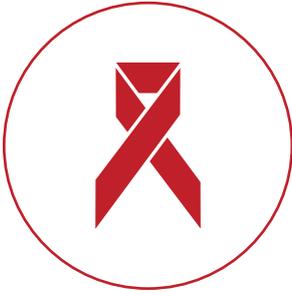
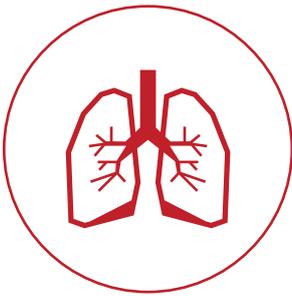


ENSURING THAT ESSENTIAL MEDICINES ARE ALSO AFFORDABLE MEDICINES: CHALLENGES AND OPTIONS



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Preface

This paper provides an overview of key historical developments, focused on the experience of increasing access to HIV medicines. Using the Essential Medicines List as a guide for prioritization, it then discusses some of the recent challenges and possible approaches to address them.

This paper does not necessarily represent the views of the World Health Organization or UNITAID.

Abbreviations

ARVs	Antiretroviral medicines
CIPIH	Commission on Intellectual Property Rights, Innovation and Public Health
DAAs	Direct-acting antivirals
EDL	Essential Drugs List
EML	Essential Medicines List
FDC	Fixed-dose combination
GSPOA	Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property
HCV	Hepatitis C virus
R&D	Research and development
TRIPS	(Agreement on) Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization
WTO	World Trade Organization
WHO	World Health Organization
WTO	World Trade Organization

Introduction

In May 2015, the World Health Organization (WHO) added several important medicines, including for the treatment of cancer, tuberculosis and hepatitis C, to its Model List of Essential Medicines [1], commonly known as the Essential Medicines List (EML). The uniqueness of these medicines – aside from their value as treatments for devastating illnesses – is their high price. Now that WHO has named these medicines as essential, they must be made both available and affordable. As innovative new medicines are increasingly patented around the world, and are thus available only at monopoly prices that prevent widespread access, a public policy response is needed to address the intellectual property challenges associated with essential treatments.

When the EML was first conceived as a tool for governments and health-care providers seeking to meet the health needs of their populations, medicines were added to the list when scientific data demonstrated their importance and when they could be made widely available at low cost. However, with new medically necessary treatments priced to break the budgets of health-care systems worldwide, both in high-income countries and in developing ones, it is time to acknowledge that the paradigm for the EML has shifted.

Several WHO experts stated in March 2015 that the Expert Committee on the Selection and Use of Essential Medicines, which recommends which medicines should be included on the EML, would have to face challenging questions on cost-effectiveness and affordability [2]. The Expert Committee in its report published in May 2015 explicitly called on WHO to “take actions at global level to make these medicines more accessible and affordable, especially as related to treatments for hepatitis C” [3].

If people around the world are to have access to essential medicines, the presence of these medicines on the EML is necessary, although it is not sufficient, to ensure that access. When WHO deems medicines to be medically essential, this should – as the Expert Committee asserted – be grounds for governments and other stakeholders to take action to ensure that the medicines are made available and affordable.

Of course, affordable prices alone are not enough to secure access to new essential medicines. Health and regulatory systems need to be sufficiently robust to take up new treatments and deliver them safely, clinical guidance needs to

BOX 1

Selected new medicines on the EML

Medicine	Disease	Disease burden	USA retail price/course of treatment
bedaquiline	multidrug-resistant tuberculosis	Multidrug-resistant tuberculosis (MDR-TB) is an increasing problem. Worldwide, 9.6 million people fell ill with TB in 2014. WHO estimates that approximately 480 000 cases of MDR-TB have occurred; about 9.7% of those had extensively drug-resistant TB. MDR-TB accounts for 3.3% of new TB cases and 20% of recurring cases [4].	US\$ 30 000 for 6 months [12]
delamanid	multidrug-resistant tuberculosis		US\$ 3180-4258 per month [13]
terizidone	multidrug-resistant tuberculosis (as an alternative to cycloserine)		
linezolid	multidrug-resistant tuberculosis		US\$ 70-4298 per month [13]
sofosbuvir	hepatitis C	WHO estimates that, worldwide, 130-150 million people have chronic HCV infection, and that one third of them will develop liver cirrhosis or hepatocellular carcinoma [5].	US\$ 84 000 for a 12-week course of treatment [14]
simeprevir	hepatitis C		US\$ 66 360 for a 12-week course of treatment [14]
daclatasvir	hepatitis C		
ledipasvir/sofosbuvir	hepatitis C		US\$ 94 500 for a 12-week course of treatment [14]
ombitasvir/paritaprevir/ritonavir	hepatitis C		Approximately 700 000 died from HCV-related illness in 2013 [6]. 4-5 million are co-infected with HIV [7].
bendamustine	chronic lymphocytic leukaemia (CLL) follicular lymphoma	Leukaemia incidence was 351 965 in 2012 (CLL is a sub-type) [8]. Non-Hodgkin lymphoma (of which follicular lymphoma is a sub-type) incidence was 385 741 in 2012 [9].	
imatinib	chronic myeloid leukaemia (CML) gastrointestinal stromal tumour	CML is a rare disease and there are minimal data, but experts writing for the EML estimated that there are 1 or 2 cases per 100 000 people each year [8]. Gastrointestinal stromal tumour incidence is estimated to be 14.5 per million [10].	US\$ 92 000 per year [15]
rituximab*	diffuse large B-cell lymphoma chronic lymphocytic leukaemia follicular lymphoma	Leukaemia incidence was 351 965 in 2012 (CLL is a sub-type) [8]. Non-Hodgkin lymphoma (of which follicular lymphoma and diffuse large B-cell lymphoma are sub-types) incidence was 385 741 in 2012 [9].	US\$ 21 186 (indicative price in high-income countries) [16]
trastuzumab*	early stage HER2 positive breast cancer metastatic HER2 positive breast cancer	Breast cancer overall incidence is approximately 1.67 million women [9]; HER2 is overexpressed in 20-30% of breast cancers [11].	US\$ 4500 per month or US\$ 54 000 per year [17]

* Biological products.

be available on the use of complex treatments in resource-limited settings, and operational research may be needed to develop experience and new knowledge about the use of new medicines in specific settings.

Nevertheless, affordability of essential medicines is a key prerequisite for expanding treatment and care. Other key elements are sufficient demand, financing for procurement, and a regulatory environment that is responsive to health needs. This paper deals with the intellectual property issues linked to affordability and access to new essential medicines.

Actions to ensure the affordability of patented medicines could include: negotiating with manufacturers for better prices; making use of flexibilities under the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement); and encouraging the production of low-cost, quality generic versions, including through licensing of relevant patents. In the longer term, delinking of payment for the cost of research and development for needed new essential medicines from the price of the final product should be considered.

HIV, affordability and the EML

Since its first publication in 1977 with 207 medicines, the EML - then called the Model List of Essential Drugs - has guided governments, international organizations, NGOs and other health-care providers in the selection of medicines designated as “of utmost importance, basic, indispensable and necessary for the health and needs of the population” [18]. Today, more than 150 countries have national essential medicines lists [19], and 19 editions of the WHO Model List have been published. Selection criteria include efficacy, safety and relative/comparative cost-effectiveness within the therapeutic category. The list is regularly updated in order to respond to new needs, drug resistance, medical advances, scientific developments and new evidence with regard to efficacy and safety. Affordability is also considered in order to take account of limited health budgets and prevent the purchase of non-essential expensive medicines to the detriment of treating other diseases, although the approach to affordability has changed over time as more medically necessary drugs carry increasingly higher prices.

The HIV crisis raised the first major challenge to the affordability criteria. The 1999 revision of the EDL excluded most antiretroviral medicines (ARVs) for treating HIV as too expensive for health systems to bear [20]. At the time, the predominant treatment regimen for HIV cost upwards of US\$ 10 000 per person per year. By 1999, however, nearly 20 million people had already died of HIV and the virus was continuing to kill 8000 people a day. There were 13 million children orphaned due to AIDS and almost 35 million people were living with a virus that could be treated but mainly was not [21]. To deem ARVs non-essential risked making the EDL irrelevant.

In 2001, WHO began a consultation process to examine the way in which new medicines were included in the WHO Model List of Essential Drugs [22]. The consultation tackled several issues of cost, such as whether high costs should prevent a medicine from being added to the list, even if it was safe, effective and needed to treat a priority health problem like HIV; and whether global comparisons on cost-effectiveness could be meaningful, given the wide variation in medicine costs around the world [23].

In a series of new procedures [23] arising from this consultation process, WHO decided that the cost of a medicine could not be the reason to exclude it if it met other criteria, and that cost-effectiveness comparisons should be made within a therapeutic

area (e.g. “identifying the most cost-effective medicine treatment to prevent mother-to-child transmission of HIV”). These new procedures also changed the term “essential drugs” to “essential medicines” and established a more systematic, transparent, participatory and evidence-based approach to selecting medicines for inclusion, as

BOX 2

The role of civil society action

Progress in access to essential medicines for the treatment of HIV would not have happened without the mobilization of civil society. Civil society organizations, often working in partnership with international NGOs and local treatment activists, drove a process of change that led to widespread scale-up of HIV treatment. Examples of work by civil society include:

- international mobilization for financing for HIV treatment that led to the establishment of the Global Fund and UNITAID;
- advocacy for the establishment of national HIV treatment programmes;
- advocacy for health-friendly patent laws and practices, such as in 2005 when India amended its 1970 Patents Act to ensure compliance with TRIPS;
- legal actions in national courts using the human right to health to ensure access to ARVs;
- the campaign against the 39 pharmaceutical companies that had brought suit against the government of South Africa, alleging that the Medicines and Related Substances Control Amendment Act, No. 90 of 1997, violated TRIPS and the South African constitution, forcing them to drop the case;
- requests filed for compulsory licensing of patents on HIV medications;
- patent grant oppositions launched in India;
- influence on international negotiations, such as those at the WTO that led to the adoption of the Doha Declaration on TRIPS and Public Health;
- advocacy at WHO in support for the WHO prequalification programme;
- influence on access policies by pharmaceutical companies (e.g. by advocating for the Medicines Patent Pool);
- contributions to price monitoring and transparency, such as the key example of MSF's Untangling the Web of Antiretroviral Price Reductions;
- participation in the governance of new global health organizations.

The intense and large-scale involvement of civil society organizations was essential in driving HIV treatment scale-up. Other diseases have so far not sparked mobilization on the same scale, which raises the question as to how access to treatment will be assured (e.g. for new treatments for hepatitis, TB and cancer). More importantly it raises the question of why global advocacy movements have been needed to ensure that essential medicines are available and affordable when access to these life-saving treatments should be ensured as a basic human right to health.

well as improving links between the list and WHO treatment guidelines. As a result, the 2002 Essential Medicines List included 12 ARVs.

