

III. Medical technologies: the innovation dimension

Chapter II has described the main elements of the policy framework for innovation and access. This chapter considers how this policy framework applies to innovation in medical technologies. It reviews the factors that have spurred innovation in medical technologies in the past, identifies how current models of R&D are evolving, and charts the role of established and new participants in the innovation process, including in the context of neglected diseases, emerging pathogens with pandemic potential and antibacterial treatments. It also covers the role of IP, particularly patents, in the R&D system.

The chapter reflects the fact that, over the past decade, health policy-makers have paid greater attention to the innovation dimension, considering in particular:

- The kinds of collaborative structures, incentive mechanisms, sources of funding and informatics tools that are required in order to build more effective and more broadly based and inclusive innovation processes, and recognizing the changing innovation and development models in the private sector
- How to ensure that medical research activities focus increasingly on areas neglected so far.

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A. Historical pattern of medical R&D

Key points

- R&D in the pharmaceutical sector evolved in typically large, privately owned companies where both R&D and marketing were carried out in-house. Initially, production was widely licensed out by originator companies. Later, however, marketing and the distribution of new medicines were exclusively taken care of by the originator companies.
- Global R&D expenditures by pharmaceutical companies and the number of patent applications have increased substantially between 2004 and 2019.
- Concerns have been raised that the development of new drugs is lagging behind, and about the limited improvement in the therapeutic benefit offered by new medicines over existing treatments.
- While a decline in R&D pharmaceutical productivity has been observed, there are indicators signalling a possible reversal.

1. Innovation for medical technologies in context

Innovation in medical technologies is distinct from innovation in general. It is characterized by several distinguishing features:

- The high costs of R&D and the concomitant high risk of failure
- The important role of public-sector input, such as in basic research funding and making infrastructure available, and in terms of influencing the market for finished products
- The inherent ethical component of medical research, and the potential negative impact on public health of closely held or overly restrictive management of technology and IP
- The need for a rigorous regulatory framework to assess medical technologies in terms of their quality, safety and efficacy.

It is important to understand historical trends in medical R&D and the development of the modern pharmaceutical industry, which provide the context for the dynamics of current developments and the challenges facing the existing innovation system and overall R&D landscape.

2. From early discoveries to “wonder drugs”

The modern pharmaceutical industry grew out of the European chemical industry in Germany and Switzerland, based on a growing understanding of organic chemistry and dyestuffs. France, the United Kingdom and the United States had joined this industry by the beginning of the 20th century, at which point there were still few

medicines available to treat basic infectious diseases. In the early 20th century, there was widespread opposition in academic circles to the patenting of innovation.¹ While there are cases in which scientific discoveries and production methods have been patented, there are many other cases in which they have not.² Prior to the 1930s, the pharmaceutical industry did not invest in R&D to any great extent. However, the discoveries that certain chemicals and microorganisms could be used to treat infections led to the development of a range of products that served as antibacterial agents. Manufacture at industrial scale proved to be another challenge. For example, it was only in 1939, ten years after Alexander Fleming discovered penicillin, that mass manufacture of penicillin got under way in facilities of the US Department of Agriculture. Subsequently, private pharmaceutical companies were enlisted to develop and market the medicine. Penicillin and sulphanilamide formed the basis of a generation of new “wonder drugs”. They were developed in collaboration with teams of researchers from both not-for-profit organizations and private enterprise. IP has played varying roles in the history of different antibiotics.

By the 1960s, more than 50 new patents had been filed in relation to sulfa drugs. These patents were primarily process patents as many countries at the time did not allow product patents on pharmaceuticals. Numerous process patents were taken out on penicillin. It is argued that these patents were not key to the development of improved processes. No one company was able to gain market control, as most fundamental process patents were owned by the US Department of Agriculture, which had a policy of licensing the patents to any company seeking to manufacture penicillin (Quinn, 2013). In the absence of patents, companies developing improved manufacturing processes entered arrangements to mutually share information and samples (Quinn, 2013). The incentivizing role of IP is more obvious in the development of later antibiotics, which involved the search for new exclusive

molecules.³ Synthetic penicillin reflects the changed role of patents in the antibiotics industry, with patents for synthetic penicillin being filed in the United Kingdom by the Beecham Group in 1960. The Beecham Group has stated that the original decision to expand drug research into semi-synthetic penicillin would not have taken place without the incentives of patent protection (Taylor and Silberston, 1973). While patenting by pharmaceutical companies increased soon after the flourishing of antibiotic manufacture, it is difficult to say whether there was a causal link between antibiotics innovation and IP.⁴

3. Growth and evolution of the pharmaceutical industry

The turmoil of war and migration, among other factors, led to the shift of leadership in the pharmaceutical industry from Europe, particularly Germany, to the United States, although trans-Atlantic rivalries continued to be sharp. The mid-1940s saw the rise of the United States-based pharmaceutical industry, and several factors influenced this, including the introduction of regulation on prescription drugs and changes in how patent law was applied.⁵ The interplay between these two specific factors helped develop the modern, vertically integrated pharmaceutical firm that undertakes both in-house R&D and marketing. From 1950 to 1970, the ratio of R&D investments to sales revenues in the US pharmaceutical industry more than doubled, while the ratio of advertising expenses to sales revenues was even higher. Most of the marketing expenditure comprised the cost of informing and influencing doctors on prescription medicines. The period from the late 1940s onwards saw an increase in the grant of both product and process patents for pharmaceuticals.⁶ During the period 1950–1970, the pharmaceutical industry returned consistently higher levels of profit than most manufacturing companies at that time. The period from the mid-1940s to 1970 saw a boom in innovations based on organic and natural products chemistry, which, in turn, led to the isolation and synthesis of vitamins, corticosteroids, hormones and antibacterial agents. The following years were marked by the industry moving from chemistry-based R&D and manufacturing to pharmacology and life-sciences-based activities. Also during this period, most countries increased the stringency of their new drug approval processes, following the 1962 Kefauver–Harris Amendments to the US Federal Food, Drug, and Cosmetic Act, and a phased system for developing new medicines was established – the so-called “Phase I–IV” system for clinical trials (see Chapter II, section A.6(b)). Prescription drugs came to dominate pharmaceutical sales and profits – for example, in the United States, prescription drugs comprised only 32 per cent of consumer expenditures in 1929, but by 1969, this share had increased to 83 per cent (Malerba and Orsenigo, 2015).

Tight control of R&D and marketing was necessary because these companies derived most of their revenues

from a very small number of successful products (Comanor, 1986; Malerba and Orsenigo, 2015). The basis for competition among these companies changed from price factors to non-price factors, such as research and advertising outlays and outputs. This model helped to incentivize innovation – the US R&D-based pharmaceutical industry moved from an average of 20 new products per year in the 1940s to an average of 50 new products per year in the 1950s.

4. From non-exclusive licensing to restricted production

An early example of non-exclusive licensing can be seen in the story of insulin (see Box 3.1).

In the early years of the US pharmaceutical industry – until around 1950 – there was widespread licensing of patented medicines for production by other pharmaceutical companies, which had a salubrious effect on price over time, even during the patent term. For example, streptomycin, for which a patent was granted in the United States in 1948 to scientists at Rutgers University, was licensed on an unrestricted basis at a royalty rate of 2.5 per cent. In the specific case of penicillin, the United States price fell from US\$ 4,000 per pound in 1945 to just US\$ 282 per pound in 1950 (Temin, 1979).

However, in the period up to 1960, a key development in the United States was that innovative companies began to exclusively manufacture products themselves, without licensing them to others. This enabled them to restrict output and generate larger profits. A practice of licensing with high royalty payments could potentially have delivered the same profits to these innovator companies, but such royalty payment rates would have had to be very high in the face of inelastic demand (i.e. where consumer demand for a product does not change appreciably in response to a small increase in price). By one estimate, when demand is inelastic, the royalty rate required to yield a return equivalent to an exclusive, single-supply model would be 80 per cent (Temin, 1979). As an early example of exclusive production, the wholesale price of tetracycline in 1948, before the introduction of generic versions of this medicine in the United States, was US\$ 30.60 per 100 capsules, whereas the production cost for the same quantity was just US \$ 3.00, thus generating a profit rate of 920 per cent. Such high royalty rates were commercially unprecedented, as royalty rates at that time were typically just 2.5 per cent. The 2.5 per cent rate – the royalty rate at which streptomycin was licensed – would have applied in a US Federal Trade Commission (FTC) decision relating to a compulsory licence for tetracycline. This FTC decision did not subsequently enter into force for other reasons (Scherer and Watal, 2002), while in the United Kingdom, a “Crown use” licence – which nowadays would be classed as a type of government-use licence – was granted to the National Health Service to import generic tetracycline.⁷

Box 3.1: IP and licensing in the discovery of insulin

In 1922, researchers at the University of Toronto developed insulin as the substance that is life saving in patients with type 1 diabetes. At the time, the code of ethics of the University required health goods to be free from gain. After extensive deliberation and consideration of precedents, such as a patent on adrenaline (see section D.4(a)), the University decided to apply for patent protection on insulin and to commercialize the medicine in the interests of the medical profession. To that effect, the University set up an Insulin Committee to develop appropriate licensing terms and to manage relations with industry in conformity with the ethical code of doctors and in patients' interests. This choice was motivated by the intention to prevent a commercial monopoly, regulate the conditions of marketing and control the quality of industrial production. An exclusive licence was agreed with a manufacturer for a limited period of one year. The manufacturer improved the production processes and filed its own patent application on the improvement. This led to discussions between the manufacturer and the University about patent dependency and ownership. While the licence contained a grant-back clause for this situation, that clause did not concern the United States. The discussions were resolved through an agreement. The manufacturer ceded its patent to the University and gained legal certainty for continued production using the improved process without costly litigation. The University kept control over the insulin patents in the United States. In addition, the parties agreed on a patent pool. Any further licensees of the University's insulin patents were required to place any further patents on insulin into a common patent pool administered by the University. The University's (non-exclusive) licence agreements enabled the University to implement the principles of its insulin licensing policy and to establish control over the pricing and advertising of the end product. The manufacturer was able to maintain a strong advantage over competitors due to its early investments in process development and manufacture (Cassier and Sinding, 2008).

These conditions of exclusivity and product differentiation extended beyond antibiotics to all medicines obtained through R&D. For instance, the first generation of steroids was widely licensed, while the second generation of synthetic steroids was exclusively produced by patent-owning companies (Temin, 1979).

As early as 1959, the report of the US Senate Subcommittee on Antitrust and Monopoly (Kefauver Committee) accused the industry of price gouging through duplicative research and insignificant molecular modifications to create newly patentable but therapeutically equivalent products. Sceptical views expressed in the current global debate about the benefits of competition, and the appropriate level of returns for innovation in the context of biomedical R&D, echo some of these early criticisms. Senator Kefauver pointed to the huge mark-ups between raw material costs and the final price of a drug; his congressional hearings also exposed a variety of unsavoury marketing practices. Senator Kefauver proposed mandatory cross-licensing of drug patents, pricing limits and marketing restrictions, in order to lower drug prices. These proposals did not ultimately make it into the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act of 1962, which gave the FDA the authority to postpone or reject new drug applications. A number of European countries followed with similar legislation conceived to ensure the quality and safety of medicines.⁸

5. Trends in R&D

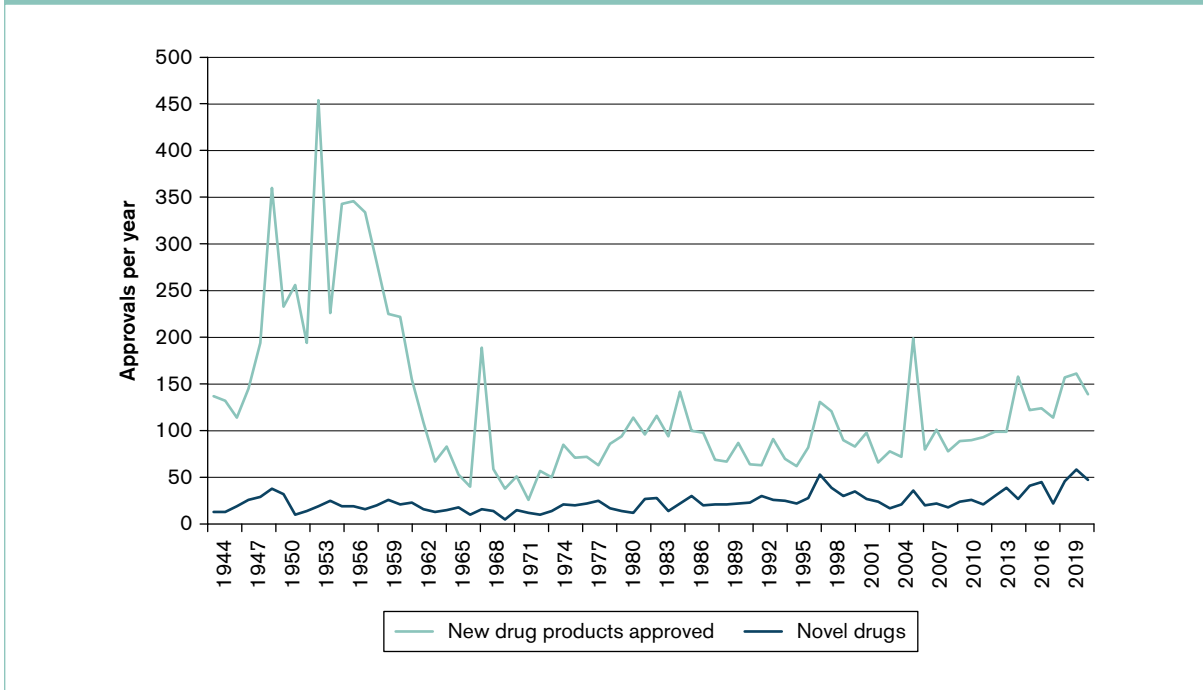
This section describes trends in R&D by looking at a number of indicators, namely, patent activity, R&D

investments and the number of medicines approved each year, as well as the characteristics of these medicines.

Trends in approvals of medicines by the FDA from 1943 to 2019 are shown in Figure 3.1. It displays trends in both approvals of new drug products, which include all approved medicines, including new dosage forms and new indications for medicines that have previously been approved, and approvals of novel drugs, that is, medicines that had never previously been approved in any form. Levels of approvals of new drug products were very high until around 1960, which likely reflects the fact that a wide range of products that did not need approval prior to the establishment of the Federal Food, Drug, and Cosmetic Act in 1938 now needed approval to remain on the market. From around 1960, the number of new products approved per year has varied substantially from year to year but has shown an overall upward trend to 2019. Compared with new product approvals, a far smaller number of approvals concern novel drugs. The number of novel drug approvals has risen slowly but steadily, from lows of 5–23 in the 1960s to a record 59 in 2018.

Figure 3.2 illustrates the parallel trends in R&D expenditures by originator pharmaceutical companies, PCT publication numbers and novel drug approvals. Global R&D expenditures by originator pharmaceutical companies have increased substantially, from an estimated US\$ 118 billion in 2004 to US\$ 182 billion in 2019. When compared with sales, this increase is less pronounced, with R&D expenditures as a proportion of sales rising from 17 per cent in 1995 to 20 per cent in 2018 for a group of large pharmaceutical companies in the United States (see Figure 3.2). Over the same period, yearly PCT patent publications for pharmaceuticals rose

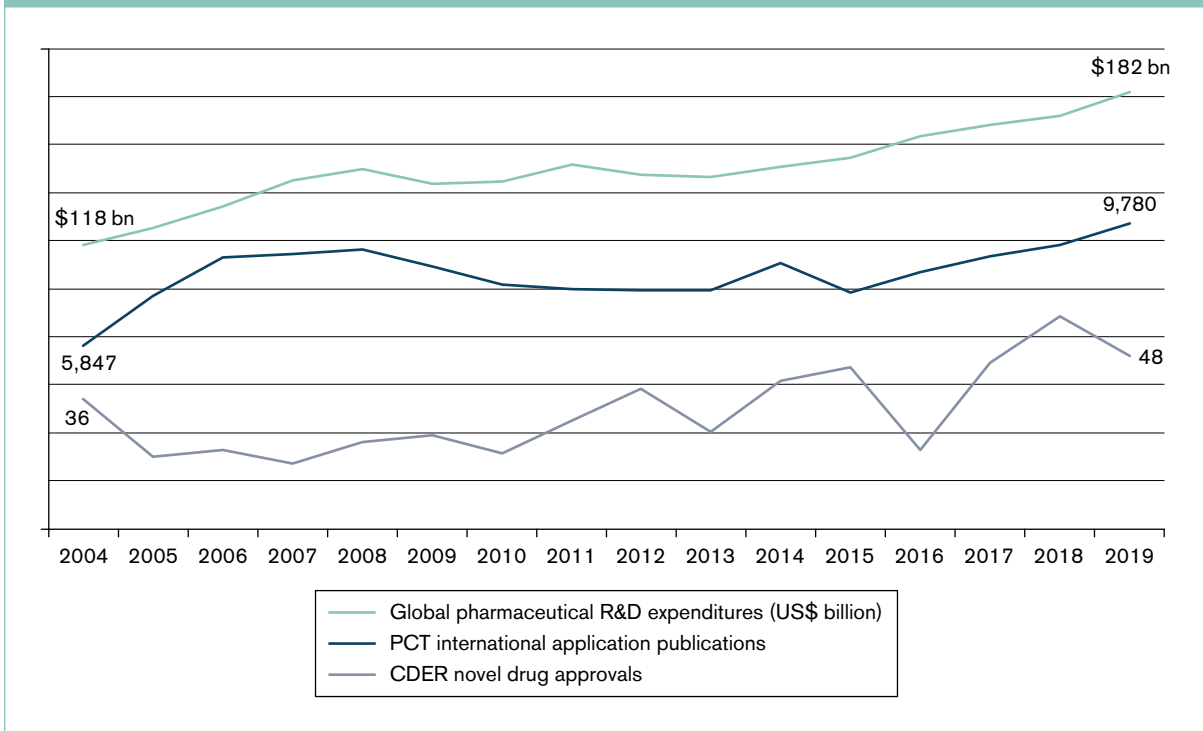
Figure 3.1: Approvals of medicines by the US Food & Drug Administration, 1944–2019



Sources: United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER).

Note: “New drug products” means all products approved under new drug applications and biologics licence applications. “Novel drugs” means new molecular entities approved under new drug applications and new therapeutic biologics approved under biologics licence applications. Data are from the US Food and Drug Administration.⁹ Local maxima at years 1996 and 2004 are in part due to changes in the FDA approval process, rather than true increases.¹⁰

Figure 3.2: Global R&D expenditures, PCT international application publications on pharmaceuticals and novel drug approvals in the United States, 2004–2019¹¹



Sources: EvaluatePharma estimates, in *World Preview* (2013, 2015, 2017, 2019); United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER); WIPO Statistics Database.

from 65,000 to 95,000, and the number of novel drugs approved by the FDA CDER rose from 36 in 2004 to 48 in 2019. A rising number of novel drugs are orphan drugs (i.e. medicines that treat rare diseases (see section B.6)), increasing from 20 per cent in 1999 to 44 per cent in 2019 (see Figure 3.3).

At the same time, concerns have been raised that the development of new drugs is lagging behind, along with concerns about the level of additional therapeutic benefit offered by new medicines over existing treatments.¹² Particular concern has been drawn to antimicrobials, where no new classes of antibiotics have been approved in the last three decades (see section C.2).

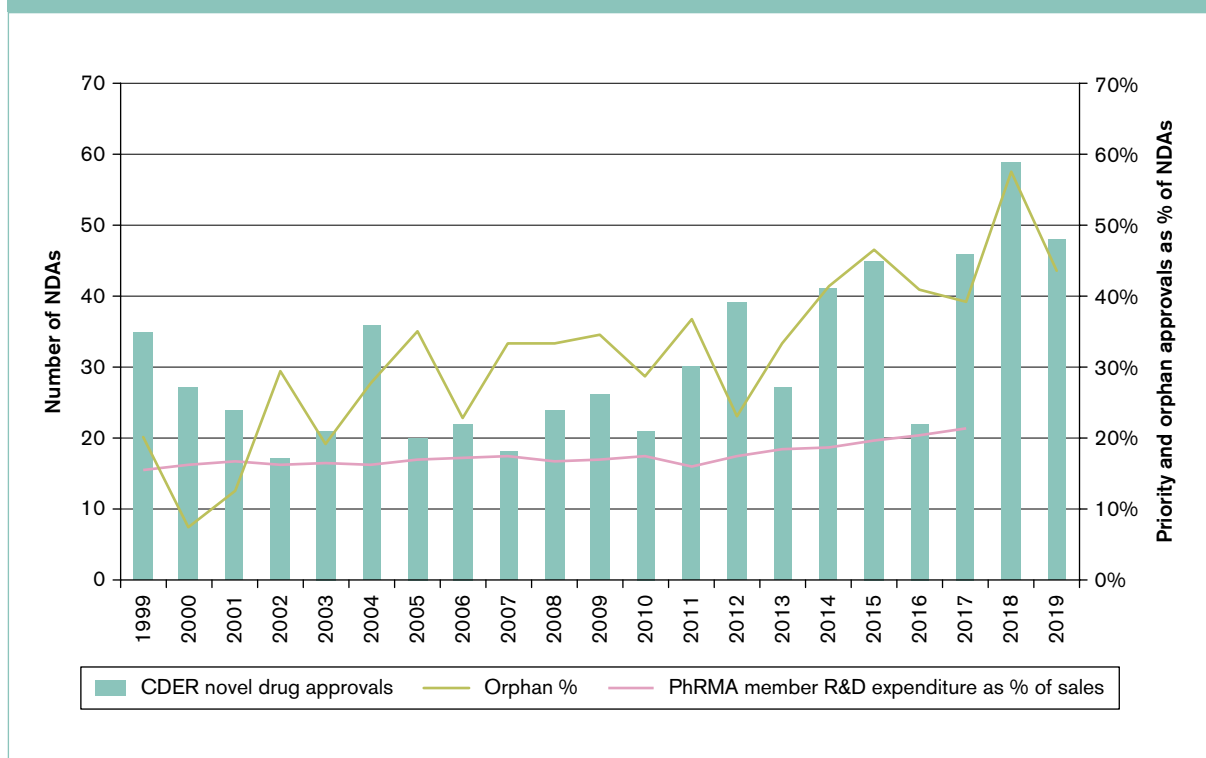
In the same vein, concerns have been expressed that the rate of innovation may be declining, though there is no consensus explanation for these trends. One explanation may be that “the low-hanging fruit have been picked”, while another may be that it is due to problems with the incentive structure in the biomedical innovation system (Bloom et al., 2017). It has also been observed that the adoption of new health technologies has become an increasingly complex exercise, due to the different environments involved, such as regulatory approval processes and multiple interactions among various stakeholders, including governments and regulatory authorities and private and public research actors, such as companies and universities (Cornell University, INSEAD and WIPO, 2019).

The economic literature indeed confirms a decline in R&D pharmaceutical productivity – defined in the literature as the ratio of R&D outputs measured by the rate of introduction of new molecular entities (NMEs) to actual R&D inputs, and thus pharmaceutical R&D expenditures (Griliches, 1994; Pammolli et al., 2011). One explanation could be that pharmaceutical R&D inputs and outputs are hard to measure (Pammolli et al., 2011); other authors wonder whether the costs of R&D expenditures are overstated, for example, by failing to account for inflation in R&D input costs (Cockburn, 2006; Griliches, 1994; Pammolli et al., 2011). Beyond some measurement issues, the concern is that diminishing returns on pharmaceutical R&D may be decreasing incentives to invest in new breakthrough drugs in important future fields (Gordon, 2018; Deloitte, 2018).

However, there are indicators signalling a possible reversal of the productivity in medical R&D (Cornell University, INSEAD and WIPO, 2019). For example, there has been a substantial increase in the number of Phase I and Phase II clinical trials since 2015. It remains to be seen whether that increase results in a corresponding increase in novel drug approvals.¹³

Patent filings in pharmaceuticals, biotechnology and medical technology have been growing over the last four decades (see Figure 3.4). Patents on medical technology grew faster than patents on pharmaceuticals or biotechnology.

Figure 3.3: Novel drug approvals, percentage with orphan designation and R&D expenditure as percentage of sales, 1999–2019¹⁴



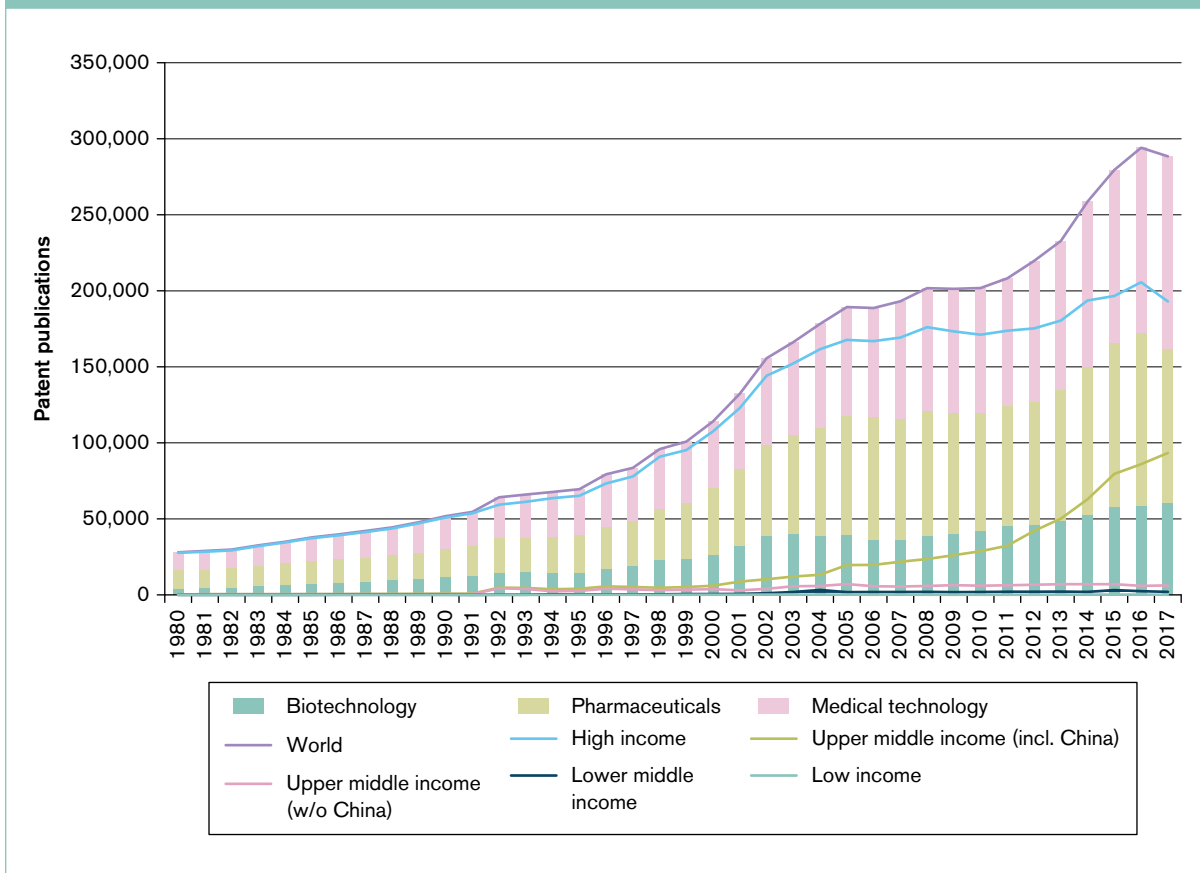
Sources: EvaluatePharma estimates, in *World Preview* (2013, 2015, 2017, 2019); United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2019 PhRMA Annual Membership Survey; WIPO Statistics Database.

