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.

Contents

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.

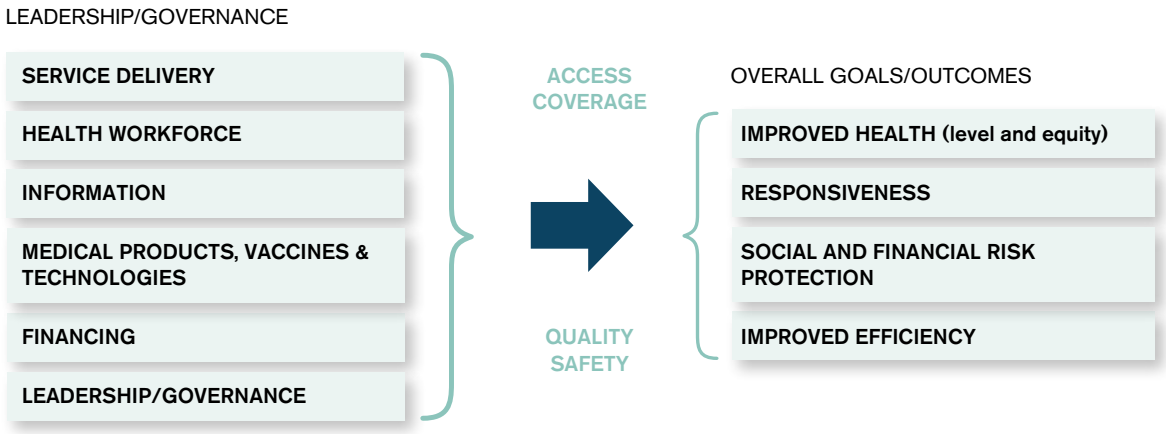
Access to medicines and other medical technologies rarely depends entirely on a single factor. This section describes the main health-systems-related determinants of access to medicines and medical technologies at the interface of health, intellectual property (IP) and trade. The section first explains 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



THE SIX BUILDING BLOCKS OF A HEALTH SYSTEM: AIMS AND DESIRABLE ATTRIBUTES

- Good **health services** are those which **deliver** effective, safe, quality personal and non-personal health interventions to those who need them, when and where needed, with a minimum waste of resources.
- A well-performing **health workforce** is one which works in ways that are responsive, fair and efficient to achieve the best health outcomes possible, given available resources and circumstances, i.e. there are sufficient numbers and mix of staff fairly distributed; they are competent, responsive and productive.
- A well-functioning **health information system** is one that ensures the production, analysis, dissemination and use of reliable and timely information on health determinants, health systems performance and health status.
- A well-functioning health system ensures equitable access to essential **medical products, vaccines and technologies** of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use.
- A good **health financing** system raises adequate funds for health, in ways that ensure people can use needed services, and are protected from financial catastrophe or impoverishment associated with having to pay for them.
- **Leadership and governance** involves ensuring strategic policy frameworks exist and are combined with effective oversight, coalition-building, the provision of appropriate regulations and incentives, attention to system design, and accountability.

Source: WHO.

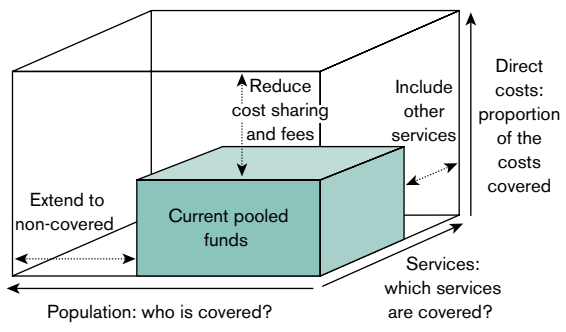
and has become a leading, unifying goal for health in the context of sustainable development. UHC means that all individuals and communities have access to quality health services without financial hardship (WHO, 2017h). It includes the full spectrum of essential, quality health services, from health 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).

Figure 4.2: The three dimensions of universal health coverage



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).