In 2003, WHO and UNAIDS launched the “3 by 5” initiative to provide ARV treatment to 3 million people by 2005 [24], following the establishment of the Global Fund in 2002. Both initiatives were key to expanding access to ARVs in developing countries, and this was aided by their recognition as essential medicines and the increased availability of generic versions. The response to the HIV crisis was driven by unprecedented global mobilization and civil society action [25].

The message was clear: cost alone was no longer a criterion by which an essential medicine could be excluded from the list. The implication was that steps should be taken to make listed drugs affordable.

In parallel to this process, the first generic ARVs began to be manufactured in India. Demand was spurred by their designation as “essential” coupled with their prequalification by WHO [26]. A concerted international effort to mobilize funding to treat HIV created a market for generic ARVs and led to robust competition. The price of ARVs fell more than 99%. As the price came down, the number of people who could access treatment grew, with the result of longer and healthier lives for many people. AIDS deaths fell, and so did new infections with HIV – to the point where, a decade later, a world with no new infections is something that can be envisioned for the future.

The HIV crises demonstrated three things: 1) the need for medically important drugs to be included on the list, 2) the power of EML inclusion as an impetus for bringing prices down, and 3) global public mobilization and civil society action are key aspects of changing medicines policies.

Intellectual property rights and the narrowing policy space for essential medicines

The policy space that allowed for the manufacturing of low-cost essential ARV drugs in the early 2000s has narrowed as key generics-producing countries such as India have implemented the World Trade Organization's TRIPS Agreement. TRIPS sets out minimum standards for the protection of intellectual property rights. Members of the WTO can no longer exclude entire fields of technology, such as medicines, from patentability.¹ Providing a minimum 20-year patent term for pharmaceutical products is obligatory.

The robust generic competition that brought down prices of early HIV medicines has become harder to achieve, both for newer HIV medicines and for medicines to treat other diseases that have a major impact on global public health – notably hepatitis C, cancer and tuberculosis, all of which can be better treated with the effective, and unfortunately expensive, new medicines just added to the EML. This new era of essential medicines does not benefit from the same political mobilization that led to action to address the HIV crisis.

Imatinib, added to the EML in May 2015, is a medicine that has helped nearly double the 5-year survival rate for chronic myeloid leukaemia from 31% in the early 1990s to 60% today [27]. Imatinib was originally priced at US\$ 30 000 a year in 2001, but by 2012 a group of more than 100 physicians from all continents with expertise in chronic myelogenous leukaemia wrote in the journal *Blood* that, after it became a blockbuster treatment, the price of imatinib had risen to US\$ 92 000 a year. Generic imatinib, manufactured in India where a protracted legal case ended in the rejection of imatinib patents, is priced at between US\$ 2004 and US\$ 2112 a year [28].

BOX 3**Primary patent expiry date of selected new medicines on the EML**

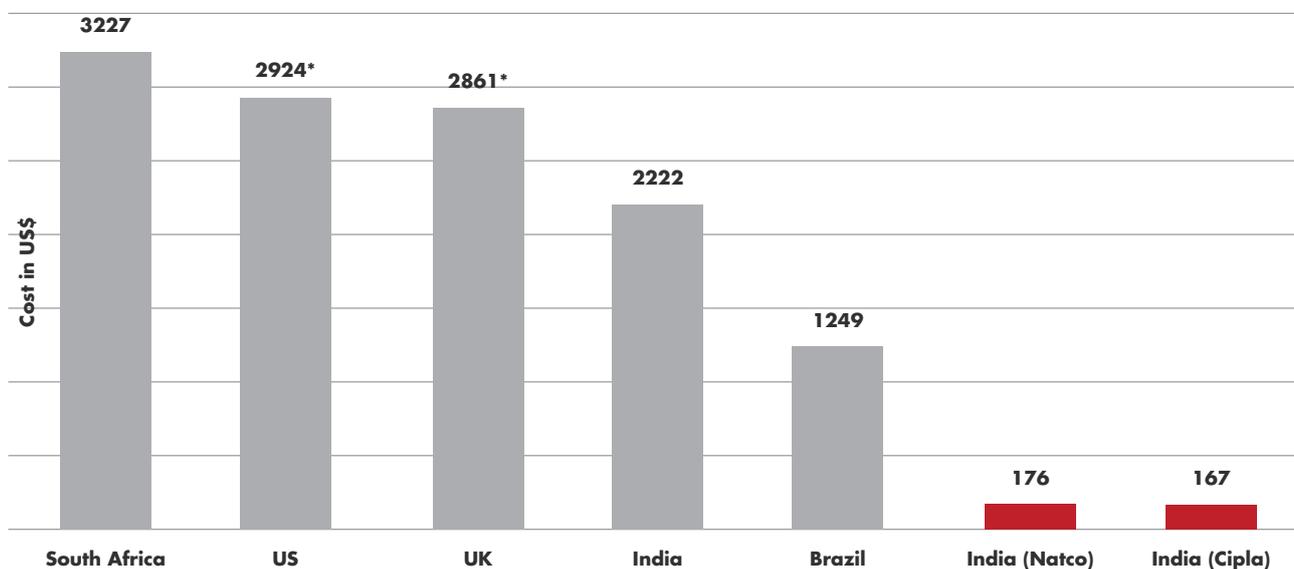
Medicine	Company	Primary patent number(s)	Expected date of expiry of the patent
Tuberculosis			
bedaquiline (Sirturo)	Janssen	WO 2004/011436	July 2023
delamanid (Delyba)	Otsuka Pharmaceutical	WO 2004/033463 WO 2005/042542	October 2023 October 2024
terizidone (Terivalidin, Tericox)			Base compound patent expired
Hepatitis C			
sofosbuvir (Sovaldi)	Gilead	WO2005003147A2 - base compound WO2008121634A2 - prodrug	April 2024 March 2028
simeprevir (Olysio, Galexos, Sovriad)	Janssen	WO2007014926A1	July 2026
daclatasvir (Daklinza)	Bristol-Myers Squibb	WO2008021927A2	August 2027
ledipasvir	Gilead	WO2010132601A1	May 2030
ombitasvir	AbbVie	WO2010132601A1	June 2030
Cancer			
bendamustine (Treakisym, Ribomustin, Levact and Treanda)	Marketed by Cephalon in the USA	WO2006076620	January 2026
Imatinib (Gleevec, Glivec)	Novartis	WO9509852 WO9903854 (secondary patent)	September 2014 2018
rituximab* (Rituxan, MabThera and Zytux)	Biogen Idec, Genentech, Roche, Chugai Pharma, Zenyaku Kogyo and AryoGen, depending on location	WO8804936 WO9411026	2008 November 2013 Several formulation patents – 2019 – 2020
trastuzumab* (Herceptin)	Roche	WO8906692	2009

* Biological products.

Developing countries have in the past sought to keep the prices of (essential) medicines low by excluding them from patentability. In 1991, for example, the Andean Community adopted a declaration that “inventions related to pharmaceutical products included in the WHO Model List of Essential Drugs” should not be patentable [29]. India did not grant product patents for medicines until 2005. This enabled the development of a vibrant generic pharmaceutical industry that plays a key role the supply of medicines to the developing world.

BOX 4

Cost of imatinib brand Gleevec (blue bars) and cost of generic imatinib per patient per month (red bars), in US\$



* Public procurement price

Source: Médecins Sans Frontières, India, 2013.

Health and trade

Post-TRIPS, this type of policy measure became impossible, although countries have tried in different ways to address the interaction of the EML and patents. Venezuela, with support from the Andean group and other developing countries, particularly South Africa, proposed at the Third Ministerial Conference of the World Trade Organization (WTO) in Seattle in 1999 to amend TRIPS Article 27.3 (b) to create a new exception to patentability for medicines on the EML. A counter-proposal led by the European Community was “to issue . . . compulsory licences for drugs appearing on the list of essential drugs of the World Health Organization” [30]. At that time, only about 11 of the 306 products on the EML were patented in certain countries and ARVs were not on the WHO list [31]. The adoption of the European proposal would have seriously limited the scope of compulsory licensing. Nevertheless, both proposals gave special treatment to medicines on the WHO list. The Seattle ministerial conference did not reach

a conclusion but concerns over the effect of globalization of patent rules on access to essential medicines remained on the agenda not only of the WTO but also of other intergovernmental organizations, including WHO [33]. These concerns led to the development of certain principles related to trade and health and the recognition that access to essential medicines is a key component of the fulfilment of the human right to health [19].

BOX 5

Communication from Venezuela on TRIPS^a

II. REVIEW OF THE TRIPS AGREEMENT IN THE YEAR 2000

The TRIPS Agreement itself is delicately poised between rights and obligations in various areas of intellectual property. However, there are many aspects and areas of interest to the developing and least-developed countries which are left unregulated by the final text of the Agreement. In this connection, it is important to begin a full review and possible renegotiation of the TRIPS Agreement from the development standpoint, taking into account the scope and interpretation which should be given to special and differential treatment and the identification of the policy areas necessary for the achievement of this objective. Venezuela considers that, among other things, a review should involve the following:

...

3. Extend the list of exceptions to patentability in Article 27.3(b) of the TRIPS Agreement to include the list of essential drugs of the World Health Organization, in order to develop the principles established in Article 8 of the Agreement.

^a Proposals regarding the TRIPS Agreement (paragraph 9(a)(ii) of the Geneva Ministerial Declaration), communication from Venezuela, WT/GC/W/282 [32].

In 2001, WTO members in Doha, Qatar, adopted the Doha Declaration on the TRIPS Agreement and Public Health [34] which states that “the TRIPS Agreement does not and should not prevent members from taking measures to protect public health.” The Doha Declaration established health as the clear priority over commercial interests and offered useful guidance for countries struggling with the affordability of new and highly-priced medicines. Paragraph 4 is often referred to as the core of the declaration because it signals the primacy of the protection of public health over the protection of intellectual property (see Box 6).

BOX 6

Paragraph 4, Doha Declaration on TRIPS and Public Health

“We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members’ right to protect public health and, in particular, to promote access to medicines for all.”

Human rights and health

Access to essential medicines has also been recognized as a human right by the international community. Article 12 of the 1966 International Covenant on Economic Social and Cultural Rights recognizes the right of everyone to “the enjoyment of the highest attainable standard of physical and mental health” including through a health-care system that is “economically accessible to all” and details the steps that states should take to achieve this [35]. Adopted in 2000, General Comment 14 on the implementation of the Covenant specifically mentions the need for governments to ensure the availability of essential drugs “as defined by the WHO Action Programme on Essential Drugs” [36]. The Millennium Development Goals further commit the international community to “provide access to affordable essential drugs” in developing countries [37]. They were followed by the Sustainable Development Goals, which also contain a commitment to “provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health” [38].

In 2006, the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH) published a report stating that “access to drugs cannot depend on the decisions of private companies but is also a government responsibility” [39]. This statement echoes the central notion of the essential medicines concept and the various human rights instruments that refer to the obligations of governments to protect and promote public health, including by ensuring the availability of essential medicines. Yet with the globalization of patent standards, the power to decide who will have access to new medicines and who will not seems to have shifted into the hands of private companies.