This puts medical technologies among the top five fastest-growing technology fields since 2016, the other four being IT-related fields. After strong catch-up, medical technology patents are now as numerous, with about 100,000 worldwide. Upper-middle-income countries have significantly increased patenting activity in health technologies from 2005 to 2017.

in biotechnology, such as single-cell analysis and genetic engineering, raise hopes of acquiring a better understanding of biological processes that may eventually help to find cures for diseases such as Alzheimer's disease, cancer and HIV/AIDS. Modern IT based on the power of big data is widely expected to enable major advances in pharmaceutical and biomedical research, medical technology and health care. The realization of these hopes will depend on a policy, innovation and development environment that supports these efforts, as well as equitable access to any new technologies.¹⁵

The future of biomedical innovation is expected to involve and combine a number of emerging and disruptive technologies, such as biotechnology and IT. Developments

Figure 3.4: Patent publications by technology: performance by sector, income group and world, 1980–2017



Source: Cornell University, INSEAD and WIPO (2019).

B. The current R&D landscape

Key points

- The conventional innovation model of the pharmaceutical industry is leading to structural changes. These changes include an increasing number of mergers and acquisitions, outsourcing of R&D activity and more R&D collaborations, as well as greater focus on R&D in cancer and orphan medicines.
- There is an increasing debate about medicine pricing that has been triggered by prices of new medicines, including in high-income countries.
- The public sector has a significant impact on the innovation cycle at various stages, through financing and undertaking R&D, helping to shape private companies' R&D priorities, and the way in which health products are regulated, procured and disseminated.
- Developing pharmaceutical products and bringing them to market is usually costly and time consuming. However, limited data make it difficult to produce a reliable, independent assessment of the true costs of medical research.
- There are many different mechanisms for promoting innovation. Intellectual property rights (IPRs) are a useful incentive mechanism, but the IP system cannot incentivize inventions in areas where there is no market. The innovation cycle is not self-sustaining in disease areas where markets are small and health services are underfunded, such as in neglected diseases or antimicrobials.
- Vaccines are different from medicines in many respects. The process of proving the safety and efficacy of a vaccine always requires a full regulatory dossier. There has been a significant increase in the development of new vaccines, and new models of innovation, coupled with a growing number of vaccine manufacturers in low- and middle-income countries (LMICs), which are also increasingly engaged in research.
- Access to results from clinical trials is in the interest of science and public health and is necessary for evidence-based decision-making. The WHO has established a global network of clinical trials registries that facilitates access to information on clinical trials. Open access policies for sharing data are important and need to comply with requirements regarding personal data and ethics.

This section reviews the environment in which companies and other public and private entities carry out research, against the background of the evolution outlined in the preceding section.

1. A time of challenges and opportunities for pharmaceutical R&D

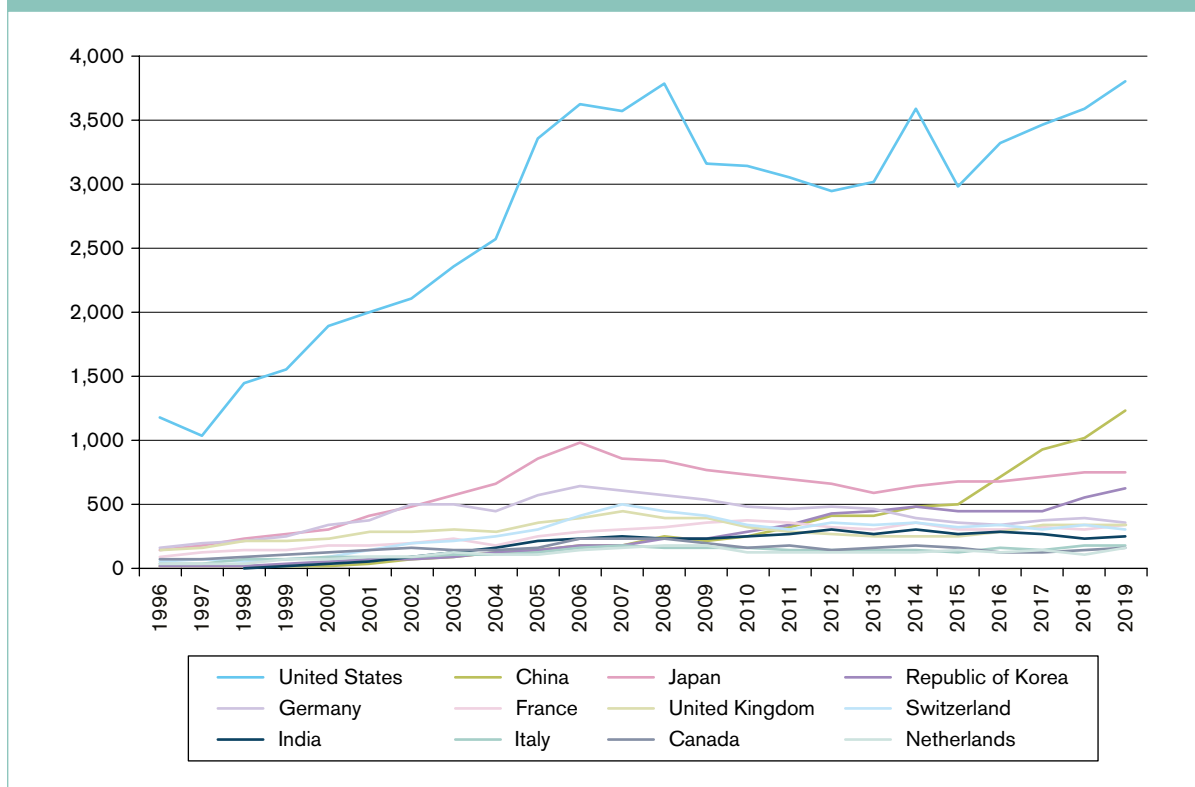
The market for pharmaceuticals is rapidly growing and changing, and the market for prescription pharmaceuticals is projected to reach US\$1.2 trillion globally by 2024 (EvaluatePharma, 2018). The global market is undergoing numerous transformations:

- In OECD countries, retail pharmaceutical expenditure per capita rose 2.3 per cent annually, on average, in the period 2003–2009, but decreased by an average 0.5 per cent annually in the period 2009–2015.¹⁶ At the same time, global spending on prescription drugs increased from to US\$ 455 billion in 2004 to US\$ 789 billion in 2017, and is projected to rise to US\$ 1,204 billion in 2024.¹⁷

- The share of worldwide prescription drug sales represented by biotherapeutic products increased from 17 per cent to 25 per cent between 2010 and 2017 (EvaluatePharma, 2018) and is projected to reach 31 per cent by 2024 (see also Chapter II, section A.6(d)).
- There is increasing political, regulatory and payer scrutiny of prescription drug prices in high-income markets.
- An increasing share of global sales will come from LMIC markets.¹⁸
- Smaller companies are becoming more important in biomedical R&D. Large pharmaceutical R&D companies no longer have the sole advantage of an important tool in drug discovery, namely, high-throughput screening, which is being combined with artificial intelligence (AI), machine learning and DNA-encoding to increase R&D productivity by small companies (Brazil, 2018).

The worldwide sales for originator medicines have increased in absolute terms since 2011 (EvaluatePharma, 2018), and the originator pharmaceutical industry continues to have stable and high profit margins compared with other industries.¹⁹

Figure 3.5: Top countries of origin of PCT publications in the field of pharmaceuticals, 1996–2019



Source: WIPO Statistics Database.

The biopharmaceuticals sector remains one of the most R&D-intensive industry sectors globally (European Commission, 2018b). In absolute terms, the United States continues to lead in R&D expenditures in the life sciences sector, far outstripping, for example, the European Union, Japan and Switzerland.²⁰ The United States is also the top country of origin of international applications filed under the PCT in the field of pharmaceuticals from 1996 to 2019 (see Figure 3.5).

Low R&D efficiencies (i.e. high R&D costs and low new drug approval rates), predominantly until 2015, have led major pharmaceutical companies to implement various changes to their business models (Schuhmacher, Gassman and Hinder, 2016). These include:

- Increased R&D collaborations. R&D is increasingly collaborative, involving partnerships between life sciences companies, academia, non-profit organizations and government entities.²¹ These enable R&D partners to share financial risk, widen their competencies and access enlarged skill sets and technologies.²²
- An increasing share of the R&D pipeline being commanded by cancer treatments. At the same time, prices of cancer medicines at launch are rising, while, among recently approved medicines, only a few offer meaningful clinical benefits (see Box 4.13) (Kim and Prasad, 2015; Davis et al., 2017; Vivot et al. 2017; Grössmann et al., 2017).
- A higher share of products for rare diseases (orphan drugs). Orphan drugs, which constituted 10 per cent of global prescription drug sales in 2010, accounted for 16 per cent in 2017 and are projected to represent 22 per cent by 2024 (EvaluatePharma, 2018). Orphan drugs are developed for small patient populations but benefit from a number of regulatory and financial incentives and often achieve high revenues (see section B.6).
- Strategic mergers and acquisitions (M&A) activity. Pharmaceutical companies increasingly use M&A to compensate for revenue losses caused by price drops following patent expiry, access strategically important technology and acquire promising R&D pipeline products (EvaluatePharma 2018).²³ In 2019, it was estimated that 69 per cent of the portfolios of high-growth pharmaceutical companies (i.e. companies that have consistently outgrown the market for more than 12 years) came from acquisitions or licensing in 2015 (Albrecht et al., 2016). M&A strategies are increasingly diverse, with pharmaceutical companies pursuing acquisitions of non-traditional, technology-oriented businesses (Deloitte, 2018). M&A also forms an important part of the growth strategy of small and medium-sized enterprises (SMEs), with many relying on investment or acquisition by larger pharmaceutical companies to progress through the costly clinical trial process (Herbert, 2018). Acquisitions of generic companies by R&D-based companies and vice versa

have blurred the traditional boundary between R&D-based companies and generic drugs companies. Horizontal integration through M&A among the big companies has led to a concentration of market shares. In addition, mergers most often lead to reduced R&D activity as companies will merge or close R&D centres that were acquired (Gilbert, 2019; Comanor and Scherer, 2013) (see also Chapter II, section B.2(c)).

- R&D cuts and outsourcing. A number of major pharmaceutical companies have cut the size of their R&D units to reduce costs and increase efficiencies (Herbert, 2018). Internal R&D cuts have been accompanied by an increased focus on outsourcing of R&D activities,²⁴ for example, capital-intensive activities such as high-throughput screening (HTS), saving pharmaceutical companies the expense of investing in in-house infrastructure (Brazil, 2018).
- Reduced antimicrobial research. Most large pharmaceutical companies have withdrawn their antimicrobial research programmes in light of poor potential for investment returns.²⁵

The structure of the industry has also evolved:

- The wider technology sector is presenting both challenges and opportunities for the pharmaceutical industry. “Big Tech” companies are entering the pharmaceutical market, disrupting traditional business models.²⁶ On the other hand, pharmaceutical companies are increasingly partnering with or acquiring technology companies, with a view to increasing their digital capabilities (Deloitte, 2018). Effective utilization of data is a key industry focus, with R&D stakeholders focusing on developing their internal technical and data capabilities and identifying potential external data sources (Deloitte, 2018).
- Start-ups are more prominent, particularly in the development of next-generation therapies. One 2019 report notes that, while only a few big pharmaceutical companies are developing next-generation therapies, more than 250 start-ups are focused on gene-based therapeutic solutions.²⁷ The rise of collaborative R&D models (between pharmaceutical companies), the outsourcing of key R&D services and the growth of digital networks has provided start-up companies with access to technologies and technological infrastructure that might have been inaccessible in the past (Brazil, 2018).
- Middle-income markets are increasingly important. The market for pharmaceuticals and medical devices in some middle-income economies is growing rapidly, driven by increased prosperity, health-care reform, local government incentives and overall rising demand for health care.²⁸ While multinationals already have a firm foothold in these markets, local companies are experiencing strong growth, attributed to lower production costs, the success of locally

adapted products and government support.²⁹ Some pharmaceutical companies from certain middle-income economies increased their share of global revenues by a factor of 26 (from US\$ 4.5 billion to US\$ 119 billion) from 2005 to 2015.³⁰

- Medical device companies are also showing signs of a similar trajectory. For example, Chinese medical device companies are already growing much faster than their American counterparts.³¹ While many companies in these contexts specialize in “frugal engineering” – making low-cost, simplified versions of existing technologies suitable for LMICs – they are increasingly investing in the development of new products.³²

The latest wave of innovation in pharmaceuticals, gathering pace from around 1980, is based on advances in the discovery and application of biotechnology. The growing use of bioinformatics in virtual R&D to create computer models of organs and cells offers significant potential for tailored drug discovery and development (PwC, 2008). The decoding of the human genome in the late 1990s spurred hopes of a new wave of innovation in personalized medicine. The first gene- and cell-based therapies were approved in the 2010s, including, for example, sipuleucel-T for prostate cancer in 2010, tisagenlecleucel for leukaemia in 2017 and voretigene neparvovec-rzyl for a genetic cause of blindness in 2017 (approval dates given are for the FDA), with more in development (see Boxes 2.3 and 2.4).³³ Despite scepticism towards genomics being able to deliver more precise diagnostics and medicines (Pray, 2008), sometimes termed “precision medicine” (see Box 4.17), benefits are beginning to be seen for some diseases, but these are mostly limited to a small number of countries, due to high prices and, in some cases, high infrastructure requirements.

There has been an increasingly intense focus on prices of new, innovative medicines, not just in poorer countries but, increasingly, in high-income country markets such as Europe and the United States. This has led to a debate on medicine pricing as well as on the social value of “me-too”-type medicines. The 2006 Congressional Budget Office report summed up the situation as follows:

“The more accurately a drug’s price reflects its value to consumers, the more effective the market system will be at directing R&D investment towards socially valuable new drugs. However, prices can only serve that directing role to the extent that good information exists about the comparative qualities of different drugs and that consumers and health-care providers use that information.” (USCBO, 2006, p. 5)

Certain criticisms of the industry notwithstanding, there is little doubt that modern medicines and technologies have contributed to longevity, especially in countries that have access to newer medicines (Lichtenberg, 2012).

Box 3.2: Adaptation of medical devices to developing-country needs – the example of portable electrocardiographs

Electrocardiography (ECG) records the electrical activity of the heart, assisting in diagnosis of heart conditions. Traditional ECG machines are a widely used diagnostic tool and are commonplace in hospitals. However, they are bulky (about the size of a briefcase), often show readings by printing on custom-format paper and are relatively expensive.

Handheld ECGs were invented in 2007. They were designed to extend the capability of a traditional ECG to a rural populations in LMICs, to help combat the rising number of deaths caused by cardiovascular diseases (GE Healthcare, 2011; Immelt et al., 2009). Rural populations in LMICs are particularly vulnerable, due to their very limited access to qualified health professionals, medical devices and essential medicines to combat cardiovascular diseases.

The first handheld ECG machine, developed in 2007, cost around US\$ 800, compared with traditional units that ranged from US\$ 2,000 to US\$ 10,000. The next generation of portable ECG machines was developed with a built-in screen to allow instant viewing of ECGs, eliminating the need to print them, thereby saving costs and paper (GE Healthcare, 2011; Immelt et al., 2009). They also included wireless technology, which enables health-care workers to perform ECGs in remote areas and immediately transfer the test results to physicians who can interpret them. Due to its efficacy, the portable ECG is now also being used in rural areas in high-income countries.

Changes are also occurring in the way innovation is taking place in medical devices (see Box 3.2). Increasingly, private-sector medical devices companies are seeking to specifically design new devices and health-care delivery models that can be adapted to the needs of LMICs. These actions reflect a growing level of commitment among companies to serve long-neglected markets; they also reflect companies' increased interest in the commercial opportunities arising from addressing the health needs of people who inhabit the middle and bottom levels of the socio-economic pyramid. As a result, companies are committing greater resources towards evaluating local and regional barriers, and they are creating tailored products and services to meet specific cultural or geographic needs. One of the outcomes of this development is devices that are more adapted to the needs of LMICs. Such devices are also less costly than those designed for markets in high-income countries and are thus more affordable. The design of the devices may also serve to enhance accessibility (Cornell University, INSEAD and WIPO, 2019).

2. The key role of public-sector research in medical R&D

The ecosystem of pharmaceutical R&D has evolved such that, in a broad sense, there is a “division of labour” between the public sector and the private sector, in which the public sector concentrates more on upstream research that provides basic scientific knowledge on the mechanisms of disease, while the private sector undertakes downstream research, translating basic research into medical products. The public sector thus significantly influences the innovation cycle by shaping research priorities, at least

with regard to basic research (WHO, 2006a; USCBO, 2006; Cornell University, INSEAD and WIPO, 2019).

The public sector also plays an important role in the innovation cycle at subsequent stages. For example, governments control the quality of health products through their regulatory frameworks, which determine whether a product gets to the market and, if so, how quickly. Additionally, the public sector plays a critical role in the delivery phase of health products because governments are usually the main purchasers of health products and they often organize the distribution and delivery of such products.

The story of the development and commercialization of monoclonal antibody-based therapies provides an example of how public and private enterprise can cooperate in the development of new drugs (see Box 3.3).

It is estimated that government agencies worldwide provided around US\$ 42 billion in health research funding annually (2011–2014), of which about 60 per cent was from the US National Institutes of Health (NIH) (Viergever and Hendriks, 2016). Non-profit entities play an important role in the funding of biomedical research, mainly in high-income countries – the Howard Hughes Medical Institute in the United States and the Wellcome Trust in the United Kingdom are good examples. Public investments can also have a “multiplier” effect; in the United Kingdom, it has been demonstrated that every 1 per cent increase in investments in public medical research is associated with a 0.8 per cent increase in private pharmaceutical R&D investments (Sussex et al., 2016).

Numerous analyses have identified the large contributions of public-sector research to biomedical R&D (Kneller, 2010).

Box 3.3: Monoclonal antibodies

Monoclonal antibodies are a type of immunotherapy drug used widely in oncology, autoimmune diseases and other areas. They are of high importance in both clinical and economic terms, and are now key treatments for numerous cancers and autoimmune conditions.

The techniques underlying the development and manufacture of monoclonal antibodies were developed at the UK Medical Research Council Laboratory of Molecular Biology (LMB), a public research institute. The pioneering researchers at LMB received a Nobel Prize for their work in developing these techniques.³⁴

LMB researchers developed one of the first therapeutic monoclonal antibodies, adalimumab, for rheumatoid arthritis, working in a spinoff company called Cambridge Antibody Technology, on commission from a German chemical manufacturer (Marks, 2015).

After adalimumab, a large number of monoclonal antibody medicines have been brought to market by pharmaceutical companies, using LMB technology. Medicines developed using LMB technology include, for example, the breast cancer treatment trastuzumab, leukaemia/lymphoma treatment rituximab, and bevacizumab, used in treating both colorectal cancer and wet age-related macular degeneration, a common cause of blindness. All three medicines are on the WHO Model List of Essential Medicines. Monoclonal antibodies are also used in many important diagnostics (Marks, 2015).

The LMB has received substantial royalties for the use of the monoclonal-antibody-related technologies in developing immunotherapies, which have, in certain years, comprised a significant part of the LMB's budget.³⁵

A 2011 study suggested medicines developed in the public sector have had, on average, a greater effect on improving public health than other medicines (Stevens et al., 2011). The methodologies of these analyses do not capture basic research, which underlies drug discoveries, for example, by identifying the molecular mechanisms of diseases that new drugs could target. A more recent analysis that included basic research found that public funding contributed to all new drugs approved in the United States over the period 2010–2016, and more than 90 per cent of this funding represented basic research related to the biological targets for drug action rather than the drugs themselves (Cleary et al., 2018).

The pharmaceutical industry spent an estimated US\$ 177 billion on R&D in 2017.³⁶ In many cases, the public and private sectors can work in synergy, with the private sector building upon basic research done in the public sector. The public and private sectors can also come together as PPPs. One example is the European Union's Innovative Medicines Initiative (IMI and IMI2), under which a large number of public–private consortia undertake joint research projects, with private entities matching public investments with in-kind contributions (such as staff time).³⁷ In some cases, public research funders attach conditions to funding to ensure that the public benefits from products developed from public research (see also Chapter IV, section C.3(c)). For example, in the United States, the NIH has developed provisions that would require licensees of IP generated through NIH-funded research to submit a plan of how public health needs for the product will be met (Stevens and Effort, 2008). Similar provisions are used by, for example, the Wellcome Trust³⁸ and CARB-X (see Chapter IV, section C.3(c)).

3. Medical R&D costs

One of the main arguments put forward by industry with respect to the need for strict protection of IPRs is the high cost of R&D for new medical products, with IP protection affording firms confidence that R&D costs can be recouped once the product is approved. There are, however, few sources of data publicly available that enable the true costs of medical research to be assessed. A number of estimates have been published, quantifying the average cost of bringing a new medicine to market. Costs greatly depend on the type of medicine in question. There is a huge difference in costs between a medicine based on a new chemical entity (NCE) not previously used in any pharmaceutical product, and an incremental modification of an existing medicine.

Costs of pharmaceutical R&D can be viewed in various ways. “Out-of-pocket” costs describe actual cash expenditures by the developer. These costs can be further risk adjusted to account for the cost of a failed drug candidate. The costs can also be “capitalized”; capitalized costs include the theoretical losses incurred from investing in pharmaceutical R&D instead of an alternative investment that would have earned returns at a certain percentage over the years before the R&D yields a successful product. One series of studies has estimated the risk-adjusted out-of-pocket cost of bringing an NCE to market at US\$ 114 million (US\$ 231 million capitalized) in 1987, US\$ 403 million (US\$ 802 million capitalized) in 2000, and US\$ 1.4 billion (US\$ 2.6 billion capitalized) in 2013 (DiMasi et al., 1991; DiMasi et al., 2003; DiMasi et al., 2016). Both lower and higher estimates are available,

ranging from US\$ 100 million to US\$ 5 billion (DNDi, 2014; Morgan et al., 2011; Herper, 2012; Prasad and Mailankody, 2017). In some disease areas, returns on R&D investments can be very large; for example, in oncology, for drugs approved during the period 1989–2017, sales of final products brought in US\$ 14.50 for every US\$ 1.00 invested in R&D (Tay-Teo et al., 2019).

The long timelines for pharmaceutical development also contribute to high costs and risk. Bringing a pharmaceutical product from the laboratory stage to marketing stage takes a long time and entails the additional burden of complying with stringent regulatory approval processes, thus resulting in a small number of successful products. An analysis of novel medicines (new active substances) found that mean time from filing of the first patent application to launch of the medicine in the United States was 12.8 years, whereas the mean time from launch to expiry of patent or other forms of exclusivity was 13.5 years (Aitken and Kleinrock, 2017).

The estimates of pharmaceutical R&D costs noted in the preceding paragraphs concern the investments, practices and performance of multinational pharmaceutical companies, reflecting, for example, their choices of disease areas to invest in, drug candidates to take forward in development, and so on. They may not necessarily apply, therefore, to drug development in other models of R&D, such as within a product development partnership. For example, Drugs for Neglected Diseases *initiative* (DNDi), which has developed one NCE and seven improved treatments for neglected diseases (see Box 3.12), estimates that, based on its experience, developing an improved treatment costs EUR 4 million–32 million, and developing an NCE costs EUR 60 million–190 million, including the cost of failures (DNDi, 2019).³⁹

All of these estimations rely on many variables, such as the estimated average length of development, the average size and costs of clinical trials and the probability of success, in that products will finally make it to market. In addition, it is difficult to verify the underlying data, as this is not disclosed for the most widely cited studies. Some of the estimates of pharmaceutical R&D costs, such as the figures in the studies by DiMasi et al. (see in this section above), have been widely discussed (e.g. Love, 2003; Avorn, 2015). There are doubts about the usefulness of such estimations, as costs vary widely between companies and also between the private sector and the public sector (see Chapter IV, section A.4(f)).

Orphan drugs, which, in 2018, were the most common type of novel drug approved in the United States (see Figure 3.3), may have lower R&D costs than non-orphan medicines, for example, due to the smaller size of the clinical trials needed to gain approval. A recent analysis of medicines approved by the FDA in the period 2000–2015 estimated that capitalized clinical trial costs for new molecular entities with orphan designation were

50 per cent lower than costs for non-orphan medicines (Jayasundara et al., 2019).

