has been estimated to be about 50 per cent (Holloway and van Dijk, 2011) and, in many cases where medicines are dispensed, the instructions given to the patient and the labelling of the dispensed medicines are inadequate.

The development of evidence-based clinical guidelines is an important tool to promote rational selection and use of medicines. Such development, however, is challenging, especially with regard to NCDs. The pharmaceutical industry is heavily engaged in this disease area because of the long-term market potential of treatments for chronic diseases, which requires a careful analysis and management of potential conflicts of interest among the industry, patient organizations, professional associations, health insurance companies and public-sector organizations.⁵⁴

Box 4.6: The WHO Model List of Essential Medicines

Essential medicines are “those that satisfy the priority health care needs of the population [...] Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility” (WHO, 2003c).

The first EML was published in 1977. Selection criteria were developed relating to safety, quality, efficacy and total cost (Mirza, 2008; Greene, 2010). The EML contains more than 400 medicines and includes treatment options for HIV/AIDS, TB, malaria, reproductive health and NCDs, such as cardiovascular disease, cancer, chronic respiratory disease and diabetes, based on the best available evidence.⁵⁵ In 2007, the first EML for children was developed and published (WHO, 2007b).

The EML lists medicines by their international non-proprietary name (INN), also known as the generic name, without specifying a manufacturer. The list is updated every two years by the WHO Expert Committee for the Selection and Use of Essential Medicines, using a transparent, evidence-based process. The Expert Committee considers applications based on criteria of effectiveness, safety, public health relevance and comparative cost-effectiveness.⁵⁶

The EML contains many old and well-established medical products, such as oxygen, paracetamol, penicillin, etc. As a result, the majority of medicines on the EML are off-patent and generic versions are widely available, including medicines for the main NCDs (Beall and Attaran, 2016). However, in every EML review cycle, applications are made to add newer, patented, expensive medicines to the EML, and the Expert Committee has to balance comparative cost-effectiveness against other criteria in evaluating proposed additions.

Before 2002, expensive medicines were often not included on the EML as the selection criteria emphasized the need for low-priced medicines. The main criterion for selection today is effectiveness. In the evaluation process, information on comparative cost and cost-effectiveness must be presented, for example, as cost per case prevented or cost per quality-adjusted life year (QALY) gained. Cost can still be relevant for the selection within a therapeutic class, to identify the best value for money if efficacy is comparable (van den Ham et al., 2011). If an expensive but cost-effective medicine is placed on the EML, this implies that it must become available and affordable (Magrini et al., 2015). First-line ARVs were the first notable example of this new approach when they were added to the EML in 2002, when they could cost more than US\$ 10,000 per patient per year (see section B.1 below).

8. Effective and efficient procurement mechanisms

Procurement and supply chain systems for medical products are part of a complex system that is dependent on effective infrastructure, information management systems, policies and regulatory systems and human resources, as well as on budgeting and financial systems. Procurement systems and mechanisms must respond to changing environments, manage risks, specify products of appropriate quality and ensure value for money. Linkages to financing, price control policies and practices are also recognized as part of an ongoing business process of informed decision-making.

(a) Principles for effective procurement

Procurement systems are designed to obtain selected medicines and products of good quality, at the right time, in the required quantities and at costs that offer appropriate value for money. The WHO has developed a series of operational principles in procurement systems, the purpose of which is to increase access through lower prices and uninterrupted supply (WHO, 2001b).

These principles are:

- Establish division of different procurement functions and responsibilities to ensure appropriate checks and balances and avoid unintended conflict of interest, along with pre- and in-service training to ensure that staff can accommodate the needs of each level and function.
- Ensure transparency of procurement and tender procedures, follow written procedures throughout and use explicit criteria to award contracts.
- Provide for a reliable procurement and logistics management information system that allows planning and monitoring of procurement.
- List drugs by their INN/generic name on procurement and tender documents and generally avoid the use of brand names.
- Quantify procurement orders based on past consumption with appropriate adjustments as needed, provided that such data are available and reliable.
- Finance procurement using reliable mechanisms, which must be adequately funded.
- Purchase and plan quantities for realistic economies of scale that are consistent with the use of the product, for example, its shelf life.
- Assure quality of purchased medicines, according to international standards.
- Obtain appropriate value for money without compromising quality.
- Monitor decentralized procurement activities to ensure price equity.

Parties to the revised WTO Agreement on Government Procurement (GPA)⁵⁷ are also bound to provide for competitive, non-discriminatory and transparent tendering for public procurement in the health sector covered by the Agreement (see Chapter II, section B.4). Further guidance on how to organize efficient procurement of medical technologies can be obtained from different sources. The World Health Organization Good Governance for Medicines programme offers a technical support package for tackling unethical issues in the public pharmaceutical sector (Baghdadi-Sabeti and Serhan, 2010). The WHO has developed a model quality assurance system for procurement agencies (WHO, 2006b). The World Bank has prepared guidelines containing standard bidding documents and a technical note for use by implementing agencies procuring health-sector goods through international competitive bidding.⁵⁸ For the purpose of combating HIV/AIDS, these guidelines have been adapted in a separate decision-maker's guide.⁵⁹

(b) Tendering

Tendering can lead to substantial cost reductions. A 2013 study examined the determinants of prices for originator and generic drugs across a significant number of countries. The study mainly focused on drugs to treat HIV/AIDS, TB and malaria in LMICs. The analysis shows that tendered procurement that imposes quality standards attracts multinational generic suppliers and significantly reduces prices of originator and generic drugs, compared with their respective prices to retail pharmacies. Specifically, it finds that "The evidence from HIV/AIDS, TB, and malaria drugs shows that procurement reduces originator and generic prices by 42.4 per cent and 35 per cent, compared with their respective retail pharmacy prices" (Danzon et al., 2015).

This is confirmed by a 2019 study of the South African tendering system for medicines, comprising all pharmaceutical tender contracts issued by the South African Government between 2003 and 2016. The prices of medicines in most tender categories in the public health-care system dropped by an average of around 40 per cent or more. The prices of medicines procured for the public system through tenders were almost always lower than those sold in the private system. Tenders generally remained moderately to highly competitive over time (i.e. Herfindahl-Hirschman indexes < 2,500), although the number of different firms winning contracts decreased in many categories (Wouters et al., 2019).

However, studies also point out that, while tenders can reduce acquisition costs, they may expose the health-care systems to risks, including drug shortages and quality trade-offs, and, ultimately, compromise patient health outcomes if defective tendering practices are employed. Risk factors include non-transparent tender

practices, a lack of consistency, unclear tender award criteria, a focus on lowest price only, single-winner tendering and, generally, a lack of impact monitoring. It is therefore recommended to ensure that tenders are well planned, managed and conducted, in order for them to be advantageous. Such “good tender practices” include the clear definition of requirements to be used as selection criteria in addition to acquisition costs, and for monitoring of the tender success (Maniadakis et al., 2018).

(c) Procurement and patent information

While, generally, the supplier is responsible for ensuring that all necessary rights to products, including IPRs, have been secured in accordance with the specifications in tender documents and procurement contracts, procurement agencies also have to consider the patent status of products early in the procurement process. The content and sources of patent information are further explained in Chapter II, section B.1(b)(viii)–(xi).⁶⁰

(d) Collective negotiation and pooled procurement

Collective negotiation takes multiple forms, including mechanisms for information sharing, joint tenders, and pooled procurement (“purchasing done by one procurement office on behalf of a group of facilities, health systems or countries” (MSH, 2012)). Pooled procurement is a strategy that can reduce prices, enhance access for small volume purchases and facilitate access to quality-assured markets.

Economies of scale and long-term prospects of supply, which are prevalent in most public-sector procurement systems, enable suppliers to lower their prices in some cases. With medicines that are typically procured in small volumes, such as several paediatric medicines, pooling procurement promotes improved planning and can stabilize prices. Forms of collective negotiation, including pooled procurement in the health sector, occur in multiple forms and include both public and privately operated mechanisms. They are used at various levels of scale (e.g. a group of private hospitals sharing a joint procurement system) and for a variety of product categories. In high-income countries, large insurance and reimbursement systems support the purchase of medicines and other medical technologies that are acquired through pooled procurement. Anecdotally, there has been an increase in interest in collective negotiation and pooled procurement from LMICs, but financing and the involvement of multiple relevant actors can complicate their establishment and compromise their ability to succeed. In public-sector procurement, many countries use a central procurement mechanism (see Box 4.7). They are often best placed to achieve economies of scale and negotiate best prices. Any pooled procurement mechanism must be fully integrated into the national procurement and supply chain system, including policy, regulatory, logistics, distribution, finance and management information systems.

Successful pooled procurement schemes have reported substantial reductions in the unit price of medicines. Some well-known examples include the Organisation of Eastern Caribbean States (OECS), the Pan American Health Organization (PAHO) Strategic Fund for Essential Public Health Supplies, the PAHO Strategic Fund for Vaccines,

Box 4.7: Cost reduction/improvements in value for money in the health-care sector through centralized procurement: the example of Ecuador

Health expenditure in Ecuador is of considerable economic significance, accounting for 9 per cent of GDP and 10 per cent of the public budget. Pharmaceutical expenditure represents 16 per cent of total health expenditure.

On average, the value of public procurement of medicines in Ecuador is estimated at US\$ 260 million annually. About 70 per cent of these medicines are bought through centralized procurement.

Centralized procurement of medicines in Ecuador has allowed significant cost reduction and improvement in value for money, equivalent to an estimated US\$ 250 million–US\$ 300 million annually for the acquisition of 450 products on the National List of Essential Medicines. This represents savings of 40–70 per cent compared with conventional purchase prices.

Reported additional benefits include: (i) reduction of the time needed for the procurement and supply of medicines; (ii) improvement of the quality control and reduction of the risks associated with falsification of medicines; (iii) reduction of administrative burden related to the procurement of medicine; and (iv) sustainability of the public health system.

Source: Presentation by Daniel López Salcedo, Ecuadorian National Service on Public Procurement, delivered at the 7th Joint Trilateral Symposium WHO, WIPO, WTO, Geneva, 26 February 2018 (available at: <https://www.who.int/phi/3-DanielLopezSalcedo.pdf?ua=1>). Figures as updated by the author in July 2019.

the African Association of Central Medical Stores and the Group Purchasing Program of the Gulf Cooperation Council (GPP/GCC). The OECS, a self-financing public-sector monopsony, has consistently reported substantial reductions in the unit price of medicines. In 2001–2002, an annual survey of 20 popular medicines available in the OECS region found that prices under the pooled procurement scheme of the OECS were 44 per cent lower than individual country prices (OECS, 2001). The GPP/GCC also demonstrated that improved procurement can reduce costs and enhance the efficiency of health service. The PAHO Strategic Fund is another example of pooled procurement. The Fund was developed by the PAHO Secretariat at the request of member states. Currently, 23 PAHO member states participate in this strategic fund, which was created to promote access to quality, essential public health supplies in the Americas. The Global Fund employs a Pooled Procurement Mechanism as a cost-effective way of ensuring efficient procurement of ARVs, rapid diagnostic kits for HIV and malaria, artemisinin-based combination therapies and long-lasting insecticidal nets (Global Fund, 2010, 2018).

Recent developments in European pooled procurement mechanisms are outlined in Box 4.8.

(e) Reliable health and supply systems

Another precondition for providing access to medicines is a reliable, functioning health system that is able to supply patients with needed medical technologies of adequate quality in a timely manner. These systems include the ability to forecast needs, as well as to procure, store, transport and inventory medicines and medical devices and distribute them appropriately. Supply systems remain weak and fragmented in many developing countries.

Without improvement, access to medicines and other needed medical technologies will remain a formidable challenge. Adequate regulatory capacity is also required to ensure access to safe and effective medicines for both imported and domestically manufactured medicines.

For policy-makers, the key issues are: to integrate medicines more directly into health-sector development; to create more efficient mixes of public–private–NGO approaches in medicines supply; to have regulatory control systems that provide assured quality medicines; to explore creative purchasing schemes; and to include traditional medicines in the provision of health care (WHO, 2004).

Box 4.8: Examples of European pooled procurement initiatives: the Benelux Initiative and the Joint Procurement Mechanisms

Benelux Initiative

The Benelux Initiative began with the health ministers of Belgium and the Netherlands announcing in 2015 that they would explore collaboration on pharmaceutical policy. This example is important as it leveraged existing legislation on economic development and trade to other sectors, such as agriculture and military spending. Luxembourg, Austria and Ireland have since joined the initiative. Members of the initiative collaborate on, among other things, horizon scanning (anticipating the effect of upcoming medicines approvals), sharing expertise and pursuing mutual recognition of health technology assessments (HTAs), joint pricing negotiations for some medicines, and sharing of best practices and policy experience.⁶¹

Benelux's joint HTA and negotiations are in the pilot phase. Until now, Benelux has conducted two joint pricing negotiations. The first, a negotiation for Orkambi (lumacaftor/ivacaftor), a new treatment for cystic fibrosis, failed after an agreement could not be reached. The second negotiation was successful, reaching a pricing agreement for Spinraza (nusinersen), a new treatment for spinal muscular atrophy.⁶²

Joint Procurement Mechanism

Noting the weaknesses in procurement of influenza vaccines and medications encountered during the H1N1 influenza pandemic in 2009 (European Commission, 2014b), the European Council and the European Parliament stressed the need for the introduction of a joint procurement mechanism for medicines, and in particular for pandemic vaccines, to allow Member States, on a voluntary basis, to benefit from such group purchases.⁶³ Subsequently, Decision No 1082/2013/EU introduced joint procurement procedures, to be based on a Joint Procurement Agreement determining the practical arrangements governing that procedure, and the decision-making process with regard to the choice of the procedure, the assessment of the tenders and the award of the contract.⁶⁴ Following the initial signing by a number of EU member states in 2014 the Joint Procurement Agreement had 37 signatories as of April 2020.⁶⁵

The scope of the JPA includes all potential medicines, medical devices, other services and goods that could be used to mitigate/treat a life threatening or otherwise serious hazard to health of biological, chemical, environmental or unknown origin which spreads, or entails a significant risk of spreading, across the national borders of EU member states, and which may necessitate coordination at Union level in order to ensure a high level of human health protection (European Commission, 2014b). The JPA specifies what procurement procedures would be followed.⁶⁶ Participation in a JPA procedure is voluntary. In 2019, 15 EU member states signed “framework contracts” under the JPA with a vaccine manufacturing company, giving them “guaranteed access to a defined part of the production capacity of the company” for up to six years.⁶⁷

9. Sustainable financing

Sustainable financing of health systems is a prerequisite for a steady supply of medicines and other medical technologies. Per capita expenditure on health care tends to be low in low-income countries, although a large proportion usually goes to medicine purchases – between 20 per cent and 60 per cent of health spending.⁶⁸ The WHO Commission on Macroeconomics and Health (CMH) recommended that developing countries increase budgetary outlays for health by 2 per cent of GNP by 2015 compared with levels in 2001, with the goal of achieving universal access to essential health services. According to the WHO Global Health Expenditure Database, domestic general government health expenditure increased steadily from 2.8 per cent to 3.2 per cent of GDP from 2000 to 2017 in middle-income countries, and in low-income countries, it was at 1.4 per cent in both 2000 and 2017, fluctuating between these years.⁶⁹ The CMH also recommended that donor countries commit significant financing and investment to health R&D by coordinating with and drawing additional resources from international and intergovernmental organizations (WHO, 2001a). Policy-makers should have as objectives, among others: to increase public funding for health, including for essential medicines; to reduce out-of-pocket spending by patients, especially the poor; and to expand health insurance coverage (WHO, 2004). On average across all countries, 32 per cent of all health expenditures are made out of pocket, rising to 36 per cent in LMIC in 2017.⁷⁰ A 2019 WHO and World Bank report estimated that 927 million people spend more than 10 per cent of their household budget on health care, and nearly 90 million people are pushed into extreme poverty each year because of out-of-pocket health expenses.⁷¹ Since 2001, the world has seen a significant increase in international funding for essential medicines in certain disease areas, vaccines and other medical products, such as antimalarial bed nets, for distribution to poorer countries, including through mechanisms such as the Global Fund; Unitaid; Gavi, the Vaccine Alliance; the US President's Emergency Plan for AIDS Relief (PEPFAR); the Clinton Health Access Initiative (CHAI); and other international initiatives. This has vastly improved access to these products in many countries. Such donor assistance and development loans can help fund health-sector financing, but they must also be provided on sustainable terms.

A commitment of the government to adequately and sustainably fund the national health system is the key condition for reaching universal (health) coverage, meaning that all people in a country have access to adequate health services.

10. Manufacturing and technology transfer

Most countries import medicines, diagnostics, vaccines and other medical products from the global market.

A number of LMICs aspire to build and strengthen their domestic medical products industry (Dong and Mirza, 2016). Trends show that local production is growing and diversifying in some countries.⁷² However, the evidence that local production results in increased access to medical products is inconclusive (WHO, 2011b). While Ghana, for example, has taken measures to support the development of local production, it has also faced important challenges (see Box 4.9).

Egypt is a successful example of tackling the hepatitis C epidemic through local production. As key patents for sofosbuvir (a key hepatitis C medication, see section B.5) were either not filed or rejected in Egypt, 18 generic versions were available in 2017, many of which were locally produced. This competition has achieved very low prices. Coupled with significant government commitments to expand screening and treatment, this has led to a high number of patients newly accessing treatment. In 2016, Egypt alone accounted for 40 per cent of all patients starting hepatitis C treatment globally (WHO, 2018e).

In order to become economically viable and sustainable, local manufacturers, particularly those based in low-income countries, have to address a number of challenges, including:

- the lack of a conducive policy environment and policy coherence across sectors
- an inconsistent regulatory framework and enforcement, and lack of capacity to perform the required level of regulatory oversight
- an insufficient IP framework
- the lack of appropriately trained technical staff
- dependence on imported raw materials, including active pharmaceutical ingredients (APIs), and technologies
- weak physical infrastructure, such as electrical supply, water and roads
- the lack of economies of scale
- the lack of competitiveness relative to international supply
- inaccessible or unattractive access to capital and foreign exchange
- high import duties and taxes
- the lack of capacity for needs-based innovation and R&D
- weak linkages for collaboration and cooperation within sectors
- the lack of a framework for collaboration among partners and stakeholders.

Policy coherence associated with local production is crucial to achieving sustainable public health and industrial development benefits. The framework diagram depicted in Figure 4.4 outlines the main relevant factors

Box 4.9: Developing local production capacities in Ghana: support measures and challenges

The development of the domestic pharmaceutical industry has been identified as a key priority by the Government of Ghana.⁷³ Actions taken for that purpose included the Government and the United States Pharmacopeial Convention (USP) setting up the Centre for Pharmaceutical Advancement and Training in 2013. In addition, four local pharmaceutical companies were supported with funding from the Export Development and Agricultural Investment Fund (EDAIF) in 2014/2015 in their efforts to upgrade to international good manufacturing practice (GMP). A GMP Roadmap was developed in 2015 in a joint effort of the Food and Drugs Authority of Ghana and local industry, with technical assistance from the United Nations Industrial Development Organization (UNIDO), under which local manufacturing companies were assessed for GMP compliance.⁷⁴ Furthermore, imports of certain finished products that can be produced locally were banned and price preferences applied for local manufacturers in public procurement.

Notwithstanding the Government's efforts to strengthen the pharmaceutical sector, local companies still find it difficult to compete with their international competitors.⁷⁵ In 2018, medicines produced locally were estimated to account for around 30 per cent of the domestic pharmaceutical market, largely representing over-the-counter and simple generics. Continuing challenges for the local industry include high production costs, poor GMP compliance, limited product portfolios and manufacturing inefficiencies, caused by, among other factors, limited technical know-how and capital for new formulation developments, as well as the performance of bioequivalence studies.

from both an industrial policy (Box A) and a public health policy (Box B) perspective. The framework shows that there are shared goals between these two perspectives and that the objectives of industrial policy can also help to meet those of public health (Box C). The government's role is to provide a range of direct and indirect support, including financial incentives, and to help ensure coherence across the entire policy arena (Box D) to ensure that patients are benefiting from increased access to affordable quality products. The development and launch of the National Strategy and Plan of Action for Pharmaceutical Manufacturing Development (NSPA-Pharma) in Ethiopia is an example of the application of policy coherence to strengthen the local pharmaceutical industry.⁷⁶

Examples of technology transfer include:

- The support given to facilitate technology transfers under the WHO Global Action Plan for Influenza Vaccines (GAP), published in 2006. WHO has provided seed funding and technical support to 14 vaccine manufacturers in developing countries to enable domestic production.⁷⁷
- The establishment of the Utrecht Centre for Affordable Biotherapeutics (UCAB), borne from the collaboration between the University of Utrecht and WHO to facilitate the development, production and distribution of high-quality and affordable biotherapeutics in LMICs. Palivizumab, used to prevent respiratory syncytial virus infections in high-risk infants, is the first medicine that is undergoing technology transfer through UCAB.

In 2015, the TRIPS Council decided to extend the transition period under the TRIPS Agreement that exempts

least-developed countries (LDCs) from the requirement to grant and enforce pharmaceutical patents up to 2033, keeping open the option for further extensions beyond that date.⁷⁸ This transition period could provide opportunities to set up local production in LDCs for products that are still under patent protection in other countries, provided that the country has met the other challenges regarding local production (see Chapter II, section B.1(g)(v)).

11. Regulatory mechanisms and access to medical technologies

Improved access to medicines will only provide public health benefits if it also involves improved access to quality products. The necessary stringent quality assurance and regulation of the quality of health products is the responsibility of manufacturers, suppliers and regulatory authorities.

This section builds on Chapter II, section A.6, and focuses on WHO prequalification, medical devices regulation, regional regulatory initiatives, and the problem of substandard and falsified (SF) products.

Regulation of health technologies plays a key role in determining access to quality-assured medical products. While certain positive developments have taken place in recent years, regulatory control for medicines and medical technologies in LMICs needs to improve further. The WHO works with its member states in assessing national regulatory systems to identify gaps, develop strategies for improvement and support countries in their commitment to build national regulatory capacity. WHO (2010) provides an overview of the regulatory situation in Africa.

Figure 4.4: Local production and access to essential medical products: a framework for improving public health

(A) Industrial policy

Main objective: to develop a viable local industry that is competitive, reliable, innovative, productive and responsible.

Key factors from medical products development perspective

Competitive: offers better prices.

Reliable: complies with quality standards; ensures steady supply.

Innovative: aims for technological change and invests in research and development.

Productive: contributes to national economy through employment generation, human resource development and supporting associated industries and suppliers.

Responsible: shows corporate responsibility towards social conditions and environment.

Strategic: balances current and future demands.



(C) Shared goals of industrial and health policies for local production for improvement in access to medical products

- Strategic selection of essential medical products for local production.
- Pricing of locally produced products that governments and people can afford.
- Strict compliance with quality standards by manufacturers and effective national regulatory authorities.
- Health security – an uninterrupted supply of essential medicines.
- Innovation for development of products that are more suitable for local conditions.



(D) Government support of local production

Direct support to reduce the cost of manufacture: grants, subsidies, soft loans, provision of land, tax and duty exemptions for imported inputs for local production of essential medical products.

Indirect support of local production for improving access: invest in strengthening regulation of national medical products; develop national priority list for medical products; improve the financing of health services for expanding the domestic market; facilitate access to foreign markets; facilitate development of regional pooled procurement mechanisms; encourage regulatory harmonization; introduce appropriate pricing policies; facilitate relevant transfer of technology; support incremental innovation and production; develop appropriate intellectual property regimes; develop appropriate investment policies and facilitate joint ventures; facilitate international cooperation for local production.



(B) Health policy

Main objective: to promote health for all through universal health coverage in terms of prevention, treatment and rehabilitation.

Key factors from medical products development perspective

Universal access to medical products through public-sector supply system and/or social protection programmes.

Availability of essential medicines and diagnostics in appropriate formulations suitable for local use.

Affordable prices for government procurement agencies and for out-of-pocket expenditures by people.

Quality assurance through effective regulation.

Uninterrupted supply of essential medical products.

Rational selection and use by health managers and clinicians.

Source: WHO (2011b).

(a) WHO prequalification

The Prequalification Team (PQT; previously the Prequalification Programme), a UN initiative managed by the WHO, has contributed substantially to improving access to quality medicines in developing countries through ensuring compliance with quality standards. The programme aims to facilitate access to medical technologies that meet international standards of quality, safety and efficacy.

If a product meets the specified requirements, and if the manufacturing site complies with current GMP, both the product linked to a specific manufacturing site and details of the product manufacturer are added to a list of prequalified medicinal products. This list is published by the WHO on a publicly accessible website.⁷⁹ The PQT does not replace national regulatory authorities or national authorization systems for the importation of medical technologies.

PQT prequalifies products for a range of therapeutic areas, including HIV/AIDS, TB, malaria, neglected tropical diseases, diarrhoea, influenza and reproductive health. In addition to medicines, WHO prequalification covers *in vitro* diagnostics, vaccines and vector control products.⁸⁰ PQT has begun pilot programmes for prequalification of similar biotherapeutic products (WHO, 2017). WHO prequalification is a recognized quality standard that is used and referred to by many international donors and procurement agencies.

PQT undertakes capacity-building work to strengthen regulatory systems in certain countries, through, among other things, training of staff, workshops, technical assistance and provision of guidance documents. PQT participates in collaborative registration procedures aimed at streamlining product registration in countries where regulatory capacity is limited (see section (e) below on collaborative procedures for accelerated registration).

(b) Regulation of medical devices

Medical devices include a wide range of tools – from the simple wooden tongue depressor and stethoscope to the most sophisticated implants and medical imaging apparatus. As is the case with vaccines and medicines, governments need to put in place policies that ensure access to quality, affordable medical devices, and ensure their safe and appropriate use and disposal. Therefore, strong regulatory systems are needed to ensure the safety, effectiveness and performance of medical devices. The use of non-medical-grade silicone in breast implants manufactured by a company based in France illustrates the need for strong regulatory systems (see Box 4.10). In general, medical devices are submitted to regulatory controls and, consequently, most countries have an authority that is responsible for implementing and enforcing specific product regulations for medical devices.⁸¹ As at 2015, at least 121 WHO member states have a national regulatory authority responsible for implementing and enforcing product regulations specific to medical devices (WHO, 2017b). However, a number of LMICs still do not have an authority responsible for implementing and enforcing medical device regulations. Implementation and enforcement are complicated, due to shortages of professional biomedical engineers, a lack of harmonization in medical devices procedures and limited information. National guidelines, policies or recommendations on the procurement of medical devices are not used in the majority of countries, either because they are not available or because there is no recognized authority in place to implement them. This creates challenges in establishing priorities in the selection of medical devices on the basis of their impact on the burden of disease. The lack of regulatory authorities, regulations and enforcement of existing regulations have a negative impact on access to quality products. The WHO has published guidance on medical device regulations and health technology assessment to assist countries in establishing appropriate regulatory systems for medical devices, including a Global Model Regulatory Framework for Medical Devices.⁸²

Box 4.10: Europe: tightening controls to guarantee the safety of medical devices

The EU legal framework relating to the safety and performance of medical devices was harmonized in the 1990s.⁸³ Under this legislation, medical devices are subject to pre-market approval by for-profit independent assessment bodies (notified bodies), which were tasked with reviewing the manufacturer's design and safety data for the product. An approval from any one notified body, in any one EU member state, would allow the product to be used in all EU countries. If one notified body declined to approve the product, a manufacturer could submit their product to another notified body.

In 2010, two high-profile cases occurred, eventually leading to changes in regulations. One case concerned breast implants manufactured by a company based in France, which used non-medical-grade silicone, leading to an unusually high short-term rupture rate. Another case concerned metal hip implants – undercover journalists secured approval for a hip implant that was purposely designed to be unsafe (Bowers and Cohen, 2018). This led to new EU regulations for medical devices, including certain aesthetic devices, adopted in 2017. The new regulations, which will come into force in 2020 and 2022, will include, *inter alia*, stricter regulatory review for high-risk devices, improved transparency through a European Union-wide medical devices database and stricter post-marketing surveillance.⁸⁴

(c) Quality assurance by national medicines regulatory authorities

National medicines regulatory authorities (NMRAs) are key in ensuring the quality of medicines. However, NMRAs vary in their capacity to undertake technical assessments.

In the context of international procurement, a list of “stringent regulatory authorities” (SRA) was created. The list was created by the Global Fund, due to a need to define which regulatory authorities’ approvals would qualify a product for procurement for HIV, TB and malaria treatment programmes. Several WHO guidance documents and the WHO Prequalification Team, as well as many international actors dealing in medicines procurement, use approval by an SRA as an acceptable marker of quality for a medicine.⁸⁵

The list of SRAs represents the members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as they stood up until October 2015. Until late 2015, the ICH included EU member states, the United States, Japan, the European Free Trade Association (EFTA) represented by Swissmedic (the national medicines regulatory authority of Switzerland), Health Canada, Australia, Norway, Iceland and Liechtenstein.⁸⁶

In October 2015, ICH overhauled its membership structure and, among other things, admitted a number of new LMIC regulatory bodies as members. This change prompted a revisiting of how NMRAs are evaluated with regard to their quality assurance procedures. The WHO has proposed a new system, in which NMRAs that are assessed as having a regulatory system in line with international standards will be termed a “WHO-Listed Authority” (WLA).⁸⁷ NMRAs previously considered SRAs will be designated WLAs (“grandfathered in”), while other NMRAs may voluntarily undergo an assessment through the WHO Global Benchmarking Tool (GBT), which, on this basis, will designate WLAs.

(d) Regulatory cooperation and convergence: reducing barriers from technical regulations and assessment procedures

Most regulatory authorities are established by national legislative processes and, as such, follow their own administrative rules and technical requirements, and have established their own processes and procedures for medicines registration, although measures to increase convergence of requirements have been developed. Different legal bases, as well as different national interpretations, may exist. Challenges with implementation of technical requirements for registration

set out in international guidelines may be due to factors such as different governmental structures, cultural norms, levels of technical competence and availability of human resources, or they may be due to particular business environments. In addition, there is often a time lag between the publication of international/regional/subregional technical regulatory guidelines and their implementation by individual countries. Regional differences still exist in terms of how individual countries go about ensuring compliance with current international good manufacturing practices (GMPs), as well as numerous other regulatory requirements for ensuring quality, safety and efficacy of products. Such distinctions can influence costs and the speed with which a company obtains marketing approval.

Convergence of the different national systems, in conjunction with harmonization of technical regulations, as well as conformity assessment procedures, can remove many of the transactional and human resource costs associated with multiple regulatory submissions in each country, including multiple testing. Such convergence can result in saving scarce resources for countries as well as companies. Regulatory convergence and increasing trust in regulatory decisions made by other competent authorities should lead to: (i) more efficient resource use (e.g. international and regional sharing of scientific resources and “best practices”); (ii) better quality applications to register medicines from manufacturers; (iii) cost savings at both the company and government level; and, as a consequence, (iv) quicker access to quality essential medicines that are safe and efficacious.

New regional regulatory entities are emerging. For example, in May 2018, the African Medicines Agency (AMA) was established.⁸⁸ The AMA will coordinate existing regulatory harmonization efforts in regional economic communities and regional health organizations. It will support the establishment and strengthening of “regional centres of regulatory excellency”. The AMA is also mandated to promote the use of the African Union Model Law on Medical Products Regulation in its member states and regional economic communities.

(e) Collaborative procedures for accelerated registration

In many countries with limited regulatory resources, registration of pharmaceutical products can take considerable time. In response to this, WHO created two procedures aimed at accelerating registration of pharmaceuticals at the national level.⁸⁹

- A collaborative procedure to facilitate the assessment and accelerated national registration of WHO-prequalified pharmaceutical products (see also section (a) above), which is currently fully operational

- A collaborative procedure to accelerate registration of finished pharmaceutical products (FPPs) that have already received approval from a stringent regulatory authority (SRA) (see also section (c) above), which is currently in pilot phase.

In addition to aiming to ensure that much-needed medicines reach patients more quickly, both procedures incorporate elements of capacity-building and regulatory harmonization.

In the accelerated registration procedure for prequalified FPPs, applicants (generally companies) voluntarily express interest in applying the procedure for accelerated registration to their prequalified products. Applicants authorize the WHO to share its assessment and inspection outcomes for the specific product(s) with the NMRA(s) of the country or countries in which accelerated registration is sought. The WHO then shares information regarding its evaluation of the FPP for prequalification (i.e. assessment and inspection outcomes) with the respective NMRA. The information is shared via a secure internet-based platform, subject to confidentiality undertakings and agreed restrictions on use. If an NMRA agrees to apply the procedure to the product concerned, it commits to reaching its decision as to whether it will register the FPP within 90 days of receiving access to the WHO assessment and inspection information, and to communicate its decision to the WHO and the applicant within a further 30 days. Thirty-nine countries currently participate in the procedure.⁹⁰

In the accelerated registration procedure for FPPs approved by SRAs, the applicant will submit an FPP for registration that is the “same” (as defined by the procedure) as the SRA-approved product to participating NMRAs. The applicant – with the agreement of the relevant SRA – will share the full assessment and inspection reports for the FPP with the participating NMRAs, as well as additional data documenting potential deviations from the FPP approved by the SRA. In organizing the sharing of the reports, the applicant will help to minimize any administrative burden on participating SRAs. Participating NMRAs will use the data submitted to support their decision-making regarding registration. They will seek to issue an “accelerated” decision on registration within 90 days of their acceptance of the submission. The procedure will not interfere with their national regulatory decision-making processes, or national legislation, or the levying of regulatory fees. Similarly, it will be the NMRAs’ responsibility to reach agreement with applicants regarding specific risk-management plans and pharmacovigilance follow-up. The WHO’s role will be to facilitate cooperation among applicants, participating NMRAs and SRAs. It will be involved with application of the procedure to a specific FPP only if it considers the FPP to be of public health relevance. Twenty-two countries currently participate in the procedure.⁹¹

12. Substandard and falsified (SF) medical products

The steady increase in the production, sale and use of substandard and falsified (SF) medical products poses serious public health problems. Medical products, both originator or generic, that do not meet quality standards and contain either no, or the wrong doses of, active ingredients or different substances, can lead to treatment failure, exacerbation of disease, resistance to medicines and even death.

SF medical products are found in all parts of the world but are typically a much greater problem in regions where regulatory and enforcement systems for medicines are weakest. For example, in 2017, it was shown that the aggregate observed failure rate of tested samples of medicines in low- and middle-income countries was approximately 10 per cent, meaning that one in 10 medicines in LMICs were substandard or falsified. If one applies this rate to the unweighted combined estimates of market size for low- and middle-income countries (nearly US\$ 300 billion per year) to calculate possible expenditure on substandard and falsified medicines by these countries, the resulting total estimate is in the order of US\$ 30 billion annually.⁹² In countries with effective regulatory systems and market control, the incidence of these medicines is, however, very low – less than 1 per cent of market value, according to the estimates in the countries concerned.

(a) Types of SF medical products

The terminology used to describe SF medical products in public health debates has changed over the past two decades. A lack of clarity over definitions in this area was resolved at the 70th World Health Assembly (WHA), which replaced the previous term “substandard/spurious/falsely-labelled/falsified/counterfeit medical products” with the term “substandard and falsified medical products”, and outlined the three broad categories of products that fall under this term:⁹³

- *Substandard medical products*: Also called “out of specification”, these are authorized medical products that fail to meet either their quality standards or their specifications, or both. Medical products that fall into this category include medicines that suffered manufacturing errors, expired medical products or degraded medical products following poor transportation and storage. Manufacturers of substandard medical products are usually known, which makes it easier to keep these products away from markets by means of regulatory tools.
- *Unregistered/unlicensed medical products*: Medical products that have not undergone evaluation and/or approval by the National/Regional Medicines Regulatory Authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

In cases of emergency or extreme shortage, member states may permit the distribution of unlicensed/unregistered medicines within their territory.

- *Falsified medical products*: Medical products that deliberately/fraudulently misrepresent their identity, composition or source. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration or reproduction of an authorized medical product or the manufacture of a medical product that is not an authorized product.

These definitions were required in order to differentiate the different types of illegal medical products circulating on the market. They assist in analysing the data, assessing the threat to public health and designing more meaningful interventions.

The WHA agreed not to use the term “counterfeit”, to avoid confusion with the infringement of trademarks, and that any consideration related to intellectual property rights does not fall within this definition (see section (b)).

(b) Counterfeit medical products and the TRIPS Agreement

The TRIPS Agreement defines “counterfeit” in relation to trademarks in a general manner, not specific to the public health sector. According to footnote 14(a) to Article 51 of the TRIPS Agreement, “Counterfeit trademark goods’ shall mean any goods, including packaging, bearing without authorization a trademark which is identical to the trademark validly registered in respect of such goods, or which cannot be distinguished in its essential aspects from such a trademark, and which thereby infringes the rights of the owner of the trademark in question under the law of the country of importation”. Counterfeiting is thus a particular type of trademark infringement. It is limited to using a sign: (i) that is identical or quasi-identical to a sign registered as a third-party trademark; (ii) for goods (or services) that are identical to the goods (or services) in respect of which the trademark was registered; and (iii) without the trademark owner’s authorization. It generally entails the use of a slavish copy (a reproduction without creative input) of the protected trademark. Given the intended confusion between the genuine product and the copy, fraud is usually involved. A counterfeit medical product would thus bear a sign identical or confusingly similar to the right holder’s registered trademark in order to pass it off as the genuine product.

(c) The impact of SF medicines

All types of medicines, including both originator and generic products, can be substandard or falsified – ranging from medicines for the treatment of life-threatening conditions to inexpensive generic versions of painkillers and antihistamines. The ingredients found in such products may range from random mixtures

of harmful toxic substances to inactive, ineffective preparations. Some falsified medical products contain a declared, active ingredient and look so similar to the genuine product that they deceive health professionals as well as patients. SF products are always illegal.

The nature of the problem of SF medical products is different in different settings. In some countries, especially in high-income countries, expensive hormones, steroids, anti-cancer medicines and lifestyle medicines account for the majority of SF products sold – often by way of internet-based transactions.

In LMICs, SF medical products for the treatment of life-threatening conditions such as HIV/AIDS, TB and malaria are prevalent. While most studies have focused on anti-infectives and antimalarials, other therapeutic categories are also affected, such as cancer and epilepsy medicines (WHO, 2017g). Over the period 2013–2017, of the SF medical products reported to the WHO Global Surveillance and Monitoring System (GSMS), 20 per cent were antimalarials, 17 per cent were antibiotics, 9 per cent were anaesthetics and painkillers, 9 per cent were “lifestyle products”, such as erectile dysfunction medicines, and 7 per cent were cancer medicines (WHO, 2017k). Experience has shown that vulnerable patient groups who pay for medicines out of pocket are often the worst affected by the negative impacts of SF medical products (WHO, 2011d).

The prime motivation for the production and distribution of SF medical products is potentially large profits. A number of factors favour their production and circulation, including:

- A lack of equitable access to, and affordability of, the relevant medicines
- The presence of outlets for unregulated medicines
- A lack of appropriate legislation
- The absence or weakness of national medicines regulatory authorities
- Inadequate enforcement of existing legislation
- Complex supply chains
- Weak criminal sanctions (WHO, 2017k).

(d) How can SF medical products be combated?

The approach to dealing with substandard or unlicensed/unregulated medical products may require a regulatory intervention, whereas the approach to falsified or counterfeit medical products may involve a criminal investigation, and the risks to public health may be very different.

The strategy developed by the WHO to combat SF medical products covers prevention, detection and response. Prevention of SF medical products requires:

education and awareness-raising; ensuring access to quality, affordable medicines; promoting the rational use of medicines; supporting quality standards; and using the WHO prequalification system (see section 11(a)). Detecting SF medical products requires heightened awareness throughout the supply chain, information sharing, improving detection technologies in the field and in laboratories, and wider use of authentication technologies. Finally, effective response to detected SF medical products requires strong governance, regulatory system strengthening, and effective communication between national regulators and international surveillance networks (WHO, 2017k).

International mechanisms for information exchange and cooperation in combating SF medical products have changed over past decades. A key concern has been the need to keep a public-health-focused approach (see also section C.3(h)). In May 2012, the WHA established a new, voluntary, member-state-driven mechanism, the

WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products (see Box 4.11), aimed at preventing and controlling SF medical products and associated activities from a public health perspective, specifically excluding trade and IP considerations.⁹⁴

The enforcement measures that WTO members are required to make available to effectively combat trademark counterfeiting can usefully complement public health tools to fight SF medical products. As set out in Chapter II, section B.1(d)(i), trademarks operate as an important source identifier. They can help to uncover counterfeit products which, as do falsified medicines, misrepresent a product's identity and source, pretending that it is the genuine product. Mandatory border measures and criminal sanctions that apply to counterfeit trademark goods, and the act of trademark counterfeiting pursuant to a country's IP legislation, can thus supplement efforts to keep medical products out of markets that are potentially harmful to patients.