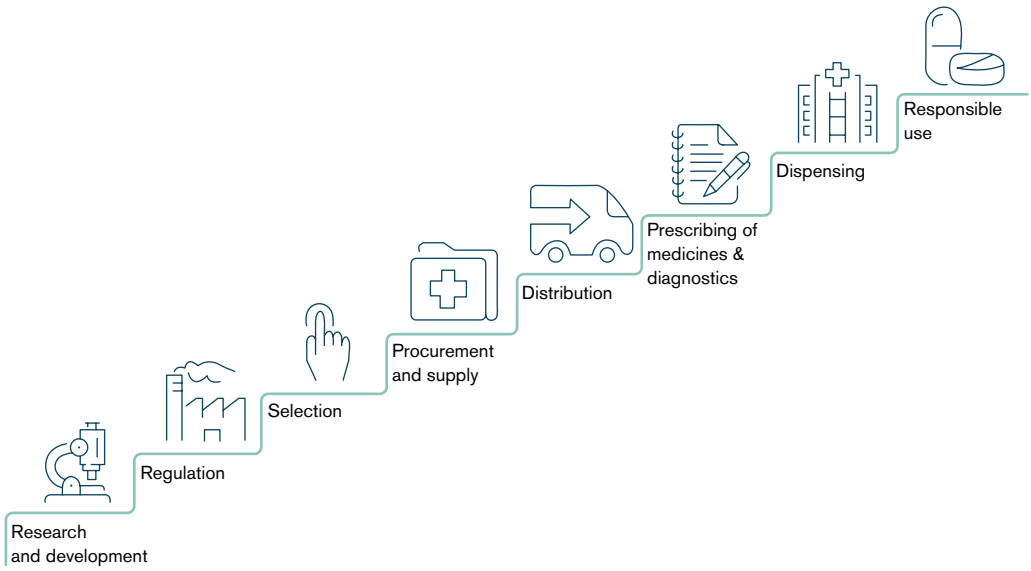
WHO conceptualizes the range of steps and factors that contribute to ensuring access to medical technologies as using the pharmaceutical life cycle, shown in Figure 4.3, which follows a medicine from discovery to use by patients.

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, NGOs[21] 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 imatinib[28] 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 Beneluxa Initiative and the Joint Procurement Mechanisms

Beneluxa Initiative

The Beneluxa 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]

Beneluxa's joint HTA and negotiations are in the pilot phase. Until now, Beneluxa 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)).

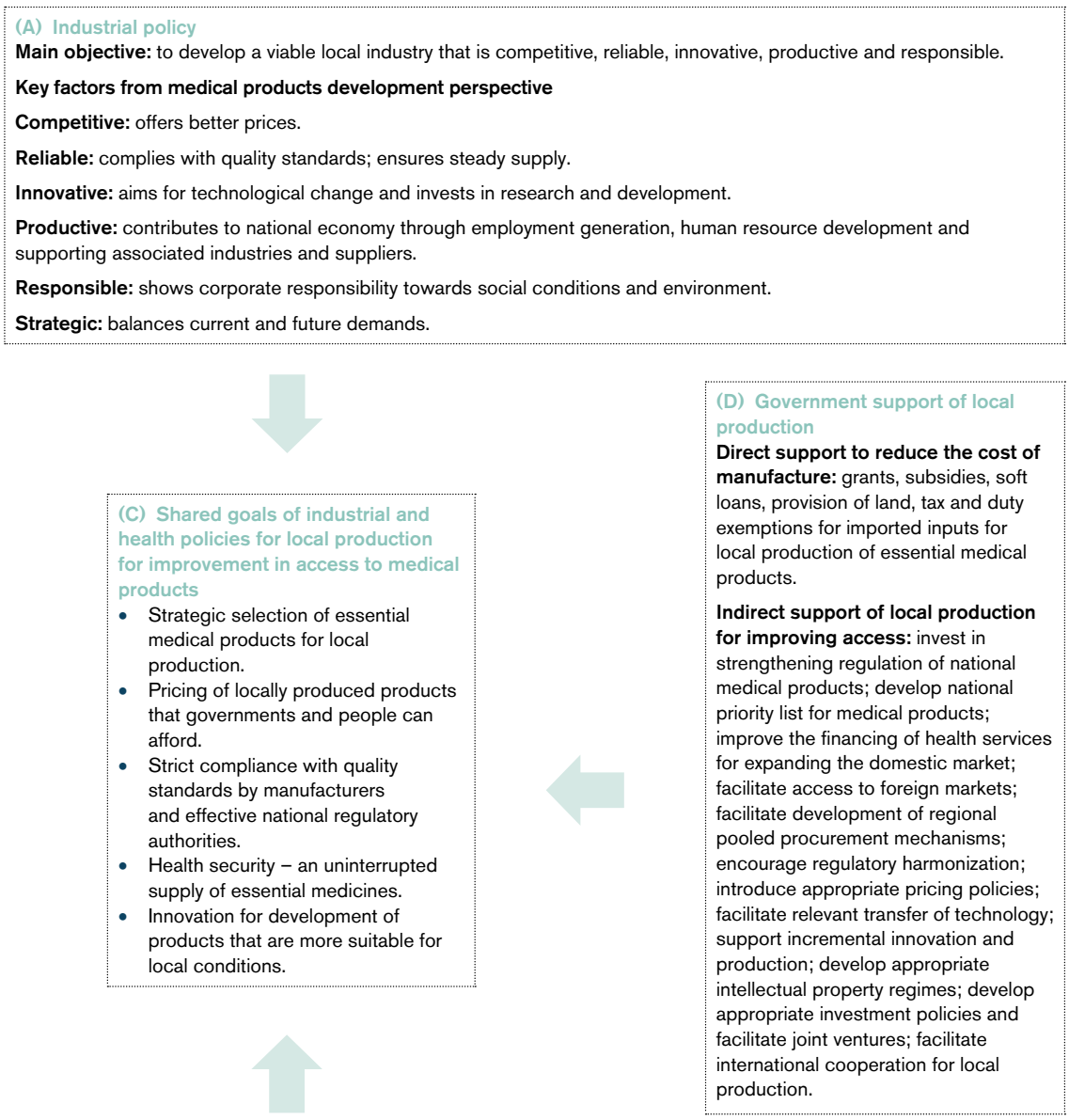
11. Regulatory mechanisms and access to medical technologies