Originator pharmaceutical companies in Europe and the United States invest about 15–20 per cent of revenues in R&D, depending on the source and year. This proportion has been on a slight upwards trend over the past two decades but is projected to decline over coming years (EvaluatePharma, 2018). According to industry reports, about one fifth of this (3–4 per cent of revenues) is spent on basic (preclinical) research, such as identifying new pharmacological targets and candidate compounds.⁴⁰ Spending on marketing and promotional activities by the industry generally exceeds R&D costs.⁴¹

While precise costs are unknown, medical R&D is very costly and highly risky. Also, many investments do not result in a return, due to product failures in the clinical trials phase. Efforts to develop a treatment for Alzheimer’s disease – the most common form of dementia – illustrate the riskiness of drug development. A large number of drug candidates have failed in Phase III, despite an apparently well-described mechanistic target (beta-amyloid) (Mullard, 2019; Makin, 2018; Langreth, 2019). Failures in Phase III are especially costly for drug developers, as investments have already been made to take the drug candidate through preclinical development and Phase I and Phase II trials (see Chapter II, section A.6(b)). Drugs developers have nevertheless persisted working in this area, as the potential market is expected to be very large.⁴²

Details on R&D costs could be important in setting up novel mechanisms for financing R&D, for example, projecting costs for a product development partnership (see Box 3.12) or evaluating how large milestone prizes need to be designed to cover R&D costs (see section C.5(c)).

4. Incentive models in the innovation cycle

The *2011 World Intellectual Property Report* (WIPO, 2011b) observes that:

“IP rights are a useful incentive mechanism when private motivation to innovate aligns with society’s preferences with regard to new technologies. But such an alignment does not always exist. In addition, it is unclear whether the IP system can incentivize invention that is far from market application, for example, basic science research.”

In reviewing the IP system in the context of the broad sweep of innovation policies, the report distinguishes three mechanisms for promoting innovation:

- Publicly funded innovation carried out by academic institutions and public research organizations

- Publicly funded research undertaken by private firms – notably, through public procurement, research subsidies, soft loans, R&D tax credits and innovation prizes
- Privately financed and executed R&D, financed through the marketplace rather than government revenues and incentivized through the IP system, which is one mechanism of government policy that promotes innovation.

(a) The innovation cycle

Innovation is often presented as a linear process that culminates in the launch of a product, but innovation in health can also be seen as a cycle (see Figure 3.6). This cycle goes from the discovery of candidate compounds to the testing and development of new products, through to the delivery of these products, and then returns to the R&D of new products (or to the optimization of existing products) through systematic post-marketing surveillance and the development of an increasingly effective demand model based on health needs.

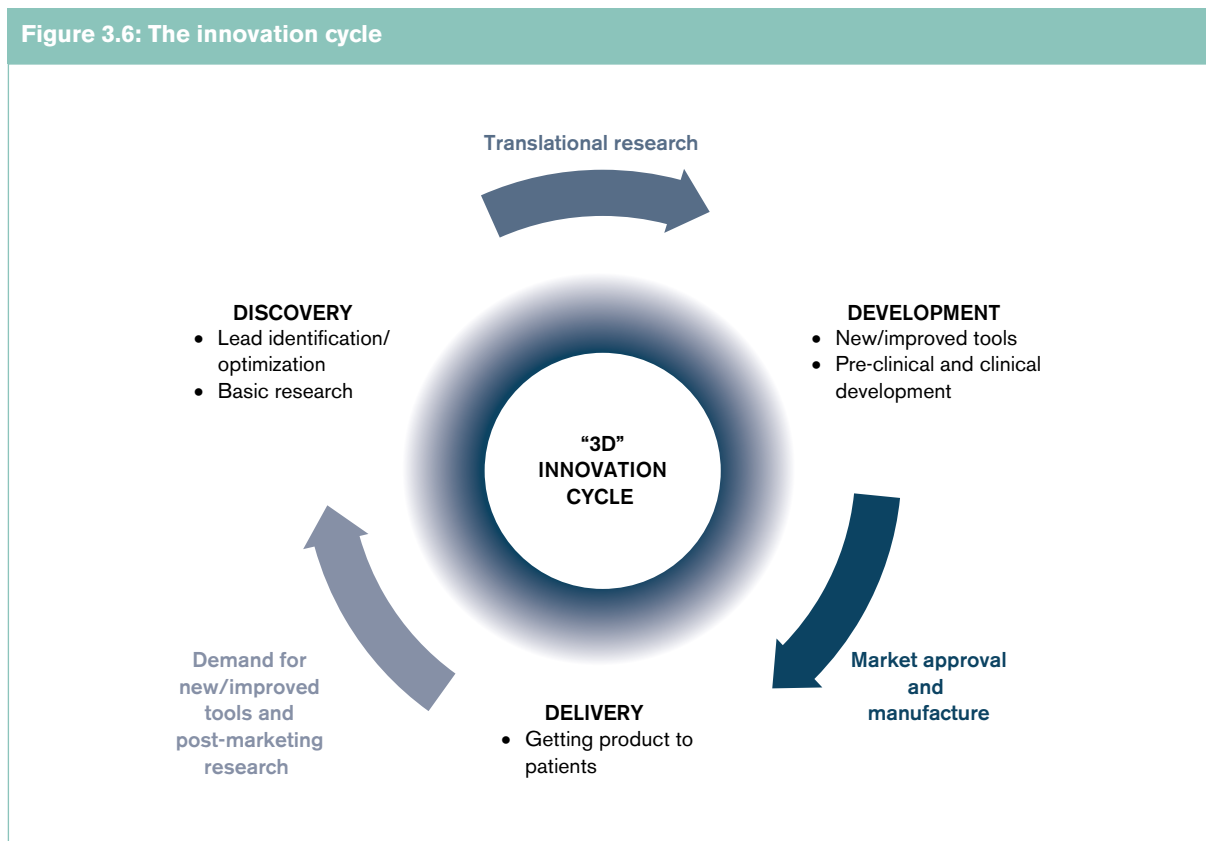
The circular model of health innovations illustrates a critical reality: the current market-driven innovation cycle works better for high-income countries where effective demand for health products is matched by the ability to pay for

them. In contrast, for diseases that predominantly affect patients in LMICs, there is a critical gap in the availability of incentives that fuel the conventional innovation cycle. While there is an urgent need for new medications for diseases that predominantly affect LMICs, that market is characterized by limited purchasing power, coupled with the lack of health insurance systems in many countries. In a similar vein, the classical innovation cycle also may not work for the development of new antibiotics, because the originator company typically cannot count on high sales volumes to recoup its investment in R&D (see section C.2 on AMR). It is also important to note that a large amount of basic research, for example, identifying drug targets, support the cycle.

(b) Absence of self-sustaining innovation cycle in the case of small markets, low incomes or low sales volumes

The CIPIH observed in this context that the IP system needs a certain type of environment in order to deliver expected results. For diseases that predominantly affect people living in poorer countries, the innovation cycle is not self-sustaining, due to low potential for revenue, underfunded health services and generally weak upstream research capacity. A similar market failure arises where sales are

Figure 3.6: The innovation cycle



Source: WHO (2006a), p. 23.

likely to be low, for example, in antibiotics and treatments or vaccines for emerging pathogens (see Chapter III, sections B.4(e), C.2 and C.3). In this type of environment, the market alone and market-based incentives, such as patent protection, cannot by themselves address the health needs of developing countries (WHO, 2006a).⁴³

This gap – between health needs and medical R&D efforts – has sparked policy debate on the effectiveness of current medical innovation structures for health needs, in particular for the specific health needs of LMICs. Equally, the compelling need to address this gap has, over the past decade, prompted an array of initiatives to find new ways of combining the diverse inputs, infrastructure and resources needed for product development. These initiatives have explored new ways of integrating these different inputs and steering candidate products through the innovation process, culminating in the delivery of safe and effective new technologies. This approach has typically made use of more collaborative structures, a wider range of non-exclusive and segmented technology licensing models and the development of pre-competitive technology platforms, as well as product development partnerships (PDPs) that harness private-sector capacities and deploy them towards the attainment of not-for-profit public health objectives. Such practical initiatives both respond to, and help to influence, the dynamics of medical innovation today, in terms of both making new technologies available and illustrating in practice the possibilities for a wider range of innovation models.⁴⁴

While it is important to trigger the requisite innovation for neglected diseases, it is also important to ensure that any new medical technologies emerging from such initiatives are affordable for the people who need them. In the existing patent-driven innovation ecosystem, the returns for investment in innovation are generally factored into the price of new-generation products. In contrast, new and innovative finance mechanisms and initiatives aim not to finance the cost of R&D through the price of the end product, thus delinking the cost of research from the price of the product.⁴⁵ These are explored further in section C, “Overcoming market failures in medical product R&D”.

There have been a few successful cases of tailoring innovation to meet identified medical needs. An example is the development of a meningitis vaccine for Africa (see Box 3.4).

(c) Building innovation networks

The CIPIH stressed that the formation of “effective networks, nationally and internationally, between institutions in developing countries and developed countries, both formal and informal” is an “important

element in building innovative capacity” (WHO, 2006a). One example of initiatives to build such collaborative networks for innovation is the European & Developing Countries Clinical Trials Partnership.⁴⁶ It funds research for the prevention and treatment of infective diseases in sub-Saharan Africa.

(d) Overview of innovation structures

A broad range of diverse innovation structures is used in the development of medical technologies. These structures can be characterized according to two factors – the degree of market-based incentives involved, and the extent to which some leverage or exclusivity is exercised over the technology. Often, innovation processes are neither situated in an entirely non-commercial context with no leverage at all maintained over technologies, nor are they a rigid, highly exclusive and entirely private model of technology development. Legal instruments alone, particularly at the international level, do not generally determine where a practical innovation strategy for a specific new technology is, or should be, located on this spectrum, and other factors typically guide choices about the mix of public and private inputs, and the management of technology.

One key feature of the innovation landscape, however, is the dividing line between “pre-competitive” and competitive inputs to innovation. Landmark research projects, such as the Human Genome Project⁴⁷ and the International HapMap Project,⁴⁸ have sought to define a pre-competitive body of data that is openly shared for wide use in research and in the development of inputs at an early stage in the product development pipeline, so as to provide a common platform for companies to compete in the development of finished products. At a later stage in the R&D pipeline, a degree of competition and differentiation between companies can promote a greater diversity of available technologies (Olson and Berger, 2011).

(e) Vaccines: a distinct challenge for innovation

Vaccine development differs from the development of small-molecule, chemically synthesized pharmaceuticals. Vaccines are complex biological entities, and there is no such thing as a “generic” vaccine. Proving the safety and efficacy of a vaccine, even if it is a “copy” of an existing vaccine, requires a full regulatory dossier containing data on pre-clinical and clinical trials. This adds years, and complexity, to the process of making and copying even existing vaccines. Vaccines are typically given to healthy individuals and, in particular, to healthy infants as a prophylaxis against a subsequent infection. Safety is

Box 3.4: New innovation models in practice: tailoring a meningitis vaccine for Africa

The successful 2010 launch of MenAfriVac highlights the role of new approaches to innovation and product development in order to address the health needs of developing countries. Prior to this, vaccines were available for various strains of meningitis, but they were too expensive for those living at risk of the disease in the so-called African meningitis belt. Moreover, they did not offer an appropriate solution for resource-poor settings. Against a background of recurrent epidemics and increasing death rates, stakeholders faced a significant innovation challenge in ensuring the production of a vaccine that would be suitable from a clinical point of view and also sustainable and affordable. The Meningitis Vaccine Project, a consortium led by the WHO and the Programme for Appropriate Technology in Health (PATH), a not-for-profit health technology organization, set about producing a vaccine for the A strain of meningitis that would cost no more than US\$ 0.50 per dose. A review of options led to a decision to develop a production process and to transfer the relevant technology to a low-cost producer in the developing world, rather than subsidizing a vaccine manufacturer in the industrialized world to undertake development and production. An innovative model for vaccine development was established, with key raw materials sourced in India and the Netherlands. The technology developed by the FDA Center for Biologics Evaluation and Research, and the technology and know-how, was transferred to Serum Institute of India Ltd to produce vaccines for clinical trials and, ultimately, full-scale production. This development model reportedly cost one tenth of the conventional estimate for producing a new vaccine. The development and introduction of this new vaccine marks a huge step towards the elimination of epidemic meningitis in sub-Saharan Africa.⁴⁹

therefore paramount, and any remote suggestion of risk to the recipient can result in withdrawal or non-authorization of the vaccine.

The cost of establishing and gaining regulatory approval for a manufacturing facility partly explains the limited number of manufacturers entering the field of vaccines and the relatively small number of qualified products and producers. Other reasons include the lack of production know-how, which can constitute an effective barrier to the viable reproduction of vaccine technologies. Vaccines also often require costly cold-chain infrastructure and only a relatively small number of doses is required to achieve immunization. Thus, profit margins can be relatively low in comparison with the manufacture of other pharmaceuticals.

These challenges mean that private manufacturers have long lacked the necessary incentives to invest in vaccines, particularly those that focus on the specific needs of developing countries. Almost all the important, innovative vaccines introduced since the 1980s have resulted from initial discoveries made by public-sector research institutions (Stevens et al., 2011).

(i) New vaccine innovation in the 21st century

The first decade of the 21st century brought a record number of new vaccines, including vaccines for meningococcal meningitis, rotavirus, pneumococcal disease and cervical cancer caused by human papillomavirus. At the same time, the market for vaccines has grown dramatically. It has multiplied more

than fivefold since 2000 and was worth more than US\$ 31 billion globally in 2016.⁵⁰

This increase in the development of vaccines is due to a number of key factors: more innovative technologies; improved understanding of immunity; investment by PDPs such as Gavi, the Vaccine Alliance;⁵¹ and, more recently, new funding sources and mechanisms such as advance market commitments (AMCs) that contribute to public funding for vaccine development (see Box 3.5). These changes continue to shape the current landscape of vaccine manufacture.

(ii) The role of developing-country manufacturers

The vaccine industry has undergone major changes.

In 2017, LMICs represented 20 per cent of the global vaccine market by value, but 79 per cent by volume (Pagliusi et al., 2018).

There is a small number of high-income-country manufacturers in the vaccine market. About 80 per cent of global vaccine sales by value comes from five large high-income-country multinational corporations that were the product of various M&A of pharmaceutical companies over the past few decades.⁵² However, in terms of volume rather than value, developing-country vaccine manufacturers claim the majority share, at more than 65 per cent in each WHO region except the European Region (WHO, MI4A and V3P, 2018).

Box 3.5: Advance market commitments in vaccines

Although vaccines are among the most effective public health interventions, few of the vaccines that have been developed address diseases that primarily affect the developing world. In the past, new vaccines typically reached low-income countries only decades after they had been rolled out in developed countries. A pilot project on an advance market commitment (AMC) for pneumococcal vaccines was launched in 2007. It was funded by Canada, Italy, Norway, the Russian Federation, the United Kingdom and the Bill & Melinda Gates Foundation. Pneumococcal disease was selected for this project, as it claims 1.5 million lives each year, mostly children in Asia and Africa.

The AMC guarantees a market to manufacturers of a novel and suitable pneumococcal vaccine, with a high introductory price of US\$ 7.00 for each dose. This price is guaranteed for about 20 per cent of the doses that manufacturers commit to sell through the AMC and is designed to help them recover the costs of establishing production capacity. In return, manufacturers have accepted to provide additional doses at a “tail price” of US\$ 3.50 for at least a decade.

Under the oversight of the World Bank and Gavi, the Vaccine Alliance, and in conjunction with UNICEF, the first AMC tender was issued in September 2009. In 2018, 149 million doses of pneumococcal conjugate vaccine (PCV) were procured through the AMC.

In December 2010, Nicaragua became the first country to immunize its children with the new vaccine. As of December 2019, 59 countries have added the AMC-purchased vaccine to their national vaccination schedules (Gavi, 2018).

Developing-country vaccine manufacturers are also increasingly engaged in research. For example, the Serum Institute of India, in collaboration with WHO and PATH, developed a meningitis A vaccine for use in sub-Saharan Africa. The Institute also developed a measles vaccine delivered by aerosol, which ultimately showed insufficient efficacy in trials.⁵³ Cuba has a vibrant research-based biotechnology industry that has developed a number of innovative vaccines, including a meningitis B vaccine, a synthetic haemophilus influenza B vaccine and a therapeutic vaccine to treat types of lung cancer.⁵⁴ It also has numerous innovative products in the pipeline. Chinese companies were, in 2019, developing hepatitis E and human papillomavirus vaccines.⁵⁵ In Brazil, the Oswaldo Cruz Foundation (Fiocruz), through its Immunobiological Technology Institute (Bio-Manguinhos), has 27 projects under development in 2019, 15 of which involve bacterial or viral vaccines.⁵⁶ Also in Brazil, the Butantan Institute has developed a novel adjuvant derived from a by-product of pertussis vaccine production.⁵⁷

5. Challenges in cancer medicines R&D

Oncology represents a large proportion of the global R&D pipeline. In 2017, 43 per cent of registered clinical trials were in the area of cancer, with more trials on cancer treatments than for the next four disease categories combined (Long, 2017). However, progress in finding cures has been slow for many types of cancer (WHO,

2018g). Data show that there is a high level of duplication in cancer R&D, with many similar clinical trials done for similar experimental compounds, but with trial results left unshared (Workman et al., 2017). At the same time, the market for oncology medicines is highly concentrated, with three companies accounting for about 50 per cent, by sales value, of the global market.⁵⁸

A large proportion of cancer medicines offer limited clinical benefits. New medicines for which evidence shows unclear or marginal therapeutic advantages pose challenges for policy-makers, regulators and clinicians, for example, in selecting which medicines to reimburse, approve or prescribe. These challenges have prompted the WHO and others to seek clearer definitions of what constitutes significant improvements over previous therapy in new cancer medicines (WHO, 2018i). One study that analysed cancer medicines approved by the EMA from 2009 to 2013 found that most drugs enter the market without evidence of benefits in survival or quality of life. Later, at a median 3.3 years after approval, 51 per cent were found to have evidence for improvements in overall survival or quality of life and 48 per cent were judged to offer a clinically meaningful benefit (Davis et al., 2017). Another study, analysing medicines for solid tumours approved by the FDA from 2002 to 2014, found an average overall survival gain of 2.1 months (Fojo et al., 2014). At the same time, one study found that solid tumour cancer medicines approved by the FDA from 2000 to 2010 caused higher rates of deaths due to toxicity than the standard of care with which they were compared in trials (Niraula et al., 2012). However, average returns on R&D investment in

cancer are high; for example, one study found that the return on investment was US\$ 14.50 for every US\$ 1.0 of investment in cancer medicine R&D, and that risk-adjusted R&D costs were recouped within a median of three years following drug launch (Tay-Teo et al., 2019).

6. Orphan drugs and orphan indications

“Orphan drugs” is a term given to medicines that treat rare diseases, including rare subtypes of common diseases (Gammie et al., 2015). The threshold for what is considered “rare” differs between countries and is generally based on the incidence of a disease in the relevant regulatory jurisdiction.⁵⁹

In response to concerns that the commercial market for these medicines may be too small to attract R&D investments, legislation has been passed in some countries to compensate for limited market size and to stimulate the development of medicines for rare diseases. Orphan drug legislation was introduced in 1983 in the United States (the Orphan Drug Act), in 1993 in Japan and in 2000 in the European Union (EvaluatePharma, 2018). Incentives include tax credits to partially compensate for clinical trial expenses, waiving of regulatory fees, accelerated approval and additional market exclusivity (details depend on the jurisdiction). For example, orphan drugs are eligible for seven years of market exclusivity in the United States (see Box 2.5) and ten years in the European Union, extended a further two years if a paediatric investigation plan is agreed (see also Chapter II, section A.6(f) for regulatory exclusivities generally).⁶⁰

In response to this legislation, the number of medicines receiving orphan designation in the United States and the European Union has increased rapidly since the turn of the century, from fewer than ten orphan drugs approved by the FDA in the decade before the introduction of the Orphan Drug Act (Giannuzzi et al., 2017) to 34 orphan drugs approved by the FDA CDER in 2018, representing 58 per cent of all novel drug approvals (see Figure 3.2).⁶¹ Orphan drugs are projected to represent nearly one quarter of prescription drug sales globally by 2024, and growth in sales of orphan drugs is expected to be double that of the pharmaceutical market overall (EvaluatePharma, 2018). In some disease areas, a majority of newly approved medicines are orphan medicines; for example, about two thirds of cancer medicines approved by the FDA in the period 2011–2015 qualified as orphan medicines (Amanam et al., 2016). This represents a significant shift in the focus of the pharmaceutical industry’s R&D efforts and is a relevant factor to consider in discussions of global health research prioritization (WHO, 2012).

At the same time, orphan drugs are priced at far higher levels than other originator medicines, and prices of orphan drugs are rising. The mean annual price of an orphan drug in the United States was US\$ 147,000 in 2017 (EvaluatePharma, 2018), and a number of orphan drugs have broken drug pricing records. For example, an orphan drug gene therapy approved to treat an inherited cause of blindness was reported to be priced at US\$ 425,000 per eye (Scutti, 2018; Miller, 2018).

It has been argued that, in some cases, companies have divided larger (non-orphan) diseases into multiple newly defined subtypes with smaller patient populations in order to benefit, in each individual indication, from orphan drug legislation incentives and bolstered ability to demand high prices (Daniel et al., 2016). Legislation attempting to curb such business practices has been enacted in Japan and was proposed, though not enacted, in the United States (Daniel et al., 2016; European Commission, 2018a). In addition, a substantial proportion of new orphan drug approvals are for new indications (new therapeutic uses) of previously approved medicines, constituting 39 per cent of orphan approvals by the FDA in the period 1983–2017 (Miller and Lanthier, 2018).

As the threshold for what regulators consider to be an orphan drug is, in general, based on the disease incidence in the particular country, in some cases, treatments that receive orphan drug designation in a country may be common diseases at the global level.

Some medicines with orphan designation are of significance in the global health context; numerous medicines added in recent years to the WHO Model List of Essential Medicines were originally approved by regulatory agencies in high-income countries as orphan drugs, such as imatinib for chronic myeloid leukaemia, and bedaquiline and delamanid (both added to the WHO EML in 2015), which are treatments for TB, the leading infectious killer globally. They nevertheless received orphan designation with the FDA and EMA, based on the relatively low prevalence of TB in the European Union and the United States.

7. Registration of clinical trials in pharmaceutical product development

Registration of clinical trials means making accessible to the public, by means of a registry, an agreed set of information about the design, conduct and administration of clinical trials.⁶² A clinical trials registry is a publicly accessible database containing entries with information about the design, conduct and

administration of clinical trials. Besides the registration of clinical trials, the publication of the results of clinical trials is equally important for public health. Patients take part in clinical trials in the hope that they will contribute to advances in medical science and they do this altruistically. Participants expect that results will be used to further scientific research. Sponsors of clinical trials will often not provide details of clinical trials that have failed, although this is valuable knowledge and could be used to help prevent a repetition of such trials, and thus help to avoid exposing patients to unnecessary risks. It would be in the interest of public health if the details of all clinical trials were to become publicly available, allowing interested parties to verify the data.

In 2017, research funders signed the “Joint statement on public disclosure of results from clinical trials”; signatories included the European Commission (for the Horizon 2020 Societal Challenge: Health, Demographic Change and Wellbeing), UK Medical Research Council, Indian Council of Medical Research, Research Council of Norway, Bill & Melinda Gates Foundation and Wellcome Trust. In the statement, the signatories pledged to develop and implement a policy with mandated timeframes for prospective registration and public disclosure of the results of clinical trials that they fund, co-fund, sponsor or support. In addition, they agreed to monitor adherence to the policies and share publicly the outputs of these monitoring processes.⁶³

The WHO maintains the International Clinical Trials Registry Platform (ICTRP).⁶⁴ The ICTRP Search Portal had 560,000 records as of the third quarter of 2019, and provides a searchable database containing the trial registration data sets. These data sets constitute international standards for clinical trials registration. The platform also has the unique ability to link together (bridging) records registered in different countries (or multi-country trials). As of 2019, the ICTRP database received more than 4,500 new clinical trial registry entries each month; the number of new clinical trials globally continues to increase.

The WHO considers the registration of all interventional trials a scientific and ethical responsibility. The rationale for the ICTRP includes the following considerations:

- Decisions about health care should be informed by all the available evidence.
- Publication bias and selective reporting make informed decisions difficult.
- Improving awareness of similar or identical trials enables researchers and funding agencies to avoid unnecessary duplication.

- Describing clinical trials in progress can make it easier to identify gaps in clinical trials research and to define research priorities.
- Making researchers and potential participants aware of trials may facilitate recruitment and increase patients’ active involvement in the clinical trial process.
- Enabling researchers and health-care practitioners to identify trials in which they may have an interest could result in more effective collaboration among researchers, including prospective meta-analysis.
- Registries checking data as part of the registration process may lead to improvements in the quality of clinical trials by making it possible to identify potential problems early in the research process.

The World Medical Association Declaration of Helsinki states that “Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject” and that “[r]esearchers have a duty to make publicly available the results of their research. [...] Negative and inconclusive as well as positive results must be published or otherwise made publicly available” (WMA, 2013). In addition to the ethical imperative, poor allocation of resources for product development and financing of available interventions, and suboptimal regulatory and public health recommendations may occur where decisions are based on only a subset of all completed clinical trials.

However, 30–50 per cent of clinical trials remain unreported across trials of different sizes and product classes (Schmucker et al., 2014; Goldacre et al., 2018). The WHO considers that the prospective registration and timely public disclosure of results from all clinical trials is of critical scientific and ethical importance. Timely results disclosure reduces waste in research, increases value and efficiency in the use of funds and reduces reporting bias, which should lead to better decision-making in health (WHO, 2015f).

Open access policies⁶⁵ are important for effective sharing of clinical trial results and individual participant data from trials, for example, for the purpose of meta-analysis (see Chapter II, section B.1(c)(iv)). As trials are registered, this sets a basis for development of individual participants’ data (IPD)-sharing. Legal frameworks are required to govern the personal and ethical aspects of data collection and use, including PIC of the persons concerned, and enable development of international norms and standards for the sharing of IPD from clinical trials.

Since 2010, the EMA has begun providing access to clinical trial data, allowing interested parties to verify the data (see Box 3.6).⁶⁶

Box 3.6: European Medicines Agency makes available clinical trials data

Following the adoption of the new EMA policy on the publication of clinical data for medicinal products for human use in October 2014,⁶⁷ the EMA started providing open access to data submitted by pharmaceutical companies in support of their regulatory applications (dossiers) in October 2016,⁶⁸ the first regulatory authority worldwide to do so. The objective of the policy is to avoid duplication of clinical trials and to encourage innovative activities to develop new medicines, and also to allow academics and researchers to reassess clinical trial data.