Box 4.11: WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products

Step 1. Reports of suspected substandard or falsified medical products submitted by public, health-care professionals, industry, supply chain, customs, police, procurers and NGOs to the national medicines regulatory authority (NMRA).

Step 2. Assessment and response by NMRA.

Step 3. NMRA Focal Point searches and reports to the WHO's surveillance and monitoring system database.

Step 4. Immediate technical assistance and alerts are issued by the WHO when requested and appropriate. Validated reports and data inform policy, procedure, processes, investment and the work of the member state mechanism.

For further information, see https://www.who.int/medicines/regulation/ssffc/publications/GSMS_Report_layout.pdf.

B. Access to health products in specific areas

Key points

- Improved availability of affordable, quality antiretrovirals (ARVs) has been responsible for a dramatic increase in the number of HIV/AIDS patients receiving treatment. While many of the older treatments are available from generic sources, more recent ARVs are still patent protected in many countries.
- With the introduction of product patents in India, generic versions of new patented treatments are only available from India after patent expiration, unless they can be produced under voluntary or compulsory licences.
- Among the key challenges to tackle rising antimicrobial resistance (AMR) is the need to ensure that core antibiotics are widely available, while also ensuring good stewardship (appropriate use) to improve patient outcomes and minimize the development and spread of resistance.
- Since 2007, tuberculosis (TB) has been the leading infectious cause of death globally. Access to newly approved medicines for multidrug-resistant TB has been limited in the first few years following approval, due to challenges including limited clinical data, lack of national registration, high prices, lack of generic versions and changing treatment guidelines.
- Non-communicable diseases (NCDs) account for the majority of deaths globally, and providing treatment for chronic diseases often causes significant financial strain. Major gaps in access to both originator and generic medicines persist. While the majority of essential treatments for NCDs are off patent and are low-cost medicines, high prices, for example, for certain patented cancer medicines, pose challenges in all countries.
- Since 2013, new, highly effective treatments for hepatitis C have been launched at very high prices, prompting wide debate on pharmaceutical pricing, including in high-income countries. This has been met with a range of approaches adopted by pharmaceutical companies, governments, advocacy groups and patients, including innovative pricing agreements, voluntary and compulsory licensing, patent oppositions and buyers' clubs.
- Paediatric formulations for many medicines have yet to be developed. Incentive systems and extensive partnerships have been established to support the development of new paediatric formulations.
- Vaccine coverage has increased globally, though it varies according to disease area. The cost of fully immunizing a child with WHO-recommended vaccines has increased dramatically, due to both more vaccines being recommended and the price of newer vaccines being relatively high. There are a limited number of manufacturers for vaccines, and barriers to market entry are greater for vaccines than for pharmaceuticals.
- Ensuring availability of appropriate, affordable, accessible and safe medical devices of good quality remains a major challenge for health systems in many countries. Other challenges include functionality, availability of key reagents or consumables, maintenance, regulation and selection, and requisite training for health-care workers. Research on access to medical devices has been limited to date.

While access to health technologies remains a problem in all disease areas, this section focuses on a number of particular areas – HIV/AIDS, antimicrobial resistance, TB, NCDs, hepatitis C virus, paediatric medicines, vaccines and medical devices – because of their specificities and importance.

1. HIV/AIDS

The treatment of HIV/AIDS, including treatment coverage, has changed dramatically since the early 1990s. The Joint United Nations Programme on HIV/AIDS (UNAIDS)

estimates that, at the end of 2017, 75 per cent of people living with HIV knew that they were HIV positive, of which 79 per cent were receiving antiretroviral (ARV) therapy. Access to ARV therapy in LMICs has grown dramatically, with coverage increasing from only 2 per cent of people living with HIV in 2000 to 62 per cent (23 million people) in 2018.⁹⁵ While new infections and mortality are declining, the number of people living with HIV (PLHIV) is rising (36.9 million in 2017).

Key drivers of this increased coverage have been community-led responses together with national and international donor commitment and decreasing prices

of ARVs. Substantial price reductions for commonly used first-line ARVs have been achieved since 2000. The annual cost of first-line regimens in low-income countries decreased from about US\$ 10,000 for a year of treatment per person in 2000 to an average price of US\$ 89 per patient per year for first-line regimens in 2017, representing a reduction of more than 99 per cent.⁹⁶ Prices for second-line regimens have also decreased notably, but remain substantially higher than first-line regimens, at an average US\$ 275 per patient per year in 2017.⁹⁷ These reductions are due to many factors, including:

- increased funding for ARV therapy
- manufacture of products in India that were not covered by product patents
- emergence of a generic ARV market creating economies of scale
- political will at national and international levels to provide treatment, due to pressure from HIV/AIDS activists
- creation and use of the WHO standard treatment guidelines
- use of compulsory licences and government use
- rejection of patent applications in key producing countries, thus enabling generic companies to compete
- price decreases for originator products and voluntary licensing agreements, and non-assert declarations,
- the Medicines Patent Pool (see Box 4.24)
- price negotiations, including by bulk purchasers
- enhanced availability of information on prices, patents and licences (see Chapter II, section B.1(b)(viii)–(ix), and section A.4(f) in this chapter).⁹⁸

The impact of patents on access to medicines has often been illustrated using the example of HIV/AIDS

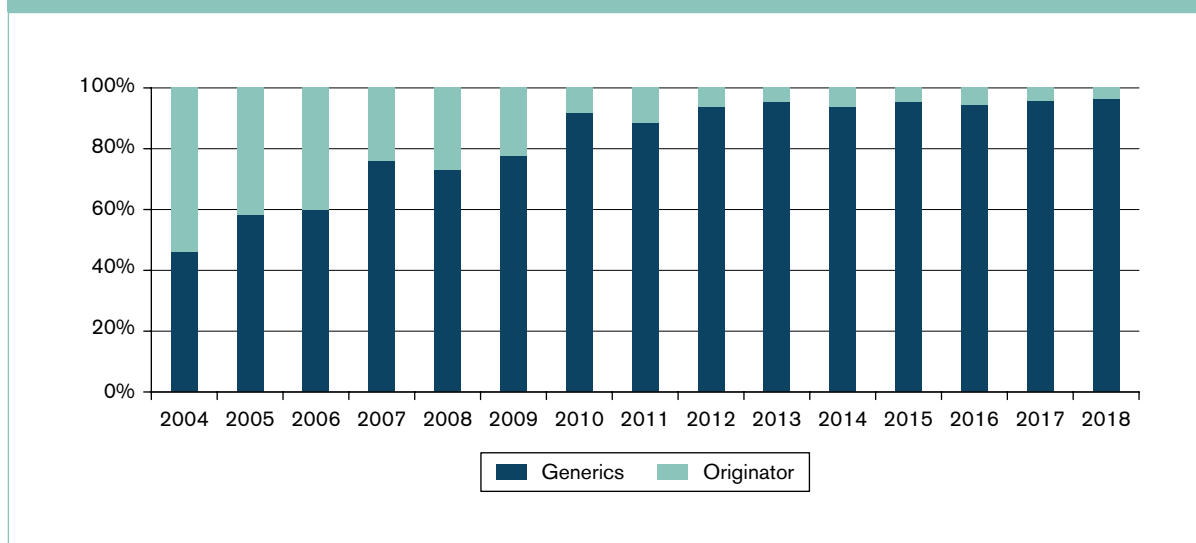
treatments – ARVs. Access to HIV/AIDS treatments has presented a unique challenge because the earliest effective treatments became available only in the late 1980s. During the major efforts to scale up treatment coverage in the early 2000s,⁹⁹ high prices for patent-protected HIV treatments posed a barrier to accessing ARV therapy in many LMICs (‘t Hoen et al., 2011). Indian manufacturers have been an important source of cheaper generic versions because, among other reasons, India did not grant pharmaceutical product patents until 2005, thus allowing India-based companies to produce generic versions of ARVs that were still under patent in other jurisdictions. Indian companies still provide most of the generic ARVs in the world. As at 2005, patent law in India provides for pharmaceutical product patents in accordance with the WTO TRIPS Agreement. This does not impact generic versions of ARVs that have been on the market previously.

The Medicines Patent Pool (see Box 4.24) has concluded licence agreements with a number of originator pharmaceutical companies that allow the production of generic medicines by other pharmaceutical companies, which can be sold in all countries that are covered by the licence agreements.¹⁰⁰

The majority of ARVs in LMICs are now generics, as shown in Figures 4.5 and 4.6.

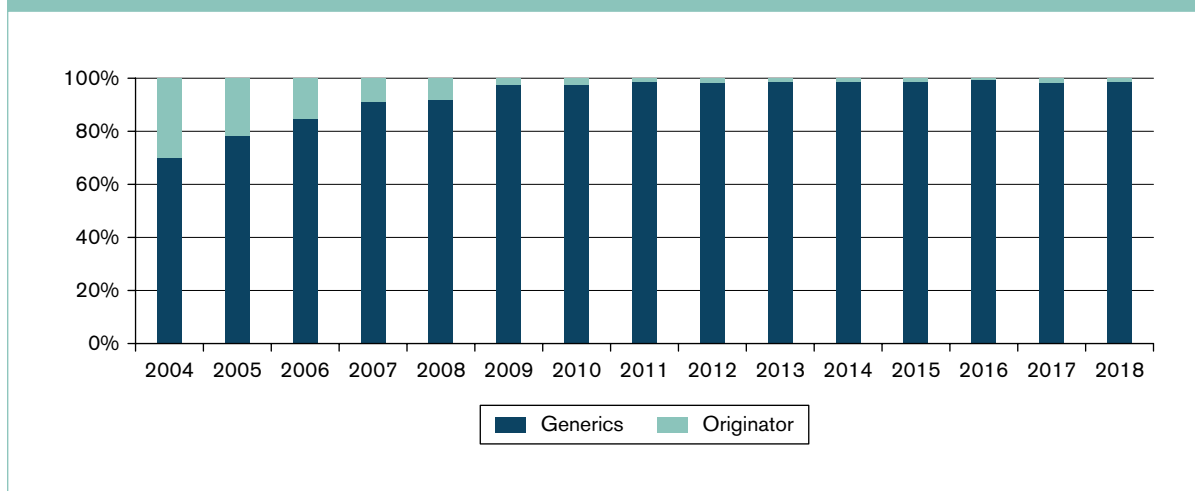
Access to low-priced ARVs continues to be essential, as governments and donor agencies strive to end the AIDS epidemic by 2030, as set out in target 3.3 of the SDGs. Low prices are also essential for governments transitioning from Global Fund financing to fully national financing.¹⁰¹ Challenges remain for newer-generation ARVs, including for WHO-recommended patented first-line treatments,

Figure 4.5: Sales revenue per year of generic and originator ARVs in LMICs



Source: WHO analysis, based on Global Price Reporting Mechanism for HIV, tuberculosis and malaria at www.who.int/hiv/amds/gprm/en/.

Figure 4.6: Sales quantities per year of generic and originator ARVs in LMICs



Source: WHO analysis, based on Global Price Reporting Mechanism for HIV, tuberculosis and malaria at www.who.int/hiv/amds/gprm/en/.

especially for upper-middle income countries that are not included in licence agreements (see Box 4.24) and have transitioned out of Global Fund financing, and in the context of pre-exposure prophylaxis.¹⁰² In this context, UN member states have committed – through, among other things, the 2016 Political Declaration on HIV/AIDS – to remove, where feasible, obstacles limiting the capacity of LMICs to provide affordable and effective HIV prevention and treatment, including by amending national law in order to: (i) optimize the use, to the full, of the TRIPS flexibilities; (ii) improve access by promoting generic competition in order to help reduce costs and by encouraging legitimate trade; and (iii) encourage partnerships to help reduce costs and to encourage development of new HIV treatments and diagnostics.¹⁰³

2. Antimicrobial resistance

The UN Interagency Coordination Group (IACG) on Antimicrobial Resistance (AMR) sees access challenges in AMR-related technologies for all dimensions of access, including availability, quality, affordability, demand and adoption, and supply and delivery (IACG, 2018). The main challenges for LMICs include a lack of needs-adapted technologies, use of SF health products, limited use of diagnostics and vaccines, inappropriate use of antibiotics, limited health system capacities, and the high cost of alternative plant protection products (see Figure 4.7).

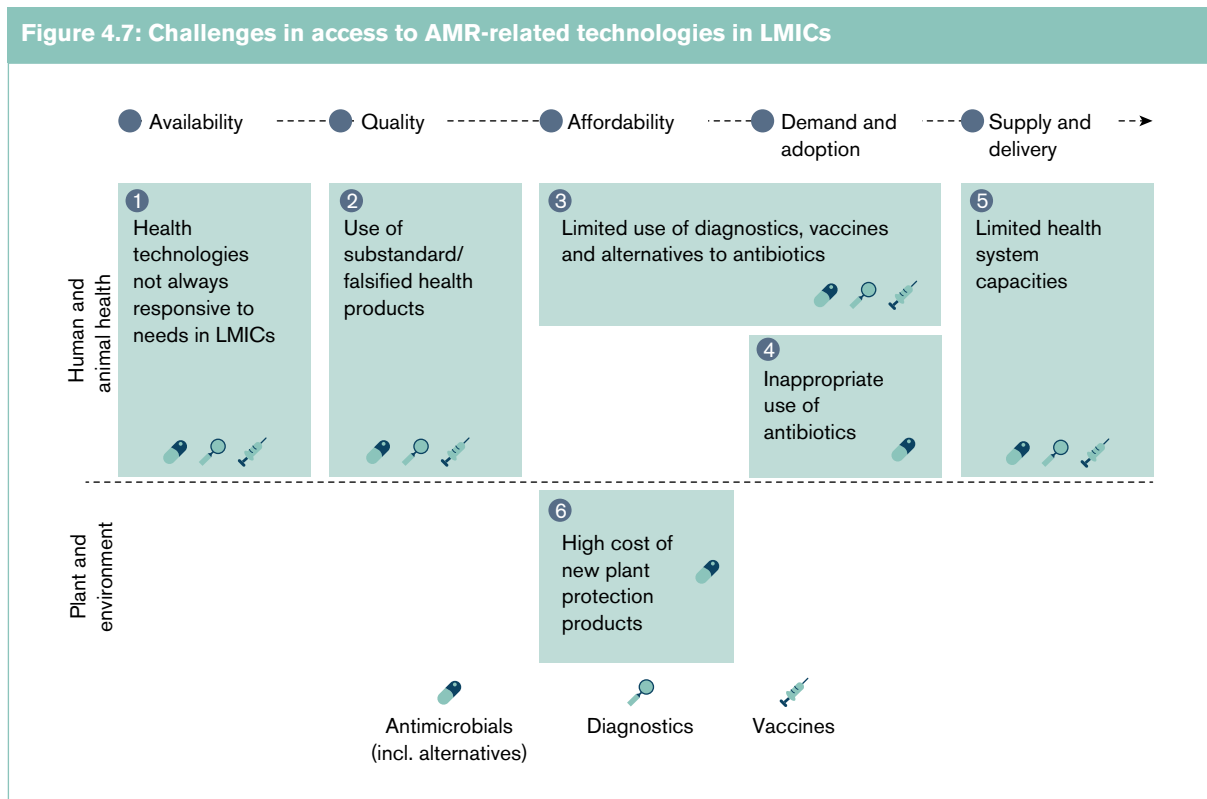
One of the key challenges for tackling AMR globally is the simultaneous need to ensure that core antibiotics are widely available, while also ensuring good stewardship – that is, appropriate antibiotic use to improve patient outcomes and minimize the development and spread of resistance.¹⁰⁴

Good stewardship of antibiotics is of paramount importance in stemming resistance. Access to antibiotics is far from adequate at present; although few precise data are available, it is estimated that almost 6 million deaths occur annually due to infectious diseases that mostly could have been treated with existing antimicrobials (Daulaire et al., 2015; Laxminarayan et al., 2016; IACG, 2019). This is despite the fact that most widely used first- and second-choice antimicrobials (“Access” group) are available as both originator and generics, as well as at low cost.

In addition, production and supply chains are fragile for many antimicrobials, due to the small number of manufacturers. This can lead to shortages around the world, which, in turn, contribute an increased risk of antimicrobial resistance in both humans and animals (Tängdén et al., 2018).

To balance the simultaneous aims of ensuring widespread availability while ensuring good stewardship, the WHO Model List of Essential Medicines (EML) uses the “AWaRe” framework, categorizing antibacterials into “Access”, “Watch” and “Reserve” groups. The Access group contains antibacterials that are first- or second-line treatments for priority infectious syndromes, and medicines in this group should be widely available, affordable and quality assured. The Watch group contains antibacterials that are considered to be at higher risk of resistance but are still recommended second-line treatments for narrow indications. The Reserve group comprises antibacterials that should be kept as a last resort (WHO, 2017f).

Initiatives providing innovative models for financing and developing new antibacterial treatments, such as GARDP and CARB-X (see Box 3.7), incorporate concerns about



Source: Antimicrobial resistance: Invest in innovation and research, and boost R&D and access, IACG Discussion Paper, June 2018, available at: https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_AMR_Invest_innovation_research_boost_RD_and_access_110618.pdf?ua=1.

simultaneously ensuring access, stewardship and innovation into their business model (see Chapter II, section A.5). GARDP is building access considerations into the whole R&D value chain, while CARB-X is including provisions in its contracts with grantees that aim to safeguard access to, and good stewardship of, the final developed antibacterial.¹⁰⁵

3. Tuberculosis

Since 2007, tuberculosis (TB) has been the leading cause of death from a single infectious agent, despite the fact that, globally, the number of new cases of TB annually is falling by about 2 per cent per year. Deaths from TB have fallen from 1.8 million annually in 2000 to 1.5 million in 2018 (1.24 million of those in HIV-negative people and 0.22 million in HIV-positive people) (WHO, 2019c). Treatment coverage for TB has increased from 35 per cent in 2000 to 69 per cent in 2018 (WHO, 2019c). Most cases of TB can be successfully treated with medicines that have been available for many decades and are low cost (WHO, 2019c). However, an estimated 484,000 new cases of TB in 2018 were resistant to, at least, the two most powerful first-line medicines, i.e. rifampicin and isoniazid (WHO, 2019c) (see also antimicrobial resistance more broadly, in Chapter II, section A.5; Chapter III, section C.2; and Chapter IV, section B.2). These cases are termed multidrug-resistant TB (MDR-TB) and are

significantly harder to treat than other TB cases – they require significantly longer treatment, require medicines with serious side effects such as hearing loss, incur far higher costs and have lower survival rates (WHO, 2016c, 2019c). Although data are limited, there is a slight trend for cases of MDR-TB to increase as a proportion of all TB cases in high-burden countries, with the burden of MDR-TB either increasing faster or decreasing more slowly than the overall TB burden in each country (WHO, 2016c, 2019c).

Currently, the world as a whole, most WHO regions and many countries with a high TB burden are not on track to reach the 2020 milestones of the End TB Strategy, of a 35 per cent reduction in the absolute number of TB deaths and a 20 per cent reduction in the TB incidence rate compared with levels in 2015 (WHO, 2019c).

One challenge is the large gaps in detection and diagnosis. Although policies are in place that require cases of TB to be notified to national authorities, only 7 million of an estimated 10 million new TB cases were reported in 2018. This gap represents a mixture of underreporting detected cases and underdiagnosis (both where people do not have access to health care or are not diagnosed once they access health care) (WHO, 2016c, 2019c).

A key focus in TB is the development of new, better medicines and regimens, and enabling universal

Box 4.12: Innovative Medicines for Tuberculosis (iM4TB) Foundation

The iM4TB Foundation, created in 2014 by the Swiss Federal Institute of Technology in Lausanne (École Polytechnique Fédérale de Lausanne (EPFL)) undertakes clinical trials to further develop a new antibiotic, PBTZ169 (macozinone), that has shown promising results against drug-resistant TB bacteria through a shortened treatment course. A patent was granted in the US in 2014, and patents have been applied for at the EPO, the Eurasian Patent Organization and China in 2015. Subsequently, the iM4TB Foundation entered into an extensive collaboration agreement with a pharmaceutical company. It has been reported that this was made possible through the Foundation's patent portfolio and the research and development data it had generated. Both triggered the interest of the company to invest in the project and to take part in the development of the new treatment. Reportedly, IPRs thus helped to secure the return on investment and facilitated in the advancement of the project.¹⁰⁶ Testing of the compound entered phase Ib trials in March 2019.¹⁰⁷

access to all medicines. TB is considered a neglected disease in terms of R&D, with serious underinvestment in research relative to the disease burden and the challenge of resistant strains. As the Innovative Medicine for Tuberculosis (iM4TB) project has reportedly shown, patents can be an important tool to secure the necessary investment to develop new medicines to treat MDR-TB (see Box 4.12).

Three new medicines – bedaquiline, delamanid and pretomanid – were approved in 2012, 2014 and 2019, respectively, for the treatment of drug-resistant TB.¹⁰⁸ These are the first new TB treatments with a novel mechanism of action approved in nearly 50 years (Brigden et al., 2015). Bedaquiline is now one of the recommended treatments for MDR-TB (WHO, 2018f). Pretomanid was developed by the product development partnership TB Alliance (see Box 3.12).

The originator launched bedaquiline in 2013 with a tiered pricing structure, with a list price of US\$ 30,000 per treatment course in high-income countries, US\$ 3,000 per course in middle-income countries and US\$ 900 per course in low-income countries (WHO, 2015c). In April 2015, the originator began a donation programme for bedaquiline, which ran until March 2019.¹⁰⁹ Delamanid was launched at a price of US\$ 1,700 for developing countries,¹¹⁰ and the originator has also announced a donation programme for this medicine.¹¹¹ In the case of bedaquiline, in 2018, the originator agreed on a price of US \$400 per course with the Government of South Africa. It has extended this price to more than 130 LMICs, as well as NGOs, eligible to purchase medicines through the Global Drug Facility.¹¹²

Roll-out of these newer treatments has been slow for various reasons, including the limited clinical data, lack of national registration, high prices and a lag in implementing new treatment guidelines (Masini et al., 2018).

For both bedaquiline and delamanid, originators have made exclusive licensing agreements with manufacturers

with local/regional expertise for certain LMICs,¹¹³ but have not licensed the treatments to the Medicines Patent Pool (MPP).

4. Non-communicable diseases

Non-communicable diseases (NCDs) accounted for 71 per cent of deaths in 2016, of which almost 80 per cent occurred in LMICs.¹¹⁴ NCDs are the most common causes of death in all world regions, with the exception of sub-Saharan Africa.¹¹⁵

According to WHO projections, the total annual number of deaths from NCDs will increase to 55 million by 2030 if “business as usual” continues (WHO, 2013a). The Global NCD Action Plan 2013–2020 includes a target “80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities”.¹¹⁶

Providing treatment for chronic diseases puts an enormous and continuous financial strain on household budgets, often necessitating catastrophic health expenditures and thus pushing families below the poverty line (Niëns et al., 2010; Jaspers et al., 2015).

For all countries, the cost of inaction far outweighs the cost of taking action on NCDs. The WHO has estimated that the total cost of implementing a combination of very cost-effective, population-wide and individual interventions to combat NCDs would amount to 4 per cent of current health spending in low-income countries, 2 per cent in lower middle-income countries and less than 1 per cent in upper middle-income and high-income countries (WHO, 2013a). Such highly cost-effective interventions include interventions aimed at decreasing tobacco and alcohol use, improving diets and physical activity, providing key medicines to people who have had, or are at high risk of having, a heart attack or stroke, and providing hepatitis B immunizations and cervical cancer screening.¹¹⁷

Box 4.13: WHO, *Pricing of Cancer Medicines and its Impacts* (2019)¹¹⁸

Global expenditures on cancer medicines are rising rapidly, growing at 5–9 per cent annually over the period 2012–2016, and these increases outpace both the rise in the number of new cancer cases and the rise in overall health expenditure.¹¹⁹

The 2019 WHO report cites a 2015 survey that found that, among LMICs, 32 per cent of cancer medicines included in the 2015 EML were available only if patients covered the full cost of the medicine and 5 per cent are not available at all; in low-income countries the proportions were 58 per cent and 8 per cent, respectively. The survey found that the most-often-cited barriers to access were budgetary constraints in high-income and upper-middle-income countries, and lack of suppliers or lack of commercial motivation in lower-middle- and low-income countries (Cherny, Sullivan et al., 2017).

Health-care systems, even in high-income countries, are, in many cases, unable to provide affordable universal access to cancer medicines due, in many cases, to high prices of originator cancer medicines (Cherny, Sullivan et al., 2016). For example, the United Kingdom's health-care cost regulator, NICE, has in recent years rejected trastuzumab emtansine and palbociclib for breast cancer (later approved following discounts), as well as tisagenlecleucel-T for lymphoma, primarily on cost grounds.¹²⁰

With some important exceptions, many newer cancer medicines offer limited clinical benefits (e.g. small or no improvement in survival), often at the risk of added toxicity (Cherny, Dafni et al., 2017; Davis et al., 2017). Despite this, investment in cancer medicine R&D has a high level of return on investment (Tay-Teo et al., 2019). The WHO concluded that current approaches to managing the prices of cancer medicines are insufficient and have not resulted in outcomes that meet health policy and budgetary objectives.

The WHO report recommended a number of policy options to improve the accessibility and affordability of cancer medicines, which can be summarized as strengthening pricing policies, improving the efficiency of cancer medicines procurement, improving transparency in pricing and R&D costs, promoting cross-sector and cross-border collaboration, managing demand-side factors such as restricting the promotion of medicines, and realigning incentives for R&D (see also Chapter III, section B.5).

Shifts in the pipeline of cancer medicines may also translate to new access barriers. Many new cancer medicines are biotherapeutic products for which typically generic competition occurs later than for small-molecule treatments (see Chapter II, section A.6(d)). Additionally, many new cancer medicines are approved for indications that are based on molecularly defined cancer subtypes, such as the HER2-positive subset of breast cancers. In these cases, specialized diagnostic technologies are a prerequisite for use of the medicine but are often not available in resource-limited settings.

An increasing proportion of new oncology medicines are approved with “orphan” designation (see Chapter III, section B.6). Medicines with orphan designation are medicines for rare indications (i.e. a rare disease or a rare subtype of a more common disease). The increasing proportion of novel medicines approved with orphan designation is especially striking in oncology: 14 of 18 novel medicines approved for oncological indication in 2018 had orphan designation.¹²¹ Orphan medicines are priced at higher levels than other originator medicines, in part due to their smaller patient populations.

Demographic and epidemiological transitions have placed focus on access to the medical technologies that are needed to treat NCDs. Major gaps in access to both originator and generic medicines for chronic diseases persist.¹²² A study comparing the mean availability of 30 medicines for chronic and acute conditions in 40 developing countries found that availability of medicines for chronic diseases was lower than for acute conditions in both public- and private-sector facilities (Cameron et al., 2011). Low public-sector availability of essential medicines is often caused by a lack of public resources or underbudgeting, high prices, low availability of

medicines, inaccurate demand forecasting and inefficient procurement and distribution.¹²³ The Lancet Commission on Essential Medicines Policies found that “[a]ffordability is particularly problematic when medicines must be taken on a continuing basis, such as for the management of chronic communicable or non-communicable conditions” (Wirtz et al., 2017).

The WHO regularly conducts surveys of countries to assess capacity to respond to NCDs. In 2017, all 194 WHO member states responded, with the majority of countries reported having basic technologies generally

available for screening, diagnosis and monitoring of NCDs in primary-care facilities in the public health sector (WHO, 2018b). The majority of countries responded that essential medicines for the management of the four main NCDs were generally available in the public health sector. The most readily available medicines were thiazide diuretics (used for high blood pressure), available in 90 per cent of all countries, and aspirin (used for heart attack and stroke prevention), available in 88 per cent of all countries. However, steroid inhalers (used for asthma and chronic obstructive pulmonary disease) were generally available in the public sector in only 6 per cent of low-income countries and 35 per cent of LMICs, and insulin in 39 per cent of low-income countries and 51 per cent of LMICs. The medicine with the lowest availability captured in the survey was oral morphine – a key palliative care medicine – available in only 32 per cent of countries in all income categories (WHO, 2018b).

The majority of essential treatments for NCDs are off patent and are low-cost medicines (NCD Alliance, 2011; Mackey and Liang, 2012). On the other hand, in the last few revisions of the WHO EML, a number of patented

NCD medicines have been added. These include imatinib, dasatinib, nilotinib and rituximab for leukaemias, trastuzumab for breast cancer, bevacizumab for wet age-related macular degeneration (a cause of blindness), abiraterone for prostate cancer, adalimumab for certain autoimmune disorders, dabigatran for certain cardiovascular conditions, erlotinib for lung cancer, lenalidomide for multiple myeloma and nivolumab for metastatic melanoma.¹²⁴ A 2019 WHO study on the pricing of cancer medicines and its impacts is summarized in Box 4.13. The example of access to insulin is discussed in Box 4.14.

Governments are employing a range of measures to limit behavioural risk factors for NCDs, such as tobacco consumption, physical inactivity, unhealthy diet and the harmful use of alcohol, and these measures may relate to trade policy. For instance, labelling requirements on food or beverages to inform consumers about NCD risk factors, or measures regulating the formulation of such products, are relevant to the WTO TBT Agreement (see Chapter II, section B.3(b)(ii)). Effective coordination between health and trade officials at the national level is important to ensure that such measures are coherent across both trade and health priorities.

Box 4.14: Access to insulin

Insulin is a fundamental part of the treatment of diabetes, and people living with type 1 diabetes (about 5 per cent of total diabetes burden) depend on daily insulin for survival. Insulin was discovered as a life-sustaining treatment for type 1 diabetes at the University of Toronto in 1922 (Rosenfeld, 2002). The University of Toronto employed a non-exclusive licensing strategy for their patents on insulin, with the objective of ensuring access to the product (see Box 3.1). While, at first, therapeutic insulin was manufactured by purifying it from the pancreata of cows and pigs, in the 1980s, advances in molecular biology led to the insulins manufactured in genetically engineered microorganisms.

A 2016 survey found that insulin was available more than three quarters of the time in about 70–90 per cent of middle-income countries (depending on the type of insulin) and 40 per cent of low-income countries.¹²⁵

Numerous factors are contributing to the lack of access to insulin. Price is one, in particular when patients need to pay out of pocket. The insulin market is not very competitive as three manufacturers control 96 per cent of the global insulin market in terms of volume (Beran et al., 2016).

While nearly all compound patents on the most widely used insulins have expired, patents on insulin delivery devices are still in force (see also Box 3.14) (Kaplan and Beall, 2016; Luo and Kesselheim, 2015; Beall et al., 2016; Beran et al., 2016). The most widely used delivery devices include pre-filled pens and reusable pens, in which the insulin-containing cartridge can be replaced. These devices offer an alternative to the older method of self-administering insulin, in which a normal disposable syringe is used to draw insulin from a vial and inject it. The devices are easier to use than the vial-and-syringe method, have special, thinner needles, making injections less painful, and are believed to increase patient adherence. Insulin in pen devices is substantially more expensive than insulin in vials.¹²⁶ Pen devices are used by nearly 90 per cent of people who use insulin in Europe and 95 per cent in Japan.¹²⁷ Pen devices are far less commonly used in LMICs: a 2016 survey found that insulin pens were available more than three quarters of the time in 67 per cent of middle-income countries and 25 per cent of low-income countries (International Diabetes Federation, 2016).

Insulins are biotherapeutics, and the general challenges for bringing a similar biotherapeutic product to market apply (see Chapter II, section A.6(d)). Lastly, insulin analogues – newer versions of insulin with small modifications to the protein structure – have come to dominate high-income markets and represent a growing share of LMIC markets (Beran et al., 2016). These insulins are more expensive than older (regular) insulin.¹²⁸ The first similar biotherapeutic product versions of insulin analogues were approved in 2014 in the European Union and in 2015 in the United States.¹²⁹

5. Hepatitis C virus

The global prevalence of chronic hepatitis C virus (HCV) infection was estimated to be 71 million in 2015, and an estimated 1.75 million new infections occurred worldwide in 2015 (WHO, 2017c). The WHO regions with the highest prevalence of HCV infection are the Eastern Mediterranean Region and the European Region (WHO, 2017c). The number of deaths due to HCV is rising and was 1.34 million in 2015. Only 20 per cent of HCV-infected persons had been diagnosed, of which 7 per cent had started treatment (WHO, 2017c). In 2015, the leading causes of new HCV infections were unsafe health-care procedures and injection drug use (WHO, 2017c). Unsafe injections have decreased notably, although in some regions needles and syringes are frequently reused (WHO, 2017c).

The treatment of hepatitis C has undergone a revolution in the past decade. New direct-acting antivirals (DAAs), such as sofosbuvir, which was approved in 2013 in the United States and 2014 in the European Union,¹³⁰ offer a cure in more than 90 per cent of chronic HCV infections. Prior to the development of DAAs, cure rates were 40–70 per cent and treatments were associated with severe adverse effects.¹³¹ Soon after their approval, numerous DAAs were added to the EML and WHO treatment guidelines (WHO, 2018d), which recommend three different alternative treatment combinations, marketed by two different originator companies.¹³² The high launch prices in the United States and Europe led to an intensive debate. A 2016 analysis found that treatment with sofosbuvir/ledipasvir – the dominant DAA combination at the time – was not affordable for most OECD countries, with costs equivalent to more than two years of annual average wages in Poland, Slovakia, Turkey, and Portugal (Iyengar et al., 2016). These new treatments entered the market at very high prices. Treatment has been unavailable, rationed or delayed due to high prices. For example, a 2018 study found that 22 European countries placed restrictions on reimbursement of DAAs based on disease stage.¹³³ In Switzerland, as in the United Kingdom, treatment was initially limited to patients with serious liver damage, although patients with mild or no liver damage would have benefited from earlier treatment.¹³⁴

In the United States, the high launch price of sofosbuvir led to a Congressional investigation into its pricing and marketing, which found that the originator company's pricing scheme was designed to maximize revenue, and that there was no evidence that the originator's costs in acquiring rights to, and developing, sofosbuvir factored into setting the price.¹³⁵

Lack of access to these highly effective treatments has been met by a range of responses by the originator companies, governments, advocacy groups

and patients: innovative pricing agreements, voluntary licensing, compulsory licensing, patent oppositions and buyers' clubs (see Box 4.15).

The patent-holder company for the most widely used DAA – sofosbuvir – signed voluntary licensing agreements with Indian generics companies for the first time in 2014, which cover four key DAAs (sofosbuvir, ledipasvir, velpatasvir and voxilaprevir) and allow supply to more than 100 countries.¹³⁶ The agreements also allow the licensed manufacturers to supply these DAAs to any country that is not included in the licensed territory but has issued a compulsory licence. The Government of Malaysia issued a compulsory licence on sofosbuvir in 2017 (see Box 4.21). Around the same time, the patent holder extended its VL scheme to include Belarus, Malaysia, Thailand and Ukraine (WHO, 2018e). Four DAAs have been licensed to the Medicines Patent Pool: daclatasvir (that can be used in combination with sofosbuvir), glecaprevir/pibrentasvir and ravidasvir.¹³⁷

In Brazil, the Ministry of Health rationed access to DAAs while negotiating with the originator for price reductions. While Brazil eventually secured a 90 per cent price reduction compared to US list prices, following the rejection of certain patent claims and other patents pending, the Ministry of Health also procures a generic version that was developed by a public–private partnership (da Fonseca et al., 2019).

Australia negotiated an agreement with the patent holder for sofosbuvir and other key DAAs wherein the government will pay about AUD 1 billion over five years for an unlimited number of treatments – sometimes termed the “subscription” model. In this way, it delinks price from volume. A key advantage of this approach is that treating a maximal number of patients is incentivized, as per-patient expenditure decreases. According to Moon and Erickson (2019), based on Australian Government projections for the number of patients that will be treated, this lump-sum payment would equate, at the per-patient level, to a price discount of almost 90 per cent compared with the US list price. The State of Louisiana is reportedly exploring a similar model (Moon and Erickson, 2019).

Early patent analyses by the WHO showed that patents on key DAAs had not been applied for or had not been granted in certain countries, allowing for local production (WHO, 2016d). Two examples are Egypt and Pakistan, where local generics companies manufacture sofosbuvir; these countries represent more than half of all people who started DAA treatment in 2016 (WHO, 2018e). Patent oppositions filed by civil society organizations have led to the rejection of some key patent applications for sofosbuvir in Brazil, China, Egypt and Ukraine. Generics have entered the market in Brazil, Egypt and Ukraine (see Chapter II, section B.1(c)).¹³⁸ In China, three manufacturers have

Box 4.15: Buyers' clubs

Buyers' clubs are organizations that assist patients in purchasing lower-priced medicines from overseas. Buyers' clubs may provide advice on legal, practical and pharmacological aspects.

The FixHepC buyers' club for hepatitis C medicines, for example, recommends online pharmacies that it considers trustworthy, manages the shipment process and offers to quality-test a sample of the product once it arrives.¹³⁹ FixHepC enrolls buyers in clinical trials, which it claims provides them with a degree of legal protection.¹⁴⁰ Another example is the Cystic Fibrosis Buyers Club in the United Kingdom, which offers information on how to contact a generic supplier of cystic fibrosis medicines.¹⁴¹

Although buyers' clubs may vary in their approach, in the two examples above, individual imported shipments of medicines are ordered by the patients themselves and are of a quantity that provides treatment for the patient alone. Buyers' clubs may also facilitate the importation of generic versions that are not approved in the patient's country of residence; in such a case, the patient faces a risk that the product will not be a quality medicine. Some buyers' clubs offer to batch-test such generics.

Buyers' clubs were established during the AIDS crisis in the late 1990s and early 2000s, for example, in the United States and Thailand.¹⁴² Apart from hepatitis C buyers' clubs, more recently, buyers' clubs have been set up for pre-exposure prophylaxis (PrEP) for HIV (see section B.1), cancer medicines and multiple sclerosis medicines.¹⁴³

filed applications for generic sofosbuvir with the national medicines regulatory authority.¹⁴⁴ Civil society has opposed patent grant at the EPO, which has ruled to uphold one of the sofosbuvir patents under opposition, in reduced form (this ruling has been appealed).¹⁴⁵

Another aspect of the DAA market is that there has been competition among various patent-protected DAA combinations marketed by different originator companies, translating into price reductions.¹⁴⁶

In the majority of LMICs, DAAs are now available from generic manufacturers at relatively low prices; an estimated 60 per cent of people with HCV infection live in countries that could procure generic DAA. Expansion of hepatitis C treatment still faces numerous challenges, even where generic DAAs are available, due to the multiple other programmatic challenges: for example, coverage of screening and diagnostic services remains low – 80 per cent of cases remain undiagnosed globally, and confirmatory testing for hepatitis C is still prohibitively expensive in many countries. In general, stronger national government responses are needed, with national treatment plans, mobilization of resources and regulatory actions to improve access to treatment (WHO, 2018e). This experience with novel, highly effective hepatitis C treatments illustrates how patent law and licensing can be used to contribute to achieving universal treatment access.

6. Paediatric medicines

For many medicines, paediatric formulations have not yet been developed (Ivanovska et al., 2014). The WHO, with partners, has identified priority medicines for paediatric formulation development, including medicines for HIV, TB and neonatal care.¹⁴⁷ Availability of paediatric medicines

is low in many LMICs. One study found that, in 14 African countries, a given paediatric formulation was available in 28–48 per cent of primary health-care clinics. Availability at retail or private pharmacies tended to be higher, ranging between 38 per cent and 63 per cent (Robertson et al., 2009).

There are a number of reasons for the lack of research in paediatric medicines. Markets for paediatric medicines tend to be more fragmented than those for adult formulations. The reasons for such fragmentation include the fact that, of necessity, doses of medicines for children are determined by body weight. In addition, paediatric medicines must be available in flexible dosage forms, pleasant tasting and easy for children to swallow.¹⁴⁸ In order to provide more incentives to pharmaceutical companies to develop new paediatric formulations, some geographical regions, including Europe and the United States, have introduced paediatric patent term extensions or market exclusivity periods that provide for an additional period of market exclusivity for the product if a paediatric formulation is developed.

Because paediatric formulations are a niche and potentially economically unattractive market, improving access requires extensive collaboration between the public and private sectors. One international effort to improve access to paediatric medicines is Unitaid's work in the area of paediatric ARVs. In cooperation with the Clinton Foundation, Unitaid has provided predictable funding for the large-scale purchase of paediatric ARVs, creating incentives for producers of paediatric ARVs.¹⁴⁹ These efforts have resulted in an increase in the number of suppliers and a decrease in the price of quality AIDS medicines for children.¹⁵⁰

In 2013, under the coordination of WHO, a series of workstreams was established, bringing together multiple

partners – including funders, implementing organizations and research organizations – to better address various needs in the paediatric ARV market. These collaborative workstreams set priorities for development of new paediatric ARV medicine formulations, provided technical guidance on certain types of clinical studies of ARV medicines in children, developed a standard Paediatric ARV Formulary to enable optimal treatment of children and coordinated the procurement of paediatric ARVs for approximately 70 LMIC programmes (Penazzato et al., 2018). To bring these workstreams together and build upon these collaborations, the Global Accelerator for Paediatric Formulations (GAP-f) was launched in 2018 by multiple stakeholders, covering the whole life cycle of paediatric formulation development, from prioritization to development and delivery.¹⁵¹

7. Vaccines

National immunization programmes are a highly effective public health tool for the prevention of illness and the spread of infectious diseases, and they are almost always cost-effective in terms of public health outcomes (WHO, 2011a). Protecting more children through vaccination with existing vaccines and the introduction of new vaccines in immunization programmes represents an important contribution to achieving the SDGs, including Goal 3, “By 2030, end preventable deaths of newborns and children under 5 years of age”.