This creates a tension between countries' obligations under TRIPS and their obligation to their populations to protect and promote health. The CIPIH made over 50 recommendations, including that WHO should develop a more coherent action plan and strategy to deal with the challenges that arise from new, and more global, intellectual property policies (See Box 13). On the basis of these recommendations, countries negotiated the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA), adopted in 2008 by the World Health Assembly. The GSPOA calls for "promoting competition to improve availability and affordability of health products consistent with public health policies and needs" and recommends specific actions, including actions that deal with intellectual property barriers to the availability of generic essential medicines [33].

The GSPOA was followed, in 2012, by the Consultative Expert Working Group on Research and Development: Financing and Coordination, which recommended the establishment of a biomedical R&D treaty [40]. The idea of an international agreement on R&D has been debated since an initial proposal was made by Hubbard & Love in 2004 [41]. Over the years, it has received support from a number of governments, scientists, Nobel laureates, civil society organizations and other experts [42–44]. Calls for better rules were echoed more recently by heads of research and international organizations proposing a Global Biomedical R&D Fund and Mechanism for Innovations of Public Health Importance [45].

While the fulfilment of basic human rights is primarily a state obligation, in the case of patented medicines one also has to recognize the responsibility of the patent-holding pharmaceutical company. In the words of UN Special Rapporteur on the right to health, Paul Hunt: "Society has legitimate expectations of a company holding the patent on a life-saving medicine... Because of its critical social function, a patent on a life-saving medicine places important right-to-health responsibilities on the patent holder. These responsibilities are reinforced when the patented life-saving medicine benefited from research and development undertaken in publicly funded laboratories" [46].

In 2008, the UN Special Rapporteur on the right to the highest attainable standard of health submitted to the United Nations General Assembly a report containing guidelines for the pharmaceutical industry on access to medicines titled Human rights guidelines for pharmaceutical companies in relation to access to medicines [47]. Specific right-to-health responsibilities of companies holding patents to life-saving medicines were further developed in a report of the UN Special Rapporteur following a right-to-health mission to GlaxoSmithKline [48]. These include:

- "The seminal right-to-health responsibility is to take all reasonable steps to make the medicine as accessible as possible, as soon as possible, to all those in need, within a viable business model. For example, as soon as the new medicine is marketed at higher prices (usually in high-income countries), the patent holder

has a right-to-health responsibility to put in place a range of mechanisms, such as differential pricing between and within countries, to enhance access for all those who cannot afford those prices.

- Also, the patent holder has a right-to-health responsibility to develop formulations for children, the elderly, pregnant and lactating women, and extremes of climate.
- The agreement with society places a responsibility on the patent holder to take these steps, expeditiously and effectively, by way of deliberate, concrete, and targeted measures.
- If the patent is worked without these steps being taken, the patent holder is in breach of its right-to-health responsibilities.
- The success of a patent holder's actions will sometimes depend upon states, donors and others fulfilling their responsibilities. Nonetheless, the patent holder has a right-to-health responsibility to do what it can" [48].

The right-to-health standards offer a normative framework against which companies can be held accountable, which is useful for monitoring companies' policies and actions. However, enforcement mechanisms to ensure that companies act on their responsibility for human rights are lacking. Anand Grover, who followed Paul Hunt as Special Rapporteur for the right to health, sought to give teeth to the normative framework developed by Hunt. Grover suggested establishing direct legal obligations of pharmaceutical companies at the international level and holding pharmaceutical companies directly accountable under international human rights law, including obligations for direct compensation to victims and the granting of compulsory licences [49].

In 2012, the Global Commission on HIV and the Law, an independent body convened by the United Nations Development Programme (UNDP), went a step further and recommended the development of a new intellectual property regime under the aegis of the United Nations Secretary-General that is "consistent with international human rights law and public health requirements, while safeguarding the justifiable rights of inventors". It further recommended that, until such a system is in place, "the WTO must suspend TRIPS as it relates to essential pharmaceutical products for low- and middle-income countries" [50].

While the suspension of TRIPS may not happen in the near future, the emphasis on human rights in the pursuit of access to patented essential medicines is likely to increase, in particular since a growing number of countries recognize the right to health as a constitutional right and individuals have used such constitutional rights to obtain access to essential medicines [51].

At the end of 2015, United Nations Secretary-General Ban Ki-moon established a UN High-Level Panel on Access to Medicines with the mandate “to review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies”. The scope of the work of the panel is global and ambitious; it will address access challenges relating to access to medicines globally [52].

A practical tool

The EML is a tool for the practical implementation of the internationally agreed principle that intellectual property should not stand in the way of measures to promote the human right to health and access to essential medicines as a component of that right. Affordability is no longer a prerequisite for the inclusion of a medicine in the EML; instead, inclusion must become a reason to ensure that treatments become affordable and thereby a ground, if not an obligation, for governments to act when the pricing of essential medicines prohibits their use by people in need.

Chapter notes:

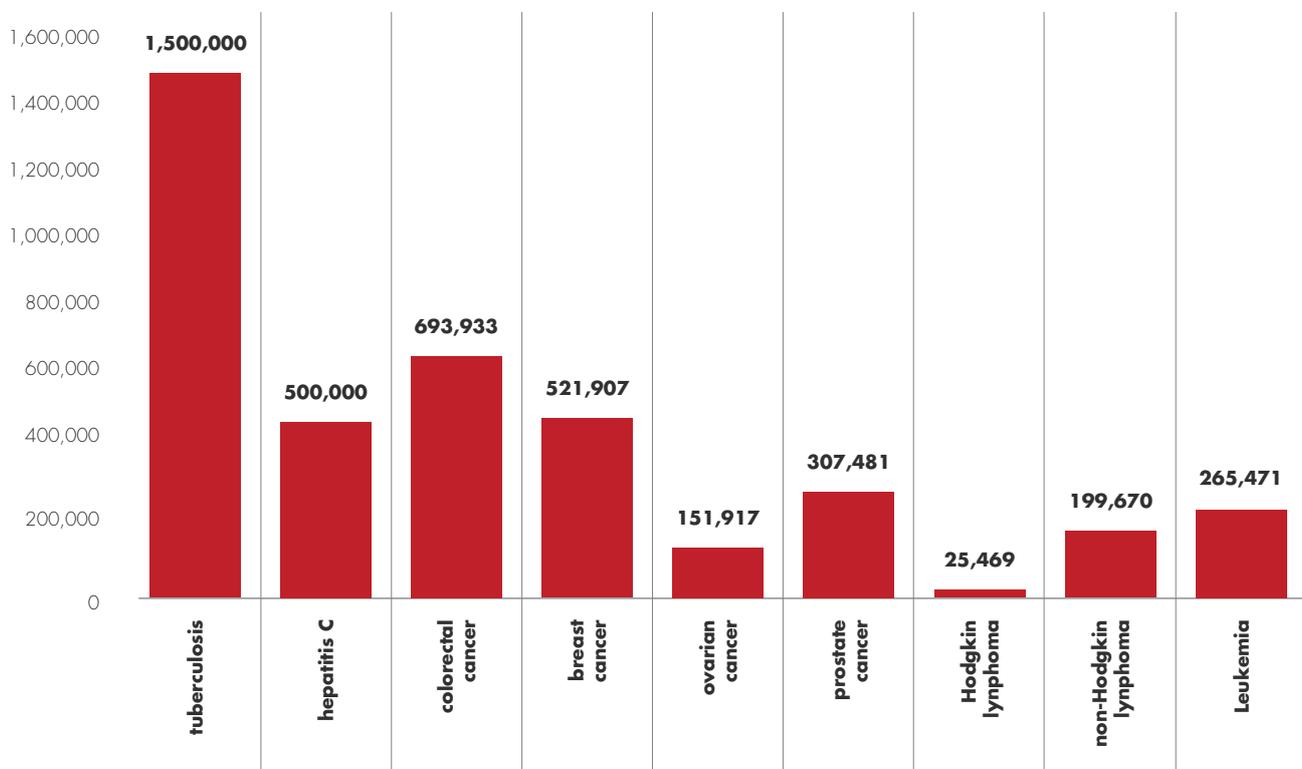
¹ See Article 27 of the TRIPS Agreement. A few exceptions listed in articles 27.2 and 27.3 allow certain exclusions from patentability (e.g. animals other than microorganisms). There is also a waiver allowing least developed countries to delay their obligation under TRIPS with regard to granting and enforcing pharmaceutical patents until at least 2033.

The challenges of hepatitis C, cancer and tuberculosis

New medicines added to the EML in May 2015 present a key opportunity to exercise the EML as a tool for access. The game-changing medicines for hepatitis C, several cancers and tuberculosis on the EML are badly needed, but they are currently priced out of reach.

BOX 7

Mortality rates, in number of deaths per year



Sources: WHO TB Factsheet, data from 2014 (<http://www.who.int/mediacentre/factsheets/fs104/en/>); WHO Hepatitis C Factsheet, data last updated July 2015 (<http://www.who.int/mediacentre/factsheets/fs164/en/>); and Globocan, 2012 (<http://globocan.iarc.fr/Default.aspx>)

Hepatitis cure for all within reach (only with access to new medicines)

Chronic hepatitis C affects 130–150 million people globally [5], while liver diseases associated with it killed approximately 700,000 people in 2013 [7]. Until recently, treatment for hepatitis C virus (HCV) was difficult to administer, limited in efficacy, difficult to undergo, frequently caused debilitating side-effects, and was expensive. However, with the arrival on the market of new direct-acting antivirals (DAAs), a widely-available cure is within reach – a cure that is easy to administer, has limited side-effects and is associated with a good sustained viral response.

The medicines are sufficiently effective for HCV eradication to be conceivable if those who need the medicines had ready access to them. But sofosbuvir (SOF), currently the backbone of any HCV treatment regimen and one of the medicines added to the EML in May 2015 [53], can cost up to US\$ 1000 a pill, or US\$ 84 000 for a 12-week course of treatment. The price of a full regimen combining SOF and ledipasvir can amount to US\$ 95 000 [54]. Another DAA – simeprevir – which was added to the list in 2015 [55], is priced at US\$ 66 360 for 12 weeks, and also must be combined into a treatment regimen. A recent study estimated that the costs of production for a 12-week course of SOF treatment could be as low as US\$ 101 with generic competition and a robust market [57].