In addition, the European Union adopted a regulation in 2014 that requires an EU Clinical Trials Portal and Database to be established.⁶⁹ The portal will be a “single entry port” for regulatory submissions, streamlining and harmonizing regulatory review, and for accessing clinical trial data, and is expected to be opened in 2020.⁷⁰ Clinical trial information will be accessible to the public, unless the confidentiality of the information can be justified on certain grounds. A summary of the results of a clinical trial and a summary for laypersons shall be submitted in the database within one year of the end of the clinical trial in all EU member states, irrespective of its outcome. Additionally, the clinical study report shall be submitted 30 days after a marketing authorization for a medicinal product has been granted, the procedure is completed or the marketing authorization application is withdrawn.

The terms of use for the EMA clinical data publication website clarify that the clinical reports are protected by copyright or other IPRs (see Chapter II, section B.1(e)) and can be considered commercially valuable when used for commercial and regulatory purposes. Therefore, they may only be viewed on the screen using the interface provided by the EMA and not be used for the purpose of submitting an application to obtain a marketing authorization or any extension or variation thereof anywhere in the world, nor may the user make any unfair commercial use of the reports (see Chapter II, section B.1(c)).⁷¹

C. Overcoming market failures in medical product R&D

Key points

- Market mechanisms, such as intellectual property rights (IPRs), do not work for incentivizing medical R&D for diseases that disproportionately affect people in developing countries. For neglected diseases, a key factor is the limited purchasing power of both governments and patients in the countries where such diseases predominate and a chronic lack of investment in R&D.
- While a huge research gap for neglected diseases remains, the health R&D landscape and the share of the global disease burden have been changing since 1990 and funding of R&D for neglected diseases has increased, predominantly from the public sector.
- Stewardship, innovation and access are three key objectives in addressing antimicrobial resistance (AMR). The current antimicrobial development pipeline is insufficient to address the increasing resistance seen in priority pathogens. The lack of investment in R&D to address AMR has been discussed in numerous political fora, and a number of reports have analysed the problem and suggested solutions.
- The WHO R&D Blueprint is a global strategy and preparedness plan to ensure that targeted R&D strengthens emergency responses by bringing medical technologies to populations and patients during epidemics.
- In 2012, the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) made recommendations for new and innovative models of financing R&D, including establishing a binding global instrument for R&D and innovation for health.
- New innovation mechanisms and models aimed at increasing R&D to find effective treatments for neglected diseases have been discussed and implemented at international and national levels. Examples include the Drugs for Neglected Diseases *initiative*. An innovative model set up in cooperation among multiple stakeholders is WIPO Re:Search Sharing Innovation in the Fight Against Neglected Tropical Diseases.
- Product development partnerships have significantly increased the number of products in development for diseases that predominantly affect developing countries.

In the traditional, dominant model of financing pharmaceutical R&D, private investments in R&D are incentivized by the promise of potential profits once a product reaches the market. The promise of potential profits is supported by the expectation that relatively high prices can be charged to payers during the protection period of the IPRs and/or regulatory exclusivity schemes. Market failures arise, for example, in cases in which the target patient population and/or relevant payers will not be able to pay, or where there is a small market for other reasons. Examples of such market failures, and current initiatives seeking solutions to the failures, are outlined in this section. Much of the debate over market failures in biomedical R&D has centred around neglected diseases, and, since the early 2010s, AMR and pathogens of epidemic potential, such as Ebola virus disease. Many proposals for incentivizing R&D, including incentive mechanisms alternative and supplementary to IPRs, as well as novel models of funding R&D, have been made.⁷²

1. Diseases disproportionately affecting people in developing countries

There is a particular problem in incentivizing medical R&D for diseases that disproportionately affect people in

developing countries, as the market mechanisms, such as IPRs, do not work in this case. A key factor is the limited purchasing power of both governments and patients in the countries where such diseases predominate; unlike for other diseases, there is no positive spill-over from drug development targeted at more affluent markets. This section deals with the challenges of medical innovation in diseases that affect disproportionately people in developing countries.

Both the CIPIH (WHO, 2006a) and the GSPA-PHI refer to diseases that disproportionately affect people in developing countries. This concept is based on the three types of diseases distinguished by the Commission on Macroeconomics and Health (WHO, 2001a):

- Type I diseases are found in both rich and poor countries and affect large numbers of vulnerable populations in both. Examples of communicable diseases include measles, hepatitis B and haemophilus influenzae type B. Examples of NCDs include diabetes, cardiovascular diseases and tobacco-related illnesses.
- Type II diseases are incident in both rich and poor countries, but with a substantial proportion of cases in poor countries. Examples of such diseases include HIV/AIDS and TB. While both diseases are present

in rich and poor countries, more than 90 per cent of cases occur in poor countries.

- Type III diseases are those that are overwhelmingly or exclusively incident in developing countries. Examples of such diseases include African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis).

Type II and Type III diseases are often referred to as neglected diseases. These also include the neglected tropical diseases (NTDs) that are a specific focus of the work of WHO and affect more than one billion people, as well as neglected aspects of diseases that affect high-income countries, for example, HIV vaccine research and certain genotypes of hepatitis C.⁷³

The distribution of NTDs is restricted by climate, in particular by its effect on the distribution of vectors and reservoir hosts. In most cases, there appears to be a low risk of transmission beyond the tropics. Unlike influenza, HIV/AIDS and malaria and, to a lesser extent, TB, most NTDs present little threat to the inhabitants of high-income countries, thus triggering less attention. They are relatively neglected by the pharmaceutical research that is needed to develop new diagnostics and medicines and to make accessible interventions to prevent, cure and manage the complications of these diseases.

The situation has been characterized by a chronic lack of investment in R&D to find effective treatments for neglected diseases. The innovation effort is starkly disproportionate to the public health challenge posed by such diseases.

In 1990, the Commission on Health Research for Development found that of the US\$ 30 billion global investment in health research in 1986, only 5 per cent, or US\$ 1.6 billion, was devoted specifically to health problems of developing countries, although an estimated 93 per cent of the world's burden of preventable mortality occurred in the developing world.⁷⁴ Later, based on this data, the Global Forum for Health Research coined the term “10/90 gap” to highlight the gap between the share of the global disease burden and the resources devoted to addressing it. In a 2015 analysis, it was found that poverty-related and neglected diseases represent 14 per cent of the global burden of disease but attract only 1.3 per cent of global R&D expenditure (von Philipsborn et al., 2015).

While a huge research gap for neglected diseases still exists, both the health research landscape and the share of the global disease burden have been changing positively since 1990. The G-FINDER survey reported that the funding of R&D for neglected diseases was more than US\$ 3 billion in 2017, representing the first (small) year-on-year increase since 2012. The three “top tier” diseases – HIV/AIDS, TB and malaria, received 70 per cent of funding, leaving only 30 per cent of funding in the neglected diseases area available for carrying out

research on all other neglected diseases (Chapman et al., 2017). Significantly more money is spent on development of new medicines than on vaccines. Only a small proportion of neglected disease R&D spending – less than 10 per cent for most disease categories – goes to diagnostics. Funding comes predominantly from the public sector. In 2016, the public sector provided almost two thirds (US\$ 2.0 billion, 64 per cent) of global funding, with high-income countries contributing 96 per cent of this. The philanthropic sector contributes US\$ 671 million (21 per cent) and the private sector invested US\$ 497 million (16 per cent) (Chapman et al., 2017). A 2017 survey found 685 product candidates for neglected diseases, of which 57 per cent targeted HIV, TB or malaria. The most common type of treatment in the pipeline was vaccines (Young et al., 2018).

WHO strategies in this area include the 2021–2030 road map for neglected tropical diseases, the End TB Strategy, and the Global Technical Strategy for Malaria 2016–2030.

2. Antimicrobials and antimicrobial resistance

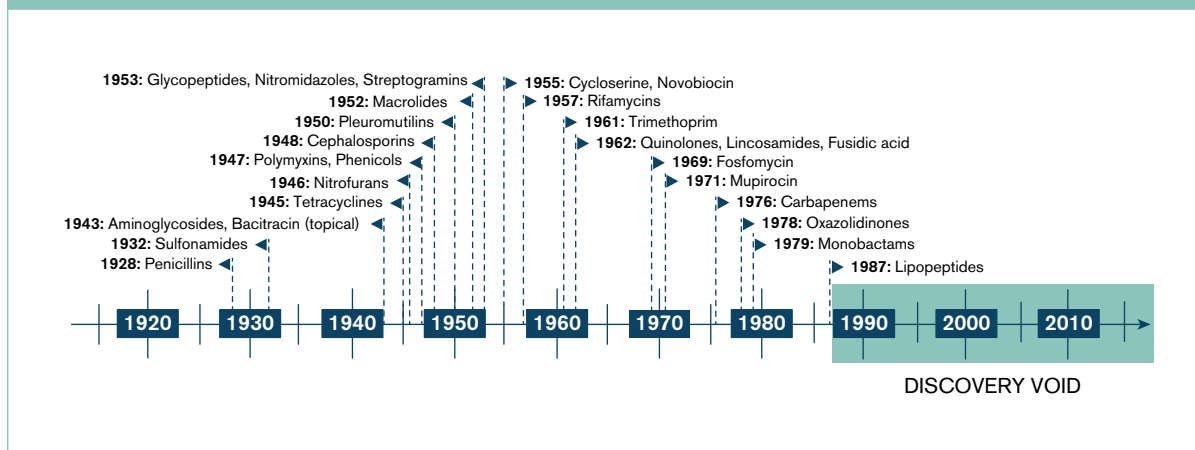
While it is challenging to come up with concrete numbers,⁷⁵ it is increasingly obvious that the disease burden caused by AMR is high and increasing steadily in both high-income countries and LMICs:

- The European Centre for Disease Prevention and Control (ECDC) estimates that infections with resistant bacteria in the European Union and European Economic Area accounted for 33,110 attributable deaths and 874,541 DALYs in 2016, which is comparable to the combined disease burden of influenza, TB and HIV/AIDS.⁷⁶
- The US Centers for Disease Control estimate that in the United States each year, at least 2 million people get an antibiotic-resistant infection, causing more than 35,000 deaths.⁷⁷

While infections with antibiotic-resistant bacteria affect all age groups, the elderly and infants are disproportionately affected and suffer from a significantly higher burden of disease. One study estimated that, globally, 214,000 neonatal sepsis deaths are attributable to resistant pathogens each year, a vast majority of them in LMICs (Laxminarayan et al., 2016). In Europe, health-care-associated infections dominate, representing about 63.5 per cent of the total burden of AMR infections (Cassini et al., 2019).

Many of these infections could be prevented through strengthened infection prevention and control, using available tools and ensuring access to clean water, sanitation and hygiene in health facilities (WASH (water, sanitation and hygiene) practices).

Figure 3.7: Timeline of the discovery of different antibiotic classes in clinical use



Source: ReAct, available at: <https://www.reactgroup.org/antibiotic-resistance/course-antibiotic-resistance-the-silent-tsunami/part-3/nearly-empty-pipeline/>.

The current antimicrobial development pipeline is insufficient to address increasing resistance of priority pathogens. Following the period of high discovery rates of new antibiotics in the mid-20th century, scientific challenges and a lack of investment resulted in very few new classes of antibiotics being developed. Of the approved classes of antibiotics, none were discovered in the last three decades (see Figure 3.7). For Gram-negative bacteria, which are, overall, the more dangerous category, all of the approved classes of antibiotics were discovered before 1965 (Deak et al., 2016).

Private-sector pharmaceutical companies have steadily divested from antimicrobial R&D; in 2019, only three large pharmaceutical companies were still active in this field, while 23 have abandoned it since 1980.⁷⁸ Less than 5 per cent of venture capital investments in pharmaceutical R&D between 2003 and 2013 was invested in antimicrobials research, and investments decreased over this period.⁷⁹ As of September 2019, 32 new antibiotics that target therapeutics and 4 combinations that target WHO priority pathogens were in the pipeline (WHO, 2019a). However, most of the private-sector development remains focused on existing classes of antibiotics, where the risk of failure is significantly lower (Jenner et al., 2017). In addition, an expert group identified 36 older, “forgotten” antibiotics – that is, antibiotics that are no longer manufactured – that may be useful if brought back to the market (Pulcini et al., 2016).

Private investments are insufficient to fill the current R&D gap, although the market potential varies widely among new, superior and “me-too” antibiotics. The fact that new antibiotics must compete with existing generic treatments and should be used sparingly to slow the development of resistance limits their market potential.⁸⁰ In addition, the market-driven R&D model does not direct investment to the most urgent public health needs, such as fighting multidrug-resistant pathogens,

where the patient population is still relatively small. Besides new antimicrobials, new and affordable point-of-care diagnostics are also urgently needed to support responsible and prudent use of antimicrobials.

The lack of investment in R&D to address AMR has been discussed in numerous political fora, and a number of reports have analysed the problem and suggested solutions. Examples include the UK Review on Antimicrobial Resistance and the DRIVE-AB report.⁸¹ The IACG suggested that one way of optimizing and increasing the impact of funding for R&D in this area would be through “delinking” mechanisms (see section C.5).⁸²

A combination of push strategies (e.g. direct funding, research grants, government laboratories or tax credits) that support research inputs and pull strategies (e.g. milestone prizes, new reimbursement models or market entry rewards) that reward research output would stimulate investment and the development of new products. The importance of delinkage was underlined in the Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance in 2016. While countries have not reached consensus on how to sustainably finance new pull and existing push mechanisms, in recent years, a number of regional and global initiatives have been established (see Box 3.7).

In addition to product development, critical needs include applied and interventional research on preventing AMR development and transmission, promoting appropriate and prudent use, improving animal husbandry, preventing hospital-acquired infections and gathering further evidence on antimicrobial residues in the environment and their impact. In many cases, improved infection prevention and control measures offer better value for money and a quicker solution than developing new health technology solutions.

Box 3.7: Initiatives to revitalize the antimicrobial pipeline**The WHO priority pathogens list and antibacterial pipeline analysis**

As part of implementation of the Global Action Plan on Antimicrobial Resistance, the WHO has produced a list of priority antibiotic-resistant pathogens (priority pathogens list, or PPL).⁸³ The WHO also produces analyses of the current clinical development pipeline for antibacterial agents, to assess the extent to which the pipeline addresses priority pathogens.

These analyses are intended to guide R&D efforts, by identifying where R&D efforts should be directed and where there are research gaps.

The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)

CARB-X is a global partnership based at Boston University, launched in 2016.

CARB-X provides financial, scientific and business support to accelerate R&D on new agents to combat pathogens identified as priorities by the WHO and US Centers for Disease Control. The aim of CARB-X is to support R&D projects through the pre-clinical and Phase I stages, so that they are able to attract further private or public investments from other sources for later development.⁸⁴

The Global Antibiotic Research and Development Partnership (GARDP)

GARDP is a not-for-profit drug developer that addresses global public health needs by developing affordable new or improved antibiotic treatments. GARDP was established in 2016 by the WHO and Drugs for Neglected Disease *initiative* (DNDi; see Box 3.12). GARDP is an important element of the Global Action Plan on Antimicrobial Resistance, which calls for new PPPs to encourage R&D of new antimicrobial agents and diagnostics.

GARDP's R&D strategy is based on global health priorities, target product profiles and R&D roadmaps. GARDP aims to deliver four new treatments by 2023, and currently has four R&D programmes, focusing on sexually transmitted infections, neonatal sepsis, paediatric antibiotics and antimicrobial memory recovery (revisiting previously abandoned research projects). GARDP plans to implement the principle of delinking the costs of R&D from product revenues, to ensure affordability as well as sustainable quality production.⁸⁵

The Global Antimicrobial Resistance Research and Development Hub (Global AMR R&D Hub)

The Global AMR R&D Hub,⁸⁶ established in May 2018 under the lead of the German Federal Government, is open to countries and observers and aims at improving coordination of, and increasing investment in, R&D for AMR. By December 2019, the Global AMR R&D Hub plans to launch an online Dynamic Dashboard that will present all AMR R&D investments globally, including data from the human, animal, plant and environment health sectors.

The International Centre for AMR Solutions (ICARS)

Established by the Government of Denmark in 2018, ICARS is an international One Health knowledge and applied research partnership, committing to working closely with low- and middle-income countries to support intervention and implementation research to tackle AMR.⁸⁷ It aims at translating aspects of national action plans and policies into evidence-based practices on the ground, while building capacity and capability within countries.

3. The WHO R&D Blueprint for Action to Prevent Epidemics

In 2014 and 2015, the world experienced the largest and longest Ebola outbreak in history. The outbreak showed that new models were needed for coordinating and financing R&D for preventing and treating pathogens of epidemic potential such as Ebola virus and others (see Box 3.12). As a direct response, the WHO developed the R&D Blueprint.

The R&D Blueprint is a global strategy and preparedness plan to ensure that targeted R&D will strengthen the

emergency response by bringing medical technologies to populations and patients during epidemics.⁸⁸ Under the R&D Blueprint, the WHO follows a systematic approach to ensure that missing vaccines, treatments and diagnostics for each blueprint pathogen are developed at least to clinical Phase II to ensure better preparedness in case of a major outbreak. The basis is a list of priority blueprint pathogens with pandemic potential that the WHO considers the greatest threats (see Box 3.8), which is regularly updated. For each pathogen, the WHO systematically reviews all the treatments that are on the market (if any) and in development and identifies gaps. Based on the specific virus and the research landscape, the WHO,

in collaboration with all stakeholders, defines research priorities to fill remaining gaps, which could be a vaccine, treatment or diagnostics, depending on the medical needs. Based on this, the WHO develops target product profiles for missing products, defining the characteristics of each. The target product profiles are guiding researchers and funders such as the Coalition for Epidemic Preparedness Innovation (CEPI) and the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) to invest in and develop the missing tools.⁸⁹

Box 3.8: WHO R&D Blueprint for Action to Prevent Epidemics: priority list as at February 2018⁹⁰

- Crimean-Congo haemorrhagic fever (CCHF)
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever (RVF)
- Zika virus disease
- Disease X

Note: Disease X represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease, and so the R&D Blueprint explicitly seeks to enable cross-cutting R&D preparedness that is also relevant for an unknown “Disease X” as far as possible.

4. WHO Expert Working Groups on R&D financing

The WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) examined the financing and coordination of R&D, and reviewed proposals for new and innovative models of financing R&D. The CEWG report was published in 2012.

The criteria for assessing the proposals included: public health impact; efficiency/cost-effectiveness; technical, financial and implementation feasibility; role of IP; delinking; access, governance and accountability aspects; and capacity-strengthening potential.⁹¹ A detailed presentation and analysis of each of these proposals is set out in Annex 3 of the 2012 CEWG report (WHO, 2012) (see Box 3.9).

The CEWG also developed principles that should guide health R&D funding allocation more generally, in particular, that health research and development should be needs driven and evidence based and be guided by the following core principles: affordability, effectiveness, efficiency and equity.⁹²

5. Novel approaches to biomedical R&D

This section presents examples of initiatives that explore novel models of biomedical R&D. It includes information on various WHO developments. This section also reviews

Box 3.9: 2012 CEWG report: key recommendations

Approaches to R&D:

- Open knowledge innovation, pre-competitive R&D platforms, open source and open access schemes, and the utilization of prizes, in particular, milestone prizes
- Equitable licensing and patent pools

Funding mechanisms:

- All countries should commit to spend at least 0.01 per cent of GDP on government-funded R&D aimed at addressing the health needs of developing countries in relation to product development.

Pooling resources:

- Between 20 per cent and 50 per cent of funds raised for health-related R&D aimed at addressing the needs of developing countries should be channelled through a pooled mechanism.

Strengthening R&D capacity and technology transfer:

- Address the capacity needs of academic and public research organizations in developing countries.
- Utilize direct grants to companies in developing countries.

Coordination:

- Establish a global health R&D observatory and relevant advisory mechanisms under the auspices of the WHO.

Implementation through a binding global instrument for R&D and innovation for health:

- Formal negotiations on an international convention on global health R&D should be initiated.⁹³

the role of PDPs and the efforts of research-based pharmaceutical companies in addressing neglected health areas.

There is a drive to find alternative and innovative ways to undertake needs-based research. New initiatives aimed at increasing R&D to find effective treatments for neglected diseases are under way, involving a diverse group of actors and a large number of collaborative partnerships. An example of an innovative model set up in cooperation among multiple stakeholders is WIPO Re:Search (see section C.8).

One important concept that evolved from this discussion is that of delinking the price of the final product from the costs of R&D. This concept is based on the fact that patents allow developers to recoup the costs and make profits by charging a price in excess of the costs of production. This way of financing R&D is considered to constitute a barrier to access to medicines where it results in product prices that the health system, or patients paying out of pocket, cannot afford. The principle of delinkage is based on the premise that the costs and risks associated with R&D should be rewarded, and incentives for R&D provided, other than through the price of the product. This type of delinkage is particularly advocated in the case of financing R&D for neglected diseases and new antibiotics.⁹⁴

Delinkage can be facilitated by both push mechanisms and pull mechanisms. Push mechanisms are incentives that provide funding to begin an R&D project, such as grant funding or tax credits for investments in R&D. Pull mechanisms are incentives that offer rewards for certain achievements in the R&D process, such as milestone prizes (e.g. awarded upon entry into Phase I, II, or III trials) or end prizes. The following section, while not exhaustive, describes some of these approaches. Assessments of many related proposals can be found in the reports of the WHO Expert Working Group on Research and Development: Financing and Coordination and the CEWG.

(a) Monitoring health R&D

Improving the availability of information on financial flows in health R&D and the state of the R&D pipeline can support policy responses to fill research gaps. Following the recommendation of the CEWG (see Box 3.9), the Global Observatory on Health R&D has been established within the WHO Secretariat to monitor and analyse relevant information on health R&D for neglected diseases. The Global Observatory on Health R&D is a global initiative that aims to help identify health R&D priorities based on public health needs, by consolidating, monitoring and analysing relevant information on the health R&D needs of developing countries, building on

existing data collection mechanisms and supporting coordinated actions on health R&D.⁹⁵

A number of other initiatives also contribute to understanding the financial flows and pipeline of health R&D, for example, G-FINDER, which publishes data on neglected disease R&D funding,⁹⁶ WHO analyses of the pipeline for antibacterial medicines⁹⁷ and the reports of Treatment Action Group on the pipeline for medicines for HIV, TB and hepatitis C virus.⁹⁸

(b) Grants

Grants are a common method for financing public-sector research. A grant may enable an SME to, for example, undertake initial research for a medicine on a neglected disease and bring a potential new medicine through Phase I trials, at which stage it may be possible to attract commercial funding.

While grants can be useful for stimulating R&D, they provide no guarantee that a viable drug will ultimately be delivered. This is because grants are paid irrespective of the results achieved.

Innovative financing mechanisms that utilize “push” funding include Unitaid (see Box 3.10) and CARB-X (see Box 3.7).

(c) Prizes

Prizes work as a pull mechanism in R&D by offering rewards for success, thereby making investment more attractive and the delivery of a specific product more likely (see Box 3.11). There are two categories of innovation inducement prizes: the first is awarded for reaching a specified milestone in the R&D process; the second rewards the attainment of a specified endpoint (such as a new diagnostic, vaccine or medicine with a particular profile in terms of performance, cost, efficacy or other important characteristics). Such prizes pre-specify certain characteristics of the product (i.e. target product profiles) that the winner, it is hoped, will ultimately develop. Other prizes can recognize innovations that bring substantial benefits to society without seeking a pre-specified product.

While inducement prizes would provide incentives for drug development, they would also aim to delink R&D costs from the prices of medicines. The effect that such prizes could have on innovation and access would largely depend on the size of the prize fund, the application and design of the medicines developed and the manner in which they align research efforts with health priorities, while aiming to leverage access by keeping prices of finished products low.

Box 3.10: Unitaid⁹⁹

Created in 2006, Unitaid is an international organization, hosted by the WHO, that invests in innovations for global health. Unitaid's work supports access to products that prevent, diagnose and treat diseases more quickly, affordably and effectively.

Unitaid researches and identifies new health solutions with potential to alleviate the burden of HIV/AIDS, TB and malaria, as well as HIV co-infections such as hepatitis C and human papillomavirus. Through calls for proposals, Unitaid finds partners best qualified to put key innovations into practice. These partners receive grants from Unitaid to fast track access and reduce the costs of more effective medicines, technologies and systems. In this way, Unitaid's investments establish the viability of health innovations, allowing partner organizations to make them widely available.

With regard to IPRs, Unitaid's flagship project is the Medicines Patent Pool, which negotiates voluntary licences with originator companies (see Box 4.24).

Since its establishment, Unitaid has received approximately US\$ 3 billion in contributions from donors, the main donors being France, the United Kingdom, Brazil, the Bill & Melinda Gates Foundation, Norway, the Republic of Korea, Chile and Spain. Innovation is at the core of Unitaid, and a key source of income is innovative financing, particularly the airline tickets levy implemented by Chile, France and the Republic of Korea. To date, Unitaid has received nearly US\$ 2 billion from such innovative financing mechanisms, accounting for two thirds of total contributions.

Box 3.11: Examples of prize schemes**The Longitude Prize**

The Longitude Prize is for an affordable, accurate, fast and easy-to-use test for bacterial infections that allows health professionals worldwide to administer the right antibiotics at the right time.¹⁰⁰

The Life Prize

The Life Prize (previously the "3P Project"), launched by Médecins Sans Frontières and run by the International Union Against Tuberculosis and Lung Disease, is a proposed initiative that, among other things, would incentivize the development of new TB treatments by offering milestone prizes for a product that fits a target product profile (Brigden et al., 2017).

The EU prize for innovative vaccine technology

The European Commission offered a EUR 2 million "inducement prize" to a research team offering novel solutions to improving temperature stability of vaccines, as refrigerating vaccines presents a major challenge in many LMICs. Submissions were received from 49 competitors; the prize was awarded to a German company (European Commission, 2014a).

The Horizon 2020 prize to reduce misuse of antibiotics

The European Commission offered a EUR 1 million prize for a rapid point-of-care test to identify which upper respiratory tract infections can be treated without antibiotics. Such a test could support a reduction in unnecessary use of antibiotics, a driver of antimicrobial resistance.¹⁰¹

US Patent and Trademark Office Patents for Humanity programme

The US Patent and Trademark Office (USPTO) Patents for Humanity programme awards prizes to applicants who develop innovations to address pressing global needs.¹⁰² Awardees receive a certificate to accelerate the examination of their patent applications before the USPTO, as well as certain re-examination or appeal proceedings. The programme has rewarded innovation in medical devices adapted for difficult environments: one of its 2018 winners developed a portable, low-water kidney dialysis machine for use in areas that lack infrastructure required for traditional dialysis. Unlike the other examples above, the Patents for Humanity programme does not issue specific target product profiles.