The prioritization and targets for the use of vaccines globally were outlined in the Global Vaccine Action Plan (GVAP), which covered the decade 2011–2020. While many of the goals that were set in this strategy have not yet been achieved, including the eradication of polio, the last decade has seen significant progress in the development, introduction and uptake of new vaccines (WHO, 2018d). In order to meet the SDGs by 2030, and increase coverage and reduce inequities in vaccination, the WHO post-2020 immunization agenda is under development.¹⁵²

The degree of access to vaccines varies according to disease area. In 2018, 86 per cent of children across the globe received three full doses of diphtheria-tetanus-pertussis-containing (DTP3) vaccine, and the same proportion received the final dose of the polio vaccine, while coverage for other vaccines included in the Expanded Programme on Immunization was lower: 86 per cent for the first dose of a measles-containing vaccine but 69 per cent for the final dose; only 47 per cent for the final dose of the pneumococcal vaccine; and 35 per cent for the final dose of the rotavirus vaccine. By the end of 2018, the human papillomavirus (HPV) vaccine had been introduced in 90 countries, and the global coverage had increased from 3 per cent in 2010 to 12 per cent in 2018.¹⁵³ The work of Gavi, the Vaccine Alliance has contributed significantly to the immunization of children in developing countries (see Box 4.16).

Box 4.16: Gavi, the Vaccine Alliance

Gavi, the Vaccine Alliance (Gavi) (formerly known as the Global Alliance for Vaccines and Immunization), a public–private partnership, funds access to new and under-used vaccines for children living in the poorest countries in the world. By the end of 2018, Gavi had contributed to the immunization of more than 690 million children immunized through routine support and more than 770 million people immunized through vaccination campaigns, globally, saving more than 10 million lives in the long term (Gavi, 2019).

From its launch in 2000 until the end of 2018, US\$ 17 billion has been contributed by donors to Gavi.¹⁵⁴ Gavi also provides support to strengthen national health systems and civil society organizations, to improve vaccine delivery to developing countries eligible for Gavi funding (47 eligible countries in 2018, defined as having a per capita gross national income equal to or less than US\$ 1,580 over the last three years).¹⁵⁵

While the majority of routine immunizations recommended by WHO are administered to infants, children and adolescents, vaccines administered to adults also play an important role in public health, including, for example, the seasonal influenza vaccine.

Vaccines are also playing an increasingly critical role in responding to outbreaks and ensuring national health security. The medical response to the Ebola outbreaks in 2014 and 2015 was driven primarily through the use of an experimental vaccine.

One major challenge within the vaccination success story is the rising costs of the standard immunization schedule for children. Between 2001 and 2014, the WHO immunization schedule grew from covering six diseases to covering 12, and, using the lowest-price vaccines available through Gavi/UNICEF, the cost increased by a factor of 68. Vaccines that drove this increase include the haemophilus influenzae type B (Hib), pneumococcal (PCV), rotavirus and HPV vaccines.¹⁵⁶ In addition, many middle-income countries are not Gavi eligible or will soon be “graduating” beyond eligibility, which translates into higher vaccination costs to national budgets.¹⁵⁷ Significant gaps exist in coverage for newer vaccines such as for HPV, rotavirus and pneumococcal disease. They remain relatively expensive, in part due to the limited number of producers.¹⁵⁸

There are numerous barriers to entry for the vaccine market that may be contributing to the low number of competitors. First, vaccine manufacture is complex. Vaccines are biologicals, making many of the challenges associated with biologicals development and manufacture applicable to vaccines (see Chapter II, section A.6(d)). Compared with pharmaceutical manufacture, vaccine manufacture is considered to be more dependent on know-how, and, in

general, requires a dedicated manufacturing facility to be built for each vaccine.¹⁵⁹ These factors contribute to the limited number of manufacturers of pandemic influenza vaccines (see Chapter III, section B.4(e)(ii) and section E) and explain why there is a limited market for seasonal influenza vaccines in developing countries.¹⁶⁰

Nevertheless, IP can also pose barriers to competition in vaccine manufacture. For example, patents on the genetic code of viruses used in the vaccine – such as patents on the HPV DNA – and patents on process technologies – such as patents on the technology needed for conjugation (a process that bolsters the immune response to the vaccine), which is key for the pneumococcal conjugate vaccine (PCV) – may pose a block to prospective competitive manufacturers.¹⁶¹ On the other hand, licensing can be instrumental to advancing the development of candidate vaccines. Only IP-protected technology can be licensed.¹⁶² For example, for Ebola Zaire, Ebola Sudan and Marburg viruses, a pharmaceutical company holding patents specific to the candidate vaccines entered into an exclusive licensing agreement with a vaccine institute and transferred certain patent rights to the institute. Based on this partnership, the vaccine institute announced its intention to continue the development and seek regulatory approval for the vaccines.¹⁶³ In addition, an IP management strategy can support the implementation of research and access strategies, including ethical principles (see Box 3.1 and section C.3(b)–(c) in this chapter).

In the area of pandemic influenza, a 2007 WIPO working paper,¹⁶⁴ prepared upon request from the WHO, found relatively few patents that claim H1N5 virus DNA as such, instead finding use claims to be more prevalent. A 2011 WIPO report,¹⁶⁵ also prepared upon request by the WHO, did not identify patent documents that included claims on a virus or derivative of a virus.

MSF has filed legal challenges on PCV-13 patents in India and the Republic of Korea, with a view to enabling more affordable versions from prospective competitors to enter the market.¹⁶⁶ In December 2019, the patent opposition proceedings were pending in India. The patent in the Republic of Korea was upheld by the Supreme Court, causing a local manufacturer who had already completed Phase III development of a competitor version to cease preparation for commercialization (MSF, 2018). No impact of these patent oppositions on access can be asserted at this point in time.

There are numerous other significant challenges in improving immunization coverage, apart from the price and supply of the vaccines, such as the difficulty in reaching populations in remote regions, weak health and logistical support systems, a lack of understanding about the importance of vaccines and, in certain cases, misconceptions about the safety of vaccines, especially in poorer populations (WHO, 2018d).

8. Medical devices

Medical devices are indispensable in the prevention, diagnosis, treatment and management of medical conditions. Medical devices comprise a great range of products, including: medical equipment for long-term use, such as imaging and radiology equipment; surgical instruments; in vitro diagnostics; single-use devices, such as syringes and stents; implantable devices, such as hip prostheses; reagents; and sterilization equipment. Therefore, it is difficult to generalize across medical devices with regard to access considerations. Ensuring availability of appropriate, affordable, accessible and safe medical devices of good quality remains a major challenge for health systems in many parts of the world.

Optimal use of medical devices is, to a large extent, dependent on a functioning health system, including necessary human resources. It is also dependent on financing systems for reimbursement and the available infrastructure. Lastly, most medical devices require a consumable input, such as electricity or consumable materials. If this input is not available, the device cannot be used even if it is available.

The maturation of the concept of “essential” medicines has led to discussions about the application of the framework to other medical technologies. The effectiveness of such devices might be dependent on the level of care, infrastructure and epidemiology in a specific region.

Little published research is available on the issue of access to medical devices. The implementation of priority/essential/reference lists for medical devices, in contrast to medicines, is complicated by the lack of analogous “generics” – medical devices do not follow the same regulatory concept of a reference (originator) product and equivalent generic products – making it more difficult for decision-makers to define which devices to select, procure and use. Technical specifications are required in order to undertake bidding processes, and, following the awarding of a contract, procurement, supply, technical installation and training are needed. Following this, the availability of consumables and sources of power must be ensured.

New assessment and readiness tools are being developed by the WHO to monitor the availability and functionality of medical devices for health-care facilities, health centres and hospitals.¹⁶⁷ These tools will support the monitoring of progress, for example, in the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases, which includes a target of achieving 80 per cent availability of basic technologies required to treat NCDs by 2020.¹⁶⁸

Devices are usually protected by different patents. For example, a blood glucose monitor – like those used daily by many people living with diabetes – can be covered

by patents relating to its user interface, software, battery, memory, power management system, integrated circuits and wireless or internet connectivity.

IP rights and their management are important for various stages of the product life cycle. For example, the R&D and marketing stages often rely on non-disclosure agreements, patent, design, trademark and copyright protection. For example, molecular diagnostics have been protected by patents on foundational technologies, such as nucleic acid amplification testing (NAAT) technologies, which underly, *inter alia*, newer tests for hepatitis C, HIV, malaria, MDR-TB and certain cancers.¹⁶⁹

In hepatitis C, the patent portfolio held by one company on the hepatitis C virus was reportedly such that any competitor developing a treatment or diagnostic devices for hepatitis C would need to secure licenses on these patents (Driehaus, 2012). The holder of these patents

has in some cases provided non-exclusive licences, which enabled it to achieve income from royalties, enabled competition, and further R&D on the hepatitis C virus by pharmaceutical companies. In other cases, where licensing agreements could not be reached, this reportedly delaying the development of treatments and diagnostic devices (National Research Council, 2003).

Hogarth et al. (2012) describe how a manufacturer of diagnostics for HPV, the leading cause of cervical cancer, protected a dominant market position for its HPV test in the United States by winning a series of IP infringement lawsuits against competitors (Hogarth et al., 2012; Hopkins and Hogarth, 2012). A 2018 report by Association de lutte contre le SIDA (ALCS, Association to Fight AIDS, Morocco) examined issues of access to devices used in assessing the level of fibrosis (liver scarring) in hepatitis C cases in Morocco (Association de lutte contra le SIDA, 2018).

C. Intellectual-property-related determinants of access

Key points

- There is no single determining factor for access to a protected product or technology. The impact of intellectual property rights (IPRs) on access to medical technologies depends on how they are regulated nationally and how they are managed by the right holder.
- The current international IP regime gives countries responsibility for designing their domestic IP systems in compliance with international agreements while also taking into account different considerations, such as the stage of their social, economic, developmental and other objectives, including in the area of public health. However, the implementation and use of these flexibilities in domestic law has its own complexities.
- The definition of patentable subject matter and exclusions from patentability, as well as of patentability criteria and their application in practice, may have a considerable impact on access to health technologies.
- Substantive examination and review procedures help to ensure the quality of patents and address the problem of erroneously granted patents. This has implications for market entry by generic producers.
- The regulatory review exception allows potential competitors to use a patented invention during the patent term without the consent of the patent owner for the purpose of obtaining marketing approval for a prospective generic product. This facilitates timely market entry of generic medicines upon expiry of the patent.
- WTO members are free to determine the grounds for granting compulsory licences. Such grounds can include public interest in general and are not limited to public health emergencies.
- Compulsory licences and government-use authorizations have been used to import cheaper generic medicines or to produce them locally, as well as to remedy anti-competitive conduct.
- In 2003, the Special Compulsory Licensing System was introduced to enhance access to medicines by removing a legal barrier to export patented medicines under compulsory licence to countries without sufficient local manufacturing capacities that need to import medicines. This led to an amendment of the TRIPS Agreement in 2017.
- Companies have increasingly entered into voluntary licensing agreements with generic manufacturers with pro-access terms and conditions, as part of their corporate social responsibility programmes. This trend has been reinforced by the creation of the Medicines Patent Pool in 2010. A limited number of public-interest research institutions have put in place socially responsible licensing policies which aim to ensure the accessibility of the end product in resource-poor settings.
- As clarified by the Doha Declaration, WTO members are free to determine their exhaustion regime. The choice of the exhaustion regime is one of the factors that impact upon whether parallel importation can take place.
- Some countries provide for the possibility of compensating the patent holder, upon request, for the delay encountered in patent grant procedures or the time taken to obtain regulatory approval through statutory mechanisms to extend the term of the patent or similar instruments.
- The TRIPS Agreement includes comprehensive standards to enable IPR holders to enforce their rights. These standards may have a bearing on public health, in particular when medicines are traded across borders. These standards can be instrumental in preventing counterfeit health technologies from entering markets, while also ensuring that free trade in legitimate products, including generic medicines, is not subject to legal barriers.
- Certain provisions in free trade agreements (FTAs) and international investment agreements (IIAs) are of relevance to the health technologies sector. The most common IP provisions in FTAs that affect the pharmaceutical sector are: definitions of patentability criteria; patent term extensions and similar instruments; regulatory exclusivities; linkage of regulatory approval with patents; and enforcement of IPRs, in particular as regards the scope of border measures. In the past decade, many FTAs have also reaffirmed the Doha Declaration and, in particular, the right of the parties to take measures to protect public health.

This section focuses on the IP-related determinants for improving access. It builds on the overview of the IP system and policy discussed in Chapter II, section B.1, and focuses on its impact on access to medical technologies. In contrast, Chapter III, section D considers the IP system from the perspective of innovation.

IP law and its practical implementation interact with access to technologies in a complex manner. For example, a finished medical product typically combines numerous inputs and innovations, some of which may be protected by IPRs, which are potentially held by different parties. There is no single determining factor for access to a protected product or technology. Much depends on: how the acquisition, maintenance and enforcement of IPRs are regulated under the applicable national law; how such law is applied in practice; where IPRs are applied for; for how long the IPRs are exercised; who holds the IPR; and how the IPR holders choose to exercise – or not to exercise – their rights.

The current international IP regime – as defined by the TRIPS Agreement, the respective WIPO treaties and a number of regional agreements – sets minimum standards of IP protection. However, it gives countries responsibility for designing their national IP systems in compliance with these international agreements while also taking into account different considerations, such as the stage of their social, economic and cultural development, as well as specific interests and needs, including in the area of public health. The public policy options and other options afforded to members under the TRIPS Agreement are commonly referred to as “flexibilities.”¹⁷⁰ Resolutions adopted by the Human Rights Council,¹⁷¹ the World Health Assembly¹⁷² and the UN General Assembly,¹⁷³ the WHO Global Strategy and Plan of Action on Public Health, Innovation and IP¹⁷⁴ and the 2030 Agenda for Sustainable Development refer to the right of developing countries to use to the full the provisions in the TRIPS Agreement regarding flexibilities. While the TRIPS Agreement and the Doha Declaration have provided the context for the use of policy options under the TRIPS Agreement, the practical implementation of any flexibility has its own complexity and involves, beyond legislation, execution and operation of the law by administrative bodies and courts, underpinned by administrative and judicial procedures, and may pose constraints to various stakeholders in using an existing national legal framework.¹⁷⁵ Some WIPO member states stated that the insufficient local legal and technical expertise to incorporate and implement the TRIPS flexibilities into the national law and policy was one of the major problems in making full use of them.¹⁷⁶ A web of bilateral/regional/plurilateral/multilateral agreements can make transposing international agreements into domestic law complex. FTAs can pose a particular challenge. In particular, asymmetrical negotiating power can reduce the abilities of parties to those agreements to use flexibilities.¹⁷⁷ Moreover, the

constructive ambiguity of international treaties, including FTAs, can lead to different understandings about the full range of options available for implementation, but may also offer flexibility to implement commitments from these agreements in a manner that is responsive to domestic policy needs. The complexity of practical implementation is another factor that can complicate the use of flexibilities; this includes the transparency of and availability of judicial and administrative procedures, institutional capacity, national governance and internal coordination within the national government.

This chapter categorizes and sets out these flexibilities and other IP-related determinants of access in the pre-grant and post-grant stages.

1. Determinants of access prior to patent grant

Pre-grant patent issues essentially relate to questions such as what is considered patentable subject matter, what subject matter is specifically excluded, and how specific criteria for patentability are defined and applied by patent offices. Both the rules regarding patentability, and how they are applied in practice, ultimately determine the boundaries of a right to exclude others from using protected inventions and thus can have considerable (but not always decisive) impact on access to that technology. Erroneously granted patents potentially impede access and further research, and are not in the public interest. Detailed explanations on patentability criteria (patentable subject matter, novelty, inventive step/obviousness, industrial applicability/usefulness and disclosure) are provided in Chapter II, section B.1(b)(iii). The following, while not exhaustive, describes a number of particular issues that are relevant for access to medical technologies. Issues relating to the patenting of medical indications of known products are discussed in Chapter III, section D.4(c)).

(a) Diagnostic, surgical or therapeutic methods for the treatment of humans or animals

Diagnostic, surgical or therapeutic methods for the treatment of humans or animals are often excluded from patentability under national/regional patent laws, consistent with the option for members to exclude from patentability provided for in Article 27.3(a) of the TRIPS Agreement. Where such an exclusion has been implemented, it typically derives from concerns that a doctor should be free to apply the method of treatment that best suits a patient, without having to secure approval from a patent holder.¹⁷⁸ A judgment in the United Kingdom explains the reason for the exclusion as “merely

to keep patent law from interfering directly with what the doctor actually does to the patient".¹⁷⁹ The rationale for rejecting patent protection for medical treatment methods was also tied to the area being conceived as non-economic.¹⁸⁰ Yet the rationality of such an approach has been questioned by the UK courts: if a patent right is a fair price to pay for the extra research incentive, why should patent protection for diagnostic and treatment methods, which may offer incentives for research into a new treatment regimen, be denied?¹⁸¹ This exclusion usually applies only to treatment or diagnostic methods carried out on a *living* human or animal body and, as such, carrying out the method separately from the body will be sufficient to make a method patent eligible. Some laws expressly clarify that this exclusion does not apply to any apparatus or product (such as medical devices) that may be used for the purpose of diagnosis, surgery or therapy. In some countries, inventions concerning diagnostic, surgical or therapeutic methods for the treatment of humans or animals are not patentable because they are not regarded as inventions that meet the requirement of industrial applicability.¹⁸² In the United States, the right to enforce patents on a medical activity has been limited following a case in which a surgeon obtained a medical process patent on a stitchless technique used in cataract surgery and sued to collect royalties from an ophthalmologist using and teaching the procedure. The surgeon was prohibited from enforcing his patent.¹⁸³ Legislation was subsequently passed to deprive patent

holders of remedies against medical practitioners using process patents in the course of medical activities, even if infringement is found.¹⁸⁴

The decisions of the Supreme Court of the United States in the cases *Mayo Collaborative Services v Prometheus Laboratories* and *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals* (see Box 4.17) give some clarification on the patentability of diagnostic and treatment methods in the United States; however, this area may become complicated as precision medicine becomes more commonplace.

(b) Patent examination and patent registration

From the perspective of access to medical technologies, it is important to be aware of the changes that can be made during the patent examination and grant procedure. Patent claims that are made in the published patent application should be differentiated from the claims contained in the patent as granted. There is no guarantee that an application will mature into a patent, and any claims in an issued patent may be much narrower than what was originally sought. Only the claims as granted determine the legal scope of the right (for guidelines for the examination of pharmaceutical patents, see Box 4.18).

Box 4.17: Precision medicine and the patentability of diagnostic and treatment methods

The term "precision medicine", also called "personalised medicine", describes the tailoring of medical treatment to the individual characteristics of a patient.¹⁸⁵ Often, precision medicine refers to the increasingly common diagnostics and treatment methods wherein the dosage of a medicine is tailored to the specific patient's metabolic characteristics (Leucht et al., 2015; Madian et al., 2012). In the United States and in other jurisdictions, this has raised patentability questions, which, in general, centre on whether such diagnostics/methods are claiming a "law of nature" *in itself* – a specific pharmacokinetic (i.e. metabolic) relationship. In 2012, the Supreme Court of the United States found a certain diagnostic method to be insufficiently distinct from the laws of nature and, as a result, that diagnostic method did not meet the patent-eligible subject matter standard of Section 101 of the US Patent Act. In *Mayo Collaborative Services v Prometheus Laboratories (Mayo)*, the patented method determined the most effective dose of medicine to treat autoimmune gastrointestinal diseases by identifying the precise relationship between the medicine's effectiveness and the levels of its metabolites in the blood. The Court in *Mayo* established a two-step framework: (1) is the patent claim directed at an ineligible patent concept such as a law of nature and, if it is, (2) do the claims have additional features that reflect a genuine application of that law of nature or an "inventive concept", that is, adding something other than what is a well-understood, routine, conventional activity? The Court then decided that Prometheus Laboratories' diagnostic method claims were not sufficiently distinct from the laws of nature to meet the patent-eligible subject matter standard of Section 101 of the US Patent Act. In 2018, the Court applied the two-step framework to treatment methods in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals* and found that a treatment method based on the metabolization of a schizophrenia medicine based on genotype was patent eligible as the patent was not directed at patent-ineligible content. The patent did not just identify the existence of a relationship between the metabolization of a medicine and the genotype, as the patent had done in *Mayo*, but it applied that relationship in a specific treatment method (dose adjustment). Following these decisions, the USPTO issued its 2019 Revised Patent Subject Matter Eligibility Guidance, which elaborated the applicable legal test for subject matter eligibility (USPTO, 2019).

Box 4.18: Guidelines for the examination of pharmaceutical patents: developing a public health perspective

To support patent examiners' work and also ensure that all patentability criteria are met, many patent authorities have established search and examination guidelines that describe in detail the application of national/regional patent law to particular circumstances. WIPO has published a collection of links to the guidelines produced by a range of patent offices.¹⁸⁶ In addition, the International Bureau of WIPO, following consultations with the International Searching and Preliminary Examining Authorities under the Patent Cooperation Treaty (PCT), published the PCT International Search and Preliminary Examination Guidelines.¹⁸⁷

The International Centre for Trade and Sustainable Development (ICTSD), the WHO and the United Nations Conference on Trade and Development (UNCTAD) have published guidelines for the examination of pharmaceutical patents in the form of a working paper. The guidelines are intended to be a contribution towards the improvement of transparency and efficiency of patentability examination for pharmaceutical inventions, particularly in developing countries (Correa, 2007). Based on this publication, the United Nations Development Programme (UNDP) has published guidelines for the examination of patent applications relating to pharmaceuticals, considering the examination of pharmaceutical patents from a public health perspective (Correa, 2016).

To obtain information about the grant, the validity of the patent, as well as the eventual scope of patent protection, it is necessary to review the patent itself and its legal status, including whether a patent has been amended or corrected, or whether a patent has lapsed due to non-payment of maintenance fees. This needs to be done for every jurisdiction, since considerable variation may exist. Further, some claims may have been rejected by one patent office, but may have been granted by another. Such variations in the scope of patents within a patent family are especially likely to occur between jurisdictions that provide for substantive examination and jurisdictions that only provide for registration – thus deferring to later judicial proceedings, if any, the question of patent scope or validity.

(c) Patent quality

Quality is an essential aspect of the patent system to ensure that it serves its purpose of promoting innovation, contributing to dissemination and transfer of technology and fostering technological, social and economic development of the country concerned. Errors can occur in patent grant and administration. Such errors can be burdensome for right holders, third parties and the patent administration. Erroneously granted patents may lead to costly litigation and delay entry of generic versions, thus negatively impacting access to medicines. They can also become problematic with regard to patent linkage, for instance, when the grant of marketing approval for medicines is linked with patent status (see Chapter II, section A.6(g)). The regulatory agency may refuse to register generic products based on the existence of patents that should not have been granted in the first place.

To ensure that patent procedures meet the required standards and deliver high-quality results, many patent offices around the world have introduced quality management measures. Such systems measure outputs aimed at promoting higher quality standards and continued patent system improvements.

Quality management measures comprise certain general principles: a patent office should be clear about its functions and provide the necessary resources (staff, premises, equipment and training)

to deliver its functions effectively; procedures should be properly documented and feedback mechanisms (internal and external customer communication) should be provided to identify problems and opportunities so that procedures could be improved to avoid recurrence of problems; staff responsibilities should be clear and, to the extent possible, objectives should be measurable; and regular and comprehensive quality reviews should be carried out.¹⁸⁸ For example, at the international level, the PCT Common Quality Framework for International Search and Preliminary Examination, which is set out in Chapter 21 of the PCT International Search and Preliminary Guidelines, requires International Authorities under the PCT to establish quality management systems containing certain features that are important for ensuring effective search and examination according to the requirements of the PCT. The quality reports are published on a dedicated website.¹⁸⁹

2. Pre-grant and post-grant review procedures

Depending on national rules, third parties often have the option of filing oppositions against a patent either before or after the grant, or of filing observations during the patent examination process. India, for example, provides both a pre-grant and a post-grant opposition system. The character of both examination and opposition procedures

have an impact on what types of inventions are ultimately patented, and thus can be decisive in relation to market entry by generic producers. Opposition grounds typically include the lack of patentability or of novelty of the invention, insufficiency of disclosure for a person skilled in the art, or extension of the protected subject matter beyond what has been disclosed in the original filing of the patent application.

Opposition proceedings usually take place before administrative bodies specifically designed to handle pre-grant and post-grant proceedings, including post-grant review (see Box 4.19). Some countries provide other mechanisms such as re-examination.

Opposition proceedings are designed to ensure that patents are not granted on claimed inventions that do not satisfy the patentability requirements. For example, an opponent might submit prior art documents showing that the claimed invention had already been publicly disclosed.¹⁹⁰ Opposition procedures are thus a tool that can contribute to higher quality of patents and legal certainty. However, data sources indicate that, overall, a small proportion of patents are opposed.¹⁹¹ For example, between 2013 and 2017, the German Patent and Trademark Office granted about 75,000 patents, of which 1,800 have been challenged in opposition proceedings between 2014 and 2018. Half of the challenged patents have been maintained as granted or in limited form – thus, more than 98 per cent of the granted patents remained valid.¹⁹² In Chile, between 2013 and 2017, between 3,419 and 3,807 patent applications were filed each year, while between 299 and 604 oppositions were submitted annually.¹⁹³

Some countries provide a re-examination mechanism, under which a patent application or a patent is re-examined at the request of the patentee or third party based on the grounds as provided under the applicable law.

In countries where a patent application is published before a patent grant, third parties can analyse the claimed invention before the patent office takes a decision. In some of these countries, third parties may submit prior art relevant to the patentability of the claimed invention without participating in the subsequent procedure.

Similarly, many patent laws allow decisions of a patent office to grant a patent to be challenged by a third party, often without the need to do so within a certain period of time, before an administrative review body, such as an appeal board in a patent office, or before a court.

The European Commission's Pharmaceutical Sector Inquiry report (European Commission, 2009a) highlighted the importance of opposition procedures in the pharmaceutical area (see section C.2). Before the EPO, the opposition rate was much higher for the pharmaceutical sector than

for organic chemistry. While generic companies almost exclusively opposed secondary patents (i.e. patents on improvements or on related aspects of a medicine as opposed to the basic molecule itself), they prevailed in approximately 60 per cent of final decisions rendered by the EPO, including the Boards of Appeal, between 2000 and 2007. In an additional 15 per cent of cases, the scope of the patent opposed was restricted. On average, these procedures took more than two years. The report stated that litigation could be seen as an efficient means of creating obstacles for generic companies.¹⁹⁴ Any revocation, restriction or confirmation of secondary patents considerably affects the legal certainty regarding the validity of the patents.

The majority of interested parties in an opposition proceeding are rival companies, but they may also include patient organizations, public health groups and individuals, among others. Since at least 2001, patent opposition procedures have been used by civil society groups concerned with the affordability of medicines.¹⁹⁵ Where patent oppositions lead to the rejection of patent applications or invalidation of patents, this may allow earlier generic market entry and price reductions. More recently, patent oppositions filed by civil society groups have mostly concerned medicines for HIV and hepatitis C, with a smaller number concerning newer TB medicines, cancer medicines, and others.¹⁹⁶

The filing of patent oppositions on sofosbuvir in Thailand was followed by the originator including Thailand in the territory of its voluntary licences (see section B.5) (Silverman, 2017a; Kittittrakul, 2018a). The inclusion of Thailand in the voluntary licences may allow estimated budgetary savings of 38–93 per cent (Kittittrakul, 2018b). Patent oppositions filed by civil society in Argentina were followed by government procurement of generic versions for first-line HIV treatment and withdrawal of the patent application for PrEP medicines (see section B.1), in both cases allowing substantial savings.¹⁹⁷

The MSF Access Campaign hosts an online database of patent oppositions containing 114 applications, 191 oppositions and 90 drugs across 36 organizations as at November 2019.¹⁹⁸

3. Post-grant determinants of access

A number of important determinants of access to medical technologies relate to the management of patent rights post-grant. They include the regulatory review exception, compulsory licensing and government use, licensing agreements more broadly, parallel imports and IPR enforcement. The WIPO database on Flexibilities in the Intellectual Property System allows searches for implementation of flexibilities in national IP laws in

Box 4.19: The US Patent Trial and Appeal Board

In 2012, the US Patent Trial and Appeal Board (PTAB) was established. As well as resolving issues arising from the United States having moved from a first-to-invent to a first-to-file system, the PTAB hears post-grant review trials and *inter partes* review, new proceedings introduced by the 2012 America Invents Act to replace *inter partes* re-examination. Post-grant review and *inter partes* review are procedures by which a third party can challenge any patent if there is a reasonable likelihood that they will prevail with respect to one challenged claim. These new proceedings were introduced to ensure matters are resolved quickly, with statutory time limits being set for their completion. Post-grant review also differs from *inter partes* re-examination by providing more available grounds for challenging a patent. Since the implementation of the America Invents Act, there has been a dramatic increase in post-grant challenge in the United States, including of pharmaceutical and biotechnology patents.¹⁹⁹ Between 2012 and 2017, patents from the pharmaceutical and biotechnology industries formed around 10 per cent (772) of the 7,557 petitions for *inter partes* review. Of these, 389 were petitions involving patents listed in the FDA Orange Book (USPTO, 2018). By the end of 2017, the PTAB found 19 per cent of petitioned Orange Book-listed patents to be unpatentable.²⁰⁰

selected jurisdictions.²⁰¹ The research group Medicines Law & Policy maintains a non-exhaustive database of instances when authorities have taken or considered taking measures for public health reasons under national law within the flexibilities provided for by the TRIPS Agreement (see Box 2.15).²⁰²

(a) Exceptions and limitations to patent rights

This section describes certain exceptions and limitations to patent rights that provide safeguards for access to medical technologies. While exceptions for regulatory review purposes, compulsory licences and government use have a direct bearing on access to medical products and are discussed below, research exceptions relate to innovation and are therefore discussed in Chapter III, section D.5(a).

(i) *Regulatory review (or “Bolar”) exception*

During the process of obtaining marketing authorization, the applicant has to produce a first batch of the product, which may be considered an infringement of a related patent. Because regulatory approval may take several years, the inability to use the patented invention during the approval process, prior to patent expiration, would delay market entry of generic versions.

The regulatory review exception mitigates this situation by, in general, entitling anyone to use a patented invention during the patent term without the consent of the patent holder for the purposes of developing information to obtain marketing approval.²⁰³ This exception thus favours market entry by competitors immediately after the end of the patent term, and is, therefore, an instrument that is specifically designed to ensure early access to generic medicines.

Article 30 of the TRIPS Agreement states that WTO members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties. The panel in the 2000 WTO case of *Canada – Pharmaceutical Patents* found that Canada’s regulatory review exception was permitted by Article 30 of the TRIPS Agreement.²⁰⁴ A draft reference document discussed within the WIPO Standing Committee on the Law of Patents lists 69 countries and the European Union having legislation on a regulatory review exception.²⁰⁵ Two regional instruments address the regulatory review exception: (i) in the European Union, Directive 2001/82/EC related to veterinary medical products and Directive 2001/83/EC relating to medicinal products for human use; and (ii) Andean Community Decision No. 689.²⁰⁶ The WIPO draft reference document maps the approaches taken by countries in the national implementation of this important policy tool within patent laws. Developed and developing countries alike have tended to follow the Canadian form of an exception permitted under WTO rules. Other countries consider that their general research exception is broad enough to cover use of a patented technology for the purposes of regulatory review, and some laws expressly state this (see also Chapter III, section D.5(a)). In the United States, the safe harbour provision of 35 U.S.C. §271(e)(1) allows use of a patented invention that is reasonably related to the development and submission of information under a federal law that regulates the manufacture and sale of medicines.²⁰⁷

In most countries where a regulatory review exception exists, an explicit provision is contained in IP or patent legislation. The acts permitted under the regulatory review exception generally include “exploitation” or “working” of the invention, which are necessary to obtain marketing approval. Some jurisdictions go into significant detail about the types of acts

permitted by the exception, with some including import and export, if import or export is required to seek and obtain marketing authorization.²⁰⁸ The scope of the exception is closely linked to its final objective of obtaining marketing authorization, which has been broadly interpreted in some countries. Other questions, such as applicability of this exception to third-party suppliers and to acts carried out to obtain regulatory approval in other countries, have been answered to varying degrees. The applicable law in India, for example, states that activities made for the purpose of obtaining regulatory approval in other countries are covered.²⁰⁹ The subject matter of this exception ranges from pharmaceutical chemicals, to reference medicines and pharmaceuticals, but also to medical devices. Despite limited empirical evidence, a 2016 study commissioned by the European Union suggests that the broadening of this exception to cover any medicines and marketing authorizations in any country could create savings between EUR 23 million and EUR 34.3 million per year.²¹⁰

The implementation of the regulatory review exception has not been without challenges. WIPO member states have reported two particular difficulties with the regulatory review exception: first, the implementation of regional instruments in national laws has caused difficulty as these instruments have been observed as lacking scope and clarity, particularly in the absence of relevant jurisprudence.²¹¹ For example, the Netherlands reported that the precise scope of “trials and studies” referred to in the EU Directives was unclear without guidance from the Court of Justice of the European Union (CJEU). Second, there is a lack of awareness about this exception among users who may benefit from it.

The feasibility of this exception depends on patent status data and other relevant patent information, for example, expiration data on pharmaceutical patents, which is not always readily available or easy to interpret.²¹² However, significant work at national and international level is ongoing to make such information more accessible (see Chapter II, section B.1(b)(viii)–(xi)). Moreover, the efficiency of administrative procedures by regulatory authorities will also impact the proper functioning of this exception.

(ii) *Compulsory licensing and government use*

Compulsory licensing allows the exploitation of a patented technology during the patent term without the consent of the patent holder, but with the authorization of competent national authorities. This authorization may be given to a third party, or, in the case of government use, to a government agency or to a third party authorized to act on the government’s behalf. The term “compulsory licensing” is often used to refer to both forms of authorization, although they can have important operational distinctions. A 2018 study identified 81 compulsory licences and government-use licences in the pharmaceutical sector between 2001 and 2016 (‘t Hoen et al., 2018).

Compulsory licences

A WIPO draft reference document published in 2019 identified 156 countries and territories that provide for compulsory and government-use licenses under their respective legal frameworks.²¹³ The document found that the term “compulsory licensing” is often used to refer to both forms of authorization, while the beneficiaries of these two forms of licences can be different and such licences may have operational distinctions. Several regional instruments also contain provisions on compulsory licences. In cases where the national law does not provide a specific exception, provisions on compulsory licences may be applied through the membership of a regional agreement.²¹⁴ To explain the public policy objectives for a compulsory licensing mechanism, countries refer to striking a balance between the interest of patentees and of third parties and/or the public interest and/or society; preventing abuses that may result from the exercise of exclusive rights; and promoting the public interest at large, such as situations of public interest and emergency motivated by considerations of public health, nutrition and national security.²¹⁵ Some possible grounds for compulsory licensing are suggested in Article 5A of the Paris Convention (e.g. abuse of patent rights, including failure of the patent holder to work the invention) and in Article 31 of the TRIPS Agreement (e.g. national emergency and public non-commercial use). However, this list is not exhaustive. The Doha Declaration (discussed below) confirmed what was already implicit in the TRIPS Agreement – that WTO members have the freedom to determine the grounds upon which compulsory licences are granted. Compulsory licences are thus not limited to public health emergencies or other urgent situations, as is sometimes mistakenly believed. A range of grounds have been set out in national laws, such as:

- **Non-working or insufficient working:** Many countries provide that where a patentee fails to work a patent in its jurisdiction, or where such working by the patentee is insufficient, a compulsory licence may be granted, provided that all other requirements are met. Some national laws simply state that if a patentee is not working the invention or is not sufficiently working the invention without any legitimate justification, a third party may request a compulsory licence. In many countries, the laws do not expressly provide a definition of the terms “non-working” and “insufficient working”.²¹⁶ In some countries, the laws provide detailed provisions clarifying the circumstances that may be applicable, including the types of activities by the patentee that are considered as “working”. Examples include whether importation of the patented invention is considered as “working” in the country,²¹⁷ and the situations under which working by the patentee is not considered “sufficient”, for example, the demand for the patented product not being

satisfied in the local market on reasonable terms. Non-working or insufficient working of the patent by the right holder can be justified by legitimate reasons of a technical, economic or legal nature, for example, being impeded by public regulations.

- Anti-competitive practices: Some countries provide specific provisions under the patent law that allow the granting of a compulsory licence, in order to remedy an anti-competitive practice engaged in by the patentee, for example, price-fixing, denying a competitor access to an essential facility or those anti-competitive practices as specifically defined by national legislation. In certain countries, such as the United States, the use of licences to address competition concerns is not regulated by patent or other IP laws, but such licences may be granted as a result of proceedings under general competition (antitrust) laws.
- Public interest: Many countries allow the grant of compulsory licences on grounds of public interest, without further defining the term. Public interest could include the non-availability of the patented product, such that reasonable needs of the public are not being met. In some cases, the laws refer to more specific health-related situations, such as a compulsory licence on a patent relating to diagnostics, or on a patent concerning a biotechnological research tool. Health-specific grounds can, for example, be found in France and Morocco. Under provisions of the licence d'office dans l'intérêt de la santé publique, the health minister can seek the grant of a compulsory licence if the product or method is made available by the right holder in insufficient quantity or unsatisfactory quality, or if the prices charged are abnormally high.²¹⁸ More general references to public interest can be found in the legislation of, for example, the Czech Republic, Finland, the Netherlands and Norway.²¹⁹ Indian legislation provides as a ground for compulsory licensing that “the reasonable requirements of the

public with respect to the patented invention have not been satisfied”.²²⁰

- National emergency or circumstances of extreme urgency: Some laws provide for the possibility of compulsory licences on the grounds of national emergencies and circumstances of extreme urgency, national security and public health in general. However, a national emergency or extreme urgency is not a prerequisite for a compulsory licence under the TRIPS Agreement.
- Dependent and blocking patents: Many countries provide for the possibility of requesting a compulsory licence where a patent (second or “dependent” patent) cannot be exploited without infringing another patent (first or “blocking” patent). Article 31(l) of the TRIPS Agreement provides that such compulsory licences can only be granted if the second invention is an important technical advance of considerable economic significance and that, where a compulsory licence is granted to the holder of a second (dependent) patent to use a first (blocking) patent, the holder of the first patent shall also have a right to a cross-licence to use the second patent.

Government use

A number of national laws explicitly entitle the government, or a third party authorized by the government, to use a patented invention without authorization of the patent holder. A WIPO draft reference document identified 62 member states where the applicable law provides for such an exception.²²¹ The grounds may vary but typically relate to public policy objectives such as national security or health. The patentee usually shall be notified of the government use and its scope. Some national laws require such notification “unless national security requires otherwise” or “unless it appears to the relevant authority that it would be contrary to the public interest to do so”.²²² For examples of government use licenses, see Boxes 4.20 and 4.21.

Box 4.20: Government-use licences: efavirenz and lopinavir/ritonavir in Thailand

In 2005, more than half a million Thai citizens were HIV positive. Although the Thai Government had made a commitment in 2003 to provide free ARV treatment to all who needed it, the cost of doing so rose significantly when newer, better and more expensive treatments became available. In November 2006, the Ministry of Public Health issued a decree providing for the use of the patent rights relating to efavirenz; it authorized the state-owned Government Pharmaceutical Organization (GPO) to import or produce efavirenz. The patent holder was entitled to receive a royalty of 0.5 per cent of GPO's total sales value.²²³ The price of treatment reduced from US\$ 511 per patient per year to US\$ 106.²²⁴ Following the declaration of government use for the ARV treatment lopinavir/ritonavir (LPV/r) in 2008, the price of treatment reduced from US\$ 2,200 per patient per year to US\$ 793²²⁵ with a 0.5 per cent royalty rate.²²⁶ The number of patients in Thailand using LPV/r has reportedly increased from 39 to 6,246.²²⁷ In response to Thailand's government-use licence, the originator reduced the price for 40 middle-income countries for both the soft-gel and the heat-stable version of LPV/r (Campaign for Access to Essential Medicines, 2011).