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



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, 2017l). 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]

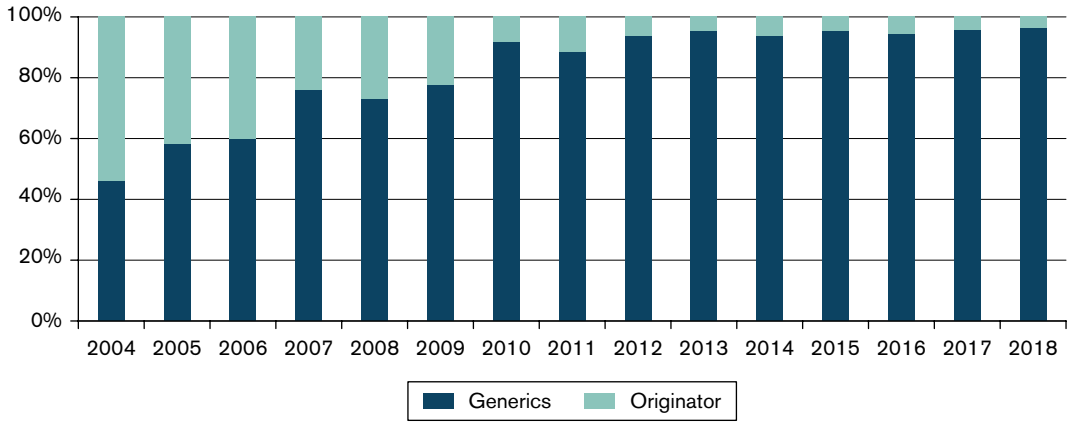
The impact of patents on access to medicines has often been illustrated using the example of HIV/AIDS treatments – ARVs. Access to HIV/AIDS treatments has presented a unique challenge because the earliest effective treatments became available only in the late 1980s. During the major efforts to scale 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.

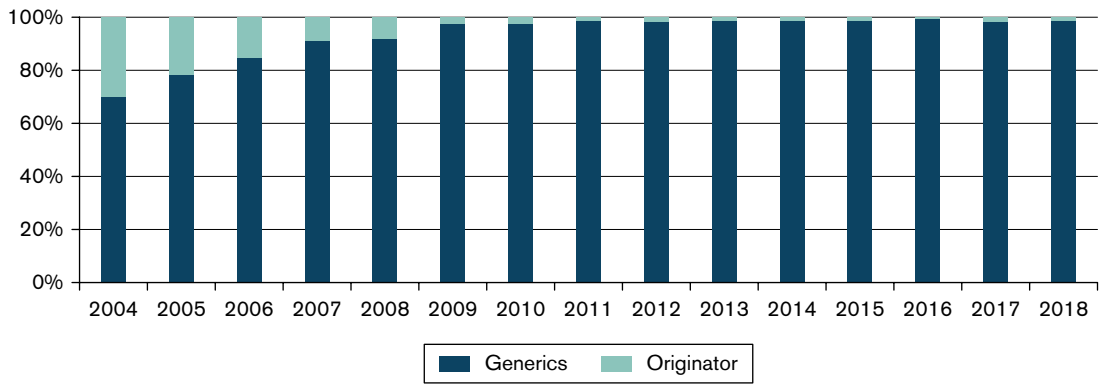
Access to low-priced ARVs continues to be essential, as governments and donor agencies strive to end the AIDS epidemic by 2030, as set out in target 3.3 of the SDGs. Low prices are also essential for governments transitioning from Global Fund financing to fully national financing.[101] Challenges remain 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]