Prizes can have a favourable impact on the development of, and access to, health products. For example, certain requirements relating to IP management may be imposed on a prize winner, including allowing free use of the technology by the public sector or developing countries, in order to promote competition for supply. Some prize schemes include such IP requirements (e.g. the Life Prize), while others do not (e.g. the Patents for Humanity programme) (see Box 3.11). Where IP management is not integrated into the prize mechanism, access to the resulting technology will not be influenced by the awarding body and will depend on the patent holder's business strategy.

(d) Advance market commitments and advance purchase commitments

AMC agreements aim to create greater incentives for the R&D of a specific product, through either market creation or risk reduction. AMC agreements operate as contracts between a purchaser (normally a government or an international financing agency) and suppliers. They usually contain some form of agreed guarantee with regard to price or volume. By effectively guaranteeing a market, pharmaceutical companies are incentivized to undertake R&D.¹⁰³ Box 3.5 provides an example of how AMCs can be implemented.

(e) Priority review vouchers

A priority review voucher (PRV) is a scheme that aims to reward companies that develop health products that address small markets or limited patient groups, as is the case also with neglected diseases. The PRV entitles a company to receive priority review (i.e. quicker review by the responsible regulatory authority) for any additional health products that would not otherwise qualify for priority review. A company can use this scheme to advance the marketing date of a potential "blockbuster" product, thus generating increased and earlier revenues from that product.

A PRV scheme was introduced in the United States in 2007. Under this scheme, companies that obtain marketing approval from the FDA for a product to treat or prevent one of 16 NTDs are entitled to receive a PRV. In 2012, the scope of eligibility was extended to include rare paediatric diseases,¹⁰⁴ and, in 2016, was extended to include "medical countermeasures" (health products that could be used for public health emergencies stemming from a terrorist attack or a naturally occurring "emerging" disease).¹⁰⁵ PRVs have now more often been issued for rare paediatric diseases than for neglected diseases (see Table 3.1).¹⁰⁶ A PRV can be used by the recipient for any future product filing, or it can be sold to another

company at a rate determined by the market: PRVs have been sold numerous times, for amounts ranging from US\$ 67.5 million to US\$ 350 million (see Figure 3.8; Ridley and Régnier, 2016).

Since this scheme was introduced in the United States, a number of PRVs have been issued (see Table 3.1). The first PRV was issued in April 2009 for the development of an antimalarial drug, and the second, in December 2012, for bedaquiline, the first anti-TB drug in 40 years (see Chapter IV, section B.3).

Some argue that the value of the voucher is too small to have meaningful impact on the allocation of R&D resources by large pharmaceutical companies. A voucher might be attractive for smaller companies, but these companies are less likely to progress a health product through to development phase in view of the large costs of that phase. The value of a voucher is uncertain since it does not guarantee that an additional company product will, in fact, ultimately be approved by the regulatory authority, nor does it guarantee that the time saved by a priority review will actually exceed one year. It has been argued that the value of PRVs has decreased because they were granted too often (Ridley and Régnier, 2016).

The PRV mechanism can also be used to finance non-profit drug development initiatives. The WHO Special Programme for Research and Training in Tropical Diseases (TDR) partnered with a non-profit pharmaceutical company to develop moxidectin for the treatment of onchocerciasis, an NTD. The prospect of obtaining a PRV enabled the non-profit pharmaceutical company to raise US\$ 13 million from a social impact investment fund to develop moxidectin, as the revenue from selling the PRV is expected to be significant (see Figure 3.8) and would be reinvested in the NTD sector, offering the funder a "multiplier" effect. In 2018, the FDA approved moxidectin and awarded a PRV (Olliaro et al., 2018).

(f) Tax breaks for companies

Many countries provide tax credits for R&D expenditures, enabling companies to account for expenditure on R&D against their tax liabilities. In the United Kingdom, tax credits were introduced with the express goal of incentivizing research on vaccines for HIV/AIDS, TB and malaria, though this tax credit was discontinued in 2017 due to low uptake (Rao, 2011; HM Revenue & Customs, 2016). Tax credits are also provided for orphan (rare disease) products in some countries (see section B.6).

Tax credits cannot by themselves remedy the absence of market incentives for neglected diseases. As long

Table 3.1: PRVs issued, 2009–2019

Year awarded	Disease	Category	Product
2009	Malaria	ND	artemether/lumefantrine
2012	Tuberculosis	ND	bedaquiline
2014	Morquio A syndrome	RPD	elosulfase alfa
2014	Leishmaniasis	ND	miltefosine
2015	High-risk neuroblastoma	RPD	dinutuximab
2015	Rare bile acid synthesis disorders	RPD	cholic acid
2015	Hereditary orotic aciduria	RPD	uridine triacetate
2015	Hypophosphatasia	RPD	asfotase alfa
2015	Lysosomal acid lipase (LAL) deficiency	RPD	sebelipase alfa
2016	Cholera	ND	single-dose live oral cholera vaccine
2016	Duchenne muscular dystrophy	RPD	eteplirsen
2016	Spinal muscular atrophy (SMA)	RPD	nusinersen
2017	Duchenne muscular dystrophy	RPD	deflazacort
2017	Batten disease	RPD	cerliponase alfa
2017	Chagas	ND	benznidazole
2017	B-cell acute lymphoblastic leukaemia	RPD	tisagenlecleucel
2017	Mucopolysaccharidosis (MPS) VII	RPD	vestronidase alfa
2017	Biallelic RPE65 mutation-associated retinal dystrophy	RPD	voretigene neparovec-rzyl
2018	X-linked hypophosphatemia (XLH)	RPD	burosumab-twza
2018	Onchocerciasis (river blindness)	ND	moxidectin
2018	Lennox-Gastaut or Dravet syndrome	RPD	cannabidiol
2018	Smallpox	MTMC	tecovirimat
2018	Malaria	ND	tafenoquine
2018	Adenosine deaminase-severe combined immunodeficiency (ADA-SCID)	RPD	elapegamase-lvlr
2018	Primary haemophagocytic lymphohistiocytosis	RPD	emapalumab-lzsg
2019	Fascioliasis	ND	triclabendazole
2019	Cystic fibrosis	RPD	tezacaftor/ivacaftor
2019	Dengue	ND	dengue tetravalent vaccine
2019	Spinal muscular atrophy	RPD	onasemnogene abeparovec-xioi

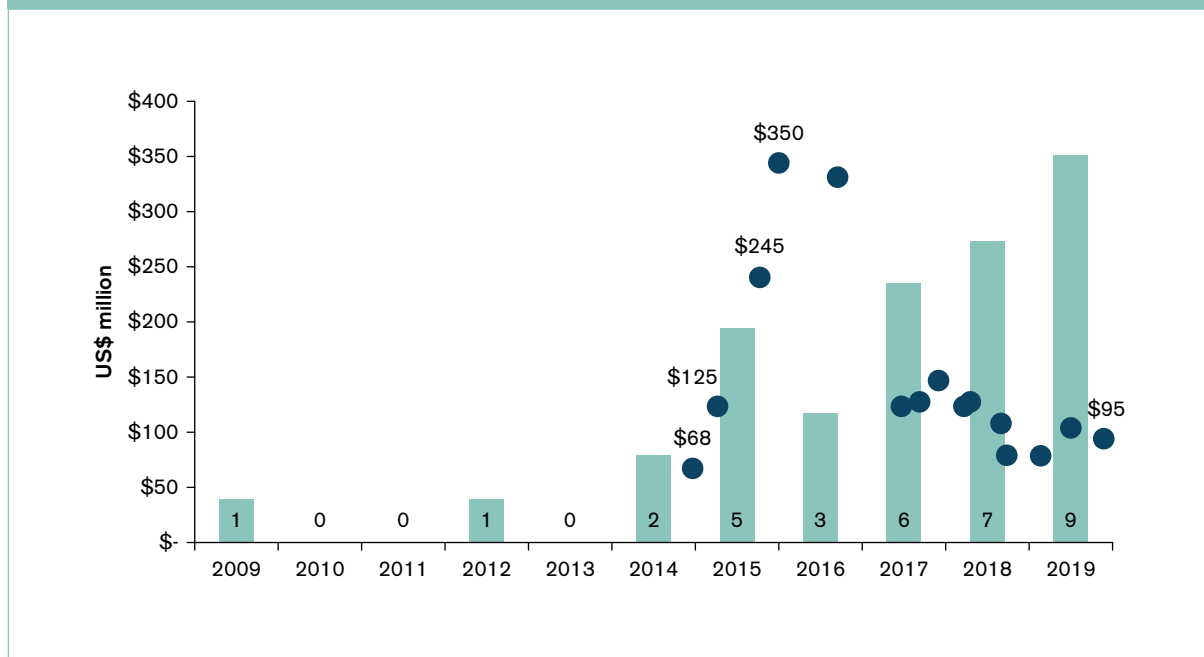
Source: Adapted from www.priorityreviewvoucher.org, a website maintained by David Ridley, one of the authors of the PRV.

Notes: ND = neglected disease; RPD = rare paediatric disease; MTMC = material threat medical countermeasure.¹⁰⁷

as a company has to recover a substantial amount of its investment in R&D for a drug through revenues, tax credits cannot effectively drive innovation for products for which there is no demand. Some commentators have questioned the application of tax credits for profitable products (Bagley, 2018; Hughes and Poletti-Hughes, 2016).

Tax credits cannot help where companies are operating at a loss – as is the case with some biotechnology companies in their start-up phase, before they have launched any approved product onto the market. Another disadvantage of the introduction of tax breaks is that they may simply subsidize R&D that a company would have undertaken anyway.

Figure 3.8: Number and sales values of PRVs



Source: <http://priorityreviewvoucher.org>.

(g) Patent pools

A patent pool is an agreement between at least two patent owners to group their patent rights relating to a specific technology and to license the rights to use these patents to each other and to third parties, subject to certain conditions, such as the payment of royalties. Pooling the relevant patents necessary to use a technology, or to produce downstream products, allows licensees to enter into only one licence agreement with one legal entity and has been advocated as a tool to be used in R&D for neglected diseases. Patent pools have been used since the 19th century in different industry sectors. Early patent pools were aimed at fixing prices and keeping competitors out of the market, and thus came into conflict with competition law. Today, most patent pools aim to enable access to new technologies and to foster downstream competition. By reducing transaction costs for licensees, patent pools provide easy access to all patented technologies needed to produce standardized products. The audio-visual industry, for example, has adopted pooling as an instrument to facilitate licensing of standard technology and has established a number of successful patent pools.¹⁰⁸ The success of patent pools depends on two key factors: (i) the participation of key patent holders, as, without their participation, the patent pool can be held hostage by patent holders outside the pool; and (ii) ensuring that administrative costs for the patent pool are kept low (Merges and Mattioli, 2017). Competition concerns can also arise from patent pools, as they may provide an opportunity for possible anti-competitive behaviour. It is thus important to ensure that licensing terms are worldwide and non-exclusive and any analysis should

examine whether the patent pool encourages collusive behaviour (WIPO, 2014b). An illustration of potential competition concerns for patent pools is the European Commission’s investigation of a patent pool agreement for non-invasive prenatal testing in 2014, based on its block exemption for technology transfer agreements¹⁰⁹ and its guidelines on technology transfer agreements.¹¹⁰

In the field of pharmaceutical inventions, with funding from Unitaid, the Medicines Patent Pool (MPP) was established to pool patents for ARVs and has since expanded its scope of work (see Chapter IV, section C.3(b)). The MPP voluntary licences provide the freedom to develop new treatments, such as fixed-dose combinations – single pills composed of several medicines – and special formulations for children.

The Broad Institute of MIT and Harvard University entered into discussions about a potential patent pool to make CRISPR gene-editing technology (see Box 2.3) more widely available by streamlining the non-exclusive licensing procedure and limiting the duration of a licence for commercial research developing human therapeutics.¹¹¹ However, uncertainty around patent status related to questions of ownership,¹¹² and uncertainty around the scope of patents involved (Jewell and Balakrishnan, 2017), have made patent pooling difficult. This underlines the need for patent information, including through patent landscape reports, to support patent pool initiatives (see Chapter II, section B.1(viii)).

Patent pooling was also discussed as a possible solution to clear patent thickets to facilitate a response to SARS.¹¹³

(h) Open source drug discovery and development

Open source drug discovery and development builds on two principles borrowed from open source software development. First, open source drug discovery is based on the idea of collaboration, that is, organizing and motivating groups of independent researchers to contribute to research projects. Second, it is based on an open approach to IP that makes the outcome of that research generally available, through either the public domain or the use of customized licences (Maurer, 2007; Masum and Harris, 2011).

The success of open source models in the IT sector (e.g. web technology and the Linux operating system) and biotechnology sector (e.g. human genome sequencing) highlights both the need and the potential to initiate a similar model in health care, such as an open source model for drug discovery. Several open source drug discovery projects are currently under way.¹¹⁴ Most have secured financing either in the form of government grants or from philanthropic sources. These funds are used to cover administrative expenses and may also be used to fund access to laboratories and computer facilities and payment to researchers. Similarly, examples of open source data platforms are emerging, including the TB-Platform for Aggregation of Clinical TB Studies,¹¹⁵ Worldwide Antimalarial Resistance Network¹¹⁶ and Infectious Disease Data Observatory for Ebola.¹¹⁷ These platforms can be particularly useful in drug repurposing, where an existing drug can be used to treat another disease and where a significant amount of pre-clinical and clinical data already exists (Balasegaram et al., 2017).

However, the results of open source initiatives have been limited to date. Initiatives thus far have been on a relatively small scale, including in terms of funding. While they seem ideally suited to promoting pre-competitive research, the model would likely have to be combined with financing models to cover the costly development phases. Biopharmaceutical firms have used different organizational modes (i.e. licensing agreements, non-equity alliances, purchase and supply of technical and scientific services) to enter into relationships with different types of partners, with the aim of acquiring or commercially exploiting technologies and knowledge. These relationships can include large pharmaceutical companies, biotechnology product firms, biotechnology platform firms and universities.

(i) *A global binding framework for R&D and a pooled fund for R&D*

In adopting the GSPA-PHI, the World Health Assembly (WHA) called for “further exploratory discussions on the utility of possible instruments or mechanisms for essential health and biomedical R&D, including, inter alia, an essential health and biomedical R&D treaty”.¹¹⁸

The CEWG recommended that WHO member states negotiate a global convention or a treaty under the auspices of Article 19 of the WHO Constitution, aimed at providing effective financing and coordination mechanisms to promote R&D. Countries would, among other things, invest 0.01 per cent of their GDP in R&D for Type II and Type III diseases and in R&D for the specific needs of developing countries in relation to Type I diseases. Part of these contributions would be collected in a pooled fund at the global level (WHO, 2012).

WHO member states agreed to explore, evaluate and independently monitor existing mechanisms for contributions to health R&D for such diseases and, if needed, develop a proposal for effective mechanisms, including pooling resources and voluntary contributions.¹¹⁹ The WHO TDR explored implementation of a pooled fund, and published concrete proposals to set up a voluntary fund to finance neglected disease research.¹²⁰ Six “demonstration projects” were selected as precursors to such a fund, but WHO member states have not, ultimately, pursued the concept. Sufficient funding to finance the demonstration projects did not materialize (WHO, 2017d).

6. Product development partnerships

The term “public–private partnership” (PPP) is usually used to describe an initiative that consists of a partnership between government and at least one private-sector company. Today, such partnerships manage a large proportion of all neglected diseases drug development projects worldwide. PPPs have common characteristics:

- They integrate public- and private-sector approaches, and generally use industry practices in their R&D activities.
- They manage neglected diseases R&D portfolios, and they target one or more neglected disease.
- They are created in order to pursue public health objectives rather than commercial gains, and also to provide funding to cover existing research gaps.
- They ensure that the developed products are affordable (WHO, 2006a).

It is difficult, however, to clearly identify the common denominator in all initiatives that are identified as PPPs. Some may not be true “public–private” partnerships, in the sense that they may not have partners from both the public and private sectors (Moran et al., 2005). The broader category of product development partnerships (PDPs) embraces such initiatives that do not necessarily have a public- or private-sector partner, and thus do not qualify as PPPs in the strict sense. It therefore encompasses equally public-health-driven,

Box 3.12: Examples of successful product development partnerships**DNDi**

DNDi is a collaborative, patient-needs-driven, non-profit R&D organization that aims to bridge gaps in existing R&D in essential drugs for neglected diseases. Since its establishment in 2003, DNDi has developed a number of new treatments for neglected diseases, including one NCE, two new fixed-dose combinations, three improved treatment regimens and two new paediatric formulations.¹²¹ DNDi currently has more than 30 projects in its pipeline.¹²² Together with the WHO, DNDi has initiated GARDP, a not-for-profit research and development organization developing and delivering new or improved antibiotic treatments (see Box 3.7).

To ensure access to the end product, DNDi utilizes non-exclusive licences and contractual commitments from industrial partners to sell the products on a cost-plus basis. By negotiating access commitments at a very early stage in the R&D process, DNDi delinks the costs of R&D (financed with DNDi funding) from the final price of the product (maintained at the lowest-possible sustainable level by the manufacturing partner).

This approach is illustrated in the example of artesunate and amodiaquine (ASAO), a new fixed-dose combination for malaria, which DNDi developed with various public- and private-sector partners, while retaining ownership of the related IP. DNDi then licensed IP to a pharmaceutical company for the industrial production, registration and distribution of ASAO in Africa and other developing countries, under a “no-profit-no-loss” price. In addition, ASAO can be freely produced and distributed by any other pharmaceutical company in the world. A more recent example is fexinidazole, the first NCE to be developed by DNDi, in collaboration with Sanofi. Fexinidazole was rediscovered by DNDi when searching for compounds with anti-parasitic activity among those for which development was abandoned for strategic reasons in the 1980s. As part of the collaboration, DNDi was responsible for pre-clinical, clinical and pharmaceutical development, and Sanofi for industrial development, registration, production and distribution of the drug. In December 2017, Sanofi submitted fexinidazole to the EMA, which issued a positive opinion in early 2019. The Democratic Republic of Congo approved the medicine in late 2018.

Vaccine R&D efforts to tackle the threat of Ebola

Over the period 2013–2016, an unprecedented outbreak of Ebola virus disease took place in West Africa, prompting a wave of interest and funding for R&D in Ebola vaccines. Initiatives created partially in response to the outbreak include the WHO R&D Blueprint for Action to Prevent Epidemics and the Coalition for Epidemic Preparedness Innovations (see section C.3).

At the time of the outbreak, a number of vaccine candidates were in the pipeline but had stalled at various stages of development due to a lack of funding (Reardon, 2014). The most mature candidate, rVSV-ZEBOV, was originally developed by the Public Health Agency of Canada, licensed to NewLink Genetics, which then sold exclusive rights to MSD (the name under which Merck and Co. Inc. operates outside the United States and Canada).¹²³ Phase I clinical trials were undertaken in 2014 by a broad coalition of public and private partners, in order to allow Phase II trials during the Ebola outbreak. In 2016, Gavi, the Vaccine Alliance signed an agreement with Merck to use the vaccine for future outbreaks of Ebola. Having shown a high level of efficacy in a Phase III trial (Henaou-Restrepo et al., 2017; Cross et al., 2018), rVSV-ZEBOV was submitted for review by the FDA in 2018.¹²⁴

Other vaccine candidates are also in development and similarly involve multiple public and private-sector partners.¹²⁵

TB Alliance

TB Alliance is a not-for-profit product development partnership dedicated to the discovery, development and delivery of better, faster acting and affordable TB drugs. TB Alliance was established in 2000, at a time when there were no TB drugs in clinical development.¹²⁶

TB Alliance manages the largest pipeline of TB drugs in history, which comprises candidates in all phases of clinical development and is directed to different parts of the TB epidemic, including treatments for drug-sensitive TB, drug-resistant TB and improved paediatric formulations for first-line TB treatments.¹²⁷

Under a collaboration agreement with Janssen, TB Alliance managed key parts of the later-stage clinical development of bedaquiline, a novel treatment for drug-resistant TB (see Chapter IV, section B.3).¹²⁸ TB Alliance has also recently received FDA approval for pretomanid, another treatment for drug-resistant TB.¹²⁹

not-for-profit organizations that use private-sector approaches to develop new products in conjunction with external partners. This study uses the term PDP, not PPP, as it is more descriptive of new structures for medical innovation.

The emergence of PDPs since the late 1990s, drawing together actors from the public and private sectors, has been a major development in efforts to focus R&D towards diseases that disproportionately affect LMICs. These new partnerships have been constituted in a number of ways, but usually with the involvement of non-profit organizations, foundations and industry. Previously, the majority of funds for PDPs were provided by the philanthropic sector, but, in 2017, government funding overtook philanthropic funding.¹³⁰ These partnerships have significantly increased the number of products in development for diseases and conditions that predominantly affect developing countries, and they play an important role in identifying pathways and overcoming bottlenecks in research for neglected diseases.

In 2017, funding to PDPs involved in research into neglected diseases amounted to US\$ 508 million. This represented 14 per cent of global funding for research on neglected diseases. Four PDPs – the Programme for Appropriate Technology in Health (PATH), Medicines for Malaria Venture (MMV), the International AIDS Vaccine Initiative (IAVI) and Drugs for Neglected Diseases *initiative* (DNDi) – accounted for over half of all PDP funding.¹³¹

PDPs form alliances with stakeholders drawn from the public and private sectors because PDPs and these entities have the potential to capitalize on the opportunities that each may offer the other. PDPs are performing the service of integrating inputs from different branches of a very diverse industry. PDPs also seem to have lower research costs than research-based pharmaceutical companies, for a number of reasons. PDPs benefit from lower capital costs as a result of their capacity to leverage in-kind inputs. They also benefit from the fact that they do not have to fund a fully loaded development pipeline. Instead, they select their projects from a pool of existing projects in the public and private domains. On the other hand, their costs could be expected to increase substantially as more projects enter large-scale Phase III trials. In this case, the PDP cost-efficiency profile would probably change, since late-stage failures are more expensive than early-stage failures (Moran et al., 2005). DNDi and the initiatives that emerged in response to the 2014–2016 Ebola epidemic are examples of public–private collaboration and PDPs. PDPs have a pressing imperative during public health crises, such as the Ebola epidemic, that calls for strong and efficient

collaboration globally and locally – while urgency is often defined and experienced locally, readiness and response requires global cooperation.¹³² Examples of needs-driven partnerships can be found in Box 3.12.

7. Research for neglected diseases: the role of pharmaceutical companies

Research-based pharmaceutical companies are increasingly engaged in philanthropic research. Aggregated contributions make the industry the second largest sponsor of research for neglected diseases in 2017, after the US NIH and ahead of the Bill & Melinda Gates Foundation.¹³³ A number of companies have established dedicated research institutes to develop new products targeting diseases that disproportionately affect developing countries, or participate in cooperative projects and PDPs, thus sharing assets and knowledge. Table 3.2 gives details of some industry-supported R&D centres that are dedicated to research in neglected diseases. In total, research-based pharmaceutical companies were reported in 2017 to be engaged in 109 projects aimed at developing new medicines and vaccines for diseases that have been prioritized by the WHO TDR. Of these projects, 90 per cent are collaborative, involving over 50 universities, NGOs and other public- and private-sector institutes.¹³⁴

Treatment coverage for NTDs increased by 76 per cent from 2008 to 2015. Global NTD treatment is highly reliant on treatment donations by a few pharmaceutical companies; the number of tablets donated has quadrupled, from 353 million in 2009 to more than 1.5 billion in 2015.¹³⁵ There was a decrease in reported private-sector R&D projects, from 132 in 2012 to 109 in 2017 (IFPMA, 2013, 2017), but, overall, private-sector investments in NTD R&D have increased notably, from US\$ 345 million in 2008 to US\$ 554 million in 2017 (though this increase represents, in part, a greater number of companies providing data).¹³⁶

8. WIPO Re:Search – Mobilizing intellectual property for global health

The WIPO Re:Search public–private consortium,¹³⁷ led by WIPO in partnership with the Seattle-based NGO BIO Ventures for Global Health (BVGH), accelerates the discovery and development of medicines, vaccines and diagnostics for NTDs, malaria and TB by catalyzing the sharing on concessionary terms of IP assets, compounds, data, clinical samples, technology and expertise among

Table 3.2: Pharmaceutical industry centres dedicated to NTDs R&D

Company	R&D centre	Location	Active since
AbbVie	AbbVie	North Chicago, IL, US	2009
AstraZeneca	Cambridge Biomedical Campus (CBC)	Cambridge, UK	2015
Celgene	Celgene Global Health	Summit, NJ, US	2009
GSK	Diseases of the Developing World Center	Tres Cantos, Spain	2002
Merck	R&D Translational Innovation Platform "Global Health"	Geneva, Switzerland	2014
Merck & Co. Inc. (operates as MSD outside the United States and Canada)	MSD Wellcome Trust Hilleman Laboratories	New Delhi, India	2009
Novartis	Novartis Institute for Tropical Diseases (NITD)	Emeryville, CA, US	2002
	Novartis Institutes for BioMedical Research (NIBR)	Emeryville, CA, US	2016
	Genomics Institute of the Novartis Research Foundation (GNF)	La Jolla, CA, US	2010
Eisai	Eisai Inc. Andover Research Institute	Andover, MA, US	1987
	Eisai Pharmaceuticals India Pvt. Ltd.	Visakhapatnam, India	2007
	Tsukuba Research Laboratories	Tsukuba, Ibaraki Prefecture, Japan	1982
Sanofi	Marcy l'Etoile Research and Development Campus	Lyon, France	Vaccines (Dengue) since the 90s; Medicines since 2015

Source: Information provided by the International Federation of Pharmaceutical Manufacturers and Associations.

members. The WHO supports WIPO Re:Search through the provision of technical advice.

WIPO Re:Search unites the scientific expertise and creative thinking of academic, non-profit and government investigators, the first-hand disease knowledge of researchers in endemic countries and the material assets and R&D experience of global pharmaceutical companies, to drive innovation and product development for the world's poorest populations. As at January 2020, WIPO Re:Search had 146 members in 42 countries (including 35 African organizations), and had facilitated 156 research collaborations. Ten ongoing collaborations have achieved key product development milestones (e.g. positive "hits" or activity against pathogens or drug targets of interest).