BOX 8

Hepatitis C medicines, prices and estimated minimum cost of production

Medicine	Price range per bottle in high-income countries [56]	Lowest recorded price per bottle in Egypt and India [56]	Global sales, 2014 (US\$ millions)	Estimated minimum cost of production for a 12-week course of treatment [57]
sofosbuvir	US\$ 14 000–20 590	US\$ 161 (India)	US\$ 10 283m [58]	US\$ 68–136
simeprevir	US\$ 9166–14 865	US\$ 241 (Egypt)	US\$ 2302m [59]	US\$ 130–270
daclatasvir	US\$ 1128–14 899	US\$ 175 (Egypt)	US\$ 201m [60]	US\$ 10–30
ledipasvir	Sold as an FDC*			US\$ 93
ombitasvir	Sold as an FDC*			
ledipasvir + sofosbuvir	US\$ 12 604–\$4890	US\$400 (Egypt)	US\$ 2127m [58]	US\$ 193
ombitasvir + paritaprevir + ritonavir	US\$ 15 344–20 215	US\$400 (Egypt)	US\$ 48m [61]	

*FDC = fixed-dose combination.

An investigation from the United States Senate Committee on Finance found that Gilead's pricing strategy for sofosbuvir was based on "maximizing revenue, regardless of the human consequences. There was no concrete evidence in emails, meeting minutes or presentations that basic financial matters such as R&D ... factored into how Gilead set the price" [62–64].

Generics manufacturers and civil society organizations have filed patent oppositions in India and in Europe [65]. In 2014, Gilead granted voluntary licences for its DAAs, including sofosbuvir, to generics manufacturers in India for the supply of these medicines in 91 low- and middle-income countries. Gilead has also offered some tiered pricing plans [66]. Countries outside the scope of the licence, however, cannot automatically benefit from the generic supply unless they issue a compulsory licence [67]. Gilead has since expanded its agreements which now cover 101 countries [68].

Bristol-Myers Squibb (BMS) in 2014 announced its plan to license the patents for daclatasvir with a licence territory of 90 countries [69], but no agreement was signed until 23 November 2015 when the Medicines Patent Pool and BMS announced an agreement for daclatasvir in 112 low- and middle-income countries [70,71]. Other companies producing HCV medication have not announced any patent licensing policies.

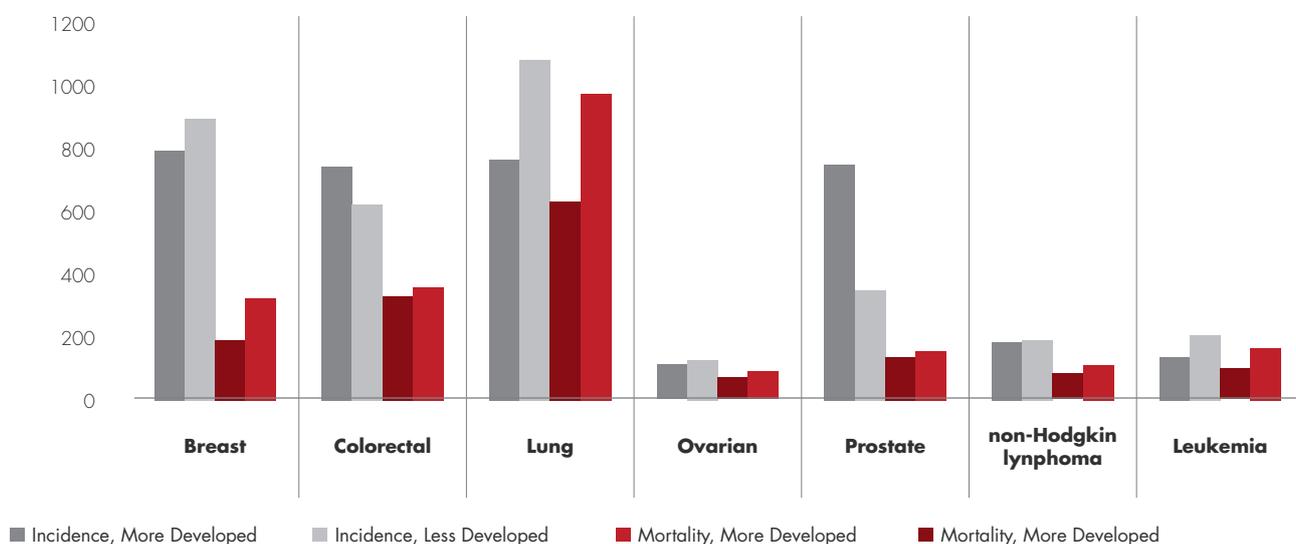
The new hepatitis C medicines are the first for which significant access problems are global; poor and rich countries alike are struggling to pay for these new medicines. The gap between monopoly prices and what is possible with a robust, competitive market is the difference between potential HCV treatment for all and treatment rationing due to limited health budgets. While licences secure generic production, a number of high-burden middle- and high-income countries cannot benefit from generic availability directly. This shows that other measures for accessing lower-priced DAAs, including the use of TRIPS flexibilities, remain essential until companies license under terms that can cover all in need.

Closing the cancer treatment gap

Cancer is among the world's leading causes of death. According to WHO, in 2012 there were 14 million new cases of cancer and 8.2 million cancer deaths [72]. These rates are set to rise, especially in developing countries where access to treatment often lags behind what is available in wealthier nations.

Even when a higher cure rate is possible – breast cancer and paediatric cancer, for instance, have an 80% long-term survival rate in the USA – this is often not achieved in low-income settings because of “a lack of access to well established and effective treatment and care” or in middle-income countries where often “treatment is only affordable for certain segments of the population, and... good outcomes remain skewed toward those who can pay,” according to the Union for International Cancer Control, which was invited by WHO to review cancer medicines for inclusion in the EML [73].

TABLE 9
Incidence and mortality rates of key cancers



Source: Globocan; data from 2012 (globocan.iarc.fr).

The International Agency for Research on Cancer reported in 2012 that, despite similar incidences of breast cancer in low- and high-income countries, the mortality rate was significantly higher in low-income countries (324 000 people versus 198 000) owing to a lack of early detection and access to treatment facilities [74]. Trastuzumab, a key breast cancer drug, was recently added to the EML. There has previously been criticism of the medicine's high prices [75].

The authors writing in the journal *Blood* said that, while “innovation and discoveries must be rewarded”, key cancer drugs such as imatinib (mentioned above) were costing over US\$100 000 per person per year which was “unsustainable” and harmful to patients [15]. The authors called for a dialogue on cancer medicines to ensure that prices are fair to innovators but not so high as to threaten the lives of patients unable to afford them.

Other cancers for which new drugs have been added to the list – colorectal cancer and lung cancer in particular – carry higher mortality-to-incidence ratios in low- and middle-income countries, demonstrating the acute need for more affordable access to care.

The case of biological medicines

Trastuzumab and rituximab, cancer medicines newly added to the EML, are known as “biological products”. Unlike most traditional small-molecule medicines manufactured through chemical processes, biological products are usually made or derived from human and/or animal materials [76]. By 2020 the projected global biologics market will be worth US\$ 250bn. The market for “biosimilars”, the generic equivalent of biological medicines, is expected to be worth up to US\$ 25bn by then [77].

Regulatory measures surrounding medicines, and particularly biological medicines, can act as further hurdles to the production of lower-cost biosimilars, even after the main patent of the medicine has expired.

Many drug regulatory agencies register generic versions of traditional “small-molecule medicines” based on studies that show the generic product is bioequivalent to the originator product. Regulatory requirements for generic biologicals or biosimilars are often more complex and require more extensive studies to demonstrate that the product is indeed similar in its action and safe to use. Some have expressed concern that these requirements are not always needed from a health perspective and instead serve the needs of originator companies who seek to maintain their market domination as long as possible [78].

Biosimilars for trastuzumab are being, or have been, prepared for the European and Indian markets where the medicine has recently come off patent [79,80], but those too may be priced out of reach [81]. Legal pathways for the registration of biosimilars have existed in the European Union (EU) since 2005. In the USA, the Food and Drug Administration (FDA) has been establishing standards for the authorization of biosimilars (an abbreviated licensure pathway for biosimilar biological products) following the passage the Affordable Care Act in 2010 [82].

Some developing countries such as Argentina, Brazil and Mexico have their own guidelines for the development of biosimilars. For instance, Colombia issued updated guidance for the registration of biosimilar products in 2015 that included an “abbreviated route” or “fast track route” for the registration of biosimilars [89].²

BOX 10

10. Price of a one-year course of trastuzumab in US\$ [83]

Country	Originator	Generic
USA	54 000 [84]	
United Kingdom	25 000 [85]	
South Africa	46 748 [83]	
India	16 392 [86] 28 182 [83]	14 000 [87] 24 000 [85] (Emcure) 11 600 [81] (Biocon)
China	54 000 [88]	

Treating the rising problem of multidrug-resistant and total-drug-resistant tuberculosis

Tuberculosis infected 9 million people in 2013, 1.5 million of whom died from the disease. More than 95% of people who die from TB live in low- and middle-income countries [90]. Worse, resistance to standard TB antibiotics has become widespread, with multidrug-resistant TB (MDR-TB) infecting 480 000 people in 2013, with about 9% of them having “extensively-resistant strains” of MDR-TB, with even fewer treatment options. Bedaquiline, newly added to the EML, is one of the first new TB drugs in decades and is an especially critical tool for treating MDR-TB. It is priced at three levels for high-, middle- and low-income countries at US\$ 30 000, US\$ 3000 and US\$ 900 respectively for a 6-month course of treatment. However, this still puts it out of reach for many patients according to Médecins Sans Frontières which wrote an open letter to the manufacturer asking to bring the price down [91].

With disease burdens and prices this high, action for affordability is essential. The following section discusses how affordability of new essential medicines can be achieved.

Options for achieving affordable access to patented Essential Medicines

Prices of many new medicines are kept artificially high due to market monopolies sustained by patents and/or data protection rules that establish market exclusivity for the originator product for certain periods. The justification for these artificial monopolies is to allow innovators to recoup their investment and to create incentives for the investment in the development of new medicines. However, it is not acceptable if the result of this policy is the exclusion of groups of people from benefitting from these innovations. Because the high price bears no relation to the actual cost of medicines production, there are ample reasons and scope for measures to bring the price of essential medicines down.

Governments can, for instance, negotiate a better price with the originator, or work to facilitate access to less costly generic products. The latter can be achieved through voluntary licences granted by the patent holder or through non-voluntary measures such as compulsory licences or government use licences. The following section outlines strategic options to ensure populations have affordable access to new essential medicines.

Price negotiations

Governments, health providers and procurement agencies can negotiate with the originator company of a patented medicine for discounted prices for certain territories. This can be challenging, especially for countries that cannot exercise leverage in the negotiation.

In some cases, companies engage in tiered pricing. This allows for the same medicine to be sold at varying prices in different countries, or in different market segments within the same country (e.g. public and private sectors), depending on what a particular market can bear. Tiered pricing can be particularly useful in situations where the market is too small or too uncertain to inspire robust competition, or where acute need demands a fast access strategy [92].³

However, studies indicate that in most cases tiered pricing does not guarantee affordability or availability and is not as effective as robust generic competition for achieving the lowest sustainable medicines prices [92].