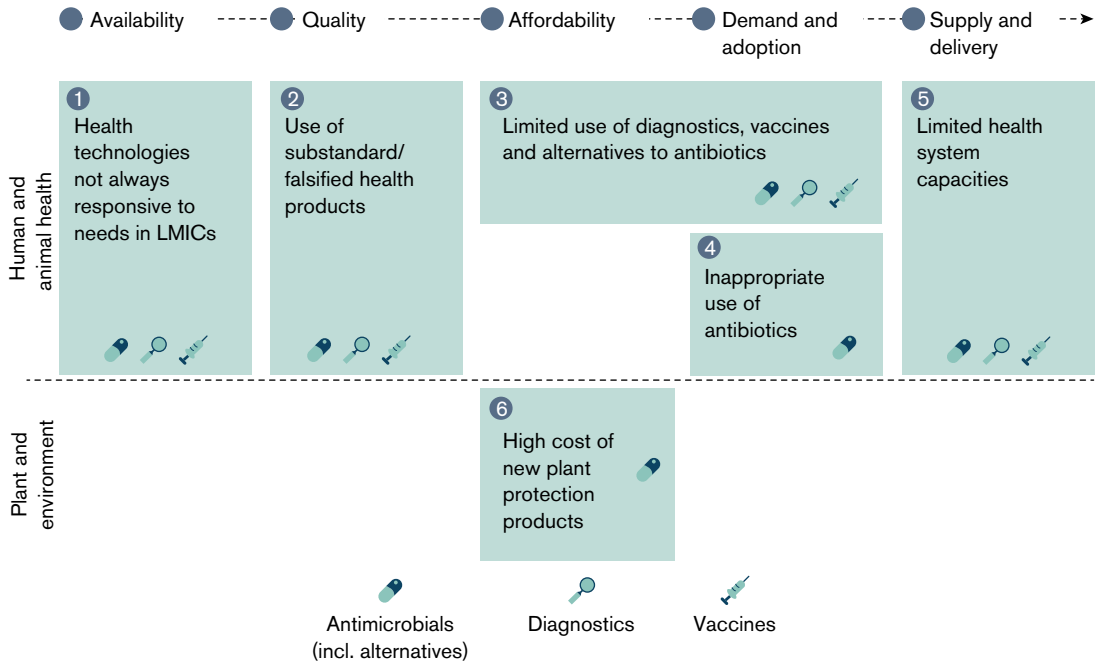
Good stewardship of antibiotics is of paramount importance in stemming resistance. Access to antibiotics is far from adequate at present; although few precise data are available, it is estimated that almost 6 million deaths occur annually due to infectious diseases that mostly could have been treated 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