Sharing of assets and participation in collaborations is optional. The terms and conditions of each collaboration are governed by licence agreements and other agreements individually negotiated by the participating entities. Such agreements must be consistent with the WIPO Re:Search Guiding Principles,¹³⁸ which

organizations agree to abide by as a condition of consortium membership. The Guiding Principles include the following provisions:

- All licences granted for R&D and manufacture anywhere in the world are to be royalty free.
- For any products developed under a WIPO Re:Search collaboration agreement, providers of the relevant IP are to provide royalty-free licences for product use and sale in all LDCs. Providers are also to consider in good faith the issue of product access for all developing countries, including those that do not qualify as LDCs.

The Consortium Structure

- The WIPO Re:Search Resource Platform,¹³⁹ operated by WIPO, is an interactive online tool designed to facilitate information sharing and spur collaborations. It enables users to view and retrieve information on WIPO Re:Search members, collaborations and IP assets, such as compounds available for licensing

through WIPO Re:Search. All the information is publicly available.

- The WIPO Re:Search Partnership Hub – operated by BVGH – leads collaboration development and management activities. It identifies investigators and companies with complementary capabilities and needs, and then introduces those parties to determine if there is reciprocal interest in collaborating. If so, the Partnership Hub facilitates communications between partners to align on milestones and agree on timelines and responsibilities. Once legal agreements are in place between the participating entities, the Partnership Hub provides alliance management support to help ensure successful outcomes. Depending on the specific needs of the collaboration, such support includes coordination of regular update calls,

recruitment of additional partners with needed expertise, and assistance in identifying relevant and high-value award opportunities.

The WIPO Re:Search Fellowship Programme

Between 2013 and 2019, the Government of Australia provided funds in trust to WIPO Re:Search to support, *inter alia*, research and training of scientists from Africa and the Indo-Pacific region. These funds were employed to create targeted research and training fellowships focused on NTDs, malaria and TB. This programme arranged 20 fellowships for scientists from LMICs at advanced laboratories in North America, Europe and Australia. The fellowships enabled the sharing of IP, knowledge and experience among hosts and fellows, and engendered long-lasting professional relationships and networks.

D. Intellectual property rights in the innovation cycle

Key points

- International legal standards can have a major impact on innovation systems. The choices made at the regional and national levels within the international legal frameworks are key. Similarly, the management of IP – often shaped by overall innovation structures – can have a direct impact on R&D outcomes and access.
- Patent law is only one element of the innovation process. The role of patent law in developing new medical technologies depends on its legal and administrative design and on specific decisions by individual parties during the development process. Patents do not have the same importance for all industries.
- Pre-grant patent issues of particular relevance to innovation include the patenting of material that exists in nature, patenting of incremental innovation and certain patent filing strategies referred to as “evergreening”, and granting of patent protection on a known product for which a new medical indication has been identified.
- Incremental innovation can improve the safety, therapeutic effect or method of delivery of an existing medicine or vaccine. Whether such inventions merit the granting of a patent is judged on a case-by-case basis.
- Post-grant issues affecting health technology R&D discussed in the study include the patenting of research tools in the field of biopharmaceuticals, the existence of a research exception in national patent laws, licences as tools for partnership building, cooperation and technology transfer, and freedom to operate (FTO) analysis as a basis for a risk-management decision in relation to R&D, product launch and commercialization.

Following the introduction to IPRs in Chapter II, section B.1, this section looks at the impact of IPRs on innovation in the pharmaceutical sector, with a particular focus on patent-related issues. It first examines the interdependence of the international, regional and national framework, and the importance of choices made with respect to the management of IPRs, then proceeds to analyse questions related to patentability in the pre-grant phase, as well as issues related to the use of patents in the post-grant phase. It concludes with an overview of issues regarding freedom to operate.

1. IP management within the broader legal and policy framework at national and international levels

While the international legal dimension of IPRs is critically important to the medical innovation ecosystem – and has garnered much attention in policy debate – it is essential to consider the various layers of IP law and policy, which ultimately influence the directions that research takes. Provisions of the TRIPS Agreement, for instance, can be understood as part of the interplay between international and domestic law and policy frameworks. Policy measures with bearing on medical technologies range from the strategies of individual projects to the standards of international law:

- General policies and strategies for management of IP at the institutional or project level, whether within the private, public or philanthropic sector, and including

practical choices, such as whether or not to file for a patent, and, if so, where; and how to exercise the ensuing rights

- National innovation policy settings, including targeted incentive initiatives, and policies for the management of publicly funded medical research
- National legislative settings, including IP laws and their interaction with other aspects of the regulatory system, such as competition policy and regulation of medicines
- International cooperation on public health and specific international initiatives, including on neglected diseases research
- The international legal framework, comprising a complex of so-called “hard law” and “soft law” instruments and standards spanning trade and investment, IP, public health, human rights, bioethics and related areas.

Consequently, while international legal standards can have a major impact on innovation systems (e.g. in requiring pharmaceutical inventions to be patentable), the choices made at the regional and national levels within the international legal framework are key (e.g. in determining and applying specific patentability criteria under national law). Similarly, the choices made by a public-sector research programme or a private-sector company regarding the management of IP can have a direct impact on R&D outcomes and access. These choices for IP management are often shaped by overall innovation structures, such as those discussed in section B.4 above.

Table 3.3: IP issues that may arise at each stage of the product development pipeline

Innovation planning for health outcomes	Initiating research on unmet public health needs	Initial choices on presence and absence of IP protection	Beyond the initial research: proof of concept and scaling-up	Clinical trials and regulatory approval	Manufacture and distribution	Distribution and marketing phase
<ul style="list-style-type: none"> Setting IP policies and management strategies, including clarifying questions of ownership, access and control over research outcomes. Surveys of existing technology as research inputs and patterns of ownership (according to patent holder, and territorial effect of patents in force), to identify potential partners and possible barriers, as well as avenues for productive new research. Assessment of freedom to operate, status of existing technology, in addition to prospects for technology partnering, access and pooling options. 	<ul style="list-style-type: none"> IP or non-IP incentives for private investment in research and other contributions (including financial and other resources, background technology, infrastructure, scientific and technology management expertise, management of regulatory processes, risk exposure and opportunity cost). Negotiation of terms and conditions covering R&D, including using IP when negotiating guarantees of development and access to finished product; negotiation or implementation of public-interest safeguards to ensure adequate access to research outcomes. Establishing and implementing publication and IP management policies for researchers. 	<ul style="list-style-type: none"> Following initial research outcomes and their subsequent elaboration, the decision at an institution or company level whether or not to seek IP protection on particular innovations and in which jurisdictions, guided by an overall product development, commercialization and diffusion strategy. Decisions at national and regional levels concerning the patentability of the research outcome according to patent grant criteria. Management of know-how, confidential information and other forms of IP. 	<ul style="list-style-type: none"> IP arrangements in negotiations on financing and conducting clinical trials, and in attracting further investment, philanthropic support or allocation of public resources. Other incentives trigger innovation in certain fields, e.g. through "orphan disease" schemes. Assessment of the IP implications of moving beyond a pure research phase into the preliminary stages of full drug development. 	<ul style="list-style-type: none"> Arrangements for generating, protecting and accessing clinical trial data; incentives for investing in this process, and the laws and policy settings that govern this; mechanisms for facilitating or reducing the cost of regulatory approval, such as push and pull incentives, e.g. AMCs. IP aspects of issues, such as mutual recognition of regulatory approvals, sharing of data, negotiating or otherwise ensuring access to, and use of, clinical trial data. 	<ul style="list-style-type: none"> Access to necessary manufacturing, excipient and adjuvant drug delivery and platform technologies. IP management strategies for effective global outcomes (including different ownership in different markets or jurisdictions; different approaches to control or licensing of IPRs in rich and poor countries; role of IP in tiered pricing; "march in" rights and other forms of guarantees of access to public- or philanthropic-funded research). Requirements of national competition policies. 	<ul style="list-style-type: none"> Monitoring and enforcing access guarantees, such as licensing provisions providing for effective access for particular patient groups and requirements for timely introduction of medicines to specified markets. Managing IP that may be relevant to improvements and new indications, and regulatory approval; fulfilling access commitments. Assessing the implications of regulations governing the use of IP in the marketplace, e.g. measures against anti-competitive practices.

2. Intellectual property and the product development process

An overview of relevant IP issues that arise at each stage of the product development pipeline can help to clarify the linkages between specific issues and choices within a narrower operational context, and the overarching policy objective of improved public health outcomes (see Table 3.3). Each of these issues is not a narrow “technical” question that can be considered entirely in isolation. Rather, the successful development and diffusion of a new technology is a consequence of the combined impact of choices taken at each of these steps.

The debate on the value and practical impact of the patent system, in particular, in delivering needed medical technologies has highlighted two key points:

- Patent law is not a stand-alone innovation system. It is only one element of the innovation process, and one which can be deployed differently in diverse innovation scenarios. Patent law has little bearing on many other factors that lead to the successful development of technologies, for example, the nature and extent of demand, commercial advantages gained by marketing and ancillary services and support, commercial and technical viability of production processes, and compliance with regulatory requirements, including through effective management of clinical trials data.
- The role of the patent system in developing a new medical technology depends not only on legislative and regulatory settings but also on a variety of choices made by individuals at different stages of the development process as to whether and when to obtain patent rights and how to exercise them. They may rely on exclusive commercial positions or draw from a range of non-exclusive and open licensing structures, waivers of rights and specific non-assertion undertakings (see Chapter IV, section C.3(c)). Notably, in the case of not-for-profit initiatives in public health, these approaches are not necessarily aimed at securing financial advantages. Instead, they are aimed at leveraging access to technologies.

Patents do not have the same importance for all industries. In addition, they have quite different impacts on markets, as is illustrated by the comparison between the medical devices industry and the pharmaceutical industry (see Table 3.4).

3. Patent filing strategies in the public and private sectors and the exercise of patent rights

Apart from the provisions of the national or international law and their interpretation by the courts, the patent filing strategies of applicants could determine the innovation

and imitation landscape for medical technologies. Filing a patent application involves a series of decisions regarding the specific invention(s) for which patents are to be sought, including the practical purpose for which they are sought, in which jurisdictions, in whose name, with whose funds and when.

Factors determining whether or not a patent application is filed may range from whether the technology is a better solution than any currently available options, to the size of the potential market for the technology or the likelihood of competition. For public-sector researchers, notably in the field of public health, considerations tend to be focused on concerns about how the decision to patent or not patent the technology would advance the institutional or policy goals of their particular research establishment, and whether a patent would help secure suitable partners for downstream product development. When determining patent strategies, the capital requirements needed to further develop the technology into a medical product must be considered, including the need to license any other proprietary technology, the cost of satisfying any regulatory requirements, and the prospects of attracting investment or partners to finance or co-develop these requirements if they cannot be met in-house.

From the inventor’s perspective, patent protection may not be the best strategy if, without it, secrecy can be maintained and the technology cannot be reverse engineered. Similarly, patenting would not be the best strategy if competitors were able to easily develop alternatives that are not covered by the patented claims (i.e. they could design around them) or it was likely to be difficult to ascertain whether competitors were using them without authorization.

Patent application filing strategies determine the countries or territories in which protection is to be sought. Fees must be paid for the grant and maintenance of each patent in each separate country or territory, which can be expensive, and may not be justified in markets where the patent is unlikely to be used. The Patent Cooperation Treaty (PCT) enables a single patent application to be filed with effect in all PCT contracting states (see Chapter II, section B.1(b)(ii) and Box 2.8). Since national processing of an application only takes place in the subsequent national phase, patent applicants can use the international phase to decide in which PCT contracting states they will eventually seek patent protection.

Patent filing strategies can be offensive or defensive. An offensive strategy aims to leverage exclusive rights over a technology in order to extract economic returns from either exclusive use of the patented technology or licensing arrangements. A defensive patent strategy is aimed solely at protecting the inventor’s or patent owner’s freedom to operate (FTO) using its own technology, by avoiding a situation in which a competitor obtains exclusive rights

to it. Equally, patent holders may waive patent rights, or grant a royalty-free licence, or declare that they will not assert certain patents once acquired in certain territories, for certain uses, or in general.

There are differences between private and public patenting strategies. Private-sector entities – mostly publicly traded or privately held companies – aim to generate a return on their shareholders’ investment. In contrast, public-sector and public-interest entities generally conduct research with the aim of serving a general or specific public interest and do not produce commercial products. They focus on smaller portfolios of fewer patents, which typically contain broader claims over key results of upstream research. These patents can be licensed to private-sector entities that have capacity to carry out additional R&D. This, in turn, may lead to delivery of products to the public, and, at the same time, may generate revenue for public-sector entities.

Some countries have adopted policies to encourage research institutions and universities to obtain patents based on inventions arising from publicly funded research. The best-known example of such a policy is the US Bayh-Dole Act of 1980.¹⁴⁰ Similar measures have been adopted in other countries, such as South Africa’s Intellectual Property Rights from Publicly Financed Research and Development Act of 2008 and the Philippine Technology Transfer Act of 2009. Such policies, and a general trend towards more active management of technologies created through publicly funded research, are leading to the steady accumulation of publicly held patent portfolios, including on key upstream technologies that provide platforms for a range of new medical technologies.

PDPs that focus on R&D for new products aimed at addressing neglected health needs may also have

distinct patent filing and IP management strategies (see section C.6).

4. Pre-grant issues: questions of patentability

This section considers selective aspects of patent law that are especially relevant to the innovation dimension of medical technologies.¹⁴¹

(a) Patenting material that exists in nature

While modern biotechnology plays an increasing role in pharmaceutical R&D and production, patents have been granted on biotechnological inventions since the 19th century.¹⁴² For instance, German patent DE 336051 was granted in 1911 to Friedrich Franz Friedmann on the production of a therapeutic against TB involving the continued vaccination of tubercle bacilli obtained from turtles.

The maturing of genetic engineering, including the rise of genome editing techniques such as CRISPR, has been accompanied by an intense public debate about the desirability and appropriateness of applying patent law to modern biotechnology. Important legislative and administrative steps have been taken to clarify some of these issues, such as Directive 98/44/EC of the European Parliament and of the Council on the legal protection of biotechnological inventions¹⁴³ and the USPTO revised Guidelines for Determining Utility of Gene-Related Inventions of 5 January 2001 (USPTO, 2001). Some jurisdictions require that the function of a gene needs to be clearly identified and to be related to the claimed part of the gene sequence.¹⁴⁴

Table 3.4: The different roles of patents in the medical devices industry and the pharmaceutical industry¹⁴⁵

Medical devices industry	Pharmaceutical industry
<i>Characteristics:</i> Medical devices are mainly based on mechanical/electrical technology, IT and systems engineering. The trigger for innovation typically arises from a clinician’s practice.	<i>Characteristics:</i> Pharmaceutical products are based on chemistry, biotechnology and genetics. Fundamental research and applied research, including that based on traditional knowledge, are the basis for innovation.
<i>Patents:</i> Given the interplay among many fields of art, technically complex devices may be protected by hundreds of patents covering the structure, function and/or methods of using the device.	<i>Patents:</i> Active ingredients/chemical compounds are usually covered by a small number of patents, with additional patents addressing variations of such ingredients/compounds, e.g. salts and esters, polymorphs, ways of delivery or formulations.
<i>Design and invent around:</i> In the field of medical devices, to opt for an unprotected design and thus invent around patents is relatively common because alternative technical solutions can be found. This, in turn, enables the creation of greater competition in the market through alternative types of devices, with variations and continuous iterative improvements produced by other companies within the patent term. Competition, coupled with the continuous need and pressure for innovation, lead to relatively short commercial life cycles of about 18–24 months, which is much shorter than the potential patent term of 20 years. However, while the product may change frequently, the technology may be continuously used in successor products.	<i>Design and invent around:</i> In the pharmaceutical area, to invent around patents is often more difficult. Patents covering chemical compounds can exclude competitors from producing comparable products for the entire patent term. In general, pharmaceuticals, if proven efficacious and safe, can enjoy a long commercial life cycle of about 10–20 years or more without undergoing significant changes. Patents will thus be exploited until the end of the patent term.

Box 3.13: Patenting products of nature – the *Myriad* case

BRCA-1 and BRCA-2 are two genes linked to susceptibility to breast and ovarian cancer. The risk of getting cancer increases if these genes show certain mutations. Identifying the mutations is therefore important for diagnosis and for monitoring women at higher risk. Myriad Genetics Inc., in collaboration with others, obtained product patents on the isolated DNA coding for two genes, BRCA-1 and BRCA-2, on a related screening method, and on methods of comparing or analysing BRCA sequences. As a product patent protects not only the functions disclosed in the patent but also all other possible future therapeutic uses of the gene, concerns were raised that the patents held by Myriad Genetics could serve as a disincentive to carrying out further research on possible functions of this gene and the development of diagnostic methods, and impact on access to such tests. Opposition proceedings before the European Patent Office (EPO) led to revocation and restriction of respective European patents in 2004 (Von Der Ropp and Taubman, 2006). Where the patents were in force, Myriad Genetics adopted a restrictive licensing policy that, in practice, only allowed Myriad to perform the complete sequence analysis in their laboratories in the United States (Matthijs and van Ommen, 2009). Public health concerns were raised about the issue of having only one source for diagnostic testing.

In 2013, the Supreme Court of the United States decided that Myriad did not create or alter any of the genetic information encoded in the BRCA-1 and BRCA-2 genes or in their DNA.¹⁴⁶ The Court held that a naturally occurring DNA segment is a product of nature and is not patent eligible merely because it has been isolated.¹⁴⁷ Accordingly, it rejected Myriad's patent claims on the BRCA-1 and BRCA-2 genes. On the other hand, the Court found that claims relating to "complementary DNA" (cDNA), being synthesized in a laboratory from naturally occurring messenger RNA (mRNA) were patent eligible. Notably, the Supreme Court did not consider the patent eligibility of any of Myriad's method claims.

Since the 2013 decision, the number of BRCA tests offered by laboratories in the United States has grown substantially, although the tests vary in how extensively BRCA genes are assessed for mutations (Toland et al., 2018).

In 2015, the patentability of BRCA-1 was also considered by the High Court of Australia.¹⁴⁸ Like the Supreme Court of the United States, the High Court of Australia found that the BRCA-1 was a naturally occurring phenomenon, and that the isolation of nucleic acid comprising the gene lacked the inventiveness necessary to qualify for patent eligibility.¹⁴⁹ The Court also noted the "chilling effect" that the relevant claims, if granted, would have on the use of any isolation process in relation to the BRCA-1 gene.¹⁵⁰

In 2018, the USPTO issued guidance on subject matter eligibility to support patent examiners considering claims relating to naturally occurring products in the wake of the *Myriad* decision. Research found that the *Myriad* decision has also been used to reject patent claims for non-DNA products (Aboy et al., 2018). Some have argued that the *Myriad* decision has led to more time and money being spent on patent applications, as, for example, many applications require a second round of patent examination (Aboy et al., 2018). One study argued that companies may keep information about natural phenomena and correlations as trade secrets rather than relying on patent protection to secure a return on investment, with a potential negative impact on research and patient care (Dreyfuss et al., 2018). For example, an administrative complaint has been filed against Myriad for not supplying genomic data that had been compiled on individuals,¹⁵¹ with Myriad maintaining its database as a trade secret (Conley et al., 2014). Ultimately, however, the new generation of genetic research and diagnostic practice does not always require the isolation of genes, and thus does not generally infringe claims to isolated sequences (Holman, 2014).

A 2001 WIPO survey¹⁵² provides information about national legislation of WIPO member states related to the protection of biotechnological inventions under patent and/or plant variety protection systems, including information as to which countries might admit the patenting of genes, cells or plant varieties. A WIPO study in 2010 looked at how countries have implemented exclusions from patentable subject matter, and exceptions and limitations to patent rights related to biotechnological inventions.¹⁵³ WIPO collates information about exclusions from patentable subject

matter in national/regional patent laws in a database hosted by the SCP.¹⁵⁴

One specific biotechnology patent law issue that is relevant to pharmaceutical production relates to the patentability of material existing in nature, or synthesized or extracted chemical compounds that already exist in nature. A distinction is made between a naturally occurring compound and an artificially extracted and isolated compound. The latter is considered to be a new entity and patentable subject matter in some jurisdictions.¹⁵⁵

In 1911, Japan granted a patent (No. 20785) for an isolated, naturally occurring substance, aberic acid (now termed thiamine, or vitamin B1) from rice bran, which had been identified for the prevention of beriberi, a disease caused by a lack of vitamin B1. The same year, a US court upheld a patent granted to an inventor who had isolated adrenalin from the human suprarenal gland, purified it and identified that it could be used in the treatment of heart disease.¹⁵⁶

Biotechnology invention has entered into the realm of genetics. Patents have been filed, and granted in some cases, for technologies that genetically modify the gene code. For example, a spin-out company holds the patent for gene expression systems using alternative splicing in insects, a technique that has been used to create genetically modified strains of dengue-fever-transmitting mosquitos. While, in many cases, existing patentability criteria are applied by patent law practice and by the courts to determine the patentability of biotechnology inventions, patenting material that exists in nature is not without controversy, as is the application of technology as such. Concerns have been raised about biosafety and unpredictable consequences.¹⁵⁷ A case in the US courts illustrates how controversy also extends to the patenting of human genes (see Box 3.13). As technology develops, for example, DNA editing tools that could rewrite the DNA of sperm, eggs or embryos destined for live births, there may be an increased role for policy-makers. Calls have already been made for the adoption of a moratorium on heritable genome editing.¹⁵⁸ In 2018, the WHO established an expert panel to examine the challenges associated with genome editing. The panel is tasked with making recommendations on appropriate governance mechanisms for human genome editing.¹⁵⁹

(b) Incremental innovation and evergreening

Incremental innovation can improve the safety, therapeutic effect or method of delivery of an existing medicine or vaccine, or improve the efficiency with which it can be manufactured, with positive outcomes for public health. Patents can be granted on incremental innovations if they meet the patentability criteria. Thus, the application of the inventive step/non-obviousness criterion¹⁶⁰ also has implications for incremental innovation.¹⁶¹ The SCP has published a study assessing the application of inventive step in the chemical sector, including pharmaceuticals.¹⁶²

(i) Examples of incremental innovation

Frequently, the first approved formulations of a drug are followed by changes in the formulation or route of administration that improve the effectiveness of the

treatment. These incremental innovations include, for example:

- New dosage forms that increase adherence: Controlled-release formulations, which permit less frequent administration (e.g. once daily rather than twice daily), potentially increasing adherence; more stable drug levels; decreased side effects; formulations for sustained delivery, or sublingual or rapid-dispersion tablets, which are easier to take than capsules and give a more rapid effect.
- New dosage forms with improved efficacy: Frequently, the addition of an excipient or a second active ingredient (a fixed-dose combination) can improve the efficacy of a drug and/or convenience of use. There are numerous examples of new dosage forms with improved efficacy, such as the inclusion of corticosteroids with antivirals, and the coformulation of antiretroviral drugs.
- New formulations with improved storage characteristics: Reliance on the cold chain is a barrier to access for many drugs that lose their activity when stored out of the cold chain. Products with improved heat stability (or simply decreased storage volume) are easier to ship and to store, enabling access in resource-poor settings. Examples include vaccines (oral polio vaccine, nasal influenza) that can be stored in a fridge rather than a freezer and oral drugs that can be stored at room temperature.
- New routes of delivery: Many drugs are first approved for administration by injection, a route which limits ease of access. Formulations allowing alternative routes of administration (e.g. oral, nasal, topical patch) can simplify administration and/or effectiveness. Examples include oral forms of antibiotics and nasal vaccines.
- Improved drug delivery devices: Products such as an inhaler or an injector pen combine a medicine with a delivery device. Combination drug product devices can be updated and patented incrementally if the patentability criteria are met for each incremental innovation (see Box 3.14) (Beall and Kesselheim, 2018). Such improvements to the device do not extend patent protection for the medicine. It may be, however, that the improved device offers the most efficient way to administer the medicine. Patents can be perceived as a barrier to access the medicine to be delivered by the device in cases where the device cannot be easily invented around. Protection of such incremental innovation through patent or regulatory regimes could be linked to increased prices and prolonged lack of generic competition.

Other incremental innovations related to a known, approved drug can have a significant impact on effectiveness. For example, improved processes for production can decrease the cost of manufacture. Improved processes for purification can decrease the contamination of the drug with residual potentially toxic substances.

Box 3.14: Examples of drug-device combinations

The EpiPen is an example of the complexities posed by the protection of the drug delivery device. Epinephrine (adrenaline) by auto-injector is the first-line treatment for anaphylaxis, a severe allergic reaction that can result in death. The EpiPen auto-injector device allows a patient to self-administer epinephrine, a drug first synthesized more than 100 years ago (Bennett, 1999). The EpiPen provides a dose of adrenaline through a spring-loaded needle that can penetrate the skin through clothing, allowing rapid administration in anaphylaxis. A hypodermic auto-injector was first patented in 1977. Although the EpiPen in its current form was first approved in 1987, it is covered by five patents on the drug delivery device that incrementally cover the auto-injector and the needle cover. Rights to commercialize EpiPen were acquired by a company in 2007. Prices were increased; in the United States, the price for a pack of two EpiPens was listed at US\$ 608 in 2017, a 500 per cent increase on the price in 2009.¹⁶³ There has been little competition in the field of auto-injectors. EpiPens are made of multiple parts, and it is difficult to achieve a reliable and sufficiently different design that does not infringe on the existing patents, especially when FDA rules standardized the way these devices work to mitigate the potential that the redesigned device will not meet clinical and safety needs. However, in 2018, the FDA issued draft guidance intended to streamline the approval of devices when the differences in design do not affect the clinical effect or safety profile.¹⁶⁴ The first generic alternative of the EpiPen was approved by the FDA in 2018.¹⁶⁵

Another example is asthma metered-dose inhalers (MDIs). In 2008, new US regulations required MDIs containing chlorofluorocarbon (CFC) propellants to be banned due to the effect of CFCs on the ozone layer. Leading up to the ban, new devices using hydrofluoroalkane (HFA) propellants were developed, approved and protected by patents. New HFA MDIs entered the US market at substantially higher prices than the older CFC MDIs, and mean costs increased (Gross, 2007; Jena et al., 2015).

An analysis of the effect of device patents found that, for device/medicine combination products in which the device is inseparable from the administration of the medicine, the additional protection provided for the medicine by the device patent, beyond patents on the medicine, was a median 4.7 years for products that had both device and medicine patents listed in the FDA Orange Book, and a median nine years for products that had only device patents listed (Beall et al., 2016).