Voluntary licensing and patent pools

Companies may also decide to provide licences for their patented medicines under certain terms and conditions. Such licences are called “voluntary licences” and provide the freedom to manufacture and sell generic versions of a medicine, even where patents exist.

Public-health oriented voluntary licensing has become a new norm for HIV medicines following the creation of the Medicines Patent Pool in 2010 (see Box 14), which brought unprecedented transparency and greater focus on treatment needs to the terms and conditions of licences. Prior to the creation of the pool, the terms of most voluntary licences were kept secret, making it hard to understand the options and limitations of such agreements.

An expansion of the scope of work of the Medicines Patent Pool to all essential medicines for which licenses are not currently available would accelerate the availability of lower-priced generic versions of new essential medicines while providing remuneration to the patent holder. Remuneration, or royalty payments, could be tiered to reflect the different levels of ability to pay in various territories. WHO and UNDP have provided guidelines for the remuneration of non-voluntary use of medical technologies that could be used for that purpose [93].

TRIPS flexibilities

The TRIPS Agreement allows countries to maintain a measure of flexibility in implementing their intellectual property regimes and also contains several clauses that can be used to protect public health. The freedom to implement TRIPS in accordance with national needs allows countries to, for instance, have stringent patentability criteria in order to ensure that only significant innovations are patented, to have simple procedures for the use of compulsory licensing and government use, and to have a patent opposition system open to the public.

The TRIPS flexibilities were affirmed in 2001 with the adoption of the Doha Declaration on TRIPS and Public Health which listed several legal mechanisms contained in TRIPS to increase, protect and promote access to medicines for all.

BOX 11

Data exclusivity

What is data exclusivity?

Data exclusivity prohibits for a certain period of time the use of pharmaceutical test data for drug regulatory purposes, which will delay the registration and thereby the marketing of generic medicines, regardless of the patent status of the product. The TRIPS Agreement does not mandate data exclusivity but, in Article 39.3, it requires the protection of undisclosed test data and other data, the origination of which involves a considerable effort, against unfair commercial use. This can, however, be achieved without creating market exclusivity.

Generic medicines, biosimilars and data exclusivity

Generic medicines and biosimilar medicines can be authorized for use only once the period of data exclusivity on the original “reference” medicine has expired. Data exclusivity periods can differ per country. In the EU, this means that the reference medicine must have been authorized for at least 10 years before a generic medicine or a generic biological medicine can be registered. In the USA, the data exclusivity period for small molecules is 5 years and for biologicals it is 12 years. Many countries do not provide data exclusivity; those that do have different periods of exclusivity, which are shorter than in the EU and the USA. Through trade negotiations of the Trans Pacific Partnership Agreement the USA tried to extend the data exclusivity period for biologicals in other countries to 12 years but did not succeed because of opposition by other TPPA countries that expressed concern about resulting rising health-care costs. The mandatory period for data exclusivity for biologicals under the TPP is 5 years, and may be 8 years under certain circumstances.

(See also: http://www.unitaid.eu/images/marketdynamics/publications/TPPA-Report_Final.pdf, accessed 1 February 2016; <http://www.politico.com/story/2015/10/trade-trans-pacific-partnership-214419>, accessed 1 February 2016).

Paragraph 5 affirmed the right of states to grant compulsory licences, and the “freedom to determine the grounds upon which such licences are granted”, among other mechanisms. Like voluntary licences, compulsory licences allow generic manufacture even where a patent is in force; unlike voluntary licences they do not require the consent of the patent holder. Paragraph 6 promised that the WTO would work to facilitate exports of medicines produced under a compulsory licence to countries that rely on other countries to produce; this promise resulted in 2003 in the adoption of the “August 30 decision” and subsequently a decision to amend TRIPS [94]. Paragraph 7 extends the transition period for least developed countries (LDCs) for the implementation of pharmaceutical product patents and the protection of undisclosed test data from 2006 to at least 2016. Since many LDCs had already granted those rights, it also allows LDCs to not enforce such rights. On 24 February 2015, LDCs requested an extension of this transitional period until a country is no longer classified as an LDC [95]. Subsequently, on 3 November 2015 WTO members reached an agreement to extend the pharmaceutical waiver for LDCs until 2033 [96]. This means that in LDCs there should be no patent barriers to making generic medicines available until at least 2033.

BOX 12

Data exclusivity in TPP countries [97]

Country	Pharmaceuticals (years)	Biologicals (years)
Australia	5	5
Brunei	0	0
Canada	8	8
Chile	5	5**
Japan	8	8
Malaysia	5***	5***
Mexico	5	5**
New Zealand	5	5
Peru	5	5**
Singapore	5	5
United States of America	5	12
Vietnam	5	5
European Union	10	10

*Excludes further extensions for paediatric approval, orphan designation, new indications and other incentives.
**It is uncertain whether RDP will apply to biologicals in Chile, Mexico and Peru. These countries do not specifically grant RDP to biologicals.
***Malaysia begins counting RDP from the date a product is approved and given data protection in its originator country and allows for up to five years RDP from that date.

The CIPIH and GSPOA recommendations on intellectual property and public health

The CIPIH made 50 recommendations (see Box 13 for highlights). It was followed by the Global Strategy and Plan of Action on Public Health, Innovation, and Intellectual Property (GSPOA) that laid out eight strategic elements for increasing R&D on and access to innovative health products, including measures related to applying and managing intellectual property rights for public health [33]. The GSPOA recommended, inter alia: “Support the production and introduction of generic versions, in particular of essential medicines, in developing countries through the development of national legislation and/or policies” and “Consider... taking appropriate measures to prevent the abuse of intellectual property rights.”

One example of such a measure would be an intervention to remedy the non-working of a patent. In most patent systems, a patent owner must “work his or her invention” in order to maintain the monopoly, and an invention “not worked or insufficiently worked in the country” may be subject to non-voluntary licensing [98]. A patented product that is priced at the level the community cannot afford can be regarded as a patent “not worked”. It is the equivalent of refusing to make the innovation available and is ground for government intervention. For example, Section 146 of the Indian Patents Act mandates that a patent holder must disclose the extent to which he/she has commercially “worked” the patent. The rationale for this requirement is that it helps evaluate if the patent holder has satisfied the reasonable requirements of the public, which in the case of a medicine patent would mean providing access to the patient population that needs the treatment. Should the patent holder fail to make its product available on the scale needed, the patent is susceptible to a compulsory licence. Such a compulsory licence was issued three years ago for a patented anticancer drug sorafenib tosylate (sold under the brand name “Nexavar”) on the grounds that it was exorbitantly priced at about US\$ 4500 a month and was hardly available to the patient population [99].

It is important to maintain the policy space that the TRIPS Agreement allows to ensure access to medicines and to avoid so-called “TRIPS-plus” provisions such as those demanded in trade agreements that might restrict access to, or the ability to produce, generic medicines [100].

BOX 13

Main recommendations of the CIPIH report [39]

Governments should:

- avoid provisions in bilateral trade agreements that could reduce access to medicines in developing countries;
- increase funding for research projects run by public–private partnerships and by developing countries, and make that funding more sustainable;
- develop advance purchase schemes to contribute to the development of vaccines, medicines and diagnostics;
- incorporate digital libraries of traditional medical knowledge into their patent offices' data to ensure that data contained in them are considered when patent applications are processed;
- make available reliable information on the patents they have granted;
- amend their laws to allow compulsory licensing for export consistent with the TRIPS Agreement;
- eliminate tariffs and taxes on health-care products.

Governments of developing countries should:

- promote health research that is in line with public health needs;
- promote the use of research exemption as part of their patent law;
- invest appropriately in health delivery infrastructure;
- improve financing of the purchase of medicines and vaccines;
- make use of compulsory licensing provisions, where this will promote innovation or access to medicines.

WHO and other international agencies should:

- develop a global plan of action to secure more sustainable funding to develop new products and make those products more accessible;
- encourage the creation of patent pools where this would facilitate product development;
- monitor the impact of intellectual property rights from a public health perspective.

Companies should:

- adopt transparent and consistent pricing policies;
- reduce prices for developing countries;
- avoid filing patents or enforcing them in low-income developing countries in ways that would inhibit access to their products.

Sustainable supply of low-cost generic essential medicines

If patents are barriers to access to new essential medicines, the following options should be explored:

- Establish a voluntary licensing mechanism for medicines on the EML. Companies should offer voluntary licences for essential medicines, including through patent pooling. Voluntary licences should have terms and conditions that aim at maximizing access and are conducive to public-health needs. One way to ensure that licences are public-health oriented is for them to go through the Medicines Patent Pool (see Box 14). Legal scholars have previously recommended the extension of the Medicines Patent Pool framework to cover all essential medicines coupled with international financing mechanisms in order to ensure affordable access to essential medicines under patent and fair royalty payments [101].

In case patent holders refuse to license, governments can take action in the following manner:

- Issue compulsory licences to generic companies to encourage the production of low-cost versions of essential medicines. Predictable compulsory licensing for essential medicines is possible under the TRIPS Agreement. While Article 31 (a) of the TRIPS Agreement requires that compulsory licences should be considered on their individual merits, legal scholars have pointed out that it is possible to impose such licences on medicines that are reasonably deemed to be essential [102].
- Make “government use” of patents to allow for the procurement of low-cost versions of essential medicines. Government use is a form of compulsory licensing whereby the government, or third parties authorized by the government, make use of the patent without consent of the patent holder. The TRIPS Agreement refers to this as “public non-commercial use”.⁴
- In all cases of licensing, royalties should be payable so that originators are remunerated. Such royalties can be determined on the basis of the UNDP royalty guidelines that link royalty rates to the gross domestic product (GDP) of the country [93].

Governments and the international community should also take steps to further expand sources of generic production beyond India, which currently is the major supplier of key medicines in low-and middle-income countries, through technology and know-how transfer, and through development cooperation networks and partnerships.

BOX 14

The Medicines Patent Pool

In 2010 UNITAID established the Medicines Patent Pool for HIV medicines. The function of the MPP is to negotiate patent licences that will allow the production and supply of generic ARVs as well as the development of adapted formulations such as paediatric ARVs. Since 2010, the MPP has signed agreements for 12 ARVs for countries that account for 87-94% of people living with HIV in the developing world and for one medicine for an HIV opportunistic infection. The MPP has sublicense agreements with 14 generics manufacturers.

The MPP works with UNITAID, the Drugs for Neglected Diseases initiative (DNDi) and the Clinton Health Access Initiative (CHAI) in the Paediatric HIV Treatment Initiative (PHTI) to accelerate the development of appropriate paediatric fixed-dose combinations.

In November 2015, the scope of work of the MPP was expanded to include HCV and TB. The MPP signed its first HCV licence with BMS the same month.

Source: www.medicinespatentpool.org, accessed 1 February 2016.

Sustainable development of future essential medicines

Making medicines affordable cannot be to the detriment of investment in the development of future essential medicines. Current spending on expensive medicines in many mostly high-income countries ensures generous profit margins for corporations and steers investments into the development of new potentially profitable medicines – rather than steering investment towards meeting the most pressing medical needs.