Figure 4.7: Challenges in access to AMR-related technologies in LMICs



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 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 enrols 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 Assembly[172] and the UN General Assembly,[173] the WHO Global Strategy and Plan of Action on Public Health, Innovation and IP[174] 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; Kittitrakul, 2018a). The inclusion of Thailand in the voluntary licences may allow estimated budgetary savings of 38–93 per cent (Kittitrakul, 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 licenses 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$ 793[225] 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, *inter alia*, 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, *inter alia*, 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 $176 per month (3 per cent of the price charged by the patent holder), with a 6 per cent royalty rate.[250]
	2013	Dasatinib	CL	Not issued	Leukaemia	Patent expired in 2020.
	2015	Saxagliptin	CL	Not issued	Type 2 diabetes	Application rejected.[251]
Indonesia	2004	Nevirapine, lamivudine	GUL	Issued	HIV/AIDS	GUL in 2012 renews the GUL issued in 2004 and 2007, and, by adding six more medicines to the licence, covers all HIV/AIDS treatments. GULs are granted until the end of the patent period (in the case of TDF, November 2024), with a 0.5 per cent royalty rate. The Ministry of Health can sub-license to pharmaceutical companies.[252]
	2007	EFV	GUL	Issued	HIV/AIDS	
	2012	Abacavir, didanosine, efavirenz, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lopinavir/ritonavir, tenofovir disoproxil fumarate (TDF), emtricitabine/tenofovir disoproxil fumarate	GUL	Issued	HIV/AIDS; Hepatitis B	
Italy	2005	Imipenem-cilastatin	CL	Issued	Antibiotic	CL granted as remedy to anti-competitive behaviour.[253]
	2007	Finasteride	CL	Issued	Prostatic hyperplasia	CL granted as remedy to anti-competitive behaviour and to allow parallel export to neighbouring markets with expired patent protection.[254]
Malaysia	2003	Zidovudine, zidovudine/lamivudine	CL	Issued	HIV/AIDS	Monthly costs of HIV treatment reduced from US$ 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 use[270] 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 Berkeley[296] 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 rare[301] (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 Principe, 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 2013[317] 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 disproxil/ 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.

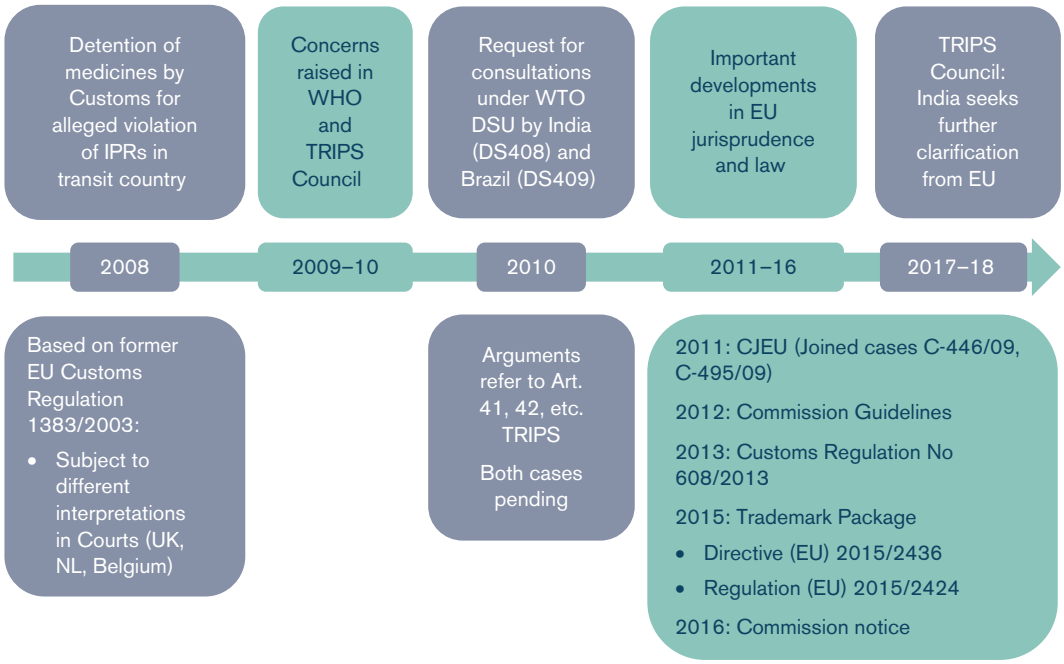
The TRIPS Agreement (Article 41) obliges all members to guarantee, under their law, access to effective, affordable, fair, equitable and transparent procedures to enable IPR holders to enforce their rights (see Chapter II, section B.1(f)). The application of these procedures must avoid the creation of 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 systems[341] and contact lenses[342]).

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 2015/2436[347] 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 2016[353] 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 framework[355] 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	✓		✓					