Thailand has also authorized government-use licences on pharmaceutical products used to treat heart attacks, strokes and cancer (see Table 4.1).

Box 4.21: Government-use licences: hepatitis C treatment in Malaysia

The prevalence of hepatitis C in Malaysia has been estimated at 454,000 or 2.5 per cent of the population in the age range of 15 to 64 years (McDonald et al., 2014). A national treatment programme for hepatitis C was established in January 2017 and, in September 2017, Malaysia became the first country to issue a government-use licence for a direct-acting antiviral. Due to this licence, Malaysia was able to import or locally produce generic sofosbuvir while paying a royalty fee to the originator company. It has obtained generic versions of sofosbuvir for US\$ 33–US\$ 35 per 28-day course, compared with the US\$ 11,200 price reported earlier in 2017 for the originator version. After issuing the government-use licence, Malaysia was included in the originator's voluntary licensing scheme for sofosbuvir, ledipasvir and velpatasvir (WHO, 2018e) (see also section B.5).

TRIPS requirements for compulsory licences and government use

Article 31 of the TRIPS Agreement sets out certain conditions regarding the way in which compulsory licences and government-use authorizations should be issued. Notably, each case must be considered on its individual merits (Article 31(a)); prior efforts to negotiate a voluntary licence are normally required; and the licence must ordinarily be limited to predominantly supplying the domestic market (Article 31(f)). There are limitations regarding scope and duration (Article 31(c)). The right to use the patent must not be exclusive (Article 31(d)); neither may it be assignable to any third party (Article 31(e)). The patent holder has normally a right to receive adequate remuneration based on the economic value of the authorization (Article 31(h)) and a right to apply for a judicial or administrative review that could lead to termination of the use or licence (Article 31(g)).

The requirement that prior efforts be made to negotiate a voluntary licence for a reasonable period of time has been interpreted in different ways in national laws. The requirement to negotiate may be waived in situations of national emergency, in other circumstances of extreme urgency or in cases of public non-commercial use (Article 31(b)). The right holder is, however, entitled to receive notification about the use in these cases. In cases where the use of the patent is authorized without the consent of the patent holder, to remedy adjudicated cases of anti-competitive practices, WTO members are not obliged to apply these conditions

(Article 31(k)). In such cases, the licence need not be predominantly for the supply of the domestic market (thus allowing exports of unlimited quantities) and the amount of remuneration can be different (i.e. it would generally be a lesser amount or nothing at all).

The limitation of compulsory licences and government use to predominantly for the supply of the domestic market, found in Article 31(f) of the TRIPS Agreement, was revised following the Doha Declaration to allow production of pharmaceutical products under a compulsory licence exclusively for export under certain terms and conditions. In effect, Article 31(f) limits the quantity that could normally be exported under a standard compulsory licence, which was identified as a potential problem for countries that had insufficient manufacturing capacity or no domestic manufacturing capacity in the pharmaceutical sector, and therefore wished to import such products. The entry into force of Article 31*bis* of the TRIPS Agreement made the Special Compulsory Licensing System (the System) a permanent part of the Agreement, providing a secure legal pathway for the production and export of generic medicines to other members that rely on the import of the needed medicines for the treatment of their patients (see section 3(a)(iii) below).

Country experiences

A WIPO draft reference document found that, despite the existence of compulsory licensing provisions in national laws, the mechanism has been rarely used in most jurisdictions.²²⁸ While it is difficult to collect information about the requests and grants of compulsory licences, the available data show that, during the last decade, the use of compulsory licences has increased in relation to pharmaceutical patents, compared with other product types.²²⁹ Compulsory licences have been issued on a range of grounds, including addressing specific public health needs, unaffordable medicine prices, remedying anti-competitive behaviour and enabling access for owners of dependent patents (see Table 4.1).

The bargaining power created by just the legal possibility of a compulsory licence can benefit countries, even where a compulsory licence is not actually granted. For example, the Brazilian Government has demonstrated that legislation that provides for the effective and expeditious use of compulsory licences can be a useful asset in negotiating lower prices for ARV medicines (Abbott and Reichman, 2007). Using the threat of compulsory licensing, the Brazilian Government negotiated significant price reductions on efavirenz and nelfinavir in 2001, lopinavir in 2003, the combination of lopinavir and ritonavir (LPV/r) in 2005 and tenofovir in 2006. In 2007, after negotiations with

the patent-owning companies, the Brazilian Government issued a compulsory licence for efavirenz, an important ARV drug used by one third of Brazilians receiving treatment through a national programme. Less than two months after the compulsory licence was issued, the first shipment of generic efavirenz was received from India, where there was no patent on this product. Brazil reported to the TRIPS Council that it had taken two years to produce the medicine locally, partly because the patent law does not require applicants to disclose all the information necessary for the commercialization of an end product.²³⁰ After the licence was issued, the price dropped from US\$ 1.59 per dose for the originator product to US\$ 0.43 per dose for the imported generic version of the medicine.²³¹ It is estimated that the Brazilian Government's policies, including the use of TRIPS flexibilities, saved approximately US\$ 1.2 billion on ARV drug purchasing costs between 2001 and 2005 (Nunn et al., 2007).

In high-income countries, licences have been granted, among other reasons, as a result of action taken by competition authorities in order to address practices having an impact on access and innovation in the field of medical technology. In 2002, for example, the US Federal Trade Commission (FTC) requested the cross-licensing of a patent on tumour necrosis factor to a Swiss company in the course of merger review proceedings. The licence permitted the Swiss company to compete with a US patent owner. In 2005 and 2007, the Italian Competition Authority investigated abuses of dominant position by two large pharmaceutical companies that refused to license rights to their pharmaceutical products. The result was that royalty-free compulsory licences were issued, with the expectation that the resulting generics would be exported to other European countries where the patents concerned had already expired.²³²

Outside competition law contexts, compulsory licensing has also occasionally been considered or "threatened" by high-income countries when faced with high pharmaceutical prices. In 2017, the Ministry of Health of the Netherlands started to explore compulsory licensing of high-priced medicines (Silverman, 2017a). In 2019, a UK health minister reported that the government was considering issuing a Crown Use licence (a type of government-use licence) for the cystic fibrosis medicine lumacaftor-ivacaftor, after a pricing deal had not been reached with the originator following three years of negotiations (McConaghie, 2019). In Germany, compulsory licences have been used as a litigation tool (see Box 4.22). Diverging views on the impact of compulsory licenses on innovation and access have been expressed, namely, as regards

the repercussions on R&D and access, as well as the role in procurement processes.

Economic studies on the relationship between compulsory licensing and welfare in general, or specifically in relation to the changes in pharmaceutical R&D, are limited.²³³ One study found that compulsory licences granted in developing countries were not detrimental to research efforts in developed countries and did not impact these markets for the medicines concerned.²³⁴

A 2019 WIPO study identified a report about a case in which, in response to a compulsory licence, a pharmaceutical company withdrew all products pending registration and decided not to register new pharmaceutical products in that country.²³⁵ Results of a 2013 study suggested "that patents are generally associated with faster launch, higher prices, and higher sales, and that the importance of patents varies across country income groups" and concluded, "On average, access to new pharmaceuticals has increased with TRIPS: the probability of new product launch increased, as did quantities sold, conditional on price. While patents are also associated with higher prices, there is some evidence that prices in poorer countries have fallen, though not to the level of off-patent products." This study also found that, in LMICs, the price premium for patented products compared with generic products was lower subsequent to the implementation of the TRIPS Agreement and saw as a possible reason an increase in the use of price controls, governments' bargaining power or the threat of compulsory licensing (Kyle and Qian, 2014).

Cases of cost savings for governments and consumers have been reported following compulsory licensing, including, for example, those outlined in Table 4.1 and the case of ARVs in Brazil, outlined above.

Countries have issued government-use licences, mostly to import generic medicines from third-country suppliers. Additionally, "government use declarations" are used in the context of international procurement by UNICEF and other international bodies to enable the import of generic medicines, especially HIV medicines.²³⁶

It has been reported that, in some cases, governments face political and economic pressure not to issue compulsory licences. A 2017 WIPO study gathered reports of constraints faced by countries in making full use of TRIPS flexibilities, identifying reports of cases of political and economic pressure from some industrialized countries and/or pharmaceutical industries, which had intervened in the governments' decision-making process regarding issuance of compulsory licences. Such cases were

Box 4.22: Compulsory licences as a litigation tool

The grant of a preliminary compulsory licence by the German Federal Patent Court in August 2016, affirmed by the German Federal Court of Justice in July 2017,²³⁷ illustrates how a compulsory licence can be used as a tool in litigation between the parties in judicial proceedings. The particularity of this case is that it involved two originator pharmaceutical companies.

The case involved the two originator pharmaceutical companies, MSD and Shionogi, who both held European patents related to a medicine using the active ingredient raltegravir for the treatment of HIV. MSD received approval for its medicine Isentress (in which raltegravir is the active compound) in 2007, while the Shionogi patent (EP 1422218) was granted in 2012. MSD opposed that patent before the EPO, followed by unsuccessful licence negotiations between the companies. Shionogi brought an infringement action before the Regional Court of Düsseldorf in 2015. In defence, MSD submitted a request for the grant of a compulsory licence in preliminary proceedings to the Federal Patent Court in order to have legal certainty for the commercialization of its product while both the infringement case and the opposition before the EPO were pending.

The preliminary compulsory licence was granted under Sections 24 and 85 of the German Patent Act. The Court decided that the public interest required the grant of the compulsory licence (under German law, the public interest must call for the grant of a compulsory licence) because, otherwise, certain sensitive patient groups, including pregnant women, infants and children, remained without medication since no approved equivalent alternative products were on the market.

In October 2017, the EPO revoked the patent and confirmation or revocation of the preliminary decision on the compulsory licence was thus rendered obsolete.

In a subsequent case in September 2018, the Federal Patent Court (3 LiQ 1/18) refused the grant of a compulsory licence in an otherwise comparable constellation. In that case, the Court did not recognize a public interest in the grant of a compulsory licence because patients had access to essentially equivalent medicines, among other reasons.²³⁸

Table 4.1: Selected country experiences with compulsory licences and government-use licences

Disclaimer: This table is not exhaustive. While every effort has been made to verify this information against primary sources such as judicial decisions, Presidential Decrees or official WTO documents, this has not always been possible as not all information is in the public domain and no official comprehensive registry or database exists.

Country	Year	Medicine	Type of licence	Outcome	Indication (non-exhaustive)	Further information
Brazil (see section C.3(a)(ii), "Country experiences")	2001	NFV	CL	Not issued	HIV/AIDS	Licence considered – price discounts secured.
	2005	LPV/r	CL	Not issued	HIV/AIDS	
	2007	Efavirenz (EFV)	CL	Issued	HIV/AIDS	By 2012, the estimated savings for the Brazilian Government reached US\$ 236.8 million. ²³⁹ Local production impossible for two years after grant of CL, during which time generic imported from India. ²⁴⁰
Colombia (see Box 4.2)	2014	Imatinib mesylate	CL	Not issued	Leukaemia	Price control applied.
Ecuador	2010	Ritonavir (RTV)	CL	Issued	HIV/AIDS	Maximum price for 30 x 100 mg RTV tablets set at US\$ 29.40 from US\$ 289.99, 4 per cent royalty rate based on tiered royalty method (TRM) ²⁴¹ or 0.42 per cent of the US price. ²⁴²
	2013	Abacavir/lamivudine (ABC/3TC)	CL ²⁴³	Issued	HIV/AIDS	Maximum price for ABC set at US\$ 6.11 from US\$ 24.83. 5 per cent royalty rate based on TRM. ²⁴⁴ A 30–70 per cent saving on the cost of purchase has been reported by the Ecuadorian Ministry of Public Health. ²⁴⁵

(Continued)

Table 4.1: (Continued)

Country	Year	Medicine	Type of licence	Outcome	Indication (non-exhaustive)	Further information
	2014	Etoricoxib	CL	Issued	Rheumatoid arthritis	IEPI reports the grant of these CLs with a suggested saving potential of between 23 per cent and 99 per cent. Price of etoricoxib reported to reduce from US\$ 0.84 per tablet to US\$ 0.0084. ²⁴⁶
		Mycophenolic acid	CL	Issued	Kidney transplant	
		Sunitinib	CL	Issued	Kidney cancer	
		Certolizumab	CL	Issued	Rheumatoid arthritis; Crohn's disease	
Germany	1995	Interferon gamma	CL	Issued and cancelled in review procedure	Rheumatoid arthritis	The public interest did not call for the grant of a CL. Court found, <i>inter alia</i> , alternative treatments were available. ²⁴⁷
	2016	Raltegravir	CL	Issued	HIV/AIDS	Preliminary CL granted to a pharmaceutical company involved in an injunction procedure with another pharmaceutical company. ²⁴⁸ The patent was eventually invalidated (see Box 4.22).
	2018	Alirocumab	CL	Not issued	Cholesterol-lowering treatment	The public interest did not call for the grant of a CL. Court found, <i>inter alia</i> , alternative treatments were available. ²⁴⁹
India	2012	Sorafenib tosylate	CL	Issued	Liver and kidney cancer	CL required generic manufacturer to provide the medicine free to at least 600 patients per year and sell the medicine at no more than US \$176 per month (3 per cent of the price charged by the patent holder), with a 6 per cent royalty rate. ²⁵⁰
	2013	Dasatinib	CL	Not issued	Leukaemia	Patent expired in 2020.
	2015	Saxagliptin	CL	Not issued	Type 2 diabetes	Application rejected. ²⁵¹
Indonesia	2004	Nevirapine, lamivudine	GUL	Issued	HIV/AIDS	GUL in 2012 renews the GUL issued in 2004 and 2007, and, by adding six more medicines to the licence, covers all HIV/AIDS treatments. GULs are granted until the end of the patent period (in the case of TDF, November 2024), with a 0.5 per cent royalty rate. The Ministry of Health can sublicense to pharmaceutical companies. ²⁵²
	2007	EFV	GUL	Issued	HIV/AIDS	
	2012	Abacavir, didanosine, efavirenz, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lopinavir/ritonavir, tenofovir disoproxil fumarate (TDF), emtricitabine/tenofovir disoproxil fumarate	GUL	Issued	HIV/AIDS; Hepatitis B	
Italy	2005	Imipenem-cilastatin	CL	Issued	Antibiotic	CL granted as remedy to anti-competitive behaviour. ²⁵³
	2007	Finasteride	CL	Issued	Prostatic hyperplasia	CL granted as remedy to anti-competitive behaviour and to allow parallel export to neighbouring markets with expired patent protection. ²⁵⁴
Malaysia	2003	Zidovudine, zidovudine/lamivudine	CL	Issued	HIV/AIDS	Monthly costs of HIV treatment reduced from US\$ 315 to US\$ 58. 4 per cent royalty rate offered but refused. Increase in HIV treatment programme capacity from 1,500 to 4,000 by reducing the costs by 81 per cent. ²⁵⁵
	2017	Sofosbuvir	GUL	Issued	Hepatitis C	See Box 4.21.
Russia	2018	Lenalidomide	CL	Issued	Multiple myeloma	Price of generic version of lenalidomide was about 20 per cent below the price for which first patentee offered medicine on Russian market. ²⁵⁶
Spain	2015	Sofosbuvir	CL	Not issued	Hepatitis C	The Supreme Court ruled that granting of compulsory licences in cases of public interest is at the discretion of the government, and not an obligation imposed by the law. ²⁵⁷

Table 4.1: (Continued)

Country	Year	Medicine	Type of licence	Outcome	Indication (non-exhaustive)	Further information
Switzerland	2019	Pertuzumab	CL	Not issued	Breast cancer	Request, submitted by a nongovernmental organization, was refused by the government. ²⁵⁸
Thailand	2006	Efavirenz	GUL	Issued	HIV/AIDS	See Box 4.20.
	2007	Lopinavir/ritonavir	GUL	Issued	HIV/AIDS	See Box 4.20.
		Clopidogrel	GUL	Issued	Cardiovascular disease	73 baht per day reduced to 7 baht per day with a 0.5 per cent royalty rate. ²⁵⁹
	2008	Letrozole	GUL	Issued	Breast cancer	First example of CL for an NCD. Price per tablet reduced from US\$ 7.35 to US\$ 0.19 ('t Hoen, 2014) Saving of US\$ 88 million to US\$ 102 million per year reported (Mohara et al., 2012).
		Docetaxel	GUL	Issued	Breast and lung cancer	Saving of US\$ 46 million to US\$ 53 million reported (Mohara et al., 2012).
Erlotinib		GUL	Issued	Lung cancer	Saving of US\$ 6 million to US\$ 8 million per year reported (Mohara et al., 2012).	
United Kingdom	2015	T-DM1	CL	Not issued	Breast cancer	CL requested by patient group following plans to remove T-DM1 from list of cancer treatments paid for by UK Government (Kmietowicz, 2015a). Price discount negotiated. ²⁶⁰
	2019	Lumacaftor-ivacaftor	GU	Not issued	Cystic fibrosis	A Crown Use licence was requested by a patient group. ²⁶¹ The UK Government considered issuing a Crown Use licence (a type of government-use licence) after a pricing deal had not been reached with the originator following three years of negotiations (McConaghie, 2019). A few months after the government announced that it was considering a Crown Use licence, a confidential pricing deal was agreed (Parsons, 2019).

Note: CL = compulsory licence; GUL = government-use licence

reported in, for example, Brazil, Colombia, India, South Africa and Thailand.²⁶² The document concluded that anecdotal cases suggest that the fact that a compulsory licence has not been used does not necessarily mean that the policy objective has been compromised. The WIPO document noted that no credible conclusion can be drawn on the impact of full use of patent flexibilities on access to medicines, let alone the impact of constraints to such use, due to the lack of data sufficient to permit empirical impact analysis.

(iii) *The Special Compulsory Licensing System: an additional flexibility aimed at enhancing access to medicines*

Paragraph 6 of the Doha Declaration mandated the TRIPS Council to find a solution to the difficulties faced by

countries with insufficient or no manufacturing capacities in the pharmaceutical sector in making effective use of compulsory licensing. This resulted in the 2003 WTO General Council decision to establish the framework for special compulsory licences, which is an additional flexibility aimed at facilitating exports of medicines to these countries.

The Special Compulsory Licensing System (sometimes termed the Paragraph 6 System) initially took the form of a waiver of the obligations of an exporting member under Article 31(f) and 31(h) of the TRIPS Agreement regarding compulsory licences under certain conditions.²⁶³ In 2005, WTO members unanimously agreed to adopt the Protocol Amending the TRIPS Agreement (the Protocol)²⁶⁴ with the aim of providing a secure legal pathway for access to medicines. It has special significance as the first amendment agreed to

any of the WTO multilateral trade agreements since their adoption in 1994. The Protocol came into force in January 2017. This made the System a permanent part of the amended TRIPS Agreement (see Article 31*bis*, the Annex to the TRIPS Agreement and the Appendix).

The entry into force of the amended TRIPS Agreement was welcomed by WTO members because it “marks a significant step forward for the members of the WTO” (LDC Group), “provides legal certainty to our quest for affordable medicines” (African Group), and signals “to everyone that this Organization is not only about trade liberalization” and that “the System is part of a broader picture which includes other important aspects” (South Africa).²⁶⁵ To follow up on members’ calls for work to be launched on how to make effective use of special compulsory licences as a practical procurement tool for medicines, the WTO Secretariat organized capacity-building workshops at regional level that included sessions dedicated to the implementation and practical use of the System.²⁶⁶

Intended by WTO members to contribute to global efforts to strengthen the legal framework for access to medicines, the Special Compulsory Licensing System has also been endorsed by the 2008 WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI), as well as a number of UN Declarations.²⁶⁷

The System applies where a country needs to import medicines to deal with a public health problem, but a potential exporting country faces a legal impediment because Article 31(f) of the TRIPS Agreement limits supply under a compulsory licence predominantly to the domestic market. The special export licence under the System is free of this constraint, enabling and requiring the full production under a compulsory licence to be exported. Accordingly, the situation addressed by the System would arise only when a country wishes to obtain a particular pharmaceutical product, and:

- The product cannot be produced domestically at all, or in sufficient quantities, due to lack of capacity
- The preferred producer of the particular product (normally, the cheapest supply that best meets regulatory and quality requirements) is located in a country where a patent is in force on that product and needs a compulsory licence in that country to produce for export
- Export of the non-predominant part of the production in the country hosting the supplier would not satisfy the needs of the importing country.

The System therefore does not apply to most procurement scenarios, for example: when affordable

supplies are already available from countries where no patent is in force; when prices for the originator product can be reduced through negotiation to an affordable level without recourse to a compulsory licence; or when the originator company agrees to grant a voluntary licence to a generic producer.

The System includes measures to ensure that products reach their intended beneficiaries and are not diverted elsewhere. Such measures may include specific labelling or marking, special packaging and/or special colouring/shaping of the products, but these ways of distinguishing products should be feasible and should not have a significant impact on price. Industry experience with other forms of labelling and packaging for specific markets, for example, in cases of tiered pricing, donation and philanthropic procurement schemes,²⁶⁸ may provide practical examples for how to distinguish products without incurring significant costs.

Annex III provides more detailed information on the operation and use of the System.

Practical experiences

As at early 2020, one special export licence under the System has been exercised. In that instance, the licence was used by a Canadian company to ship medicines to Rwanda (see Box 4.23). Ghana reportedly considered using the System in 2005 when it declared an emergency situation with regard to HIV/AIDS and granted a government-use authorization order to import generic HIV/AIDS medicines (although a declaration of emergency is not a requirement for using the System).²⁶⁹ Imports were initially intended to be sourced from Canada, where the products were patented, but Ghana later chose to import the products from generic manufacturers in India, where no patent applied. Another potential use²⁷⁰ concerned an Indian company’s applications, filed in September 2007 with the Indian Patent Office, to manufacture and export to Nepal several anti-cancer pharmaceuticals patented in India, including erlotinib. Reportedly, the applicant later withdrew the applications. As an LDC, Nepal was automatically entitled to use the System, but it had not notified the WTO that it wished to import these medicines, which is a prerequisite for use of the System.

TRIPS Council assessment of the operation of the System

The TRIPS Council reviews the System each year and reports to the WTO General Council on how the System has been implemented and used, its operational context, and the status of acceptances of the TRIPS Amendment by WTO members that are yet to complete their domestic

Box 4.23: Case study on supply of ARVs to Rwanda

In 2004, Médecins Sans Frontières (MSF) approached a Canadian company to produce a triple-combination ARV (zidovudine, lamivudine and nevirapine). MSF initiated this move in the absence of any specific request from an importing country. The company obtained marketing approval in Canada in 2006, less than six months after the date of its application. The three medicines combined in the product were each covered by a separate patent owned by a separate company. In July 2007, the company sought, without success, voluntary licences from the three patent holders.

In July 2007, Rwanda sent the WTO a brief notification of its intention to import 260,000 packs of the triple-combination ARV, reserving the right to modify the estimated quantity. It said it would not allow patent holders to enforce any patents on the product that may have been granted in its territory. As an LDC, Rwanda was not obliged to state anything else.²⁷¹ In September 2007, under the System, the company applied for a compulsory licence in Canada that would allow it to export a set volume over a two-year period. The Canadian Government granted the compulsory licence and notified the WTO in October that it was using the System as an exporting country.²⁷²

Canada reported that, in October 2007, the Rwandan Government issued a public tender for this triple-combination ARV.²⁷³ The Canadian company had originally offered its ARV at the no-profit price of US\$ 0.39 per tablet. There were indications that at least four Indian generic manufacturers could supply the product at a lower price. Canada reported that, if Rwanda had procured the ARVs from these manufacturers, it would not have needed to use the System at all, since the products were not patented in India. However, during the tender process, the Canadian company halved its price to US\$ 0.195 per tablet. In May 2008, the company announced that it had won the tender.

In line with the terms of Canada's Access to Medicines Regime (CAMR) and the System itself, the tablets shipped to Rwanda were distinguished from the version manufactured for the Canadian market by the mark "XCL" and white colouring, instead of the standard blue. The packaging bore an export tracking number issued by the Canadian Government. Details of the product, its distinguishing characteristics and the shipment were posted online. Two shipments reached Rwanda in September 2008 and September 2009.²⁷⁴

acceptance procedures.²⁷⁵ While no conclusions have been reached as a result of these discussions, various WTO members have voiced a range of views, including the following diverse observations on whether the System is fulfilling its intended function:

- As a consequence of the System only being used once, some WTO members have expressed the view that the System is overly complex and have questioned its practical applicability.²⁷⁶ It is essential to clarify whether constraints on its use were built into the System, thus necessitating its reform, or whether such constraints were a consequence of how individual countries chose to implement it.
- Potential users of the System may be deterred by concerns about political or trade ramifications associated with the use of compulsory licensing.²⁷⁷
- The CAMR was successfully utilized, and only a very small portion of the three-year time period was taken up with procedures associated with the System. Much of the time that elapsed between the regulatory review of the medicine in question and the actual shipments was attributable to other factors.²⁷⁸
- The limited use of the System is not an appropriate measure of its success, as no delegation demonstrated evidence of obstacles to its use when such use was required.²⁷⁹ A single case demonstrated that the System could work when necessary, and that it could play a

supportive role in the wider effort to improve access to essential medicines, given that alternative ways of procuring the needed medicines are often available.²⁸⁰

- The System is not a panacea to solve all public-health-related problems.²⁸¹ Rather, it is part of a broader picture that includes other important aspects that have an impact on innovation and access, such as infrastructure, tariffs, innovative financing mechanisms, partnerships and cooperation (including at the regional level) and regulatory frameworks.²⁸²
- Patent protection for pharmaceutical products in India could make it more difficult in the future to procure generic versions of new medicines. Under such circumstances, the System might assume a greater significance.²⁸³

In the TRIPS Council, discussions are ongoing on how to make effective use of the System and to overcome any constraints on its use.²⁸⁴ To facilitate these discussions, the WTO Secretariat's 2016 Note on Technical Cooperation in the TRIPS Area summarized the key issues and questions for further consideration.²⁸⁵ These included the need to put the System into context, including as regards procurement and regulation of medicines, to raise awareness about it, including among procurement officers, to consider its economic viability for potential generic suppliers, to design domestic implementation measures in a manner supportive of the use of the System, etc.

Scope for potential future use of the System

The vast majority of countries that are traditional exporters of medicines have introduced legislation to enable export under the System. It is expected that this will support any future use.²⁸⁶ There has been negligible notification of demand from potential beneficiaries who are faced with this particular scenario. No developing country has notified the WTO that it has a general intention to use the System. Countries are entitled to notify their expected needs for medicines at an early stage in the procurement planning process, without having to give a commitment to adhere to the quantities notified or to commit to proceed with imports under the System should preferable alternatives arise, even at a late stage in the procurement process. Such early notification by one or more importing countries is intended to increase the practical likelihood of potential exporters responding to the opportunity to use the System.

One key question is whether, and, if so, in what circumstances, the use of the System could have been appropriate but did not occur. A further question concerns the extent to which affordable medicines are already available without the need for compulsory licences for export. Reported procurement experiences suggest that many medicines were already available as generic exports from countries where no patent was in force. Where generic medicines are available from non-patented sources, the System does not need to be used. This situation may change in future as the progressive impact of changes to pharmaceutical patentability in key export countries such as India makes it less likely that newer generations of medicines will be so readily available in generic versions for export. In addition, the availability of the System provides a legally secure basis for effective use of compulsory licensing for countries with either no or limited production capacity, thus strengthening their hand in negotiations on price without necessarily leading to the grant of a compulsory licence. Past experience with procurement processes, such as in Brazil regarding the ARV medicine *nelfinavir* in 2001 (see section C.3(a)(ii) "Country experiences"), shows how the mere threat of the use of compulsory licensing can succeed in inducing lower prices. Finally, the limited role of the System thus far may also be partly due to the fact that many countries procure needed medicines through international procurement programmes, which may have other means of leveraging lower prices. Examples of such programmes include those run by PEPFAR, the CHAI, the Global Fund, UNICEF and Unitaid.

Debate centres on the necessity to establish an adequate commercial basis for potential suppliers under the System, in order to respond to needs that have been signalled in notifications to the WTO. The System expressly recognizes the need for economies of scale in the context of its provisions on regional trade agreements, also referring to the possibility for parties to such agreements to make joint notifications.

The special export licence is one legal pathway that can be followed, but, as for any compulsory licence, it does not in itself make the production of a medicine economically viable. Sufficient scale and predictability of demand are prerequisites for making it practically and commercially viable for companies to undertake the regulatory, industrial and commercial steps required to produce and export a medicine under such a licence. Regional approaches to procurement and joint notifications by countries with similar needs for accessible medicines offer pathways to aggregating demand under the System, thus enabling an effective response to the needs identified.²⁸⁷

(b) Voluntary licensing agreements

An owner of a patent can allow the use of IP voluntarily with third parties through licensing agreements. A licence is a contract in which the patent holder allows another party to use the IP, either in return for a payment of royalties (or some other consideration) or free of charge, for a certain field of use, in a certain territory (which may be for the life of the patent). The ability of voluntary licensing agreements to reflect the interests of both parties depends on the knowledge and experience of negotiating such licence agreements. In terms of public health, the ability to negotiate licences which have terms and conditions that consider public health needs is crucial. In the framework of their corporate responsibility programmes, research-based pharmaceutical companies, in the years since the adoption of the Doha Declaration, have increasingly used licence agreements to allow generic producers to manufacture and distribute generic versions of their products within a defined geographical area.

In some disease areas, originator companies have agreed to non-exclusive licences with manufacturers to produce and sell generic versions of patent-protected products, sometimes within a limited number of countries. These agreements are often referred to as "voluntary" licensing agreements, as opposed to compulsory licences (Beyer, 2012). For an overview of current licensing agreements, see the MedsPaL database maintained by the Medicines Patent Pool (see Box 2.11).

Companies began to use this type of voluntary licensing agreement to a greater extent after the adoption of the Doha Declaration. Initially, voluntary licences were used only for HIV medicines, the scope and territory were rather limited and some of the agreements were triggered by interventions from third parties. Today, most companies that own IP covering products for the treatment of HIV/AIDS have signed licence or immunity-from-suit agreements with various generic producers, or have issued non-assert declarations on their HIV/AIDS products.

The trend to license HIV/AIDS products to generic companies increased further with the creation of the Medicines Patent Pool in 2010 (see Box 4.24).

Box 4.24: The Medicines Patent Pool

The Medicines Patent Pool (MPP) was established in 2010 by Unitaid as a public health patent pool.²⁸⁸ The MPP negotiates IP licence agreements with patent-holding pharmaceutical companies, wherein the patent holder allows the MPP to grant sublicences to manufacturers in LMICs to make and sell generic versions in a certain territory. The MPP's mandate was initially focused on HIV, then expanded to include TB and hepatitis C, and, in 2018, was expanded to include patented essential medicines more broadly.²⁸⁹

As of December 2019, the MPP has signed IP licence agreements with eight IP-holder originator companies and two universities, covering 13 HIV medicines, 3 hepatitis C medicines, 1 investigational TB treatment, and 1 platform technology. Through these agreements, the MPP has signed sublicences with 22 generic manufacturers and one not-for-profit medicine developer.²⁹⁰

The MPP has pioneered the development of a public-health-oriented approach to voluntary licensing. MPP licence agreements are transparent (i.e. available in full on the MPP's website), include quality requirements for generic versions, are non-exclusive to enable competition, include disclosure of company patent information and include waivers for data exclusivity (see Chapter II, section A.6(f)).

The geographical coverage for MPP licences ranges from 92 to 131 countries. Nearly all key HIV medicines are now covered in MPP licences, and MPP licences have allowed estimated savings of US\$ 1.06 billion over the period 2012–2018, with MPP-facilitated generic products providing 22 million patient-years of treatment in this period.²⁹¹ Between 87 per cent and 91 per cent of people living with HIV in developing countries are covered by MPP adult licences, depending on the medicine.²⁹²

In addition to negotiating and administering licensing agreements, the MPP maintains the MedsPaL database (see Box 2.11), which provides information on patent status for HIV, TB and hepatitis C medicines, as well as many medicines on the EML.²⁹³ The MPP also collaborates with the WHO to prepare joint projections on the use of ARVs in LMICs and is a partner in GAP-f (see section B.6).²⁹⁴

In some cases, voluntary licences have been criticized for their limited geographical scope, which excludes some LMICs – in most cases, they operate in upper-middle income countries. For example, the licence agreement signed by the MPP with Gilead Sciences in 2011 led to a vigorous debate among public health groups about the added value of this agreement and role and mandate of the MPP in that regard.²⁹⁵

Voluntary licences have been agreed outside the MPP mechanism, including licences for key hepatitis C medicines (see section B.5). In some of those cases, it is difficult to assess licence agreements as the terms and conditions are not disclosed. In general, in voluntary licensing agreements, the licensors allow others to serve the high-volume, low-profit markets in poor countries with a high disease burden.

The Access to Medicines Foundation uses licence agreements as one of the main indicators in their ranking of pharmaceutical companies (see Box 4.25).

(c) **Socially responsible licensing policies and management of IP developed at public institutions**

Socially responsible licensing (SRL), also termed global access licensing, describes an approach to IP management used by some public-interest research

institutions and/or public research funders. In SRL, the institution/funder adopts a policy that any licensing agreements on IP resulting from its research must include contractual requirements ensuring that the end product is accessible in resource-poor settings. For example, if a university discovered a promising compound and licensed it to a private entity, it would include in the contract various clauses aimed at ensuring equitable access. Such clauses could, for example, include a requirement to not assert the patent rights in LMICs, a requirement to sell at lower prices in LMICs or a requirement to develop an access plan.

The SRL approach has been recommended by the CEWG (see Chapter III, section C.4) and other entities. A number of research institutions and research funders have implemented SRL-type policies (Nguyen et al., 2018; Guebert, 2014; Stevens and Effort, 2008). Examples include the University of California at Berkeley²⁹⁶ and the University of Manchester in the United Kingdom.²⁹⁷ In the United States, AUTM (formerly known as the Association of University Technology Managers) has recommended that technology transfer offices (TTOs) ensure that licensing agreements covering medical innovations account for neglected individuals or communities.²⁹⁸ The Bill and Melinda Gates Foundation requires projects to have predefined global access strategies in place, and reserves its right to require a humanitarian licence in order to achieve global access.²⁹⁹ The Wellcome Trust also places similar requirements on recipients of its research grants.³⁰⁰

Although some universities have endorsed global access policies premised on SRL, such as the AUTM policies, in practice, social responsibility clauses in university IP contracts remain rare³⁰¹ (Guebert and Bubela, 2014).

Discussions around SRL grew following a debate concerning patents held by Yale University over stavudine, a substance that had been synthesized in 1966 and discovered to have reverse transcriptase inhibitor properties by researchers at Yale in the early 1990s. This research was supported by federal grants. The University had exclusively licensed production, marketing and distribution to a company that sponsored Phase III clinical trials of the medicine.³⁰² Although the University had not applied for patents in most developing countries, stavudine was patented in South Africa (Patent ZA8707171).³⁰³ When MSF began providing ARV treatment in South Africa, the medicine was being sold at prices that were 34 times higher than generic versions available in other countries.³⁰⁴ In December 2000, MSF approached the South African division of the licensee company for permission to import generic stavudine, but was advised to approach the patent holder, Yale University. Under pressure from civil society, the student body, research communities and the inventor of stavudine (in March 2001), the licence agreement was revised and the company reached an immunity-from-suit agreement with a generic medicines company in South Africa, allowing the marketing of stavudine in South Africa and other African countries (’t Hoen, 2009; Beyer, 2012).

(d) March-in rights

In the US, the Bayh-Dole Act (1980) gives the federal government “march-in rights” over patents on technologies developed by a small business firm or non-profit organization through federal funding, whereby the government may require, on certain grounds and upon reasonable terms, the patent holder to grant a

“nonexclusive, partially exclusive, or exclusive license” in any field of use to a “responsible applicant or applicants”. It may grant such a licence directly if the patent holder refuses.³⁰⁵ Grounds for asserting such “march-in rights” include, among others, that the invention is not being used for a practical application or it is necessary to alleviate unsatisfied health or safety needs.³⁰⁶ “March-in rights” can also be included in licensing agreements as part of an SRL approach to IP management in public-sector research institutions (Stevens and Effort, 2008).

(e) Open source licensing

Inspired by the open source software movement, open source licensing is the practice of licensing patents, for royalty-free use by third-party users for a specific purpose on the condition that any improvements that are developed are licensed on the same terms. While providing patents free of charge has been presented as a way to exercise patent rights while encouraging collaboration, cutting costs and catalyzing innovation (Ziegler et al., 2014), specific open source licensing schemes have had limited success in practice. CAMBIA, a private non-profit research institute based in Australia, set up the Biological Innovation for Open Society (BiOS) project to develop new tools for biological innovation using an open source licensing model for its patent for transferring genes in plants. However, the online community set up through BiOS ended in 2008 with no significant improvements to the tool and no compliance with the licence terms.³⁰⁷

(f) Exhaustion of rights and parallel imports

Parallel imports refer to genuine products first put on the market in another country and imported through a channel parallel to the one authorized by the right holder. Parallel imports are not counterfeit, and the right holder has had

Box 4.25: Access to Medicine Index

The Access to Medicine Foundation (AMF) is an international non-profit organization dedicated to improving access to medicines. It publishes the Access to Medicine Index, which ranks pharmaceutical companies according to their strategic and technical efforts to enhance global access to medicines. The aim is to develop a transparent means by which pharmaceutical companies can assess, monitor and improve their own performance and their public and investment profiles, while building a platform on which all stakeholders can share best practices in the area of global access to medicine.

The Index ranks 20 pharmaceutical companies on their efforts to provide access to medicines, vaccines and diagnostic tests to people living in 106 countries. The Index for 2018 covered 77 priority diseases, conditions and pathogens, including neglected tropical diseases, the ten most important communicable diseases and the ten most important non-communicable diseases, in terms of their health burden on the countries included in the Index, as well as maternal health and neonatal infections. Rankings are based on a large number of indicators that measure activities across areas, such as R&D, patent policy, pricing and philanthropy. The Index provides reports on each company’s leading practices and the changes the company has made since publication of the previous Index report. The reports also suggest areas for improvement.³⁰⁸

the opportunity to receive payment for the first sale. They are sometimes referred to as “grey market goods”.

“Exhaustion” is a legal doctrine according to which the IPR holder cannot prevent the further distribution or resale of goods after consenting to the first sale. In such a situation, the right holder is considered to have “exhausted” its rights over these goods (the exhaustion doctrine is also known as the “first-sale doctrine”). The exhaustion doctrine is applicable to patents and other IPRs, including trademarks and copyright. It can play a role in enabling access to medicines, as the decision by a country to adopt international, regional or national exhaustion is an important factor in determining whether medical products can be imported (or reimported) from other countries where prices are lower. Other important factors impacting on parallel importation are the rules regarding the regulatory approval regime and private law governing the contract between the manufacturer and its distributors. In case of abuse of IPRs to prevent parallel importation where this would otherwise be permissible, competition law can also serve as a useful corrective tool.

Countries have employed several options in regulating the exhaustion regime so as to best serve their domestic policy objectives. In many cases, different exhaustion regimes apply to patents, trademarks and copyright. However, WTO members are required to apply exhaustion regimes in a non-discriminatory way with regard to the nationality of the right holder.

The following section considers exhaustion in relation to patents in the pharmaceutical sector. In a 2014 survey by WIPO, 76 member states indicated that their applicable laws provided exhaustion of patent rights, among which there are four countries where this exception is provided under case law.³⁰⁹

(i) International exhaustion

Some countries apply a regime of “international exhaustion”, meaning that IPRs over goods are exhausted after the first sale by or with the consent of a right holder located anywhere in the world. In a 2014 survey by WIPO, 19 member states indicated that they have adopted a regime of international exhaustion of patent rights in their domestic laws. Argentina, Armenia, Chile, China, Costa Rica, the Dominican Republic, Kenya, Mauritius, Pakistan and Viet Nam, as well as the Andean Community, figure among these 19.³¹⁰ An international exhaustion regime may facilitate access to medicines as the right holder cannot prevent the further distribution or resale of goods after consenting to the first sale. On the other hand, a regime of international exhaustion may deter companies from engaging in differential pricing (see Chapter II, section C).

A number of countries do not specify rules on exhaustion in their IP laws; rather, they leave it to the courts and administrative practice. In 2017, the Supreme Court of the United States adopted a rule of international exhaustion for patent rights, finding that the first-sale doctrine applies to patent law.³¹¹ This rule could support the parallel importation of pharmaceutical products in the United States. This will, however, depend on other factors, including contractual arrangements and health regulations that require these products to meet several conditions before they can be parallel imported.