This spending could be organized differently. Separating, or “delinking” the payment for the cost of developing medicines from the price of medicines for patients [103] is critical to ensuring that innovators are rewarded while needed treatments are developed and remain affordable.

Delinkage models can be found, for example, in the Drugs for Neglected Diseases Initiative [104], which carries out nonprofit drug development on diseases that primarily affect low- and middle-income countries. Delinkage can also take the form of a prize fund – an alternative incentive model that

offers a cash prize in return for the development of a specified target medicine. Prizes can carry the requirement that products should not be patented or that intellectual property is licensed. Further downstream, a similar result can be achieved through patent buy-outs that remunerate the originator for R&D investment but allow generic competition. International collaboration by groups of countries is likely to be required in order to share the cost burden of these new innovation models.

Delinkage will also help fix incentive problems that are inherent in the monopoly-based system of drug development – namely, that dependence on artificially high prices to recoup the cost of drug development only incentivizes research on diseases suffered by people who can afford to pay. This is likely to become an even wider conversation as current medicines prices outstrip the health budgets of even wealthy economies and needed essential medicines are not developed.

Chapter notes:

² This has provoked questions from the USA and the EU at the WTO Committee on Technical Barriers to Trade, a forum where regulations that create unwarranted barriers to trade are discussed (see: <http://keionline.org/node/2085>, accessed 1 February 2016).

³ For an example of a small market situation, see the Medicines Patent Pool's agreement on valganciclovir to treat cytomegalovirus (CMV) retinitis: (<http://www.medicinespatentpool.org/medicines-patent-pool-and-roche-sign-hiv-medicines-agreement-focus-on-preventing-blindness-in-people-living-with-hiv/>, accessed 1 February 2016).

⁴ For example, Thailand issued government use licences for medicines to treat HIV/AIDS and cancer between 2006 and 2008. Thanks to this policy, nearly 85 000 additional people were able to access needed treatments, and considerable savings were made for the health system of Thailand. See: Yamabha I, Mohara A, Tantivess S, Chaisiri K, Teerawattananon Y. Government use licences in Thailand: an assessment of the health and economic impacts. *Globalization and Health*. 2011;7:28 (<http://www.globalizationandhealth.com/content/7/1/28>, accessed 1 February 2016).

Conclusions

The label “Essential Medicine” should have consequences. It seems self-evident that when a proven effective medicine to treat a disease exists it should be made available and affordable to the patient and the community. When the market fails to do this, governments need to act. This will require dealing with patent and regulatory issues and may need international collaboration. A lack of action in this regard by governments and companies means depriving a population from access to important medical innovations and thus failing duties and responsibilities under human rights law.

Countries can take measures at the national level but this risks country-by-country and medicine-by-medicine controversies related to intellectual property. Access to essential medicines should be predictable and requires a global approach and greater international collaboration.

Several tools are at the disposal of governments and the international community to help avoid the pitfalls of monopoly pricing and to ensure greater affordability as a critical precondition to greater access to essential medicines.

Actions that governments and the international community can take include:

- *Engage in price negotiations* with the originator company for discounts in certain territories. This approach is useful when a medicines market is very small. However, in general it is less effective than robust competition in bringing prices down.
- *Use TRIPS flexibilities:* The WTO TRIPS Agreement affirms the rights of governments to grant compulsory licences, and to decide when such licences are appropriate. It also allows least-developed countries the right not to enforce pharmaceutical product patents for a period of time, and contains an amendment to help countries that are incapable of manufacturing medicines to import them under a compulsory licence. Governments should be wary of bilateral or multilateral trade agreements that seek to erode these rights.
- *Implement the CIPIH and GSPOA recommendations:* These two WHO processes resulted in concrete recommendations for governments and others seeking to increase access to medicines, including

- to explore sustainable funding/incentive schemes for medicine development and purchase,
 - to avoid trade agreement provisions that could reduce access to medicines,
 - to make use of compulsory licensing provisions,
 - to support the production and introduction of generic medicines, and
 - to consider taking measures to prevent abuse of intellectual property rights.
- *Ensure sustainable supplies of low-cost generics*, including through voluntary or compulsory licensing or “government use” of patents. The international community should consider extending the mandate of the Medicines Patent Pool to include all essential medicines.
 - *Ensure sustainable development of future essential medicines* through models that delink the cost of medicines development from the final price of the medical product. Such models could include:
 - nonprofit drug development such as practiced by DNDi,
 - cash prizes as an alternative to patents (known as “prize funds”), or
 - patent buy-out schemes.

The recent shifts in the WHO Essential Medicines paradigm demand a bold approach to avoid unnecessary delays in making these medicines available to the populations in need.

REFERENCES

1. WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers. Press release. Geneva: World Health Organization; 2014 (<http://who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/>, accessed 19 January 2016).
2. Magrini N, Robertson J, Forte G, Cappello B, Moja LP, de Joncheere K et al. Tough decisions on essential medicines in 2015. *Bull World Health Organ.* 2015;93:283–284 (<http://www.who.int/bulletin/volumes/93/4/15-154385.pdf?ua=1>, accessed 19 January 2016).
3. Executive Summary. The selection and use of essential medicines (2015). Report of the 20th WHO Expert Committee on the Selection and Use of Essential Medicines. Geneva: World Health Organization; 2015 (http://www.who.int/medicines/publications/essentialmedicines/Executive-Summary_EML-2015_7-May-15.pdf?ua=1, accessed 19 January 2016).
4. Global tuberculosis report 2015, 20th edition. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1, accessed 19 January 2016).
5. Hepatitis C Factsheet. Geneva: World Health Organization; 2015 (<http://www.who.int/mediacentre/factsheets/fs164/en/>, accessed 9 February 2016).
6. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;385:117-71.
7. The Gap report 2015. Geneva: UNAIDS; 2014 (http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf, accessed 9 February 2016).
8. Union for International Cancer Control. Review of cancer medicines on the WHO List of Essential Medicines: chronic myelogenous leukemia. Geneva: World Health Organization; 2014 (http://www.who.int/selection_medicines/committees/expert/20/applications/CML.pdf?ua=1, accessed 19 January 2016).
9. GLOBOCAN 2012. Estimated cancer incidence, mortality and prevalence worldwide in 2012. Lyon: International Agency for Research on Cancer; 2012 (<http://globocan.iarc.fr/Default.aspx>, accessed 19 January 2016).
10. Union for International Cancer Control. Review of cancer medicines on the WHO List of Essential Medicines: gastrointestinal stromal tumor. Geneva: World Health Organization; 2014 (http://www.who.int/selection_medicines/committees/expert/20/applications/GastrointestinalStromalTumour.pdf?ua=1, accessed 7 February 2016).
11. Mitri Z, Constantine T, O'Regan R. The HER2 receptor in breast cancer: Pathophysiology, clinical use, and new advances in therapy. *Chemother Res Pract.* 2012;2012:743193 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3539433/>, accessed 19 January 2016).

12. AIDS-Free World et al. Open letter: Reducing the price of bedaquiline. 10 September 2014 (http://www.msfaccess.org/sites/default/files/bedaquiline_pricing_letter_2014_sept_10_compressed_.pdf, accessed 15 February 2016).
13. Clayden P. Price of MDR TB drugs could be greatly reduced with competitive generic manufacture. HIV treatment bulletin (<http://i-base.info/htb/29373>, accessed 15 February 2016).
14. Hepatitis C medicines technology and market landscape. Geneva: UNITAID; February 2015 (http://www.unitaid.eu/images/marketdynamics/publications/HCV_Meds_Landscape_Feb2015.pdf, accessed 15 February 2016).
15. Experts in chronic myeloid leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood*. 2013;121(22):4439–42 (<http://www.bloodjournal.org/content/121/22/4439>, accessed 19 January 2016).
16. Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries. Closing the Cancer Divide: A blueprint to expand access in low and middle income countries. Boston: Harvard Global Equity Initiative; 2011 (http://gtfccc.harvard.edu/fs/docs/icb.topic1063570.files/ccd_report_111027.pdf, accessed 15 February 2016).
17. Staton T. FDA approves Roche's pricey new Herceptin partner, Perjeta. *FiercePharma*, 11 June 2012 (<http://www.fiercepharma.com/story/fda-approves-roches-pricey-new-herceptin-partner-perjeta/2012-06-11>, accessed 15 February 2016).
18. The selection of essential drugs. Report of a WHO Expert Committee. Geneva: World Health Organization; 1977 (WHO Technical Report Series, No. 615; http://apps.who.int/iris/bitstream/10665/41272/1/WHO_TRS_615.pdf, accessed 19 January 2016).
19. Hogerzeil HV. Essential medicines and human rights: what can they learn from each other? *Bull World Health Organ*. 2006;84:371-5 (<http://www.who.int/bulletin/volumes/84/5/371.pdf>, accessed 19 January 2016).
20. Chirac P, Laing R. Updating the WHO essential drugs list. *Lancet*. 2001;357(9262):1134.
21. Report on the global HIV/AIDS epidemic: June 2000. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2000 (http://data.unaids.org/pub/report/2000/2000_gr_en.pdf, accessed 19 January 2016).
22. Laing R, Waning B, Gray A, Ford N, 't Hoen E. 25 years of the WHO essential medicines lists: progress and challenges. *Lancet*, 2003;361:1723-9 (<http://apps.who.int/medicinedocs/documents/s17543en/s17543en.pdf>, accessed 19 January 2016).
23. The selection and use of essential medicines. Report of the WHO Expert Committee, 2002 (including the 12th Model List of Essential Medicines). Geneva: World Health Organization; 2003 (WHO Technical Report Series, No. 914; <http://apps.who.int/medicinedocs/pdf/s4875e/s4875e.pdf>, accessed 19 January 2016).

