

“Ellen ’t Hoen is a towering figure in the movement for access to medicine. Truly indispensable.” – Dylan Mohan Gray

PRIVATE PATENTS AND PUBLIC HEALTH

CHANGING INTELLECTUAL PROPERTY RULES
FOR ACCESS TO MEDICINES

Ellen ’t Hoen



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Ellen 't Hoen
January 2016

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*I dedicate this book to the memory of Dr Andrew Herxheimer,
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**PRIVATE PATENTS
AND PUBLIC HEALTH**
Changing intellectual
property rules
for access
to medicines

Ellen 't Hoen

INTRODUCTION

Millions of people around the world do not have access to the medicines they need to treat disease or alleviate suffering. Strict patent regimes interfere with widespread access to medicines by creating monopolies that maintain medicines prices well beyond the reach of those who need them.

The magnitude of the AIDS crisis in the late nineties brought this to the public's attention when millions of people in developing countries died from an illness for which medicines existed, but were not available or affordable. Faced with an unprecedented health crisis—8,000 people dying daily—the public health community launched an unprecedented global effort that eventually resulted in the large-scale availability of quality generic HIV medicines and a steady scale-up in access to those medicines. This has allowed nearly 13 million people¹ to lead longer, healthier lives. However, trends in international intellectual property law could impact many of the policy tools used to scale up HIV treatment.

Developments in global health and specifically access to medicines policies are now at an important juncture. Impressive progress has been made in access to medicines for HIV and many lessons can be learned from that experience. But it is important to examine whether those lessons can be applied for other diseases. Today's pharmaceutical patent regime affects almost all medicines developed since 1995 in most

countries. The high prices of new medicines, such as for cancer, tuberculosis and hepatitis C, cause huge access challenges globally, in both developed and developing countries. These new global challenges pose the question of whether the public health approaches to medicines patents developed in response to the HIV/AIDS crisis are exclusive to HIV or whether they can be applied more broadly.

This book provides a history of the parallel developments in global public health and international patent laws: detailing the current situation, how we got here, and how we can move forward to best protect the future of medical innovation as well as the lives that will depend on it. **This book is an update of an earlier account that was published in 2009: *The Politics of Pharmaceutical Monopoly Power: Drug Patents, Access, Innovation and the Application of the WTO Doha Declaration on TRIPS and Public Health.***²

It is divided into the following chapters:

INTRODUCTION: Patents and patients are today at a critical juncture; the global HIV epidemic and the international response to it is the critical case study to best understand why.

CHAPTER 1: Ending Global Diversity in Patent Laws: The formation of the World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) resulted in the first enforceable international standards for patent protection and, as a result, in problems for public health. This chapter explores how TRIPS came about, and details the growing tensions between the public health community and those looking for greater intellectual property protection.

CHAPTER 2: Turning the Tide: The growing patent/patient tension resulted in the 2001 Doha Declaration on TRIPS and Public Health, the pivotal point in international negotiations about patents and medicines. This chapter details its key provisions, and explains how those provisions should be interpreted.

CHAPTER 3: From Declaration to Application: Since 2001, governments and other actors around the world have used Doha principles and flexibilities to implement key policy changes to improve access to medicines. This chapter presents data and analysis on how these principles and provisions have been used over the last decade and a half.

CHAPTER 4: Closing the Policy Space: TRIPS was meant to strike a balance between protecting innovators and protecting the public interest; it contains several flexibilities to ensure that balance can be maintained. But regional trade agreements and other trends are shrinking that space

by binding countries to more stringent ‘TRIPS-plus’ rules. This chapter details TRIPS’ key flexibilities for public health, and how recent trends threaten to limit their use.

CHAPTER 5: The New Frontiers: The HIV epidemic laid bare the conflicts between patent regimes and a growing need for the life-saving medicines those regimes priced out of reach. But HIV is not the only disease for which high prices are a problem. This chapter details several of the newest frontiers of health needs and high prices: cancer, hepatitis C and tuberculosis.

CHAPTER 6: Fixing the Broken R&D System: At the heart of the price/patent debate is the question of how to support the expensive research and development (R&D) that leads to pharmaceutical innovation, while also guaranteeing access to the products of that innovation. The system as it currently stands is broken and fails to incentivise R&D for diseases that have profound public health impact but little market promise. This chapter outlines international efforts to address this concern, especially the ‘delinkage model’ and a proposed International R&D Agreement.

CHAPTER 7: Restoring the Balance: There is a crying need to restore the balance in the patent system, and to explore alternative ways to ensure neither new innovation nor the health needs of the global population are ignored. The lessons of HIV can inform this process, but there are other factors at work as well. This chapter evaluates the HIV experience and the extent to which past success can guide future action, as well as details where new strategies are needed.

WHY PATENTS MATTER TO PATIENTS

“We have no model which would meet the need for new drugs in a sustainable way. You can’t expect for-profit organisations to do this in a large scale. If you want to establish a system where companies systematically invest in this kind of area [low-cost medicines for developing-countries], you need a different system.”

- Former Novartis CEO, Daniel Vasella, in the *Financial Times*, September 2006³

New essential medicines can help people lead longer, healthier lives. Unfortunately, they are often priced to exclude many of those who need them most, and there are many diseases for which new medicines are never made or brought to market in the first place. This is due in a large

part to the way that innovation is currently rewarded through the patent system.

Patents are a form of intellectual property (IP). IP refers to the legal rights that result from intellectual activity in the industrial, scientific, literary and artistic fields. IP has two branches: industrial property (e.g. inventions (patents), trademarks, industrial designs, geographical indications) and copyright (and related rights). IP law aims at safeguarding creators and other producers of intellectual goods and services by granting them certain time-limited rights to control the use made of those innovations. Patents are relevant to access to medicines because they can increase the price of a medicine.

Governments grant patents to people who invent something new, non-obvious and useful. A patent holder can prevent others from making, using, importing, or selling their invention for a certain period of time without his or her consent. In exchange, the public is meant to benefit from the sharing of scientific advancements. The patent system is intended to strike a balance between incentivising innovation, protecting innovators, and ensuring maximum public benefit from innovation.

Today's system, particularly within the area of pharmaceutical innovation, is out of balance. It provides excessive financial rewards to patent holders, mostly large pharmaceutical companies. Patent holders may use the de facto monopoly created by the patent to ask the highest possible price for their products, which excludes those who cannot pay from access.

This is particularly hard-felt in developing countries where people often pay out of pocket (rather than through insurance or social security) and cannot afford to pay high prices for medicines that are under patent. But high pricing of medicines is increasingly posing challenges for high-income countries too.

A recent example is sofosbuvir, a medicine that is part of a 12-week treatment of hepatitis C, which can cause a potentially lethal infection of the liver. The production cost of sofosbuvir is estimated to be US\$ 68–136⁴ for a course of treatment. However, the company that holds the patent sells it for up to US\$ 84,000⁵, a difficult price for even developed countries to afford.⁶ The cancer drug imatinib (brand name Gleevec in the United States (US), Canada and South Africa; Glivec elsewhere; hereafter Glivec) also demonstrates the huge differences between a monopoly price and a generic price. South Africa pays over US\$ 3,227 per patient per month for the branded product Glivec, while in India where the patent was not

granted, the drug is priced at US\$ 170 for a month's treatment.⁷ In the US, the price of Glivec has nearly tripled since its introduction in 2001; it now costs US\$ 92,000 a year.⁸

Monopoly pricing is justified by the industry to compensate for the cost of R&D of new drugs. Without patents, pharmaceutical R&D will come to a standstill, they argue. It is, of course, true that commercial companies will not invest in the development of a new product if a competitor that did not have to make such investments can market the product immediately after drug regulatory approval. This is called the 'free-rider' issue and the patent system is designed to deal with the free-rider issue by creating a monopoly for the innovator.

But recent years have shown an unprecedented increase in drug prices, far greater than what is necessary to sustain the R&D efforts of the industry. Cancer drug prices have doubled in the US in the last decade, from an average of US\$ 5,000 a month to US\$ 10,000⁹ a month. Prices of new cancer medications are rising at a higher rate than public and private spending on health care, creating challenges even for health systems and individuals in high-income countries.

The profit-motive is also responsible for pharmaceutical company neglect of key public health issues. It is not profitable or not profitable enough—and therefore not commercially interesting—for companies to invest in the development of medicines for people with limited or no purchasing power. Not-for-profit drug development organisations are working to fill gaps in drug development for certain neglected diseases, but they struggle with securing funding for their R&D activities.¹⁰

“Unfortunately, the standard economic model for drug development, in which industry takes all of the risk in R&D and gets a return on investment from successful products, does not work for diseases that primarily impact low-income countries and developing healthcare systems,” said Andrew Hollingsworth, policy manager of the Association of the British Pharmaceutical Industry, in the United Kingdom newspaper, *The Observer*, in response to questions about the role of the pharmaceutical industry in dealing with the Ebola outbreak in West Africa.¹¹

The message that the needs of people in developing countries are not part of the pharmaceutical industry's commercial priorities was repeated by Bayer's CEO Marijn Dekkers seven years later in 2013. Responding to the Indian compulsory licence that allowed for generic manufacture of the cancer drug sorafenib (Nexavar) in India, he said: “Is this going to have a big effect on our business model? No, because we did not develop

this product for the Indian market, let's be honest. We developed this product for Western patients who can afford this product, quite honestly. It is an expensive product, being an oncology product."¹²

Out of concern for access to low-cost versions of new medicines, developing countries like India used to restrict the patent term for medicines, or not allow medicines to be patented at all. This changed after the World Trade Organization (WTO) was established in 1995. The WTO requires almost all its members to grant and enforce patents, or face penalties. This has resulted in the gradual globalisation of an incentive system that leaves unprofitable health needs unmet and creates huge challenges to accessing treatments that do exist, but are priced at a level most people in low- and middle- income countries cannot afford.

With new medicines—notably on hepatitis C and cancer—increasingly priced at levels that even high-income countries cannot afford, the pressure on this system is growing. The world is now at a critical juncture, and it is time to examine the experience of the last two decades of a globalised patent system and determine the best way to move forward.

Nowhere have the many challenges at issue played out so starkly than through the HIV crisis.

HOW THE HIV PANDEMIC CHANGED EVERYTHING

The HIV crisis brought about important changes in global public health. As the first major international public health emergency in an era of newly-minted international patent rules, it exposed fault lines in the systems available for coping with disease in affordable, effective ways, as well as serious differences in perspective between different stakeholders. It is therefore the critical case study on patents, patients, and the on-going struggle to ensure innovation on, and access to, essential medicines. The extent to which lessons learned from HIV can be applied to other illnesses is still unclear, but to understand the history of patents and HIV is to begin to understand what is at stake in the debate.

The access to AIDS medicines crisis hit a crescendo just after countries had, in 1995, created the WTO, and with it, TRIPS—setting out global standards for the protection of IP. The TRIPS Agreement created the obligation for all WTO members to grant patents with a minimum of 20 years and the obligation to grant patents in all fields of technology. Before TRIPS, many developing countries did not grant pharmaceutical product patents and/or they limited patent terms, which allowed a generic

medicines industry to flourish in some of those countries. Generic companies made relatively new products available at lower prices; these products would have been expensive or unavailable had they been patent-protected.

• *For more information on TRIPS and generic medicines, see Chapter 1, “Globalising the patent regimes of wealthy nations”*

The TRIPS Agreement was negotiated without any involvement of the health community. But the HIV crisis focused the health community’s attention on the issue; as a result, its influence on the actual implementation of TRIPS has been much more significant.

In 1996, medical breakthroughs ushered in highly active antiretroviral therapy (HAART), which combined several (usually three) different classes of antiretrovirals (ARVs) into one treatment regimen that attacked the virus at various places in its life cycle. This new treatment strategy promised to change HIV infection from a death sentence into a manageable chronic disease. But there was a catch. The life-saving medicines were purchasable only from originator companies, which produced them in small quantities carrying paralysing price tags of US\$ 10,000 to US\$ 15,000 per person per year, and controlled the patents to maintain their monopoly.

When, in early 2000, the world turned its long overdue attention to the HIV/AIDS crisis in the developing world, people realised a better solution was necessary. By that time, 24.5 million people were living with HIV in Africa¹³—and only one in a thousand had access to HAART. AIDS was killing nearly 8,000 people a day. The high price of HIV/AIDS medicines and the staggering loss of lives called into question the relationship between patent protection and public health.

Producers of generic versions of ARVs, mostly from India, offered them at lower prices, but controversies broke out over patents on ARVs in the countries needing those medicines. In other words, importing medicines from India into a country where those medicines were patented proved to be a problem. Medicines patents in many countries restricted procurement agencies such as UNICEF, the International Dispensary Association (IDA), and non-governmental organisations (NGOs) like Médecins Sans Frontières (MSF) from distributing generic ARVs made in India.

Health groups, treatment activists and health professionals demanded greater flexibility in the application of patent law where health is concerned and campaigned for measures to protect public health and promote access to medicines.

In 1998, a group of 39 pharmaceutical companies along with the Pharmaceutical Manufacturers Association of South Africa sued the South African government over its medicines act, which included provisions to increase access to lower-priced medicines. One of their arguments was that the act was not in accordance with the TRIPS agreement. At the time, nearly a fifth of the South African population was living with HIV.¹⁴

Massive public outcry against the companies who had filed suit against South Africa eventually led them to back down in 2001 from a case described in the United Kingdom newspaper, *The Guardian*, as a humiliating “PR disaster.”¹⁵

In advance of the November 1999 WTO Ministerial Conference in Seattle, NGO demands for recognition of the primacy of public health over patents grew stronger, spurred by the need for wider access to medicines for HIV and concerns about company resistance to that access in places like South Africa. The conference collapsed with no agreement, in part due to concerns about the WTO’s effect on public health.

- *For more information, see Chapter 1, “Health at the centre of trade talks”*

A few months later, at the next WTO ministerial in Qatar in 2001, members adopted the Doha Declaration on TRIPS and Public Health. The declaration gave countries practical tools and political confidence to take measures to overcome patent barriers that impeded access to medicines. It was a direct response to the demands by developing countries struggling with the AIDS epidemic and supported by the public health community and treatment activists.

The Doha Declaration signalled a sea change in thinking about patents and medicines. It is at the root of a cascade of activities aimed at reformulating IP protection as a social policy tool for the benefit of society as a whole, rather than a mechanism to protect only limited commercial interests.

- *For details on the Doha Declaration, see Chapter 2*

Meanwhile, Indian generic manufacturers in 2001 began to take advantage of a clause within the TRIPS agreement allowing certain developing countries to delay implementation of patents on medicines until 2005. In 2001, the Indian generic manufacturer, Cipla, announced that it would make a generic triple ARV therapy for HIV for \$350 per person per year; it was not long before other generic producers followed.

The price of a drug is related to the degree of competition among producers. In the case of ARVs for HIV, it was only after competing generic products arrived on the market that originator drug companies agreed to a dramatic reduction in their prices.¹⁶ If generic competition increases, in general, prices come down.

In 2002, the World Health Organization (WHO) added several HIV medicines to its Essential Medicines List (EML), which provides guidance for governments seeking to meet the priority health needs of their populations. It also established a mechanism, the Prequalification of Medicines Programme (PQP), to ensure the quality of medicines procured by United Nations (UN) agencies and others. The PQP helped scale up access to treatment by providing a stringent, straightforward way to validate the quality of generic medicines and formulations such as so-called fixed-dose combinations, which combine several medicines in one pill.

• *For more on the PQP, see Box 2, “The Quiet Revolution at the WHO”*

Financing for treatment became available through various mechanisms, beginning with the launch of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002, the launch of the President’s Emergency Plan for AIDS Relief (PEPFAR) in 2003 and UNITAID in 2006.

On 1 December 2003, WHO and UNAIDS declared the lack of HIV/AIDS treatment to be a global public health emergency. They launched the “3 by 5” campaign, to get 3 million people on antiretroviral treatment by 2005. The political momentum of the campaign, combined with new funding from governments, the Global Fund, and PEPFAR, and later from UNITAID (established by a coalition of developed and developing country governments to undertake strategic market interventions to increase treatment availability for HIV, tuberculosis and malaria), allowed countries to begin purchasing HIV/AIDS medicines in large volumes. Yet to optimise buying power and cover all patients needing treatment, the price of the ARVs would have to be lowered drastically. The world came together to make this happen.

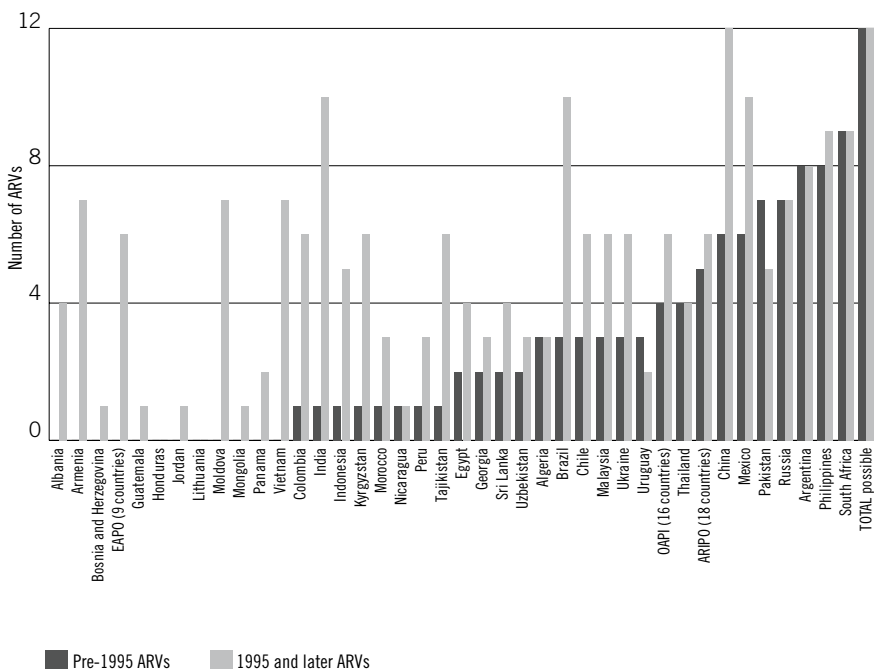
Fifteen years later, more than 13 million people globally receive ARV treatment, mostly in the form of low-cost generic medicines.¹⁷ In sub-Saharan Africa, 87% of the people who know their HIV status are receiving ARVs. Almost 76% of those on ARVs have achieved viral suppression, according to UNAIDS.¹⁸ Globally, however, 61–63% of people who need treatment still do not yet receive it.¹⁹

In 2011, the US National Institutes of Health published a report²⁰ that found treatment with ARVs decreased the chance of HIV transmission to a partner by 96%. This news finally promised a way to break the back of the AIDS epidemic, if all who needed medicines could get access to them. At the same time, improved tolerability profiles of new HIV medicines and continued studies allowed the WHO to continue recommending HIV positive people start on therapy earlier in the disease progression, culminating in a new recommendation on 30 September 2015 to “treat all” people exposed to or at high risk of HIV exposure.²¹

But the 2005 deadline for developing countries (with the exception of least-developed countries) to fully implement the TRIPS Agreement meant a closing window for many of the generic medicines manufacturers who had become the leading drug suppliers to people living with HIV in the developing world. Generic versions of drugs brought to market before TRIPS went into effect could still be manufactured. But newer, better tolerated treatment regimens preferred by the WHO faced patent barriers.

- *For more on this closing policy space, see Chapter 4*

FIGURE 1 PATENT APPLICATIONS FOR ANTIRETROVIRALS (ARVS) BEFORE AND AFTER 1995



ARIPO African Regional Intellectual Property Office (covers 18 countries)
OAPI Organisation Africaine de la Propriété Intellectuelle (covers 16 countries)
EAPO EurAsian Patent Office (covers 9 countries)

SOURCE

ARV Patents on the rise? An analysis of ARV patent status in 75 low- and middle-income countries, *Presentation to the XIX AIDS Conference*, Washington, DC, 2012, available here: <http://www.medicinespatentpool.org/wp-content/uploads/ARV-Patenting-Trends-FINAL2.pdf>

After the adoption of the Doha Declaration and the establishment of funding mechanisms for the treatment of HIV, countries started to use TRIPS flexibilities to access lower-priced generic medicines. This was done on a fairly large scale, often in the context of government procurement. In particular, there has been widespread use of two flexibilities: the least-developed country (LDC) waiver, or Paragraph 7 mechanism, which allows LDCs to not grant or not enforce pharmaceutical product patents; and the use of compulsory licensing, including government use, which allows procurement of medicines even when they are patented.

- *For more information, see Chapter 3, “The practical application of the Doha Declaration”*

Some companies also engaged in voluntary licensing of ARV patents, sometimes in response to non-voluntary measures by governments. Licences, whether voluntary or compulsory, allow for the manufacture and supply of generic medicines, even where a patent is otherwise in force.

In 2010, UNITAID established the Medicines Patent Pool (MPP) for HIV medicines to ensure licences related to patents needed to produce WHO-recommended ARVs were available to generic producers. This created a predictable system of licences with terms and conditions formulated to serve public health.

- *For more on the MPP, see Chapter 3, “Medicines Patent Pool”*

While the fight against HIV is not yet over, huge strides have been made and continue to be made in scaling up access to life-saving ARVs. The critical question now is whether the HIV story is one that will repeat for other disease areas. Highly-priced medicines for hepatitis C and some cancers have sparked debates reminiscent of those around HIV in the late 1990s. But the policy space that allowed the original HIV treatment scale-up is increasingly closing. At the same time, new issues in patents and access to medicines are emerging.

- *For more information, see Chapter 4, “Trade agreements closing in on TRIPS flexibilities” and Chapter 5, “Pharmaceutical innovation and access”*

But first, we will take a look at the details of that policy space, starting with the agreement that began it all, TRIPS.

TIMELINE OF EVENTS RELATED TO ACCESS TO MEDICINES AND INTELLECTUAL PROPERTY

- 1957–1962 In the late 1950s and early 1960s, the United States invokes government use powers on a routine basis to order generic medicines from abroad, regardless of the patent status of the products.
- 1965 Pfizer Corporation unsuccessfully challenges the United Kingdom’s routine use of compulsory licences (“Crown use”) for the provision of generic medicines to the National Health Service.
- 1969–1992 Canada issues 613 compulsory licences for importation and/or local production of medicines as part of its cost containment measures.
- 1990s Highly active antiretroviral therapy (HAART) becomes available in Europe and North America, changing AIDS from a lethal disease to a chronic illness.
- 1995 Establishment of World Trade Organization (WTO) and the adoption of the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS).
- 1995 UNAIDS created.
- 1996 Brazil starts offering universal free antiretroviral (ARV) treatment to people living with AIDS.
- 1996 (May) The World Health Assembly (WHA) adopts the Revised Drug Strategy and strengthens the World Health Organization’s (WHO) mandate in the area of intellectual property; the WHA requests the WHO “to report on the impact of the work of the WTO with respect to national drug policies and essential drugs and make recommendations for collaboration between WTO and WHO, as appropriate.”
- 1997 Brazil starts granting pharmaceutical product patents.
- 1998 The South African Pharmaceutical Manufacturers Association and 39 mostly multinational pharmaceutical companies bring 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.
- 1999 Médecins Sans Frontières (MSF) launches its international Campaign for Access to Essential Medicines.

- 1999 (March) MSF, Health Action International (HAI) and Consumer Project on Technology (CPTech, now Knowledge Ecology International) organise the first meeting on compulsory licensing of AIDS medicines, held at the UN in Geneva.
- 1999 Seattle WTO Ministerial meeting collapses. For the first time, delegates officially discuss the consequences of the WTO TRIPS Agreement for access to medicines.
- 2000 (May) US President Clinton issues Executive Order 13155 supporting sub-Saharan African countries in using measures such as compulsory licensing to allow production and import of generic AIDS drugs, without fear of trade retaliation.
- 2000 (May) Multinational drug companies announce price reductions for AIDS drugs.
- 2000 (July) The 13th International AIDS conference takes place in Durban, South Africa. This was the first time that the conference was held in a developing country.
- 2001 (February) The Indian generic medicines manufacturer, Cipla, announces triple-ARV AIDS treatment for US\$ 350 per patient per year.
- 2001 (April) Following a global public outcry against the 39 drug companies' actions in South Africa, the companies are compelled to drop their lawsuit.
- 2001 (November) The Fourth WTO Ministerial Conference adopts the Doha Declaration on TRIPS and Public Health.
- 2001 WHO launches the Prequalification of Medicines Programme to ensure the quality of medicines for HIV/AIDS, tuberculosis and malaria.
- 2002 WHO includes ARV medicines in its Essential Medicines List for the first time.
- 2002 The Global Fund to Fight AIDS, Tuberculosis and Malaria is established.
- 2002 WTO adopts the decision to exempt WTO least-developed country (LDC) members from the obligation to grant or enforce patents on pharmaceutical products, or to protect pharmaceutical test data, until 1 January, 2016. This decision implemented Paragraph 7 of the Doha Declaration, also known as the LDC pharmaceutical waiver.

- 2003 The WHO starts the “3 by 5” initiative to expand access to HIV treatment to 3 million people by 2005.
- 2003 Thailand offers universal access to ARVs to people living with AIDS.
- 2003 WTO adopts the ‘August 30th’ decision to allow drugs to be produced under a compulsory licence predominantly for export.
- 2003 In South Africa, the Treatment Action Campaign (TAC) wins its case against GlaxoSmithKline (GSK) and Boehringer Ingelheim before the Competition Commission, which found the companies guilty of anti-competitive practices.
- 2003 President’s Emergency Plan for AIDS Relief (PEPFAR) is launched in the United States.
- 2003 The Drugs for Neglected Diseases Initiative (DNDi), a not-for-profit drug development organisation, is founded.
- 2003 The United Kingdom Commission on Intellectual Property Rights publishes its report, concluding that the new global architecture for intellectual property has serious drawbacks for developing countries, particularly for access to medicines.
- 2005 (March) India amends its 1970 Patents Act to introduce pharmaceutical product patents, as required by the TRIPS Agreement.
- 2006 (January) The Indian Patent Office rejects the patent application by Novartis for imatinib mesylate (Gleevec).
- 2006 (March) The Indian Network of People Living with HIV/AIDS and the Manipur Network of Positive People file at the Kolkata patent office in India a pre-grant opposition to GSK patent application for AZT/3TC (Combivir).
- 2006 (May) Novartis sues the Indian government over its amended Patents Act, attempting to overturn the provision (Section 3d) that establishes higher patentability criteria. The criteria were aimed at only granting patents to highly innovative products, thereby preventing frivolous patenting and ‘evergreening’ of patents.
- 2006 Establishment of UNITAID, a new mechanism for the purchase of medicines, financed by a tax on airline tickets.
- 2006 WHO Commission on Intellectual Property Rights, Innovation and Public Health publishes its report, leading the World Health Assembly to establish the

- Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG).
- 2006 (August) GSK announces the withdrawal of its patents and patent applications for a specific formulation of AZT/3TC that was the subject of civil society actions in India and Thailand.
- 2006–2008 Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) negotiations take place in Geneva.
- 2007 (May) World Health Assembly asks the director general of WHO in resolution 60.30 “to encourage the development of proposals for health-needs driven research and development for discussion at the Intergovernmental Working Group that includes a range of incentive mechanisms including also addressing the linkage between the cost of research and development and the price of medicines, vaccines, diagnostic kits and other health-care products and a method for tailoring the optimal mix of incentives to a particular condition or product, with the objective of addressing diseases that disproportionately affect developing countries.”
- 2007 United States government establishes the Food and Drug Administration Priority Review Voucher to incentivise neglected drug and vaccine development.
- 2007 (July) Rwanda notifies the WTO that it intends to use the “August 30” system to import medicines produced under a compulsory licence.
- 2007 (October) In the first use of the “August 30” system, Canada issues a compulsory licence for the production of a triple fixed-dose combination ARV for export to Rwanda.
- 2007 The World Intellectual Property Organization (WIPO) adopts the WIPO Development Agenda to ensure that development considerations form an integral part of WIPO’s work.
- 2008 (January) Thailand issues compulsory licences for four anti-cancer drugs: docetaxel, letrozole, erlotinib, imatinib.
- 2008 The WHA adopts the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property drawn up by the IGWG.

- 2009 Dutch custom officials seize HIV and other medicines upon the suspicion they were counterfeit. In reality, the products were legitimate essential medicines, prequalified by the WHO and approved by the United States Food and Drug Administration, on their way from India to treatment programmes in developing countries.
- 2010 UNITAID establishes the Medicines Patent Pool (MPP). The MPP concludes its first licence agreement with the US National Institutes for Health.
- 2012 WHO Consultative Expert Working Group (CEWG) recommends the start of multilateral negotiations on a medical R&D agreement.
- 2012 WHO, WIPO and WTO publish a joint report “Promoting Access to Medical Technologies and Innovation” signalling greater collaboration between the organisations on public health issues.
- 2012 India issues first medicine compulsory licence for liver cancer drug, sorafenib tosylate (Nexavar).
- 2012 (October) Treatment advocates establish a patent opposition database. The database shows a wide variety of legal cases targeting a number of medicines patents in low- and middle-income countries.
- 2013 (April) Indian Supreme Court upholds the rejection of a patent for Novartis’s cancer drug, Glivec, and section 3(d) of the Indian Patents Act.
- 2013 FDA approves sofosbuvir, a new medicine to cure hepatitis C. The company, Gilead, prices it at US\$ 84,000 per treatment or US\$ 1,000 per pill.
- 2013 WTO adopts decision to exempt LDCs from the obligation to implement the TRIPS obligations until July 2021 (with the exception of Articles 3, 4 and 5 related to national treatment and most-favoured nation treatment), or until such a date on which they cease to be an LDC member, whichever date is earlier.
- 2013 GSK CEO, Andrew Witty, calls US\$ 1 billion R&D cost figure, a frequently cited statistic on what it costs to develop a new drug, “one of the great myths of the industry.”
- 2014 Gilead announces voluntary licences with 11 Indian generic companies for hepatitis C medicines, but excludes countries

- with important disease burden from the geographical scope of the licences.
- 2015 (January) India rejects a patent application by Gilead related to a hepatitis C drug, sofosbuvir, following an opposition by civil society.
- 2014 (March) Ebola outbreak in West Africa first reported. By July 2015, 11,000 people will have died.
- 2014 (November) Tufts study updates its cost figures for pharmaceutical R&D and claims it now costs \$2.6 billion to develop and bring a new medicine to market.
- 2015 (March) An LDC-based company, Incepta Pharmaceuticals in Bangladesh, brings generic sofosbuvir to market for US\$ 10 a pill.
- 2015 (May) WHO includes new highly-priced medicines for cancer, hepatitis C and multi drug resistant tuberculosis on the WHO Essential Medicines List. Several of these medicines are widely patented.
- 2015 (September) The first World Hepatitis Summit takes place in Glasgow. Participants ask for access to more affordable hepatitis C medication and licensing through the Medicines Patent Pool.
- 2015 (September) WHO recommends treatment with ARVs for all HIV positive people and those at “substantial risk,” bringing the number of people who should be on treatment to 37 million.
- 2015 (October) Trans-Pacific Partnership Agreement (TPP) negotiations conclude, and introduce the obligation to provide market exclusivity for biologics based on test data protection of five to eight years. During this period, a biosimilar product cannot be registered.
- 2015 (November) WTO LDC members are granted an extension of the 2002 ‘pharmaceutical waiver’ that exempts LDCs from implementing or enforcing pharmaceutical product patents and which was scheduled to run out in January 2016.
- 2015 (November) UN Secretary-General establishes a High-Level Panel on Access to Medicines.