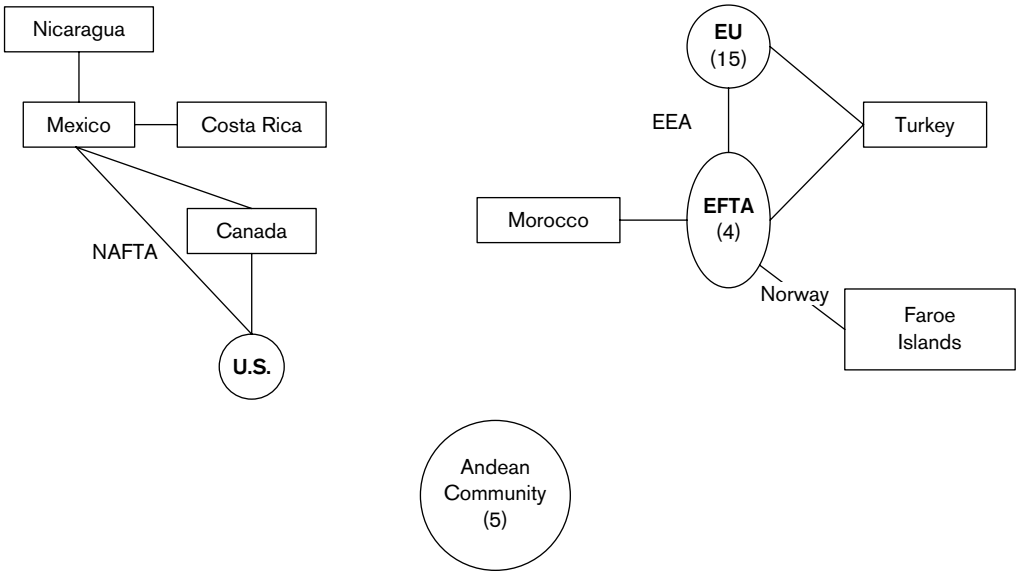
Notes: The entries reflect mandatory provisions that add to existing TRIPS obligations. The names of parties to FTAs are those used in the WTO. The source of the agreements is the Database of Regional Trade Agreements, available at: http://rtais.wto.org/UI/PublicMaintainRTAHome.aspx.

[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/cptpp-ptpgp/sectors-secteurs/ip-pi.aspx?lang=eng.

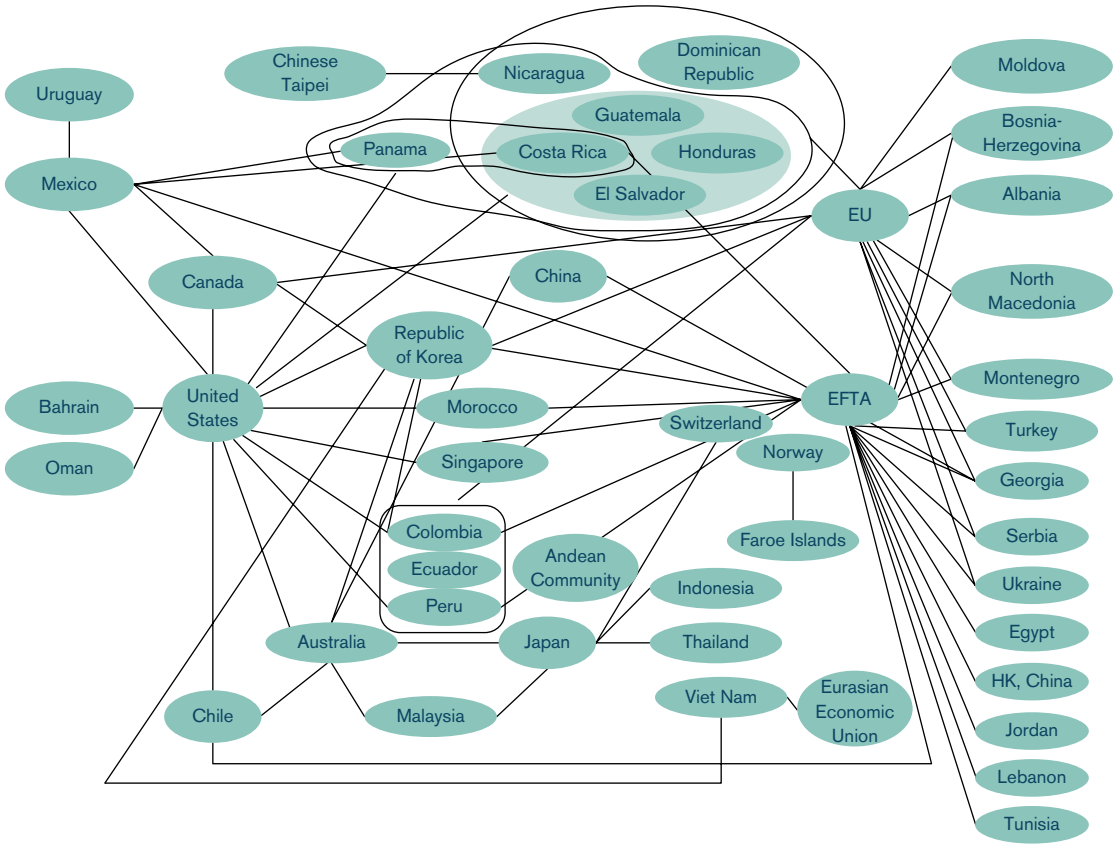
[2] See Declaration of the EU Party on Data Protection of Certain Regulated Products: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1399559252828&uri=CELEX:22012A1215(01). The Declaration also states that the relevant legislation of the Central American parties, "by providing protection periods 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

Year 2000



Year 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) Model[386] – 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.