24. The 3 by 5 initiative. UNAIDS and the World Health Organization (<http://www.who.int/3by5/en/>, accessed 19 January 2016).
25. 't Hoen E, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents and access to medicines for all. *J Int AIDS Soc.* 2011;14:15 (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3078828/>, accessed 19 January 2016).
26. 't Hoen E, Hogerzeil HV, Quick J, Sillo H. A quiet revolution in global public health: the World Health Organization's prequalification of medicines programme. *J Pub Health Pol.* 2014;35(2):137-61(25).
27. Leukemia – chronic myeloid – CML: Statistics. Cancer.Net. (<http://www.cancer.net/cancer-types/leukemia-chronic-myeloid-cml/statistics>, accessed 19 January 2016).
28. 't Hoen E. A victory for global public health in the Indian Supreme Court. *J Pub Health Pol.* 2013;34(3):370-4.
29. Decision 344: Common Regime on Industrial Property, Article 7(e). SICE Foreign Trade Information System. Washington (DC): Organization of American States (<http://www.sice.oas.org/trade/JUNAC/decisiones/DEC344e.asp>, accessed 19 January 2016).
30. Common working paper of the EC, Hungary, Japan, Korea, Switzerland and Turkey to the Seattle ministerial declaration, Nov 29, 1999 (<http://www.jmcti.org/2000round/common01.pdf>, accessed 9 February 2016).
31. Scholtz M. Views and perspectives on compulsory licensing. Conference on AIDS and Essential Medicines and Compulsory Licensing, Geneva, 27–29 March 1999.
32. Venezuela position on TRIPS. GRAIN. 6 August 1999. (World Trade Organization document WT/GC/W/282; <https://www.grain.org/article/entries/2110-venezuela-position-on-trips>, accessed 19 January 2016).
33. The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. Geneva: World Health Organization; 2011 (http://www.who.int/phi/implementation/phi_globstat_action/en/, accessed 19 January 2016).
34. Declaration on the TRIPS agreement and public health. Adopted on 14 November 2001. Geneva: World Trade Organization; 2001 (http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm, accessed 19 January 2016).
35. International Covenant on Economic, Social and Cultural Rights. Geneva: Office of the United Nations High Commissioner for Human Rights; 1966 (<http://www.ohchr.org/EN/ProfessionalInterest/Pages/CESCR.aspx>, accessed 19 January 2016).
36. Substantive issues arising in the implementation of the international covenant on economic, social and cultural rights. General Comment 14 (2000). New York (NY): International Network for Economic, Social & Cultural Rights (ESCR-NET); 2006 (<http://www.escr-net.org/docs/i/425238>, accessed 19 January 2016).
37. Millennium Development Goals and beyond. Goal 8: Develop a global partnership for development. New York (NY): United Nations; 2015 (<http://www.un.org/millenniumgoals/global.shtml>, accessed 19 January 2016).

38. UN Sustainable Development Summit 2015. New York (NY): 25-27 September 2015 (<http://www.who.int/mediacentre/events/meetings/2015/un-sustainable-development-summit/en/>, accessed 7 February 2016).
39. Public health, innovation and intellectual property rights. Report of the Commission on Intellectual Property Rights, Innovation and Public Health. Geneva: World Health Organization; 2006 (<http://www.who.int/intellectualproperty/report/en/>, accessed 19 January 2016).
40. Resolution WHA66.22. Follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. In: Sixty-sixth World Health Assembly, Geneva, 20-28 May 2013. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/150173/1/A66_R22-en.pdf?ua=1&ua=1, accessed 19 January 2016).
41. Hubbard T, Love J. A new trade framework for global healthcare R&D. *PLoS Biol.* 2004;2(2);e52. doi:10.1371/journal.pbio.0020052.
42. Proposal by Bangladesh, Barbados, Bolivia and Surinam. Proposal for WHO discussions on a biomedical R&D treaty, 9 April 2009 (http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Suriname_R_DTreaty.pdf, accessed 19 January 2016).
43. Dentico N, Ford N. The courage to change the rules: a proposal for an essential health R&D treaty. *PLoS Med.* 2005;2(2);e14. doi:10.1371/journal.pmed.0020014.
44. An essential health and biomedical treaty. Submission by Health Action International Global, Initiative for Health & Equity in Society, Knowledge Ecology International, Médecins Sans Frontières, Third World Network (TWN). 22 June 2011 (http://www.who.int/phi/news/phi_1_joint_submission_en.pdf, accessed 19 January 2016).
45. Balasegaram M, Bréchet C, Farrar J, Heymann D, Ganguly N, Khor M et al. A global biomedical R&D fund and mechanism for innovations of public health importance. *PLoS Med.* 2015 May 11;12(5):e1001831 .
46. Hunt P. Promotion and protection of all human rights, civil, political, economic, social and cultural rights, including the right to development. Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Health. Annex: Mission to GlaxoSmithKline. United Nations General Assembly; Human Rights Council: No. A/HRC/11/12/Add.2, 5 May 2009. New York (NY): United Nations; 2009 (http://www.who.int/medicines/areas/human_rights/A_HRC_11_12_Add_2.pdf, accessed January 2016).
47. Hunt P. Promotion and protection of all human rights: human rights questions, including alternative approached for improving the effective enjoyment of human rights and fundamental freedoms. The right to health: report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. United Nations General Assembly: No. A/63/263, 11 August 2008. New York (NY): United Nations; 2008 (http://www.who.int/medicines/areas/human_rights/A63_263.pdf, accessed 19 January 2016).

48. Hunt P, Khosla R. Are drug companies living up to their human rights responsibilities? The perspective of the former United Nations Special Rapporteur (2002-2008). *PLoS Med.* 2010;7(9):e1000330. doi:10.1371/journal.pmed.1000330.
49. Grover A, Citro B, Mankad M, Lander F. Pharmaceutical companies and global lack of access to medicines: strengthening accountability under the right to health. *J Law Med Ethics.* 2012;40(2):234-250.
50. Global Commission on HIV and the Law. Risks, rights and health. New York (NY): United Nations Development Programme; 2012 (<http://www.hivlawcommission.org/index.php/report>, accessed 19 January 2016).
51. Pehudoff SK. Health, essential medicines, human rights and national constitutions. Geneva and Amsterdam: World Health Organization and Vrije Universiteit Amsterdam; 2008 (http://www.who.int/medicines/areas/human_rights/Pehudoff_report_constitutions_2008.pdf, accessed 19 January 2016).
52. United Nations Secretary-General's High-Level Panel on Access to Medicines. New York (NY): United Nations. (<http://www.unsgaccessmeds.org/the-process/>, accessed 19 January 2016).
53. Essential medicines selection: Sofosbuvir – addition – EML. Geneva: World Health Organization; 2015 (http://www.who.int/selection_medicines/committees/expert/20/applications/sofosbuvir/en/, accessed 19 January 2016).
54. Harvoni cost in USA, Canada, Europe, Egypt, India and more (<http://esofosbuvir.com/harvoni-cost-in-usa-canada-europe-egypt-india/>, accessed 9 February 2016).
55. WHO Model List of Essential Medicines application: Simeprevir 150mg capsule. (http://www.who.int/selection_medicines/committees/expert/20/applications/Simeprevir.pdf, accessed 19 January 2016).
56. Andrieux-Meyer I, Cohn J, Affonso de Araújo ES, Hamid SS. Disparity in market prices for hepatitis C virus direct-acting drugs. *Lancet Global Health.* 2015;311:e676-e677. doi: 10.1016/S2214-109X(15)00156-4 (<http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2815%2900156-4/fulltext>, accessed 19 January 2016).
57. van de Ven N, Fortunak J, Simmons B, Ford N, Cooke GS, Khoo S et al. Minimum target prices for production of direct-acting antivirals and associated diagnostics to combat hepatitis C virus. *Hepatology.* 2015;61(4):1174-82. doi: 10.1002/hep.27641 (<http://www.ncbi.nlm.nih.gov/pubmed/25482139>, accessed 19 January 2016).
58. Gilead Sciences announces fourth quarter and full year 2014 financial results. Press release. Foster City (CA): Gilead; 3 February 2015 (<http://www.gilead.com/news/press-releases/2015/2/gilead-sciences-announces-fourth-quarter-and-full-year-2014-financial-results>, accessed 19 January 2016).
59. Johnson & Johnson 2014 Annual Report (p. 5). New Brunswick (NJ): Johnson & Johnson; 2014 (http://files.shareholder.com/downloads/JNJ/1074108325x0x815170/816798CD-60D9-4653-BB5A-50A66FD5B9E7/JNJ_2014_Annual_Report_bookmarked_.pdf, accessed 19 January 2016).

60. Bristol-Myers Squibb 2014 Annual Report (p. 36). New York (NY): Bristol-Myers Squibb Company; 2014 (http://s2.q4cdn.com/139948097/files/doc_financials/annual%202014/BMS-2014-Annual-Report.pdf, accessed 19 January 2016).
61. AbbVie reports fourth-quarter and full-year 2014 financial results. Financial release. Chicago (IL): AbbVie; 30 January 2015 (<http://www.abbvieinvestor.com/phoenix.zhtml?c=251551&p=irol-newsArticle&id=2012116>, accessed 19 January 2016).
62. Caret R, Harvey T, Gerber J. Wyden-Grassley Sovaldi investigation finds revenue-driven pricing strategy behind \$84,000 hepatitis drug. Press release. Washington (DC): United States Senate Committee on Finance; 1 December 2015 (<http://www.finance.senate.gov/ranking-members-news/wyden-grassley-sovaldi-investigation-finds-revenue-driven-pricing-strategy-behind-84-000-hepatitis-drug>, accessed 19 January 2016).
63. Gilead slide presentation. Aside from access and physician demand, there are a number of softer issues that could affect Gilead's final pricing decision. (<https://docs.google.com/document/d/16m9tH0lq7sv-Z9006QgBhtdV5VRwmeE4oVcBcm6uTQc/edit>, accessed 19 January 2016).
64. Waarom farmaceuten niets zeggen over hoe hun medicijnprijzen worden bepaald. De Correspondent, 6 January 2016 (<https://decorrespondent.nl/3853/Waarom-farmaceuten-niets-zeggen-over-hoe-hun-medicijnprijzen-worden-bepaald/460423143136-33662a62>, accessed 19 January 2016).
65. Hepatitis C: Doctors of the World - Médecins du Monde opposes Sofosbuvir patent in Europe. Press release. Paris: Médecins du Monde; 10 February 2015 (<http://www.businessinsider.com/r-natco-moves-to-oppose-gilead-hepatitis-c-drug-patent-in-india-source-2014-10?IR=T>; <http://www.medecinsdumonde.org/gb/Doctors-of-the-World-Medecins-du-Monde-is-filing-a-patent-challenge-to-Gilead-s-patent-on-sofosbuvir-at-the-European-Patent-Office>, accessed 19 January 2016).
66. Silverman E. The hepatitis C scorecard: Gilead is trouncing AbbVie, but at a price. New York (NY): The Wall Street Journal; 12 February 2015 (blogs.wsj.com/pharmalot/2015/02/12/the-hepatitis-c-scorecard-gilead-is-trouncing-abbvie-but-at-a-price/, accessed 19 January 2016).
67. Gilead announces generic licensing agreements to increase access to hepatitis C treatments in developing countries. Press release. Foster City (CA): Gilead; 15 September 2014 (<http://www.gilead.com/news/press-releases/2014/9/gilead-announces-generic-licensing-agreements-to-increase-access-to-hepatitis-c-treatments-in-developing-countries>, accessed 19 January 2016).
68. Chronic hepatitis C treatment expansion: generic manufacturing for developing countries. Fact sheet. Foster City (CA): Gilead; August 2015 (<http://www.gilead.com/~media/files/pdfs/other/hcvgenericagreementfactsheet.pdf?la=en>, accessed 19 January 2016).
69. MSF responds to BMS commercial strategy for hepatitis C drug daclatasvir in developing countries. Statement, speeches, letters. Geneva: Médecins Sans Frontières; 3 November 2014 (<http://www.msffaccess.org/content/msf-responds-bms-commercial-strategy-hepatitis-c-drug-daclatasvir-developing-countries>, accessed 19 January 2016)