1

ENDING GLOBAL DIVERSITY IN PATENT LAWS: The TRIPS Agreement

GLOBALISING THE PATENT REGIMES OF WEALTHY NATIONS

In 1958, the economist Fritz Machlup wrote: “If we did not have a patent system, it would be irresponsible, on the basis of our present knowledge of its economic consequences, to recommend instituting one. But since we have had a patent system for a long time, it would be irresponsible, on the basis of our present knowledge, to recommend abolishing it.” He emphasised that the latter statement “refers to a country such as the United States of America—not to a small country and not a predominantly nonindustrial country”²²; for such countries, he felt the patent system best remains unimplemented.

Still, 37 years later, the World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) came into being, globalising intellectual property (IP) requirements that had only recently been adopted by rich nations. TRIPS was part of a set of international treaties agreed upon at the end of the Uruguay Round of negotiations within the General Agreement on Tariffs and Trade (GATT); this round concluded with the creation of the WTO and was intended to encourage trade among members of the new organisation.

What was an agreement that created monopolies—which inherently restrict free trade and competition—doing in an institution whose main

purpose was to encourage free trade and global competition? What were the forces behind the adoption of the TRIPS Agreement?

The TRIPS Agreement signalled a fundamental change in that, for the first time, global minimum requirements for the creation and protection of IP were enforceable through the WTO.

Before TRIPS, pharmaceutical patent law, policies and practices differed immensely among countries, particularly between developed and developing countries. The patenting of essential goods such as medicines and foods was long considered an act against the public interest. When Indian Prime Minister Indira Gandhi addressed the World Health Assembly (WHA) in 1982, she said: “The idea of a better ordered world is one in which medical discoveries will be free of patents and there will be no profiteering from life and death.”²³

When the Uruguay Round launched in 1986, 49 of the 98 members of the Paris Convention excluded pharmaceutical products from patent protection, 10 excluded pharmaceutical processes and 22 excluded chemical processes.²⁴ Countries varied in the periods of protection granted and/or set out other conditions that restricted patent holders’ rights. Such exceptions were also common in Western countries. For example, the following European countries excluded pharmaceutical products from patentability: France (until 1960), Switzerland (until 1977), Italy (until 1978), Sweden (until 1978) and Spain (until 1992).²⁵

BOX 1 THE PARIS CONVENTION

The Paris Convention for the Protection of Industrial Property, signed in Paris, France, on 20 March 1883, was one of the first multilateral IP agreements. It is administered by the World Intellectual Property Organisation (WIPO) and has today 173 contracting parties. As a result of the Paris Convention, national systems for the protection of IP, including patents, of any contracting state are accessible to the nationals of other states party to the Convention.

In developing countries that did not grant pharmaceutical product patents and/or had limited patent terms, a generic industry and competition was able to flourish. India’s 1970 Patents Act, for example, provided for process patents but not product patents; this law encouraged the development of a generics industry that reverse-engineered its own

versions of new medicines that were often patented elsewhere. As a result, developing countries had for many years been able to rely on countries such as India, Egypt, Israel, Jordan, Brazil and Argentina for their supply of affordable medicines.²⁶

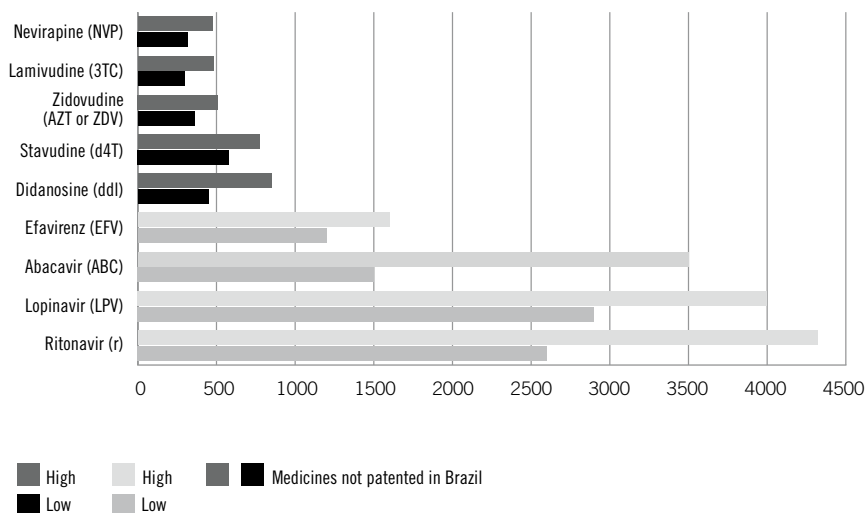
Developing countries that did not grant pharmaceutical product patents at the date of application of the TRIPS Agreement (1 January 2000) were allowed under the transitional rules to delay the implementation of product patents until 2005. Countries that made use of this transition period were, however, obliged to have “mailbox” provisions to receive patent applications during the transition. India was one of the few countries to make full use of the TRIPS transition provisions. It did not start to grant product patents until 2005.

The establishment of successful AIDS treatment programmes such as those of Brazil and Thailand—countries that offered universal access to HIV treatment beginning in 1996 and 2003, respectively—were possible, in part, because key pharmaceuticals were not patent-protected and could be produced locally at much lower costs. These were primarily ‘first line’ drugs that are used when patients first begin HIV treatment. The production of ARVs in Brazil created a larger market for ARV active pharmaceutical ingredients (APIs), making it possible for Indian companies to start production of APIs in large volumes; the resulting economies of scale allowed for dramatically reduced prices and dropped the price. The price of the triple ARV combination lamivudine/nevirapine/stavudine, which at the time was the WHO-recommended first line treatment, dropped from US\$ 15,000 to US\$ 66 per patient per year and was available as a twice-a-day fixed-dose combination (three-in-one) pill.

In Figure 2 below, the dark grey bars represent products that could be produced in Brazil because they were not patent protected there. Brazil’s purchasing power reduced the price of the API on the global market, which helped to create large scale, low-cost production of ARVs.²⁷

FIGURE 2 PRICES OF ACTIVE PHARMACEUTICAL INGREDIENTS²⁸

2005 Prices of Active Pharmaceutical Ingredients, in US\$ per kilogram

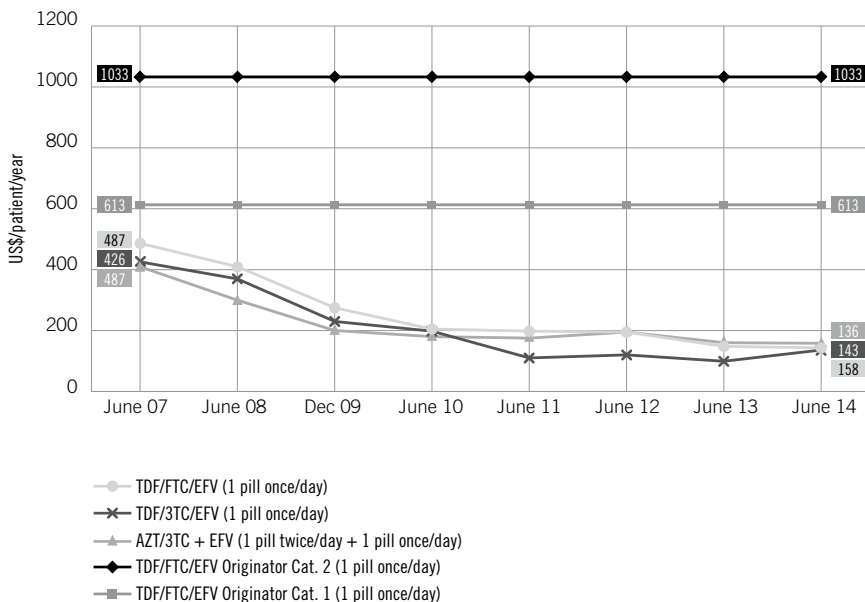


SOURCE

E Pinheiro, A Vasan, JY Kim, E Lee, JM Guimier, and J Perriens, "Examining the production costs of antiretroviral drugs," *AIDS*, 20, no. 12 (22 August 2006): 1745-52, <http://www.ncbi.nlm.nih.gov/pubmed/16931939>

Today, the updated WHO-recommended first line treatments, based on tenofovir (combined with lamivudine and efavirenz or emtricitabine and efavirenz), are available for US\$ 95–143 from generic suppliers. In developing countries where patents prevent purchasing generics, and which therefore depend on price discounts from the originator company, the treatments are available for US\$ 613–1,033. MSF has been monitoring the prices for ARV treatment since 2007, and it is noteworthy that the generic price has been on a steady decline, while the price of the originator products has remained the same since 2007.

FIGURE 3 THE EVOLUTION IN PRICE OF DIFFERENT FIRST-LINE REGIMENS



SOURCE

MSF's *Untangling the Web of Antiviral Price Reductions*, 17th edition.²⁹

Following the full implementation of TRIPS in 2005 in India and several other developing countries that did not previously grant pharmaceutical patents, reverse engineering by generic companies became far more difficult without a licence, either voluntary or compulsory.

As a result, access to affordable new drugs also became more difficult. And patent disputes on new treatments for HIV, hepatitis C, cancer, cardiovascular and other non-communicable diseases, and rare diseases, have become more common.^{30,31}

HEALTH AT THE CENTRE OF TRADE TALKS FROM GENEVA TO SEATTLE AND DOHA

CONCERN GROWS AT THE WORLD HEALTH ORGANIZATION

In 1996, the annual meeting of the WHO's member states, the WHA, debated for the first time the effects of new WTO trade rules on access to medicines. This debate was long overdue, considering that the WTO agreements were negotiated without input from health experts and had already gone into effect. It nevertheless unleashed a series of activities that would lead to the adoption of the WTO Doha Declaration on TRIPS and Public Health in 2001.

A WHA resolution in 1996 gave the WHO a mandate to monitor and study the effects of trade agreements, and particularly the TRIPS Agreement, on public health. In 1998, the WHO published the first guide with recommendations to member states on how to implement TRIPS while limiting the negative effects of higher levels of patent protection on medicines availability.³²

WHO's involvement in trade issues did not come without controversy. In fact, the response to WHO's guidance on TRIPS and public health from the United States (US) and a number of European countries was fiercely negative. In particular, the US, working very closely with drug-company lobby groups, pressured the WHO to withdraw the publication, calling the book "an outrageous and biased attempt to mold international opinion."³³ The publication was initially withdrawn. The controversy over the publication was fuelled by a turf war between the WTO and the WHO over the competency to make pronouncements on trade agreements and the US and European Union's (EU) position that it was none of WHO's business to meddle in trade and IP matters. In the background was also the legal challenge by 39 drug companies to South Africa's medicines act, a case that would come to a head in 2001 (see Introduction, "How the HIV pandemic changed everything").

The then WHO Director General Dr Gro Harlem Brundtland, who had just taken office, stood firm. She invited various parties to express their views and published those together with the original text of the guide. But she resisted pressures to withdraw the publication as no significant factual errors could be found in it. She only changed the colour of the cover from red to blue.³⁴

The WHO's involvement in trade and IP issues would remain highly controversial in the years that followed. The simple emphasis that the

WHO placed on public health needs over trade interests was perceived as a threat to the commercial sector of the industrialised world. In particular, a greater role for the WHO in issues related to TRIPS created considerable concern within the pharmaceutical industry, which lobbied hard against it.

A draft resolution discussed at the 1998 WHO Executive Board, the governing body of the WHO responsible for preparing the annual WHA, called on WHO member countries to ensure that public health, rather than commercial interests, would have primacy in pharmaceutical and health policies. The resolution further referred to TRIPS and asked the WHO director general to analyse the effects of new trade agreements on health and to develop measures to counter these effects in a 'Revised Drug Strategy'. In 1998, in response to this and in reference to "considerable concern among the pharmaceutical industry," the European director general for trade's position was that "no priority should be given to health over intellectual property considerations."³⁵ The WHO Executive Board established an ad-hoc group chaired by France to prepare for the discussions on the Revised Drug Strategy at the WHA in 1999.

The issue of trade agreements with regard to IP and access to medicines had been put on the agenda of the WHO and was there to stay. The Executive Board ad-hoc group organised a five-day meeting, including a one-day hearing with interested parties. It concluded its work with a proposed resolution that was sent to the 52nd WHA.³⁶

The resolution was adopted by the WHA in May 1999 and strengthened the WHO's role in IP issues. The text no longer called for the "primacy of health over trade," but noted the importance of "ensuring that public health interests are paramount in pharmaceutical and health policies."³⁷ This nevertheless put health advocates at the table of trade negotiations, as subsequent developments at the WTO TRIPS Council and the Doha WTO ministerial conference would show. The resolution also urged countries to look into the options they have under current trade rules to safeguard access to essential medicines, a clear reference to the flexibilities available under the TRIPS Agreement. These flexibilities include compulsory licensing, which allows governments to overcome patents and produce, import, export, and market generic versions of a patented drug (see Chapter 4, "TRIPS and its built-in flexibility"). Most importantly, the assembly requested that the WHO assess the health implications of trade agreements, which was understood to mean the WTO TRIPS Agreement, with a view to assisting countries in mitigating the negative effects of this agreement.

NGOS ADVOCATE FOR HEALTH PRIMACY OVER PATENTS

Non-governmental organisations (NGOs) also increased their involvement in the trade and health debates and focussed their attention on the WTO. In anticipation of the 1999 Seattle WTO ministerial conference, there was a flurry of activity that strengthened the IP knowledge base that NGOs had and their ability to mobilise quickly in relation to the issue.

Fuelled by the “health primacy” debates at the WHA and against the backdrop of the court case between South Africa and thirty-nine pharmaceutical companies claiming some of South Africa’s provisions to increase access to medicines were not compliant with TRIPS,³⁸ a coalition of groups consisting of Health Action International (HAI), the Consumer Project on Technology (CPTech, now Knowledge Ecology International or KEI), Act Up–Paris, the Health GAP Coalition, Oxfam, and the Access to Medicines Campaign of Médecins Sans Frontières (MSF) came together. These groups worked in close collaboration with national treatment action groups in various countries, notably in Thailand, Brazil, India, Malaysia, Indonesia, Kenya, South Africa and others.

In March 1999, MSF, HAI and CPTech organised the first meeting on compulsory licensing of AIDS medicines, held at the UN in Geneva. Later that year, a larger coalition of NGOs organised a global conference in Amsterdam on access to medicines. At the Amsterdam conference, participants called for health to be made a priority at the WTO Seattle negotiations and demanded a balance between the rights of patent holders and the rights of citizens in IP rights regulations. These views were shared by representatives of UNDP, WHO, WTO, members of the governments of the Netherlands and Thailand, and NGOs attending the Amsterdam conference. The meeting brought together 350 participants from 50 developing and developed countries, from the private and public sectors.³⁹

NEGOTIATIONS ON TRIPS AND PUBLIC HEALTH AT THE WTO, 1999–2001

The debate on TRIPS and public health started at the WTO in late 1999 at the ministerial in Seattle. While not on the official agenda, the issue of public health and access to medicines received attention for a number of reasons.

First, the European Commission prepared a Common Working Paper that proposed developing countries be allowed to issue “compulsory

licences for drugs appearing on the list of essential drugs of the World Health Organization.”⁴⁰ However, only about 15 of the 306 products on the WHO Model List of Essential Drugs at that time were widely patented,⁴¹ and HIV medicines had not yet been included on the list. The European proposal would have at the time limited the use of compulsory licensing—which was primarily needed for the expensive drugs that had not yet been added to the Model List—rather than making sure it became a useful tool to overcome patent-related access barriers such as prohibitive pricing.

Second, then US President Bill Clinton chose Seattle as the venue to declare a change in US policy with regard to IP rights and access to medicines. The US government had come under fierce attack from AIDS activists because of its policies in South Africa. In particular, Vice-President Al Gore was criticised for being the envoy of the US pharmaceutical industry in its attempts to challenge the South African Medicines Act.⁴² Under the new policy, the US Trade Representative and the US Department of Health and Human Services would together establish a process to analyse health issues that would arise in the application of US trade-related IP law and policy. In his speech, President Clinton referred specifically to the situation in South Africa and the HIV/AIDS crisis, declaring: “The United States will henceforward implement its health care and trade policies in a manner that ensures that people in the poorest countries won’t have to go without medicine they so desperately need.”⁴³

Tens of thousands of protestors descended on Seattle during the conference to voice objection to the WTO’s effect on matters such as environmental protection, labour rights and health. Inside the meeting itself, delegates struggled and failed to find common ground on hot-button issues, notably agriculture, while several developing country delegates expressed frustration at being excluded from debates before and during the meeting.⁴⁴ After three days, the ministerial conference collapsed without an agreement.

In May 2000, President Clinton confirmed the announced change in US policy by issuing an Executive Order on Access to HIV/AIDS Pharmaceuticals and Medical Technologies, supporting the use of compulsory licences to increase access to HIV/AIDS medication in sub-Saharan Africa.⁴⁵ Although this policy change contributed to breaking the taboo on the use of compulsory licensing in the health field, attention to TRIPS and medicines at the WTO was diverted by the collapse of the

Seattle ministerial, which left all matters on the table unresolved. At the time, an editorial in the magazine *Pharmaceutical Executive* commented: “Unlikely as it seems, the pharmaceutical industry may have reason to thank the demonstrators who brought Seattle and the ministerial meeting of the World Trade Organization (WTO) to a standstill. Had the demonstrators not disrupted the gathering, the forecast for global pharma might be much cloudier.”⁴⁶ However, outside the WTO, the debate on access to medicines, TRIPS, and compulsory licensing grew more intense.

The period between the failed Seattle WTO ministerial conference in 1999 and the next ministerial meeting in Doha in 2001 saw a number of developments that had a profound effect on the debate over access to medicines and IP. First, trade disputes arose between Western countries with big pharmaceutical industries and developing countries that tried to bring the price of medicines down. The legal conflict in South Africa, where the pharmaceutical industry (initially supported by the European Commission and the US government) had taken the government of Nelson Mandela to court over a medicines act, came to a head in 2001 when companies were compelled to drop the case in the face of global outcry (see Introduction, “How the HIV pandemic changed everything”). The case had focussed the world’s attention on the severe constraints that pharmaceutical patents and their enforcement by the industry could have on the health care of poor people. Second, there was increased attention to the devastating effects of the AIDS crisis in the developing world. And third, national treatment programmes that relied on locally-produced generic ARVs began to experience the consequences of aggressively enforced pharmaceutical patents on AIDS drugs.

All of this formed the backdrop against which the WTO held its ministerial conference in Doha, Qatar in November 2001.

BOX 2 THE QUIET REVOLUTION AT THE WHO: PRE-QUALIFICATION OF MEDICINES AND ACCESS TO HIV TREATMENT⁴⁷

While the spirited debates on access to medicines and patents were taking place at the WTO, a quieter revolution took place at the WHO medicines programme. At issue was the quality assurance of ARVs, which were relatively new compounds. Most regulators in generic drug manufacturing countries (such as India, South Africa and China), as well as in potential recipient

countries, had no experience with these products, including ‘fixed-dose combinations’ (FDCs) bringing together several medicines in one pill.

FDC ARVs were an important advance in HIV/AIDS treatment, particularly in resource-poor settings where a ‘one pill twice a day’ regimen would help increase adherence to treatment, reduce the risk of developing resistance, and simplify the supply chain. Indian firms were the first to produce an FDC of a WHO-recommended first-line combination.⁴⁸ They could do so because there were no patent barriers in India to putting three compounds of different originator companies together in one pill. The price of the first generic triple combination by Cipla in 2001 was US\$ 350 and soon dropped to less than US\$ 140 per person per year. This medicine, a combination of lamivudine, stavudine, and nevirapine—compounds developed by three different originators—was sold under the name ‘Triomune’.

These generic ARVs needed quality assurance quickly: buying the costly originator medicines was not an option, nor were originators making the recommended treatments in patient-friendly one pill twice a day combination tablets. In 2001, the WHO established the Pre-qualification of Medicines Programme (PQP) to take on the task. Initially focussing on medicines for HIV, tuberculosis and malaria, the PQP over the last 13 years has been especially important in scaling up HIV treatment.

In 2002, the PQP published its first list of 41 approved formulations of ARVs and other medicines. The International Federation of Pharmaceutical Manufacturers (IFPMA), a trade organisation representing the interests of large pharmaceutical companies, was quick to question whether WHO’s assessment standards were sufficiently strict. They warned against counterfeit and substandard medicines.⁴⁹ But the industry seemed to be most concerned about its loss of markets as the role of the generics industry in the supply of low-cost AIDS medicines increased.

This list of pre-qualified medicines opened up a supply of quality-assured, low-cost generic ARVs for global procurement and helped to establish the market for generic ARVs. The Global Fund to fight AIDS, Tuberculosis and Malaria, created in 2002, subsequently adopted a policy that restricts use of its immense purchasing power to products approved by stringent regulatory authorities or prequalified by WHO. This became the norm for global health funders. In 2003, the PQP approved Cipla’s first generic FDC of three ARVs in one pill. The triple FDCs, produced only by generic companies, came to symbolise the great savings that generics could achieve.

The PQP is strict and does not hesitate to delist products when the applicant’s dossiers are not up to standard. This happened for the first time

in 2004 when WHO delisted five generic ARVs because of irregularities in the paperwork,⁵⁰ signalling to generics that the PQP had teeth.

In 2004, the US government established its own process for approving ARVs for procurement using President's Emergency Plan for AIDS Relief (PEPFAR) money, called the US Food and Drug Administration's Tentative Approval Mechanism. The US government did not want to rely on the WHO PQP but also realised that if PEPFAR did not take advantage of low-priced generic ARVs and bought instead from US or European drug companies, it would not be able to reach as many people with the available money. While initially the US FDA's Tentative Approval Mechanism was seen as a direct competitor to the WHO programme, today both agencies collaborate.

As of November 2015, the PQP has prequalified 418 medical products, including 255 for HIV/AIDS, 79 for tuberculosis and 43 for malaria.⁵¹ It has expanded its activities to APIs and clinical testing sites, as well as several other disease areas. It is estimated that 80% of the people receiving treatment for HIV access generic ARVs; the vast majority of generic ARVs passing through international procurement agencies are prequalified by the WHO.

The PQP's importance goes beyond procurement. It has raised the bar for quality assurance of medicines: its standards are recognised and promoted by others, helping to expand quality medicines production. For example, Medicines Patent Pool licences—which offer the possibility of generic production even when a patent exists—require that producers play by WHO PQP quality rules. It is an important strength of the programme that it carries out its work regardless of the patent status of the medicines it pre-qualifies.

2

TURNING THE TIDE:

The WTO Doha Declaration on TRIPS & Public Health

THE WTO DOHA DECLARATION ON TRIPS AND PUBLIC HEALTH

The fourth World Trade Organization (WTO) ministerial conference in 2001 in Doha, Qatar responded to the public health concerns fuelled by the HIV/AIDS crisis by adopting the Doha Declaration on the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) and Public Health. The Doha Declaration, as it is widely known, affirmed the sovereign right of governments to take measures to protect public health, including the use of compulsory licensing and parallel importation. It also allowed least-developed countries (LDCs) not to grant or enforce pharmaceutical product patents until at least 2016.

The Doha Declaration was a pivotal point for the debate on access to medicines and intellectual property (IP). In its seven paragraphs, the Declaration: recognised the growing concerns over HIV and other diseases; firmly established the primacy of public health concerns over IP; firmly supported interpretations of TRIPS allowing governments to take action necessary to protect the health of their populations; and set out plans to cope with the particular plight of LDCs and countries lacking the capacity to make their own medicines. This chapter provides an introduction to the Doha Declaration, its key provisions, and what each of them mean.

PROVISIONS OF THE DOHA DECLARATION: PARAGRAPHS 1–5 AND 7

The Doha Declaration contains seven paragraphs (see Annex 2 for full text). The first four paragraphs set out the scope, background and basic principles of the Declaration. Paragraph 1 reads:

“We recognize the gravity of the public health problems afflicting many developing and least-developed countries, especially those resulting from HIV/AIDS, tuberculosis, malaria and other epidemics.”

Notably, the Declaration covers “health problems” without restrictions. Paragraph 1 highlights the examples of “HIV/AIDS, tuberculosis, malaria and other epidemics,” but this text is meant to illustrate some of the problems, not to limit the use of the Doha Declaration to these three diseases or epidemics only.⁵²

Paragraph 2 was included to signal that WTO members recognised that IP was not the only factor that affected access to medicines. It reads:

“We stress the need for the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) to be part of the wider national and international action to address these problems.”

Some members, particularly the United States (US), strongly pushed the notion that factors other than IP were the cause of access problems. In one submission, in order to illustrate why patents were not relevant, the US argued that some people were so poor they could never afford to buy medicines, even at the most competitive prices.⁵³

Paragraph 3 reads:

“We recognize that intellectual property protection is important for the development of new medicines. We also recognize the concerns about its effects on prices.”

The significance of this text is that it recognises the link between patents and high medicines prices and the difficulties this creates for developing countries.

Legal scholar Carlos Correa commented: “The consensus achieved on patent protection’s impact on drug prices may be considered one of the major political achievements of the developing countries in the Doha Ministerial Declaration.”⁵⁴

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 IP, and reads:

“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.”

Paragraph 4 is critical because it gives priority to public health considerations and clarifies that this principle is not restricted to certain selected provisions of TRIPS, but rather stretches out over the entire TRIPS Agreement. The line “measures to protect public health” is not limited to medicines only, but also refers to vaccines, diagnostics and other health tools needed to facilitate the use of these products.

BOX 3 COMPULSORY LICENSING AND PARALLEL IMPORTATION

‘Compulsory licensing’ enables a competent government authority to license the use of a patented invention to a third-party or government agency without the consent of the patent holder against a payment of “adequate remuneration.”

‘Parallel imports’ are cross-border trades in a patented product, without the permission of the patent holder. Parallel imports take place when there are significant price differences for the same good in different markets.

Paragraphs 5, 6 and 7 are the substantive sections of the Declaration. Paragraph 5 lays out the key measures and flexibilities within TRIPS (see Chapter 4, “Trips and its Flexibilities”), such as compulsory licensing, that can be used to overcome IP barriers to access to medicines. It reads:

“Accordingly and in the light of paragraph 4 above, while maintaining our commitments in the TRIPS Agreement, we recognize that these flexibilities include:

a) In applying the customary rules of interpretation of public international law, each provision of the TRIPS Agreement shall be

read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles.

b) Each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.

c) Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

d) The effect of the provisions in the TRIPS Agreement that are relevant to the exhaustion of intellectual property rights is to leave each Member free to establish its own regime for such exhaustion without challenge, subject to the MFN [most favoured nation] and national treatment provisions of Articles 3 and 4.”

The use of the term “include” in the first sentence of this paragraph makes it clear that the flexibilities in implementing TRIPS are not limited to those listed in the Doha Declaration. Paragraphs 4 and 5(b) identify compulsory licensing as a key measure for developing countries to limit the exclusive rights of patent holders and to identify alternate sources of medicines, whether through local production or importation. It strengthens countries’ rights to use compulsory licensing and is unambiguously clear on the fact that there are no limitations as to the grounds for issuing compulsory licences. Paragraph 5(c) reiterates countries’ freedom to determine what is a national emergency or circumstance of extreme urgency. This clause is important because TRIPS waives certain procedural requirements, such as prior negotiation with the patent-holder, if a compulsory licence is issued in a situation of emergency or urgency. It does not mean that a compulsory licence can only be applied in cases of emergency or urgency. This is a common misunderstanding regarding TRIPS.

Paragraph 5(d) resolves once and for all the question of whether TRIPS authorises parallel trade by noting that TRIPS leaves “each Member free to establish its own regime for such exhaustion without challenge.”

Parallel importation refers to the import and resale in a country, without the consent of the patent holder, of a patented product that has been legitimately put on the market of the exporting country. The sale of the patented medicine is deemed to “exhaust” the patent holder’s rights.

Parallel import or “exhaustion” generally refers to the importation of the patented product; however, one can also imagine parallel trade in generic products, such as those produced under a licence agreement and thus put on the market legitimately.⁵⁵

Paragraph 6 deals with production for export under a compulsory licence. Article 31 (f) of the WTO TRIPS Agreement limits the use of compulsory licensing to “predominantly for the domestic market.” Countries without local production capacity would have great difficulty finding sources of low-cost medicines in a world where medicines are patented almost everywhere. Countries recognised in Doha that this restriction causes problems for countries that rely on importation for their supply of medicines. However, the key issue of how to ensure that products manufactured under a compulsory licence could be exported to countries without domestic production capacity remained unresolved in Doha. The Doha Declaration promised to find an “expeditious solution” to this problem in Paragraph 6, which read:

“We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002.”