(ii) National exhaustion

Other countries apply the exhaustion doctrine with respect to IPRs, but only to the extent that the first sale takes place within its own territory. This is called “national exhaustion”. Under this regime, the rights of the IP owner are exhausted, but only with respect to goods that have been put on the market in the country with the right holder’s consent, thus enabling the right holder to prevent parallel importation from third-country sources. In a 2014 survey by WIPO, 27 member states indicated that they that have opted for this type of exhaustion for patents in their domestic laws. These countries include, for example, Albania, Belarus, Bhutan, Bosnia and Herzegovina, Brazil, Croatia, El Salvador, The Gambia, Madagascar, the Republic of Moldova, Morocco, the Russian Federation, São Tome and Príncipe, Serbia, Sudan, Tajikistan, Tanzania, Turkey and Uganda.³¹²

(iii) Regional exhaustion

A third option is “regional exhaustion”. The first sale of goods in the region by the right holder (or a sale made with his or her consent) exhausts any IPRs over those products – not only domestically but within the entire region – and therefore, parallel imports within the region cannot be opposed, based on IPRs.³¹³ In a 2014 survey by WIPO, 22 member states indicated that they had opted for this type of exhaustion regime.³¹⁴ Under such a regime, the right holder can still use IPRs to prevent goods from being imported from outside the region in question.

(iv) Policy options for exhaustion regimes

Article 6 of the TRIPS Agreement provides that “nothing in this Agreement shall be used to address the issue of exhaustion of intellectual property rights” for the purposes of WTO dispute settlement, as long as the doctrine is applied in a way that does not discriminate according to the nationality of the right holder. The Doha Declaration clarified that the effect of this provision is to leave each WTO member free to establish its own regime for exhaustion without challenge, provided that right holders

from all WTO members are not discriminated against. This clarification is reflected in the different choices that members throughout the world have made with respect to exhaustion.

Some countries have adopted mixed exhaustion regimes. Their laws generally apply a particular exhaustion regime, but for specific cases they apply another exhaustion regime. In Switzerland, while the exhaustion regime in general depends on the place where the product has first been put onto the market, for medicines, a national exhaustion regime applies.³¹⁵ Rwanda adopted the Law on the Protection of Intellectual Property in 2009 (Law No. 31/2009) which provides for a system of national exhaustion of patent rights with the possibility of international exhaustion for specific products. Article 40 empowers the Minister to declare patent rights exhausted on the advice of a government agency or upon request of an interested party. The Law lists several grounds on which such an authorization can be given and provides that the authorization can be revoked if the parallel importer fails to fulfil the purpose of the Minister's declaration, or if the conditions that gave rise to the declaration cease to exist.

The choice of exhaustion regime is only one of the factors determining whether parallel imports can take place. Another important aspect is the contract concluded between the right holder and the distributor. For example, if such a contract prohibits the distributor from re-exporting the goods concerned, the right holder could argue that engaging in parallel importing constitutes an act violating the distributor's contractual obligations, independently of whether his or her IPRs are exhausted or not. Some FTAs explicitly preserve for the patent owner the right to contractually limit parallel imports. In such situations, competition law can play an important role as a potential correcting factor. For example, Switzerland applies international exhaustion in the field of trademarks. In a competition law case in that country, a Swiss company was shown to have continuously applied a contractual clause until 2006 as part of a licence to an Austria-based firm. This clause prohibited the licensee from exporting to Switzerland the products it had manufactured in Austria under licence. In 2009, the Swiss Competition Commission imposed a fine on the company, as it considered that such a clause constituted a vertical agreement that would significantly affect competition on the Swiss market and it, therefore, struck down the clause.³¹⁶ This decision was confirmed by the Swiss Administrative Court in December 2013³¹⁷ and the Swiss Federal Court in June 2016.³¹⁸

Another important factor that determines whether parallel imports can take place is the set of health regulations for market approval of medicines. Any country may prohibit parallel imports of different versions of the same

pharmaceutical product if those versions lack marketing approval in the country of importation – even if the country embraces an international exhaustion regime.

(g) Patent term extension and supplementary protection certificates

National laws set out the period of time during which the patent can remain in force (the “patent term”) (see Chapter II, section B.1 (b)(iii)). Applicable law may provide for longer periods of exclusivity for pharmaceutical products through: (i) statutory extension of the patent term; or (ii) application of additional mechanisms, such as supplementary protection certificates (SPCs) in the European Union. Extensions may be given to compensate for time taken to obtain regulatory approval. In the United States, an extension may include time taken in clinical development and a PTA may compensate for a delay in patent grant. Unlike products in most other fields of technology, pharmaceutical products must undergo regulatory review in order to ensure safety and efficacy. The regulatory review process can considerably curtail the patent protection period that holders of pharmaceutical patents would otherwise enjoy.

Patent term extensions and SPCs are legally distinct tools but have a similar effect. A 2019 WIPO survey, to which 26 countries responded, identified 24 countries as providing patent term extensions or SPCs.³¹⁹

Many different views have been expressed about the impact of patent term extensions or SPCs on public health. Some argue that such extensions do not incentivize R&D that addresses unmet health needs and hinder access to medicines because they delay the market entry of generic medicines.³²⁰ Others are of the view that extensions are favourable from a public health perspective because they may support medical innovation and thus improve public health in the long run.³²¹

(i) *Statutory mechanisms to extend the term of a patent*

A number of WTO members, such as Australia, Colombia, Costa Rica, the Dominican Republic, Israel, Japan, the Republic of Korea and the United States, make available an extension of the patent term beyond the minimum of 20 years required by the TRIPS Agreement.³²² In some countries, administrative delays in the grant process or the patent prosecution can also result in extensions to the term of patent protection to compensate the right holder for any unreasonable curtailment of the patent term. For example, the United States provides for a PTA in the case that the USPTO does not grant a patent within three years of patent filing (PTAs and patent term extensions are different

instruments).³²³ Patent term extensions for delays regarding the grant of the patent and also for regulatory delays are a common feature in many FTAs.³²⁴

(ii) Supplementary protection certificates

In the European Union, supplementary protection certificates (SPCs) are available to holders of patents on pharmaceutical products under Regulation (EC) No 469/2009.³²⁵ The aim of the Regulation is to compensate for the lag between patent application and the grant of regulatory approval for pharmaceuticals. SPCs are available for products that satisfy particular requirements, such as being protected by a valid patent and being in possession of marketing authorization in the particular member state, and confer the same rights as conferred by the basic patent and shall be subject to the same limitations and the same obligations.³²⁶ The Court of Justice of the European Union (CJEU) confirmed, *inter alia*, that “it is not the purpose of the SPC to extend the protection conferred by that patent beyond the invention which the patent covers. [...] [T]o accept that an SPC could grant [...] protection which goes beyond [...] the invention it covers, would be contrary to the requirement to balance the interests of the pharmaceutical industry and those of public health”.³²⁷ Following this judgment, the Court in the United Kingdom revoked the SPC.³²⁸

SPCs are national rights and granted by an EU member state (i.e. by a national patent office and not by an EU institution). To consider all interests at stake, including public health, SPCs are limited to a duration of five years.³²⁹ SPCs aim at securing a combined maximum period of 15 years of protection under both the patent and the SPC from the time the medicinal product in question first obtains market authorization.³³⁰ As a result of combining both periods, SPCs are often granted for a period shorter than five years.

A Dutch study found that, while these measures have proved compensatory by providing a return on investment, it appears that they have a limited value in incentivizing investment into R&D (de Jongh et al., 2018). However, a study commissioned by the European Commission found that a longer effective patent protection period stimulates spending on pharmaceutical R&D, although it delays reduced prices following the entry of generics into the market (Copenhagen Economics, 2018).

While Article 3(b) and (d) of Regulation (EC) No 469/2009 states that an SPC can only be granted when a product is subject to the first valid authorization to place the product on the market, a 2012 ruling of the CJEU suggests that an SPC can be granted to the new therapeutic use of the already authorized active ingredient. The product subject to the SPC, in this scenario, is the therapeutic use and not the active ingredient (Schell, 2013). Since 2007, under Regulation (EC) No 1901/206 (that amended, among other things, the earlier SPC Regulation)³³¹, the European Union has allowed for an additional six-month protection under an SPC in return for the completion of clinical studies of a product's effectiveness and safety in children.

An analysis by Medicines for Europe (an association representing European generic and biosimilar medicines manufacturers) suggested that SPCs in the European Union expired later than corresponding dates of SPC-like instruments in Canada, China, India, the Republic of Korea and the United States, in the majority of cases.³³² Some examples of the extension of market protection offered by SPCs for essential medicines are shown in Table 4.2.

In 2019, the European Union introduced an exception (the so-called “SPC manufacturing waiver for export”) to allow EU generic firms to manufacture SPC-protected pharmaceuticals for export to non-EU markets where no

Table 4.2: Comparison of expected patent expiry dates and dates of SPC expiry in France, for selected medicines on the WHO EML

Medicine	Disease treated*	Expected compound patent expiry	Expiry of SPC protection in France**	SPC number in France
Abacavir/lamivudine	HIV	2016	2019	FR05C0022
Atazanavir	HIV	2017	2019	FR05C0030
Raltegravir	HIV	2022	2023	FR08C0026
Tenofovir disoproxil/ emtricitabine	HIV	2017	2020	FR05C0032
Sofosbuvir	Hepatitis C	2028	2029	FR14C0082
Trastuzumab (powder for injection)	Breast cancer	2012	2014	FR04C0007
Imatinib mesylate	Leukaemia	2013	2016	FR02C0012

Notes: * May also be approved for other indications. ** Patent and SPC expiry dates are cited from Institut national de la propriété industrielle Patent Database Search. Patent expiry assumed as 20 years after filing, available at: <https://bases-brevets.inpi.fr/en/home.html>.

patent exists.³³³ Another exception allows generic firms to make and store products in the six months before expiry of the SPC for the purpose of entering the market of any member state upon expiry of the corresponding certificate (EU day-one entry).³³⁴ While these waivers are aimed at promoting competitiveness of the European Union's generic industry, contributing to wider supply of pharmaceutical products,³³⁵ the originator industry has expressed concern it could result in increased litigation and suggested it could trigger investments in secondary patents (Wingrove, 2019).

SPCs can only be granted to products that are subject to the administrative authorization procedure as set out in Directive 2001/83/EC (Medicinal Products Directive). Medical devices are authorized by a certification mark indicating the health and safety standard (CE mark) and can therefore not be awarded an SPC. Some patent offices have nevertheless considered CE certification as equivalent to marketing authorization issued in accordance with the Medicinal Products Directive, while other patent offices have ruled that SPC protection is not justified for CE-certified devices. In a case referred to the CJEU by the German Federal Patent Court, the applicant applied for an SPC for paclitaxel on the basis of the CE certification for a paclitaxel-eluting stent. The CJEU ruled that it is not possible to obtain SPC protection for an active ingredient contained in a medical device/medicine combination on the basis of CE-mark approval of the medical device/medicine combination.³³⁶

(h) Enforcement of IP

An overview of IP enforcement standards is set out in Chapter II, section B.1(f). This section looks at issues of enforcement that are specifically linked to access to medicines.

The TRIPS Agreement (Article 41) obliges all members to guarantee, under their law, access to effective, affordable, fair, equitable and transparent procedures to enable IPR holders to enforce their rights (see Chapter II, section B.1(f)). The application of these procedures must avoid the creation of barriers to legitimate trade and must provide for safeguards against their abuse. The TRIPS Agreement requires WTO members to provide for: (1) civil (or administrative) procedures and remedies on the merits of a case; (2) provisional measures; (3) border measures; and (4) criminal procedures. In the area of civil procedures, the main remedies foreseen in the case of IP infringement include injunctions (Article 44), damages (Article 45) and other remedies, such as the destruction or disposal outside the channels of commerce of IP-infringing goods and of materials and implements primarily used for the manufacture of such goods (Article 46). These remedies must be

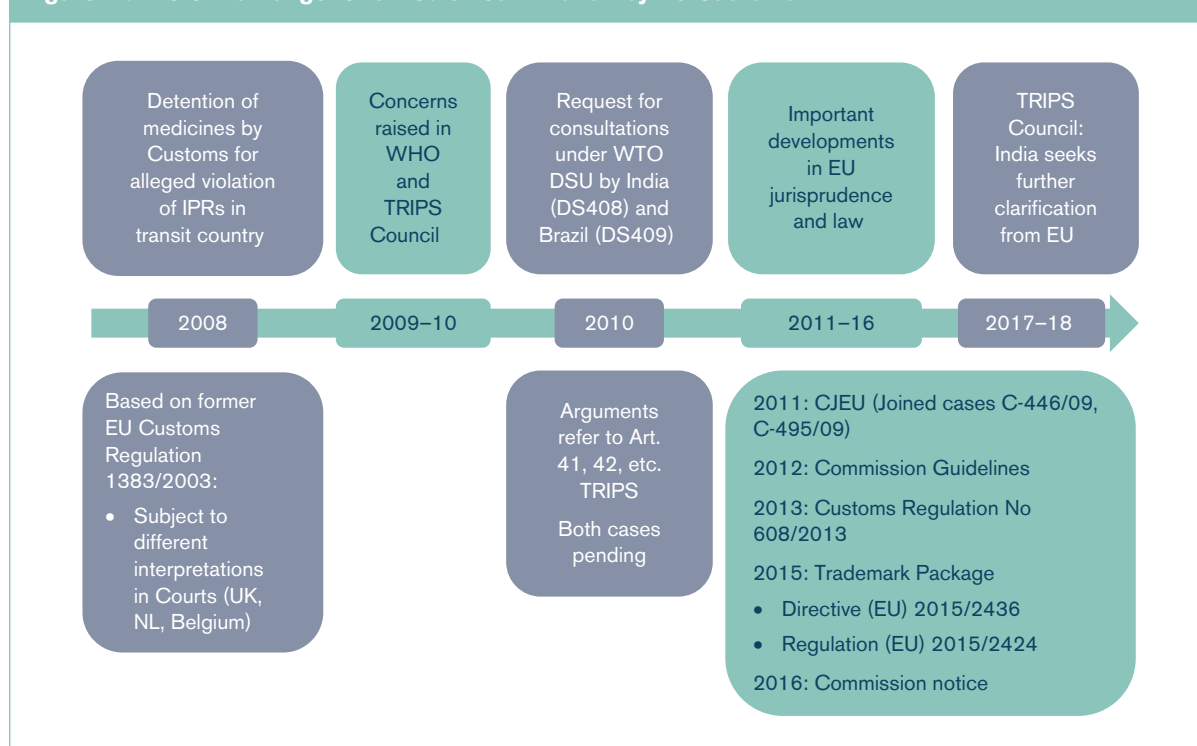
available for all categories of IP covered by the TRIPS Agreement, including patents, undisclosed information (such as test data), trademarks and copyright. WTO members have the option to entitle an IPR holder to a right of information against an infringer concerning involved other persons and about distribution channels (Article 47).³³⁷

In the case *eBay Inc. v. MercExchange L.L.C. (eBay)*, the Supreme Court of the United States addressed the question of when permanent injunctions should be issued against patent infringements.³³⁸ Prior to *eBay*, permanent injunctions – prohibiting the infringer from continuing to engage in the infringing activity – were issued as remedy in nearly all patent cases where infringement was found to occur. In *eBay*, the Supreme Court rejected this “general rule” and ruled that issuance of a permanent injunction must meet the conditions set out in a four-factor test: “[a] plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction”. Since *eBay*, there have been numerous cases in which US courts grant monetary remedies in lieu of permanent injunction, that is, allowing the infringer to continue use of the patented invention without authorization by the patent holder. These remedies have often taken the form of running royalties set by the court.³³⁹ Such cases have concerned both non-medical and medical patents. In some cases concerning medical patents, the “public interest” part of the four-part test has been emphasized in denying permanent injunction on infringing patents (e.g. cases concerning cardiovascular implants,³⁴⁰ contraception systems³⁴¹ and contact lenses³⁴²).

In the area of cross-border trade in medical products, public health and free trade interests intersect. The common objective is to ensure that counterfeit medical products do not come to markets, while free trade in legitimate medical products, including generic medicines, is not subject to unnecessary legal barriers to prevent movements of medicines between countries. This common objective is reflected as a general principle in the enforcement section of the TRIPS Agreement (Article 41.1).

The TRIPS Agreement requires members to adopt procedures to enable a right holder who has valid grounds for suspecting that the importation of counterfeit trademark or pirated copyright goods may take place to lodge an application in writing with competent authorities, administrative or judicial, for the suspension by the customs authorities of the release into free circulation of such goods.³⁴³ However, there shall be no obligation to apply such procedures to goods in transit.³⁴⁴

Figure 4.8: Detention of generic medicines in transit by EU Customs



Source: WTO Secretariat.

The detention of generic medicines transiting EU territory and subsequent developments in multilateral organizations, as well as in EU law and jurisprudence, represent an interesting case study (see Figure 4.8). In 2008, EU Customs detained a number of consignments of generic medicines in transit, mostly originating from India and destined for developing countries in Latin America and Africa. While there was no suggestion that the medicines were infringing any IPRs in the country of origin nor in the countries of destination, detention by Customs took place, in the vast majority of cases, on grounds of alleged infringement of patent rights in the transit country. This action was based on former EU Customs Regulation (EC) No 1383/2003, which was subject to different interpretations in the courts of EU member states. The consignments concerned were subsequently released.

In May 2010, India and Brazil initiated dispute settlement proceedings, claiming violation of the GATT obligation to allow freedom of transit, as well as various TRIPS provisions on patent rights and enforcement, and arguing, in particular, that IPR enforcement should not affect legitimate trade in generic medicines.³⁴⁵ Both cases are pending. There has been no request for the establishment of a dispute settlement panel.

In 2013, the European Union replaced Regulation (EC) No 1383/2003 with Regulation (EU) No 608/2013. Recital 11 of Regulation (EU) No 608/2013 clarifies that Customs, when assessing a risk of IPR infringement of medicines in transit, should consider whether there is a

substantial likelihood of diversion of these medicines onto the EU market.³⁴⁶

In 2015, the European Union adopted new trademark legislation consisting of Directive (EU) No 2015/2436³⁴⁷ and Regulation (EU) No 2015/2424,³⁴⁸ as now codified in Regulation (EU) No 2017/1001.³⁴⁹ They entitle the right holder to take action against counterfeit goods, including where these are not released for free circulation in the European Union.³⁵⁰ The entitlement lapses, however, if the declarant or holder of the goods provides evidence that the right holder is not entitled to prohibit the placing of the goods on the market of the country of final destination. Recital 19 of Regulation (EU) No 2017/1001 on the European Union Trade Mark and Recital 25 of Directive (EU) 2015/2436 recall the need for appropriate measures to ensure the smooth transit of generic medicines and, for that purpose, clarify that the right holder should not take action based upon similarities between international non-proprietary names for active ingredients in the medicines and related trademarks.³⁵¹

At the TRIPS Council meeting in June 2016, a number of developing countries expressed concerns about the European Union's trademark legislation and questioned how it related to the Customs Regulation (EU) No 608/2013.³⁵² A European Commission Notice of July 2016³⁵³ clarified that Customs should avoid detention of medicines under Regulation (EU) 608/2013, unless they are intended to be placed on the EU market or unless the goods bear a mark identical or essentially identical to the

trademark protected in the EU. In TRIPS Council meetings in 2017 and 2018, India submitted follow-up questions to the European Union, seeking further clarification on the practical effects of the updated legal framework and the guidance provided by the 2016 Commission Notice.³⁵⁴

The case illustrates the importance of ensuring that enforcement provisions do not create unnecessary barriers to legitimate trade in generic medicines that are transiting through a third country. For this purpose, there is clearly a need to distinguish between counterfeit and generic medicines, in order to avoid definitional issues becoming a *de facto* barrier to access to generic medicines (definitional issues are also discussed in section A.12 of this chapter).

4. Patent information and its relationship with public health policy

Access to patent information is an area of increasing importance for the procurement of medical products. When making procurement decisions relating to the purchasing of the best-priced quality products, procurement agencies may also need to consider the patent status of the products and the legal status of those patents in specific markets. The content and the sources of patent information are explained in Chapter II, section B.1(b)(viii)–(xi).

5. Review of relevant provisions in free trade agreements

This section provides an overview of the IP standards set down in certain free trade agreements (FTAs), which are of particular relevance to the medical technologies sector, as well as investor–state dispute settlement (ISDS) provisions in FTAs and international investment agreement. After looking at the major actors in FTAs, it also provides an overview of studies that have attempted to estimate the potential economic impact of these standards on the pharmaceutical sector and potential implications for access to medical technologies. To conclude, the role played by international organizations is briefly discussed.

Since the 1960s, trade agreements have focused on reducing barriers to trade applied “at the border”, such as import tariffs and port of entry inspections. Since the 1990s, FTAs tend to focus on “behind the border” measures, which affect the domestic regulatory framework³⁵⁵ and are envisaged to facilitate investment and foster incorporation into global value chains (see Box 4.27). These often include measures that relate to IP (see Table 4.3). The number of FTAs including such provisions has increased considerably in the period from

2000 to 2019. Many agreements also contain provisions on other relevant disciplines, such as the application of sound procurement practices (see Chapter II, section B.4) and competition policy (see Chapter II, section B.2 and Chapter IV, section D.2).

As at June 2016, all WTO members have at least one FTA in force.³⁵⁶

FTAs started developing around “hubs”, including the United States, the European Union and the European Free Trade Area, which became increasingly interconnected. Figure 4.9 illustrates the evolution of FTAs negotiated from 2000 until 2019.

Major FTAs negotiated since 2013 include: the Eurasian Economic Union;³⁵⁷ the Comprehensive Economic and Trade Agreement (CETA) between the European Union and Canada;³⁵⁸ the African Continental Free Trade Agreement (AfCFTA);³⁵⁹ the Comprehensive and Progressive Agreement for Trans-Pacific Partnership (CPTPP);³⁶⁰ the United States–Mexico–Canada Agreement (USMCA);³⁶¹ and the trade agreement between the European Union and MERCOSUR.³⁶² Some have extensive interregional coverage, integrate important markets and aim at harmonizing regulatory regimes. Although most modern FTAs negotiated by the European Union, EFTA or the United States contain provisions pertaining specifically to pharmaceuticals and/or health technologies, the European Union–Mercosur agreement does not contain such provisions.

The analysis of the implications of FTAs on public health has traditionally focused on IP provisions. The following subsection will therefore review selected IP provisions in FTAs. That said, disciplines on trade in goods, services and investment can also have a bearing on innovation and access to medical technologies. For example, access could be limited by non-tariff measures such as import licences for pharmaceutical products and/or encrypted goods, as well as restrictive distribution regimes.

(a) Review of selected IP provisions

When the TRIPS Agreement entered into force in 1995, there were 44 FTAs in force that had been notified to the WTO. At the time of writing, December 2019, the number of notified FTAs had surpassed 300.³⁶³ Some merely reaffirm the principles of the TRIPS Agreement. Many contain obligations to accede to a range of WIPO conventions and treaties, for example, the Paris Convention, the Patent Cooperation Treaty, the Patent Law Treaty or the Trademark Law Treaty. They reaffirm the principles of non-discrimination (i.e. national treatment and most-favoured-nation treatment) enshrined in the TRIPS Agreement (see Chapter II, section B.1(a)–(b)). Additionally, certain standards found in FTAs that

Table 4.3: Provisions in selected FTAs with a bearing on access and innovation in the pharmaceutical sector

FTA	Entry into force	Patentability	Patent term extension, SPCs and similar instruments	Compulsory licensing	Exhaustion	Regulatory exclusivities	Patent linkage	Enforcement	Side letters/ reaffirmation of Doha Declaration
EU–Japan	February 2019		≤ 5 years (marketing approval process only)			≥ 6 years		✓	✓
Hong Kong, China–Georgia	February 2019								✓
Comprehensive and Progressive Agreement for Trans-Pacific Partnership (CPTPP) ¹	December 2018	(suspended) ✓	(suspended) ✓ (marketing approval process only)			(suspended) ≥ 3 years (new indication/formulation/method of administration) ≥ 5 years (new product) ≥ 5/≥ 8 years (new biologics)	✓	✓	✓
EFTA–Philippines	June 2018	✓						✓	✓
China–Georgia	January 2018								✓
Turkey–Singapore	October 2017								✓
EFTA–Georgia	September 2017	✓	≤ 5 years			≥ 6 years (plus ≥ 1 year for new therapeutic indications)		✓	✓
EU–Canada (CETA)	September 2017		≤ 2–5 years			≥ 6/≥ 8 years		✓	✓
Canada–Ukraine	August 2017							✓	✓
Honduras–Peru	January 2017							✓	✓
Eurasian Economic Union (EAEU)–Viet Nam	October 2016							✓	
Costa Rica–Colombia	August 2016							✓	✓
Colombia–Korea, Republic of	July 2016								✓
Korea, Republic of–New Zealand	December 2015								
Australia–China	December 2015								✓
China–Korea, Republic of	December 2015							✓	✓
Mexico–Panama	July 2015							✓	✓
Canada–Korea, Republic of	January 2015							✓	✓

(Continued)

Table 4.3: (Continued)

FTA	Entry into force	Patentability	Patent term extension, SPCs and similar instruments	Compulsory licensing	Exhaustion	Regulatory exclusivities	Patent linkage	Enforcement	Side letters/ reaffirmation of Doha Declaration
EFTA–Bosnia and Herzegovina	January 2015		≤ 5 years			≥ 8/≥ 10 years (plus ≥ 1 year for new therapeutic indications)		✓	
Japan–Australia	January 2015						✓		
Australia–Korea, Republic of	December 2014	✓							✓
EU–Moldova	September 2014		≤ 5 years (6 months extension for paediatric use)		✓	≥ 5/≥ 7 years (plus ≤ 1 year for new therapeutic indications)		✓	✓
EU–Georgia	September 2014		≤ 5 years (6 months extension for paediatric use)		✓	≥ 6 years (plus ≤ 1 year for new therapeutic indications)		✓	✓
EFTA–Central America (Costa Rica, Guatemala and Panama)	August 2014		✓ (marketing approval process only)			≥ 5 years		✓	✓
Switzerland–China	July 2014					≥ 6 years		✓	✓
EU–Ukraine	April 2014 (EU) January 2016 (Ukraine)	✓	✓ (6 months extension for paediatric use)			≥ 5 years		✓	✓
EU–Central America	August 2013					Protection through non-discrimination principles ²		✓	✓
Costa Rica–Singapore	July 2013								✓
Costa Rica–Peru	June 2013							✓	✓
EU–Colombia and Peru/Ecuador	March 2013 (EU and Peru) August 2013 (Colombia) January 2017 (Ecuador)		✓ (marketing approval process only)			5 years (Parties may regulate exceptions for reasons of public interest, situations of national emergency or extreme urgency)		✓	✓
Korea, Republic of–Turkey	May 2013								
Australia–Malaysia	January 2013							✓	
EFTA–Hong Kong, China	October 2012	✓				≥ 8 years		✓	
United States–Panama	October 2012	✓	✓			Reasonable period (normally 5 years)	✓	✓	✓

(Continued)

Table 4.3: (Continued)

FTA	Entry into force	Patentability	Patent term extension, SPCs and similar instruments	Compulsory licensing	Exhaustion	Regulatory exclusivities	Patent linkage	Enforcement	Side letters/ reaffirmation of Doha Declaration
EFTA–Montenegro	September 2012	✓	≤ 5 years			≥ 8/≥ 10 years (plus ≤ 1 year for new therapeutic indications)		✓	
United States–Colombia	May 2012	✓	✓			Reasonable period (normally 5 years)	✓	✓	✓
United States–Korea, Republic of	March 2012	✓	✓			≥ 5 years (new product) ≥ 3 years (product containing previously approved chemical entity)	✓	✓	✓
EU – Korea, Republic of	July 2011		≤ 5 years (marketing approval process only)			≥ 5 years		✓	✓
EFTA–Colombia	July 2011		✓ (marketing approval process only)			Reasonable period (normally 5 years)			✓
EFTA–Peru	July 2011					Reasonable period (normally 5 years)			✓
EFTA–Albania	November 2010	✓	≤ 5 years			≥ 8 years		✓	
Japan–Switzerland	September 2009		≤ 5 years (marketing approval process only)			≥ 6 years		✓	
United States–Peru	February 2009	✓				Reasonable period (normally 5 years)	✓	✓	✓
United States–Oman	January 2009	✓	✓			≥ 5 years ≥ 3 years (product containing previously approved chemical entity)	✓	✓	✓
EC–CARIFORUM States	December 2008							✓	✓
EFTA–Egypt	August 2007					≤ 5 years			
EFTA–Lebanon	January 2007					≥ 6 years			
EFTA–Korea, Republic of	September 2006	✓	≤ 5 years (marketing approval process only)			Adequate number of years determined by the parties			✓
United States–Bahrain	August 2006	✓	✓			≥ 5 years ≥ 3 years (product containing previously approved chemical entity)	✓	✓	✓

(Continued)

Table 4.3: (Continued)

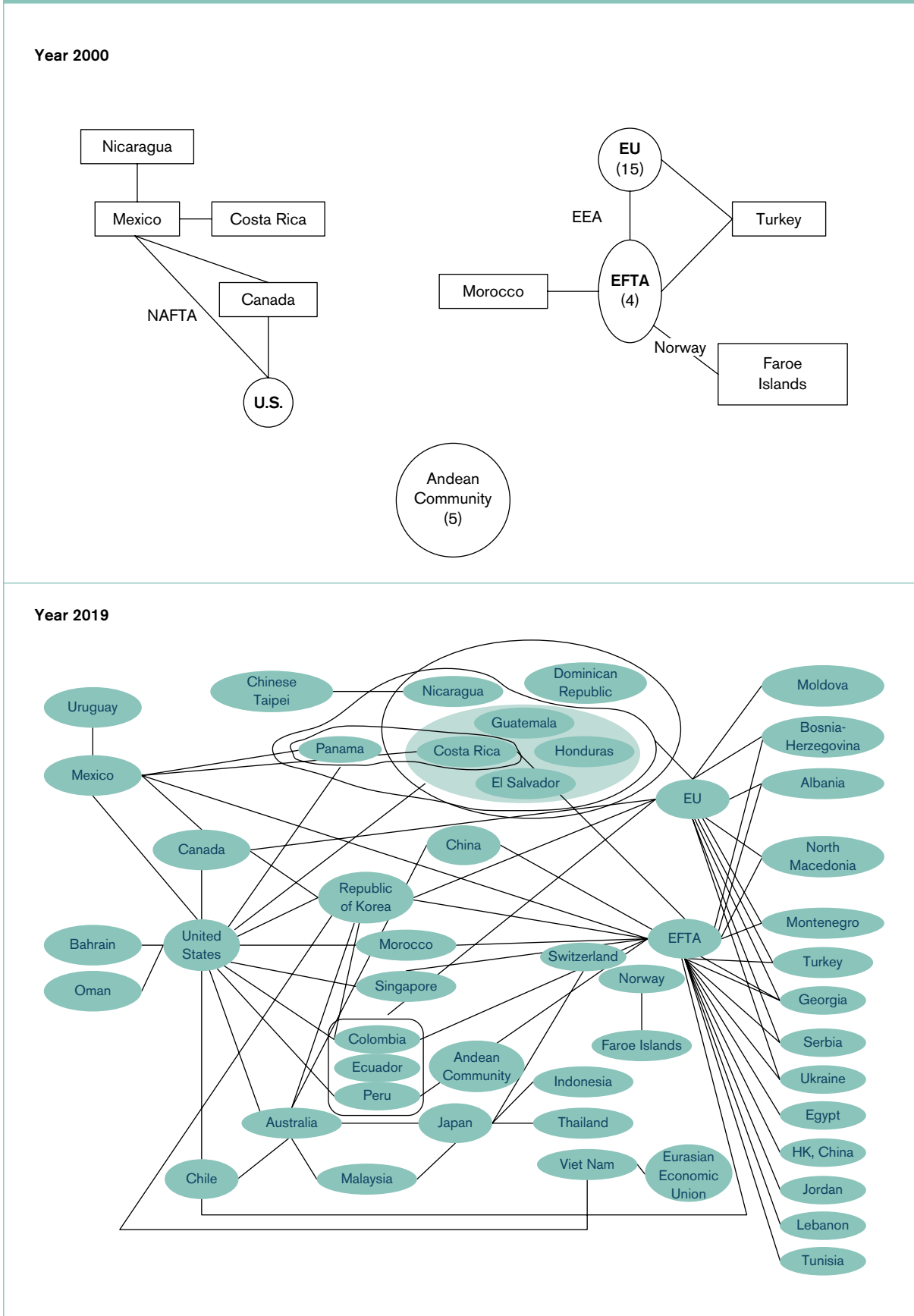
FTA	Entry into force	Patentability	Patent term extension, SPCs and similar instruments	Compulsory licensing	Exhaustion	Regulatory exclusivities	Patent linkage	Enforcement	Side letters/ reaffirmation of Doha Declaration
Dominican Republic–Central America–United States Free Trade Agreement (CAFTA-DR)	March 2006	✓	✓			≥ 5 years	✓	✓	✓
United States–Morocco	January 2006	✓	✓		✓	≥ 5 years ≥ 3 years (new clinical information)	✓	✓	✓
EFTA–Tunisia	June 2005					≥ 5 years			
United States–Australia	January 2005	✓	✓	✓	✓	≥ 5 years ≥ 3 years (new clinical information)	✓	✓	
EFTA–Chile	December 2004		✓ (marketing approval process only)			≥ 5 years			✓
United States–Chile	January 2004	✓	✓			≥ 5 years	✓	✓	✓
United States–Singapore	January 2004	✓	✓	✓		≥ 5 years	✓	✓	
EFTA–Singapore	January 2003	✓	≤ 5 years (marketing approval process)						
EFTA–Jordan	September 2002	✓		✓					
United States–Jordan	December 2001		✓ (marketing approval process only)	✓			✓	✓	
EFTA–Morocco	December 1999	✓		✓					
North American Free Trade Agreement (NAFTA)	January 1994					Reasonable period (normally not less than 5 years)			
EFTA–Turkey	April 1992	✓		✓					

Notes: The entries reflect mandatory provisions that add to existing TRIPS obligations. The names of parties to FTAs are those used in the WTO. The source of the agreements is the Database of Regional Trade Agreements, available at: <http://rtais.wto.org/UI/PublicMaintainRTAHome.aspx>.

¹ The CPTPP suspends a number of provisions in the original Trans-Pacific Partnership Agreement (TPP) chapter on IP, including as regards patents and pharmaceuticals. Agreement by all CPTPP Members is needed for these provisions to take effect. For further details, see <https://www.international.gc.ca/trade-commerce/trade-agreements-accords-commerciaux/agr-acc/optpp-ptgpp/sectors-secteurs/ip-pi.aspx?lang=eng>.

² See Declaration of the EU Party on Data Protection of Certain Regulated Products: [https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1399559252828&uri=CELEX:22012A1215\(01\)](https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1399559252828&uri=CELEX:22012A1215(01)). The Declaration also states that the relevant legislation of the Central American parties, "by providing protection periods of at least five years for pharmaceutical products [...], affords a satisfactory level of protection [...]".

Figure 4.9: Evolution of IP chapters in FTAs: developments from 2000 to 2019



Source: WTO Secretariat.

Note: Names of WTO members are those used in the WTO.

relate to patent protection and regulatory exclusivities, as well as IPR enforcement, are particularly relevant to pharmaceutical and biotherapeutic products, as well as other health technologies.

Eighty-two per cent of the FTAs that entered into force after 2005 contain IP provisions. Among these, 20 per cent contain provisions that require the parties to implement more extensive protection and enforcement of IPRs than the standards provided for in the TRIPS Agreement.³⁶⁴ Such provisions are often referred to as “TRIPS plus”. The non-discrimination principles under the TRIPS Agreement require parties to those FTAs to extend the application of any higher standards to all other WTO members (see Chapter II, section B.1(a)–(b)).

While there is no unique approach to IP standards in FTAs, certain commonalities in terms of specifying and increasing IP standards can nevertheless be observed. Provisions with a bearing on the health technologies typically cover one or more of the following subjects:

(i) Patent law

Several FTAs contain detailed provisions on various aspects of patent law. For example, some FTAs specify how patentability criteria and the requirement of sufficient disclosure are to be applied (see Chapter II, section B.1(b)(iii)). Some FTAs provide that patents must be available for inventions claimed as being at least one of the following: new uses of a known product; new methods of using a known product; or new processes of using a known product.

FTAs may include provisions foregoing the application of otherwise permissible exclusions from patentability and exceptions and limitations to patent rights in domestic law, or, on the contrary, making their application mandatory (see Chapter II, section B.1(b)(vii)). FTA provisions may thus expressly require the patentability of plants and animals (see Article 15.9.2 of the FTA between Morocco and the United States). But they may also require the parties to provide for regulatory review exception in domestic law (see section C.3(a)(i) above). Article 18.49 of the CPTPP, for example, states that “each Party shall adopt or maintain a regulatory review exception for pharmaceutical products”.

(ii) Patent term extension

A number of FTAs require the possibility of extending the 20-year term of protection, which has to be available under the TRIPS Agreement, for, among other things, pharmaceutical products. The purpose of such an extension is to compensate the patent owner for the time it takes to obtain marketing approval, or for processing

delays in the patent office. Some WTO members provide such extensions in the form of patent term extensions or adjustments, while others make supplementary protection certificates available (see section C.3(g)).

(iii) Grounds for granting compulsory licences

The TRIPS Agreement does not establish an exhaustive list of grounds for granting compulsory licences. Provisions in certain FTAs, such as Article 16.7(6) in the United States–Singapore FTA, Article 17.9(7) in the United States–Australia FTA and Article 4(20) in the United States–Jordan FTA, limit grounds to remedies under competition law, situations of extreme urgency and public non-commercial use (see section C.3(a)(ii)).

(iv) Exhaustion regime

Under the TRIPS Agreement, WTO members are free to choose the exhaustion regime that best meets their domestic policy objectives (see section C.3(f)). This freedom is confirmed in a number of FTAs. However, some FTAs specifically provide for the right of a patent owner to limit parallel imports through contracts.

(v) Regulatory exclusivities

The term “regulatory exclusivities” is explained in Chapter II, section A.6(f). The WTO TRIPS Agreement does not require WTO members to provide for regulatory exclusivities in domestic legislation.

Some FTAs specify that a period of regulatory exclusivity is required and some FTAs provide for regulatory exclusivities in the context of implementing Article 39.3 of the WTO TRIPS Agreement (see Chapter II, sections A.6(f) and B.1(c)). In some cases, regulatory exclusivities are prescribed for a number of years (see Table 4.3). Certain FTAs provide for the possibility of extending exclusivity periods. Some FTAs require the parties to apply exclusivity periods when new clinical information is submitted in support of a previously approved product covering a new indication, formulation or method of administration.

In certain FTAs, data exclusivity also covers cases in which an FTA party permits the granting of a marketing approval of regulated products on the basis of an earlier marketing approval of the same or similar product in a third country. This has the effect of preventing generic companies from relying on the test data supplied by the originator company to another country’s government, even if no test data have been supplied to the government of the country in which the generic company seeks to market its product. Parties to FTAs have implemented such obligations in different ways.³⁶⁵

A number of FTAs provide for additional data and/or market exclusivity for biotherapeutic products, beyond the exclusivity periods for small-molecule medicines (see Chapter II, section A.6(d)). In many jurisdictions, no distinction was made between biotherapeutics and small-molecule medicines in terms of data and/or market exclusivity prior to signing an FTA.³⁶⁶

For example, Article 20.49 of the USMCA as initially agreed in 2018 provided for a period of at least ten years of test data protection for new biotherapeutic products. In December 2019, the Parties agreed, among others, to make changes to the intellectual property chapter and to remove this obligation. Following ratification by all Parties, the Agreement entered into force in July 2020. During the negotiations for the TPP, the length of regulatory exclusivity for biotherapeutic products was also debated. One concern was that a lengthening of the exclusivity period for biotherapeutic products to 12 years would lead to substantially increased health expenditures.³⁶⁷ These provisions, among others, were suspended in the final text of the CPTPP.³⁶⁸

(vi) Patent linkage

While the TRIPS Agreement does not include any requirement regarding patent linkage, a number of FTAs include provisions to that effect (see Chapter II, section A.6(g)). In practice, it has been observed that countries that have agreed to patent linkage provisions in FTAs still retain some flexibility and discretion in implementing certain features of the system domestically (Son et al, 2018).

(vii) Enforcement

IPR enforcement standards in FTAs are generally of broad application and are not sector specific. A number of these standards have the potential to directly affect the pharmaceutical sector. Relevant enforcement provisions include, for example, the application of border measures to IPRs other than trademarks and copyright (for which there are already mandatory provisions under the TRIPS Agreement), as well as their application to goods in transit. In short, “border measures” allow right holders to work with customs authorities to prevent the importation of goods infringing IPRs (see Chapter II, section B.1(f) and Chapter IV, section C.3(h)).