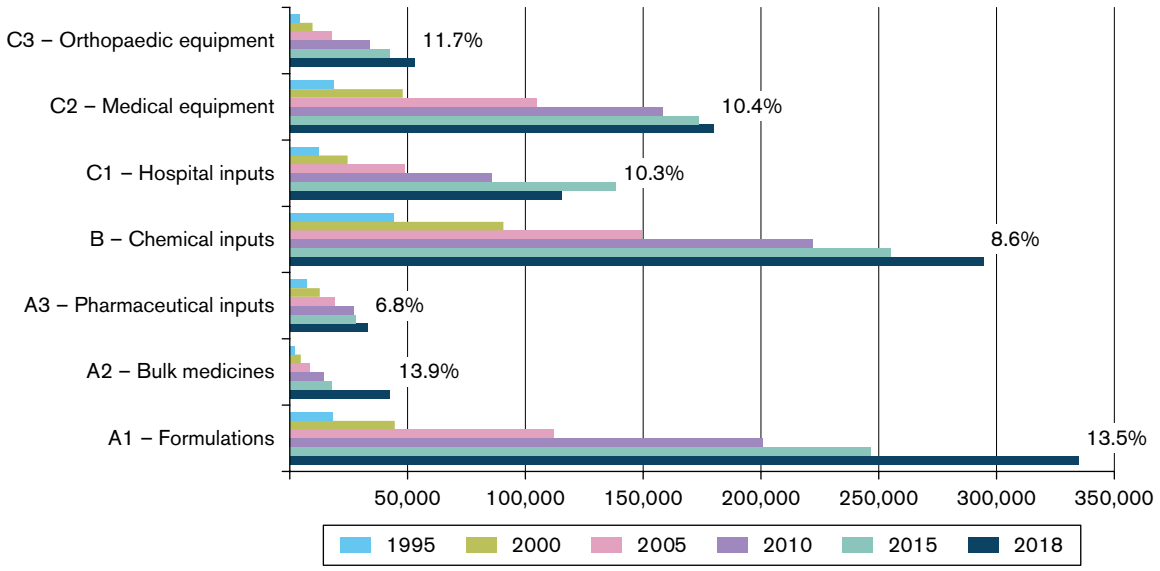
Source: WTO Secretariat. Product selection modified and updated based on "More Trade for Better Health? International Trade and Tariffs on Health Products", October 2012, Matthias Helble, WTO Staff Working Paper ERSD-2012-17.

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 Taipei[392] 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 Taipei[394] 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 Taipei[395] 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.