It took two years of difficult negotiations at the WTO to arrive in 2003 at the “August 30” decision, which established a process to allow such export on a case-by-case basis (see “Compulsory licensing for export,” in this chapter).

Paragraph 7 extends the transition period from 2006 to at least 2016 for the implementation of pharmaceutical product patents and the protection of undisclosed test data for LDC members. Since many LDCs had already granted those rights, it also allows them not to enforce such rights until at least 2016. The paragraph reads:

“We reaffirm the commitment of developed-country Members to provide incentives to their enterprises and institutions to promote and encourage technology transfer to least-developed country Members pursuant to Article 66.2. We also agree that the least-developed country Members will not be obliged, with respect to

pharmaceutical products, to implement or apply Sections 5 and 7 of Part II of the TRIPS Agreement or to enforce rights provided for under these Sections until 1 January 2016, without prejudice to the right of least-developed country Members to seek other extensions of the transition periods as provided for in Article 66.1 of the TRIPS Agreement. We instruct the Council for TRIPS to take the necessary action to give effect to this pursuant to Article 66.1 of the TRIPS Agreement.”

While Paragraph 5 provides an interpretation of existing rights under TRIPS, Paragraph 7 creates new rights for LDCs by specifically removing the obligation for LDCs to comply with Section 5 (Patents) and Section 7 (Protection of Undisclosed Information) of Part II of the TRIPS Agreement, including any obligation to enforce rights under these provisions.

The next section describes the specific issues related to LDC membership of the WTO with regard to pharmaceuticals and IP.

One thing the Doha Declaration did not address is the as-yet-unfulfilled promises of increased research and development (R&D) in exchange for higher levels of IP protection, an expectation that was part of the bargain when countries were negotiating the TRIPS Agreement.

GENERIC PRODUCTION OR IMPORTATION IN LEAST-DEVELOPED COUNTRIES

The WTO has 34 LDC members (there are currently 48 LDCs on the UN list). LDCs enjoy the largest freedom under the TRIPS Agreement, based on two decisions of the Council for TRIPS, the body responsible for administering the TRIPS agreement:

A 2002 decision exempted WTO LDC members from the obligation to grant or enforce patents on pharmaceutical products, or to protect pharmaceutical test data, until 1 January 2016. This decision implemented Paragraph 7 of the Doha Declaration. A 2015 decision extends the exemption to 2033.⁵⁶

A 2013 decision exempts LDCs from the obligation to implement the TRIPS Agreement until July 2021 (with the exception of Articles 3, 4 and 5 related to national treatment and most-favoured nation treatment), or until such a date on which they cease to be an LDC member, whichever date is earlier.

As the 2013 decision concerns the entire TRIPS Agreement, it also exempts de facto LDCs from their obligations with regard to pharmaceutical patents and data protection until at least July 2021. However, the 2002 decision specifically exempts LDCs from enforcing already granted patents and has therefore been very important in day-to-day procurement. The data presented in Chapter 3, “Practical Application of the Doha Declaration,” shows that since the adoption of the 2001 Doha Declaration, LDCs have frequently used the “Paragraph 7” exemption in day-to-day procurement of low-cost generic medicines, particularly to access medicines needed for the treatment of HIV. Between 2001 and 2009 at least 31 LDCs authorised the importation of generic ARVs with a reference to the LDC Paragraph 7 exemption. Of them, 25 were WTO members and six were WTO observers at the time of the purchase.

Some LDCs have important production capacity. Bangladesh, for example, has provided the first source of generic sofosbuvir,⁵⁷ a direct-acting antiviral needed for the treatment of hepatitis C and a medicine the entire world is struggling to access at affordable prices. One could also imagine such manufacturing capacity being developed in the African region, including in LDCs.

BOX 4 PARAGRAPH 7 OF THE DOHA DECLARATION

“We reaffirm the commitment of developed-country Members to provide incentives to their enterprises and institutions to promote and encourage technology transfer to least-developed country Members pursuant to Article 66.2. We also agree that the least-developed country Members will not be obliged, with respect to pharmaceutical products, to implement or apply Sections 5 and 7 of Part II of the TRIPS Agreement or to enforce rights provided for under these Sections until 1 January 2016, without prejudice to the right of least-developed country Members to seek other extensions of the transition periods as provided for in Article 66.1 of the TRIPS Agreement. We instruct the Council for TRIPS to take the necessary action to give effect to this pursuant to Article 66.1 of the TRIPS Agreement.”

Medicines, including those needed for the treatment of HIV, are widely patented throughout the developing world including in low-income countries.⁵⁸ In sub-Saharan Africa, the regional patent offices Organisation Africaine de la Propriété Intellectuelle (OAPI) and African Regional Industrial Property Organization (ARIPO) offer easy routes for companies to obtain patents. Twelve of the 17 OAPI members are WTO LDC members and 10 of the 19 ARIPO members are WTO LDC members.

While today, patent licensing and non-assert declarations—in which patent holders promise not to seek to enforce or ‘assert’ their patent rights under certain conditions and in certain countries—by companies that hold patents on HIV medicines are common, this was not the case in the early and mid 2000s. Even when companies had made public announcements not to enforce their patents in LDCs, procurement agents would seek assurances of government officials. In general, procurement agencies are reluctant to supply medicines that are patented, or of which the patent status is unknown, in the absence of assurances by the government. Therefore, the ability of LDCs to not enforce patents through simple declarations remains of key importance. It provides much needed legal certainty for suppliers and procurement agencies—including non-profit actors—that seek to minimise the risk of patent infringement suits.

BOX 5 THE WTO LEAST-DEVELOPED COUNTRIES

The WTO recognises LDCs as those that are designated by the United Nations (UN). There are currently 48 LDCs on the UN list, and 34 are WTO members: Angola, Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Central African Republic, Chad, Democratic Republic of the Congo, Djibouti, Gambia, Guinea, Guinea Bissau, Haiti, Lao People’s Democratic Republic, Lesotho, Madagascar, Malawi, Mali, Mauritania, Mozambique, Myanmar, Nepal, Niger, Rwanda, Senegal, Sierra Leone, Solomon Islands, Tanzania, Togo, Uganda, Vanuatu, Yemen and Zambia.

Eight more are applying for WTO membership: Afghanistan, Bhutan, Comoros, Equatorial Guinea, Ethiopia, Liberia, Sao Tomé & Principe, and Sudan. They are observers.

SOURCE

World Trade Organization, “Least-developed countries,” https://www.wto.org/english/thewto_e/whatis_e/tif_e/org7_e.htm (LDC member status quoted above accurate as of November 2015, though both membership and LDC status can change).

On 24 February 2015, Bangladesh—on behalf of the 34 LDC members of the WTO—submitted a request for an extension of the transitional period under article 66.1 TRIPS, with respect to pharmaceutical products, until a country is no longer classified as an LDC.⁵⁹ The original extension, set to expire on 1 January 2016, specifically removes the obligation for LDCs to comply with Section 5 (Patents) and Section 7 (Protection of Undisclosed Information) of Part II of TRIPS, including any obligation to enforce rights under these provisions.

Some may argue that the extension is no longer necessary because ARVs are made available through licensing and because several companies have indicated they will not assert their patents in LDCs. LDCs are systematically included in the scope of Medicines Patent Pool licences. However, not all companies provide licences for products that are needed in the treatment of HIV/AIDS, and LDCs need treatment for other diseases as well.

Licensing may seem to have become the norm for HIV-related products but this is not the case for all ARVs. And it is not the case for most other diseases increasingly affecting LDCs. The LDC request cites non-communicable diseases and, particularly, the rising incidence of cancer in their countries. The World Health Organization (WHO) in April 2015 amended its Essential Medicines List to include essential medicines for cancer, some of which are still protected by patents in many countries (see Chapter 5, “Patented essential medicines: The 2015 EML”).⁶⁰ The LDC extension is not confined to a particular disease and can be used to purchase or produce any generic medicine.

Another argument against the extension of the specific pharmaceutical waiver is that LDCs are not obliged to implement the TRIPS Agreement as whole (with the exception of some articles) until 1 July 2021. This implementation deadline may also be further extended upon request of the LDC members.⁶¹ Therefore, some will argue, the specific pharmaceutical waiver is redundant. However, to date, very few LDCs have rewritten their laws to undo previous implementation of TRIPS obligations. The specific pharmaceutical waivers, particularly the non-enforcement declarations, remain essential tools for LDCs and their suppliers of low-cost medicines. These tools do not require legislative changes and have proven to be practical and effective.

On 3 November 2015, WTO members reached an agreement to extend the pharmaceutical waiver for LDCs until 2033.⁶²

COMPULSORY LICENSING FOR EXPORT ("PARAGRAPH 6 SYSTEM")

The TRIPS Agreement stipulates that production under a compulsory licence must be “predominantly for the supply of the domestic market” (Article 31f) except when the compulsory licence is granted to remedy an anticompetitive practice (Article 31k).

This restriction limits the quantity of products that can be produced for export. This is a key issue because it could render local production of a drug uneconomical for a WTO member, even if—in principle—production was legally permissible under the compulsory licence, since they would lose any external market. This restriction also has important consequences for countries without their own production capacity that rely on imports to give effect to a compulsory licence.

The Doha Ministerial in 2001 decided to postpone a resolution of this problem, but called for an “expeditious solution” in Paragraph 6 of the Doha Declaration:

“We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002.”

However, the cooperative spirit of Doha quickly evaporated once negotiators were back in Geneva. It took the TRIPS Council nearly two years to reach an agreement to allow the export of medicines produced under a compulsory licence.

During this period, the fundamental disagreement was over whether the solution would be simple and economically feasible or complex and economically risky.

Developing countries, the WHO and non-governmental organisations (NGOs) supported a solution that would have automatically allowed export of a medicine once the importing country had expressed the need and/or issued a compulsory licence. This solution would have relied upon TRIPS Article 30, and considered export under compulsory licence to be a “limited exception” to a patent right. Article 30 of TRIPS reads:

“Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties.”

In support of a solution based on Article 30, the WHO said in the TRIPS Council on 17 September 2002:

“... WHO has published a paper, Implications of the Doha Declaration on the TRIPS Agreement and Public Health, WHO/EDM/ PAR/2002.3.⁶³ This paper describes the features of a solution to the so-called “paragraph 6 problem” which are desirable from a public health perspective. These include: a stable international legal framework; transparency and predictability of the applicable rules in the exporting and importing countries; simple and speedy legal procedures in the exporting and importing countries; equality of opportunities for countries in need of medicines, even for products not patented in the importing country; facilitation of a multiplicity of potential suppliers of the required medicines, both from developed and developing countries; and broad coverage in terms of health problems and the range of medicines.”

Thus, the basic public health principle is clear: the people of a country which does not have the capacity for domestic production of a needed product should be no less protected by compulsory licensing provisions (or indeed other TRIPS safeguards), nor should they face any greater procedural hurdles, compared to people who happen to live in countries capable of producing the product.

Among the solutions that were proposed, the limited exception under Article 30 is the most consistent with this public health principle. This solution would have given WTO Members expeditious authorisation, as requested by the Doha Declaration, to permit third parties to make, sell and export patented medicines and other health technologies to address public health needs.

In its submission to the TRIPS Council on 4 March 2002, the European Commission (EC) initially signalled openness to proposals based on an interpretation of Article 30.⁶⁴ The EC said:

“To this end, WTO Members could adopt a declaration stating that a WTO Member may, in accordance with Article 30 of the TRIPS Agreement, provide that the manufacture, on its territory, of a patented product, without the authorization of the right holder, is lawful when it is meant to supply another country which has granted a compulsory licence for the import and sale of the product concerned in its territory in order to deal with a serious public health problem.”

While negotiations went on in the TRIPS Council, the European Parliament on October 23 2002 adopted Amendment 196 to the European Union (EU) Directive 2001/83/EC relating to medicinal products for human use. This amendment reads as follows:

“Manufacturing shall be allowed if the medicinal product is intended for export to a third country that has issued a compulsory licence for that product, or where a patent is not in force and if there is a request to that effect of the competent public health authorities of that country.”

The Parliament’s amendment had no impact on the EU’s position in the TRIPS Council, which by then had abandoned its initial openness towards a solution based on an interpretation of Article 30 and was advocating a solution solely based on Article 31, which did not leave the option of an automatic exception.

NGOs supported a solution based on Article 30. In June 2002, MSF published a briefing note entitled “Why Article 30 will work. Why Article 31 will not.”⁶⁵ The note drew attention to the fact that a solution based on Article 31 would require, in many cases, two compulsory licences with all the procedural requirements that come with that process, while an exception based on article 30 of TRIPS would be automatic:

“Put yourself in the position of someone suffering from a lethal disease and in need of medicines that are unaffordable under patent. Your government has acted and issued a compulsory licence for import to your country. Would you prefer that the medicines you need could be produced and supplied to your country (a) automatically; or (b) after somebody in a different country has eventually come to a decision that, in this case, it would be allowed?”

The decisions in answer (b) could have life and death consequences for millions of people. Answer (b) is the preferred option of those who favour an Art 31 solution even though it is the less swift and sure option. The best option, answer (a), is instead the Article 30 solution.”

Unfortunately, the WTO negotiations took an entirely different direction. Months of discussions in the TRIPS Council showed a deep divide between developing countries seeking a workable solution and the industrialised world that tried to limit the scope of any solution as much as possible. In an attempt to meet the 2002 deadline, most delegations were prepared to accept a far from ideal compromise text that became known as “the December 16 Motta text,” named after the chair of the TRIPS Council. The Motta text was ambiguous on the scope of diseases, through its reference to Paragraph 1 of the Doha Declaration, which mentions AIDS, tuberculosis (TB) and malaria and other epidemics. A more appropriate basis for the scope of disease would have been Paragraph 4 of the Doha Declaration, which refers to public health problems in general. On the issue of country eligibility, the Motta text seemed to be at odds with the Doha Declaration, which called for TRIPS to be implemented in a manner to “promote access to medicines for all.” The Motta text also created cumbersome procedures to determine the eligibility of countries to use the system, and measures to prevent diversion of medicines to rich country markets.

Although the Motta text was seen as far from ideal, countries were ready to agree to it. NGOs called upon the negotiators to reject the text.⁶⁶

In the end, it was the US that vetoed the proposal. The drug companies had been lobbying fiercely to restrict the scope of diseases and eligible countries. The US considered the scope of diseases in the Motta text to be too broadly defined, and rejected the proposal and announced a unilateral moratorium on disputes. In an attempt to break the deadlock, the EC followed up on an earlier US proposal and listed diseases for which the solution could apply, and introduced an advisory role for WHO in case a member requested this.⁶⁷

This proposal was rejected by the developing countries as backtracking on the Doha Declaration and was met with a wave of objections from all over the world. In numerous letters, professional medical organisations, individual medical doctors, NGOs, consumer groups and human rights groups rejected any further narrowing of the scope of the Doha Declaration. Apart from HIV/AIDS, the list included only diseases for

which there was either no treatment or where virtually all the recommended treatments were so old as to be off patent. The negotiations in the WTO became quite bizarre, with trade negotiators trying to determine public health priorities for countries of which they often had little knowledge.

The latest attempt to make the Motta text palatable for the US came from the chair of the TRIPS Council, who proposed in January 2003 to adopt a statement saying the solution “under paragraph 6 of that Declaration [was understood] as being essentially designed to address national emergencies or other circumstances of extreme urgency.”⁶⁸ Again this proposal was rejected by the developing countries. NGOs reacted fiercely in an open letter to the WTO members and called upon the members to reject the proposal. The use of compulsory licensing was never meant to only address emergency situations. It would certainly have been unacceptable to limit the use of compulsory licensing for countries without production capacity even further, when the entire purpose of the Paragraph 6 discussions was to lift the barriers to using compulsory licensing for these very countries. At this point it had become clear that there was little left of the spirit that had led to the Doha Declaration. In particular, the US seemed to want to turn back the clock to the pre-Doha era and as it would subsequently do, in part, through its bilateral and regional trade agenda.

Finally, on 30 August 2003, a decision was adopted. The August 30 decision contained a waiver of the obligations of Article 31(f) to use compulsory licences only for export and was followed by an amendment to the TRIPS Agreement (Article 31 bis) on 6 December 2005. The amendment will replace the 30 August 2003 decision once two-thirds of WTO members have accepted it.

The deadline for the acceptance of the amendment has been extended to 31 December 2015. As of this writing, 60 out of the 161 Members have done so.⁶⁹ This does not prevent countries from implementing the Paragraph 6 system into their own patent legislation nor making use of it when required. The waiver will stay in place until Article 31b comes into force. Both the August 30 Decision and the adoption of the amendment in December 2005 were accompanied by a Chairman’s statement representing several “key shared understandings” related to the non-commercial nature of the Decision, the need to take measures against trade diversion, the need to resolve issues expeditiously and amicably and the need to bring all information gathered on the Decision’s

implementation to the attention of the TRIPS Council (see Annex 1 for the full text). It also included an annex of “best practice guidelines” listing methods to prevent diversion of drugs from the multinational drug companies’ discount and donation programmes (also available in Annex 1). The note also listed the countries that had notified the WTO that they had opted out of using the solution or had restricted it to use in emergency situations only.⁷⁰

Many have noted that the system has serious flaws. The WHO Commission on Intellectual Property, Innovation and Public Health (CIPIH) recommended that the effectiveness of the August 30th Decision “needs to be kept under review and appropriate changes considered to achieve a workable solution, if necessary.” The system has only been used once since 2003: By Rwanda for the import of medicines for HIV (see Box 6).

BOX 6 PARAGRAPH 6 SYSTEM IN PRACTICE: THE CASE OF RWANDA

The compulsory licensing for export provision (Paragraph 6 system) was only used once. On 17 July 2007, Rwanda informed the WTO that it intended to import 260,000 packs of a fixed-dose combination product of zidovudine, lamivudine and nevirapine, produced by Apotex Inc. under the brand name Apo-TriAvir, over two years. The drug would be made in Canada where the products were patented. Canada had indicated as early as 2003 that it would be willing to make the Paragraph 6 system work. This announcement set a lengthy process in motion to first adopt the system into national legislation, then develop the product, negotiate with patent holders, issue the necessary compulsory licences that allowed for production and export, make the necessary notifications to the WTO, and produce and export the final product.⁷¹ The medicines were finally delivered to Rwanda in September 2008. Canadian civil society and some lawmakers have since called for amendments to the Canadian law to ease the procedures for production for export of medicines under a compulsory licence, so far without success.⁷²

MSF’s Dr Felipe Garcia de la Vega summarised the difficulties with the Canadian implementation of the Paragraph 6 system as follows: “*When we order medicines normally, all we need to do is type up a form, send it to the supplier and pay the bill—then we receive the shipment. With this system we have to persuade a government to notify the WTO, find a company willing to produce, push to get a drug on the list of eligible medicines, wait for voluntary licence negotiations to be completed, wait for the compulsory licence*

application to be made, and then granted... For a disease that kills 8,000 people a day, not only is this not a solution, it's unacceptable."

Even Apotex called the system "costly and complicated" and its president, Jack Kay, said Canada must "fix or change the legislation if we want to meet the original intent of getting life-saving drugs to developing countries."⁷³

Given that the Rwandese order is so far the only use of the system since it was put in place, some may conclude that this provides evidence that patents do not cause problems for accessing low-cost medicines. This is not correct. More logical explanations for the lack of the use of the Paragraph 6 system lie in the complexity and uncertainty of using it, and in the fact that many of the products needed—for example, antiretroviral medicines—were not patented in India and could be produced in India without any IP barriers. Accessing products from India that are not patented therefore only required one 'traditional' compulsory licence on the importing side. Ironically, Indian producers had developed and brought to market the same combination product that was subject to the compulsory licence for export in Canada well before the Canadian producer did.⁷⁴

Developing countries in the TRIPS Council continue to question the effectiveness of the mechanism.⁷⁵ In a 2013 TRIPS Council meeting, India called for a thorough review of the Paragraph 6 system, and suggested exploring alternatives to a mechanism seen by many as too cumbersome and not conducive to the economic realities of the production and supply of generic medicines.⁷⁶ The limited experience of the case of Rwanda (see Box 6) with the mechanism would support the position that a revision is needed.

However, there are options available under the mechanism that have not been explored sufficiently. In particular, the regional waiver of the mechanism provides options for effective use of compulsory licensing by creating economies of scale.

PARAGRAPH 6 OF PARAGRAPH 6: THE REGIONAL WAIVER

The Paragraph 6 regional waiver refers specifically to the options for regional trade communities of which at least half of the members are LDCs (see Box 7).⁷⁷ To harness economies of scale, such trade communities are allowed to import (and/or produce) medicines using compulsory licences and export such medicines to other countries that belong to a regional trade agreement.

BOX 7 THE TRIPS REGIONAL WAIVER

The TRIPS regional waiver states: “where a developing or least-developed country WTO Member is a party to a regional trade agreement within the meaning of Article XXIV of the GATT 1994 and the Decision of 28 November 1979 on Differential and More Favourable Treatment Reciprocity and Fuller Participation of Developing Countries (L/4903), at least half of the current membership of which is made up of countries presently on the United Nations list of least developed countries, the obligation of that Member under Article 31(f) of the TRIPS Agreement shall be waived to the extent necessary to enable a pharmaceutical product produced or imported under a compulsory licence in that Member to be exported to the markets of those other developing or least developed country parties to the regional trade agreement that share the health problem in question.”

SOURCE

World Trade Organization, “Amendment of the TRIPS Agreement,” *Decision of the General Council 6 December 2005*, WT/L/641, 8 December 2005, https://www.wto.org/english/tratop_e/trips_e/wtl641_e.htm

In practice, this means that an LDC may import and/or produce generic versions of any medicine patented in its territory, both for its own needs and for export or re-export within and outside a trade community that it is a member of, provided that at least half of the member countries are LDCs.⁷⁸

Currently qualifying trade groups include: Southern African Development Community (SADC), East African Community (EAC), Common Market for Eastern and Southern Africa (COMESA) and the African Union (AU).

Until now countries have not made use of these provisions. However, with the growing demand for medicines to treat cancer and other non-communicable diseases that are patented in the countries that traditionally provided low-cost generics to the developing world, the situation may change. As outlined in the trilateral study by the WHO-WIPO-WTO, *Promoting Access to Medical Technologies and Innovation*, “the special export licence is one legal pathway that can be followed when it represents the optimal route to effective procurement ... Regional approaches to procurement and joint notifications by countries with similar needs for accessible medicines may offer pathways to aggregating demand under the System, thus enabling an effective response to the needs identified.”

INDIA: A MODEL OF PARAGRAPH 6 IMPLEMENTATION

The Indian implementation of the WTO Paragraph 6 mechanism could be considered a model for ensuring easy use and predictable outcome because the India Patents Act (Section 92A) provides for mandatory compulsory licences for export to address public health problems of other countries, as is evidenced by the use of the word “shall” (see Box 8).

BOX 8 INDIA PATENTS ACT, SECTION 92A

“Compulsory licence shall be available for manufacture and export of patented pharmaceutical products to any country having insufficient or no manufacturing capacity in the pharmaceutical sector for the concerned product to address public health problems, provided compulsory licence has been granted by such country or such country has, by notification or otherwise, allowed importation of the patented pharmaceutical products from India.”⁷⁹

3

FROM DECLARATION TO APPLICATION:

The practical use of the Doha Declaration since 2001

IMPLEMENTING DOHA: COMPULSORY LICENCES, GOVERNMENT USE, AND WAIVERS FOR LDCS

The 2001 Doha Declaration on the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) and Public Health signalled an important turning point in the approach to intellectual property (IP) in the area of health. But while the Doha Declaration was adopted by a consensus of World Trade Organization (WTO) members, the actual application of it has often been mired in controversy, particularly in the case of middle-income countries. Nevertheless, the use of the Doha Declaration by countries to increase access to medicines has been more extensive than is generally assumed. In particular, there has been the use of: the LDC waiver or Paragraph 7 mechanism that allows LDCs to not grant and not enforce pharmaceutical product patents; and compulsory licensing, including government use (or ‘public non-commercial use’), primarily in the procurement of medicines needed to treat HIV/AIDS.

This chapter documents the use of the measures available in TRIPS and the Doha Declaration since the adoption of the Doha Declaration in 2001. This work builds on earlier overviews of the use of certain TRIPS flexibilities^{80, 81, 82} and complements these overviews with data obtained

from medicines supply agencies that were previously not publicly available.

COMPULSORY LICENSING AND GOVERNMENT USE

Under TRIPS, governments can give others than the patent holder the right to use a patent without the authorisation of the patent holder. The term ‘compulsory licence’ is often used as an umbrella term for many types of non-voluntary authorisations to use a patent, such as ex officio licences, government use, crown use, licences to remedy anti-competitive practices, mandatory licences, and statutory licences.⁸³

Compulsory licensing is particularly relevant in cases where the patent holder refuses to license. In that case, an entity such as a supplier or a generic company can request the government to issue a compulsory licence. Such a request needs to be supported by evidence that the applicant has attempted to obtain a voluntary licence first. If a patent holder refuses to give a voluntary licence for its product, the government can step in and grant licences instead. Royalties are often paid to the patent holder under compulsory licensing agreements.

It is not a requirement to first seek a voluntary licence in the case of national emergency or other circumstances of extreme urgency. Countries are free to determine what constitutes a national emergency or other circumstances of extreme urgency. It is also important to note that a national emergency or other circumstances of extreme urgency are not necessary conditions for issuing a compulsory licence. Such a situation merely makes the compulsory licence process easier as no prior negotiations to attempt to seek a voluntary licence are needed.

A health-sensitive patent law could help facilitate strategies for greater medicines access by specifically listing some of the grounds for issuing compulsory licences, including⁸⁴:

- Lack or insufficiency of ‘working,’ (which could mean failure to ‘work’ the patent by making the product commercially available, or only making it available at prices unaffordable by the community)
- Refusal to deal (refusal of a voluntary licence);
- Anti-competitive practices;
- Emergency;
- Government use; and
- Public interest.

A government can also decide to use the patent itself. This particular form of compulsory licence is called ‘government use’. In TRIPS, government use is called “public non-commercial use.” In case of government use or public non-commercial use, there is no requirement to first seek a voluntary licence. The government can make use of the patent and subsequently inform the patent holder of this decision and of the royalty that will be payable.

The government can decide to grant a compulsory licence—including for ‘government use’ or ‘public non-commercial use’—for a variety of reasons. Some countries include in their law “high prices” of medicines, or a “lack of access to medicines” as grounds for compulsory licences. For example, French law authorises compulsory licences when medicines are “only available to the public in insufficient quantity or quality or at abnormally high prices.” A ‘government use’ licence can also be used to authorise a third party to perform certain acts that otherwise would have constituted a patent infringement. This means that a government can issue a government use licence and authorise a procurement agent to purchase and supply medicines on its behalf. Government use or ‘Crown use’ existed well before the TRIPS Agreement, and in fact was common in procurement of medicines in Europe and the US in the 1950s and 1960s (see Box 9).

BOX 9 PAST USE OF COMPULSORY LICENSING BY THE UK AND US IN MEDICINES PROCUREMENT

The United Kingdom (UK) has a history of Crown use in the provision of generic medicines to the National Health Service (NHS). The NHS would purchase medicines that were patented in the UK from producers in countries where pharmaceutical patents were not granted, mostly from Italy. The Ministry of Health ordered medicines to be bought through tendering according to standard government contracts that authorised and required the supplier to disregard patent rights. The patentee had the right to compensation from the government but could not halt the importation and use of the generic. The Pfizer Corporation challenged this practice in 1965 after the Minister of Health had authorised the purchase of a generic version of the antibiotic tetracycline from Italy for use in NHS hospitals (Pfizer vs. Ministry of Health, 1965). Pfizer’s main argument was that using drugs to treat hospital patients was not use “for” the Crown. The case went

all the way up to the House of Lords, which dismissed Pfizer's arguments and ruled in favour of the Ministry of Health. Lord Reid observed at the time of the ruling:

"... It appears to me that the natural meaning of use 'for the services of the Crown' is utilisation by members of such services in the course of their duties. Sometimes, as in the case of the armed services, that use will or is intended to benefit the whole community; sometimes it will benefit a particular section of the community and sometimes it will benefit particular individuals... Therefore the use of patented drugs for National Health Service patients is use 'for services of the Crown.'"

In 1975, renowned IP scholar Stephen Ladas commented:

"Although this power of the Ministry of Health to purchase drugs and medicines from sources independent of the patentee has been much criticised by the pharmaceutical industry, it is not likely to be affected by such criticism. Such power will be exercised if the patentee is alleged to maintain unduly high prices for these products."⁸²

The Crown use provision is still part of UK patent law today.

In the late 1950s and early 1960s, the US routinely used government use powers to procure generic medicines from abroad. Because much of Europe did not grant product patents on pharmaceuticals, medicines from the continent were often much cheaper than in the US. In 1959, the US Military Medical Supply Agency (MMSA) placed an order for generic tetracycline in Italy for US\$ 0.08 per capsule. At the time, Pfizer was charging US\$ 0.17 per capsule. When another tender was issued in 1961, Pfizer responded by reducing the price to US\$ 0.06, but the Italian supplier beat this offer by bidding US\$ 0.05 per pill. By 1963, international price competition made possible by the compulsory licensing powers of the US government had driven down the price of tetracycline to US\$ 0.0015 per capsule, less than one-tenth of Pfizer's 1959 price.

PARAGRAPH 7 OF THE DOHA DECLARATION, ALSO KNOWN AS THE 'LDC PHARMACEUTICAL WAIVER' OR 'PARAGRAPH 7 MECHANISM'

Paragraph 7 of the Doha Declaration removes the obligation for least-developed countries (LDCs) to comply with Section 5 (Patents) and Section 7 (Protection of Undisclosed Information) of Part II of TRIPS, including any obligation to enforce rights under these provisions, until 1 January 2016.