(viii) Reaffirmation of TRIPS flexibilities and Doha Declaration principles

Many FTAs contain a reaffirmation of the Doha Declaration on TRIPS and Public Health in their IP chapter. Some

FTAs confirm the parties’ agreement that the IPR standards set by the FTA affect neither their right to take measures to protect public health nor their right to use the additional flexibility made available to WTO members through the Special Compulsory Licensing System (see section C.3(a)(iii)). Some FTAs contain such provisions in the body of the agreement. In other FTAs, this has been addressed by “side letters”. Such confirmation is aimed at addressing concerns that FTA standards could limit the flexibilities available under the TRIPS Agreement and later instruments.

(b) Investor–state dispute settlement

Investor–state dispute settlement (ISDS) mechanisms, which are included in FTAs and also in international investment agreements (IIAs), provide investors (e.g. private companies) with the opportunity to sue states and claim damages in cases of alleged breaches of the FTA (Miller and Hicks, 2015; see Box 4.26). Usually, parties to an FTA or IIA have agreed to use the International Centre for Settlement of Investment Disputes (ICSID) as the forum for ISDS, where such cases are heard by a panel of arbitrators agreed between the parties.³⁶⁹

The number of known treaty-based ISDS cases has increased since the early 2000s, from 13 initiated arbitrations in 2000 to 71 in 2018.³⁷⁰ Most of these cases are outside the pharmaceutical sector. Investment chapters have become a regular component of FTAs.³⁷¹ In some of those chapters, for example Chapter 8 of CETA, IP has been classified as an investment, meaning that failure to comply with the IP provisions in the relevant FTAs could give rise to ISDS cases.³⁷²

Some cases have led to concerns that the results could affect health systems and discourage public health regulations.³⁷³ On the other hand, it has been found that IIAs do increase foreign direct investment (FDI) into countries that sign them, but only if those countries are not subsequently challenged before ICSID. Governments might lose FDI if they are taken before ICSID and suffer greater losses of FDI when they lose a dispute (Allee and Peinhardt, 2011).

Different views about the effects of ISDS cases have been reflected in recent FTA negotiations. Draft documents of the TPP, as negotiated by the original parties, contained an ISDS exclusion for tobacco-control measures. Notably, this exclusion was kept in Article 29.5 of the CPTPP. Also, in the framework of the CPTPP, New Zealand signed agreements with Australia, Brunei Darussalam, Malaysia, Peru and Viet Nam to exclude public education, health and other social services from the compulsory ISDS between them.³⁷⁴

Box 4.26: Cases under IIAs and FTAs

In two cases brought under international investment agreements (IIAs), a tobacco manufacturer brought ISDS cases against Uruguay and Australia, claiming that national restrictions on cigarette packaging and advertising infringed on trademark rights of the company. In the Australian case, the tribunal did not address the tobacco manufacturer's claims, as the tribunal ruled that the investor abused its rights (or abused the process) when it changed its corporate structure to gain the protection of an investment treaty at a time when an ISDS dispute was foreseeable, and that, therefore, the investor's claim was inadmissible.³⁷⁵ In the Uruguayan case, the tobacco manufacturer claimed numerous breaches of the Uruguay–Switzerland IIA, comprising expropriation, denial of fair and equitable treatment, impairment of use and enjoyment of the claimants' investments, failure to observe commitments under an umbrella clause and denial of justice. The tribunal dismissed all the tobacco manufacturer's claims.³⁷⁶

In another case, a pharmaceutical company brought an ISDS case against Canada, claiming that the invalidation of certain patents by Canadian courts violated the investment chapter of the North American Free Trade Agreement (NAFTA). For both medicines, patents had been found to be "invalid for lack of utility" in Canada. The claimant alleged that there had been a change in the utility requirement in Canadian patent law and that the utility requirement was arbitrary and/or discriminatory, due to being "unpredictable and incoherent", having disproportionately disadvantageous effects on the pharmaceutical sector and in practice favouring national patent holders. The tribunal concluded that there had not been a fundamental or dramatic change in Canadian patent law, the pharmaceutical company had not demonstrated that the utility requirement had been "unpredictable and incoherent", and neither had it resulted in discrimination against the pharmaceutical sector or foreign patent holders. The case was decided in favour of the State.³⁷⁷

(c) Major actors in FTAs

Table 4.3 lists selected provisions with a bearing on innovation and access in the pharmaceutical sector. The entries only reflect provisions that add to existing TRIPS Agreement obligations. The list illustrates that FTAs, which clarify for the parties how to implement existing TRIPS provisions or provide for higher standards of IPR protection and enforcement, are clustered in and around three main geographical areas, namely, the United States, the European Free Trade Association (EFTA) and the European Union:

- Since the mid-1990s, the European Union has concluded a series of association, partnership and trade agreements. As at October 2019, 43 FTAs have been notified to the WTO that are in force.³⁷⁸ The Customs Union with Turkey of 1995 and the stabilization and association agreements (which countries enter into with a view to facilitating eventual accession to the European Union) with several Central European countries,³⁷⁹ aim at aligning the level of protection to that in the European Union. A number of the earlier FTAs provide for IPR protection in line with the "highest international standards"³⁸⁰ or "prevailing international standards",³⁸¹ without defining the precise meaning of such standards – in particular, whether the reference point is multilateral agreements (such as the TRIPS Agreement) or any other standards set, for example, those set in other FTAs. Since the early 2010s, FTAs negotiated by the European Union include a detailed IPR chapter. This applies, for example, to CETA as well as the

European Union–Georgia and the European Union–Central America FTAs.

- As at October 2019, EFTA, which comprises Iceland, Lichtenstein, Norway and Switzerland, has concluded an extensive network of 29 FTAs.³⁸² In the area of IP, the majority of these agreements focus on higher standards with respect to patent term extension, regulatory exclusivities and enforcement measures at borders.
- As at October 2019, the United States has 14 FTAs in force with 20 countries, which are notified to the WTO.³⁸³ Generally, these FTAs cover IPRs in a comprehensive manner.

Most of the FTAs concluded by the European Union, EFTA and the United States contain IPR provisions related to medical technologies. This reflects the fact that they host the largest producers and exporters of such technologies (see section D.1(a)) and therefore have an interest in improving access to markets and facilitating investment. In contrast, detailed provisions on specific IPRs are usually rare, or even absent, from FTAs concluded among other countries, especially least-developed countries. However, in some of the FTAs between developing countries, detailed provisions on patents, regulatory exclusivities and/or test data protection are set out.

(d) Economic impact analysis

Each of the higher IP protection standards adopted in FTAs – either on its own or in conjunction with other

standards – has the potential to affect both the innovation of, and subsequent access to, medical technologies. The trend towards the inclusion of detailed IPR provisions continues, including in the more recent FTAs negotiated by the three major players – the European Union, EFTA and the United States. At the same time, the readiness to include public health safeguards in these agreements – either in the IP and investment chapters or in side letters – has also increased significantly.

Several studies have looked at the economic impact of IPR provisions in FTAs on the pharmaceutical sector. A 2009 study commissioned by the ICTSD estimated that the Dominican Republic–Central America–United States FTA (CAFTA-DR) would lead, depending on the scenario applied, to an increase in public spending on medicines in Costa Rica ranging from US\$ 176 million to US\$ 331 million by 2030, due to the increased proportion of active pharmaceutical ingredients subject to exclusive rights from 6–9 per cent in 2010 to 24–28 per cent in 2030. The strongest repercussions were expected from standards on patentability criteria and on test data exclusivity.³⁸⁴ A similar 2009 study for the Dominican Republic predicted a modest price increase of 9 per cent to 15 per cent for active ingredients by 2027. It found that the strongest impact by far was to be expected from provisions on data exclusivity. Interestingly, the authors also reported that information asymmetries and government policy imperfections would have a higher impact on prices than regulatory changes in the IP regime.³⁸⁵

In 2009, the ICSTD developed a simulation model – the Intellectual Property Rights Impact Aggregate (IPRIA) Model³⁸⁶ – that can be applied to various national scenarios to assess the impact of changes in the IP regime on access to medicines. It has been applied to Brazil, Colombia, Costa Rica, the Dominican Republic, Ecuador and Peru.³⁸⁷ A 2012 study prepared by two civil society organizations in Colombia found that the introduction of data exclusivity in exchange for trade preferences in 2002, and later confirmed in the FTA negotiations, has led to additional expenditure of US\$ 412 million.³⁸⁸ And a 2007 Oxfam Briefing Paper estimated that prices for medicines in Jordan had increased by 20 per cent since the conclusion of the FTA with the United States. Here

again, data exclusivity was singled out for delaying the market entry of almost 80 per cent of the generic versions of newly launched medicines between 2002 and 2006, with additional expenditures for medicines estimated at between US\$ 6.3 million and US\$ 22.04 million.³⁸⁹ The Canadian Patented Medicine Prices Review Board estimated that the introduction of cheaper biosimilars could save between CAD 332 and CAD 1.8 million per year, based on sales figures for existing biotherapeutic products in 2016.³⁹⁰

Assessing the economic impact of specific chapters in FTAs in an isolated fashion, however, may not do justice to the overall architecture of FTAs and their resulting effects in terms of wealth creation, improved living standards, and transparent and non-discriminatory procedures leading to the delivery of better value for money, among other things. Impact assessments that have been prepared by parties to a particular FTA, and that cover the effects of the FTA as a whole, are more common.

(e) The role of international organizations

The WTO monitors and raises awareness of FTAs, among other things, through the examination of notified FTAs in the Committee on Regional Trade Agreements and the regular review of national trade policies under the Trade Policy Review Mechanism. Based on Article 63.3 of the TRIPS Agreement, WTO members can also seek access to, or information on, bilateral agreements from other WTO members.

With regard to the WHO, a number of resolutions have also been adopted that call on WHO member states to take into account the flexibilities in the TRIPS Agreement and later instruments (e.g. the Doha Declaration and the Special Compulsory Licensing System) in trade agreements (see, for example, Element 5.2(c) of the GSPA-PHI adopted by World Health Assembly Resolution WHA 61.21).

The WHO Regional Office for the Eastern Mediterranean has published a policy guide for negotiators and implementers of IP provisions in bilateral FTAs (El Said, 2010).

D. Other trade-related determinants of access

Key points

- Most countries rely heavily on imports of health technologies. International trade is therefore crucial to ensuring access to these technologies.
- International trade in health-related products has grown significantly since 1995. In 2018, high-income countries accounted for 57 per cent of worldwide imports of health products, while their share of exports was 66 per cent. At the same time, the share of global exports and imports associated with certain middle-income countries has increased.
- Tariffs and non-tariff measures can have a significant impact on the price of imported medical technologies, as much as distribution costs at domestic level, including mark-ups and pharmacy dispensing fees.
- High-income countries have largely eliminated tariffs on health-related products, in line with the 1994 WTO Pharmaceutical Agreement. Tariffs applied by LMICs have also fallen significantly, but the picture is still mixed.
- Trade costs are a determining factor in price composition. To contain such costs, the WTO Trade Facilitation Agreement aims at modernizing customs systems and encourages WTO members to rationalize and simplify import-export procedures and formalities.
- Competition law and policy are relevant to all stages in the process of supplying medical technology to patients – from the development and manufacture of medical technology to its eventual sale and delivery.
- Business practices of originator companies that have been investigated by competition authorities include: strategic patenting; litigation, including sham litigation and reverse patent settlement agreements; refusal to deal and restrictive licensing practices; and life-cycle strategies, including product-hopping.
- After market entry of generics, the application of competition law to generic manufacturers is also important. Competition authorities have scrutinized excessive prices charged by pharmaceutical companies for generic medicines in view of potential infringement of competition law.
- Competition law and policy have an important role to play in public-sector procurement and distribution to maximize competition in the procurement process and prevent collusion among suppliers of medical technologies.

1. International trade and tariff data of health products

No country is entirely self-reliant in terms of the products and equipment it needs for its public health systems – most rely heavily on imports. Trade statistics, therefore, may provide valuable insights into the evolution of patterns regarding access to health-related products. The factors affecting imports influence availability as well as prices of health-related products and technologies, and thus have immediate consequences for access. Tariffs are one of the key factors influencing imports, but price and availability are also impacted by non-tariff measures, such as licences, regulations and other import formalities. In addition, national distribution costs, such as wholesale and retail mark-ups and dispensing fees, may increase prices dramatically.

Analysing trade statistics and tariffs on health-related products is difficult in the absence of a clear definition of

health products in WTO agreements and the Harmonized Commodity Description and Coding System (HS) of tariff nomenclature (used to monitor international trade). Many products – such as chemical ingredients – have both medical and non-medical end uses. In the absence of a precise definition, this section reviews tariff and trade data for health-related products designated under 413 tariff subheadings of the 2017 HS for 197 countries and territories. This definition covers products ranging from organic chemicals and pharmaceutical products to ultrasonic scanners and dentists' chairs. The products are clustered in seven groups (see Table 4.4).

(a) International trade in health-related products

There has been very significant growth in international trade in health-related products since 1995. The value of imports in the seven product groups combined rose

Table 4.4: Public-health-related products

Group A	Pharmaceutical industry	A1 Medicines for retail sale	15 tariff subheadings covering medicaments put up in measured doses and packaged for retail sale
		A2 Medicines in bulk	15 tariff subheadings covering medicaments not put up in measured doses for retail sale, i.e. sold in bulk
		A3 Inputs specific to the pharmaceutical industry	43 tariff subheadings covering inputs specific to the pharmaceutical industry, e.g. antibiotics, hormones and vitamins
Group B	Chemical inputs	B Chemical inputs of general purpose	249 tariff subheadings covering chemical inputs used by the pharmaceutical industry, as well as other industries
Group C	Medical equipment, other inputs	C1 Hospital and laboratory inputs	35 tariff subheadings covering bandages and syringes, gloves, laboratory glassware, diagnostic reagents, etc.
		C2 Medical technology equipment	39 tariff subheadings covering medical devices used in diagnosis or treatment covering furniture, X-rays, machinery, etc.
		C3 Orthopaedic equipment	17 tariff subheadings covering crutches and wheelchairs, spectacle lenses, artificial teeth, hearing aids, etc.

Source: WTO Secretariat. Product selection modified and updated based on "More Trade for Better Health? International Trade and Tariffs on Health Products", October 2012, Matthias Helble, WTO Staff Working Paper ERSD-2012-17.

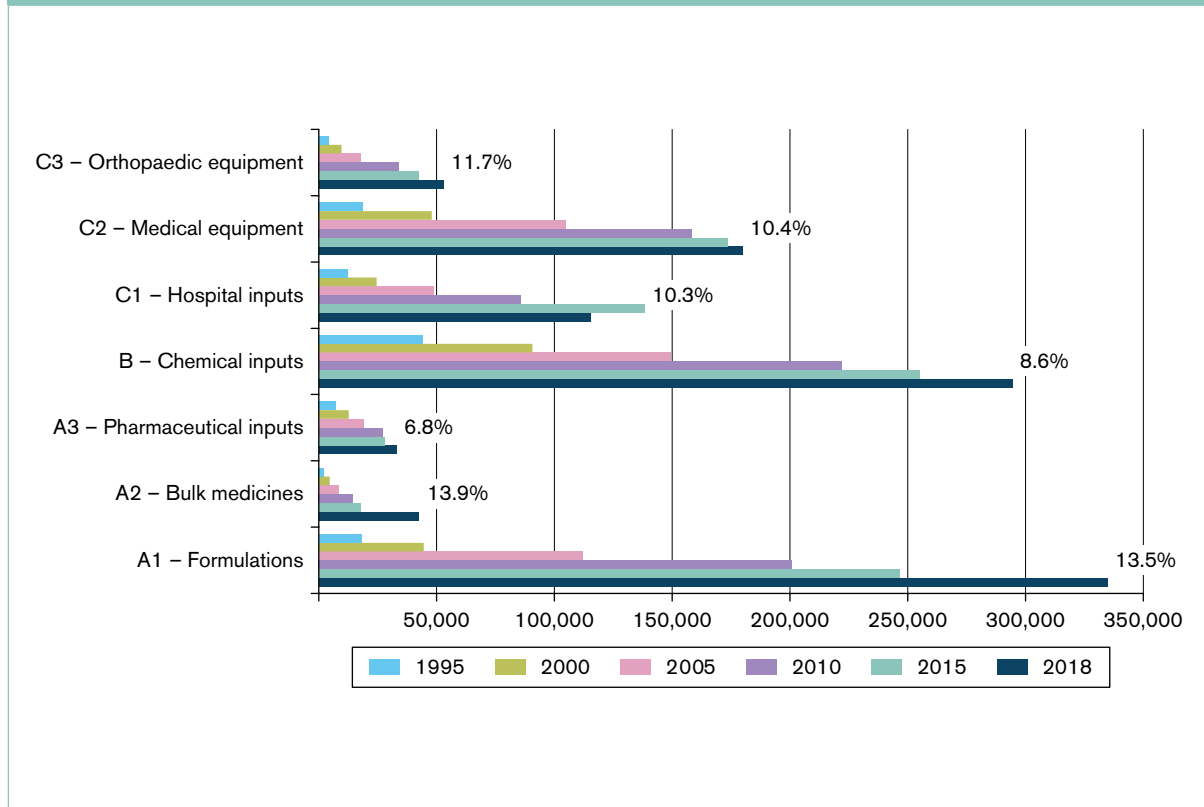
from US\$ 106 billion in 1995 to US\$ 1,052 billion in 2018. Worldwide, imports of health products were therefore multiplied by about ten – almost all product categories analysed have experienced annual compound growth rates higher than trade growth for merchandise in general.³⁹¹ In 2018, trade in health-related products accounted for approximately 5 per cent of global merchandise trade. As can be seen in Figure 4.10, imports of medicines (i.e. medicines packaged for retail sale, category A1, and medicines in bulk, category A2) experienced the highest compound annual growth rates, 13.5 per cent and 13.9 per cent, respectively. Growth in these categories was closely followed by an increase in the importance of orthopaedic equipment (category C3) and of medical technology equipment (category C2) and hospital and laboratory inputs (category C1). Medical technology equipment now represents more than 17 per cent of all imports of health products. It is worth highlighting the dynamism and importance of trade in pharmaceutical products and medicines; in fact, despite the very large spectrum of products reviewed in this analysis, formulations (category A1) alone represents around one third of total imports of all health products.

It is interesting to note that a small number of countries account for the majority of imports of public health products, although this pattern has started to change with the emergence of new players. The United States, the European Union member states, China, Japan, Switzerland and Canada account for 65 per cent of all imports of health products globally. The importance of developed-country imports may be explained by their relatively high share of private and public expenditures on health care and their greater integration into vertical supply chains, boosting trade flows (see Box 4.27). However, the share of total imports by developed

countries is slowly diminishing as new players emerge; while developed countries imported almost 70 per cent of all traded health-related products in 2010, their share dropped to 57 per cent in 2018 (see Table 4.5). China, in particular, has risen in less than a decade to become the world's third largest importer of health products. It is the world's largest importer of certain categories of products, such as medical technology equipment (category C2). In addition, other new players have emerged: The Republic of Korea, Mexico, India, the Russian Federation and Brazil, for instance, have become significant overall importers.

A small number of countries also account for the bulk of exports of public health goods (see Table 4.6), although, as for imports, that pattern has started to evolve in terms of diversification. The European Union is the world's single largest exporter of health products (33 per cent), followed by the United States (15 per cent). While developed countries and territories still account just over 66 per cent of all exports of health products, exports from some developing countries are now significant. China has risen to become the world's third largest exporter with almost 12 per cent of world exports. Exports from Singapore, India, the Republic of Korea, Canada, Mexico and Chinese Taipei³⁹² have also become significant. While the share of exports from developing countries is becoming more significant in general, their increased participation in exports of health products is most noticeable in a few specific product categories. For instance, China represents more than one quarter of all exports in some categories, such as pharmaceutical inputs (category A3, 27 per cent), chemical inputs (category B, 20 per cent) and medical technology equipment (category C2, 19 per cent). However, developing countries have not risen to become major exporters in all health product groups; for example,

Figure 4.10: Imports of health-related products 1995–2018, by value (in US\$ million) and compound growth rates, 2018



Source: Calculations by the WTO Secretariat.

Table 4.5: International trade in health-related products: share of main importers, 2018

Imports	Total %	A1 Formulations %	A2 Bulk medicines %	A3 Pharmaceutical inputs %	B Chemical inputs %	C1 Hospital inputs %	C2 Medical equipment %	C3 Orthopaedic equipment %
United States	22.5	26.9	34.7	13.2	17.2	21.7	19.9	29.5
European Union	18.5	17.1	26.6	36.6	18.1	19.4	14.8	22.4
China	11.1	7.1	3.1	4.6	12.7	8.0	22.4	5.8
Japan	5.8	6.7	2.3	3.3	6.1	5.0	4.9	7.9
Switzerland	4.7	7.0	10.1	4.1	4.1	2.8	1.6	3.3
Canada	2.8	2.9	2.6	4.3	2.3	3.7	2.3	3.5
Korea, Republic of	2.7	1.6	0.6	1.7	4.1	2.4	3.7	1.5
Mexico	2.1	0.9	0.7	1.8	2.7	2.6	3.4	1.4
India	2.1	0.4	0.6	6.0	4.2	1.4	1.8	1.2
Russian Federation	2.0	2.5	2.4	1.4	1.7	2.3	1.6	1.5
Brazil	2.0	1.8	1.0	2.9	3.2	1.8	1.1	1.1
Australia	1.7	2.0	0.9	1.9	0.7	2.1	1.9	3.1
Singapore	1.6	0.6	0.4	1.4	2.5	1.7	2.2	1.7
Chinese Taipei	1.3	1.0	0.5	0.5	2.1	1.0	1.1	0.9
Hong Kong, China	1.3	0.8	0.2	0.2	0.7	1.1	3.1	3.3
Turkey	1.1	0.9	1.3	1.1	1.4	1.5	0.7	0.8

Source: Calculations by the WTO Secretariat.

Note: Names of WTO members are those used in the WTO.

China only accounts for only 1.3 per cent of global exports of medicines packaged for retail sale (category A1).

Overall, international trade has assumed increasing importance in ensuring supplies of health-related goods. The vast majority of countries and territories reviewed are indeed net importers of health products and, in particular, of pharmaceutical products (categories A1, A2 and A3). Of the 197 countries and territories reviewed, only very few were net exporters of these products on average in the period from 2016 to 2018, including, in particular, the European Union, Switzerland, India, Israel and Singapore

(see Table 4.7). China, a net exporter in 2010, has now become the world's third largest net importer of such products (see Table 4.8).

Structural shifts were evident in general trade in health products between 1995 and 2018. Many countries have built local manufacturing capacity and, in the case of a few, have moved to a trade surplus, indicating growth and diversity in production capacity, with surpluses aimed at export markets. A number of countries (e.g. Costa Rica, India, Ireland, Jordan, Panama and Singapore) seem to have prioritized the pharmaceutical and medical

Box 4.27: The emergence of global value chains

The patterns of global production and trade have changed considerably and are now based on globally integrated production chains. Manufactured products consumed all over the world are often produced within international supply chains in which individual companies specialize in specific steps of the production process. Increasing numbers of products are composed of parts and components of various geographical origins – such products should be labelled “Made in the World” rather than “Made in (any single country)”.

The trade taking place among various stakeholders in supply chains reflects their specialization in particular activities and can thus be referred to as “trade in tasks”. The rise in global production has involved profound changes in international trade, mainly characterized by the marked increase of world trade in intermediate goods, the expansion of processing trade among developing countries and the important growth of intra-firm transactions.

Conventional trade statistics do not necessarily show the real picture of international trade in a globalized economy. For example, the “country of origin” recorded for imports of final goods is usually the last country in the production chain, and this ignores the value of production from other contributors (origins). In order to provide innovative approaches to international trade statistics, the WTO Global Value Chain initiative provides analysis and information on trade in value-added indicators.³⁹³

Table 4.6: International trade in health-related products: share of main exporters, 2018

Exporter	Total %	A1 Formulations %	A2 Bulk medicines %	A3 Pharmaceutical inputs %	B Chemical inputs %	C1 Hospital inputs %	C2 Medical equipment %	C3 Orthopaedic equipment %
European Union	33.4	48.5	50.9	28.0	24.4	30.9	21.7	28.5
United States	15.3	10.6	15.9	15.3	13.7	25.2	17.9	20.0
China	12.2	1.3	3.5	26.8	20.0	10.6	19.0	12.5
Switzerland	10.9	22.0	8.1	13.6	6.2	3.8	3.2	10.5
Japan	4.0	1.5	1.2	1.1	6.4	4.2	6.7	0.9
Singapore	3.5	1.8	5.7	4.1	5.3	2.8	3.3	4.7
India	3.0	4.3	1.7	5.0	4.3	1.7	0.5	0.6
Korea, Republic of	3.0	0.6	4.1	1.1	3.7	1.2	7.8	1.6
Canada	1.7	2.3	0.8	0.2	1.7	2.0	1.1	0.5
Mexico	1.6	0.4	0.2	0.5	0.5	3.9	3.7	3.9
Chinese Taipei	1.5	0.1	0.1	0.4	2.1	0.7	3.8	2.5
Hong Kong, China	1.2	0.4	0.2	0.1	0.8	0.8	2.7	4.5

Source: Calculations by the WTO Secretariat.

Note: Names of WTO members are those used in the WTO.

Table 4.7: Net exporters of pharmaceutical products (categories A1, A2, A3), average 2016–2018

Exporter	Trade balance US\$ million
European Union	80,399
Switzerland	38,716
India	11,401
Israel	4,363
Singapore	4,203
Panama	304
Cuba	193
Jordan	94

Source: Calculations by the WTO Secretariat.

Note: Names of WTO members are those used in the WTO.

Table 4.8: Net importers of pharmaceutical products (categories A1, A2, A3), average 2016–2018

Importer	Trade balance US\$ million
United States	-55,313.38
Japan	-17,472.52
China	-11,086.42
Russian Federation	-8,824.96
Brazil	-5,308.62
Australia	-5,250.85
Saudi Arabia, Kingdom of	-4,549.73
Canada	-3,799.33
Venezuela	-3,068.04
Viet Nam	-3,049.13
Turkey	-3,001.50
Korea, Republic of	-2,731.61
Chinese Taipei	-2,671.86
United Arab Emirates	-2,402.01
Mexico	-2,342.76
Egypt	-2,042.96
Thailand	-1,957.61
Colombia	-1,734.01
South Africa	-1,723.03

Source: Calculations by the WTO Secretariat.

Note: Names of WTO members are those used in the WTO.

equipment sector in national development strategies. China doubled its share of world exports of health products (all categories combined) from 6 per cent in 2010 to 12 per cent in 2018.

Global value chains open new manufacturing and integration opportunities. For instance, Israel, the Republic of Korea and Singapore have grown to become significant exporters of bulk medicines (category A2). India has become a major exporter of pharmaceutical inputs (category A3), and Malaysia, Chinese Taipei³⁹⁴ and Thailand are now important exporters of chemical inputs (category B), some of which are used to manufacture health-related products. Similarly, Costa Rica, Mexico, Singapore, Chinese Taipei³⁹⁵ and Thailand and are important exporters of orthopaedic equipment (category C3).

While some developing countries represent a small proportion of exports of health products from the global point of view, these products may, nonetheless, represent a significant share of national exports. For instance, health products (all categories combined) represent one third of total exports in Costa Rica (34 per cent) and Panama (31 per cent), and they make up a substantial share of the total exports of the Dominican Republic (16 per cent) and Israel (16 per cent).

In conclusion, vigorous growth in health-related products and strong global demand mean that development strategies targeting the production and trade of health-related products offer developing countries and territories promising avenues for economic growth and diversification.

Likewise, for some countries, imports are highly significant domestically, even if they comprise a small share of global imports. Imports of health-related products represent 5 per cent or more of all imports for 91 countries and territories reviewed, with this share rising to 35 per cent in Panama, 18 per cent in Switzerland, 12 per cent in Brazil, 11 per cent in the Central African Republic and 10 per cent in Colombia, Costa Rica, Burundi, Malawi and Argentina (see Table 4.9).

Between 1995 and 2018, substantial, and widening, variations in per capita imports of health-related products could be observed in countries at different levels of development (see Figure 4.11), highlighting stark differences in access to medicines. Developed countries' per capita imports in current US dollars multiplied 19-fold, from US\$ 10.9 in 1995 to US\$ 206 in 2018. By contrast, in 2018, per capita imports of health products stood at US\$ 21 in developing countries and US\$ 5.9 in LDCs. Nonetheless, per capita imports more than doubled in both developing countries and LDCs between 2005 and 2018. In the case of LDCs, which produce few medicines and rely very heavily on imports, these import statistics are reasonable indicators of overall consumption

Table 4.9: Share of health product imports in total national imports, 2018

Country	Share of national imports %
Panama	35
Switzerland	18
Brazil	12
Central African Republic	11
Colombia	10
Costa Rica	10
Burundi	10
Malawi	10
Argentina	10
Lebanon	9
United States	9
Russian Federation	9
Togo	9
European Union	8
Japan	8
Rwanda	8
Ecuador	8
Iran	8
Israel	8
Uganda	8

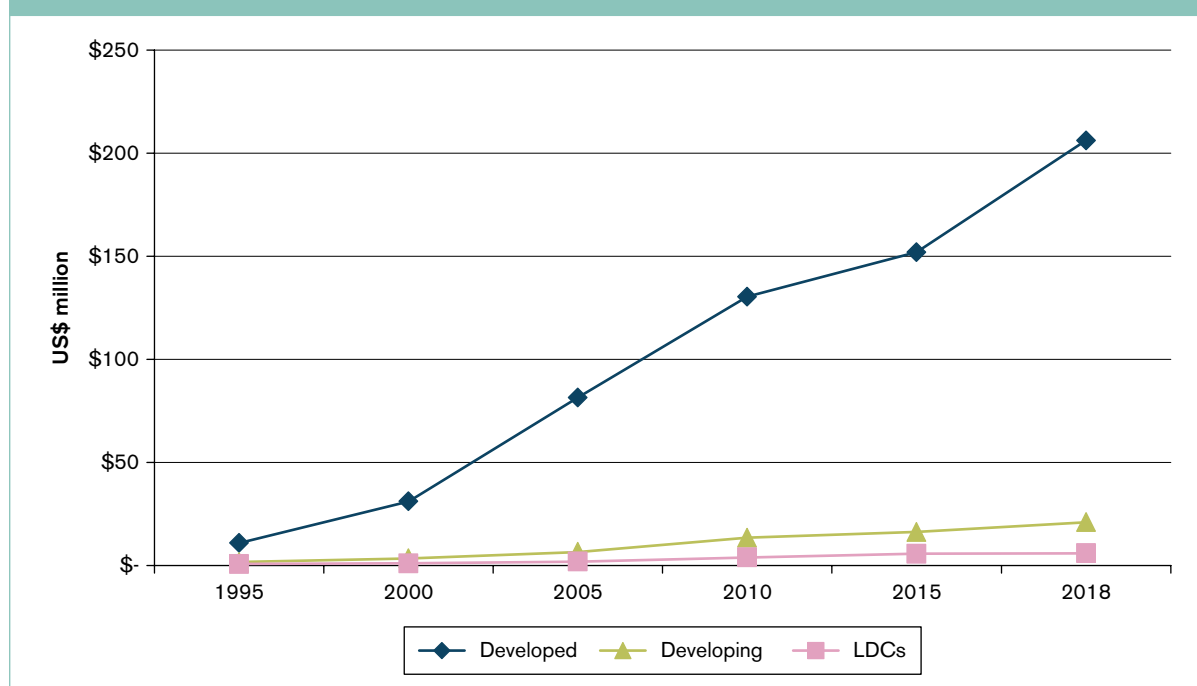
Source: Calculations by the WTO Secretariat.

of medicines; therefore, despite some improvement, the relative level of importation remains very low, particularly given the high disease burden in LDCs.

(b) Tariff policy for health-related products

Tariffs or import duties on pharmaceuticals affect prices, protection for local production capacity and generation of revenue (Olcay and Laing, 2005). The WHO has recommended that countries “reduce or abolish any import duties on essential drugs” (WHO, 2001c). Initiatives such as the Malaria Taxes and Tariffs Advocacy Project call for the reduction of tariffs on certain products, including treated mosquito nets, artemisinin-based combination therapies, diagnostic tests, insecticides and related equipment (see Boxes 4.28 and 4.29). Patterns of tariffs applied to the seven health-related product groups therefore have a direct bearing on access.

Some of the highest average tariff rates are in force in countries that rely exclusively or heavily on imports to satisfy their public health needs. For instance, the average tariff rate applied to imports of medical technology equipment (category C2) was 25.9 per cent in Djibouti, 10.6 per cent in Cuba, 9.4 per cent in Argentina, 9.1 per cent in India and 9 per cent in Brazil. Similarly, imports of medicines for retail sale or in bulk (categories A1 and A2) were subject to average tariff rates of 10 per cent or above in Nepal, Morocco, the Democratic Republic of Congo, Djibouti, Pakistan and India. Seventeen developing countries and LDCs applied average tariff rates of 10 per cent or above to hospital and laboratory inputs (category C1).

Figure 4.11: Per capita imports of pharmaceutical formulations 1995–2018

Source: Calculations by the WTO Secretariat.

Box 4.28: How tariff reductions can save human lives: the example of mosquito nets

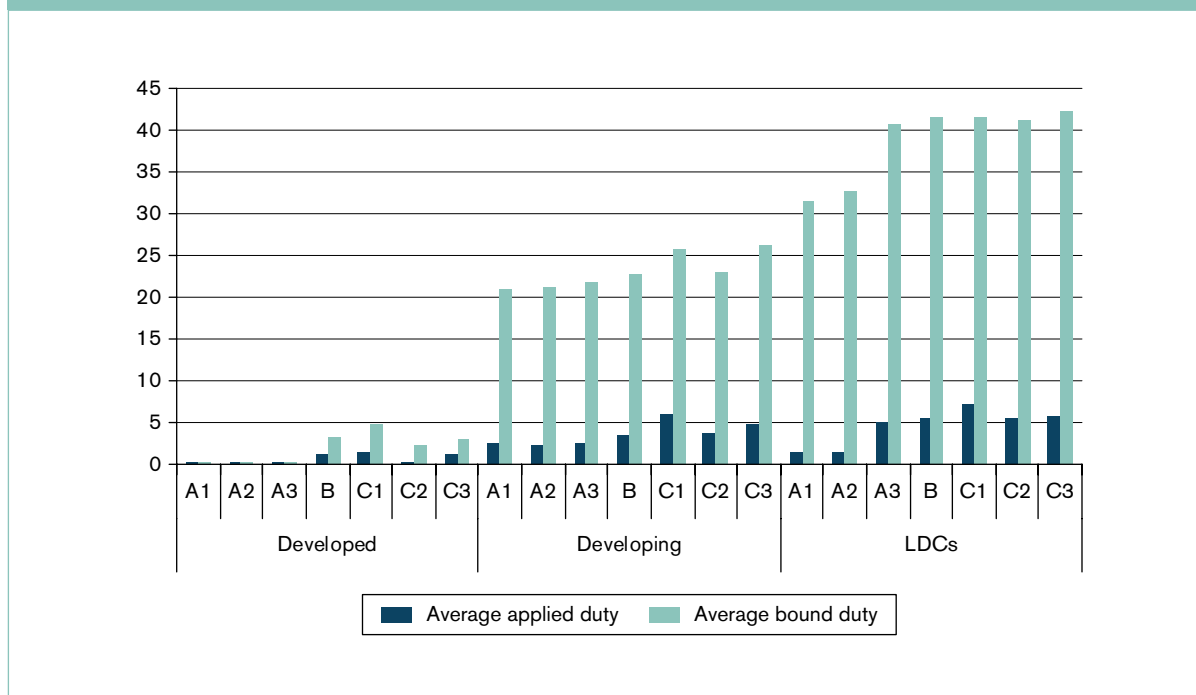
Despite excellent progress having been achieved in recent years, malaria continues to have a devastating human impact. In the absence of an efficient vaccine, the use of insecticide-treated mosquito nets (ITNs) remains one of the most effective prevention means. Yet many countries – in particular, in sub-Saharan Africa, the region most exposed to malaria – continue to impose import tariffs on ITNs.

A 2017 WTO Working Paper estimated that the imposition of import tariffs in sub-Saharan Africa has suppressed demand for more than 3 million ITNs between 2011 and 2015, while fiscal income derived from these duties was very limited. Had these 3 million ITNs been available, almost 2.9 million malaria cases and close to 5,200 deaths could have been avoided. Although these estimates should be interpreted with caution, they illustrate the significant negative human impact that import duties on malaria prevention means can have.

While many countries apply concessions or exemptions to ITNs imported by humanitarian institutions and NGOs, these are often bound to specific conditions and can be granted in a discretionary manner. Concessions granted in the form of repayment of import tariffs and other duties are often subject to considerable time lags and additional costs. The Working Paper found that the best policy is to bring tariffs on ITNs and other anti-malarial products to zero, coupled with measures to expedite and facilitate their importation.

Source: Klau, Arne (2017), “When bad trade policy costs human lives: tariffs on mosquito nets”, WTO Staff Working paper, available at: https://www.wto.org/english/res_e/reser_e/ersd201714_e.pdf.

Figure 4.12: Tariffs on health-related products: simple applied average versus WTO simple bound average rates, by product category, 2018



Source: Calculations by the WTO Secretariat.

Governments can increase tariffs applied to health-related products at any time, as long as such increases are within the limits of tariff ceilings that WTO members prescribe for themselves (called bound duty rates or “tariff bindings”). Sometimes, the gap between tariffs actually applied and the maximum WTO legal ceiling is very substantial (see Figure 4.12), creating uncertainty among traders about whether the effectively applied

tariff rates might be increased. Substantial cuts in bound rates to align them with actual rates, promote stability and predictability in tariff rates, and could promote trade and investment in health products.

It should be noted that the impact of tariffs may be nuanced by particular circumstances that are not captured in this analysis. For instance, governments sometimes apply special

concessionary tariff regimes for certain strategic products, for example, waiving import duties on pharmaceuticals or health-related products in order to improve access. Several countries are reported to apply such tariff exemptions for public health commodities, especially for not-for-profit purchasers (Krasovec and Connor, 1998).

FTAs frequently include provisions for preferential treatment between the agreement signatories. This may include reducing or removing import tariffs, which, in turn, results in more favourable market access than that afforded by multilateral (WTO) commitments. This section of the study only considers tariffs applied in the absence of such preferential deals, i.e. on a most-favoured-nation (MFN) basis. The difference can be very significant for LDCs and developing countries; for example, syringes may be imported free of tariffs from a country with preferential market access, but they may be subject to a 16 per cent tariff when imported from other WTO members. As a result, procurement of health-related products is skewed towards partners in FTAs. A comparison of preferential tariff rates with those applied in the absence of preferences reveals that, for Brazil, China, Mexico, India, South Africa and Turkey, preferential tariffs for all three product groups (A, B and C) fell between 2005 and 2009 and were lower than the WTO MFN rate (by at least 0.4 per cent). The gap between preferential treatment and MFN treatment has thus widened, with the lowest tariffs applying to medicines (A) and the highest tariffs applying to medical devices (C).

Overall, but with significant exceptions, tariffs on health-related products have reduced substantially during recent years, and only represent one of the cost factors in the complex equation that determines access and affordability.

However, remaining tariffs often represent a cost increase at the beginning of a value chain, so their impact on final prices may be magnified considerably by add-ons applied in the national distribution chain (excise taxes, distribution services, mark-ups and retail services), based on that higher import cost.

Apart from their impact on prices, tariffs also affect the conditions for local production initiatives – in terms of the cost of inputs such as chemical ingredients, the competitiveness and export focus of local producers, and the protection afforded by tariffs on imported products. The trend towards lower tariffs for specific and general chemical inputs into the pharmaceutical industry (categories A3 and B1) may help boost competitiveness of the local pharmaceutical industry. The tariff data above do not provide conclusive insights into the effectiveness of efforts to build up local production capacities. However, it would seem that tariffs are losing overall significance in these policy efforts. Box 4.28 outlines sectoral tariff negotiations related to public health in the GATT and the WTO.

Box 4.29: Sectoral tariff negotiations in the GATT and the WTO

During the Uruguay Round trade negotiations, some countries agreed to negotiate tariff reductions in specific economic sectors.³⁹⁶

In 1994, Canada, the European Communities,³⁹⁷ Japan, Norway, Switzerland and the United States concluded the WTO Pharmaceutical Agreement. They were joined by Macao, China, after its accession to the WTO in 1995. These countries cut tariffs on pharmaceutical products and chemical intermediates used for their production (the “zero-for-zero initiative”), including all active ingredients with a WHO international non-proprietary name (INN). They agreed to periodically review and expand the list of items covered. The last such expansion took place in 2010.

Also during the Uruguay Round, some WTO members agreed to harmonize tariffs on chemical products, bringing them to zero, 5.5 per cent and 6.5 per cent, in what is referred to as the “chemical harmonization” initiative.