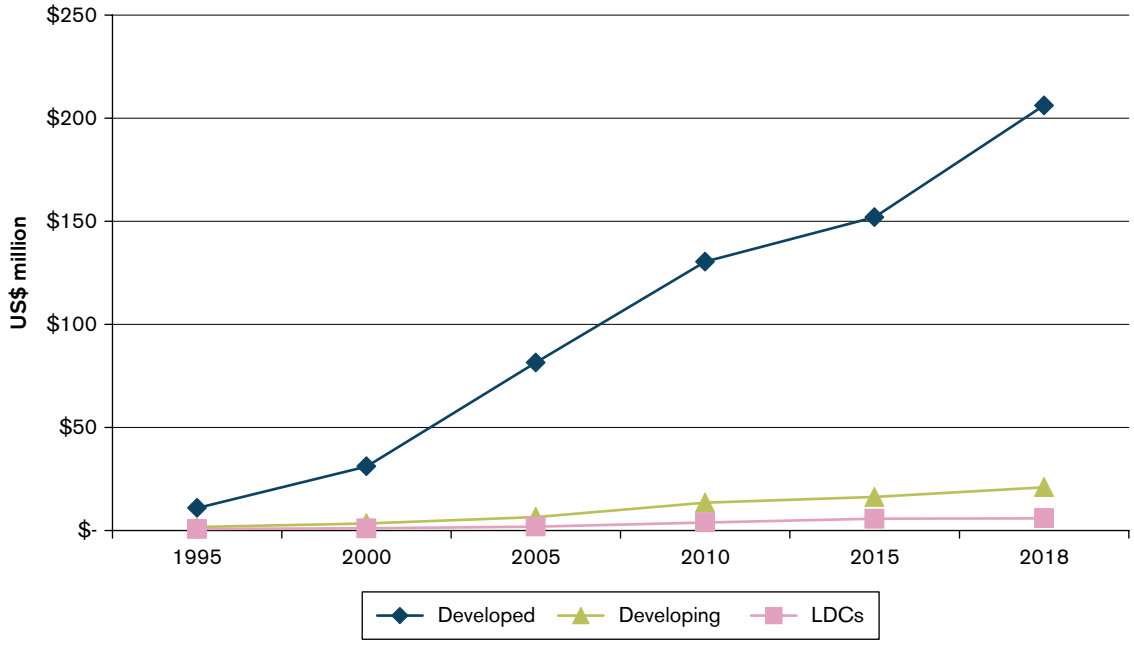
of medicines; therefore, despite some improvement, the relative level of importation remains very low, particularly given the high disease burden in LDCs.

(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 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

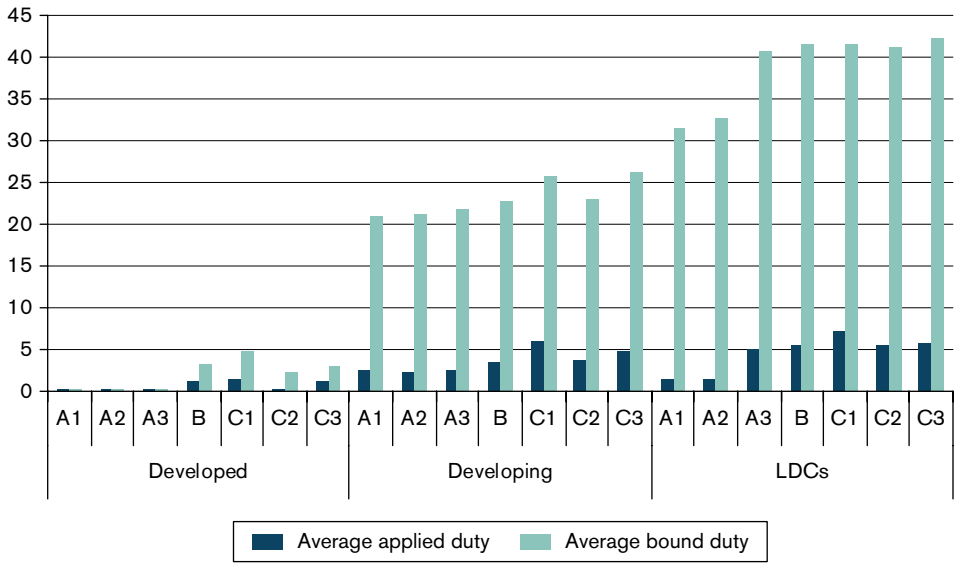
Despite excellent progress having been achieved in recent years, malaria continues to have a devastating human impact. In the absence of an efficient vaccine, the use of insecticide-treated mosquito nets (ITNs) remains one the most effective prevention means. Yet many countries – in particular, in sub-Saharan 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 Agreement[399] 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 caries 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 investigations[407] related to the pharmaceutical sector that underwent judicial review. The European Commission Pharmaceutical Sector Inquiry Final Report's main recommendations[408] 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 developments[420]

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 sector[421]

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 Korea[426]

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 antivirus 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 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).

Box 4.40: Jurisprudence on competition authority scrutiny to enable competition through off-label use[451]

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 Brazil[452]

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.

Similarly, a Health Market Inquiry conducted by the Competition Commission of South Africa (CCSA) in 2019[453] 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 recommendations[456] 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).

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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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209 Section 107A(a) of the Patents Act of 1970 of India.

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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.

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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.

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219 WIPO document SCP/21/4 Rev., p. 15, para. 50.

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.

224 See https://www.msf.org/sites/msf.org/files/utw_14_eng_july2011.pdf, p. 26.

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230 WTO document IP/C/57, para. 19, see Chapter II.

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