Paragraph 7 of the Doha Declaration was implemented through a 2002 decision by the TRIPS Council exempting WTO LDC members from the obligation to grant or enforce patents on pharmaceutical products, or to protect pharmaceutical test data, until 2016. LDCs have requested a further extension of the waiver until they graduate to developing country status.⁸⁵ This request was not granted by the WTO; instead, a 17-year extension that will prolong the waiver until 2033 was agreed.⁸⁶

The practical implication of the Paragraph 7 mechanism is that an LDC, through simple declaration, can authorise the importation or production of a medicine regardless of its patent status in the country. The mechanism has been used on a large scale by LDCs to allow the importation of medicines, especially those needed for the treatment of HIV/AIDS.

USE OF DOHA FLEXIBILITIES: EXAMINING THE NUMBERS

The following section documents cases of practical use of the TRIPS flexibilities in the area of pharmaceuticals since the adoption of the Doha Declaration to date. The overview provides information about the use of the following types of flexibilities:

1. Compulsory licences granted by a government or government authority:
 - Following a request by a third party (CL) for import or production.
 - For government use in the context of procurement/importation (GU).
 - As a remedy for anti-competitive practices.
2. Use of the LDC pharmaceutical waiver (paragraph 7 mechanism) in the context of procurement/importation.

The sources used to collect the information include:

- Reports in the general media;
- Reports in professional medical and legal literature;
- Declarations made by governments;
- Procurement documents obtained from procurement agencies (International Dispensary Association (IDA) and UNICEF Supply).

While the information presented here is extensive, it is not necessarily exhaustive. There are likely other instances of the use by governments of TRIPS flexibilities that are not documented and/or of which information is not publicly available. Nevertheless, this overview provides one of the more complete sets of information to date, particularly because of the information from procurement agencies which was previously not available.

RESULTS: COMPULSORY LICENCES GRANTED BY A GOVERNMENT OR GOVERNMENT AUTHORITY

The table below shows 34 instances of compulsory licensing in 24 countries for reasons of access to treatment. These instances include compulsory licence grants as well as rejected or withdrawn applications for a compulsory licence. Twenty instances concerned medicines to treat HIV/AIDS, two for anthrax, two for avian flu, two for cancer, one for migraine, one for prostate enlargement, one for erectile dysfunction, and one for infection. The compulsory licence instances took place between 2001 and 2014. Of the instances, three concerned high-income countries, 26 concerned 18 developing countries, and three concerned LDCs. Of the 34 compulsory licence instances documented, eight were not executed and one application is pending. Three LDCs used GU licences: Mozambique and Zambia for local production of antiretrovirals (ARVs), and Rwanda in the context of the WTO Paragraph 6 system (see Box 6). The table below also shows the use of compulsory licensing by three high-income countries. Canada and the US announced compulsory licences for Bayer's ciprofloxacin to prepare sufficient stock of the medicines in case of anthrax attacks. Italy issued a number of compulsory licences in the context of antitrust cases, including: on 21 June 2005, for imipenem/cilastatin, a broad spectrum antibiotic marketed by Merck Sharp and Dohme (MSD); on 26 February 2006, for sumatriptan succinate, a GlaxoSmithKline (GSK) product to treat migraine headaches; and on 26 March 2007, for the active ingredient finasteride, an MSD product to treat benign prostate enlargement and male baldness. The licences are royalty-free. The Italian antitrust authority cited refusal to license as the grounds for the compulsory licence and mentioned anticipated price reductions, promotion of more widespread use of generics, and benefits for consumers when it announced its decisions.⁸⁷

TABLE 1 COMPULSORY LICENSING INSTANCES BETWEEN 2001 AND 2014

CLASSIFICATIONS:

HIC = High-income country

DC = Developing country

LDC = Least-developed country

ORIGINATORS:

BI = Boehringer Ingelheim

BMS = Bristol-Myers Squibb

GSK = GlaxoSmithKline

MSD = Merck, Sharp and Dohme

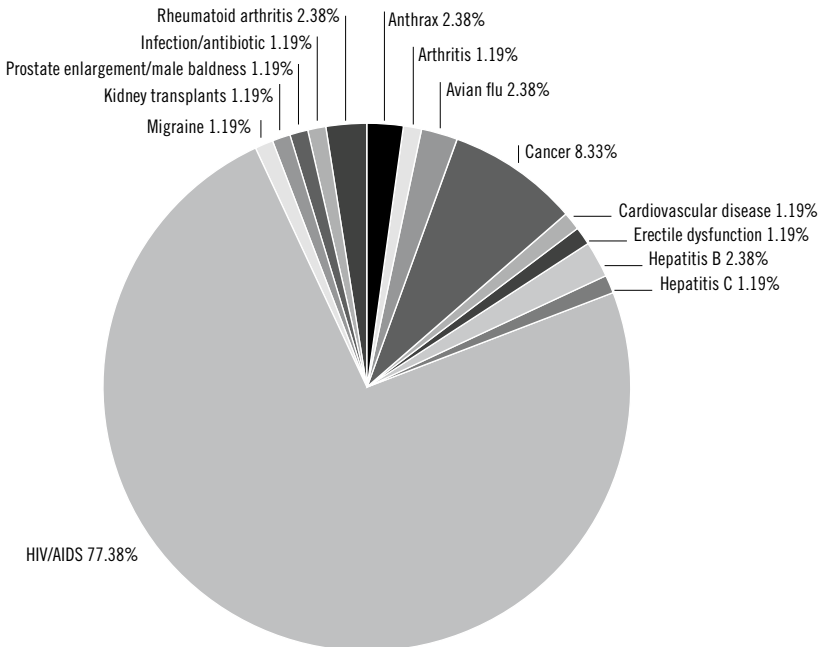
COUNTRY	DATE	CLASSIFICATION	COMPOUND	ORIGINATOR	DISEASE
Argentina*	2005	DC	oseltamivir	Roche	Avian flu
Brazil*	2001	DC	nelfinavir	Roche	HIV/AIDS
Brazil	2007	DC	efavirenz	Merck	HIV/AIDS
Cameroon*	2005	DC	NVP,3TC, 3TC+AZT	BI,GSK	HIV/AIDS
Canada*	2001	HIC	ciprofloxacin	Bayer	Anthrax
Canada	2007	HIC	3TC+NVP+AZT	GSK,BI	HIV/AIDS
China	2005	DC	3TC/d4T/NVP	GSK,BMS,BI,	HIV/AIDS
China	2007	DC	3TC/d4T/NVP and LPV/r	GSK, BMS, BI, Abbott	HIV/AIDS
Ecuador	2010	DC	ritonavir	Abbott	HIV/AIDS
Ecuador	2012	DC	abacavir/3TC	GSK	HIV/AIDS
Ecuador	2014	DC	etoricoxib	Merck	Arthritis
Ecuador	2014	DC	mycophenolate sodium	Novartis	Kidney transplant
Ecuador	2014	DC	sunitinib	Pfizer	Cancer
Ecuador	2014	DC	certolizumab	UCB	Rheuma- toid arthritis
Egypt	2002	DC	sildenafil	Pfizer	Erectile dysfunction
India	2012	DC	sorafenib tosylate (Nexavar)	Bayer	Cancer of the liver
Italy**	2005	HIC	imipenem/ cilastatin	MSD	Infection/ antibiotic
Italy**	2006	HIC	sumatriptan	GSK	Migraine
Italy**	2007	HIC	finasteride	MSD	Prostate en- largement/ male baldness
Ivory Coast	2007	DC	ARVs (specified)	Various	HIV/AIDS
Kenya*	2004	DC	ARVs	GSK, BI	HIV/AIDS
Korea*	2002	DC	imatinib	Novartis	Cancer
Mongolia	2007	DC	specified medicines	Various	Various
Mozambique	2004	LDC	NVP, D4T, 3TC	BI, BMS, GSK	HIV/AIDS
Pakistan	2006	DC	ARVs (specified)	Various	HIV/AIDS

COUNTRY	DATE	CLASSIFICATION	COMPOUND	ORIGINATOR	DISEASE
Papua New Guinea	2007	DC	ARVs	Various	HIV/AIDS
Peru*	2014	DC	atazanavir	BMS	HIV/AIDS
Philippines	2005	DC	ARVs and other meds	Various	HIV/AIDS
Rwanda	2007	LDC	3TC/NVP/AZT	GSK, BI	HIV/AIDS
South Africa*	2003	DC		GSK, BI	HIV/AIDS
Taiwan (Chinese Taipei)	2005	DC	oseltamivir	Roche	Avian flu
US*	2001	HIC	ciprofloxacin	Bayer	Anthrax
Zambia	2004	LDC	3TC, NVP, D4T	GSK, BI, BMS	HIV/AIDS
Zimbabwe	2002	DC	all ARVS	Various	HIV/AIDS

* Compulsory licence not executed. For details, see Table 6.

** Compulsory licence in the context of measures against anti-competitive practices.

FIGURE 4 INSTANCES OF COMPULSORY AND GOVERNMENT USE LICENCES (PER DISEASE AREA)



BOX 10 COMPULSORY LICENCES IN ECUADOR

On October 23, 2009, Ecuador's President, Rafael Correa, declared "access to medicines used for the treatment of diseases that affect the Ecuadorian population and are priorities for public health", a matter of public interest, and that "compulsory licences may be granted for patents on any human use medicine that may be necessary for treatment." Following this decree, the patent office has received 32 applications for compulsory licences. Ecuador has issued compulsory licences to allow for lower-cost generics of six products to be made available for the treatment of HIV, cancer, with kidney transplant and arthritis. Civil society groups in Ecuador have been involved in the advocacy for access to new medicines.⁸⁸

BOX 11 THE CASE OF THE GLIVEC COMPULSORY LICENCE APPLICATION IN KOREA

On January 30, 2002, the People's Health Coalition for Equitable Society, the Association of Physicians for Humanism, and the Korean Pharmacists for Democratic Society requested a compulsory licence for Glivec (imatinib), a drug used in the treatment of chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumour (GIST). The basis for the request was the high price that Novartis had set.

The request was rejected a year later⁸⁹ by the Korean patent office, on the following grounds:

- "1) If Glivec is imported at a lower price, it will be possible to reduce the financial burden of patients who desperately require Glivec to treat leukaemia. However, CML is not a disease that is infectious or may cause an extremely dangerous situation in our nation or society. If nevertheless a compulsory non-exclusive licence is granted for Glivec merely due to its high price, the basic purport of the patent system, which is to grant an exclusive right and interest to an inventor, thereby inspiring the public with inventive mind and striving for the development of technology and industry, will then become meaningless. Accordingly, the two conflicting interests above should be considered to determine whether a compulsory non-exclusive licence should be granted for Glivec.
- 2) All of the CML patients (including those who in chronic phase) are currently covered by health insurance. The patients actually bear about

10% of the price fixed and announced by the Ministry of Health & Welfare. The supply of Glivec is now stable. Also, it is possible to import pharmaceutical products for self-care purposes according to Article 14 of the Foreign Trade Act and Article 7 of the Foreign Trade Management Regulations. In consideration of such present situations relating to the supply of Glivec, a compulsory licence for the patented invention (Glivec) is not considered to be necessary for the public interest as prescribed in Article 107, Paragraph 1(3) of the Patent Act.”⁹⁰

RESULTS: INSTANCES OF GOVERNMENT USE SINCE 2001

The following table shows instances of government use by countries from 2001 to 2014. The table shows 51 instances of government use (GU) licences, of which only one was not executed. This concerned the GU for the cancer drug imatinib, which was suspended by Thailand in 2008 when the originator company offered a drug donation^{91,92}. There were 46 instances concerning medicines for use in HIV/AIDS programmes, including ARVs and medicines for opportunistic infections such as tuberculosis and hepatitis B. Thailand issued a GU licence for four cancer drugs and one cardiovascular medicine. Often the specific medicines were not identified or the GU declaration was for “all medicines, including ARVs” such as in the case of Zimbabwe (see Box 12). Many of the documented GU licences were issued in the context of procurement of medicines from not-for-profit supply agencies such as UNICEF supply and the IDA.

TABLE 2 GOVERNMENT USE OF MEDICINES PATENTS

DATE	COUNTRY	WTO CLASSIFICATION AT TIME OF GU	COMPOUND	DISEASE
2011	Azerbaijan	Observer	ARVs (specified)	HIV/AIDS
2005	Belarus	Observer	ARVs	HIV/AIDS
2005	Cambodia	LDC	Medicines related to HIV+OI	HIV/AIDS
2005	Chad	LDC	ARVs	HIV/AIDS
2005	Congo, Republic of	DC	Medicines related to HIV+OI	HIV/AIDS
2007	Congo, Republic of	DC	ARVs	HIV/AIDS
2014	Congo, Republic of	DC	ARVs	HIV/AIDS
2004	Cuba	DC	ARVs	HIV/AIDS
2007	Cuba	DC	ARVs	HIV/AIDS
2008	Cuba	DC	ARVs	HIV/AIDS
2005	Eritrea	Not WTO member	ARVs	HIV/AIDS
2004	Ethiopia	Observer	ARVs	HIV/AIDS
2005	Gabon	DC	ARVs	HIV/AIDS
2006	Gabon	DC	ARVs	HIV/AIDS
2013	Gabon	DC	ARVs	HIV/AIDS
2006	Georgia	DC	ARVs	HIV/AIDS
2005	Ghana	DC	ARVs	HIV/AIDS
2005	Guatemala	DC	ARVs	HIV/AIDS
2004	Guinea	LDC	ARVs	HIV/AIDS
2005	Guinea	LDC	ARVs	HIV/AIDS
2009	Equatorial Guinea	Observer	ARVs	HIV/AIDS
2005	Guyana	DC	ARVs	HIV/AIDS
2005	Haiti	LDC	ARVs	HIV/AIDS
2005	Honduras	DC	ARVs	HIV/AIDS
2008	Honduras	DC	ARVs	HIV/AIDS
2004	Indonesia	GU	ARVs (specified)	HIV/AIDS
2012	Indonesia	GU	ARVS (specified)	HIV/AIDS
2012	Indonesia	DC	TDF	Hepatitis B
2013	Iran	DC	ARVs (specified)	HIV/AIDS
2004	Lesotho	LDC	ARVs	HIV/AIDS
2005	Liberia	Observer	ARVs	HIV/AIDS
2003	Malaysia	DC	ARVs (specified)	HIV/AIDS
2004	Mauritania	LDC	ARVs	HIV/AIDS
2005	Mozambique	LDC	ARVs	HIV/AIDS
2005	Myanmar	LDC	ARVs	HIV/AIDS
2008	Philippines	DC	ARVs	HIV/AIDS

DATE	COUNTRY	WTO CLASSIFICATION AT TIME OF GU	COMPOUND	DISEASE
2006	Sao Tome Principe	Observer	ARVs	HIV/AIDS
2006	Senegal	LDC	ARVs	HIV/AIDS
2008	Sudan (North)	Not a member	ARVs	HIV/AIDS
2007	Sudan (South)	Observer	ARVs and other meds	HIV/AIDS
2005	Swaziland	DC	ARVs	HIV/AIDS
2005	Tajikistan	DC	ARVs	HIV/AIDS
2006	Thailand	DC	ARV (specified)	HIV/AIDS
2007	Thailand	DC	ARV (specified)	HIV/AIDS
2007	Thailand	DC	clopidogrel	Cardio-vascular disease
2008	Thailand	DC	letrozole	Cancer
2008	Thailand	DC	docetaxel	Cancer
2008	Thailand	DC	erlotinib	Cancer
2008	Thailand	DC	imatinib	Cancer
2004	Ukraine	DC	ARVs	HIV/AIDS
2003	Zimbabwe	DC	all medicines	HIV/AIDS

BOX 12 EXAMPLE OF A GOVERNMENT USE DECLARATION: ZIMBABWE 2003

Statutory Instrument 32 of 2003.

[CAP. 26:03 Declaration of Period of Emergency on (HIV/AIDS) Notice, 2003

The Minister of Justice, Legal and Parliamentary Affairs, in terms of section 34 as read with section 35 of the Patents Act [Chapter 26:03], hereby makes the following notice:—

1. This notice may be cited as the Declaration of Period of Emergency on (HIV/AIDS), Notice, 2003.
2. The Minister hereby declares an emergency for a period of five years with effect from 1st January 2003 to 31st December 2008 for the purpose of enabling the State or a person authorised in writing by the Minister under section 34 of the Act—
 - (a) to make or use any patented drug, including any antiretroviral drug,

used in the treatment of persons suffering from HIV/AIDS or HIV/AIDS-related conditions;

(b) to import generic drugs used in the treatment of persons suffering from HIV/AIDS or HIV/AIDS-related conditions.

Supplement to the Zimbabwean Government Gazette dated 17th January, 2003. Printed by the Government Printer, Harare.

RESULTS: USE OF THE LDC PHARMACEUTICAL WAIVER (PARAGRAPH 7 MECHANISM)

The table below documents 32 instances of 24 LDCs invoking their rights under the Paragraph 7 mechanism or LDC pharmaceutical waiver of 2002. Two LDC ‘observers’ (meaning they were not WTO members yet) referred to the WTO’s rules for LDCs when declaring no intent to enforce medicines patents and authorising the importation of generic medicines. In 11 instances, countries invoked the mechanism for all medicines; in 18 instances, countries specified that they invoked the mechanism for medicines needed in the treatment of HIV/AIDS. The instances took place between 2004 and 2009.

All of the instances were in the context of procurement from not-for-profit procurement agencies. Such agencies seek legal assurance that they can supply without threats of patent infringement suits. The Paragraph 7 mechanism has proven to be a very effective mechanism to provide such legal certainty. The concern for legal action by patent holders was not imaginary, certainly not in the early 2000s when Africa knew several legal battlegrounds over medicines patents. The most notorious of these was the 1998 South African court case (see Introduction, “How the HIV pandemic changed everything”).

But there were others. In 2000, GSK took legal action in Ghana against a drug distributor and the generic drug maker Cipla to prevent the supply of generic version AZT/3TC, an HIV treatment product sold by GSK under the brand name Combivir.⁹³ In 2005, the year in which all developing country members of the WTO who were not LDCs had to comply with TRIPS, Ghana issued GU licence to allow the import of generic medicines after declaring HIV/AIDS a national emergency.⁹⁴

**TABLE 3 LDC USE OF THE PHARMACEUTICAL WAIVER
(DOHA PARAGRAPH 7 MECHANISM)**

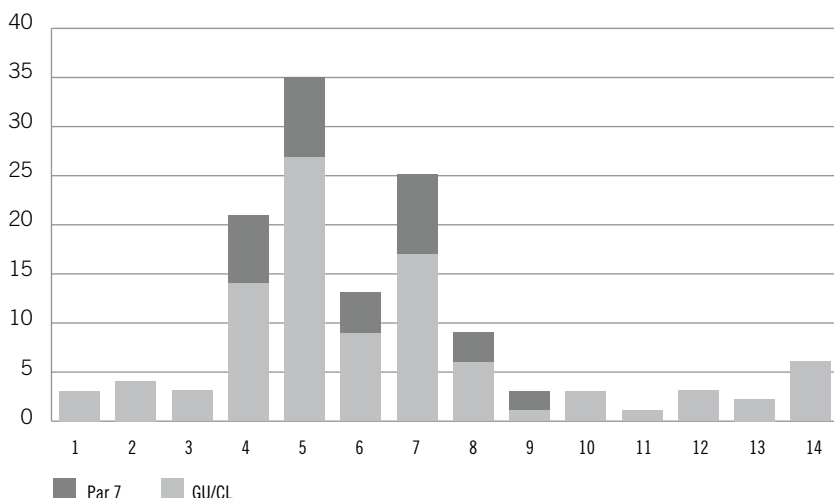
DATE	COUNTRY	WTO CLASSIFICATION	COMPOUND(S)	DISEASE(S)
2005	Angola	LDC	All medicines	All
2004	Benin	LDC	ARVs	HIV/AIDS
2007	Benin	LDC	ARVs	HIV/AIDS
2009	Benin	LDC	ARVs	HIV/AIDS
2005	Burkina Faso	LDC	All medicines related to HIV+OI	HIV/AIDS
2005	Burundi	LDC	All medicines related to HIV+OI	HIV/AIDS
2004	CAR	LDC	ARVs and all other medical supplies	HIV/AIDS
2005	CAR	LDC	All medicines related to HIV+OI	HIV/AIDS
2007	Chad	LDC	All medicines	All
2007	Comoros	Observer LDC	All medicines related to HIV+OI	HIV/AIDS
2007	Djibouti	LDC	ARVs	HIV/AIDS
2005	DRC	LDC	ARVs	HIV/AIDS
2004	Gambia	LDC	ARVs	HIV/AIDS
2007	Gambia	LDC	All medicines	All
2005	Guinea Bissau	LDC	ARVs	HIV/AIDS
2006	Lesotho	LDC	All medicines	All
2004	Malawi	LDC	All medicines	All
2005	Malawi	LDC	ARVs	HIV/AIDS
2006	Mali	LDC	All medicines	All
2007	Nepal	LDC	All medicines	All
2008	Nepal	LDC	All medicines	HIV/AIDS
2004	Niger	LDC	All medicines	All
2005	Niger	LDC	ARVs	HIV/AIDS + other
2007	Rwanda	LDC	All medicines	All
2009	Sierra Leone	LDC	ARVs (specified)	HIV/AIDS
2007	Sudan	Observer LDC	All medicines	All
2008	Tanzania	LDC	All medicines	All
2004	Togo	LDC	All medicines	HIV/AIDS
2008	Togo	LDC	ARVs (specified)	HIV/AIDS
2006	Uganda	LDC	ARVs (specified)	HIV/AIDS
2004	Zambia	LDC	ARVs and all other medical supplies	All
2006	Zambia	LDC	ARVs and all other medical supplies	All

OBSERVATIONS

The use of TRIPS flexibilities has been most extensive in the context of the procurement of HIV medicines. By 2004, funding for HIV treatment was starting to become available through the Global Fund, the Presidents Emergency Plan for AIDS Relief (PEPFAR), UNITAID (2006) and other agencies. It was in the donors' interest that money for the procurement of HIV medicines was used efficiently and not wasted on over-priced branded products.

Countries sometimes used a mix of flexibilities and grounds in their procurement, perhaps in an effort to provide a maximum level of assurance to the suppliers. For example, a GU declaration was often made in conjunction with a statement about the public health needs constituting an emergency. LDCs sometimes used GU even though they could resort to the Paragraph 7 mechanism. Sometimes non-WTO members referred to Doha flexibilities even though they would not need to or it would not have been applicable in their situation.

Not all compulsory licence (CL) instances presented here were granted or executed. For example, Thailand suspended the CL for imatinib after the patent-holding company established a donation program. Brazil did the same once it obtained a lower price for one of the ARVs. These instances of CL use are nevertheless interesting because they illustrate that even the threat of the use of compulsory licensing can lead to a response by the patent holder to offer a better price, offer a voluntary licence or provide access to the product in question.

FIGURE 5 USE OF TRIPS FLEXIBILITIES, 2001–2014

A surge in the use of TRIPS flexibilities can be seen from 2004 to 2007. This can be explained by the fact that most cases concerned HIV products for which funding had become available. The instances of use of TRIPS flexibilities tapered off after 2008. By that date, companies had begun to change their approach and implemented non-assert strategies for LDCs and sub-Saharan African countries and started to grant licences to generic producers. For the procurement agencies it was not always necessary to seek government use or the invocation of the Paragraph 7 mechanisms by LDCs for follow-up orders once those statements were on file. This is not to say that the need for CLs had become defunct. In particular, middle-income countries to this day struggle to access lower-cost ARVs because they are often not able to benefit from licences and external funding sources. Middle-income countries are also subject to greater scrutiny and trade pressures by rich countries that often make them reluctant to exercise their rights under TRIPS/Doha.

In 2010, UNITAID created the Medicines Patent Pool, which negotiates licences for HIV medicines and today has agreements with all but two of the ARV patent holding companies for supply to low- and middle-income countries that are home to 82–87% of the people living with HIV. The existence of the MPP makes non-voluntary measures

redundant in those countries⁹⁵ (see “The Medicines Patent Pool” in this chapter).

A slight increase in compulsory licences is again visible in 2014. Interestingly, these mostly concern medicines for the treatment of non-communicable diseases (NCDs). All instances related to non-HIV medicines in developing countries took place between 2007 and 2014 (with the exception of the CL application for a cancer drug in Korea in 2002, described in Box 11). The NCDs represent the new frontier of access to medicines struggles in low- and middle-income countries that are seeking ways to provide care for cancer patients, heart disease patients and others in a cost effective manner. The focus of the use of TRIPS/Doha flexibilities may shift to NCDs now that medicines patenting is a global phenomenon and prices of newly patented essential medicines remain high.

CONCLUSIONS

Most of the GU-type compulsory licences and non-enforcement measures by LDCs documented here in relation to ARVs concern decisions by the ministry of health in day-to-day procurement practices. These measures did not require lengthy court procedures or presidential decrees, but were instead simple statements of the intention to make public non-commercial use of the patents or declare a non-enforcement of medicines patents to alleviate the HIV crisis. Many of these licences have not made newspaper headlines. And why should they? Procuring quality low-cost medicines should be part of a routine function of health officials and not be mired in controversy. This practice is reminiscent of the procurement carried out by the UK and the US in the late 1950s and 1960s (see Box 9).

HIV procurement in the early to mid-2000s shows that routine use of Doha/TRIPS measures have been effective in increasing access to low-cost ARVs, in particular first-line fixed-dose combination (FDC) ARVs that were only available from Indian generic producers. The use of TRIPS/Doha flexibilities in ARV procurement is in stark contrast with the politicisation of compulsory licensing for medicines to treat cardiovascular disease and cancer, a practice that continues to attract the opposition of countries like the US and the EU.

THE USE OF THE DOHA DECLARATION BEYOND HIV/AIDS

From 2008 onwards, some countries started to use the TRIPS flexibilities to gain access to lower-cost treatment for diseases other than HIV/AIDS. This is explicitly allowed under TRIPS. The Doha Declaration further clarifies this when it states: “Each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted.”

Nevertheless, countries that took advantage of these flexibilities in TRIPS have met with resistance, both internally (from people worried about economic repercussions) and externally from countries and companies looking to push for stronger patent protections. Below are case studies from Thailand, India, and the EU.

COMPULSORY LICENCES ON CANCER MEDICINES IN THAILAND

In 2008, Thailand issued a compulsory licence for the cancer drug imatinib (Glivec), price being the main reason.⁹⁶ The price of a 100mg tablet of the originator brand costs 917 Baht (US\$ 29.30), while the generic version cost 50–70 Baht (US\$ 1.59–2.23), representing a price differential of almost 20 times the amount for the patented version. A government assessment of the effect of the compulsory licence concluded that by 2009, the increased availability of imatinib in the Thai health care system resulted in a gain of 2,435 quality adjusted life years (QALYs).

The Thai Health Intervention and Technology Assessment Program (HITAP) carried out an assessment of the effects of the compulsory licence measures focusing on health impact, health-related economic impact, impact on trade and foreign investment. The study also included a survey of the views of key Thai and international stakeholders to assess the psychosocial impact: healthcare workers, researchers/academics and civil servants, government officials, the private sector, non-governmental organizations (NGOs) and foreign stakeholders.⁹⁷ It is interesting to note in the context of this study that the stakeholders interviewed about the Thai compulsory licences were more supportive of the use of such a measure for HIV than for NCDs. One explanation for this is the common misunderstanding that compulsory licences are not legal unless there is a state of emergency or extreme urgency and, therefore, not suitable for use in chronic NCDs.

The assessments carried out by HITAP show clear benefits in terms of access to treatment. The study estimated the increase in the number of

patients with access to the four anti-cancer drugs over the five-year study timeframe as follows: 8,916 patients for letrozole; 10,813 for docetaxel, 1,846 for imatinib; and 256 for erlotinib.

The results in terms of QALYs gained as a result of the compulsory licences were as follows (in order of drugs with the greatest health gains):

- Letrozole: 3,656 QALYs gained;
- Imatinib: a total of 2,435 QALYs gained (1,384 QALYs for Chronic Myeloid Leukaemia, or CML, patients; 1,051 QALYs for Gastrointestinal Stromal Tumour, or GIST, patients); and
- Docetaxel: 1,251 QALYs gained.

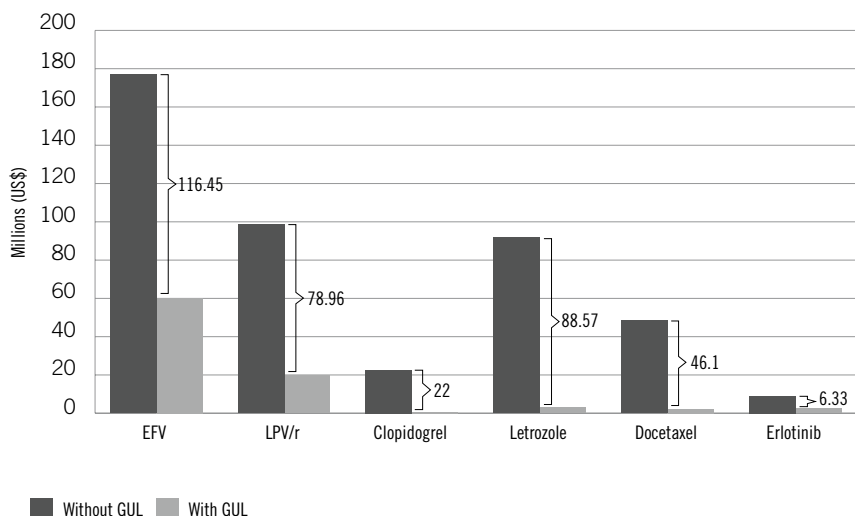
There was no QALY data available for erlotinib.

Considering that these medicines are used to fight life-threatening diseases, not issuing licences and extending the availability of the products to people suffering from cancer would have been inhumane.