70. HCV developing world strategy. New York (NY): Bristol-Myers Squibb (<http://www.bms.com/responsibility/access-to-medicines/Pages/HCV-developing-world-strategy.aspx>, accessed 19 January 2016).
71. The Medicines Patent Pool signs licence with Bristol-Myers Squibb to increase access to hepatitis C medicine daclatasvir. Press release. Geneva: The Medicines Patent Pool; 23 November 2015 (<http://www.medicinespatentpool.org/the-medicines-patent-pool-signs-licence-with-bristol-myers-squibb-to-increase-access-to-hepatitis-c-medicine-daclatasvir/>, accessed 19 January 2016).
72. Cancer. Fact sheet, No 297. Geneva: World Health Organization; 2015 (<http://www.who.int/mediacentre/factsheets/fs297/en/>, accessed 19 January 2016).
73. Shulman L, Torode J. Preface and methodology: 2014 cancer medicines review (review of cancer medicines on the WHO list of essential medicines). Geneva: Union for International Cancer Control; 2014 (http://www.who.int/selection_medicines/committees/expert/20/applications/UICC_EMLreview-preface_methodology2014.pdf?ua=1, accessed 19 January 2016).
74. Latest world cancer statistics. Global cancer burden rises to 14.1 million new cases in 2012: marked increase in breast cancers must be addressed. Press release. Lyon: International Agency for Research on Cancer; 2013 (http://www.iarc.fr/en/mediacentre/pr/2013/pdfs/pr223_E.pdf, accessed 19 January 2016).
75. Breast cancer drug costing tens of thousands of pounds more than other treatments 'unaffordable' for NHS. Press release. London: National Institute for Health and Care Excellence; 23 April 2014 (<https://www.nice.org.uk/news/press-and-media/breast-cancer-drug-costing-tens-of-thousands-of-pounds-more-than-other-treatments-unaffordable-for-nhs>, accessed 19 January 2016).
76. Data exclusivity / generics / biosimilars. Regulatory and procedural guidance. London: European Medicines Agency (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000211.jsp&mid=WC0b01ac0580031b0a, accessed 19 January 2016).
77. Murphy B. Debate over naming of biosimilars intensifies ahead of WHO meeting. London: The Pharmaceutical Journal; 11 June 2015 (<http://www.pharmaceutical-journal.com/news-and-analysis/news/debate-over-naming-of-biosimilars-intensifies-ahead-of-who-meeting/20068663.article>, accessed 19 January 2016).
78. Copies of biotechnology-derived medicinal products ("biosimilars"): the European Medicines Agency (EMA) makes a timid shift towards a more pragmatic approach. Medicines in Europe Forum and ISDB; October 2013 (<http://english.prescrire.org/en/79/207/46302/3009/2506/SubReportDetails.aspx>, accessed 19 January 2016).
79. 2 patents down, 1 to expire: herceptin biosimilar coming to EU. Biosimilar News; 11 April 2014 (<http://www.biosimilarnews.com/2-patents-down-1-to-expire-herceptin-biosimilar-coming-to-eu>, accessed 19 January 2016).

80. Biosimilars of trastuzumab. Generics and Biosimilars Initiative Online (GaBi); 19 September 2014. Updated November 2015 (<http://www.gabionline.net/Biosimilars/General/Biosimilars-of-trastuzumab>, accessed 19 January 2016).
81. Kresege N, Gokhale K. Roche herceptin copy's price still out of reach in India. Bloomberg Business; 21 January 2014 (<http://www.bloomberg.com/news/articles/2014-01-20/roche-herceptin-copy-s-price-still-out-of-reach-in-india>, accessed 19 January 2016).
82. Purple Book. Lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Silver Spring (MD): U.S. Food and Drug Administration (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>, accessed 19 January 2016).
83. Knowledge Ecology International trastuzumab price survey (https://docs.google.com/spreadsheets/d/1VDdTUAD1yqH-gPq1D_p0f6bwChkjnK7-Khlz0MU72hY/pub?gid=2#, accessed 9 February 2016).
84. Proposal for the inclusion of trastuzumab in the WHO Model List of Essential Medicines for the treatment of HER2-positive breast cancer. Washington (DC), San Francisco (CA) and New York (NY): Knowledge Ecology International, University of California San Francisco, and Universities Allied for Essential Medicines, and Young Professionals Chronic Disease Network (YP-CDN); 30 November 2012 (http://www.who.int/selection_medicines/committees/expert/19/applications/Trastuzumab2_8_2_A_Ad.pdf, accessed 19 January 2016).
85. 't Hoen E. Access to Cancer Treatment: A study of medicine pricing issues with recommendations for improving access to cancer medication. Report prepared for OXFAM, 2 May 2014 (<https://www.ciaonet.org/attachments/27387/uploads>, accessed 7 February 2016).
86. Staton T. India's Biocon promises herceptin biosim launch by fiscal year-end. Fierce Pharma. 21 August 2013 (<http://www.fiercepharma.com/story/indias-biocon-promises-herceptin-biosim-launch-fiscal-year-end/2013-08-21>, accessed 19 January 2016).
87. Rajagopal D. Cancer drugs made by Emcure, Roche still expensive for patients. The Economic Times. 1 February 2013 (http://articles.economictimes.indiatimes.com/2013-02-01/news/36684537_1_cancer-drugs-roche-herceptin, accessed 19 January 2016).
88. Chen W, Jiang Z, Shao Z, Sun Q, Shen K. An economic evaluation of adjuvant trastuzumab therapy in HER2-positive early breast cancer. Value in Health. 2009;12(3);S82-S84 (<http://www.ispor.org/consortiums/asia/ViH/An-Economic-Evaluation-of-Adjuvant-Trastuzumab-Therapy.pdf>, accessed 19 January 2016).

89. Colombia issues further draft guidelines for biologicals. Generics and Biosimilars Initiative Online (GaBi). 12 June 2015 (<http://gabionline.net/Guidelines/Colombia-issues-further-draft-guidelines-for-biologicals>, accessed 19 January 2016).
90. Tuberculosis. Fact sheet, No. 104. Geneva: World Health Organization; October 2015 (<http://www.who.int/mediacentre/factsheets/fs104/en/>, accessed 1 February 2016).
91. Bothamley G, Furin J. Reducing the price of bedaquiline. Open letter from AIDS-Free World to Dr Stoffels of Janssen Pharmaceuticals Companies of Johnson & Johnson. 10 September 2014 (http://www.msfaccess.org/sites/default/files/bedaquiline_pricing_letter_2014_sept_10_compressed_.pdf, accessed January 2016).
92. Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution? A critical analysis of tiered pricing to improve access to medicines in developing countries. *Global Health*. 2011;7:39 (<http://www.globalizationandhealth.com/content/7/1/39>, accessed 19 January 2016).
93. Remuneration guidelines for non-voluntary use of a patent on medical technologies. Health Economics and Drugs. TCM Series, No. 18. Geneva: World Health Organization; 2005 (http://www.who.int/hiv/amds/WHOTCM2005.1_OMS.pdf, accessed 19 January 2016).
94. Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health: Decision of the General Council. Geneva: World Trade Organization; 1 September 2003 (https://www.wto.org/english/tratop_e/trips_e/implem_para6_e.htm, accessed 19 January 2016).
95. Request for an extension of the transitional period under article 66.1 of the trips agreement for least developed country members with respect to pharmaceutical products and for waivers from the obligation of articles 70.8 and 70.9 of the trips agreement. Communication from Bangladesh on behalf of the LDC Group. World Trade Organization Council for Trade-Related Aspects of Intellectual Property Rights (IP/C/W/605). 23 February 2015 (<http://www.ip-watch.org/weblog/wp-content/uploads/2015/02/LCD-pharma-waiver-proposal-Feb-2015.pdf>, accessed 19 January 2016).
96. Shashikant S. Unconditional 17-year exemption from pharmaceuticals patents agreed. TWN Infor Service on Intellectual Property Issues (Nov15/01). London: Third World Network; 3 November 2015 (http://twon.my/title2/intellectual_property/info.service/2015/ip151101.htm, accessed 19 January 2016).
97. Mezher M. Trade talks stumble of biologics data exclusivity. Regulatory Affairs Profession Society; 11 February, 2015 (<http://www.raps.org/Regulatory-Focus/News/2015/02/11/21309/Trade-Talks-Stumble-over-Biologics-Data-Exclusivity/#sthash.9nLxqUdp.dpuf>, accessed 19 January 2016).

98. Fields of intellectual property protection, chapter 2. Geneva: World Intellectual Property Organization. (<http://www.wipo.int/export/sites/www/about-ip/en/iprm/pdf/ch2.pdf>, accessed 19 January 2016).
99. Basheer S, Samuel R. Bayer's Nexavar and the "working" of compulsory licensing. Mind the patent (information) gap! Spicy IP, April 2015 (<http://spicyip.com/wp-content/uploads/2015/04/Report-on-Bayer-for-writ-Finalized.pdf>, accessed 19 January 2016).
100. Promoting access to medical technologies and innovation: intersections between public health, intellectual property and trade. Geneva: World Health Organization, World Intellectual Property Organization and World Trade Organization; 2012 (http://www.wipo.int/edocs/pubdocs/en/global_challenges/628/wipo_pub_628.pdf, accessed 19 January 2016).
101. Abbott F. Intellectual property and public health: meeting the challenge of sustainability. Global Health Programme Working Paper, No. 7/2011; FSU College of Law, Public Law Research Paper, No. 566. 15 November 2011 (<http://ssrn.com/abstract=1965458>, accessed 19 January 2016).
102. Reichman J, Hasenzahl C. Non-voluntary licensing of patented inventions: historical perspective, legal framework under TRIPS, and an overview of the practice in Canada and the USA. Issues paper, No. 5. Geneva: UNCTAD-ICTSD Project on IPRs and Sustainable Development; 2003 (http://www.ictsd.org/downloads/2008/06/cs_reichman_hasenzahl.pdf, accessed 19 January 2016).
103. Thiru's blog. WHO/WIPO/WTO trilateral report: human rights, de-linkage and the R&D treaty. Knowledge Ecology International. 15 February 2013 (<http://keionline.org/node/1650>, accessed 19 January 2016).
104. Pécoul B. Time for a reality check for neglected diseases. DNDi Viewpoint. February 2014 (<http://www.dndi.org/advocacy/viewpoint/1757-2014-feb-pecoul.html?highlight=WyJkZWxpbmthZ2UiXQ==>, accessed 19 January 2016).

UNITAID Secretariat

Chemin de Blandonnet 10
– BIBC III – 8th Floor
1214 Vernier Switzerland

T +41 22 791 55 03
F +41 22 791 48 90
unitaid@who.int
www.unitaid.org

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