Participants in the WTO Information Technology Agreement (ITA) have agreed to eliminate tariffs on a number of health-related products. The ITA is a plurilateral agreement under which participating WTO members liberalize their imports of information and communication technology products. The ITA, originally adopted in 1996, was expanded in 2015 to cover additional products.³⁹⁸ As a result, 55 WTO members have agreed to eliminate tariffs on 201 high-tech products with an international trade valued at over US\$ 1.3 trillion per year (approximately 10 per cent of world trade in goods today). Among the products covered in that expansion, several are used in health-related services, including electrocardiographs, ultrasonic scanners, magnetic resonance imaging machines and pacemakers. Tariff elimination for such products should be fully implemented by 2019.

In addition to tariffs, the availability and price of health-related products is influenced by costs and delays related to their importation and exportation. Import licences or authorizations, sampling, testing, conformity assessment procedures (see Chapter II, section B.3(b)), certification or inspections, etc., increase trading costs and cause delays. Trade costs are a determinant factor in price composition, particularly in landlocked and least-developed countries, where transportation, distribution and logistical costs tend to be highest. Simple, efficient and transparent import-related documents and procedures contribute to low trading costs and, thus, lower prices. The WTO Trade Facilitation Agreement aims at reducing trade-related costs, including as regards the import of medical technologies (see Box 4.30).

Box 4.30: The WTO Trade Facilitation Agreement

The WTO Trade Facilitation Agreement³⁹⁹ contains provisions that aim to modernize customs systems and will encourage WTO members to rationalize and simplify their import-export procedures and formalities. As a result, implementation of all the provisions of the Agreement could reduce members' trade costs by an average of 9.6 per cent to 23.1 per cent, with African countries and LDCs expected to experience the biggest potential reductions. Globally, trade-related costs could be reduced by an average of 14.3 per cent. To the extent that trade costs are typically passed on to consumers, the implementation of the WTO Trade Facilitation Agreement could make a direct contribution to more affordable health products.

2. Competition law and policy

The importance of competition (antitrust) law and policy in promoting innovation and ensuring access to medical technologies derives from its cross-cutting relevance to all stages and elements involved in the process of supplying medical technology to the patient – from the development and manufacture of such technology to its eventual sale and delivery (see Chapter II, section B.2).

In the pharmaceutical sector, different originator companies compete for the development of new medicines. Once a pharmaceutical product has been developed, one of the main determinants of access to it is affordability, for example, the final price paid by a health-care provider (such as a hospital) or the consumer. The prices charged by manufacturers, whether originator or generic, are an important factor in determining this final price, and competition between different manufacturers has been found to have a beneficial effect on the affordability of and access to pharmaceuticals. Two forms of competition take place. The first is between-patented-product competition, which is competition between manufacturers of different originator medicines within a given therapeutic class. The second is competition between the originator companies and producers of generic products (as well as among the generic companies themselves), usually after expiry of the patent. Equally, competition issues, for example, in the distribution of pharmaceuticals, can drive up prices. While a full analysis of all competition policy issues involved is beyond the scope of this study, this section outlines a number of areas in which competition policy has direct relevance. The main focus in this section is on the link with the access dimension.

What follows is a review of the main competition cases and investigations carried out in health-care-related

markets. Different jurisdictions apply their own specific procedural rules. Hence, in some jurisdictions, first-instance decisions are made by competition agencies themselves (this is the case of the European Commission); in other jurisdictions, the competition agency carries out the preliminary investigation and the first-instance decision is made by either a specialized court (e.g. in Canada and South Africa) or an ordinary court (e.g. in the United States). The following discussion has to be read in this light. Some of the investigations presented have not yet resulted in a decision (whether by a competition agency or by a court) and should be interpreted as being simply informative, as they may result in allegations being dropped by competition agencies themselves or agencies' decisions being turned down by the courts.

A number of developed- and developing-country jurisdictions have been involved in addressing anti-competitive practices in the pharmaceutical sector. Some competition authorities have carried out sector-wide inquiries and published reports to gain a better understanding of competition concerns in the pharmaceutical sector and to identify relevant markets. A number of competition authorities have conducted investigations of specific cases and charged fines or brought legal cases against alleged violators. Both approaches are discussed in the sections below in the context of application of competition law to manufacturers of originator and generic products.

International organizations play an important role in contributing to policy discussion in this area. Institutions such as UNCTAD, UNDP and the OECD support member states in developing and implementing competition law in health care.⁴⁰⁰ In 2018–2019, some WTO members, building on the existence of competition-related provisions in the TRIPS Agreement,⁴⁰¹ called for a discussion of the interface between IP and competition law and policy with a particular focus on the pharmaceutical sector. For this purpose, they invited members to share national experiences and best practices regarding the use of competition law and policy to achieve public health objectives. Some other members, however, considered that the TRIPS Council was not the appropriate forum for such a discussion and cautioned against an overly broad interpretation of relevant TRIPS provisions.⁴⁰²

(a) Application of competition law and policy to manufacturers of originator products

Originator companies can use a variety of strategies to delay the market entry of generics, of which certain strategies may attract competition authority scrutiny. Some of the key approaches applied by originator companies, identified in the European Commission's

Pharmaceutical Sector Inquiry Final Report (European Commission, 2009a), include:

- Strategic patenting to extend the scope and duration of exclusivity
- Litigation, including reverse patent settlement agreements
- Life-cycle strategies, including strategies that aim to switch patients from products facing patent expiry to newer, more expensive products
- Other strategies, including interventions before national regulatory authorities and/or pricing and reimbursement bodies.⁴⁰³

The following examples describe some business practices that have been investigated by competition authorities.

(i) *Strategic patenting*

The 2009 European Commission Pharmaceutical Sector Inquiry Final Report found that originator companies file for numerous patent applications (on process, reformulation, etc.) in addition to the base patent, with the aim of creating several layers of defence against generic competition.⁴⁰⁴

It showed that individual blockbuster medicines were protected by almost 100 INN-specific EPO patent families, which, in one case, led to up to 1,300 patents and/or pending patent applications across the EU member states. The report referred to such a multitude of patents as a “patent cluster”. It described the effect of this strategy: generic companies, even if they manage to invalidate the base patent before its regular expiry, still cannot enter the market.

The report describes the filing of divisional patent applications as another strategy used by originator companies. This strategy involves keeping subject matter that is contained in a parent application pending even if the parent application as such is withdrawn or revoked. Divisional patent applications allow the applicant to divide out from a patent application (parent application) one or several patent applications (divisional application).

Divisional applications must not go beyond the scope of the parent application. The division must be made while the parent application is still pending, leading to separate applications, each with a life of its own. These applications have the same priority and application date as the parent application, and, if granted, have the same duration as the parent application. In cases where the parent application is refused or withdrawn, the divisional application remains pending.

The European Commission stated that both practices are aimed at strategically delaying or blocking the market entry of generic medicines by creating legal uncertainty for generic competitors.⁴⁰⁵ However, in a European Commission 2019 list of cases, no competition law cases have been reported related to the creation of “patent clusters” or the use of divisional patent applications themselves as violations of competition law.⁴⁰⁶ Moreover, over the past ten years, the Commission reports three investigations⁴⁰⁷ related to the pharmaceutical sector that underwent judicial review. The European Commission Pharmaceutical Sector Inquiry Final Report’s main recommendations⁴⁰⁸ were in fact of a regulatory nature, proposing to establish a Community patent and a unified specialized patent litigation system in Europe,⁴⁰⁹ welcoming the EPO’s initiative to ensure high-quality patents and recommending that EU member states ensure speedy administrative procedures, e.g. for generic medicines approval and to promote transparency in generic-medicines-related advertisement campaigns.

In Brazil, an investigation by the competition authority into alleged violations of competition law through strategic patenting, among other things, is pending.⁴¹⁰ In South Africa, the competition authority has investigated strategic patenting in combination with abuse of dominance/excessive pricing (see Boxes 4.31 and 4.36).

(ii) *Patent litigation*

Originator companies can be plaintiff or defendant in patent litigation. In that regard, in particular, “sham litigation” and reverse patent settlements (also termed

Box 4.31: Competition investigation into strategic patenting – cases from South Africa

In June 2017, the Competition Commission of South Africa (CCSA) initiated two investigations for abuse of dominance in relation to IP-protected oncology medicines.

While the investigation remains ongoing, allegations include patent strategies as a way to delay or prevent entry of generic alternatives of breast cancer medicines in South Africa.⁴¹¹ The CCSA is scrutinizing whether these patenting strategies were used to engage in excessive pricing, exclusionary conduct and price discrimination with regard to the sale and supply of trastuzumab (medicines to treat breast and gastric cancer) and crizotinib (medicines to treat lung cancer). A final decision of the Commission is pending.

“pay-for-delay” agreements) have emerged as a focus of competition agencies’ enforcement action.⁴¹²

Litigation proceedings initiated by patent holders can constitute a deterrent to market entry of generics irrespective of the final outcome. Courts may grant preliminary injunctions in favour of patent holders while litigation is pending and before the ultimate determination of the validity of patents is made. In that regard, the pharmaceutical sector has come under close scrutiny under abuse of dominance rules in so-called sham litigation cases.⁴¹³ Under this strategy, a patent holder brings a patent infringement suit that is “objectively baseless”, the sole purpose of which is to create costs and delays to market entry for a prospective competitor (Zain, 2014). Competition authorities have recently fined originator companies for sham litigation, for example, in the United States and Brazil (see Box 4.32).⁴¹⁴

On the other hand, settlement agreements can be reached during opposition proceedings or patent litigation between generic manufacturers and originator companies. Patent disputes, like any other types of lawsuit between private entities, may legitimately be settled in order to avoid costly litigation. However, such settlements can have effects that restrict competition and can therefore be undesirable from the standpoint of competition policy. Competition authorities have found that settlement agreements sometimes include negotiated restrictions on the generic company party to the litigation entering the market in return for a cash payment or other benefit granted by the originator company to the generic company. Such reverse patent settlement agreements

(“pay-for-delay” agreements) have been identified as anti-competitive as they delay generic entry and maintain higher prices.

A landmark case, *FTC v. Actavis*, was decided by the Supreme Court of the United States in 2013, in which the Court ruled that, while such settlements may fall within the scope of the exclusionary rights conferred by the patent, this does not shield such agreements from antitrust scrutiny. This ruling opened the path for a “rule-of-reason”⁴¹⁸ assessment of reverse settlement agreements under US competition law (see Box 4.33).

Other jurisdictions have adopted guidelines and/or brought cases against pharmaceutical companies concluding such agreements (see Box 4.34 on the European Union and Box 4.35 on the Republic of Korea).⁴¹⁹

(iii) Refusal to deal and restrictive licensing practices as abuse of dominance

In some jurisdictions, and in particular circumstances, the refusal of an IP right holder to license the protected technology may be considered an anti-competitive abuse of dominance (see Box 4.36). Compulsory licensing can arguably provide an effective remedy in circumstances in which a refusal to license may be abusive in character. However, it is important to note that refusals to license *per se* are not necessarily actionable abuses. On the contrary, the right of such refusal is implicit in the grant of the IP rights.

Box 4.32: Action against sham litigation in the pharmaceutical sector in Brazil

In a case that received attention in Brazil,⁴¹⁵ the Brazilian Administrative Council for Economic Defence (CADE) fined a company approximately US\$ 8.4 million in June 2015 for filing sham litigation claims. According to CADE, the company actions met the three requirements necessary for establishing sham litigation according to Brazilian case law: (1) implausibility of the claims; (2) provision of erroneous information; and (3) unreasonableness of the means used. CADE noted that, as a result, the originator managed to keep competitors out of the market between 2007 and 2008. As a result of the sham litigation, São Paulo’s health department paid three times more for the medicine in question in comparison with the period prior to the patent expiry. Four further sham litigation cases in the pharmaceutical sector are or have been under investigation in Brazil. In three cases, no sufficient elements of sham litigation were found.⁴¹⁶ The fourth case is pending.⁴¹⁷

Box 4.33: Reverse patent settlement ruling by the Supreme Court of the United States and subsequent developments⁴²⁰

In its 2013 landmark decision, the Supreme Court of the United States established specific considerations for lower courts to apply when considering patent settlements, including analysis of the genuine adverse effects on competition that may result from the settlement, and special consideration to the payment, that is, the existence of large and unexplained payments, which may serve as an indicator of the power of the patentee to bring about anti-competitive harm in practice.

Since this ruling, the FTC has published two staff reports monitoring patent settlements. The report of November 2017 found 14 potentially anti-competitive patent settlement deals in fiscal year (FY) 2015, a reduction on the 21 identified in the FY 2014 report. Five settlements in FY 2015 contained both compensation to the generic company and a restriction on generic company entry. In February 2019, the FTC entered into a settlement with the last remaining defendant in the earlier landmark case.

Box 4.34: The European Union's Guidelines on Technology Transfer Agreements, monitoring and enforcement against reverse patent settlements in the pharmaceutical sector⁴²¹

Following the European Commission's Pharmaceutical Sector Inquiry (European Commission, 2009a),⁴²² the Commission has been monitoring patent settlements between originator and generic companies and publishing annual reports in order to better understand the use of this type of agreement in the European Economic Area and to identify those settlements that delay generic market entry to the detriment of the European consumer.⁴²³

In 2014, the European Commission adopted new Guidelines on the application of Article 101 of the Treaty for the Functioning of the European Union (TFEU) to technology transfer agreements.⁴²⁴ The Guidelines state that, while patent settlement agreements are, in principle, a legitimate way to find mutually agreed solutions to technology disputes, "pay-for-delay" type settlement agreements based on a value transfer from one party in return for a limitation on the entry into and/or expansion on the market of another party may be caught by Article 101 of the TFEU.

The European Commission has adopted three individual decisions against pharmaceutical companies involving reverse patent settlements. The Commission found that the agreements had caused consumer harm by delaying generic entry and unduly maintaining high prices. The decisions in two cases have been upheld in principle by the European Union General Court upon appeal. Similarly, in a decision of February 2016, when enforcing the Guidelines, the UK Competition and Markets Authority found, among other things, that an originator had abused its dominant position by entering into reverse patent settlement agreements with generic competitors.⁴²⁵

Box 4.35: Competition law enforcement against a reverse patent settlement in the Republic of Korea⁴²⁶

In the Republic of Korea, an originator and a generic producer agreed to settle a dispute relating to a patented medicine based on the following conditions: the generic manufacturer was to remove the generic product from the market, and not to develop, manufacture or sell medicines that could compete with the originator's product in the antiemetic and antiviral agent market. In return, the originator would provide the generic manufacturer with the economic profits related to the dealership of the medicine in national hospitals, as well as the right to sell an originator medicine not related to the patent.

The Korea Fair Trade Commission found that the agreement constituted an unreasonable restraint of competition, imposed a remedial order to remove the non-competition conditions of the agreement and levied fines totalling US\$ 4.4 million (KRW 5.34 billion). In February 2014, the Supreme Court of the Republic of Korea confirmed the findings of the Commission.

Box 4.36: Abuse of dominance in South Africa

In 2003, the Competition Commission of South Africa (CCSA) found that two originator pharmaceutical companies had allegedly abused their dominant position in their respective antiretroviral (ARV) markets by charging excessively high prices for their patent-protected ARVs, by refusing to give competitors access to an essential facility when it was economically feasible to do so, and by engaging in an exclusionary act.⁴²⁷

The Commission did not pursue the case since the companies undertook to:

- issue the licences to a number of domestic generic manufacturers, and
- permit the licensees to export the relevant ARV medicines to other sub-Saharan countries, charging royalties of no more than 5 per cent of the net sales of the relevant medicines.

In 2007, a third major pharmaceutical company agreed to grant licences to produce and sell ARVs, following a complaint brought before the CCSA about its refusal to license its product to generic manufacturers.

These cases concern settlements rather than fully litigated competition law decisions. The settlements reached are understood to have contributed to the substantial reduction in prices of ARVs in South Africa.⁴²⁸

In many jurisdictions, other licensing practices, the effects of which on competition are normally evaluated on a case-by-case basis, are regulated by competition law and related competition authority guidelines. Such practices, which are of concern if implemented by companies holding market power or a dominant position, may include:

- “Grant-backs” that legally grant back to the holder of a particular patent the right to use improvements made by a licensee to the licensed technology. Where such licences are exclusive, they are likely to reduce the licensee’s incentive to innovate since it hinders the exploitation of his/her improvements, including by way of licensing any such improvements to third parties.
- “Exclusive dealing requirements” requiring a licensee to use or deal only in products or technologies owned by a particular right holder.
- “Tie-ins” or “tying arrangements” requiring that a given product or technology (the “tied product”) be purchased or used whenever another product or technology (the “tying product”) is purchased or used.
- “Territorial market limitations” limiting the territories within which products manufactured under licence may be marketed.
- “Field-of-use” restrictions limiting the specific uses to which patented or other protected technologies may be put by a licensee.
- “Price maintenance clauses” stipulating the price at which products manufactured under licence may be sold. Relevant clauses in licensing contracts can either be declared invalid in patent laws or other IP laws, or invalidated as violations of (general) competition law.

As such clauses need to be evaluated taking into account their terms and the circumstances of the case at hand, some competition authorities have issued guidelines in order to provide further clarity and guidance to the private sector. International institutions can facilitate discussion in that regard.⁴²⁹

(iv) Interface of regulatory systems and competition law

Under certain circumstances, regulatory systems are used to prevent or delay generic market entry. This has also been identified as anti-competitive practice. One example of misuse of regulatory systems is seen in so-called “hard” product-switching (also termed “product hopping”). This is a strategy applied by patent holders when products are nearing patent expiry. In such cases, a patent holder first introduces to the market a new product with minor, non-therapeutic differences from the established product. The patent holder then withdraws from the market the established product, and may also increase the price

of the established product, thus forcing or encouraging patients and buyers to switch from the older product to the newer one. The established product is the “reference product” that prospective generic entrants will refer to in their approval submissions. Strategic deregistration can thus prevent competition from generic manufacturers and/or parallel importers, as prospective competitors will lack a reference product to cite in regulatory submissions.⁴³⁰ Competition cases concerning “hard” product-switching have been brought in the United States and the European Union.⁴³¹

In the European Union, the judgments of the General Court (in 2010) and the CJEU (in 2012)⁴³² established that misleading public authorities and misusing the regulatory procedures as a part of a commercial strategy to launch a follow-on product can, in certain circumstances, constitute an abuse of a dominant position. In that case, the originator selectively deregistered the marketing authorizations for an off-patent capsule version. The strategic deregistration made it impossible for generic competitors and parallel importers to compete with the originator.

(b) Competition law and policy in relation to the generics sector

The effect of generic competition, including between generic manufacturers, on medicine prices after patent expiry has been highlighted in various studies carried out by international institutions and developed jurisdictions (European Commission, 2009b). In general, these studies have found that savings from generic competition are substantial. The US FTC estimates that generic competition leads to price decreases of 20 per cent to 90 per cent, depending on the number of generic market entrants.⁴³³ The European Commission found that, on average, price levels for a sample of medicines that faced loss of exclusivity in the period 2000–2007 decreased by almost 20 per cent one year after the first generic entry. In rare cases, the decrease in the average price index was up to 90 per cent in the first year of generic entry.⁴³⁴ Other studies exploring these issues have been conducted by the Canadian Competition Bureau and the OECD.⁴³⁵

Where market entry of generics has occurred, the application of competition law to generic manufacturers is necessary in order to prevent anti-competitive practices by such companies and also oversee mergers that may restrict competition (see Box 4.37).

Competition authorities in both developed and developing countries have scrutinized “excessive prices” charged by pharmaceutical companies as a result of, and/or potential, infringement of competition law (see Box 4.38). The issue of excessive pricing in regard to generic medicines has

Box 4.37: Applying competition law to generic manufacturers

In the United States, the FTC has found cases in which generic companies have entered into anti-competitive agreements in order to control markets for generic medical technology and ancillary markets. For example, in 2000, the FTC found that one generic manufacturer concluded exclusive agreements for the supply of raw materials for producing lorazepam and clorazepate with four companies, which resulted in a dramatic increase in the price of these products. In a move designed not only to deter such behaviour but also to compensate the public for the welfare losses incurred, the FTC ordered the generic manufacturer to pay US\$ 100 million to consumers and state agencies that had suffered losses as a result of excessive prices.⁴³⁶

In the European Union, in 2013, the Italian competition authority alleged anti-competitive behaviour by a manufacturer of cholic acid – used to produce a medicine for liver diseases – who manufactured both the intermediate and the end product. The manufacturer had raised the price of the intermediate while offering selective price cuts on the end product to the customers of a competitor (a “price squeeze” strategy). The Italian competition authority intervened to ensure that the manufacturer supplies the intermediate, cholic acid, to competitors at an adequate price.⁴³⁷

been raised in a number of cases, notably in Europe and South Africa (see Box 4.39), and the issues related to excessive pricing pharmaceuticals (whether IP protected or generic) is an area of active discussion.⁴³⁸

Box 4.38: General approaches to “excessive pricing” in domestic laws

Article 102 of the TFEU prohibits, *inter alia*, imposing unfair purchase or selling prices. The CJEU established in *United Brands v. Commission* (1978) that “charging a price which is excessive because it has no reasonable relation to the economic value of the product supplied” would be an abuse under Article 102 of the TFEU. A two-part test was established to recognize an abusive price: (1) the price–cost margin is excessive; and (2) the price imposed is either unfair in itself or when compared with competing products.⁴³⁹

The South African Competition Act defines an excessive price as one that “bears no reasonable relation to the economic value of the product” and “is higher than the [economic value]”.⁴⁴⁰

The Canadian Competition Act identifies “unreasonable enhancement of price” based on a patent right as grounds for remedies such as the court-ordered granting of licences on the relevant patent(s).⁴⁴¹

In 2018, an OECD report highlighted similarities among recent (2016–2018) “excessive pricing” competition cases. These cases have concerned:

- medicines that have long been off patent
- sudden and significant price increases of generic products that have long been in the market
- essential pharmaceutical products with no reasonable prospect of the entity responsible for providing them for patients not purchasing them, leading to demand that is extremely price inelastic
- medicines for which there was no prospect of timely market entry for alternative products, due to supply constraints, the regulatory framework or the limited size of the market
- situations in which regulatory interventions were perceived to be unable to provide an appropriate response to the price increase.⁴⁴²

Box 4.39: Examples of “excessive pricing” cases concerning pharmaceuticals

In 2017, both the European Commission and the Competition Commission of South Africa (CCSA) investigated against a generic producer based in South Africa for excessive pricing of cancer medicines, including chlorambucil, melphalan and busulfan – all of which are off patent.⁴⁴³ This is the European Commission’s first investigation into excessive pricing practices in the pharmaceutical industry. In October 2017, the CCSA dropped the investigation as an excessive pricing case could not be sustained.⁴⁴⁴ As at August 2019, the European Commission investigation is still ongoing. The Italian competition authority had already adopted an infringement decision against the company in 2016, imposing a EUR 5 million fine for abuse of dominance by setting excessive prices for the same medicines in Italy. On appeal, the Italian First Grade Administrative Court had confirmed the decision.⁴⁴⁵

The UK Competition and Markets Authority (CMA) has brought cases based on an excessive pricing charge in a number of instances, including regarding an anti-epileptic medicine.⁴⁴⁶ In that case, however, the Competition Appeals Tribunal concluded that the CMA did not correctly apply the legal test for excessive pricing.⁴⁴⁷ In January 2018, the Danish Competition Council ruled that a pharmaceutical distributor that public-sector buyers relied on had abused its dominant position by charging excessive prices.⁴⁴⁸

For a case concerning an originator company accused of excessive pricing, exclusionary conduct and price discrimination, see Box 4.31.

While, in the United States, excessive pricing in itself is not considered an antitrust infringement, cases of collusion among generic suppliers to fix prices have been investigated by competition authorities.⁴⁴⁹ In 2019, more than 40 US states initiated parallel cases investigating generic medicine manufacturers. Pharmaceutical producers were accused of fixing prices of more than 100 different medicines and dividing markets for medicines among themselves, rather than competing on price.⁴⁵⁰

Competition cases in European Union member states have addressed the off-label use of medicines (see Box 4.40).

(c) Application of competition policy to other actors in the health sector

Competition needs to be ensured with regard not only to manufacturers but also other actors in the health-care and retail sectors. Both restrictions of competition along the value chain (vertical restriction) and market restraints

Box 4.40: Jurisprudence on competition authority scrutiny to enable competition through off-label use⁴⁵¹

In 2014, the Italian national competition authority found that two pharmaceutical companies had entered into an anti-competitive agreement aiming to discourage and limit off-label use of the first company's oncology medicine for ophthalmologic treatment as it would compete with the second company's medicine in this market. The arrangement between the two undertakings included the dissemination of misleading information to the European Medicines Agency, health-care professionals and the general public. This information concerned adverse reactions resulting from the off-label use of one of their products in the context of scientific uncertainty, in order to discourage the use of the oncology medicine for the therapeutic indication identified in the market authorization of the other. After having been fined approximately EUR 90 million each by the Italian authority, the companies appealed to the Italian courts and the Italian Council of State. The Council of State asked the CJEU for a preliminary ruling. The CJEU held that a national competition authority may include in the definition of the relevant market medicinal products, the market authorization of which does not cover the treatment of a specific condition, but which are used for that purpose and are thus actually substitutable with the former. The CJEU found that an arrangement discouraging such use constitutes a restriction of competition "by object" as it reduces the competitive pressure resulting from the off-label use on the use of the other product.

Box 4.41: Hospital merger in Brazil⁴⁵²

A merger case reviewed by CADE (Brazil's competition agency) concerned two health-care providers: a cooperative medical service, which, in addition to offering individual, family and cooperative health plans, also had its own accredited laboratories, clinics, oncology service, various physiotherapy centres and a hospital; and a regional hospital in a form of a joint stock company also offering individual, family and cooperative health insurance. The competition agency considered that the two providers covered at least two separate segments of health-care services, namely: (i) hospital medical services; and (ii) diagnostic medicine support services.

In this specific case, CADE defined the relevant geographical market for hospital medical services as falling within the radius of 10 km of the hospitals in question. In order to analyse the degree of concentration resulting from the merger, CADE used the Herfindahl-Hirschman index (HHI). Before the merger, the HHI of the market was 3,855.3. After the merger, the HHI would have been 7,317.6. Due to this projection of a very strong concentration in the market as a result of the merger, CADE rejected the merger.

in the health-care or retail sectors (horizontal restrictions) can have highly detrimental effects on access to medical technology. This includes a lessening of competition through mergers. For example, a hospital merger case was considered by Brazil's competition agency and rejected because of the strong concentration in the market (see Box 4.41).

Similarly, a Health Market Inquiry conducted by the Competition Commission of South Africa (CCSA) in 2019⁴⁵³ reported a high level of concentration in the hospitals market in South Africa (see Box 4.42). In that regard, the Inquiry recommended, *inter alia*, that the CCSA address the situation through effective merger review and provide guidance to practitioner associations on desirable pro-competitive conduct.⁴⁵⁴

Vertical mergers between different companies that operate along the value chain can pose a threat to competition (see also Chapter II, section B.2(c)). For example, the US antitrust authorities have investigated mergers between pharmacy benefit managers (PBMs) and other players in the health sector.⁴⁵⁵ In addition to carrying out a range of other activities, PBMs help determine which prescription medicine claims to reimburse. Therefore, preservation of their neutrality is essential in maintaining competition.

Cartelization can restrict competition horizontally. Associations of pharmacies or pharmacists have been found in several OECD countries to have coordinated prices or restricted entry to the profession. In some

Box 4.42: The 2019 Health Market Inquiry of the Competition Commission of South Africa

In September 2019, the CCSA published the findings and recommendations⁴⁵⁶ of its Inquiry into the health-care sector, initiated in 2014.

Among other issues, the Inquiry reviewed interrelationships among various markets in the private health-care sector, including contractual relationships between and within different health service providers, the contribution of these interactions to private health-care expenditure, the nature of competition within and between these markets and ways in which competition could be promoted. It also included a consumer survey and public participation by various stakeholders, including patients covered by various medical schemes. The procurement dimension of these issues is also discussed in the report. At the end of the Inquiry, the Commission provided recommendations, including on approaches to regulatory issues and pricing.

cases, the associations restricted the ability of individual pharmacists to deal with third-party payers individually, thus establishing control over possible defectors and stabilizing cartel agreements. In a commitment decision in 2011, the Lithuanian competition authority addressed possible vertical price coordination in agreements between manufacturers and wholesalers. These agreements included a provision requiring that the wholesalers and manufacturers coordinate retail prices of medicines, and possibly resulting in prices of medicines being raised for the patients. Such a clause was deleted from the agreements after intervention of the competition authority.⁴⁵⁷

At the same time, both public-sector initiatives and contracted or franchised NGO participation in the retail market have been found to increase competition and

improve access to low-priced medical technology. For example, Uganda has contracted non-profit organizations to provide health services, and has allowed them to establish retail pharmacy outlets selling medical technology at affordable prices.

(d) The role of competition policy with regard to public procurement markets

The role of public-sector procurement and distribution is not to be underestimated. Competition policy is relevant in two key respects.

First, good procurement policies can maximize competition in the procurement process. Moreover, it can be cost-effective to procure bulk quantities of medicines.⁴⁵⁸ However, this may mean that a balance needs to be struck between achieving the lowest price in a given tender (through bulk purchases) and maintaining a competitive market structure over the medium to longer term. In that regard, a 2019 study in South Africa found that appropriately designed competitive tenders did not result in longer term lessening of competition (Wouters et al., 2019).

Second, competition policy has an important role to play in preventing collusion among suppliers of medical technology. Although transparency is generally considered conducive to integrity in the procurement process, it can also facilitate anti-competitive behaviour by, for example, facilitating the ability of competitors to match each other's prices. Competition policy and law therefore need to complement general procurement regulations and practices in order to guard against such behaviour, and competition authorities should be encouraged to monitor anti-competitive behaviour with regard to not only competition in private markets but, equally, competition in public markets for medical technology (Anderson et al., 2011).

Endnotes

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- 10 See Chakradhar and Khamsi (2017); Thomas (2015).
- 11 Thomas, 2015, p. 500.
- 12 See OECD data, available at: https://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_PHMC; see also Wouters et al., 2017; OECD, 2018.
- 13 See OECD (2018), pp. 143–146, for a general discussion of the generic market in OECD member states, generic policy options, and their strengths and weaknesses.
- 14 Interestingly, Australia has generic substitution policies, whereas England does not. Nevertheless, the relative volume of generics dispensed in England is much higher, suggesting that generic prescription policies are more effective than pharmacy substitution of generic medicines.
- 15 Amongst other things, the new price-disclosure scheme includes a shorter disclosure cycle (6 months compared to 18 months under the previous regime) and no longer factors in the price of originator brand medicines when determining the reimbursement price for generics; see the *National Health (Pharmaceutical Benefits) Regime 2017* (Cth).
- 16 For a general overview of pricing policies, see OECD (2008).
- 17 See <http://pmprb-cepmb.gc.ca/home>.
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- 19 See Angela Acosta, Regulation of Prices of Medicines in South America: Results and Concrete Strategies of Colombia, available at: <https://issuu.com/isagsunasur4>.
- 20 See Circular No. 7, 2009.
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- 26 See also the submission of the Ministry of Health of Colombia to WIPO's Standing Committee on Patents, as reported in WIPO document SCP/27/6, paras. 4–10.
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- 172 WHA, Resolutions WHA56.27, WHA57.14, WHA59.26 and WHA60.30.
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- 180 *National Research Development Corporation v. Commissioner of Patents (1961)* RPC 134.
- 181 “[...] patents are provided to encourage research [...] there would be less of a research incentive to find such methods if new treatment regimes [sic] are not, in principle patentable’ per Jacob J in *Teva Industries Ltd v Instituto Gentili SpA* [2003] EWHC Civ 5; [2003] FSR 29 at [80].
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- 183 *Pallin v. Singer*, 36 USPQ 2d 1050.
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- 191 WIPO documents SCP/14/5, 17/9, Annex, and 18/4, Annex I. All documents available at: https://www.wipo.int/meetings/en/topic.jsp?group_id=61.
- 192 WIPO document SCP/30/11, para. 90.
- 193 Presentation by the Delegation of Chile to SCP 29, Sharing session on approaches used by delegations to ensure the quality of the patent grant process within IP offices, including opposition systems, any challenges faced and how they have been overcome, available at: https://www.wipo.int/meetings/en/details.jsp?meeting_id=46447.
- 194 See http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf.
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- 201 The WIPO Database on Flexibilities in the Intellectual Property (IP) System is available at <https://www.wipo.int/ip-development/en/agenda/flexibilities/database.html> and contains data drawn from WIPO documents, namely, CDIP/5/4 Rev., CDIP/7/3 Add, CDIP/13/10 Rev, and CDIP/15/6 Corr. The references to laws were accurate at the date of publication of the above-mentioned documents in 2010, 2012 and 2015, respectively. Users are advised to cross-check laws in WIPO Lex to ensure that the most up-to-date version of the law is referenced. Regularly updated information on national laws regarding prior art, novelty, inventive step (Obviousness), grace period, sufficiency of disclosure, exclusions from patentable subject matter and exceptions and limitations of the rights is available at: https://www.wipo.int/scp/en/annex_ii.html.
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- 206 WIPO document SCP/28/3, paras. 15–24.
- 207 *Momenta Pharm., Inc. v. Teva Pharm. USA Inc. 809 F.3d 610* (Fed. Cir. 2015), cert. denied sub nom., *Amphastar Pharm., Inc. v. Momenta Pharm., Inc.* (US Oct. 3, 2016).
- 208 Chile, Israel, Latvia, Pakistan, Peru and the United States.
- 209 Section 107A(a) of the Patents Act of 1970 of India.
- 210 WIPO document SCP/28/3, fn 110.
- 211 SCP/27/3, p. 16, para. 48.
- 212 SCP/28/3, para. 77.
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- 214 Decision No. 486 Establishing the Common Industrial Property Regime for the Andean Community of September 14, 2000; Patent Regulation of the Cooperation Council for the Arab States of the Gulf; the Agreement Revising the Bangui Agreement of March 2, 1977, on the Creation of an African Intellectual Property Organization (Bangui (Central African Republic), February 24, 1999); and at the European Union level – Directive 98/44/EC of the European Parliament and of the Council of July 6, 1998 on the legal protection of biotechnological inventions and Regulation (EC) No. 816/2006 of the European Parliament and of the Council of May 17, 2006 on compulsory licensing of patents relating to the manufacture

- of pharmaceutical products for export to countries with public health problems. Section 3(12) of the Protocol on Patents and Industrial Designs within the Framework of the African Regional Intellectual Property Organization (ARIPO) and Article 12 of the Eurasian Patent Convention (EAPO) provide the possibility of a grant of a compulsory licence with respect to the patents issued by these respective Organizations in accordance with the national law of the member country concerned.
- 215 WIPO document SCP/30/3, Annex, part 2: Objectives and Goals of the Compulsory Licensing.
- 216 WIPO document SCP/30/3, Annex, para. 104.
- 217 This issue was raised in consultations requested by the United States with Brazil under the WTO dispute settlement mechanism. The mutually agreed solution can be found in WTO document WT/DS199/4.
- 218 See Article L613-16 of the French Code de la propriété intellectuelle and Article 67 of Morocco's Loi relative à la propriété industrielle.
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- 220 The Patents Act of India, 1970, with amendments updated as of 11 March 2015, Article 84(4).
- 221 WIPO document SCP/21/5 Rev.
- 222 WIPO document SCP/21/5 Rev., para. 25.
- 223 See <http://www.cptech.org/ip/health/c/thailand/thaicl4efavirenz.html>; WTO document WT/TPR/S/255, para. 171.
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- 225 See *ibid.*, p. 35.
- 226 See http://www.cptech.org/ip/health/c/thailand/thai-cl-kalettra_en.pdf; WTO document WT/TPR/S/255, para. 171.
- 227 WTO document WT/TPR/S/255, para. 173.
- 228 WIPO document SCP/30/3, Annex, para. 217.
- 229 *Ibid.*
- 230 WTO document IP/C/57, para. 19, see Chapter II.
- 231 WTO document IP/C/M/65, para. 151.
- 232 See WTO document IP/C/61, paras. 50–55; Khor, 2007, p. 18.
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- 234 Chien, 2003. The author reported that out of the six companies subjected to compulsory licences in the study's sample, only one (Merieux with respect to a US Federal Trade Commission order to lease a rabies vaccine) showed a decline in patenting subsequent to the licence. The author also finds that developing countries care about two categories of drugs: "global" drugs that are created for rich markets, but are also useful in developing countries; and drugs specific to developing countries. The paper cites research that suggests that if compulsory licences are taken in less significant markets, their impact on innovation should be marginal. For global drugs such as AIDS therapy, this would imply that compulsory licences that are limited to developing countries (i.e. ancillary markets) and do not impact the target markets for the drugs (i.e., rich countries) might not be detrimental to research efforts in the rich, developed countries.
- 235 WIPO document SCP/30/3, para. 222 and fn 339.
- 236 See 't Hoen (2009).
- 237 Decisions 3 LiQ 1/16 and X ZB 2/17. The judgements are available in German at http://www.rechtsprechung-im-internet.de/jportal/portal/t/19ke/page/bsjrsprod.psm1?pid=Dokumentanzeige&showdoccase=1&js_peid=Trefferliste&documentnumber=1&numberofresults=10908&fromdoc_todoc=yes&doc.id=MPRE135990964&doc.part=L&doc.price=0.0&doc.hl=1#focuspoint; and <http://juris.bundesgerichtshof.de/cgi-bin/rechtsprechung/document.py?Gericht=bgh&Art=en&Datum=Aktuell&Sort=12288&Seite=2&nr=79269&pos=75&anz=608>.
- 238 Sources (with references to the judgments, which are available in German only): The Rhineland Biopatent Gazette, Issue 6/2016, available at: <https://www.mhpatent.net/de/gazette/>; Rudolf Teschemacher, "German Federal Court of Justice confirms the compulsory license granted by way of a preliminary injunction for the AIDS drug Isentress; the EPO Board of Appeal then revokes the European patent", 23 October 2017, available at: <https://www.bardehle.com/ip-news-knowledge/ip-news/news-detail/german-federal-court-of-justice-confirms-the-compulsory-license-granted-by-way-of-a-preliminary-inju.html>; Joff Wild, "Recent decision opens up the possibility of more compulsory licensing in Germany", 13 November 2017, available at: <https://www.iam-media.com/frandseps/recent-decision-opens-possibility-more-compulsory-licensing-germany>; Andreas von Falck, "Compulsory Patent Licences in Germany", May 2018, available at: <https://whoswholegal.com/features/compulsory-patent-licences-in-germany>; Konstanze Richter, "Amgen defends patent for cholesterol treatment", 12 December 2018, available at: <https://www.juve-patent.com/news-and-stories/cases/amgen-defends-patent-for-cholesterol-treatment/>.
- 239 WIPO document SCP/21/12, para. 58.
- 240 WTO document IP/C/57, para. 19, see Chapter II.
- 241 Tiered royalty method (TRM) applied based on UNDP/WHO "Remuneration Guidelines for Non-Voluntary Use of a Patent on Medical Technologies" (2005) where the royalty rate is based upon the price of the patented product in a high-income country not upon the price of the generic product. This base royalty is then adjusted to account for relative income per capita or, for countries facing a particular high burden of disease, relative income per person with the disease.
- 242 IEPI, Tramite No. 000002/2010, de Concesion de Licencia Obligatoria para farmaco, del principio activo denominado RITONAVIR.
- 243 Ecuador assigned three CLs for ABC-3TC to three generic producers.
- 244 IEPI, Tramite No. 000006 (Licencia Obligatoria para Farmaco), available at: https://www.keionline.org/wp-content/uploads/ecuador_license_abc_3tc_.pdf.
- 245 WTO document IP/C/M/86/Add.1, 12 September 2017, para. 282.
- 246 See <https://www.salud.gob.ec/ecuador-concedio-nueve-licencias-obligatorias-para-medicamentos-estrategicos/>.
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- 394 Names of WTO members are those used in the WTO.
- 395 Names of WTO members are those used in the WTO.
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- 408 See https://europa.eu/rapid/press-release_IP-09-1098_en.htm?locale=en.
- 409 See <https://www.unified-patent-court.org/sites/default/files/upc-agreement.pdf>.
- 410 Administrative Proceeding no. 08012.001693/2011-91, see https://sei.cade.gov.br/sei/modulos/pesquisa/md_pesq_documento_consulta_externa.php?DZ2uWeaYicbuRZEFhBt-n3BfPLu9u7akQA8mpB9yPmszWQvh-vzUILLANuAA3bhRN6eSki6WU3piuanBBs2hSNuTy72zAcvQx153GCc3EU19b3OqUcxUDCEoDn17hN-.
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- 418 “Rule of reason” can be described as “legal approach by competition authorities or the courts where an attempt is made to evaluate the pro-competitive features of a restrictive business practice against its anti-competitive effects in order to decide whether or not the practice should be prohibited”. See <https://www.concurrences.com/en/glossary/rule-of-reason>.
- 419 Apart from developments in the United States and the European Union, Canada has addressed patent settlement agreements in its 2016 Intellectual Property Enforcement Guidelines. In the Republic of Korea, the competition authority (KFTC) has brought a case against GlaxoSmithKline (GSK) for a patent settlement relating Zofran, an antiemetic agent used to alleviate nausea. In Australia, the Productivity Commission, in its 2016 inquiry report into the IP sector, drafted a set of recommendations for the Government, including issues related to pay-for-delay agreements. In Japan, the Japanese Fair Trade Commission (JFTC) and the Competition Policy Research Center published a joint research report entitled “Competition and R&D Incentives in the Pharmaceutical Product Market” in 2015 that also addresses patent settlements. In India, a 2015 study on competition in the pharmaceutical markets commissioned by the Indian Competition Commission (CCI) reports mostly on the US and EU approaches to patent settlements, describing the Hatch-Waxman Act as a “unique system”. For further discussion and references, see Anderson, Pires de Carvalho and Taubman (eds.), 2020.
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- 428 See <http://cyber.law.harvard.edu/people/tfischer/South%20Africa.pdf>; Seventh United Nations Conference to review the UN Set on Competition Policy. Geneva, 6-10 July 2015. Roundtable on: Role of Competition in the Pharmaceutical Sector and its Benefits for Consumers. Contribution by South Africa, available at: https://unctad.org/meetings/en/Presentation/CCPB_7RC2015_RTPharma_SouthAfrica_en.pdf.
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- 431 In the US: *New York v. Actavis PLC*, 787 F.3d 638 (2d Cir. 2015) and in the EU: Judgment of the General Court of 1 July 2010, *AstraZeneca AB and AstraZeneca plc v Commission*, T-321/05; Judgment of the Court of Justice of 6 December 2012, *AstraZeneca AB and AstraZeneca plc v European Commission*, C-457/10. See also Antonella Salgueiro (2019), “Product Switching, valid strategy or anti-competitive consumer coercion?” in Anderson, Pires de Carvalho and Taubman (eds.) (2020).
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- 433 See Statement of Federal Trade Commission Chairman Jon Leibowitz, Pay-for-Delay Press Conference, 13 January 2010, available at: <https://www.ftc.gov/sites/default/files/documents/reports/pay-delay-how-drug-company-pay-offs-cost-consumers-billions-federal-trade-commission-staff-study/100113stmtleibowitzpdf.pdf>. See also www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm.