EFFECTS ON EXPORT TRADE AND FOREIGN DIRECT INVESTMENT

Domestic criticism of the Thai compulsory licences was often driven by a concern for adverse economic effects as a result of trade sanctions by trading partners such as the US. Thailand's trade status was downgraded by the US from the 'Watch List' to the 'Priority Watch List' under its Special 301 provisions where it records what it views as IP violations in other countries. The US also withdrew three Thai export products from the Generalized System of Preferences (GSP), a trade preference programme that eliminates tariffs on certain goods for certain developing countries in order to facilitate trade, in 2007, but granted GSP status to eight new products in the same year. The GSP withdrawal, therefore, did not adversely affect the overall export status. The study also did not find any adverse effects on foreign direct investment. In conclusion, compulsory licences for HIV and cancer drugs in Thailand have been important for increasing access and lowering the cost of patented medicines, with no short-term adverse economic effects.

FIGURE 6 COST SAVINGS BY DRUG THROUGH THE USE OF GOVERNMENT USE LICENSING (GUL) POLICY (IN MILLION US\$)



SOURCE

Thai Ministry of Health quoted in “Use of Compulsory Licenses, Selected National Experiences,”⁹⁸ published by UNCTAD.

COMPULSORY LICENCES ON MEDICINES IN INDIA

In India, the price of newer generations of cancer medicines posed an important challenge in a country seeking to expand universal cancer care for its population. The Ministry of Health recommended in January 2013 compulsory licensing (referring to both Section 84 and Section 92 of the Patent Act, 1970) of the patents on three anti-cancer drugs: dasatinib (originator: Bristol-Myers Squib, or BMS), trastuzumab (originator: Roche) and ixabepilone⁹⁹ (originator: BMS) to the Department of Industrial Policy and Promotion (DIPP).¹⁰⁰ In July 2015, a compulsory licence request was made for a patent related to saxagliptin, a diabetes drug marketed by AstraZeneca.¹⁰¹

Dasatinib is a medicine used primarily to treat several types of leukaemia. MIMS India listed two prices for dasatinib in 2013, one from originator Bristol-Myers Squibb (BMS) and one from Natco Pharma Ltd., which makes a generic version of dasatinib. The difference is telling, as seen in Table 4.

TABLE 4 RETAIL PRICE OF A DASATINIB (50MG) TABLET IN US\$

BRAND NAME	COMPANY	PRICE PER TABLET (50MG)
Dasanat	Natco Pharma Ltd.	2.33
Sprycel	Bristol-Myers Squibb	52.20

SOURCE

Mims.com (2013).

BMS and Natco had been engaged in a patent infringement battle over dasatinib. A Delhi High Court injunction in June 2012 prohibited Natco from continuing to sell the product.¹⁰² At least 2,500 patients were on treatment using Natco's generic dasatinib, until it was withdrawn following the Delhi High Court order in June 2012.

Independent of the DIPP process, in 2013 the generic company BDR Pharmaceuticals also applied for a compulsory licence to be able to produce and market dasatinib.¹⁰³ BDR said its generic dasatinib would be available to patients at Rs. 135 (US\$ 2.20) per tablet. BMS's estimated comparable price is about Rs. 2,761 (US\$ 43.57) per tablet. BDR offered to pay a royalty and make the product available for free to a certain percentage of patients. This request for a compulsory licence, however, was rejected on procedural grounds—failure to meaningfully engage in obtaining a voluntary licence from the patent owner—on 29 October 2013.¹⁰⁴

The DIPP in October 2014 deferred the decision to grant a compulsory licence for dasatinib. The CL was recommended by the Ministry of Health.¹⁰⁵

Trastuzumab (brand name Herceptin) is used to treat breast cancer. In August 2013, in the face of mounting pressure, Roche relinquished its patent for trastuzumab in India making the issuance of a compulsory licence redundant.¹⁰⁶ Roche did this after the Kolkata patent office had revoked patents related to trastuzumab.^{107,108}

A few months later in 2013, generic companies Biocon and Mylan received marketing authorisation in India for their biosimilar trastuzumab products, which they each market under separate brand names.¹⁰⁹

As of May 2015, trastuzumab is on the WHO Model List of Essential Medicines (EML). In November 2012, Knowledge Ecology International (KEI), the University of California, San Francisco, Universities Allied for Essential Medicines (UAEM) and the Young Professionals Chronic Disease Network submitted trastuzumab for inclusion in the EML. In their application they point out that one possible supplier of trastuzumab

suggested the drug could be manufactured for US\$ 31 per gram, or US\$ 242 per year, roughly 1% of the lowest Roche price. The current Roche prices range from US\$ 3,000–9,000 per gram. In comparison, one gram of gold cost US\$ 42 on 4 November 2013.¹¹⁰ However, countries where the medicine is patented will need to resort to compulsory licensing (in the absence of a voluntary licence) to access the generic price.

TABLE 5 PRICE OF TRASTUZUMAB FOR A ONE-YEAR COURSE IN US\$¹¹¹

This table provides prices as quoted in different sources for trastuzumab.

COUNTRY	ORIGINATOR	GENERIC
US	49,000	
UK	25,000	
India	16,392 ¹ 28,182 ³	14,000 ² 24,000 ³ (Emcure) 11,600 ⁴ (Biocon)
China	54,000 ⁵	
South Africa	46,748 ³	

SOURCES

- 1 Tracy Staton, “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>
- 2 Divya Rajagopal, “Cancer drugs made by Emcure, Roche still expensive for patients,” *The Economic Times of India*, 1 February 2013, http://articles.economictimes.indiatimes.com/2013-02-01/news/36684537_1_cancer-drugs-roche-herceptin
- 3 From the KEI trastuzumab price survey.¹¹²
- 4 Naomi Kresge and Ketaki Gokhale, “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>
- 5 Wen Chen, Zeifei Jiang, Zhimin Shao, Qiang Sun, and Kunwei Shen, “An Economic Evaluation of Adjuvant Trastuzumab Therapy in HER2-Positive Early Breast Cancer,” *Value in Health*, 12, no. 3 (2009): S82 – S84, <http://www.ispor.org/consortiums/asia/ViH/An-Economic-Evaluation-of-Adjuvant-Trastuzumab-Therapy.pdf>

To date India has granted one compulsory licence (based on Section 84 of the Patents Act), in 2012 for the cancer drug, sorafenib tosylate (originally marketed by Bayer as Nexavar), for the treatment of liver cancer.¹¹³ This marked India’s first, and so far only, granted compulsory licence.

The sorafenib CL has led to huge controversy and fierce response from the industry and policy makers in countries that are home to multinational pharmaceutical companies, particularly in the US. In 2013, 170 members

of Congress wrote to President Obama complaining about the compulsory licence for sorafenib and expressing concerns over the potential of more compulsory licences to follow.¹¹⁴ Additionally, 40 senators wrote to Secretary of State John Kerry to express similar concerns, and business groups established a new coalition—the Alliance for Fair Trade with India—focussing on India’s IP policy¹¹⁵, which it called “unfair” and harmful to American business. India’s IP policy has been the subject of high-level discussions between India and the US and provoked an out-of-cycle review by the US Trade Representative.¹¹⁶

COMPULSORY LICENCES ON HEPATITIS C MEDICINES IN EUROPE

In 2015, KEI-Europe petitioned the government of Romania to issue a compulsory licence for medicines needed in the treatment of hepatitis C.¹¹⁷

Romania has one of the highest hepatitis C infection rates in Europe. New antivirals to cure hepatitis C have become available in Europe but are priced highly. For example, the best price in France for a 12-week course with sofosbuvir/ledipasvir fixed-dose combination sold by Gilead under the brand name Harvoni is € 46,000 (US\$ 51,500)¹¹⁸ The US price for the sofosbuvir/ledipasvir combination product (Harvoni) is US\$ 94,000.

Considering that the gross domestic product per capita in Romania is around US\$ 9500, such prices will keep these lifesaving medicines out of the hands of people with hepatitis C unless more affordable sources become available. Generic manufacturers and global health groups have filed patent grant oppositions to sofosbuvir patents in India and other countries, including at the European Patent Office.¹¹⁹

THE ‘ALMOST COMPULSORY LICENCES’

The decision to issue or the announcement of a compulsory licence does not always lead to the actual granting of a compulsory licence. But this does not mean that such decisions or announcements are without effect. Sometimes the announcement of the intention to issue compulsory licences can be sufficient to provoke a response from the patent holder to lower the price or to make the product available otherwise, for example, through voluntary licensing. Thus, the potential to issue compulsory licences can be as important a policy tool as the compulsory licences themselves.

This happened in the case of the US and Canada¹²⁰, both of which had announced compulsory licences for ciprofloxacin to respond to a possible

anthrax outbreak in case of terror attacks in 2001. Bayer, the patent holder, responded with price discounts and commitments for the supply of stockpiles.¹²¹

TABLE 6 INSTANCES OF COMPULSORY AND GOVERNMENT USE LICENCES NOT (YET) GRANTED OR SUSPENDED

COUNTRY	DATE	CLASSIFICATION	COMPOUND	DISEASE	REASON
Argentina	2005	DC	oseltamivir	Avian flu	No patent
Brazil	2001	DC	nelfinavir	HIV	Price discount
Cameroon	2005	DC	NVP, 3TC, 3TC+AZT	HIV	No response
Canada	2001	HIC	ciprofloxacin	Anthrax	Price discount
Kenya	2004	DC	multiple ARVs	HIV	Voluntary licence
Korea	2002	DC	imatinib	Cancer	Rejected (See Box 11)
Peru	2014	DC	atazanavir	HIV	Pending
South Africa	2003	DC	multiple ARVs	HIV	Voluntary licence
Thailand*	2008	DC	imatinib	Cancer	Suspended after donation by originator
US	2001	HIC	ciprofloxacin	Anthrax	Price discount

DC = WTO developing country

HIC = WTO high-income country

*Concerning a government use licence

There are other reasons why compulsory licences are not granted when announced. Argentina announced in 2005 plans to issue compulsory licences for oseltamivir (brand name Tamiflu, manufactured by Roche) to allow local production of the product as part of their pandemic flu preparedness plans. It later became clear that the patent for oseltamivir was never granted in Argentina. Taiwan, around the same time, issued a compulsory licence for the production of oseltamivir to ensure sufficient supply in case of an epidemic outbreak, though they said they would use it only in case stockpiles of the branded drug ran dry.¹²²

These compulsory licensing plans provoked a response from the patent holder. Roche, in an attempt to avoid a public relations fall-out and further compulsory licences, announced later in 2005 that it

would make voluntary licences available for generic production of oseltamivir.¹²³

Kenya came close to issuing compulsory licences for ARVs in 2004 after a local medicine manufacturer, Cosmos, won a tender to provide ARVs that were patented in Kenya. However, the companies concerned, GSK and BI, subsequently granted voluntary licences.¹²⁴

Thailand suspended its compulsory licence for imatinib, a drug needed for the treatment of CML, a specific type of cancer of the blood, on the condition that the originator drug would be provided free to low-income patients under the government health insurance scheme and the Novartis Glivec International Patient Assistance Program (GIPAP).

Brazil abandoned its plans to issue compulsory licences for HIV medications five times after price discounts were obtained.

The conclusion that the threat of a compulsory licence can lead to a positive outcome is also supported by the findings of Beall and Kuhn.¹²⁵ They identified 24 episodes of compulsory licensing in 17 countries (for 22 products, 16 concerning drugs for HIV/AIDS), of which only half led to the actual granting of a licence. They also note that countries that signalled their intention to grant compulsory licences, but in the end did not, nevertheless benefited from price reductions, for example, through discounts or voluntary licensing by the patent holder.

A MOVE TOWARDS VOLUNTARY LICENSING: CREATING A PATENT POOL

Increasing recognition on the part of pharmaceutical companies that actions needed to be taken in order to ease tensions between the need for medicines and high prices resulted in an uptick of voluntary licences. The need to have greater predictability in licensing led to the proposal to establish a Medicines Patent Pool that would bring all IP together in one place to ensure generic production in patient-friendly formulations.

THE MEDICINES PATENT POOL

The idea for a patent pool to facilitate public-health oriented voluntary licences for medicines was first discussed at the 2002 International AIDS Conference in Barcelona when a small group of treatment activists came together to listen to a presentation about the 1917 US government-mandated airplane patent pool by James Love, director of KEI. A patent pool is a licensing arrangement between several entities holding patents

related to a particular type of technology, in which they agree to share their IP with each other and/or with third parties. Patent pools often form around complex innovations in which several parties own patents that could block development.

Airplanes were one such complex innovation. The airplane patent pool was established in 1917 by the US government in response to the refusal of patent holders to offer licences to the patents they held and which were necessary to scale up production of military airplanes—a key ambition by the US government now that it had entered World War I. The US government mandated access to those patents and royalty rates were set at 1%.¹²⁶

When such a measure could be taken by a government to increase the production of military airplanes, surely something similar could be done in the face of the HIV crisis. A medicines patent pool would respond to the need for a more structured and predictable approach towards voluntary licensing and move away from the hand-to-hand combat that had become the mainstay in increasing access to medicines needed to treat HIV/AIDS. For that to happen, it was necessary to establish an independent public health-driven entity that would take on the negotiations with patent holders, manage the licences, and ensure uptake by generic manufactures.

The plan for a medicines patent pool found an ear at UNITAID in 2006, following a presentation by KEI and Médecins Sans Frontières (MSF) to the UNITAID board that assessed the feasibility of the project.

In 2008, patent pools were discussed by the World Health Assembly and referenced in the World Health Organization (WHO) Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA; see Chapter 6, “Pharmaceutical Innovation and Health Needs”; also article 4.3(a) in the GSPOA¹²⁷) and later in the Consultative Expert Working Group (CEWG) Report that grew out of the Global Strategy. The CEWG considered patent pools for medicines a feasible mechanism to accelerate the availability of low-cost newer medicines in developing countries. In 2008, UNITAID¹²⁸ decided in principle to move ahead with the plan to establish a patent pool for medicines. The Medicines Patent Pool (MPP) was established in 2010, following the positive results of the feasibility study, to ensure the availability of patent licences in low- and middle-income countries, beginning with medicines for HIV.

During the discussions at the UNITAID board, the Doha Declaration was brought forward by countries that wanted to ensure that the MPP was set up according to its basic principles. They sought to avoid any risk creating restrictions of the policy space the Doha Declaration had clarified

by setting up a mechanism that was based on negotiating voluntary licences. They sought assurances that the MPP would take on the principles of the Doha Declaration. The memorandum of understanding between UNITAID and the MPP, as well as the MPP's constitution, refer to the obligation to make sure that terms and conditions negotiated are consistent with the WHO GSPOA and other international instruments and declarations, which is a reference to the Doha Declaration.¹²⁹

The brand new initiative received an early boost when the US National Institutes of Health became the first licensor and committed patents it held related to the ARV, darunavir, to the MPP in 2009. The agreement came with a strong endorsement from the US government. The White House blogged about it under the title "US Government first to share patents with Medicines Patent Pool."¹³⁰ This high level political endorsement helped to establish the MPP as a recognised entity and encouraged companies to engage with it.¹³¹ Engagement with pharmaceutical companies was not at all a given when the initiative took off; some were openly hostile to the idea. For example, Dominique Limet, CEO of pharmaceutical company ViiV, said in July 2010 to the *Financial Times*: "The pool's key focus has been political in getting access to IP without explaining how it will work. It's not the issue. It's about the will and money to invest in new drugs, and ensuring there is enough demand and infrastructure to ensure access. The €4.7 million they will spend could save thousands of lives [by buying drugs]."¹³² The first commercial company to enter into negotiations with the MPP was Gilead Sciences, which in 2011 licensed its IP related to products to treat HIV and hepatitis B to the MPP. Other companies, including ViiV, would follow soon.

The MPP offers a predictable remedy to the effects of HIV medicines patenting by negotiating licences with HIV medicines patent holders and by licensing out to generic producers that have the capacity to make low-cost quality HIV treatments. The availability of licences makes treatments more affordable because it makes generic competition possible. The MPP also works to encourage the development and production of fixed-dose combinations of ARVs, in accordance with the recommendations of the WHO and the development of adapted formulations, such as ARVs for children. It contributes to quality assurance of the medicines by requiring in its sub-licence agreements that generic companies seek WHO prequalification or stringent regulatory approval.

The MPP creates the availability of sources of low-cost generic production that otherwise would not exist because of patents. This is important for a

number of reasons: it provides low-cost generics for people in the countries that are part of the agreements. It also provides a benchmark for other actors to either negotiate with the patent holder a better price or seek other solutions to access the medicine. It sets new public health norms and standards for voluntary licensing. And because it sets those new norms, it also offers the possibility for countries outside the scope of the agreements to benefit from the generic supply through compulsory licensing. For example, Peru is currently contemplating a compulsory licence for atazanavir. BMS holds the atazanavir patent in Peru until 2018, and Peru today pays on average US\$ 12.85 per 300 mg of the drug, sold under the brand name Reyataz. Bolivia, which can access generic products, pays US\$ 0.50 per 300 mg. Peru is not in the scope of the MPP's agreement with BMS; however, public-health oriented provisions negotiated by the MPP mean that generic manufacturers using the MPP licence to make atazanavir will be able to export it to Peru if the country issues a CL.¹³³

There are also important challenges and limitations to the MPP. In particular, participation in the MPP by patent holders is voluntary. While all ARV patent holders are currently engaging with the MPP, and of those all but two have signed agreements, the MPP does not have the power to force reluctant patent holders to the negotiation table. The MPP also has no power to dictate terms and conditions to a company that is not willing to accept them. For example, a company can seek to limit the geographical scope of the licence. Also, the MPP so far has been primarily limited to HIV, while problems of access to medicines exists in many other areas of health.

Important advantages of the MPP are that it negotiates licences from a public health perspective and seeks the broadest possible application in terms of number of countries and people that can benefit from the agreement. The licences are predictable and transparent. The MPP's transparency with regard to the licence agreements is unprecedented: all agreements are made public on the organisation's website, where they are open to scrutiny by others. This is important for building trust in the work of the MPP, but also to help improve the agreements. Prior to the MPP, the terms and conditions of voluntary licences were largely kept secret. But by allowing others to scrutinise the outcome of the negotiations, areas of improvements have been identified and led to changes in the agreements. The MPP proactively engages with the generic industry and others to ensure uptake of the licences, to encourage the development and production of priority products and to ensure products meet quality standards. UNITAID remains a key strategic partner to the

MPP as its main funder and an expert in market dynamics for improving global health. It is fair to say that the changing norms with regard to IP protection that were a result of the Doha discussions created an environment in which the establishment of a medicines patent pool for HIV was possible.

After five years of operation, the MPP has had important successes:

- It has signed voluntary licences on 12 priority ARVs with six patent holders and 59 sub-licences with 14 generic manufacturers. It additionally signed one licence on a priority treatment for hepatitis C as well as an agreement to increase access to a key opportunistic infection in people living with HIV, cytomegalovirus retinitis (CMV-retinitis).
- Generic companies with licences from the MPP have supplied more than 7 million patient years of WHO-recommended ARVs in 117 countries, including 41 countries that were previously unable to benefit from generic competition for such medicines.
- The MPP's licences enable the manufacturing of generic adult formulations of ARVs and their sale in countries where between 87% and 93% of people with HIV in the developing world live. This includes all 34 low-income countries and, depending on the licence, between 55% and 80% of middle-income countries, representing a significant increase over licences prior to the establishment of the MPP.
- The MPP's agreements have saved the international community US\$ 119.6 million through lower prices of ARVs.¹³⁴
- MPP sub-licensees, between January 2012 and June 2012, supplied 4.3 million patient-years (the equivalent of one year's treatment for 4.3 million people) with formulations of tenofovir disoproxil fumarate (TDF). TDF is WHO-recommended first-line treatment for HIV.
- In the coming years, the MPP is expected to generate total savings of between US\$ 1.18 and 1.4 billion.¹³⁵

The MPP, in collaboration with the Drugs for Neglected Diseases Initiative (DNDi) and UNITAID, has embarked on innovation projects to ensure HIV medicines suitable for use by children are developed. The first child-friendly WHO-recommended HIV treatment resulting from this collaboration was approved by the US Food and Drug Administration in June 2015.¹³⁶

On 6 November 2015, the MPP announced that its mandate had been expanded to include hepatitis C and tuberculosis.¹³⁷ Shortly thereafter, the MPP announced its first licence on a hepatitis C drug, daclatasvir, with BMS.¹³⁸

4

CLOSING THE POLICY SPACE:

Trade agreements and TRIPS-plus measures

TRIPS AND ITS BUILT-IN FLEXIBILITY

The World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) provides flexibility in implementation and specifically contains a number of public interest safeguards. Many of these safeguards can be traced back to developing countries' concerns expressed during the negotiations of the TRIPS Agreement about the effects of stricter intellectual property (IP) rules on their ability to access new technologies, including medicines. The Doha Declaration further reinforced and expanded the flexibilities.

The preamble to TRIPS points out that the purpose of the Agreement was not to protect the private interests of a small group of IP rights-holders, but rather, to serve the wider goals of trade, economic development and the public interest. It warns in the first paragraph that IP itself could become a barrier to trade. It defines IP as a means to an end, not as an end in itself. This idea is reflected in the fifth clause of the preamble to TRIPS, which reads: "Recognizing the underlying public policy objectives of national systems for the protection of intellectual property, including developmental and technological objectives."

TRIPS Article 1.1 indicates that it sets out the “required” minimum standards. Where it reads that countries “shall not be obliged” to implement more extensive protection, Article 1 also reflects the fact that these standards are the maximum countries were prepared to agree on. Article 1.1 reads:

“Members shall give effect to the provisions of this Agreement. Members may, but shall not be obliged to, implement in their law more extensive protection than is required by this Agreement, provided that such protection does not contravene the provisions of this Agreement. Members shall be free to determine the appropriate method of implementing the provisions of this Agreement within their own legal system and practice.”

According to legal scholar Carlos Correa, Article 1.1 of TRIPS provides protection against demands for higher standards than TRIPS requires and outlaws unilateral sanctions such as Section 301 of the US Trade Act.¹³⁹

The stated objective of the TRIPS Agreement includes reference to social and economic welfare, thereby stipulating that TRIPS does not only create and protect the private rights of innovators but also serves the broader public interest. This objective is laid out in Article 7, which reads:

“The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.”

The inclusion of this objective was the result of proposals made by developing countries that were concerned about their ability to obtain cutting-edge technologies under an IP system that ran ahead of their level of industrial development. Article 7 also made clear that IP protection should be seen as a social policy tool designed to benefit societal and economic welfare. The TRIPS objectives together with Article 1.1 give countries leeway in how the Agreement can be interpreted and implemented.

Developing countries’ concerns were also at the root of TRIPS Article 8, which allows for measures “to protect public health and nutrition, and to

promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement.”

Developing countries also obtained transition periods for the implementation of the TRIPS Agreement to allow them to reach a certain level of economic development before being bound to the norms of TRIPS. Today only the WTO’s least-developed country (LDC) members continue to enjoy such transition periods.

The 2001 Doha Declaration strengthens the notion even further that the TRIPS Agreement should serve a greater public good. It further expands the freedom countries have to implement TRIPS in a manner that takes into account specific needs with regard to health and access to medicines.

The TRIPS Agreement sometimes specifically mentions the term ‘flexibility’, for example in Paragraph 6 of the preamble, which says “[...] the special needs of the least-developed country Members in respect of maximum flexibility in the domestic implementation of laws and regulations in order to enable them to create a sound and viable technological base.”

But all of these clauses do not take away from the fact that the TRIPS Agreement obliges countries to give up much of the diversity and flexibility in IP law and practices that existed beforehand. ‘Flexibilities’ is a term used to refer to the remaining room to manoeuvre when implementing the TRIPS Agreement.

The term flexibilities gained greater meaning in the context of the TRIPS and public health discussions that commenced in the early 2000s and has since then come to refer to policy space available in IP law to protect public health.

The World Intellectual Property Organization (WIPO) secretariat has identified the following flexibilities in the context of public health:

- Compulsory licences and government use;
- Exhaustion of rights (parallel importation);
- Research exemption; and
- Regulatory review exception (Bolar-type exception; that is, an exception to facilitate regulatory approval of generic medicines by allowing use of patented material before the end of the patent term).

TRIPS leaves, however, larger policy space than the areas listed above, and allows for a degree of differentiation in the implementation of its

provisions. The fact that the TRIPS Agreement provides minimum standards implies that variation in national implementation is indeed possible.

Some elements that allow for differentiation are clearly described in the Agreement, such as the transition periods for implementations by certain groups of countries. Others are more implicit, such as the freedom to formulate requirements for patentability or the implementation of the requirements with regard to the protection of undisclosed test data in national law.¹⁴⁰ In many countries, so-called ‘data protection’ has created a non-patent-based market exclusivity for originator drug companies by prohibiting the medicines regulatory authority to refer to the originator’s clinical trial data when reviewing a generic application. Repeating clinical trials of a proven effective product would be unethical because one would have to expose a control group of patients to a placebo with no active ingredient while effective treatment is known. Generic manufacturers must therefore generally demonstrate that their product is bio-equivalent to the originator product but are not required to redo the clinical efficacy trials. For efficacy data, the regulator can refer to the clinical trial data the originator company has provided.

However, if the drug regulatory authority is not allowed to do this, market exclusivity is created because the generic company cannot be authorised to put its product on the market. The use of the originator’s file for that purpose is prohibited in the European Union (EU) for a minimum of eight years for new chemical entities (NCEs) and biologics, and in the United States (US) for five years for NCEs¹⁴¹ and 12 years for biologics.¹⁴² A biologic is a medicine derived from human or animal protein, as opposed to traditional, ‘small molecule’ medicine.

BOX 13 TRIPS ARTICLE 39.3

“Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products that utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.”

A public health-oriented approach to implementing article 39.3 of TRIPS would mean that undisclosed data is protected against unfair commercial use but this protection does not lead to barring the medicines regulatory agency from using clinical trial data it has access to in the registration process for generic medicines. Carlos Correa, for example, provides a useful overview of how the requirements of article 39.3 of TRIPS to protect undisclosed test data against unfair commercial use can happen without creating additional layers of market exclusivity⁴⁴³ (see Box 14).

BOX 14 SUMMARY OF TRIPS REQUIREMENTS WITH REGARDS TO DATA PROTECTION AND DATA EXCLUSIVITY

From Carlos Correa's *Protection Of Data Submitted For The Registration Of Pharmaceuticals: Implementing The Standards Of The Trips Agreement*⁴⁴⁴:

- *“As a condition for registering pharmaceutical products, national authorities normally require registrants to submit data relating to drugs’ quality, safety and efficacy (“test data”), as well as information on the composition and physical and chemical characteristics of the product. A particularly important issue is the direct or indirect use of the data for subsequent registration of products similar to those originally registered.*
- *The World Trade Organization’s Trade Related Aspects of Intellectual Property Agreement (TRIPS), Article 39.3, requires member countries to establish protections for submitted test data. But this requirement is in fact narrowly drawn, and countries maintain substantial flexibility in implementation. The public interest in limiting protections for data is to promote competition, and to ensure that data protections do not become the means to block the timely entrance of generic competitors to off-patent drugs. Generic competitors drive down price, thereby promoting greater accessibility of medicines.*
- *Article 39.3 requires governments to provide protection to marketing approval data only under certain conditions. Test data must be protected if national authorities require its submission. Article 39.3 does not require protection be given to already public data. Protection is required only for new chemical entities. Members have considerable discretion in defining “new,” and may exclude applications for second indications, formulations and dosage forms. And, prior to granting protection, national regulatory authorities may request the applicant to prove that the information for*

which protection is sought is the result of significant investment.

- *Article 39.3 requires countries to protect against “unfair commercial use” of marketing approval data. Countries have considerable discretion to define “unfair” in the context of their own national laws and culture. Use by the government to assess the efficacy and toxicity of a pharmaceutical or agrochemical product is not a commercial use subject to Article 39.3. Granting marketing approval to a second entrant, based on the second product’s similarity to a previously approved first product, is not a proscribed “use” under Article 39.3. These interpretations are supported by United States and Canadian Supreme Court decisions interpreting national laws.*
 - *Countries can meet their obligations to protect against “unfair commercial use” under Article 39.3 by barring “dishonest” uses of test data. This would require, for example, proscribing situations in which a competitor obtains the results of testing data through fraud, breach of confidence or other “dishonest” practices, and uses them to submit an application for marketing approval for its own benefit. It would also apply in cases where the government provides access to undisclosed testing data in order to provide an advantage to a firm which did not produce them or share their cost.*
 - *Countries are not obligated under Article 39.3 to confer exclusive rights on the originator of marketing approval data.*
 - *The pharmaceutical industry and some countries have argued for much broader coverage of Article 39.3, and for a requirement that countries confer exclusive rights on originators of marketing approval data. But these positions are not well grounded in either the text or negotiating history of TRIPS. TRIPS negotiators specifically considered and rejected language requiring grants of exclusive rights to test data.”*
-

One other important flexibility under TRIPS is the option for countries to determine patentability criteria. Countries cannot exclude entire fields of technology, such as medicines or food, as was the case before TRIPS, but they can impose requirements on patentability so as to award real innovations but restrict the number of follow-on patents (see “Patentability criteria and the evergreening of patents” in this chapter).

Countries do not always avail themselves of the flexibilities that are contained in the TRIPS Agreement. There are several reasons for this. Some countries already had IP laws when TRIPS came into being, often modelled after the laws of their former colonisers. Regional IP agreements,

often drafted in cooperation with wealthy countries, bind countries to stricter IP law than required under TRIPS. For example, the 1977 Bangui Agreement, a regional IP agreement for West African countries, was revised in 1999 to comply with TRIPS but ended up containing a number of provisions that went beyond TRIPS.¹⁴⁵ This trend of trade agreements limiting flexibilities built into the TRIPS Agreement is on the rise.

BOX 15: WIPO AND TRIPS

One would expect WIPO, the United Nations (UN) agency tasked with IP, to offer assistance to countries to ensure that their IP laws are developed in a manner consistent with their level of development, and to be particularly responsive to the health care challenges of such nations.