As a final example, the devices used to administer naloxone, an emergency treatment for opioid overdose, are under increased demand due to the epidemic of opioid abuse. Two devices are available – an auto-injector (similar to the EpiPen) and a nasal spray. Both devices are originator products that are protected by numerous patents and do not have alternatives available in the US market.¹⁶⁶ In view of access concerns, in 2018, a municipal health department, together with a civil society group, requested that the US Government authorize production of generic versions of these products without authorization from the right holder under 28 U.S.C. §1498(a).¹⁶⁷

(ii) Evergreening

Concerns have been raised that patenting of new forms, or other minor variations, of existing products that have no additional therapeutic value and display limited inventiveness can be used to prolong patent protection in an inappropriate manner, thus creating a negative effect on access to medicines, as well as on further innovation – a strategy referred to as “evergreening”. The CIPIH defined evergreening as a term popularly used to describe patenting strategies “when, in the absence of any apparent additional therapeutic benefits, patent holders use various strategies to extend the length of their exclusivity beyond the 20-year patent term” (WHO, 2006a).

In reviewing the evergreening debate, the CIPIH commented that “demarcating the line between incremental innovations that confer real clinical improvements, therapeutic advantages or manufacturing improvements, and those that offer no therapeutic benefits is not an easy

task. But it is crucial to avoid patents being used as barriers to legitimate competition”. The CIPIH recommended that governments “take action to avoid barriers to legitimate competition by considering developing guidelines for patent examiners on how properly to implement patentability criteria and, if appropriate, consider changes to national patent legislation”.¹⁶⁸

The central issue is: when does an adaptation or modification of a first patented invention itself become separately eligible for a patent? In this respect, it is important to judge every individual invention claimed in a patent on its merits. The mere fact that an innovation is incremental is not a ground for refusing the granting of a patent. In fact, most innovation is incremental by nature, since technology normally progresses in incremental steps. In order to distinguish inventions that meet the inventive step/non-obviousness criterion from others that do not meet the criterion, patent law and practice have developed and established patentability criteria that need to be met before a patent can be granted.

Some health policy-makers argue that therapeutic efficacy should be used as an additional criterion to prevent evergreening and that patent protection for incremental innovations should be granted only if the invention provides sufficient additional therapeutic benefits. While the therapeutic value of a product as such is not a patentability criterion in most jurisdictions, therapeutic advantages over what exists in the prior art¹⁶⁹ may be considered when determining inventive step. Furthermore, any intention behind patent grant – for example, to build a defensive layer of additional patents to be used against competitors – is not a relevant criterion in the granting procedure. Post-grant measures such as exceptions and limitations to patent rights, and the regulation of licensing practices, can be applied to deal with undesirable effects of validly granted patents. Thus, a patent must be available if the patentability criteria of novelty, inventive step and industrial applicability, among others, are met.

In the context of a patent system, and to the extent that the evergreening debate concerns the grant of patents (rather than how patent rights are exercised by patent holders), the debate can be considered from two angles:

- How are the patentability criteria defined by the relevant national law and interpreted by case law and practice? Many countries have revised their legislation to adopt different types of measures. Section 3(d) of India's Patents Act 1970 (see Box 3.15) and Section 26.2 of the Philippines' Intellectual Property Code are two examples of a narrow definition of patentability criteria. Countries apply different approaches, however, and various definitions and practices exist in the granting of patents to pharmaceutical inventions (e.g. for claimed inventions relating to second medical use, dosage regimes, etc.). In 2001, Brazil introduced a "prior consent" system, meaning that the Instituto Nacional da Propriedade Industrial (National Institute of Industrial Property, Brazil) (INPI) could only grant patents for pharmaceutical products and processes when consent was given by the Ministry of Health's Agência Nacional de Vigilância Sanitária (National Agency for Sanitary Vigilance, Brazil) (ANVISA).¹⁷⁰ ANVISA developed guidelines limiting secondary patents. However, a 2017 resolution (following judicial decisions that ANVISA does not have authority to examine patentability requirements) now limits the assessment to be undertaken by ANVISA to the analysis of public health risk, such as a prohibited substance.¹⁷¹ In some cases, domestic patentability criteria may reflect a party's international obligations under FTAs. For example, under the Australia–United States FTA (AUSFTA), the parties confirm that patents shall be available in their respective jurisdictions for any "new uses or methods of using a known product".¹⁷²
- How are the patentability criteria applied by examiners? Some patent offices have set up search and examination guidelines as instruments to support the examiners' work, with a view to ensuring high quality of granted patents. Such guidelines need to be regularly revised and maintained. WIPO has published a collection of links to a range of patent offices' guidelines for easy access to this information.¹⁷³ Many patent offices, for example in Brazil, China, Germany, the United Kingdom and the United States, and EPO, have established examination guidelines for pharmaceutical inventions.¹⁷⁴ Guidelines for patent examiners along similar lines as Section 3(d) of India's Patents Act 1970 were adopted by Argentina in May 2012¹⁷⁵ and the Andean Community in 2004.¹⁷⁶ In addition, patent offices need to regularly train examiners and maintain a supportive infrastructure (e.g. prior art databases).

The impact of policies targeting secondary patents has been assessed in two separate studies, with one report concluding that there had been a rise in rejections of patent application in India based on Section 3(d) following the Supreme Court decision in 2017 (Ali et al., 2017). Another study found that India, as an example of a country with more restrictive criteria for granting secondary patents, does not show a significant difference in primary and secondary patent grant rates when compared with countries such as the United States and Japan, and the EPO, where secondary patents were found to be granted at a significantly lower rate than primary patents. According to the author of this study, the restrictions on secondary patents have therefore had little direct effect on patent examination outcomes.¹⁷⁷

One question that has been raised is whether this task of ascertaining whether incremental innovation that otherwise meets the criteria for patentability offers therapeutic benefits or deters competition should be assigned to patent offices or would better be determined by competition or health authorities (Yamane, 2011).

Leaving aside the question of patentability, it must be noted that the granting of a patent on an incremental improvement of a pharmaceutical is independent from the granted patent of the original product. Specifically, it does not extend the patent term of the earlier patent. While the improved form of the medicine will be covered by the new patent, the patent protection of the original version will end with the expiration of the first patent.

However, even if the patent on the original version has expired, and a generic version could be commercialized from the mere patent point of view, it still may not be possible to bring a generic to the market for regulatory reasons, including where regulatory exclusivities apply (see Chapter II, section A.6(f)).

Box 3.15: How India defines and applies patentability criteria

When revising its patent law to comply with the TRIPS Agreement requirement that pharmaceutical products be patentable, India adopted specific patentability criteria for chemical products by introducing Section 3(d) to its Patents Act (Patents Amendment Act 2005). Section 3(d) states: “the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant” is not an invention. Section 3(d) provides the following explanation: “For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy”.

In 2007, the Indian Patent Office, following an opposition filed by a patient organization, refused to grant a pharmaceutical company a patent for the cancer drug imatinib mesylate, based on Section 3(d). In 2013, the Indian Supreme Court rejected an appeal against this decision.¹⁷⁸ It held that, while Section 3(d) did not bar patent protection for all incremental inventions, the invention, in order to be patentable, had to pass the test of enhanced efficacy as provided in Section 3(d) read with its explanation. The beta crystalline form of imatinib mesylate was a new form of a known substance, imatinib, and lacked the enhancement in efficacy required under Section 3(d). The Supreme Court decided that “efficacy” under Section 3(d) of the Indian patent law was “therapeutic efficacy”, and stated that the term must be interpreted “strictly and narrowly.” As there was no evidence offered to indicate that imatinib mesylate would produce enhanced therapeutic efficacy as compared with imatinib, the appeal against the rejection of the patent application was unsuccessful.¹⁷⁹

In 2015, the High Court of Delhi noted that the purpose of Section 3(d) is to encourage incremental innovation in pharmaceuticals. Section 3(d) determined a threshold for what subject matter qualified as the same and what qualified as a new invention under Section 2(j) of the Patents Act. Where such derivatives are considered “the same” as a known substance under Section 3(d), they will, as a matter of course, be covered by any existing patent protection for that known substance.¹⁸⁰

Finally, research in Australia on who owns follow-on innovation patents found that substantial patenting activity is undertaken by companies other than the originator, including generic manufacturers, and that such third parties hold up to three quarters of secondary patents (Christie et al., 2013; Lloyd, 2013).

(c) Medical indication claims

Article 27.3(a) of the TRIPS Agreement allows countries to exclude from patentability diagnostic, therapeutic and surgical methods for the treatment of humans or animals. In some countries that have implemented this exclusion in their law, so-called medical indication claims have emerged in practice. Such claims must not cover the method of treatment but can claim an already known product for a new medical use.

When a previously known substance, used for a certain non-medical purpose, is later found effective in the treatment of a disease, a patent application may be filed claiming the known substance specifically for the use relating to the “first medical indication” (also called “second use” or “new use”) of the known product.¹⁸¹ If the first indication or earlier use of the known substance was already medical in nature, newly filed product claims

on that substance for another medical use are labelled “second medical indication”. Such claims, if granted because all patentability criteria under the applicable law have been met, protect an already known product for the specified medical use. The TRIPS Agreement does not expressly address this question. Patent laws differ on this point.

Some patent laws specifically rule out the patenting of first or second medical indication inventions. For example, the Andean Community Decision 486, the common IP law for the member states of the Andean Community, stipulates in Article 21: “Products or processes already patented and included in the state of the art [...] may not be the subject of new patents on the sole ground of having been put to a use different from that originally contemplated by the initial patent”.¹⁸² Section 3(d) of the Indian Patents Act (2005) provides that the “new use for a known substance” is not an invention, unless there is enhanced therapeutic efficacy.¹⁸³ The 2012 Patenting Guidelines in Argentina say that therapeutic treatment methods were not considered as industrially applicable; medical indication claims were not considered as fulfilling the novelty requirement; and Swiss-type medical claims (see in this section below) would be equivalent to a medical treatment method. Therefore, such inventions were not patentable.¹⁸⁴ The Patenting Guidelines of the

Philippines,¹⁸⁵ providing guidance on Sections 22 and 26 of the Intellectual Property Code, accept first, second and further medical use claims, stating that “this new technical effect of a known substance must lead to a truly new therapeutic application, which is the treatment of a different pathology”. The Guidelines require that second and further medical uses claims must be drafted in a Swiss-type claim format. The Guidelines note that the EPO has abandoned this type of claim format. The Intellectual Property Office of the Philippines has nevertheless decided to continue to accept Swiss-type claims for subsequent medical use claims, also to help the examiners distinguish subsequent medical use claims over first medical uses.

Some jurisdictions allow first, second and further medical indication claims. This is the case, for example, under Article 54(4) and (5) of the European Patent Convention (EPC) as revised in 2000 (referred to as EPC 2000).¹⁸⁶ In essence, these provisions state that the novelty requirement does not exclude the patentability of a known substance used for a new method for treatment or diagnostic.¹⁸⁷ The European Patent Office Enlarged Board of Appeal clarified that “where it is already known to use a medicament to treat an illness, Article 54(5) EPC does not exclude that this medicament be patented for use in a different treatment by therapy of the same illness”.¹⁸⁸ It should be noted that all other patentability criteria under the EPC must be met before a patent on a known substance for a new medical use can be granted. Such a patent, however, does not extend the patent protection covering the already known medical use.

Prior to the revision in 2000, the EPC allowed patent claims on a first medical indication, but not on further medical indications. In 1984,¹⁸⁹ the EPO Enlarged Board of Appeal accepted for the EPO the practice in Switzerland to grant claims in the following form: “the use of compound X in the manufacture of a medicament for the treatment of indication Y”. Such claims were called Swiss-type medical claims. They were process claims, covering the manufacturing process of a known medicine for a novel medical indication. These claims did not cover a method of treatment for the human or animal body, which is excluded from patentability under Article 53(c) of the EPC. With adoption of the EPC 2000, which allowed claims on further medical indications under the new Article 54(5), the Swiss-type claims became obsolete in Europe, and the Enlarged Board of Appeal decided that such claims would be no longer accepted for applications with a filing or priority date as of 29 January 2011.¹⁹⁰

As illustrated in the case of fluoxetine (see Box 3.16), prices can differ widely for the same active ingredient when it is sold as a different product to treat a different condition.

A 2018 UK Supreme Court decision may illustrate implications of medical indication patents for the generics industry.¹⁹¹ The case relates to the manufacture by generics of the so-called “skinny label” products, which are for the treatment of an off-patent indication, but prescribed by doctors, sold by pharmacists and used by patients for the indication that is still patent protected, and whether the generics manufacturers infringe the patent. The decision suggests that patent infringement requires that the manufacturer could reasonably foresee the use of the medicine for the protected purpose and wants this use. As a consequence, the “skinny label” products would not infringe the patent when there is no subjective intention of the manufacturer to infringe. In this particular case, no infringement was found, also because the defendant had made it clear that it did not intend to infringe the patent by applying for a market approval explicitly excluding the patented indications and by sending warnings to pharmacies and related institutions not to prescribe and sell the medicine for the patent-protected indications.

The patentability of first, second and further medical indications is a matter of debate, and therefore exemplifies the continuing challenge in patent law of balancing access against innovation. On the one hand, opponents of medical indication patents argue that such patents impede access to medicines, reward uninventive activities and unnecessarily prolong effective patent protection for a certain medical substance. On the other hand, proponents express the view that an additional medical use can itself be inventive, and that the development and clinical testing of a second use is no less in need of incentives than the first use, and, in some cases, may be more therapeutically valuable than the first use.

Box 3.16: Second use patents: the case of fluoxetine

Fluoxetine (better known as “Prozac”) was first marketed in the United States in 1987 for the treatment of depression, and its US base patent expired about 14 years later, in 2001. However, fluoxetine was discovered to also be useful in the treatment of a second indication, premenstrual dysphoric disorder. A pharmaceutical company obtained a patent on this second use in 1990 (United States Patent No. 4,971,998) and secured regulatory approval for this indication in 2000 under the trade name Sarafem. Although both medicines contain the identical active ingredient (fluoxetine hydrochloride), at an identical dosage level (20 mg), the prices differ widely in the United States; in one pharmacy, it was found that Prozac was US\$ 0.83 per pill, while Sarafem was US\$ 9.26 per pill.

5. Post-grant issues: questions related to the use of patents

Once a patent has been granted, certain legal and practical considerations determine how it influences and impacts on the development and dissemination of the patented technology. These include options for defining the legal scope of patent rights, and approaches to their licensing. This section outlines several of these considerations that are most relevant to product development.

(a) Research exception

A research exception or experimental use exception is one of the most commonly used types of “limited exceptions” to national patent laws pursuant to Article 30 of the TRIPS Agreement. A WTO dispute settlement panel has defined the term as “the exception under which use of the patented product for scientific experimentation, during the term of the patent and without consent, is not an infringement”.¹⁹² This exception enables researchers to examine the patented inventions and to research improvements without having to fear that they are infringing the patent.

Many countries provide varying levels of exceptions for acts carried out for experimental purposes or scientific research. In general, the scope of the exception can be defined through the purpose of the research or experiment, whether it allows an experiment or research with a commercial intent, and/or how the experimental act related to the patented invention (i.e. whether it allows for research *with* or *on* a patented invention).¹⁹³

Some countries limit the exception to acts carried out without commercial or gainful intent. For example, in the United States, the US Court of Appeals for the Federal Circuit held in *Madey v. Duke University*¹⁹⁴ that using a patent without the consent of the patent holder in order to further the “infringer’s legitimate business interests” was to be considered patent infringement.

Some countries apply the research exception only to acts that explore how the invention works or seek to further improve the invention, and this is often referred to as “research on the invention”.¹⁹⁵ In these countries, using the patented invention to perform research on a different subject matter, also called “research with the invention” is not covered by the research exception. This distinction is particularly relevant for the discussion on research tools (see subsection (b) below).

Some countries define that acts, such as studies, undertaken to obtain market approval for medical technologies fall under the research exception (see Chapter IV, section C.3(a)(i)).¹⁹⁶

Where a research exception is not wide enough in a particular jurisdiction to allow research for a follow-on product, such as use of a patented research tool (see subsection (b) below), the researcher needs to obtain a licence on terms to be mutually agreed. Alternatively, compulsory licensing may allow such downstream research, subject to compliance with the requirements under the applicable national law.¹⁹⁷

The SCP identified 113 countries that provide for research exceptions.¹⁹⁸ Replies to a questionnaire from WIPO member states and regional offices provide information on various national practices regarding the experimental use and scientific research exception.¹⁹⁹

(b) Research tools

Historically, the discussion of research exceptions has largely concerned biotechnology research tools. Patentable biotechnological inventions are not necessarily end products such as new drugs, but can be “upstream” research tools that are essential for the development of “downstream” pharmaceutical products. Research tools are resources used by scientists to facilitate an experiment or produce a result. Research tools can be research techniques (e.g. gene-editing tools such as CRISPR-Cas and DNA amplification techniques), research consumables (e.g. enzymes or reagents) or research targets (e.g. genetic material used for new drugs or vaccines). Where technologies comprise DNA sequences, genetic researchers often have no way to invent around them. For example, expressed sequence tags are tiny portions of an entire gene that can be used to help identify unknown genes and to map their positions within a genome. Polymerase chain reaction is a well-known research tool or technique used to amplify small segments of DNA. Broad patenting of these types of inventions may disadvantage those wishing to use them to develop other products, while narrower claims may allow their downstream use.

Where a research exception exists (see subsection (a) above), it does not necessarily apply to use of patented research tools in all circumstances. In a number of countries, the research exception is restricted to experimental acts that are related to the subject matter of the patented invention or experimental acts *on*²⁰⁰ the patented invention, and they do not except research with the protected tool.²⁰¹ In Belgium, the text of the research exception provision states that the exception applies to “[...] acts accomplished for scientific purposes on and/or with the subject matter of the patented invention”.²⁰² Switzerland has introduced a right to a non-exclusive licence with regard to the use of research tools, for example, for cell proliferation in the field of biotechnology.²⁰³ The Appendix of WIPO document SCP/29/3 compiles various legal provisions on the research exception.²⁰⁴

Without the freedom to use research tools through exceptions to patent rights, licensing is key to enabling access to relevant technologies. While patent holders are entitled to set the terms of the licence, the scope of these terms can sometimes be restrictive.

In the United States, the NIH wants to ensure both broad access to research tools that have been developed using public funds and the preservation of opportunities for product development. To this end, the NIH promotes licensing policies that realize both product development and availability of new research tools to the scientific community.²⁰⁵ In addition, US law requires that a federal agency may only grant an exclusive or partially exclusive licence on a federally owned invention if “the public will be served by the granting of the license, as indicated by the applicant’s intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention’s utilization by the public, and that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention’s utilization by the public”.²⁰⁶

In the case of CRISPR, each of the key patent holders (some being publicly funded) have out-licensed their rights to spinoff companies that can then licence the technology exclusively in specific areas, including human therapeutics and CAR T-cell therapy, to commercial partners. As a result, while CRISPR is freely available as a research tool for academic research, broad exclusive licences are granted by the spinoff companies to other licensees, such as biopharmaceutical companies. However, these companies do not always have the capacity to work on the full range of gene targets that are included in these broad exclusive licences. This can have a negative impact on competition and create innovation bottlenecks for drug discovery and development (Contreras and Sherkow, 2017).

(c) Licensing and assignment with respect to innovation

A patent owner may lack the resources to exploit an invention and to scale up from the laboratory research stage to bring a product to market. The resources required to develop a product include the skills, facilities and capital to conduct further research; carry out tests, trials and production engineering; obtain regulatory approval; and then manufacture, market and distribute the final product. The ingenuity and competitive edge of an invention alone are not sufficient to ensure its successful implementation. In this situation, a public- or private-sector patent owner must consider whether it is in its best interests to assign the technology or to license it to another party who can develop it. Each choice offers

different degrees of control over the technology and may yield different levels of return and health benefits.

A patent assignment may include sale, or transfer free of compensation, to a PDP, for example. An assignment entails a loss of control over the technology. In general, an assignment at an earlier stage of R&D offers a lower return to the assignor than at a later stage, as the assignee is typically assuming greater uncertainty and risk. The assignor may assume obligations to provide technical advice for a certain period.

Patent licences vary in scope. An exclusive licence guarantees that the licensee will have no competition in the production and distribution of the given product, not even from the licensor. Licences can be restricted to a particular territory, and can allow or prohibit sublicences. A non-exclusive licence allows the licensor to grant other licences to other parties in the contractual territory. Licences can also be restricted to particular fields of use. This allows a licensor to grant a licence to the same patent or related patents to different parties in different fields. Patents for medical technologies are often suitable for field-of-use licences because such technologies often have multiple uses. For example, the same technology can be applied to diagnostic and therapeutic uses with respect to the same disease or different diseases. Field-of-use licensing grants the licensor greater freedom to deal with the patent with other parties in other fields of use and extract greater returns. Licences can also include options to commercialize additional compounds or fields of use that could allow the licensee to integrate additional products into its pipeline. The return from a licensee to the licensor depends on the objective of the licensor and the licensee, the degree of exclusivity, size of contractual territory, restrictions on use, options included and the duration of the licence, as well as the value of the technology itself. Alternatively, technology can be voluntarily shared, even without a formal licensing arrangement.

A licensing strategy covers an entity’s inputs as well as its outputs in the product development process. The strategy determines, in line with the entity’s overall objectives, what licensing models are to be pursued, and to what end. Public-interest IP management can promote innovation by granting licences on non-exclusive terms or, where exclusive licensing is necessary to promote further development, it can restrict the licensed field of use to reserve other areas of research that may use the same technology.²⁰⁷

(d) Patents in R&D agreements and other forms of collaboration

Medical technologies are developed through a diverse spectrum of forms of collaboration that have implications

for access post patent grant. At one end of the spectrum, traditional public-sector research places all results in the public domain, where they are freely available for use by others involved in product development. At the other end of the spectrum is the conventional vertically integrated private-sector business model, which involves conducting R&D in-house within a single company group, exercising exclusive rights to prevent its use by others, thus furthering the company's own commercial interests. Increasingly, few pharmaceutical companies have the capacity to operate in a fully integrated and entirely exclusive manner.

Between these two extremes, new forms of commercial collaboration can be found. They combine different inputs in order to deliver a complex product such as a new drug or vaccine. In the field of biotechnology, there are frequently several different licensors and other right holders by the time the final product is ready for market. Patent rights can also be leveraged in other, non-conventional ways, such as to enable access to improvements and developments of licensed technologies through open source or public health patent pools and also through commercial patent pools that enable competitors to develop products based on shared pre-competitive technology platforms (see the discussion of innovation structures in section B.4).

Collaborative research partnerships often broach the divide between the public and private sectors with research being undertaken through collaborative PPPs involving industry and universities. Increasingly, these research collaborations take place across borders and the management of IP can become more complex when dealing with multiple jurisdictions. In the United Kingdom, model agreements have been developed to support these forms of collaboration.²⁰⁸ A Fast Track Model Agreement was also produced by Public Health England to evaluate potential treatment options for Ebola and Zika virus diseases and to share the results with stakeholders for a coordinated global response.²⁰⁹

(e) Patent clusters and patent thickets

There is no generally agreed definition of the term "patent thicket". One author describes a patent thicket as a "dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology" (Shapiro, 2001). In such a situation, multiple patent rights owned by different parties have to be considered by competitors as well as new entrants into a market within that field of technology. Eventually, they must negotiate multiple licence agreements, and this may present difficulties and impede the implementation of a project. The European Commission has identified the creation of "patent clusters" by filing numerous additional patents for the

same medicine as a common strategy employed by pharmaceutical companies (European Commission, 2009). Companies reportedly file a significant number of these additional patents on variations of the same product, especially for blockbuster medicines, very late in the life cycle of a medicine, when the main patent is about to expire.²¹⁰ The Commission found that these patent clusters make it more difficult for generic competitors to evaluate whether they can develop a generic version of the original medicine without infringing one of the numerous patents filed around one medicine. The number of patents also increases the risk of potentially costly litigation for generic companies.

Patent thickets have been observed for complex technologies, such as information and communications technology (ICT) and pharmaceuticals. They can arise in technical fields where a number of companies compete at the same level and where patent ownership is fragmented. Key issues that have been highlighted with respect to patent thickets include: the high density of patents potentially impeding R&D; high, possibly excessive, licensing costs; refusal of the patent holder to grant a licence; and difficulties associated with inventing around a patent (IPO, 2011).²¹¹

Cross-licensing agreements have been proposed as a solution. However, some have argued that this measure could aggravate the issue, as it could induce competing companies to obtain larger numbers of patents in order to improve their bargaining capacity. Patent pools have also been suggested as a way to address transaction costs.²¹²

Empirical studies of patent thickets show varied results. One study found that, among academic researchers in the biomedical field, 3 per cent had abandoned a project during the preceding three years due to too many patents covering their particular research field. The study found that access to tangible research input was more problematic, as 20 per cent of academic-to-academic requests were refused.²¹³ Another study found that 40 per cent – including 76 per cent of those in the biosciences industry who responded to the survey – considered that their research was affected by difficulties in accessing patented technologies. Of these respondents, 58 per cent reported delays, 50 per cent reported changes in their research plans and 28 per cent had abandoned their research. The most common reason for changing or abandoning the research was overly complex licensing negotiations (58 per cent), followed by high individual royalties (49 per cent).²¹⁴

(f) Freedom-to-operate issues

This subsection briefly sketches the issues involved in a freedom to operate (FTO) analysis.²¹⁵

(i) Defining freedom to operate

FTO assessments are important in deciding whether to initiate or continue with R&D projects, or use or market new products. An FTO assessment is based on a legal opinion on whether the making, using, selling or importing of a specified product is free from potential infringement of third-party IP or tangible property rights. Managers use FTO analysis when making risk-management decisions in relation to R&D, product launch and commercialization. However, FTO does not mean an absolute freedom from any risk of infringing another party's IP. It is a relative assessment based on analysis and knowledge of IP landscapes for a given product, in a given jurisdiction, at a given point in time.