- 434 See http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/preliminary_report.pdf.
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- 436 See <https://www.ftc.gov/news-events/press-releases/2000/11/ftc-reaches-record-financial-settlement-settle-charges-price>.
- 437 See <https://www.agcm.it/media/dettaglio-notizia?id=ceea51cb-5be8-4965-ab1f-f854226ef174&parent=News&parentUrl=/media/news> (in Italian) and <http://www.osservatorioantitrust.eu/it/wp-content/uploads/2015/03/4763-p25366.pdf> (in Italian).
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- 439 See *United Brands Co.*, 1978 E.C.R., p. 301, paras. 248–252, available at: <https://publications.europa.eu/en/publication-detail/-/publication/32bf3aa2-d8b1-4201-81eb-a238062fcd37/language-en>.
- 440 Article 1.1 (ix) of *South Africa Competition Act*, available at: <http://www.compcom.co.za/wp-content/uploads/2017/11/pocket-act-august-20141.pdf>; and UNDP, 2017.
- 441 Section 32(1), *Competition Act*. R.S.C., 1985, c. C-34, available at: <https://laws-lois.justice.gc.ca/eng/acts/c-34/FullText.html>.
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- 444 Reuters, “South Africa watchdog drops over-charging probe into Aspen, Equity”, online version, 4 October 2017.
- 445 See European Commission (2019a).
- 446 See UK Competition and Market Authority, *Hydrocortisone tablets: alleged excessive and unfair pricing*, available at: <https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-practices>; UK Competition and Markets Authority, *Liothyronine tablets: suspected excessive and unfair pricing*, available at: <https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct>; UK Competition and Markets Authority, *Phenytoin sodium capsules: suspected unfair pricing*, available at: <https://www.gov.uk/cma-cases/investigation-into-the-supply-of-pharmaceutical-products>.
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- 450 For the complaint before the District Court of Connecticut, see <https://portal.ct.gov/-/media/AG/Downloads/GDMS%20Complaint%2051019%20FINAL%20REDACTED%20PUBLIC%20VERSION.pdf>; see also the press release of the House Committee on Oversight and Reform, available at: <https://oversight.house.gov/news/press-releases/cummings-and-sanders-see-answers-on-drug-companies-apparent-obstruction-of>.
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- 457 See also http://ec.europa.eu/competition/sectors/pharmaceuticals/antitrust_en.html; European Commission, 2019a.
- 458 For further background information, see www.oecd.org/document/25/0,3746,en_2649_37463_48311769_1_1_1_37463,00.html.

Annex I

Resolutions of the
UN General Assembly
and UN Human Rights
Council

Key Reports of the UN
Special Rapporteur on
the Right to Health

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A. Selected Resolutions of the United Nations General Assembly	294
B. Selected Resolutions of the United Nations Human Rights Council	295
C. Key Reports of the United Nations Special Rapporteur on the Right to Health	296



This Annex lists selected United Nations documents that have relevance to the scope of this study. The list is not comprehensive and inclusion in this list does not imply any evaluation of importance.

A. Selected Resolutions of the United Nations General Assembly

A/RES/74/2	Political declaration of the High-level Meeting on Universal Health Coverage: "Universal health coverage: moving together to build a healthier world" (2019)
A/RES/73/3	Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis (2018)
A/RES/73/2	Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases (2018)
A/RES/71/3	Political declaration of the High-level Meeting of the General Assembly on Antimicrobial Resistance (2016)
A/RES/66/2	Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases (2011)
A/RES/65/277	Political declaration on HIV/AIDS: Intensifying our Efforts to Eliminate HIV/AIDS (2011)

B. Selected Resolutions of the United Nations Human Rights Council

A/HRC/38/8	Human rights in the context of HIV and AIDS
A/HRC/RES/35/23	The right of everyone to the enjoyment of the highest attainable standard of physical and mental health in the implementation of the 2030 Agenda for Sustainable Development
A/HRC/RES/32/16	Capacity-building and public health (panel discussion by OHCHR)
A/HRC/RES/32/15	Access to medicines (panel discussion by OHCHR)
A/HRC/RES/23/14	Access to medicines (general resolution)
A/HRC/RES/17/14	Access to medicines (report by SR)
A/HRC/RES/12/24	Access to medicines (expert consultation by OHCHR)
E/CN.4/RES/2002/32	Access to medication in the context of pandemics such as HIV/AIDS
E/CN.4/RES/2001/71	Human rights and bioethics
E/CN.4/RES/2001/33	Access to medication in the context of pandemics such as HIV/AIDS
A/RES/68/98	Interlinkages between health and all determinants, including social, economic and environmental determinants
A/RES/67/81	Social protection and sustainable financing mechanisms for universal health coverage
A/RES/64/108	Control of emerging infectious diseases and foreign policy
A/RES/58/173	The right of everyone to the enjoyment of the highest attainable standard of physical and mental health

Note: See <https://www.ohchr.org/en/issues/health/pages/overviewmandate.aspx>.

C. Key Reports of the United Nations Special Rapporteur on the Right to Health

Dainius Pūras (since 2014)		
Year	Document symbol	Title
2016	A/71/304	Report of the SR on the right to health and Agenda 2030
Anand Grover (2008–2014)		
Year	Document symbol	Title
2014	A/69/299	Report to the General Assembly (main focus: effective and full implementation of the right-to-health framework, including justiciability of ESCR and the right to health; the progressive realization of the right to health; the accountability deficit of transnational corporations; and the current system of international investment agreements and the investor–state dispute settlement)
2013	A/HRC/23/42	Report to the Human Rights Council (main focus: access to medicines in the context of the right-to-health framework)
2012	A/67/302	Report to the General Assembly (main focus: health financing in the context of the right to health)
2011	A/HRC/17/43	Report to the Human Rights Council (main focus: report on expert consultation on access to medicines)
2009	A/HRC/11/12	Report to the Human Rights Council (main focus: right to health in the context of access to medicines and intellectual property rights)
Paul Hunt (2002–2008)		
Year	Document symbol	Title
2008	A/63/263	Report to the General Assembly

Note: See <https://www.ohchr.org/en/issues/health/pages/srrihealthindex.aspx>.

Annex II. Selected Resolutions and Decisions of the World Health Assembly

Contents

Selected Resolutions and Decisions of the World Health Assembly

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Selected Resolutions and Decisions of the World Health Assembly

Document (year)	Title
WHA72(13) (2019)	The public health implications of implementation of the Nagoya Protocol
WHA72(12) (2019)	Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and other benefits
WHA72.8 (2019)	Improving the transparency of markets for medicines, vaccines, and other health products
WHA72.5 (2019)	Antimicrobial resistance
WHA71(8) (2018)	Addressing the global shortage of, and access to, medicines and vaccines
WHA71(9) (2018)	Global strategy and plan of action on public health, innovation and intellectual property: overall programme review
WHA71(11) (2018)	Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and other benefits
WHA70.12 (2017)	Cancer prevention and control in the context of an integrated approach
WHA69.11 (2016)	Health in the 2030 Agenda for Sustainable Development
WHA69.20 (2016)	Promoting innovation and access to quality, safe, efficacious and affordable medicines for children
WHA69.23 (2016)	Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination
WHA69.25 (2016)	Addressing the global shortage of medicines and vaccines, and the safety and accessibility of children's medication
WHA68.7 (2015)	Global action plan on antimicrobial resistance
WHA68.18 (2015)	Global strategy and plan of action on public health, innovation and intellectual property
WHA67.1 (2014)	Global strategy and targets for tuberculosis prevention, care and control after 2015
WHA67.6 (2014)	Viral hepatitis
WHA67.14 (2014)	Health in the post-2015 development agenda
WHA67.20 (2014)	Regulatory system strengthening for medical products
WHA67.21 (2014)	Access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy
WHA67.22 (2014)	Access to essential medicines
WHA67.23 (2014)	Health intervention and technology assessment in support of universal health coverage
WHA67.25 (2014)	Antimicrobial resistance
WHA66.12 (2013)	Neglected tropical diseases
WHA66.22 (2013)	Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination
WHA65.19 (2012)	Substandard/spurious/false-labelled/falsified/counterfeit medical products
WHA65.22 (2012)	Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination
WHA64.5 (2011)	Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits

Document (year)	Title
WHA63.1 (2010)	Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits
WHA62.10 (2009)	Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits
WHA62.16 (2009)	Global strategy and plan of action on public health, innovation and intellectual property
WHA61.21 (2008)	Global strategy and plan of action on public health, innovation and intellectual property
WHA60.20 (2007)	Better medicines for children
WHA60.28 (2007)	Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits
WHA60.29 (2007)	Health technologies
WHA60.30 (2007)	Public health, innovation and intellectual property

Note: See also WHA 72/17 Appendix 1: Key resolutions of the health assembly and regional committees, and regional committee documents from the past 10 years relevant to access to safe, effective and quality medicines, vaccines and health products, available at: http://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_17-en.pdf.

Annex III. Special Compulsory Licences for Export of Medicines

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A. Operation of the System: context and scope

While Chapter IV, section C.3(a)(iii), outlines the policy context of the Special Compulsory Licensing System (“the System”, sometimes also referred to as “the Paragraph 6 System”) and why the System allows the grant of such licences for export of medicines in limited circumstances, this Annex provides supplementary information setting out its operation and use. The System is the only flexibility in the TRIPS Agreement that specifically entails action by (at least) two members (i.e. an importer and an exporter). It operates on the basis of notifications to the TRIPS Council by these members, which, in turn, result in the various actions described in this Annex.

1. What Is the System?

The 2001 Ministerial Doha Declaration on the TRIPS Agreement and Public Health (paragraph 6) recognized that WTO members with insufficient or no manufacturing capacity in their pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. To overcome those difficulties, WTO members adopted the System. It provides WTO members with an additional flexibility, which is a special type of compulsory licence permitting production of medicines exclusively for export. It waives, in particular, a condition that otherwise applies to compulsory licences under Article 31(f) of the TRIPS Agreement, restricting their use to predominantly for the supply of the domestic market. The System links demand in importing members with supply from exporting members. In addition, it waives the obligation on importing members to pay adequate remuneration to the right holder following the grant of a compulsory licence (Article 31(h) of the TRIPS Agreement), if such remuneration is provided for in the exporting member.

2. What products are covered by the System?

The System is available for any pharmaceutical products (including active ingredients and diagnostic kits) that are patented or manufactured under a patented process and are needed to address public health problems afflicting developing countries and least-developed countries (LDCs), especially those resulting from HIV/AIDS, tuberculosis (TB), malaria and other epidemics. This list of public health problems is based on paragraph 1 of the Doha Declaration and is now reflected in paragraph 1(a) of the Annex to the TRIPS Agreement; it is not intended to be exhaustive.

B. Legal basis

Since the entry into force of the Protocol Amending the TRIPS Agreement (the Protocol) on 23 January 2017, Article 31 *bis* of the amended TRIPS Agreement constitutes the legal basis for the vast majority of members that wish to use this additional flexibility to procure medicines. Members that are yet to adopt the Protocol, however, will continue to operate under the 2003 waiver Decision. Newly acceding members will be automatically bound by the amended TRIPS Agreement upon their accession.

C. Use of the System

This section describes which WTO members can use the System as importers and exporters, and the terms and conditions under which the System may be used.

1. Who can use the System as importers and exporters?

While all WTO members are eligible to use the System as importers, developed countries have elected not to use the System for their imports,¹ and some higher-income developing countries and territories have agreed that they would use the System as an importer only in situations of national emergency or other circumstances of extreme urgency.² Nevertheless, the System itself is not restricted to emergency situations for the other WTO members.

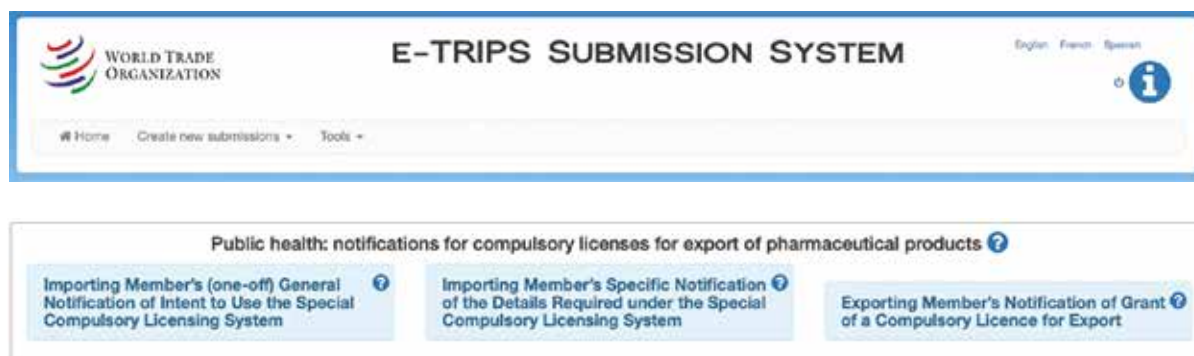
Any WTO member may participate in the System as an exporter but is under no obligation to do so. Many WTO members have implemented the System so as to enable exports to developing countries and LDCs that are not WTO members.³

2. How can the System be used by WTO members?

The essence of the System is the grant of a compulsory licence by the exporting member to meet the need(s) identified by the importing member. To do so, the following notifications are required.

1. An importing member's general notification of intent to use the System (not required for LDCs).
2. An importing member's specific notification of needed pharmaceutical product(s).
3. An exporting member's notification of a compulsory licence issued for exports to meet the needs of the importing member(s).

They are sent for information and transparency purposes to the WTO TRIPS Council. The notifications do not require approval by any WTO body.



WTO members are encouraged to use the e-TRIPS Submission System⁴ to submit the above notifications to the WTO TRIPS Council. Traditional methods of notifying remain available.

The e-TRIPS Submission System provides guidance to both WTO members that have accepted the Protocol and who operate on the basis of the amended TRIPS Agreement and those that are yet to accept the Protocol and who continue to operate under the 2003 Decision. This guidance includes the information to submit for each notification type. In addition, a detailed explanation of the notifications, including a set of model notifications, is available at the WTO website.⁵

(a) How does an importing member use the System?

(i) *Notifying general intention to use the System*

The general notification comprises the simple statement by a WTO member that it intends to use the System. A member can submit its notification at any time prior to actual use, and it does not commit it to use the System. Rather, it simply reserves the right to do so in the event of potential future need. LDCs are not required to make this notification.

(ii) *Notifying the need to import specific pharmaceutical products*

When a member wishes to create the option of importing particular products under the System, it submits a specific notification of its import needs.

The specific notification includes:

- Names and expected quantities of the product(s) the member needs to import
- If a patent is in force in the member for any of the pharmaceutical products listed, an indication that a compulsory licence has been or will be granted. LDCs

may simply indicate their intention to use the extended transition period under the TRIPS Agreement

- An indication that the member has established that it lacks the capacity to manufacture the product(s). LDCs are already deemed to have insufficient manufacturing capacity, and thus they are exempt from adhering to this requirement.

This notification can be submitted at an early stage of the procurement process, before any final decision about preferred sources of supply. It does not create any obligation to use the System should a better alternative emerge. A member is therefore free to notify expected medicine requirements as a routine step in the procurement planning process, thus facilitating assessment of the full range of access options, signalling demand for potential suppliers, and clearing the way for actual use of the System should it present the most commercially viable option.

Members pooling their procurement needs can make joint notifications. Given that the System recognizes the need for economies of scale in a regional context, joint notifications by members with similar needs open a pathway for the establishment of commercially viable levels of demand for production and shipment.

If a compulsory licence is needed on a patent in force in the importing member, that member must still respect general TRIPS Agreement requirements for compulsory licensing (see Chapter IV, section C.3(a)(ii)). The importer should thus make prior efforts to obtain authorization from the patent holder on reasonable commercial terms and conditions. This obligation does not apply, however, in cases of public non-commercial use, or if there is a national emergency or other circumstances of extreme urgency. The Doha Declaration clarifies that members have the right to determine when such situations exist. Furthermore, there is no obligation to seek a voluntary licence if the compulsory licence was issued to remedy an anti-competitive practice. To avoid double payment to the patent holder, the licensee in the importing member is exempted from the requirement under Article 31(h) of the TRIPS Agreement to pay remuneration for a compulsory licence to the patentee if payment has already been made in the exporting member.

(b) How does an exporting member use the System?

Any member can export under the System if its domestic law allows the grant of a compulsory licence to export. If there is no patent in force for the products in the exporting member, then there is no need to resort to the System. Equally, if the product is already being produced under a compulsory licence for the domestic market, the non-predominant portion of the production quantity can be exported without using the System.

Once a compulsory licence for export under the System has been issued, the exporting member submits a notification.

The exporting member's notification of the licence(s) for export contains the following details:

- name and address of the licensee(s)
- product(s) for which the licence(s) has/have been granted
- quantity(ies) for which the licence(s) has/have been granted
- country(ies) to which the product(s) is/are to be supplied
- duration of the licence(s)
- optionally, any other licence conditions and other information, such as the patent number(s)
- address of a website providing information on quantities shipped and distinguishing features of the product(s).

When granting the special licence for export, the exporting member needs to apply the standard requirements under the TRIPS Agreement for compulsory licences as implemented into domestic law, except that:

- the quantity that can be exported under compulsory licence is no longer limited to the non-predominant part of the production; rather, it requires the entire production quantity to be exported to the beneficiary countries
- the requirement for adequate remuneration in the exporting member is calculated on a different basis, namely, the economic value of the authorization in the importing member.

3. Do regulatory authorities have to approve products manufactured under a special compulsory licence?

The System is part of the IP regime and does not deal with marketing authorization for pharmaceutical products.

It remains a separate responsibility of health authorities to determine whether products are of appropriate quality, safety and efficacy, and it is up to the exporting and importing members to decide whether their respective pharmaceutical regulatory authorities will review the products manufactured under the System or whether they will rely on regulatory reviews carried out by counterpart authorities, either in the members using the System or even in another jurisdiction.

4. Which safeguards against diversion need to be put in place?

In order to ensure that products exported under the System are used to address the public health problems afflicting the importing member(s), specific safeguards against diversion apply:

- Production carried out in the exporting WTO member as a result of a special compulsory licence is limited to the quantity necessary to meet the needs of the importing WTO member(s), and the entire quantity produced must be exported to the importing WTO member(s).
- The products must have specific labelling or marks. They should have distinctive packaging and/or be specially coloured or shaped – as long as these latter requirements are feasible and do not have a significant impact on price. Before shipment, the manufacturer must post on a website details of the quantity of products it has manufactured under the compulsory licence, as well as details of the way in which it has specially labelled or packaged them. The WTO website is available for the manufacturer to publish this information, but such use is not mandatory.
- Importing WTO members must take reasonable measures within their means to prevent re-exportation. Such measures should be proportionate to these members' administrative capacity and the risk of trade diversion. Importing WTO members are entitled to receive technical and financial assistance from developed-country WTO members so as to meet this obligation.
- Other WTO members need to have in place effective legal procedures and remedies in order to prevent importation into their markets of diverted pharmaceutical products produced under special compulsory licences for export, using the means that are already to be made available under the TRIPS Agreement.

5. How can the System be used at the regional level?

Under a regional mechanism established by the System, the condition that the products produced under the compulsory licence must be used predominantly to supply

the domestic market is also waived. The purpose is to allow WTO members that are party to a regional trade agreement (RTA) to better harness economies of scale in their regional economic community and also enhance their purchasing power by combining demand to facilitate bulk imports or local production of pharmaceutical products for distribution within the relevant region. The regional mechanism enables the exporting and re-exporting of products that have been manufactured locally or elsewhere under a compulsory licence to take place more easily among WTO members that are party to an RTA, provided that:

- the RTA complies with the General Agreement on Tariffs and Trade (GATT) and the so-called Enabling Clause (the name given to a 1979 GATT Decision permitting preferential arrangements among developing countries and LDCs in goods trade)
- at least half the WTO members that are party to the RTA are LDCs
- they share the public health problem(s) in question.

The WTO does not determine which RTAs satisfy these requirements, and thus no list of RTAs qualifying for this regional mechanism is available.

The regional mechanism can thus cover pharmaceutical products manufactured within the regional trade area under compulsory licence. It can cover products manufactured elsewhere under compulsory licence and imported by one RTA party under the System. Either way, the products can be traded among the parties to the RTA without any further notification or adherence to any additional requirements other than those that apply at the time of the production in an RTA member or importation into the regional trade area under the System.

The regional mechanism does not override patents or national marketing approval requirements. Where a patent is in force for any country in the region, either a voluntary or compulsory licence would be required in the country that is seeking to use the mechanism to import medicines from another RTA member. Equally, the product should still be approved for distribution in each of the countries concerned, although this is not a TRIPS Agreement requirement.

6. What does the WTO General Council Chairman's statement add?

The General Council decisions to establish the System (2003 waiver Decision and 2005 Protocol Amending the TRIPS Agreement) were both adopted in light of statements by the General Council Chairman that reflected several key shared understandings of WTO members,⁶ notably:

- The System should be used in good faith to protect public health and should not be used to pursue industrial or commercial policy objectives;
- The requirements on product differentiation apply to active ingredients produced and supplied under the System. They also apply to finished products containing such ingredients. In general, special packaging and/or special colouring or shaping should not have a significant impact on the price of pharmaceuticals;
- In relation to the prevention of diversion of products, members and producers are encouraged to draw from and use best practices guidelines and to share information on their experiences and practices in preventing diversion;
- Importing members should include information in their notification to the TRIPS Council on how they established that they have insufficient or no manufacturing capacities in their local pharmaceutical sector.

The Chairman also noted that developed countries had agreed to opt out of the System as importers (also reflected in footnote 3 of the Annex to the amended TRIPS Agreement/2003 waiver Decision)⁷ and that 11 higher-income developing countries and territories had agreed to restrict the use of the System as importers to situations of national emergency or other circumstances of extreme urgency.

D. Domestic implementation

Members can implement the System as importers, exporters, or both.⁸ There is no obligation on WTO members to use the System in either capacity, and it remains one option among many that can be used to enable access to medicines.

1. Importing members

Importing WTO members will generally need to make legislative changes in order to exercise the option of dispensing with remuneration on imports under a compulsory licence, where remuneration has already been paid in the exporting member. While the required notification to the WTO TRIPS Council does not necessitate special legislation, such notification requirement and how to process it domestically may be usefully addressed in laws or implementing regulations. Importing WTO members are obliged to take reasonable measures to prevent the re-export of imported products but do not need to adopt special legislation. In the Philippines, the law simply

requires that the compulsory licence “shall also contain a provision directing the grantee of the license to exercise reasonable measures to prevent the re-exportation of the products imported under this provision”.⁹

2. Exporting members

Exporting WTO members typically need to make limited legislative changes in order to use the System, unless Article 31*bis* of the TRIPS Agreement is directly applicable under national law. Members that have already incorporated the TRIPS Agreement standards into their law have conditions in place that apply to compulsory licences, namely, that products manufactured under compulsory licence must be predominantly for supply of the domestic market. Therefore, at a minimum, this limitation will need to be amended so as to allow for the export of the entire quantity produced under a compulsory licence issued under the System. At the same time, the implementing legislation needs to limit the grant of the compulsory licence to the quantity which is necessary to meet the needs of the eligible importing member (as referred to in the importing member's notification(s) to the TRIPS Council) and needs to require that the compulsory licence obliges the licensee to export the full quantity of that production and to specially mark or label the products.

Exporting members implementing the System may adopt specific provisions governing the calculation of, and procedures for, the payment of adequate remuneration to the right holder (e.g. a fixed maximum royalty or prescribed calculation taking into account the economic value of the authorization in the importing member or any other reference). These provisions may specify that the licensee is obliged to pay the remuneration or that it shall be proportionally shared among all right holders in the case of multiple patents. They often also specify the competent authority, if any, to determine the level of adequate remuneration (Kampf, 2015).

3. Regional mechanism

Implementation of the regional mechanism would entail ensuring that the relevant legislation in exporting members in the region does not require that the production of the products under compulsory licence must predominantly supply the domestic market, as would be the case for standard compulsory licences under the TRIPS Agreement. For members that intend only to import, changes may be required in their domestic law so that the licensee can be exempted from paying remuneration to the right holder in a situation where a compulsory licence to import has been granted and where remuneration has already been paid in the exporting member.

Endnotes

- 1 See footnote 3 to the Annex to the amended TRIPS Agreement/the 2003 Decision (WTO document WT/L/540).
- 2 See the list contained in the Chairman's Statement, WTO documents WT/GC/M/82, para. 29 and WT/GC/M/100, para. 29.
- 3 See Kampf (2015).
- 4 The e-TRIPS Submission System is an optional online tool for WTO members to submit TRIPS-related notifications, and review materials and reports, available at: <https://nss.wto.org/tripsmembers>. WTO members must have log-in credentials provided by the WTO in order to use the e-TRIPS Submission System. To receive log-in credentials and for any other enquiries regarding notifications under the System, the WTO Secretariat may be contacted at e-TRIPS@wto.org.
- 5 See Guide to Notifications, available at: www.wto.org/english/tratop_e/trips_e/par6_modelnotifs_e.htm.
- 6 WTO documents WT/GC/M/82, para. 29 and WT/GC/M/100, paras. 28–29.
- 7 WTO document WT/L/540.
- 8 A collection of laws implementing the System is available at: www.wto.org/english/tratop_e/trips_e/par6laws_e.htm.
- 9 Rule 13 of the Implementing Rules and Regulations of Republic Act 9502 otherwise known as the "Universally Accessible Cheaper and Quality Medicines Act of 2008", notified in WTO document IP/N/1/PHL/I/10.

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Abbreviations

ABS	access and benefit-sharing
ACE	Advisory Committee on Enforcement
ACT	Access to COVID-19 Tools
ADA-SCID	adenosine deaminase-severe combined immunodeficiency
AfCFTA	African Continental Free Trade Agreement
AI	artificial intelligence
ALCS	Association de lutte contre le SIDA (Association to fight AIDS, Morocco)
AMA	African Medicines Agency
AMC	advance market commitment
AMF	Access to Medicine Foundation
AMR	antimicrobial resistance
ANVISA	Agência Nacional de Vigilância Sanitária (National Agency for Sanitary Vigilance, Brazil)
ARDI	Access to Research for Development and Innovation
ARV	antiretroviral
ASAQ	artesunate and amodiaquine
ASPI	Access to Specialized Patent Information
ATC	Anatomical Therapeutic Chemical classification system
AUTM	Association of University Technology Managers
Berne Convention	Berne Convention for the Protection of Literary and Artistic Works
BiOS	Biological Innovation for the Open Society
BTA	bilateral trade agreement
BVGH	BIO Ventures for Global Health
C-TAP	COVID-19 Technology Access Pool
CADE	Administrative Council for Economic Defence
CAM	complementary and alternative medicine
CAMR	Canada's Access to Medicines Regime
CAR T-cell	Chimeric antigen receptor T-cell
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CAS	Chemical Abstracts Service
CASE	Centralized Access to Search and Examination
CBD	Convention on Biological Diversity
CCSA	Competition Commission of South Africa
CDER	United States Food and Drug Administration Center for Drug Evaluation and Research
CDIP	Committee on Development and Intellectual Property
cDNA	complementary DNA
CEPI	Coalition for Epidemic Preparedness Innovation
CESCR	Committee on Economic, Social and Cultural Rights
CETA	Comprehensive Economic and Trade Agreement
CEWG	Consultative Expert Working Group on Research and Development: Financing and Coordination
CFC	chlorofluorocarbon
CHAI	Clinton Health Access Initiative
CIPHI	Commission on Intellectual Property Rights, Innovation and Public Health
CJEU	Court of Justice of the European Union
CL	compulsory licence
CLIR	Cross-Lingual Information Retrieval
CMA	Competition and Markets Authority (United Kingdom)
CMH	Commission on Macroeconomics and Health
CMNN	communicable, maternal, neonatal and nutritional conditions
CNPMDM	National Commission for the Price of Medicines and Medical Devices of Colombia
COVID-19	coronavirus disease 2019
CPTPP	Comprehensive and Progressive Agreement for Trans-Pacific Partnership
CRISPR	clustered regularly interspaced short palindromic repeats
CSIR	Council of Scientific and Industrial Research
CT	computed tomography
CWS	Committee on WIPO Standards

DAA	direct-acting antivirals
DALY	disability-adjusted life year
DAS	Digital Access Service
DND <i>i</i>	Drugs for Neglected Diseases <i>initiative</i>
Doha Declaration	Declaration on the TRIPS Agreement and Public Health
DSU	Understanding on Rules and Procedures Governing the Settlement of Disputes
EBS	equitable benefit-sharing
EC	European Communities
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiography/electrocardiogram
EDAIF	Export Development and Agricultural Investment Fund
EFTA	European Free Trade Association
EMA	European Medicines Agency
EMBL-EBI	European Bioinformatics Institute
EML	Model List of Essential Medicines
EOI	Expression of Interest
EPC	European Patent Convention
EPFL	École Polytechnique Fédérale de Lausanne
EPO	European Patent Office
EUIPO	European Union Intellectual Property Office
EUL	Emergency Use Listing
EXPH	Expert Panel on Effective Ways of Investing in Health
FAO	Food and Agriculture Organization of the United Nations
FCTC	Framework Convention on Tobacco Control
FDA	Food and Drug Administration (United States)
FDI	foreign direct investment
FPP	finished pharmaceutical product
FTA	free trade agreement
FTC	Federal Trade Commission (United States)
FTO	freedom to operate
FY	fiscal year
GAP	Global Action Plan for Influenza Vaccines
GAP-f	Global Accelerator for Paediatric Formulations
GARDP	Global Antibiotic Research & Development Partnership
GATS	General Agreement on Trade in Services
GATT	General Agreement on Tariffs and Trade
GBD	global burden of disease
GBT	Global Benchmarking Tool
GDP	gross domestic product
GHO	Global Health Observatory
GISRS	Global Influenza Surveillance and Response System
Global AMR R&D Hub	Global Antimicrobial Resistance Research and Development Hub
GloPID-R	Global Research Collaboration for Infectious Disease Preparedness
GMP	good manufacturing practice
GNP	gross national product
GPA	Agreement on Government Procurement
GPO	Government Pharmaceutical Organization
GPP/GCC	Group Purchasing Program of the Gulf Cooperation Council
GPRM	Global Price Reporting Mechanism
GRs	genetic resources
GSD	genetic sequence data
GSMS	Global Surveillance and Monitoring System
GSPA-PHI	Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property
GUL	government-use licence
GVAP	Global Vaccine Action Plan
HAI	Health Action International
HCV	hepatitis C virus
HFA	hydrofluoroalkane

HHI	Herfindahl-Hirschman index
HPV	human papillomavirus
HRC	United Nations Human Rights Council
HS	Harmonized Commodity Description and Coding System
HTA	health technology assessment
HTS	high-throughput screening
IACG	Interagency Coordination Group
IAVI	International AIDS Vaccine Initiative
ICE	International Cooperation for Patent Examination
ICER	incremental cost-effectiveness ratio
ICESCR	International Covenant on Economic, Social and Cultural Rights
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSID	International Centre for Settlement of Investment Disputes
ICSTD	International Centre for Trade and Sustainable Development
ICT	information and communication technology
ICTRP	International Clinical Trials Registry Platform
ICTSD	International Centre for Trade and Sustainable Development
IGC	Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore
IHR	International Health Regulations
IIA	international investment agreement
iM4TB	Innovative Medicine for Tuberculosis
IMI	Innovative Medicines Initiative
InChI	International Chemical Identifier
INN	international non-proprietary name
INPI	Instituto Nacional da Propiedade Industrial (National Institute of Industrial Property, Brazil)
IP	intellectual property
IPD	individual participants' data
IPRIA	Intellectual Property Rights Impact Aggregate
IPRs	intellectual property rights
IRP	international reference price
ISDS	investor-state dispute settlement
IT	information technology
ITA	Information Technology Agreement
ITN	insecticide-treated mosquito net
ITPCru	International Treatment Preparedness Coalition – Russia
ITU	International Telecommunication Union
IVDs	in vitro diagnostics
IVPP	influenza viruses with pandemic potential
JPA	Joint Procurement Agreement
JPM	Joint Procurement Mechanism
KIPO	Korean Intellectual Property Office
LAL	lysosomal acid lipase
LDCs	least-developed countries
LMB	UK Medical Research Council Laboratory of Molecular Biology
LMICs	low- and middle-income countries
M&A	mergers and acquisitions
Madrid System	Madrid System for the International Registration of Marks
MAT	mutually agreed terms
MDGs	Millennium Development Goals
MDI	metered-dose inhalers
MEA	market entry agreement
MedsPaL	Medicines Patents and Licences database
MFN	most-favoured-nation
MI4A	Market Information for Access to Vaccines
MMV	Medicines for Malaria Venture
MPP	Medicines Patent Pool

MPS	mucopolysaccharidosis
MRI	magnetic resonance imaging
MSF	Médecins Sans Frontières
MTMC	material threat medical countermeasure
NAAT	nucleic acid amplification testing
NAFTA	North American Free Trade Agreement
NCD	non-communicable disease
NCE	new chemical entity
ND	neglected disease
NDA	new drug application
NGO	non-governmental organization
NHS	National Health Service (United Kingdom)
NIC	national influenza centre
NICE	National Institute for Health and Care Excellence (United Kingdom)
NIH	National Institutes of Health (United States)
NME	new molecular entity
NMRA	national medicines regulatory authority
NSPA-Pharma	National Strategy and Plan of Action for Pharmaceutical Manufacturing Development
NTD	neglected tropical disease
NTM	non-tariff measure
OAPI	Organisation africaine de la propriété intellectuelle (African Intellectual Property Organization)
OECD	Organisation for Economic Co-operation and Development
OECS	Organisation of Eastern Caribbean States
OHCHR	Office of the United Nations High Commissioner for Human Rights
OIE	World Organisation for Animal Health
PAHO	Pan American Health Organization
Paris Convention	Paris Convention for the Protection of Industrial Property
PATH	Programme for Appropriate Technology in Health
Pat-INFORMED	Patent Information Initiative for Medicines
PBM	pharmacy benefit manager
PCT	Patent Cooperation Treaty
PCV	pneumococcal conjugate vaccine
PDP	product development partnership
PEPFAR	President's Emergency Plan for AIDS Relief
PIC	prior informed consent
PIEMEDS	Price Information Exchange for Essential Medicines
PIP	Pandemic Influenza Preparedness
PPE	personal protective equipment
PPL	priority pathogens list
PPP	public-private partnership
PQT	WHO Prequalification Team
PrEP	pre-exposure prophylaxis
PRV	priority review voucher
PTA	patent term adjustment
PTAB	Patent Trial and Appeal Board
PTE	patent term extension
QALY	quality-adjusted life year
R&D	research and development
RBP	reference biotherapeutic product
RPD	rare paediatric disease
RTA	regional trade agreement
RTV	ritonavir
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	similar biotherapeutic product
SCP	Standing Committee on the Law of Patents
SDGs	Sustainable Development Goals
SF	substandard and falsified

SIC	Superintendency of Industry and Commerce
SMA	spinal muscular atrophy
SME	small and medium-sized enterprises
SMTA	Standard Material Transfer Agreement
SPC	supplementary protection certificate
SPS Agreement	Agreement on Sanitary and Phytosanitary Measures
SRA	stringent regulatory authority
SRL	socially responsible licensing
T&CM	traditional and complementary medicine
TB	tuberculosis
TBT Agreement	Agreement on Technical Barriers to Trade
TCM	traditional Chinese medicine
TDF	tenofovir disoproxil fumarate
TDM	text and data mining
TDR	WHO Special Programme for Research and Training in Tropical Diseases
TFEU	Treaty on the Functioning of the European Union
TISC	Technology and Innovation Support Center
TK	traditional knowledge
TKDL	Traditional Knowledge Digital Library
TPP	tobacco plain packaging
TRIPS Agreement	Agreement on Trade-Related Aspects of Intellectual Property Rights
TRM	tiered royalty method
TTO	technology transfer offices
UCAB	Utrecht Centre for Affordable Biotherapeutics
UHC	universal health coverage
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNCITRAL	United Nations Commission on International Trade Law
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
UNEP	United Nations Environment Programme
UNHLP	United Nations Secretary-General's High-Level Panel on Access to Medicines
UNICEF	United Nations Children's Fund
UNIDO	United Nations Industrial Development Organization
USMCA	United States–Mexico–Canada Agreement
USP	United States Pharmacopeial Convention
USPTO	United States Patent and Trademark Office
V3P	WHO Vaccine Product, Price and Procurement project
VBP	value-based pricing
VL	voluntary licence
WASH	water, sanitation and hygiene
WHA	World Health Assembly
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WMA	World Medical Association
WPRO	Western Pacific Regional Office
WTO	World Trade Organization
WTO Agreement	Marrakesh Agreement Establishing the World Trade Organization
XLH	X-linked hypophosphatemia
YLD	years lost due to disability
YLL	years of life lost

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Promoting Access to Medical Technologies and Innovation

SECOND EDITION

Intersections between public health, intellectual property and trade

Medical technologies – medicines, vaccines and medical devices – are essential for public health. Access to essential medicines and the lack of research to address neglected diseases have been a major concern for many years. To promote innovation and to ensure equitable access to all vital medical technologies, policy-makers need a clear understanding of the innovation processes that lead to new technologies and of the ways in which these technologies are disseminated in health systems. This study seeks to reinforce the understanding of the interplay between the distinct policy domains of health, trade and intellectual property, and of how they affect medical innovation and access to medical technologies.

This collaborative effort by the World Health Organization, the World Intellectual Property Organization and the World Trade Organization draws together the three Secretariats' respective areas of expertise. The study is intended to inform ongoing technical cooperation activities undertaken by the three organizations and to support policy discussions. It has been prepared to serve the needs of policy-makers, as well as lawmakers, government officials, delegates to international organizations, non-governmental organizations and researchers.

The second edition comprehensively reviews the existing material and captures new developments in key areas since the initial launch of the study in 2013. Among the new topics covered by the study are antimicrobial resistance and cutting-edge health technologies. The second edition provides updated data on health, innovation trends in the pharmaceutical sector, and trade and tariffs. It includes an updated overview of access to medical technologies globally and key provisions in free trade agreements, and takes account of developments in IP legislation and jurisprudence.

ISBN 978-92-870-4997-1



WTO ISBN 978-92-870-4996-4 (print) / 978-92-870-4997-1 (electronic version)

WHO ISBN 978-92-4-000827-4 (print) / 978-92-4-000826-7 (electronic version)

WIPO ISBN 978-92-805-3174-9 WIPO Publication No. 628E/20