However, technical assistance to countries by agencies such as WIPO has not always given sufficient attention to the use of flexibilities¹⁴⁶ to protect public health and access to low-cost medicines at a time when this was most needed. WIPO's work often lacked attention to development needs and was weak on collaboration with other UN agencies, for example in the health field.

These concerns led in 2004 to demands for the formulation of a WIPO Development Agenda. The Development Agenda was adopted in 2007 and contained 45 recommendations to enhance the development focus of WIPO's work including those that focus on public health issues.¹⁴⁷ For example:

“Within the framework of the agreement between WIPO and the WTO, WIPO shall make available advice to developing countries and LDCs, on the implementation and operation of the rights and obligations and the understanding and use of flexibilities contained in the TRIPS Agreement.”

More recently, a group of Latin American and Caribbean countries have asked WIPO to update its Model Law for Developing Countries on Inventions, which dates back to 1979.¹⁴⁸ The US voiced opposition to the proposal to update the Model Law in preliminary comments, stating that the impetus for model laws is no longer present today, that a one-size-fits-all approach does not work, and that updating the Model Law would not be consistent with the WIPO Development Agenda.¹⁴⁹ It is hard to see how this latter position can be

defended considering the technological developments since 1979 and that fact that the Model Law dates from before the adoption of the Doha Declaration on TRIPS and Public Health and the WIPO Development Agenda. Most importantly, members have specifically asked WIPO for the updated Model Law in order to bring it more into line with both Doha and the Development Agenda. Of course, such an update to the Model Law might interfere with the US bilateral and regional trade agenda in which it pursues a strong IP agenda.

TRADE AGREEMENTS CLOSING IN ON TRIPS FLEXIBILITIES

TRIPS meant to protect against so-called “TRIPS-plus” measures—provisions that require more stringent IP standards than those contained in TRIPS or that limit flexibilities inherent in TRIPS. The Agreement did this by explicitly stating in Article 1.1 that countries are free but not obliged to implement more extensive IP protection than is required by TRIPS.

One could call Article 1.1 of TRIPS the anti TRIPS-plus clause. Countries expected that by agreeing to the TRIPS standards they had struck a bargain protecting them from pressures to further ratchet up national levels of IP protection. The same expectation was re-enforced when World Trade Organization (WTO) members agreed to the Doha Declaration on TRIPS and Public Health, which affirmed the importance of and countries right to use the flexibilities written into TRIPS.

That bargain has been broken by the plethora of trade agreements containing TRIPS-plus provisions that have been concluded in the last decade, including after the adoption of the Doha Declaration on TRIPS and Public Health. The US and the EU are systematically seeking higher levels of IP protection in agreements with developing countries that affect access to medicines and seriously hamper the full implementation of the Doha Declaration.

The following TRIPS-plus demands regularly feature on the wish lists of the US and/or the EU in trade talks. All of these TRIPS-plus features can delay the introduction of generic medicines and thereby affect access to medicines:

- Patent linkage: Prohibits granting of marketing approval by drug regulatory authorities during the patent term without the consent of the patent holder. These provisions effectively create a new function for health authorities in the enforcement of patents on medicines;

- 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, including biosimilar products, regardless of the patent status of the product;
- Extension of the patent term for pharmaceuticals beyond the 20 years required by the TRIPS Agreement, which will further delay generic competition;¹⁵⁰
- Extension of the scope of patent protection to allow known substances to be patented for each “new use”;
- Restrictions on the grounds for compulsory licensing; and
- Restrictions to parallel importation.

Some or all of these provisions appear in concluded agreements such as the Central American Free Trade Agreement (CAFTA),¹⁵¹ the US-Singapore Free Trade Agreement, the US-Chile Free Trade Agreement, the US-Morocco Free Trade Agreement, US-Peru Trade Promotion Agreement and other agreements that have already been signed.¹⁵² The TRIPS-plus provisions reappear, or are likely to reappear, in trade agreements being negotiated with Thailand, Panama, the Andean countries (Bolivia, Colombia, Ecuador) and the countries of the Southern African Customs Union (SACU),¹⁵³ and have also appeared in accession agreements with new WTO members, for example, China and Cambodia. They featured high on the agenda of the US Trans Pacific Partnership Agreement (TPP) team that is in talks with 11 countries on the creation of a free trade agreement. Many of them appear in the final negotiated text of the TPP, leaked in October 2015 and published in November 2015.¹⁵⁴

The US trade negotiators have also turned their attention to the national pharmaceutical coverage and pricing policies and medicines reimbursement systems of their trading partners. For example, in 2003, the US approached Australia with the following trade mandate: “the elimination of government measures such as price controls and reference pricing which deny full market access for United States products.” This led to changes in Australia’s Pharmaceutical Benefits Scheme in 2007. Those changes made it more difficult to use reference pricing for new products, thereby abandoning the Australian norm that products with a similar efficacy profile should have similar pricing.¹⁵⁵

THE TRANS PACIFIC PARTNERSHIP AGREEMENT

The more recent TPP has created tremendous concern among health advocates, not least because the negotiated texts have been closely guarded secrets of which only a few leaked portions have been publicly available. The TPP talks involve 12 countries (the US, Japan, Australia, Peru, Malaysia, Vietnam, New Zealand, Chile, Singapore, Canada, Mexico, and Brunei Darussalam) and seem, from a leaked copy of the IP chapter in October 2015, to contain TRIPS-plus standards for IP.¹⁵⁶

Public discourse and democratic scrutiny of the provisions of the TPP (and other trade agreements) are very difficult because of the lack of transparency. Negotiations take place in secret and draft negotiating text is not available until after a deal is reached.¹⁵⁷

The TPP's leaked drafts, however, give us an idea of the contours of the IP-related demands that focus on obstructing generic competition and maintaining high drug prices.¹⁵⁸ Some of those demands include:

- Patent term extensions beyond the minimum requirement of 20 years in TRIPS;
- Introduction or expansion of data exclusivity for biologics leading to market exclusivity even in the absence of patents,¹⁵⁹ and resulting in a loss of diversity in data protection laws in TPP countries (see Table 7);
- Requirements for patentability criteria that allow for the grant of secondary and new use patents, a practice that can lead to evergreening of patents and which is currently outlawed by a number of countries including India (see “Patentability criteria and evergreening of patents” in this chapter); and
- Restrictions on the use of compulsory licensing.¹⁶⁰

UNITAID, a financing mechanism for HIV, tuberculosis (TB) and malaria, made the following concerned statements over TRIPS-plus provisions in the TPP, particularly since the TPP is cast as a future model:¹⁶¹

“TRIPS-plus provisions also limit or undermine developing countries’ policy options for legislating and using TRIPS flexibilities, even though safeguards and flexibilities were included in the TRIPS Agreement to enable governments to protect public interests, including access to medicines. This has led to concerns that TRIPS-plus provisions in free trade agreements will undermine public health safeguards and objectives—notably access to medicines. These concerns are particularly pertinent with regard to the negotiation of

a Trans-Pacific Partnership Agreement, which has been positioned as a “model” for the 21st century—implying that the same or similar provisions are likely to appear in future trade agreements, including those involving developing countries.”¹⁶²

In particular, the inclusion of investor state dispute settlement (ISDS) mechanisms in trade agreements raises serious concerns. ISDS allows corporations to take legal action against countries to seek compensation for regulation that allegedly has negatively affected their investments. Such actions can further curtail flexibilities that are currently granted under TRIPS and may have a chilling affect on health regulation.¹⁶³

Concerns over the effects of the inclusion of ISDS in trade agreements for health are not hypothetical.

The drug company Eli Lilly is suing the Canadian government over losses resulting from Canada’s invalidation of secondary patents related to the previously known active ingredients atomoxetine (Strattera) and olanzapine (Zyprexa), drugs used to treat attention deficit hyperactivity disorder, schizophrenia and bipolar disorder.¹⁶⁴ Eli Lilly is using the investment chapter of the North American Free Trade Agreement (NAFTA) to support its suit.

In Australia, Philip Morris, a cigarette corporation, challenged the country’s tobacco plain packaging legislation using the 1993 Agreement between the Government of Australia and the Government of Hong Kong for the Promotion and Protection of Investments (Hong Kong Agreement).¹⁶⁵

The United Nations Conference on Trade and Development (UNCTAD) maintains a database of ISDS, which currently counts 608 cases.¹⁶⁶ In its 2015 World Investment Report, UNCTAD notes that developing countries “bear the brunt of these claims” and that most claimants (i.e., the companies) come from developed countries.¹⁶⁷ UNCTAD adds that claims against developed country governments are on the rise.

TABLE 7 DATA EXCLUSIVITY PROTECTIONS IN THE TPP NEGOTIATING PARTIES

COUNTRY	PHARMACEUTICALS – DATA EXCLUSIVITY (YEARS)	BIOLOGICS – DATA EXCLUSIVITY (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	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 data exclusivity will apply to biologics in Chile, Mexico and Peru. These countries do not specifically grant data exclusivity to biologics.

***Malaysia begins counting data exclusivity from the date a product is approved and given data protection in its originator country and allows for up to five years of data exclusivity from that date.

SOURCE

Michael Mezher, "Trade Talks Stumble Over Biologics Data Exclusivity," *Regulatory Affairs Professionals Society*, www.raps.org/regulatory-Focus/News/2015/02/11/21309/Trade-Talks-Stumble-over-biologics-Data-Exclusivity

MERITS OF THE MULTILATERAL SYSTEM

It is difficult for countries, in particular developing countries, to push back on TRIPS-plus demands in bilateral and regional trade talks. And subsequent trade agreements tend to have a ratcheting up effect on TRIPS-plus measures, as they each set new norms for IP measures. India, for example, is not part of the TPP, but norms in the TPP will indirectly affect India's patent laws, making it harder for India to resist signing on to similar legislation in future trade deals.

TRIPS-plus demands undermine the multilateral consensus where wealthy nations also have to give and take and where the public and the media can follow the deliberations and offer comment. Norm setting on

IP at the WTO, while far from ideal, has been more sensitive to health needs than is the case in bilateral and regional talks. Greater transparency and greater involvement of the health community account for this. At the WTO TRIPS Council, UN organisations such as the World Health Organization (WHO) have a voice¹⁶⁸; in bilateral and regional trade talks, the public health community is excluded from participation.

BOX 16 ACCESS TO MEDICINES, HUMAN RIGHTS AND COMPANY OBLIGATIONS

Access to essential medicines is a key component of the human right to health. Article 12 of the 1966 International Covenant on Economic Social and Cultural Rights recognises the right of everyone to “the enjoyment of the highest attainable standard of physical and mental health” including through a healthcare system that is “economically accessible to all” and details steps states should take to achieve this.¹⁶⁹ In 2000, General Comment 14 on the implementation of the Covenant specifically mentions the need for governments to ensure availability of essential drugs “as defined by the WHO Action Programme on Essential Drugs.”¹⁷⁰ Some national constitutions directly recognise the human right to health and in such countries individuals have successfully invoked human rights to gain access to life-saving medicines.

While the fulfilment of basic human rights is primarily a state obligation, in the case of patented medicines one also has to recognise the responsibility of the patent holding pharmaceutical company. After all, with patenting of essential medicines now more widespread, the power to determine who has access to such medicines has shifted to the private sector.

In the words of former 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. In relation to such a patent, the right-to-health framework helps to clarify what these terms, and expectations, are. 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.”*¹⁷¹

In 2008, Hunt submitted a report to the UN General Assembly titled “Human Rights Guidelines for Pharmaceutical Companies in Relation to Access to Medicines.”¹⁷² The report contained guidelines for the pharmaceutical industry in relation to access to medicines. Specific right-to-

health responsibilities of patent holding companies of life-saving medicines were further developed in a report of the UN special rapporteur following a right-to-health mission to GSK.¹⁷³ In Hunt's words, 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.”¹⁷⁴*

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 indeed 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 the normative framework developed by Hunt teeth. He suggested establishing direct legal obligations for pharmaceutical companies at the international level and holding pharmaceutical companies directly accountable under international human rights law, including through direct compensation to victims and the granting of compulsory licences.¹⁷⁵ So far, the UN has not taken action to implement these recommendations.

In 2012, the Global Commission on HIV and the Law, an independent body convened by the UN Development Programme (UNDP) went a step further and recommended the development of a new IP regime under the aegis of the UN Director General. The Commission specified that this regime “be consistent with international human rights law and public health requirements, while safeguarding the justifiable rights of inventors.” The

Commission 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.”¹⁷⁶

While the suspension of TRIPS will not likely happen in the near future, the emphasis on human rights in the pursuit of access to patented essential medicines will increase. In particular, since a number of countries recognise the right to health as a constitutional right and individuals have used such constitutional rights to obtain access to essential medicines.¹⁷⁷

PATENTABILITY CRITERIA AND THE EVERGREENING OF PATENTS

A patent will be granted to an inventor if the invention meets patentability criteria, which are: the invention has to be new, not obvious to a person ‘skilled in the art’ (familiar with the area the patent covers) and useful. According to the TRIPS Agreement Article 27: “... patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application.”

Under TRIPS, countries are free to determine how these patentability criteria are applied. While entire fields of technology, such as medicines or food, can no longer be excluded from patentability now that TRIPS is in force, countries can set patenting standards so as to ensure patents are awarded only for true innovation. This can help prevent the practices of follow-on patenting and ‘evergreening’—processes in which secondary patents are sought with the aim to extend market exclusivity beyond the patent term of the basic patent.

The 2003 WHO Commission on IP, Innovation and Public Health (CIPIH) defined evergreening as “a term popularly used to describe patenting strategies when, in the absence of any apparent additional therapeutic benefits, patent holders use various strategies to extend the length of their exclusivity beyond the 20-year patent term.”¹⁷⁸

The Commission recognised that “demarcating the line between incremental innovations that confer real clinical improvements, therapeutic advantages or manufacturing improvements, and those that offer no therapeutic benefits is not an easy task. But it is crucial to avoid patents being used as barriers to legitimate competition.”¹⁷⁹

This seems like a sensible recommendation considering that throwing up barriers to competition is exactly what the pharmaceutical industry

aims to achieve with its patenting strategies. In the industry’s own words “... a key element of any life cycle management strategy is to extend patent protection beyond the basic patent term for as long as possible, by filing secondary patents which are effective to keep generics off the market.”¹⁸⁰

The commercial benefits of evergreening can be significant. A study of the 1,304 patents on new molecular entities (NMEs) listed in the Food and Drug Administration’s Orange Book between 1988 and 2005 showed that secondary patent claims extended patent protection by an average of 6.3 to 7.4 years [see Table 8].¹⁸¹

TABLE 8 STUDY OF 1,304 ORANGE BOOK LISTED PATENT CLAIMS (NMEs IN THE US 1988–2005)

INDEPENDENT SECONDARY PATENTS	AVERAGE PATENT LIFE EXTENSION IN THE US (YEARS)
Independent formulation	6.5
Method of use	7.4
Polymorphs, isomers, prodrug, ester and/or salts	6.3

An overview of annual sales¹⁸² of the top 19 blockbuster medicines in history shows a range of US\$ 5 to US\$ 13.7 billion at each medicine’s peak year (the larger figure is for Pfizer’s cholesterol medication, Lipitor [atorvastatin]). The sales of Pfizer’s Lipitor fell to US\$ 2 billion in 2014 after the patent expired in November 2011.¹⁸³ By then, Pfizer had enjoyed 14.5 years of sales worth a total of US\$ 125 billion, which made Lipitor the world’s best selling drug at the time. Annual sales of billions mean that even a few months of extra market exclusivity is important. This exclusivity translates into high drug prices, as demonstrated by the 93% fall in Lipitor pricing after the generic competitors entered the market.¹⁸⁴

One can also find examples of evergreening of patents related to the treatment of HIV/AIDS. Zidovudine (AZT) was first synthesised in 1964. In 1984, the first patents related to the use in HIV were granted and in 1987 AZT was approved for use in HIV. It was one of the first ARV products on the market and sold by Burroughs Wellcome (which later became GlaxoSmithKline, or GSK).

The company filed for patents on combinations with other ARVs in 1992, 1996, and 1997. And in 1997, GSK received marketing authorisation

for the fixed-dose combination (FDC) AZT/lamivudine (3TC), which it sold under the brand name Combivir and was used in combination with a third HIV medicine. The last patent related to a combination product with AZT is to expire in 2017 (WO9818477). However, the database of the Medicines Patent Pool indicates that the company has ‘officially withdrawn’ the patent.

In 2006, following treatment campaigners’ opposition to the grant of a patent to GSK for the AZT/3TC combination, GSK withdrew its patent application. Generic versions of AZT/3TC combinations became subsequently available for a sixth of the originator price.

Around 2001, triple FDCs of ARVs became the medical gold standard. Such FDCs were available from Indian generic suppliers where patents did not create a barrier to developing and producing them. But patents on combinations inhibited the use of such FDCs where such patents were granted.

TABLE 9 AZT/3TC COMBINATION PRICE IN THAILAND IN 2006¹⁸⁵

AZT/3TC COMBINATION	PRICE PER MONTH PER PERSON (US\$)
GSK	207.00
Generic	37.50

PATENT OPPOSITIONS

In Thailand in 1998, the availability of generic HIV medicine didanosine (DDI) tablets was blocked because of a formulation patent held by Bristol-Myers Squibb (BMS). Only the powder formulation, which was not patented, was available at low cost. But this formulation was less tolerated by patients and more difficult to take. In 2000, the Thai government had considered a compulsory licence, but was warned against this move by the US. Thai AIDS groups successfully challenged the granting of the patent. BMS appealed the decision. AIDS groups hit back and launched in 2002 another patent challenge. Finally, in 2002, BMS agreed to surrender all its exclusive rights under the DDI patent in Thailand.¹⁸⁶ The generic tablets could then be made available, but after a delay caused by four years of litigation.

Had Thailand limited the grant of patents in its patent law to base compounds only, this delay would not have been necessary. The delay

could also have been avoided had Thailand felt free to move ahead with the compulsory licence. Post-grant measures such as exceptions and limitations, and licensing are specifically designed to deal with undesirable effects of granted patents.

Some countries do indeed pursue strategies to avoid the granting of patents beyond those that cover the basic innovation. The Indian Patents Act Section 3(d)¹⁸⁷ explicitly requires that patents only be granted for compounds that are truly new and innovative. For new forms and new uses of known compounds, Indian law requires patent applicants to prove significantly improved efficacy to achieve eligibility for a patent. India introduced this requirement to prevent the practice of evergreening of medicines patents by seeking follow-on patents for minor alterations to the original molecule or known compounds.

Section 3(d) has been subject to challenges by drug companies. But it has also been the basis for a number of successful pre-grant opposition procedures by generic companies and patient interest organisations. Some of the more high-profile cases include:

- the opposition to the patent for the HIV medicine tenofovir disoproxil fumarate (TDF), sold under the brand name Viread by Gilead. The patent was rejected in 2008.
- the opposition to the patent for cancer drug imatinib, sold under the brand name Gleevec or Glivec by Novartis. The patent was rejected in 2006, a decision Novartis appealed. In 2013, the Indian Supreme Court confirmed the rejection.
- more recently, the opposition to the patent for hepatitis C medicine sofosbuvir, sold by Gilead under the brand name Sovaldi. The opposition was filed in 2013; a decision is pending.¹⁸⁸

Patent oppositions have also been successful elsewhere. In June 2015, China rejected a Gilead patent for the pro-drug of sofosbuvir. This rejection was a result of a civil society initiative to oppose the patent.¹⁸⁹ Medicines patent grant oppositions on sofosbuvir are now being filed by civil society groups in various countries, including in Europe.¹⁹⁰ Patent oppositions are effective campaigning methods that draw attention to the severe consequences of the lack of affordable essential medicines. However, they have to be fought country-by-country, and patent-by-patent, and demand considerable resources and stamina of the groups involved. If successful, the positive effects of a patent rejection are considerable, as the cases of TDF and imatinib have shown.

BOX 17 COUNTERFEIT MEDICINES AND OUT-OF-CONTROL BORDER CONTROL

On 20 April 2015, *The American Journal of Tropical Medicine and Hygiene* published a series of articles on medicines quality issues, titled “The Global Pandemic of Falsified Medicines: Laboratory and Field Innovations and Policy Perspectives.”¹⁹¹ In the summary, the co-editors of the series advocate a global convention to address the technical/financial and legal dimensions of the pandemic of falsified and substandard medicines. The co-editors ask their readers to respond to their “clarion call.” Media worldwide have paid attention.¹⁹²

Such zeal should be met with caution. Efforts to combat falsified or counterfeit medicines often play into the hands of those that want to push expensive branded products. The effect can be to the detriment of the supply of legitimate low-cost, quality-assured, generic medicines.¹⁹³

Counterfeit medicines and medicine quality problems are often presented as being one and the same problem that can be addressed with the same measures. The proponents of the global convention seem to make the same mistake.

Counterfeit medicines are fake medicines, sometimes carrying a fake logo, the distribution of which is often carried out by criminal organisations. Substandard medicines are medicines that do not meet quality standards. The problem of substandard medicines is predominantly a pharmaceutical issue that needs to be dealt with by enforcing regulatory standards for quality in production and supply. Both problems need to be taken seriously. To be sure that happens, the WHO provides policy, legislative, and technical guidance.¹⁹⁴

The proponents of a draft Model Law on Medicines Crime introduce the term ‘wrongful medicines’ to mean substandard, falsified, or unregistered medicines.¹⁹⁵ These three categories represent very different issues and require different responses.

Confusion in use of these terms, deliberate or otherwise, can obstruct the availability of legitimate medicines. This was, for example, the case when EU legislation defined counterfeit so broadly that it included medicines unregistered in the EU. This legislation was used as the basis for the seizure at Schiphol Airport in the Netherlands of medicines for the treatment of HIV/AIDS. The products were held on the suspicion that they were counterfeit. In reality, these medicines were legitimate WHO-prequalified, US Food and Drug Administration approved products on their way from India to treatment programs in Nigeria funded by UNITAID.¹⁹⁶

The problem of counterfeit medicines surely needs to be addressed, but no one really knows how big a problem it is.¹⁹⁷ Emphasis on counterfeiting as the main threat to public health can prevent attention to a more serious issue: assuring the quality of medicines. A group of medicines supply experts at Médecins sans Frontières identified this problem as long ago as 2008.¹⁹⁸ The experts concluded that the best way to tackle the problem of substandard medicines is through assistance to manufacturers to help them improve pharmaceutical quality. They listed other ways to assure medicines quality: control of exports of substandard medicines, including from industrialised countries; strengthening health systems in developing countries; and having donors and purchasers enforce quality requirements in calls for tender.

Access to effective medicines that meet international quality standards depends on several factors, often interrelated:

- Affordability (often related to patent status);
- Secure and reliable supply chains;
- Quality suppliers; and
- Producers that meet international standards.

Donor policies are key to increasing access to quality-assured medicines. The Global Fund quality assurance policy, adopted in 2009 and then taken up by other donors, ensures that its resources are used to procure medicines approved for use by Stringent Regulatory Authorities¹⁹⁹ or prequalified by the WHO Prequalification Programme (PQP; see Box 2, “The Quiet Revolution at the WHO”). This policy has important implications. It strengthens drug authorities in their efforts to limit the infiltration of fake medicines and to boost and maintain quality-assured production. As a result, the number of generic manufacturers producing drugs that meet quality standards will likely increase, assuring wider availability of affordable, safe, and effective generics. There are now, for example, 16 triple FDCs to treat HIV/AIDS prequalified by WHO and priced at US\$ 100–136 per patient per year.²⁰⁰ Over 80% of the antiretroviral medicines used in treatment programs in the developing world are accessed through international procurement bodies, mostly sourced from Indian generic suppliers, and mostly prequalified by the WHO or by a stringent regulatory agency.²⁰¹ Despite the savings and health benefits the WHO PQP creates, the programme continues to struggle to find a sustainable financing base for its work. It is considering a fee-based model, which could jeopardise its independence.²⁰²

The best approach to counter the supply of illegal and dangerous medicines is ensuring the availability of affordable, quality-assured essential medicines. The scale up of treatment for HIV in low- and middle-income countries has taught us that lesson.

5

THE NEW FRONTIERS: Patents and treatment for cancer, hepatitis C, and other diseases

INTRODUCTION

The problem of high drug prices is by no means confined to HIV/AIDS, as is illustrated by the recent legal battles over cancer, cardiovascular, hepatitis C and diabetes medications in India and elsewhere.²⁰³

Nor is it any longer confined to developing countries. The high price of cancer drugs, in particular, is increasingly the subject of harsh criticism by consumers and the medical profession globally.^{204, 205}

Enormous progress has been made in access to medicines to treat HIV/AIDS. Through this process, public health approaches to intellectual property (IP) protection have been developed and have become acceptable to many stakeholders. Still, it is unclear to what extent lessons learned can be applied to other diseases. Finding out is particularly important now that new and high-priced essential medicines are included in the World Health Organization (WHO) Essential Medicines List (EML), but increasingly unaffordable in developing and developed countries alike.

PATENTED ESSENTIAL MEDICINES: THE 2015 EML²⁰⁶

In May 2015, the WHO added several important medicines²⁰⁷ including drugs for the treatment of cancer, tuberculosis and hepatitis C to its EML. The uniqueness of these medicines—aside from their value as treatments for devastating illnesses—is their high price.

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

Several WHO experts said in March that the 2015 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.²⁰⁸ The Expert Committee in its May 2015 conclusions explicitly called on the WHO to “take actions at global level to make these medicines more accessible and affordable,” especially as related to treatments for hepatitis C.²⁰⁹

If people around the world are to have access to essential medicines, their presence on the EML is necessary, but not sufficient, to ensure that access. When the WHO deems medicines medically essential, this should—as the Expert Committee asserted—be ground for governments and other stakeholders to take action to ensure that they are made available and affordable. Availability will depend, among other things, on whether the products can be made affordable for the communities that need them. And in the case of the more recent products, IP issues will affect affordability.

TABLE 10 SELECTED NEW MEDICINES ON THE WHO ESSENTIAL MEDICINES LIST, WITH PRIMARY PATENT EXPIRY DATE*

MEDICINE	COMPANY (ORIGINATOR)	EXPIRY DATE PRIMARY PATENT
Tuberculosis		
bedaquiline	Janssen	2023
delamanid	Otsuka	2023
terizidone	Sanofi-Aventis, Macleods	2024
Hepatitis C		
sofosbuvir	Gilead	2024 (2028 secondary prodrug patent)
simeprevir	Janssen	2026
daclatasvir	Bristol-Myers Squibb	2027
ledipasvir	Gilead	2030
ombitasvir	AbbVie	2030
Cancer		
bendamustine	Cephalon (US)	2026
imatinib	Novartis	2014 (2018 secondary patent)
rituximab	Roche (others)	2008 (2019-2020 secondary formulation patent)
trastuzumab	Roche	2009

* This table lists expiry dates for the primary patent and select secondary patents; there may be additional patents associated with these medicines that are not listed here and which may have later expiry dates.

SOURCE

Ellen 't Hoen and Kaitlin Mara, *Ensuring that Essential Medicines are also Affordable Medicines*, World Health Organization, http://www.unitaid.eu/images/marketdynamics/publications/Ensuring_that_essential_medicines_are_also_affordable_medicines_challenges_and_options.pdf

HIV, AFFORDABILITY, AND THE EML

Since its first publication in 1977 with 207 medicines, the EML, then called the Essential Drugs List (EDL), has guided governments, international organisations, non-governmental organisations (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.”²¹⁰ Today, more than 150²¹¹ countries have national essential medicines lists, and 18 editions of the list have been published.

Selection criteria include efficacy, quality, safety, and cost-effectiveness, and the list is regularly updated to be able 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 optimise limited health budgets and prevent the purchase of non-essential expensive medicines to the detriment of treating other diseases, though the way in which affordability is treated is changing 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) to treat HIV as too expensive for health systems to bear.²¹² At the time, the predominant treatment regimen for HIV cost upwards of US\$ 10,000 per person per year. But by 1999, HIV had killed nearly 20 million people and was continuing to kill 8,000 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 mostly was not.²¹³ To deem ARVs non-essential had become absurd and risked making the EDL irrelevant.

In 2001, the WHO began a consultation process to examine the way that new medicines were included in the WHO Model List of Essential Drugs²¹⁴. The consultation tackled several cost issues, 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 wide variation in medicines costs around the world.²¹⁵

In a series of new procedures²¹⁶ arising from this consultation process, the WHO decided 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 (for example, “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 well as improving linkages between the list and WHO treatment guidelines and technical departments. The 2002 EML included a number of ARVs.

The message was clear: cost alone was no longer a criterion for 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 spurred by their designation as ‘essential’ coupled with their prequalification by the WHO²¹⁷ and a concerted international effort to mobilise funding to treat HIV created a market for robust generic competition.

The HIV crisis demonstrated both 1) the need for medically important drugs to be included on the list and 2) the power of EML inclusion as an impetus for bringing prices down.

Table 10, above, shows that a number of the new essential medicines on the list are subject to patents, and that the expiry date of those patents are far in the future. Without deliberate action by governments and companies—as was taken to provide access to HIV treatment—these medicines will not become affordable.

The EML is a tool for the practical implementation of the internationally agreed principle that IP should not stand in the way of measures to promote the human right to public health. Affordability is no longer a prerequisite for 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 pricing of essential medicines prohibits their use by people in need.

THE CHALLENGES OF HEPATITIS C, CANCER, AND BIOSIMILARS

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

HEPATITIS C

Chronic hepatitis C, for example, affects 130–150 million people globally, and liver diseases associated with it kill 300–500,000 people a year. Additionally, 5.5 million people are co-infected with hepatitis C and HIV and consequentially suffer increased rates of both HIV-related and liver-related illnesses.

The new essential medicines to treat hepatitis C are effective enough to provide a cure for all. Until recently, treatment for hepatitis C was: difficult to administer (requiring regular hospital visits and extensive monitoring); difficult to undergo (requiring daily or weekly injections and several pills a day, and frequently causing debilitating side-effects);

often ineffective at achieving sustained viral response, especially in people co-infected with HIV; and expensive.