(ii) Freedom-to-operate strategies

The decision to undertake an FTO analysis, and to commission an FTO opinion from legal counsel or a patent attorney, is based on a preliminary risk assessment. FTO considerations are relevant at all stages of the product development cycle. In practice, however, carrying out a detailed FTO analysis and legal opinion on every product or process early in the pipeline would be impractical. This is because the detailed specifications of the product could not be known to a sufficient degree of detail and certitude. On the other hand, obtaining any needed licences at a late stage in the development process runs the risk that either no licence would be obtained or the conditions would be unfavourable and thus the bargaining flexibilities would be reduced. In addition, there could be a risk of becoming involved in a lawsuit for IP infringement.

Negotiating a licence is a straightforward way to obtain the consent of the right holder for the intended commercial activity. This approach may have the advantage of focusing on mutual interests in a deal in a way that proves beneficial for all parties. Licences may include additional information, such as know-how, regulatory data, trade secrets and trademarks. Agreements may include up-front payments, milestone payments or royalty rates, or a combination of all three, or they may be in the form of a cross-licence, whereby the licensees and the licensor grant each other certain rights. Licences may also include – and indeed frequently do – grant-backs for improvements, options on new inventions and the mutual sharing of new data. These options may be particularly relevant if long-term collaboration is sought and if further research has the potential to lead to improvements in the licensed/protected technology.

However, licence negotiations may not always lead to the desired agreement, even if a potential licensee has made reasonable efforts to obtain a licence. In such situations, a compulsory licence is a route that could possibly be explored.²¹⁶

Instead of seeking a licensing agreement or a compulsory licence, another viable strategy could be to aim to have the “blocking” patent invalidated. The blocking patent may have been granted erroneously and could therefore be challenged and invalidated. However, going into litigation can be costly and lengthy, and the outcome is often uncertain.

An additional option would be to seek a non-assertion covenant, in which a right holder confirms in a public statement that the rights will not be enforced under certain circumstances or in certain defined fields or geographies. Such agreements may be particularly relevant for “humanitarian” licensing aimed at responding to socio-economic needs. In addition, these agreements deliver the added benefit of ensuring that product liability issues are simplified (Krattiger, 2007b).

Instead of pursuing available legal options, the company may adapt the project to the IP situation. One such option could be to modify the product in such a way that no licence would be required. Such a strategy works if available alternatives exist and if the different options are analysed at an early R&D stage (i.e. when it may be easier to modify the product). The lack of alternative options may serve to incentivize further research to find a new solution for the project. Inventing around may delay product development but can lead to new inventions – and perhaps even better products – thus resulting in new IP for cross-licensing. On the other hand, inventing around may increase costs.

A review of available legal, research and financial options may lead to a decision to abandon the project. The alternative, electing to overlook existing patents and awaiting a choice by the patent holder whether or not to enforce their rights, could result in additional financial loss – particularly if there is a successful claim for damages based on knowing infringement.

Finally, FTO issues can also be resolved through M&A of competing companies.

The process of developing a sound strategy for securing FTO should consider all options, and decisions should be based on the assessment of the risks of each option in relation to the institutional context, product type and market dynamics. In practice, several options are typically pursued concurrently.

An FTO opinion provides only a snapshot of the IP related to a product at a given point in time. The patent landscape changes as patent applications are filed, and as patents are granted, expire or are invalidated. Therefore, strategies need to be regularly revised, and tactics need to be adapted in response to changing circumstances.

E. Sharing of influenza viruses and access to vaccines and other benefits

Key points

- The WHO Pandemic Influenza Preparedness (PIP) Framework for the Sharing of Influenza Viruses and Access to Vaccines and other Benefits provides a global approach to the sharing of influenza viruses with pandemic potential. It also enables the sharing of benefits derived from such viruses, including the management of related intellectual property (IP).
- The Standard Material Transfer Agreements (SMTAs) agreed under the PIP Framework stipulate that participating laboratories should not seek to obtain intellectual property rights (IPRs) on PIP biological material. In addition, these agreements provide for a range of options for biological material recipients, such as influenza vaccine manufacturers, to enter into benefit-sharing agreements.

A highly significant development in itself, given its central role in preparing for a potential pandemic, the PIP Framework serves to illustrate many of the points made in earlier sections of this chapter relating to the role of public-sector institutions and networks, capacity-building in medical innovation, sharing of benefits of the fruits of innovation, and dealing with IP in a public health context.

1. WHO Global Influenza Surveillance and Response System

The WHO Global Influenza Surveillance and Response System (GISRS) (formerly known as the Global Influenza Surveillance Network) was created in 1952 to advise WHO member states on influenza control measures. This system monitors the evolution of seasonal influenza viruses and other subtypes of influenza viruses that infect humans sporadically. Among its many responsibilities, the GISRS selects and develops candidate influenza viruses for development and production of seasonal and other influenza vaccines, including pandemic vaccines. The GISRS also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential (IVPP). Its activities have contributed greatly to the understanding of influenza epidemiology, and have facilitated effective, internationally coordinated responses to outbreaks of seasonal, H5N1, H7N9 and other influenza virus subtypes with pandemic potential.

The GISRS comprises different categories of laboratories with national influenza centres (NICs)²¹⁷ forming its backbone. Under their WHO terms of reference, NICs are requested to regularly ship representative clinical specimens/virus isolates to WHO collaborating centres²¹⁸ for in-depth antigenic and genetic analyses. To fulfil its role as a global alert mechanism for the emergence of IVPP, the GISRS relies on its members to share IVPP in a timely manner.

The re-emergence of highly pathogenic avian influenza A(H5N1) in 2003 highlighted the risk of an influenza pandemic. The inability of developing countries to secure safe and affordable access to pandemic vaccines was underscored by the global limitation of influenza vaccine production capacity. In early 2007, this situation prompted one country to announce that it would stop sharing its A(H5N1) viruses with the GISRS until it:

- Provided greater transparency of its activities
- Enabled increased access by developing countries to the benefits derived from the use of such viruses, notably vaccines.

This led to the adoption by the May 2007 World Health Assembly (WHA) of a resolution (WHA60.28) that became the basis for negotiations on a framework for the sharing of influenza viruses and other benefits.²¹⁹ Two issues were central to the discussions:

- Improving the transparency of the activities of the GISRS
- Improving fairness and equity of access to influenza vaccines and other benefits derived from the work of the laboratories in the WHO system.

2. Intellectual property rights in the context of PIP negotiations

The role of patents and, more specifically, the rules regarding what the GISRS laboratories should, or should not, do with respect to seeking patent protection on inventions developed with viruses contributed to the GISRS were core issues throughout the negotiation process. Technical papers prepared by the WHO in response to a request by member states found that: "There are no significant patent barriers to the manufacture of any of the marketed types of influenza vaccines. Some patents protect specific processes or products, but for each of the types of

Box 3.17: WIPO Patent Search Report on PIP-Related Patents and Patent Applications

The patent search report highlights several critical points:

- In the pool of patent information assembled and analysed in this report, no patent documents were identified that included claims having, as a sole and/or single element, either a complete native virion, a native viral strain, a native viral genome in its entirety, or a complete assembled complement of native viral proteins from a specific virus.
- The report discusses in detail certain patent families, represented by patent applications, where the scope of the claims is broad and could potentially be construed as covering known viral sequences, processes and compositions of matter. It is well established that issued patents frequently have narrower claims than the corresponding patent applications. Therefore, the scope of the claims in the patent applications identified and analysed in this search may very well be restricted during the patent application prosecution and grant process.
- While some patent applications from members of the WHO Global Influenza Surveillance Network are identified as falling within the scope of the search, the report does not analyse the extent to which collaborations, licences and technology transfer are taking place between these and other entities, including between and among developed and developing countries.
- A number of patent applications were identified from companies based in industrialized countries that are now co-owned by companies in developing countries. This is arguably one form of technology transfer and should be seen in the light of emerging models that facilitate broad access to new technologies, including in health, by developing countries.²²⁰

marketed vaccines, there is sufficient freedom to operate to permit manufacturers in developing and emerging economies to make the vaccine of their choice. For future vaccines based on new technologies, there are potential intellectual property barriers; however, it is not known which, if any, of those technologies could make marketable vaccines that could be sustainably produced".²²¹

In order to provide further information on patenting activity related to IVPP, the WHO, based on Resolution WHA60.28, requested WIPO to prepare a working paper on Patent Issues Related to Influenza Viruses and Their Genes, in 2007.²²² In 2011, upon request from WHO member states, WIPO presented a patent search report on PIP-related patents to the WHO Open-Ended Working Group of Member States on Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and other Benefits (see Box 3.17).

3. The PIP Framework

The PIP Framework was established in 2011²²³ to provide a global approach to the sharing of IVPP for risk assessment and response, including vaccine development, and the sharing of benefits derived from such viruses. The scope of the Framework is limited to IVPP and does not cover seasonal influenza, though discussions are ongoing as to whether its scope should be expanded to include it (WHO, 2018a). The Framework defines the materials covered under it as "PIP biological materials", meaning, in summary, IVPP samples, IVPP modified by GISRS laboratories, human clinical specimens and certain IVPP genetic material.²²⁴

The PIP Framework operates with two Standard Material Transfer Agreements (SMTAs):

- SMTA 1 governs sharing of PIP biological materials within the GISRS, that is, between NICs and WHO collaborating centres. SMTA 1 specifies terms and conditions for transferring viruses within the GISRS and allows onward transfers of the PIP biological materials only if the prospective recipient outside the GISRS has concluded an SMTA 2 with the WHO. Article 6.1 of SMTA 1 requires that neither the provider nor the recipient should seek to obtain any IPRs on PIP biological materials.
- SMTA 2 governs transfer of materials to recipients outside the GISRS. An SMTA 2 is concluded between the WHO and the prospective recipient and defines rights and obligations of the SMTA 2 parties. For example, it allows recipients of PIP biological material any further transfer of that material to a third party only if that third party has also concluded an SMTA 2 with the WHO.²²⁵ Article 4.1 of SMTA 2 sets out a list of options for benefit-sharing and requires the recipient to commit to at least two of them (see Table 3.5).²²⁶ In this manner, the Framework provides opportunities for IP holders to share IP related to pandemic influenza preparedness or response. It does not, however, compel them to do so.

In accordance with Section 6.14.3 of the PIP Framework, manufacturers using the GISRS pay annual cash partnership contributions to the WHO. The PIP Secretariat uses a set of standard operating procedures to identify manufacturers using the GISRS and divide payment of the partnership contributions among companies.²²⁷

Table 3.5: Summary of benefit-sharing options under SMTA 2

	CATEGORY A (Select 2/6)	CATEGORY B (Select 1/6)	CATEGORY C (Consider)
1	Donate % of real-time vaccine production to WHO	Donate diagnostic kits to WHO	Consider contributing to the measures listed below, as appropriate: <ul style="list-style-type: none"> • Donations of vaccines • Donations of pre-pandemic vaccines • Donations of antivirals • Donations of medical devices • Donations of diagnostic kits • Affordable pricing of pandemic products • Transfer of technology and processes • Granting of sublicences to WHO • Laboratory and surveillance capacity-building.
2	Reserve % of real-time vaccine production at affordable pricing to WHO	Reserve diagnostic kits at affordable pricing to WHO	
3	Donate antivirals to WHO	Support laboratory and surveillance capacity-strengthening	
4	Reserve antivirals at affordable pricing to WHO	Support transfer of technology, know-how and/or processes	
5	Licence on technology, know-how, processes or products needed for the production of influenza vaccines, antivirals or adjuvants to developing-country manufacturers, on mutually agreed fair terms	Licence on technology, know-how, processes or products needed for the production of influenza vaccines, antivirals or adjuvants to developing-country manufacturers, on mutually agreed fair terms	
6	Royalty-free licence to developing-country manufacturers or WHO for production of influenza vaccines, antivirals or adjuvants	Royalty-free licence to developing-country manufacturers or WHO for production of influenza vaccines, antivirals or adjuvants	

Source: WHO, available at: www.who.int/influenza/pip/benefit_sharing/SMTA2BenefitSharingOptions.pdf?ua=1.

As of December 2019, implementation of the Framework has enabled the WHO to secure more than 400 million doses of pandemic vaccine under the SMTA 2 benefit-sharing mechanism, and to collect more than US\$ 198 million through partnership contributions,²²⁸ which has been used to strengthen pandemic response capacities, including laboratory, surveillance, regulatory and risk communications.²²⁹

WHA Decision 70(10) has reaffirmed the importance of the PIP Framework in addressing present or imminent threats to human health from influenza viruses with pandemic potential, and emphasized its critical function as a specialized international instrument that facilitates expeditious access to influenza viruses of human pandemic potential, risk analysis and the expeditious, fair and equitable sharing of vaccines and other benefits.²³⁰ A “specialized international instrument” is addressed in Article 4.4 of the Nagoya Protocol²³¹ (see Chapter II, section D.4 and Box 2.21). The provision stipulates that, where a specialized international access and benefit-sharing (ABS) instrument applies that is consistent with, and does not run counter to, the objectives of the CBD and the Nagoya Protocol, the Protocol does not apply for the party or parties to the specialized instrument in respect of the specific genetic resource covered by and for the purpose of the specialized instrument. In November 2019, parties to the Nagoya Protocol were still considering potential criteria for the identification of a specialized international ABS instrument and any process for recognition of such an instrument.²³² The European Union Regulation on compliance measures for users from the Nagoya Protocol considers that the PIP Framework “constitutes a specialised international access and benefit-sharing instrument

that is consistent with the Nagoya Protocol and that should not be affected by the rules implementing the Nagoya Protocol”.²³³

4. The PIP Framework and genetic sequence data

The role of genetic sequence data (GSD) in the PIP Framework is a matter of ongoing debate among WHO member states.²³⁴ GSD can be used to analyse or synthesize physical material to develop influenza products. With the development of technology in vaccine manufacture, it is expected that, in the future, it will increasingly become possible to develop and manufacture vaccines based on GSD alone, that is, without needing access to biological materials (WHO, 2018a).

GSD are not included in the definition of PIP biological material.²³⁵ Hence, manufacturers using GSD that were developed by, or provided through, the GISRS are not required to sign an SMTA 2. However, payment of the partnership contribution is required by the PIP Framework itself for any use of information, including GSD, provided through the GISRS. Therefore, manufacturers who have received GSD, but not PIP biological material, from the GISRS must pay the partnership contribution, but would not be obliged to share benefits, for example, to share a new product with the WHO in the event of a pandemic (WHO, 2018a). The development of technology that allows development and manufacture of vaccines based on GSD alone may thus present a loophole in the PIP Framework. Discussions are under way on whether and how to make changes to the Framework in respect of these considerations (WHO, 2018a).

Endnotes

- 1 Gaudillière, 2008; Bud, 2008; Cassier and Sinding, 2008; Mowery and Sampat, 2001a; Mowery and Sampat, 2001b.
- 2 WIPO, 2015c, p. 69.
- 3 Ibid., p. 70.
- 4 Sampat, 2015, p. 19.
- 5 This section is largely based on Temin, 1979.
- 6 Streptomycin was introduced commercially in 1946 under a patent granted in 1948. However, scientists at Rutgers University who were involved in the discovery of streptomycin convinced the originator company to license it on an unrestricted basis at a royalty rate of 2.5 per cent and to assign the patents to the Rutgers Research Foundation. In the United States, competition drove down the price of streptomycin from US\$ 4,000 per pound to US\$ 282 per pound by 1950.
- 7 See *Pfizer Corporation v. Ministry of Health, Reports of Patent, Design and Trade Mark Cases* 1965, 82(8), 12 August: 261–321.
- 8 See <https://pubs.acs.org/cen/coverstory/83/8325/8325social.html>.
- 9 Figures in the graph are drawn from: US Food & Drug Administration, Summary of NDA Approvals & Receipts, 1938 to the present, available at: <https://www.fda.gov/about-fda/histories-product-regulation/summary-nda-approvals-receipts-1938-present>; US Food & Drug Administration, Center for Drug Evaluation and Research (2019), *Advancing Health Through Innovation: 2018 New Drug Therapy Approvals*, available at: <https://www.fda.gov/media/121483/download>; author's calculation based on monthly data published by US Food & Drug Administration, Original New Drug Application (NDA and BLA) Approvals, available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=reportsSearch.process&rptName=2&reportSelectMonth=12&reportSelectYear=2017&nav#navigation>.
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- 173 See <https://www.wipo.int/patents/en/guidelines.html>.
- 174 See WIPO document SCP/30/4, Further Study on Inventive Step (Part III), available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_30/scp_30_4.pdf.
- 175 Joint Resolution 118/2012, 546/2012 and 107/2012 (Ministry of Industry, Ministry of Health and National Industrial Property Institute) of 5 May 2012, published in Official Gazette of 8 May 2012.
- 176 Manual para el examen de solicitudes de patentes de invención en las oficinas de propiedad industrial de los países de la Comunidad Andina, developed by the Andean Community, EPO and WIPO, 2004, available at: http://www.comunidadandina.org/StaticFiles/201166165925libro_patentes.pdf and from the industrial property offices of Bolivia, Colombia, Ecuador, Peru and Venezuela, see https://www.wipo.int/wipo_magazine/en/2005/02/article_0008.html.
- 177 Sampat and Shadlen, 2016; see also Shedlen (2018).
- 178 *Novartis AG v. Union of India & Ors.* (2013) 6 SCC 1, 1 April 2013.
- 179 *Ibid.*, paras. 180, 187–190.
- 180 *F. Hoffmann-La Roche Ltd & Anr v. CIPLA Ltd*, RFA(OS) 92/2012 and *CIPLA Ltd v. F.Hoffmann-La Roche Ltd & Anr*, RFA(OS) 103/2012, paras. 71–74.
- 181 The issue of novelty is addressed in Chapter II, section B.1(b)(iii).
- 182 See <https://wipolex.wipo.int/en/legislation/details/9451>.
- 183 Section 3(d) of the Patents Act (2005) as amended excludes from the definition of “invention” the “mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant”.
- 184 New guidelines for examining chemical-pharmaceutical patent applications, effective as of 9 May 2012 and applicable to all pending and new patent applications, were issued in Argentina (Joint Regulation Nos. 118/2012, 546/2012 and 107/2012 issued on 2 May 2012 by the Argentine Patent Office together with the Ministries of Industry and of Health, published in the Official Gazette on 8 May 2012), available at <https://www.boletinoficial.gob.ar/detalleAviso/primera/69099/20120508>. See Anexo 4) - Considerando características farmacotécnicas (xii) - Segunda indicación médica (Nuevos usos médicos).
- 185 Revised guidelines on the examination of pharmaceutical applications involving known substances, available at: <https://www.ipophil.gov.ph/services/patent/patent-examination-guidelines/>.
- 186 See <https://www.epo.org/law-practice/legal-texts/epc.html>.
- 187 Some guidance about granting of patents by the EPO for first or further medical use of known products can be obtained from the guidelines for patent examination of the EPO, available at: https://www.epo.org/law-practice/legal-texts/html/guidelines/eg_vi_7.htm.
- 188 G 0002/08 (Dosage regime/ABBOTT RESPIRATORY) of 19 February 2010.
- 189 EPO Enlarged Board of Appeal of 5 December 1984, G 0005/83 (Second medical indication), available at: <https://www.epo.org/law-practice/case-law-appeals/recent/g830005ep1.html>.

- 190 See Notice from the European Patent Office dated 20 September 2010 concerning the non-acceptance of Swiss-type claims for second or further medical use following decision G 2/08 of the Enlarged Board of Appeal, available at: <https://www.epo.org/law-practice/legal-texts/official-journal/2016/etc/se4/p258.html>.
- 191 *Warner-Lambert Company LLC v Generics (UK) Ltd t/a Mylan and another* (2018) UKSC 56, available at: <https://www.supremecourt.uk/cases/uksc-2016-0197.html>.
- 192 See *Canada – Pharmaceutical Patents* (DS114).
- 193 WIPO SCP/29/3: https://www.wipo.int/edocs/mdocs/scp/en/scp_29/scp_29_3.pdf, Annex II, p. 10.
- 194 *Madey v. Duke University*, 307 F.3d 1351 (Fed.Cir. 2002).
- 195 See WIPO document SCP/20/4, paras. 36–40, available at: https://www.wipo.int/edocs/mdocs/patent_policy/en/scp_20/scp_20_4.pdf.
- 196 WIPO document CDIP/5/4, Annex II.
- 197 See Chapter IV, section C.3(a)(ii)–(iii).
- 198 WIPO document SCP/29/3, para. 17.
- 199 See www.wipo.int/scp/en/exceptions.
- 200 Refer to subsection (a) above for further explanation on the distinction between “research on” and “research with” a patented invention.
- 201 The following countries outline that research exceptions only apply to research “on” or relating to the patented invention: Albania; Dominican Republic; Germany; Hong Kong, China; Kyrgyz Republic; the Netherlands; Norway; Russian Federation; Switzerland and Tajikistan. See WIPO SCP/29/3, available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_29/scp_29_3.pdf.
- 202 Article XI.34. §1 er. of the Law of 19 April 2014 of Belgium.
- 203 Article 40b, Swiss Patent Law, <https://www.admin.ch/opc/en/classified-compilation/19540108/index.html>.
- 204 Appendix, WIPO SCP/29/3, available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_29/scp_29_3.pdf.
- 205 See Department of Health and Human Services, National Institutes of Health, Principles and Guidelines for Recipients of NIH Research Grants and Contracts and Obtaining and Disseminating Biomedical Research Resources: Final Note (1999), p. 72093, available at: https://grants.nih.gov/grants/intell-property_64FR72090.pdf.
- 206 35 U.S.C. §209. Licensing federally owned inventions, available at: <https://www.law.cornell.edu/uscode/text/35/209>.
- 207 The WIPO SCP has organized sharing sessions on licensing issues. In SCP 30, the WIPO Secretariat and a number of relevant institutions shared their experiences on capacity-building activities relating to negotiating licensing agreements. The Report of the Sharing Session on 24 June 2019 is available at: https://www.wipo.int/meetings/en/doc_details.jsp?doc_id=455117; all presentations are available at: https://www.wipo.int/meetings/en/details.jsp?meeting_id=50419. In SCP 32, a sharing session discussed challenges and opportunities in relation to types of patent licensing provisions in health-care technologies. Information about the WIPO SCP is available at: <https://www.wipo.int/policy/en/scp/>.
- 208 See <https://www.gov.uk/guidance/model-agreements-for-collaborative-research>.
- 209 See <https://www.gov.uk/guidance/university-and-business-collaboration-agreements-lambert-toolkit#fast-track-model-agreement>.
- 210 See <http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/>.
- 211 WIPO document SCP/12/3 Rev.2.
- 212 Ibid.
- 213 See Reaping the Benefits of Genomic and Proteomic Research, National Academy of Science, quoted after WIPO document SCP/12/3 Rev.2, available at: https://www.wipo.int/edocs/mdocs/scp/en/scp_12/scp_12_3_rev_2.pdf.
- 214 Ibid.
- 215 This section is a summary of Krattiger (2007a).
- 216 For further explanations on compulsory licences, see Chapter IV, section C.3(a)(ii)–(iii).
- 217 Section 4.3 of the PIP Framework defines NICs as meaning influenza laboratories authorized and designated by the member state and subsequently recognized by WHO to perform a number of functions.
- 218 Section 4.3 of the PIP Framework defines WHO Collaborating Centres on Influenza as influenza laboratories designated by WHO and supported by national authorities to perform certain roles within the WHO GISRS.
- 219 WHA, Resolution WHA60.28: Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits.
- 220 Source: WIPO (2011a).
- 221 See https://www.who.int/influenza/resources/technical_studies_under_resolution_wha63_1_en.pdf. See also www.who.int/vaccine_research/diseases/influenza/Mapping_Intellectual_Property_Pandemic_Influenza_Vaccines.pdf.
- 222 See https://www.who.int/influenza/resources/documents/wipo_ipdoc/en/.
- 223 WHA, Resolution WHA64.5: Pandemic influenza preparedness: Framework for the sharing of influenza viruses and access to vaccines and other benefits, available at: https://apps.who.int/gh/pip/pdf_files/pandemic-influenza-preparedness-en.pdf.
- 224 The PIP Framework, in Section 4.1, defines PIP biological materials as including: “human clinical specimens, virus isolates of wild type human H5N1 and other influenza viruses with human pandemic potential; and modified viruses prepared from H5N1 and/or other influenza viruses with human pandemic potential developed by WHO GISRS laboratories, these being candidate vaccine viruses generated by reverse genetics and/or high growth re-assortment. Also included in ‘PIP biological materials’ are RNA extracted from wild-type H5N1 and other human influenza viruses with human pandemic potential and cDNA that encompass the entire coding region of one or more viral genes”.
- 225 See WHO, Standard Material Transfer Agreement 2, Article 4.4, available at: https://www.who.int/influenza/pip/smta2_eng.pdf?ua=1.
- 226 See WHO, Standard Material Transfer Agreements 2 (SMTA2), available at: <https://www.who.int/influenza/pip/smta2/en/>.
- 227 See WHO, Partnership Contribution Collection, available at: https://www.who.int/influenza/pip/benefit_sharing/pc_collection/en/.

- 228 See WHO, PIP Partnership Contributions, as of 30 December 2019, available at: https://www.who.int/influenza/pip/benefit_sharing/pc_total_contributions.pdf?ua=1.
- 229 See, for example, WHO, 2019d.
- 230 Document WHA70/2017/REC/1, available at: http://apps.who.int/gb/ebwha/pdf_files/WHA70-REC1/A70_2017_REC1-en.pdf#page=61.
- 231 The Text of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity is available at: <https://www.cbd.int/abs/text/>.
- 232 See decision adopted by the parties to the Nagoya Protocol on Access and Benefit-Sharing, document CBD/NP/MOP/DEC/3/14, available at: <https://www.cbd.int/conferences/2018/np-mop-03/documents>; WHO 2018a.
- 233 Recital 16 of Regulation (EU) No 511/2014 of the European Parliament and of the Council of 16 April 2014 on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union, available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0511>; WHO, 2018a.
- 234 The PIP Framework uses the term “genetic sequence data”, while the discussions held under the Nagoya Protocol so far refer to “digital sequence information”. Parties to the CBD and Nagoya Protocol have not yet agreed on a definition of “digital sequence information”. However, it generally refers to information associated to genetic sequencing. “Genetic Sequence Data” and “Digital Sequence Information” are sometimes used interchangeably. WHO, 2018a. The Analysis explains that parties to the CBD and the Nagoya Protocol also use the term “digital sequence information” for information associated to genetic sequencing; see footnote 71 in that Analysis.
- 235 WHO, 2011c, Article 4.1.