The development of direct-acting antivirals (DAAs) to treat hepatitis C has therefore been a powerful breakthrough. The new DAAs can be taken orally, appear to be well tolerated and effective, and cut treatment time significantly—to 12–24 weeks (from 24–48 weeks on earlier treatments). They are also expensive.

Sofosbuvir (SOF), the DAA likely to be the backbone of any hepatitis C treatment regimen and one of the medicines added to the EML in April²¹⁸, was initially priced at US\$ 1,000 a pill, or US\$ 84,000 dollars for a 12-week course of treatment. A full treatment regimen combining SOF and ledipasvir can run up to US\$ 95,000.²¹⁹ Another DAA added to the list in April, simeprevir,²²⁰ is priced at US\$ 66,360 for 12 weeks, and also must be combined with other drugs into a treatment regimen. The cost of production for these medicines, shown in the table below, is, however, only a small fraction of the price charged. This means that there is ample scope for price reductions, provided generic companies could enter the market.

TABLE 11 HEPATITIS C MEDICINES, PRICES, AND ESTIMATED MINIMUM COST OF PRODUCTION

MEDICINE	PRICE RANGE PER BOTTLE IN HIGH INCOME COUNTRIES ¹	LOWEST RECORDED PRICE PER BOTTLE IN LOW-INCOME COUNTRIES ¹	GLOBAL SALES, 2014 (IN MILLIONS OF US\$)	ESTIMATED MINIMUM COST OF PRODUCTION FOR A 12-WEEK COURSE OF TREATMENT ²
sofosbuvir	\$14,000–20,590	\$161 (India)	\$10,283m ³	\$68–136
simeprevir	\$9,166–14,865	\$241 (Egypt)	\$2,302m ⁴	\$130–270
daclatasvir	\$1,128–14,899	\$175 (Egypt)	\$201m ⁵	\$10–30
ledipasvir	(Sold as an FDC*)			\$93
ombitasvir	(Sold as an FDC)			
ledipasvir + sofosbuvir	\$12,604–\$24,890	\$400 (Egypt)	\$2,127m	\$193
ombitasvir + paritaprevir + ritonavir	\$15,344–20,215	\$400 (Egypt)	\$48m	

* FDC = Fixed-dose combination

SOURCES

- 1 Isabelle Andrieux-Meyer, Jennifer Cohn, Evaldo S Affonso de Araújo, Saeed S Hamid, “Disparity in market prices for hepatitis C virus direct-acting drugs,” *The Lancet Global*

Health 3, No. 11: pgs. E676-e677, doi: 10.1016/S2214-109X(15)00156-4, November 2015, <http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2815%2900156-4/fulltext>

- 2 Nikolien van de Ven, Joe Fortunak, Bryony Simmons Nathan, Ford, Graham S Cooke, Saye Khoo and Andrew Hill, "Minimum Target Prices for Production of Direct-Acting Antivirals and Associated Diagnostics to Combat Hepatitis C Virus," *Hepatology* 61, no. 4 (2015): 1174-82, doi: 10.1002/hep.27641, <http://www.ncbi.nlm.nih.gov/pubmed/25482139> and also from <http://cid.oxfordjournals.org/content/early/2014/02/13/cid.ciu012.full>
- 3 Gilead Sciences, Press Releases, *Gilead Sciences Announces Fourth Quarter and Full Year 2014 Financial Results*, 3 February 2015, <http://www.gilead.com/news/press-releases/2015/2/gilead-sciences-announces-fourth-quarter-and-full-year-2014-financial-results>
- 4 Johnson & Johnson, 2014 Annual Report, pg. 5 (as brand name Olysio/Sovriad), http://files.shareholder.com/downloads/JNJ/1074108325x0x815170/816798CD-60D9-4653-BB5A-50A66FD5B9E7/JNJ_2014_Annual_Report_bookmarked_.pdf (last accessed 26 November 2015).
- 5 BMS, 2014 Annual Report, pg. 36, http://s2.q4cdn.com/1399848097/files/doc_financials/annual%202014/BMS-2014-Annual-Report.pdf (last accessed 26 November 2015).

There are several other promising new DAAs, including pipeline products that are expected to expand the range of hepatitis C treatment options, including in people co-infected with HIV.²²¹ Other DAAs are also likely to be widely patented. For example, patents related to daclatasvir²²² (Bristol-Myers Squibb (BMS); US expiry date for the base compound patent is 2026) and simeprevir²²³ (Janssen; US expiry date base compound patent is 2027) have been granted or are pending in a number of low- and middle-income countries, including India.

In September 2014, Gilead announced a licence agreement with seven Indian generic manufacturers covering 91 low- and middle-income countries for two of its medicines for the treatment of hepatitis C: sofosbuvir (SOF) and ledipasvir (LDV).²²⁴ Gilead has since expanded its agreements to 11 manufacturers in India, with three generic manufacturers to supply in Pakistan and Egypt. The agreements cover 101 countries that account for 50% of the hepatitis C disease burden.²²⁵ Patent applications are pending in India and are subject to pre-grant oppositions. BMS in 2014 announced a licence agreement for daclatasvir with a licence territory of 90 countries,²²⁶ but none was signed until 23 November 2015, when the Medicines Patent Pool and BMS announced an agreement for the DAA in 112 low- and middle-income countries.^{227, 228} The approach of other companies to patent licensing is unclear.

Hepatitis C will be the first disease profoundly impacting low- and middle-income countries in which companies are seeking patents for their hepatitis C medicines, in particular in the countries with generic

manufacturing capacity. The new hepatitis C medicines are also the first for which access problems are global; poor and rich countries alike are struggling to pay for these new medicines.

Since the cost of production of DAAs can be relatively low (for example, the cost of production of SOF is estimated to be US\$ 68–138 for a treatment course when demand increases), robust generic production will likely result in steep price decreases.²²⁹

CANCER: A LEADING CAUSE OF DEATH AND UNSUSTAINABLY HIGH PRICES

According to the WHO, cancer is one of the leading causes of death in the world, with 8.2 million deaths in 2012.²³⁰ Lung, female breast, colorectal and stomach cancers were the most commonly diagnosed cancers, accounting for more than 40% of all cancers. Lung, stomach, liver, colon and breast cancer cause the most deaths. While cancer is often categorised as a non-communicable disease (NCD), 20% of cancer deaths in low- and middle-income countries are linked to viral infections such as hepatitis and human papilloma virus (HPV).²³¹ Infection-related cancers in sub-Saharan Africa account for 33% and in China for 27%.²³²

While death rates from cancer in wealthy countries are slightly declining because of early diagnosis and the availability of treatment, this is not the case in the low- and middle-income countries. Instead, rates are rising in low- and middle-income countries, partly because of the ageing of the population. Currently 14 million people a year are diagnosed with cancer. That will increase to 19 million by 2025, 22 million by 2030 and 24 million by 2025, according to the WHO. More than 60% of the world's cancer cases occur in Africa, Asia and Central and South America.²³³

In low- and middle-income countries, however, treatment for cancer is not widely available. According to the Global Task Force on Expanded Access to Cancer Care and Control, only 5% of global resources for cancer are spent in the developing world, yet these countries account for almost 80% of disability-adjusted years of life²³⁴ lost to cancer globally.²³⁵

Access to cancer treatment is a challenge in resource-poor settings for a variety of reasons, not only because of the cost of the medicines, but the soaring prices of new anti-cancer drugs throw up additional barriers. It should therefore not be a surprise that out of the nine non-HIV-related compulsory licensing events, six concerned a cancer drug (see Chapter 3, “The practical application of the Doha Declaration”).

Cancer is a big money maker: Global oncology sales by the pharmaceutical industry accounted for US\$ 100 billion in 2015 and are expected to rise to US\$ 147 billion in 2018.²³⁶

Particularly in the situation where the product has no competitors, buyers are at the mercy of a single provider, often the patent holder. The unsustainable high pricing of new medicines is increasingly becoming an issue of global concern. In developing countries, governments and individuals struggle to pay for products that are priced at several times the level of their per capita GDP.²³⁷

TABLE 12 TOP 10 BEST-SELLING CANCER DRUGS OF 2013²³⁸

COMPANY	PRODUCT	DISEASE	ANNUAL SALES 2013
Roche	Rituxan/MabThera (rituximab)	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia	US\$ 7.78 billion
Roche	Avastin (bevacizumab)	Colorectal, lung, ovarian and brain cancer	US\$ 6.75 billion
Roche	Herceptin (trastuzumab)	Breast, oesophagus and stomach cancer	US\$ 6.56 billion
Novartis	Glivec (imatinib)	Leukaemia, gastrointestinal cancer	US\$ 4.69 billion
Celgene	Revlimid (lenalidomide)	Multiple myeloma, mantle cell lymphoma	US\$ 4.28 billion
Eli Lilly	Alimta (pemetrexed)	Lung cancer	US\$ 2.7 billion
Johnson & Johnson	Velcade (bortezomib)	Multiple myeloma	US\$ 2.6 billion
Merck, Bristol-Myers Squibb	Erbix (cetuximab)	Colon and head and neck cancer	US\$ 1.87 billion
AbbVie, Takeda, Sanofi	Lupron, Eligard (leuprolide acetate)	Prostate and ovarian cancer	US\$ 1.73 billion
Johnson & Johnson	Zytiga (abiraterone)	Prostate cancer	US\$ 1.7 billion

TABLE 13 TOP 10 LEADING COMPANIES IN THE GLOBAL CANCER MARKET BY SALES²³⁹

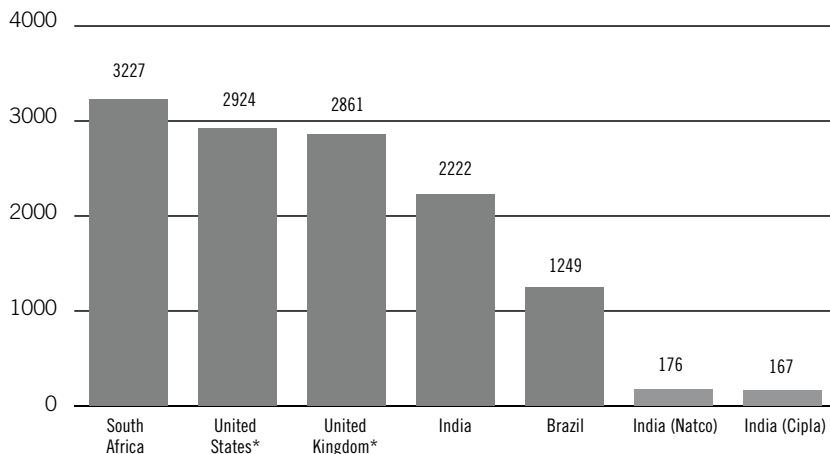
COMPANY	2014 SALES (IN US\$ BILLIONS)	2013 SALES (IN US\$ BILLIONS)
Roche	25.15	24.65
Novartis	10.26	9.50
Celgene	7.49	6.34
Johnson & Johnson	3.99	3.36
Bristol-Myers Squibb	3.53	2.94
Lilly	3.39	3.27
Takeda	3.27	3.16
AstraZeneca	2.94	3.09
Merck & Co	2.70	3.05
Amgen	2.06	1.48

Prices of new cancer medication, for example, rise at a higher rate than public and private spending on health care. This creates challenges even for health systems and individuals in high-income countries. Cancer drug prices have doubled in the United States (US) in the last decade from an average of US\$ 5,000 a month to US\$ 10,000.²⁴⁰ The United Kingdom (UK) is struggling with providing cancer treatment to National Health Service (NHS) patients.²⁴¹

THE IMATINIB (GLIVEC) CASE

Imatinib has helped nearly double the survival rate of people with chronic myelogenous leukaemia (CML).²⁴² Originally priced at US\$ 30,000 a year in 2001, a group of over 100 physicians from six continents with expertise in chronic myelogenous leukaemia wrote in the journal *Blood* that by 2012 its price had climbed to US\$ 92,000 a year after it became a blockbuster treatment. Generic imatinib, manufactured in India where a protracted legal case ended in the rejection of imatinib patents, costs between US\$ 2,004–2,112 a year.²⁴³ The authors point out that the research and development cost has long been earned back by the company and that the number of patients using imatinib continues to rise, which should lead to a reduction in price. Instead, since its introduction in the US in 2001, imatinib's price has nearly tripled.²⁴⁴

FIGURE 7 PRICE OF BRANDED GLIVEC VERSUS INDIAN GENERIC IMATINIB PER PATIENT PER YEAR IN US\$²⁴⁵



* Public procurement prices listed for these countries.

Access to imatinib for the treatment of CML is a challenge in developing countries. It is therefore no surprise that recent patent disputes centred on this product. In particular, in Thailand and India cancer has been the subject of several recent patent disputes.

TABLE 14 PATENT DISPUTES IN INDIA INVOLVING CANCER DRUGS

PRODUCT	PATENT HOLDER	DATE OF CL APPLICATION	GRANTING/ REJECTION OF CL	LICENCEE/ APPLICANT/ OPPONENT	ROYALTY	LEGAL STATUS
sorafenib tosylate (Nexavar)	Bayer	2011 (September) ¹	2012 (March) ² 2013 (March) CL upheld	Natco (CL)	6% raised to 7% (2013 by IPAB)	Bayer's appeal rejected by IPAB (4/3/13). Bayer announced appeal of the decision.
dasatinib (Sprycel)	BMS	2013 (March)	CL request Rejected 30 October, 2013 ³	BDR (CL)	NA	CL request rejected by Indian patent controller.
trastuzumab (Herceptin)	Roche	2013 (January)		NA	NA	Patent lapsed. Recommended for compulsory licence by expert panel of Ministry of Health.
ixabepilone (Ixemptra)	BMS	2013 (January)				Patent revoked on non-obviousness grounds (June 2007).
sunitinib* (Sutent)	Pfizer			Patent oppositions by Cipla, Natco.		Patent rejected non-compliance section 3(d) (April 2013).
imatinib* (Gleevec/ Glivec)	Novartis					

CL = Compulsory licence

* Pre-2005 mailbox applications

SOURCES

- 1 *Official Journal of the Patent Office*, Issue 32/2011, Date: 12/08/2011, Publication of the Indian Patent Office, available online here: <https://docs.google.com/viewer?a=v&pid=sites&srcid=ZGVmYXVsdGRvbWFpbXZcG1jeWlwZmlsZXN8Z3g6NDFFINjAxZDlyOTY0MjMyMg> (last accessed 16 November 2015).
- 2 NATCO, press release, NATCO granted compulsory licence for Nexavar, 12 March 2012. Available: <http://natcopharma.co.in/about/news/>
- 3 The Controller of Patents, Patent Office, Mumbai, C.L.A. No. 1 of 2013, In the matter of BDR Pharmaceuticals International Pvt. Ltd. Vs. Bristol-Myers Squibb Company, http://www.ipindia.nic.in/iponew/Order_30October2013.pdf

A GROWING CALL FROM DOCTORS FOR MORE REASONABLE PRICING

In recent years, more physicians have added their voices to demand more reasonable pricing of cancer medication.

In an op-ed in the *New York Times*, oncologists of the Memorial Sloan-Kettering Cancer Center described how the US\$ 11,000 a month price tag

for the colorectal cancer drug Zaltrap (ziv-aflibercept) left families without money to live on, and took a public stand not to prescribe the drug and to opt for a less costly and equally effective treatment instead.²⁴⁶

At the 2015 annual meeting of the American Society of Clinical Oncology, Dr Leonard Saltz, chief of gastrointestinal oncology at Memorial Sloan Kettering Cancer Center and one of the op-ed’s authors, told the audience:

“The unsustainably high prices of cancer drugs is a big problem, and it’s our problem ... These drugs cost too much.”

He was referring to the doubling of the monthly price for cancer drugs in the US in the last decade. Cancer drug prices are not related to the value of the drug, but rather are related to what has come before and what the seller believes the market will bear (see Tables 15 and 16).

That Saltz’s speech²⁴⁷ made headlines the world over signals that the suffering caused by the race to the top of cancer drug pricing is no longer accepted. It also signals that the issue has become a global phenomenon that requires a global response.

TABLE 15 AVERAGE PRICE OF SIX CANCER DRUGS IN FOUR COUNTRIES²⁴⁸

AVERAGE TRADE PRICE (US\$ PER UNIT)	DASATINIB (PER TABLET)	DOCETAXEL (PER INJECTION)	ERLOTINIB (PER TABLET)	IMATINIB (PER TABLET)	LETROZOLE (PER TABLET)	TRASTUZUMAB (PER INJECTION)
GENERIC						
India (total sales)		114.41	11.76	2.65	0.40	941.58
South Africa (total sales)		241.41		12.46	2.76	
UK hospital	79.06	496.18			0.40	
UK retail	79.06	825.08			0.72	
US clinic	162.39	305.73			0.18	
INNOVATOR						
India		133.85				
South Africa	48.82	245.74	44.04	36.09	4.80	2,115.61
UK hospital		602.26	57.40	43.81	4.97	317.73
UK retail		720.19	57.40	43.81	4.97	631.25
US clinic		587.49	107.66	24.11	10.10	2,907.49

TABLE 16 TARGET GENERIC COST OF SELECT CANCER MEDICINES

MEDICINE AND DAILY DOSAGE	INDICATION	US RETAIL PRICE/ PATIENT/YEAR	COST OF API/KG	TARGET GENERIC PRICE/PATIENT/YEAR
imatinib (400mg)	Chronic myeloid leukaemia	\$92,000	\$347–746	\$119–159
erlotinib (150mg)	Lung and pancreatic cancer	\$2,470	\$236	
sorafenib (400mg)	Kidney and thyroid cancer	\$122,737 ¹	\$3,000	\$1,387
dasatinib (100mg)	Chronic myeloid leukaemia	\$123,500 ²	\$5,478	\$334
trastuzumab	Breast cancer	\$54,000 ³		\$242

SOURCES

Presentation at ECCO, September 2015,²⁴⁹ except where noted below.

- 1 Knowledge Ecology International, Prices for Sorafenib, spreadsheet available online here: <https://docs.google.com/spreadsheets/d/1fGQoNLP76FOad30moA0vXjPz3lxlemp3QTOI39K3JGY/pub?output=html> (last accessed 16 November 2015).
- 2 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*, 121, no. 22:4439-42. doi: 10.1182/blood-2013-03-490003, 30 May 2013, <http://bloodjournal.hematologylibrary.org/content/121/22/4439.long>
- 3 Knowledge Ecology International, University of California San Francisco, Universities Allied for Essential Medicines, and Young Professionals Chronic Disease Network (YP-CDN), *Proposal for the Inclusion of Trastuzumab in the WHO Model List of Essential Medicines for the Treatment of HER2-Positive Breast Cancer*, 30 November 2012, http://www.who.int/selection_medicines/committees/expert/19/applications/Trastuzumab2_8_2_A_Ad.pdf

THE CASE OF BIOLOGICAL MEDICINES

Trastuzumab and rituximab, both cancer medicines newly added to the EML, are known as ‘biological products’. Unlike most traditional ‘small-molecule’ drugs manufactured through chemical processes, biological products are usually made or derived from human and/or animal materials.²⁵⁰ By 2020, the projected global biologics market will be worth US\$ 250 billion. The market for ‘biosimilars’, the generic equivalent of biological medicines, is expected to be worth up to US\$ 25 billion by then, which is 4–10% of the total.²⁵¹

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

Drug regulatory agencies register generic versions of traditional small-molecule medicines based on studies that show the generic product is bio-equivalent to the originator product. Regulatory requirements for generic biologics or biosimilars are often more complex and require more extensive studies to demonstrate that the product is indeed similar in its action to the original 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.²⁵²

Biosimilars for trastuzumab are being or have been prepared for the European and Indian markets, where trastuzumab has recently come off patent,²⁵³ though those, too, may be priced out of reach.²⁵⁴ Legal pathways for the registration of biosimilars have existed in the EU since 2005. In the US, the Food and Drug Administration has been establishing standards for authorisation of biosimilars (an abbreviated licensure pathway for biosimilar biological products) following the passage the Affordable Care Act in 2010.²⁵⁵

TABLE 17 PRICE OF TRASTUZUMAB FOR A ONE-YEAR COURSE IN US\$

COUNTRY	ORIGINATOR	GENERIC
US	49,000	
UK	25,000	
India	16,392	14,000
	28,182	24,000 (Emcure)
		11,600 (Biocon)
China	54,000	
South Africa	46,748	

SOURCE

Ellen 't Hoen, "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, available online here: https://www.oxfam.org/sites/www.oxfam.org/files/file_attachments/rr-access-cancer-treatment-inequality-040215-en.pdf

Biosimilars can only be authorised for use once the period of data exclusivity on the original ‘reference’ biological medicine has expired. Data exclusivity periods can differ per country. In the EU, this means that the biological reference medicine must have been authorised for at least 10 years before a similar (generic) biological medicine can be made available by another company. In the US, the data exclusivity period for biologics is 12 years.²⁵⁶ Many countries have different data exclusivity periods, all shorter than in the US and the EU. Through trade talks such as in the Trans Pacific Partnership Agreement the US is trying to extend the data exclusivity period in other countries to 12 years.²⁵⁷ This would create new levels of market exclusivity for originator companies not related to patents and immune to measures in patent law to deal with undesirable effects of such exclusivity.

Some developing countries, such as Argentina, Brazil, Colombia and Mexico, have developed their own guidelines for the development of biosimilars. For example, 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.^{258, 259}

Considering the savings that could come from biosimilars, it will be important for the WHO to engage in pre-qualification of biosimilars and work with national regulatory agencies to build experience, exchange information and develop standards for biosimilars regulation in resource-poor settings.

MEDICINES PRICES ARE EVERYONE’S PROBLEM NOW

Fifteen years ago, access to medicines was a developing country issue. Today, the challenge of access to new, highly-priced medicines is also an issue in high-income countries. Recently, national health systems in the UK and the Netherlands shied away from providing certain recommended medicines due to price. In the US, waiting lists for state HIV drug assistance are lengthening due to the high cost of drugs (frequently more than US\$ 20,000 per patient per year).²⁶⁰ The price of new hepatitis C medication, which can be up to US\$ 95,000 for a 12-week cure, has led to rationing and lack of access in the US and EU alike.

BOX 18 ESTABLISHING A LICENSING MECHANISM FOR MEDICINES ON THE WHO ESSENTIAL MEDICINES LIST

Companies should offer their products at prices the community can afford. From HIV, we know that a very effective way of ensuring this happens is through voluntary licensing. Voluntary licences should have terms and conditions that aim at maximising access and are conducive to public health needs. One way to ensure public health-oriented licences is for them to go through the Medicines Patent Pool (MPP; see Chapter 3, “The Medicines Patent Pool”). Legal scholars have previously recommended the extension of the MPP framework to cover all essential medicines coupled with international financing mechanisms to ensure affordable access to essential medicines under patent and fair royalty payments.²⁶¹

Countries can take measures at the national level but this risks country-by-country and essential medicine-by-essential medicine IP-related controversies. Access to the new essential medicines requires a global approach and greater international collaboration. The establishment of a licensing mechanism would prevent the type of drug-by-drug access challenges seen in the early days of HIV treatment. The recent shifts in the WHO Essential Medicines paradigm demand bold approaches to avoid unnecessary delays in making these medicines available to the populations in need.

When 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 the Essential Medicines. Predictable compulsory licensing for essential medicines is possible under TRIPS. Even though TRIPS Article 27.2 puts bounds on compulsory licensing for entire categories of products without discrimination, it is possible to impose such licences on medicines deemed to be essential.²⁶²

Make government use of patents to allow for procurement of low-cost versions of essential medicines (see Chapter 3, “Implementing Doha: Compulsory licences, government use, and waivers for LDCs”).²⁶³

In all cases of licensing, reasonable royalties should be determined so originators are remunerated. Such royalties can be determined on the basis of the United Nations Development Programme royalty guidelines that link royalty rate to the gross domestic product of the country.²⁶⁴

Compulsory licensing, including for export, will become more important especially for the new essential medicines that are likely to be patented in

producing countries such as India. For an effective use of compulsory licensing in procurement of medicines, it would be important that the World Trade Organization (WTO) Paragraph 6 system be improved (see also Chapter 2, “Compulsory licensing for export”). A key issue that needs to be addressed is the case-by-case, order-by-order procedure of the mechanism, which is not consistent with the economic and technical realities of the generic industry nor with international procurement practices. The system has a built-in review mechanism. Paragraph 8 of the 2003 Decision prescribes that the TRIPS Council annually reviews the functioning of the system in order to ensure its effective operation. These review cycles offer opportunities to seek improvements to the mechanism and to ensure that the mechanism is coherent with the economic reality of generic pharmaceutical production and procurement. The WTO has prepared a staff working paper²⁶⁵ that lists a number of issues that should be examined in the context of the evaluation.

In Western Europe, the public has largely been protected from the high cost of pharmaceutical care because the financing of healthcare does not fall on individuals. However, the economic crisis and subsequent austerity measures have put the spotlight on the fact that prices of new medicines have also become unsustainable in Europe.²⁶⁶ The consequences of high drug prices are most painfully felt in cancer care. In 2011, Roche stopped the supply of cancer drugs and other medicines to Greek state hospitals because of unpaid bills. Novo Nordisk had done the same for insulin.²⁶⁷ Roche is the world’s largest maker of cancer drugs with US\$ 25.15 billion in annual sales in 2014 (see Table 13). The Greek healthcare budget in 2011 was € 6 billion (approximately US\$ 8.3 billion).²⁶⁸

Even the more affluent European countries also struggle with the high cost of medicines. In 2012, the Dutch College for Health Insurance initially recommended excluding three medicines for the treatment of the rare Pompe and Fabry diseases, because they had become too expensive. Pompe disease is an inherited disorder caused by the build up of a complex sugar called glycogen in the body’s cells that impairs certain organs and tissues, especially muscles, from functioning normally.²⁶⁹ Fabry disease is caused by the lack of, or possession of faulty, enzymes needed to metabolise lipids. Symptoms usually begin during childhood or adolescence and include burning sensations in the hands that get worse with exercise and hot weather and small, raised, reddish-purple blemishes on the skin. Lipid storage may lead to impaired arterial circulation and increased risk

of heart attack or stroke. The heart may also become enlarged and the kidneys may become progressively involved. Other signs include decreased sweating, fever, and gastrointestinal difficulties.²⁷⁰ These diseases affect small numbers of patients in the Netherlands (Pompe, about 100 patients; Fabry, 40–50), but the treatment costs are in the millions each year: € 44 million (US\$ 49 million) for Pompe and € 11 million (US\$ 12 million) for Fabry.²⁷¹

This news sparked a national debate on the reimbursement of medicine costs and the role of the pharmaceutical industry in the development and pricing of the products. The chair of the board of the Erasmus Medical Centre in Rotterdam has called on the government to set up a not-for-profit research and development consortium for rare diseases in the EU to ensure the development of treatments for rare diseases and decrease dependency on the pharmaceutical industry.²⁷² Dr H. Schellekens, professor of medical biotechnology at the University of Utrecht and member of the Dutch medicines board, called for a radical overhaul of the innovation system, and suggested abolishing pharmaceutical patents to use the savings to invest in R&D directly.²⁷³

In the UK, some NHS trusts have denied patients innovative cost-effective treatments recommended by the National Institute for Health and Care Excellence (NICE) because they considered them too expensive. This included, for example, the cancer medication erlotinib.²⁷⁴ NICE chairman, Sir Michael Rawlins, has called the refusal to offer patients NICE-endorsed treatments unlawful and encouraged patients to seek relief in court.²⁷⁵

These stories are not isolated cases and point at the need for the world as a whole to look at the way we finance and make available important pharmaceutical innovations. It begs the question: is the patent system, recently globalised through the WTO TRIPS Agreement, really the most efficient way to go about it? Or can we design a wider variety of incentives aimed at stimulating pharmaceutical innovation that we can afford?

CONCLUSIONS: NEW MEDICINES, NEW URGENCIES IN ADDRESSING THE DRUG PRICE AND ACCESS DIVIDE

A combination of unmet need, important therapeutic advances and prohibitive pricing has created several new urgencies in public health and patents. The crippling prices of medicines for hepatitis C and cancers coupled with a rising disease burden means that governments, companies and civil society will be compelled to act.

In the meantime, what has become clear is that the high-stakes game pitting billions of dollars in risky research and development spending, billions in potential profit, and millions of human lives against each other is neither ideal nor sustainable. New ways of supporting both continued innovation and wider access must be found.

6

FIXING THE BROKEN R&D SYSTEM:

Ensuring essential innovation and access to medicines for all

THE CRISIS IN INNOVATION AND ACCESS: MISSING ESSENTIAL MEDICINES

U sing the profit-motive as the predominant means to incentivise innovation is not only problematic because it results in high prices; it also results in many needed medicines never being developed in the first place.

Over the last several decades, it has become increasingly clear that the current means of incentivising research and development (R&D) leaves many serious public health problems unaddressed—especially diseases disproportionately affecting those in developing countries, rare diseases, and lately, bacterial infections that no longer respond to antibiotics.

As with the issue of access to high-priced medicines, the case of HIV helps to illustrate the R&D issue, particularly through the struggle to treat HIV in children.

PAEDIATRIC HIV AND THE STRUGGLE TO INCENTIVISE ALL MEDICINES FOR CHILDREN

“While the last decade has seen remarkable, historic progress in the AIDS response, children are being left further and further behind,” declares a 2014 report by UNAIDS. The 3.2 million children currently living with HIV—the vast majority of whom live in sub-Saharan Africa—“are substantially less likely than adults living with HIV to obtain life-saving antiretroviral (ARV) therapy. Due to gaps in basic commodities and diagnostic technologies, as well as serious obstacles to the effective use of the health tools currently available, many children are needlessly dying.”²⁷⁶

There are many reasons children with HIV do not have access to treatment, but a major problem is the lack of HIV medicines adapted to their specific needs. A 2011 United Nations report notes that there “there are disincentives for manufacturers to produce paediatric formulations. Clinical research of children’s medicine is often difficult and costly, and paediatric medicine markets are often small and fragmented owing to the need for weight-specific strengths.”²⁷⁷

Scale-up of services to mothers with HIV is increasingly preventing mother-to-child transmission, the way 90% of children contract the virus.²⁷⁸ In wealthy countries, this has virtually eliminated the number of children contracting HIV. But in developing countries, the burden remains, and of children from age 0–14 that do have HIV, only one in four receive treatment.²⁷⁹ Because it is so rare in wealthy countries, there is little incentive for pharmaceutical companies to develop child-friendly formulations that can be easily adjusted depending on the size of the child or that taste better. The foul taste of certain ARVs makes them difficult to administer to young children. From a profit-driven perspective, children with HIV are uninteresting—they represent an economically underprivileged and shrinking market. From a health perspective, however, the human need for these medicines is clear: without treatment, 50% of HIV positive children will die before their second birthday, and four-fifths before their fifth birthday.²⁸⁰

The demographic of HIV in children puts it in the ‘neglected diseases’ category because it fails to attract commercial R&D investments. The pipeline for paediatric dosages is modest, with only a few companies active in this field.

Several non-profit initiatives have been launched over the last several years to address the problem. One of UNITAID’s earliest priorities was to

use pooled procurement to create a market for paediatric HIV medicines²⁸¹; and since 2010, the Drugs for Neglected Diseases initiative (DNDi) has been working to create better, more child-friendly ARV formulations.²⁸² And in 2014, the Medicines Patent Pool (MPP), DNDi and UNITAID together launched the Paediatric HIV Treatment Initiative to help scale up HIV treatment for children.²⁸³

These initiatives have begun to make improvements, but the systematic underinvestment in R&D for paediatric HIV means it will take time—and significant re-thinking of the way drug innovation is conducted—before children with HIV have access to the medicines that can keep them alive and healthy.

WHY THERE IS UNDER-INVESTMENT IN CERTAIN CLASSES OF MEDICINES

The patent-based incentive model for R&D causes systematic underinvestment in diseases that do not represent a profitable market, such as:

- Diseases that disproportionately affect people with little or no ability to pay (so-called “Type II and III” diseases; see Box 19);
- Diseases for which markets are fragmented or small; and
- Diseases for which the treatments need to be preserved and thus cannot be aggressively marketed, which is the case with antibiotics.

In 1990 the Global Forum for Health Research found that only 10% of the US\$ 70 billion spent on health research worldwide each year was for research into the health problems that affect 90% of the world’s population (the so-called 10/90 gap).²⁸⁴

In 2001, Médecins Sans Frontières (MSF) and the Drugs for Neglected Diseases working group (which eventually became the DNDi) published *Fatal Imbalance: The Crisis in R&D for Neglected Diseases*,²⁸⁵ which showed how skewed spending on health research affects priority setting in pharmaceutical R&D. The report analysed the outcome of 25 years of new drug development and found that only 15 new drugs out of 1393 total medicines developed between 1975 and 1999 were for tropical diseases and tuberculosis, yet these diseases accounted for 12% of the global disease burden. In contrast, over two-thirds of new drugs were ‘me too drugs’ (modified versions of existing medicines), which do little or nothing to change the disease burden. A survey of R&D pipelines of 20 pharmaceutical companies in the US, Europe and Japan showed that they were virtually empty for neglected diseases.²⁸⁶

The report used the term “market failure” to describe the lack of private sector investment for diseases affecting people living in developing countries. However, one can also argue that this is not a failure of the system but its very nature: if a medicine is not profitable enough, it will not be brought to market no matter how much it is needed. This is why the report also drew attention to the fact that the crisis in R&D was equally a public policy failure.

MSF stepped up its campaigning to demand political attention to address the imbalance in the world’s innovation system.²⁸⁷ At the same time MSF moved to establish the DNDi.

BOX 19 TYPE I, II AND III DISEASES

The MSF publication, *Fatal Imbalance*, introduced a disease classification that offered a framework that would subsequently guide much of the international policy developments on the issue:²⁸⁸

Type III: Diseases affecting exclusively developing countries, the ‘most neglected diseases’, which received little to no R&D investment (such as many neglected tropical diseases);

Type II: Diseases disproportionately, but not exclusively affecting developing countries’ (such as HIV/AIDS, tuberculosis, dengue, and malaria), which received some, but not enough, R&D investment (with HIV a possible notable exception); and

Type I: Global diseases, affecting primarily but not only ‘developed countries’ which attract substantial R&D investment but do not always lead to innovations adapted to meet needs in low- and middle-income countries and/or that are priced within reach of patients.

MISSING MEDICINES ARE ALSO A PROBLEM IN WEALTHY NATIONS

While initially, the work documenting the challenges in pharmaceutical R&D focused on neglected diseases (type III and type II diseases; see Box 19), subsequent studies showed that the problem was broader. Increasingly, it has become apparent that the failure of market-driven pharmaceutical R&D to effectively respond to certain health needs has a global impact.

Experts from the Bellagio meeting at the Rockefeller Foundation in 2012 on the implementation of the World Health Organization (WHO) Consultative Expert Working Group on Research & Development (CEWG) agreed that:

“[M]arket failures affected all countries, regardless of level of income – such as the growing problem of antimicrobial resistance and the hollow pipeline for new effective antibiotics. While acknowledging that the categories of Type I, II and III diseases were a useful analytical tool to understand why certain diseases attracted more or less private sector investment, the experts recognised that in order to generate long-term public funding from all countries, a new global framework would need to offer some benefits applicable to all countries (and not be arbitrarily limited by disease categories). Therefore, a more useful way of delineating the scope of a new framework was to identify areas of market and/or public policy failure – that is, diseases or areas of technology where the existing system had failed to deliver safe, effective, quality products that were suitable and affordable, particularly for poorer populations.”²⁸⁹

One area in which this is clear is in paediatrics. In 2005, pharmaceutical sales in the United States (US) were US\$ 250 billion, with a growth rate of 5.4%; paediatric sales were only US\$ 37 billion, the majority of which was focussed on a handful of disease areas.²⁹⁰ Companies viewed paediatric markets as risky, “with little expected return on investment.”²⁹¹ As a result, small markets for devastating illnesses such as childhood cancer are underserved. Between 1948 and 2003, the Food and Drug Administration (FDA) approved 120 new cancer drugs, but only 30 have been used in children. Several experts writing in *Nature* explained the problem:

“In the USA, approximately 60% of funding for biomedical research stems from the private biopharmaceutical sector. The next largest funder is the NIH, which supports approximately 25% of research. For childhood cancers, however, which represent a constellation of more than 100 rare and ultra-rare diseases, the biopharmaceutical sector has an almost negligible investment, resulting in virtually all research funding emanating from the National Cancer Institute (NCI), private foundations and philanthropic sources. This limitation of funding and investment from industry impacts all key areas of drug development, spanning target discovery through clinical development.”²⁹²

Industry has pointed at the lack of market incentives (many of the medicines for which paediatric formulations are needed concern off-

patent products) but also regulatory challenges²⁹³ which likely go beyond the development of formulations.

The European Union (EU) and US have given the lack of paediatric drug development some attention, which now seems to have had results. But those efforts do not take into account the needs of children in developing countries.²⁹⁴

Another group of diseases for which the market fails is so-called ‘orphan’ or rare diseases. Some of these diseases have devastating consequences, but because the market is small, government intervention has been necessary to create incentives for companies to invest in drug development for rare diseases. However, many of the drugs that result from such incentive schemes are extremely expensive (see the “Pompe and Fabry” section in Chapter 5, “Medicines prices are everyone’s problem now”).

MARKET FAILURE SPURS VULNERABILITY TO MICROBIAL RESISTANCE

Similarly, the alarming rise of antimicrobial resistance and the empty pipeline in antibiotic drug development has brought home the limitations of a market-driven R&D system that will not invest in the development of medicines if it cannot promote them actively and sell them at high price. New antibiotics need to be preserved and ideally used as little as possible, in cases of well-defined need, in order to keep them effective (the greater the exposure, the greater chance of microbial resistance developing). This makes an antibiotic medicine development an unattractive project for a commercial company. Antibiotic drug development should move into the not-for profit sphere of drug development, analogous to neglected diseases research.

A Chatham House report²⁹⁵ on new business models for sustainable antibiotics lists the following economic incentives that need fixing:

- Inadequate market incentives for companies to invest in R&D and bring new products to market at the right time;
- Inadequate market incentives to protect these valuable resources from overuse and premature resistance; and
- Inadequate market incentives to ensure global access to life-saving antibiotics.

The failure to respond to the Ebola outbreak in West Africa with effective vaccines, diagnostics and treatments²⁹⁶ further hammered home the urgent need for change, which was recognised by many, including the industry. In response to questions about the role of the pharmaceutical industry in dealing with the Ebola outbreak in West Africa, a spokesperson

for the Association of the British Pharmaceutical Industry, said: “Unfortunately, the standard economic model for drug development, in which industry takes all of the risk in R&D and gets a return on investment from successful products, does not work for diseases that primarily impact low-income countries and developing healthcare systems.”²⁹⁷

Clinical testing of a new Ebola vaccine in Guinea has since shown very promising results,²⁹⁸ but it took an unprecedented outbreak, over 11,000 deaths and extensive political mobilisation to take the vaccine candidate off the shelf where it had been sitting for 10 years after the Public Health Agency of Canada had developed it.²⁹⁹

NOT-FOR-PROFIT ESSENTIAL DRUG DEVELOPMENT: PIONEERING NEW INNOVATION MODELS

The late 20th and early 21st centuries saw the establishment of a number of not-for profit drug development initiatives to fill the R&D gap left by the profit-driven sector for type II and III diseases, especially for malaria, a number of infectious diseases, including, tuberculosis (TB) and HIV. These initiatives develop products using a business model that does not rely on high pricing to recoup R&D investments.

Funders came forward, new actors such as the Bill and Melinda Gates Foundation appeared on the scene, new industry R&D platforms were created, and new incentives for industry were developed.³⁰⁰ The issue of lack of R&D for neglected diseases became a recurrent theme in policy dialogues and industry initiatives.

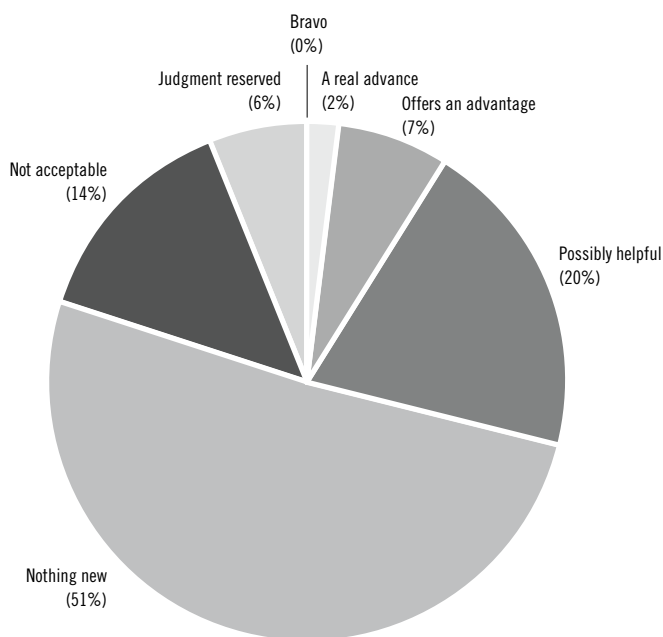
Yet in 2012, a new analysis³⁰¹ conducted by DNDi, MSF and others³⁰² found that of the 850 new drugs and vaccines approved for all diseases between 2000 and 2011, just 4% (37) were for neglected diseases. In addition, of the nearly 150,000 registered clinical trials for new therapeutic products in development as of December 2011, only 1% were for neglected diseases. This highlights the persistence of the gap between global disease burden—and thus patients’ needs—and therapeutic product development by the current R&D system.³⁰³

HIGH PRICES DO NOT NECESSARILY INDICATE ESSENTIAL INNOVATION

Suggestions for change in the pharmaceutical R&D system are often met with stern warnings of the negative effects it may have on innovation. However, the increase in drug prices has not met with a similar increase in new drug development.

A breakdown of 1,432 new drug approvals in Europe between 2000 and 2014 by *La Revue Prescrire* shows that there were no “real breakthroughs.” Further, just 9% of the new medicines offered a real advance or an advantage; 20% were deemed “possibly helpful,” and 14% were “not acceptable” (see Figure 8). Judgment was reserved in 5% of the new approvals, mostly because of lack of data. More than half (51%) of the new medicines were so-called ‘me-too’ products, which indicates that the pharmaceutical industry over-invests in products that are similar in function to what is already available on the market. This is perhaps a profitable commercial strategy, but does little to expand the therapeutic arsenal.³⁰⁴

FIGURE 8 INNOVATIVE VALUE OF NEW DRUG APPROVALS IN EUROPE, 2000–2014



SOURCE

“Année du médicament,” *La Revue Prescrire* 2015.³⁰⁵

A recent *Access to Medicines Index* review of the R&D pipeline of the top 20 R&D companies on priority diseases shows 327 relevant products in development. Of these, 190, or 54%, are for five diseases: respiratory infections (45); diabetes (45); chronic hepatitis (38); HIV/AIDS (34); and malaria (28). Very few projects (only 15, or 4%) are for maternal and neonatal health. Most non-communicable disease (NCD) medicines are developed by private entities; no access policies have been defined for any of these medicines. In other words, there may be promising products in the pipeline that are needed globally, but with the exception of HIV and malaria, companies do not develop strategies to ensure access to those medicines.³⁰⁶

CHANGING THE R&D SYSTEM: POLICY CHANGES AND CHALLENGES TO DATE

The question of whether the current global R&D system should undergo fundamental changes to respond to the health needs of the world, and what such changes would entail, has been asked with increasing urgency over the last 15 years.³⁰⁷ The challenges of medical innovation and of access to health tools (including medicines, diagnostics, and vaccines) to address global health needs are well-documented and have been the subject of a number of reports and policy recommendations.³⁰⁸

Considering that over 80% of the 7.3 billion people³⁰⁹ in the world live in low- and middle-income countries and that innovation and access problems have become increasingly global, a new global paradigm to spur biomedical innovation in areas neglected by the market-based innovation system is clearly needed. It is just not always clear how to arrive at this new paradigm.

Attempts at change remain haphazard, often stumbling from crisis to crisis, disease to disease, and often dependent on charitable contributions, leaving the status quo of the system in place. Why is more fundamental change so difficult? Several reasons are detailed below.

INTELLECTUAL PROPERTY ISSUES

Today's pharmaceutical innovation system is firmly rooted in the patent system. The 1994 adoption of the World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) globalised patent-based medical innovation, and TRIPS set global minimum requirements for the creation and protection of intellectual property (IP) enforceable through the WTO (see Chapter 1, "Globalising the patent regimes of wealthy nations").

Monopoly-based high drug pricing is justified by the industry and its supporters to compensate for the cost of R&D of new drugs. Without patents, pharmaceutical R&D will come to a standstill, they argue.

But prices asked for new medicines bear little relation to the actual cost of development; they rather reflect the dominant market position of a company that holds the patent. As a result, the patent-based innovation system has become immensely costly and does not deliver desperately needed new medicines if the profitability cannot match those of blockbuster products.

LACK OF UNDERSTANDING OF HOW MUCH DRUG DEVELOPMENT COSTS

The question of what would be a fair return on R&D investment cannot be addressed without greater transparency on the true cost of R&D. Companies guard the cost of their own R&D as trade secrets while sponsoring academic work that provides development cost estimates. Recent cost estimates for the development of a new drug by the Centre for the Study of Drug Development at Tufts University in Massachusetts set the average cost for drugs developed between 1995 and 2007 at US\$ 2.5 billion.³¹⁰ In 2012, an industry-funded study by the Office of Health Economics, came to an estimate of US\$ 1.506 billion development cost per drug.³¹¹ The table below summarises various R&D cost estimates since 1991.^{312, 313, 314}

TABLE 18 STUDIES ON R&D COSTS OF NEW DRUG DEVELOPMENT

YEAR	R&D COST ESTIMATE (IN US\$)	SOURCE
1991	231 million (1987\$)	DiMasi
1993	140–194 million (1990\$)	OTA
2002	802 million	DiMasi
2012	1.5 billion	OHE
2014	2.5 billion	DiMasi

These figures are used by the pharmaceutical industry to justify high drug prices. Though some in the industry have also expressed scepticism: GlaxoSmithKline (GSK) Chief Executive Officer Andrew Witty even called the US\$ 1 billion figure “one of the great myths of the industry.”³¹⁵

R&D costing figures of not-for-profit drug developers show that significant innovations are possible for much more modest expenditure on R&D.

In 2001, the Global Alliance for Tuberculosis Drug Development estimated the costs of successfully developing an new chemical entity (NCE) to treat tuberculosis to be approximately US\$ 36.8–39.9 million in the US, excluding costs of failure. This estimated range covers preclinical development (US\$ 4.9–5.3 million), pharmaceutical development (at least US\$ 5.3 million), and phases I through III of clinical development (US\$ 26.6 million). If one includes the estimated cost of unsuccessful projects, the estimated costs of developing an NCE are approximately US\$ 76–115 million.³¹⁶

In 2014, the DNDi published data on their R&D expenditure. The cost for an improved treatment (combination product with existing compounds) is between € 6–20 million (approximately US\$ 8.3–27 million) and € 30–40 million (approximately US\$ \$41–55 million) for the full development of an NCE. These figures do not include in-kind contributions from partners. If one applies standard attrition for the DNDi products, DNDi’s cost for the development of an NCE is estimated to be € 100–150 million. These estimates are based on real cost for products that have been or are under development by DNDi.³¹⁷

While exact estimates of R&D cost remain subject to debate,³¹⁸ we do know that new drug development is costly. The current innovation system is in need of change to become less costly and more responsive to health needs, especially to develop missing essential medicines needed to respond to global health problems. R&D models are needed that share the results of

research, that ensure transparency of clinical trial results to enable independent assessment of the value of a product and, perhaps most importantly, that include new models of financing drug development.

Pricing of medicines should reflect public investment in innovation to prevent a situation where the public pays twice: through government funded research and then again through high drug prices. New models also will need to address the monopoly-based pricing that today leads to rationing of important medicines. In the words of the *Financial Times*:

“... the licence to manufacture a treatment exclusively is not the same as one to print money. New medicines cannot come at any price — especially when the maker uses its legal monopoly to set swinging charges for vital remedies. Doctors do not wish to withhold drugs that can save lives. But there is a limit to what stretched healthcare systems can afford.”³¹⁹

DELINKAGE MODELS: A WAY FORWARD

One proposal to solve the innovation/access challenge is to ‘delink’ the cost of the R&D from the price of the product and develop new ways to share the burden of innovation cost internationally. A joint WTO, WIPO, WHO study describes delinkage as follows:

“One important concept that evolved from this discussion is the concept of delinking price of the final product from the costs of R&D. This concept is based on the fact that patents allow developers to recoup the costs and make profits by charging a price in excess of the costs of production. This way of financing R&D is viewed as constituting a barrier to access to medicines in countries where populations pay out of their own pockets for medicines and thus cannot afford to pay high prices. The principle of delinking is based on the premise that costs and risks associated with R&D should be rewarded, and incentives for R&D provided, other than through the price of the product.”³²⁰

If, for example, the R&D cost of new cancer drugs would not have to be recouped through high drug prices in a few countries, those medicines would cost less and would be more widely available.^{321, 322}

Several proposals for an international agreement on medical R&D to achieve the objectives of financing for innovation and access to those innovations have been made since 2004 (see Box 20).³²³

BOX 20 DEVELOPING A NEW INTERNATIONAL FRAMEWORK FOR PRIORITY SETTING, COORDINATION AND FINANCING OF MISSING ESSENTIAL MEDICINES

The current pharmaceutical R&D system suffers from disappointing rates of innovation, a misalignment between research investments and health priorities, and unaffordable prices for end products.

Global spending on pharmaceutical products is expected to reach US\$ 1.4 trillion by 2020,³²⁴ of which the market share of developing countries, particularly in Asia and Latin America, is growing at a rapid pace. This is money the public spends, either out of pocket or through its health insurance, social security schemes or tax-based government-provided health care. The public, however, has very little say over how this money is allocated when it come to R&D priority setting and spending.

Public policy, including at the international level, should therefore play a much greater role in steering the R&D priorities, coordinating financing and developing approaches to access to new essential medicines.

WHO can use its powers to initiate international talks about priority setting and burden sharing of the cost of essential health R&D and set new rules to allow for financing of innovation while equitable access to those innovations is assured. This would initiate international implementation of delinkage. The WHO has started doing so on a small scale. The Tropical Disease Research programme at the WHO is moving forward with plans to set up and manage a pooled research and development fund.³²⁵

The 2016 World Health Assembly, which will discuss the recommendation for a new global R&D agreement made by the Consultative Expert Working Group on R&D in 2012, offers an opportunity for a bold and ambitious approach and discussion of plans for an agreement among countries on collaboration towards and financing of essential medical R&D.

The idea of an international agreement on R&D has been debated since Hubbard and Love made an initial proposal in 2004.³²⁶ Central in those proposals are innovation models based on delinkage of the cost of R&D from the price of the end product. Examples include prize funds, patent buy-outs, open source innovation and other new financing mechanisms. An R&D agreement could be crafted under the auspices of the WHO, whose Constitution (article 19) allows for its 194 member states to negotiate formal international law.³²⁷

Key features of a new medical R&D framework should include:

- R&D priorities driven by health needs;
- Binding obligations on governments to invest in health R&D;
- Equitable distribution of contributions across countries;
- Measures to improve the regulatory environment and collaboration;
- Measures to ensure affordability of the end product;
- Access-maximising licensing practices to deal with IP issues; and
- Innovative approaches to incentivising R&D based on delinkage principles.

While both formal and informal norms (such as guidelines or global strategies) can influence the behaviour of states and non-state actors, binding international law offers several potential advantages. An important precedent was set with the 2005 Framework Convention on Tobacco Control, the first public health treaty negotiated within WHO, which has contributed significantly to global tobacco control efforts.^{328,329}

The proposals for a new global framework for medical innovation were echoed in a commentary by heads of research and international organisations in Public Libraries of Science (PloS) calling for a Global Biomedical R&D Fund and Mechanism for Innovations of Public Health Importance.³³⁰ The authors make the point that the idea of a global financing mechanism for innovation has been discussed separately for global health priorities, including for neglected diseases, antibiotics and, more recently, Ebola. These are diseases that provide limited commercial market opportunities, but that are also health priorities for all countries: low-, middle- and high-income alike. The medical tools needed to address them should be considered global public goods. They suggest that “before jumping to create multiple new mechanisms, it would make sense to consider reconciling the needs of all these areas by considering an umbrella framework for specifically funding and coordinating R&D that emphasises not only innovation but also secures access.”

The issue of access and innovation and the recommendation by the CEWG for a global agreement on medical R&D has sparked an international campaign that continues to gain support from a number of governments, scientists, Nobel laureates, civil society organisations, and other experts.^{331, 332, 333, 334} Eminent scholars, including Nobel laureates, in 2015 published a statement of support, titled “Make medicines for people

not for profit,”³³⁵ in which they support the R&D agreement and call for “a different system, based on principles of open access, open knowledge, open sharing and fair price, as well as incentives and mechanisms to encourage R&D of essential medicines according to needs of people worldwide.” They refer to mechanisms already being used that show great potential, including prize funds, patent pools, and open collaborative approaches. They further state: “As academics, researchers and scientists it is our responsibility to generate and transmit knowledge. We have a unique role to promote innovation in many fields and to ensure that our innovations are used to benefit the public.”

All proposals point at the need for greater public leadership and alternatives to the failings of the market-based innovation system and the need for a new global innovation framework. The coming years will show whether the world has the global governance capacity to respond to the new challenges and translate the recommendation for change into action.

7

RESTORING THE BALANCE:

Access to essential medicines in a post-TRIPS world

WILL A PUBLIC HEALTH APPROACH TO IP BEYOND HIV BE POSSIBLE?

The HIV crisis and the global mobilisation to provide access to treatments for the millions of people infected with HIV were at the origin of a redirection in protection of intellectual property (IP) in the global public health field. They were responsible for the Doha Declaration in 2001 that took some of the sharpest edges from the World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) concluded only five years earlier. The only amendment to TRIPS in its history was for public health, and was a direct response to the HIV treatment crisis. It introduced a special compulsory licensing mechanism for export in anticipation of TRIPS implementation by countries that provided low-priced generic medicines. The vast majority of instances of compulsory licences, government use licences and applications of the least-developed country (LDC) pharmaceutical waiver—key public health flexibilities in TRIPS and the Doha Declaration—were in the context of the procurement of HIV medicines. The HIV crisis prompted companies to change both their pricing and licensing policies. The developments around IP and HIV

also provided the policy space that led to the establishment of the Medicines Patent Pool in 2010.

HIV/AIDS and the struggle over whether public health concerns trump IP has changed the way medicines and monopolies are viewed. Researcher Suerie Moon frames it as follows: “First it [HIV/AIDS] has re-framed medicines from being understood as private goods to global public goods. Second (and relatedly), it has legitimised the idea that public health concerns may trump intellectual property protection.”³³⁶

Today, first-line antiretroviral (ARV) regimens are available from generic suppliers for US\$ 95–158, a sharp decrease from the US\$ 10,000–15,000 a decade and a half ago. Nearly 13 million people worldwide now use these medicines, according to UNAIDS.

The Doha Declaration was a very important part of the norm setting for dealing with IP in the context of health. The Doha Declaration, however, is not confined to HIV. In that context it is interesting that the Indian Supreme Court referred to the Doha Declaration in its ruling in the pre-grant opposition case concerning the anti-cancer drug imatinib (Glivec), in support of section 3(d) of the Indian patents as an important provision to protect health interest.³³⁷

A key question is whether the HIV-related re-framing is leading to changes in the approach to innovation and access to medicines for other diseases. Patents remain a blunt policy tool leading to high prices and often fail to drive R&D into areas of most need, as is shown in the cases of Ebola, antibiotics, medicines for children, and many neglected diseases. Important new medicines have been developed for the treatment for non-communicable diseases, such as cancer. But companies rarely have access strategies in place to make these medicines available in less resource-rich settings. Countries that have invoked TRIPS/Doha flexibilities for other than HIV have been subject to severe criticism and have been threatened with trade sanctions by the United States (US) and European Union (EU). The Western pharmaceutical industry continues to vigorously defend its patents and promote a TRIPS-plus agenda through bilateral and regional trade agreements, aided by the governments of the US and the EU.

The glimmer of hope for a more broadly balanced approach towards IP and health that came with the Doha Declaration seems to be vanishing in the face of bilateral and regional trade policies. For example, the US Trade Representative’s annual publication of the Special 301 reports, where it reports on what it views as IP policies damaging to US business interests in other nations, singles out countries that have public health-friendly IP

approaches.³³⁸ Full implementation of TRIPS flexibilities by low- and middle-income countries is still hampered by fear of trade retaliation by rich nations.

It is, however, clearly in the best interest of governments everywhere to find a solution to affordably treat the diseases of today and ensure a sustainable pipeline to treat the diseases of tomorrow, to avert a re-play of the crisis years of HIV. Without such a solution, there will continue to be clashes between public health interests and patents with every new essential medicine that comes to market. The recent addition by the World Health Organization (WHO) of highly priced, patented medicines to the WHO Essential Medicines List is a call for action.³³⁹

The label “WHO 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. Governments need to act when the market fails to do so. This will require dealing with patent and regulatory issues and may need international collaboration. Not acting means depriving a population from access to important medical innovations and thus ignoring basic human rights.

While the critical voices about the patent system are growing stronger,³⁴⁰ few are suggesting the abolition of the patent system. However, based on today’s knowledge of the challenges of the current pharmaceutical system for both access to new medicines and priority setting in innovation it is apparent that we need to look at alternatives.

We need a mechanism to bring the price of new, patented essential medicines down so they become affordable to the communities that need them.

Equally important is ensuring that research and development (R&D) for new essential treatments takes place. New financing models for R&D need to provide the correct incentives for innovation while keeping drug prices affordable. Such models should be based on delinkage principles, in which the cost of R&D is delinked from the price. In other words, innovation should no longer be dependent on the ability to charge high prices.

To achieve this objective of essential pharmaceutical innovation and assured access, countries will require a better system that allows for sharing of the cost and the benefits. The development of such systems will require that powerful industries, strongly attached to patent monopolies and their home governments engage.

It is too early to say whether the changing winds in the protection of medical IP brought in by the HIV/AIDS crisis a decade and a half ago will continue to affect IP law and innovation policy development. The need for change is no longer driven by unmet needs in developing countries only.

To achieve the objective of essential pharmaceutical innovation and assured access, countries will require a system that allows for sharing of the cost and the benefits. If all contribute, all will benefit. The high medicines price crisis has become a global one. The next decade will show whether the world can get together to solve it.

7

RESTORING THE BALANCE: ACCESS TO ESSENTIAL MEDICINES IN A POST-TRIPS WORLD

ANNEXES

ANNEX 1

THE GENERAL COUNCIL CHAIRPERSON'S STATEMENT ON THE AUGUST 30 DECISION

FROM 30 AUGUST 2003:

The General Council has been presented with a draft Decision contained in document IP/C/W/405 to implement paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health. This Decision is part of the wider national and international action to address problems as recognized in paragraph 1 of the Declaration. Before adopting this Decision, I would like to place on the record this Statement which represents several key shared understandings of Members regarding the Decision to be taken and the way in which it will be interpreted and implemented. I would like to emphasize that this Statement is limited in its implications to paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health.

First, Members recognize that the system that will be established by the Decision should be used in good faith to protect public health and, without prejudice to paragraph 6 of the Decision, not be an instrument to pursue industrial or commercial policy objectives.

Second, Members recognize that the purpose of the Decision would be defeated if products supplied under this Decision are diverted from the markets for which they are intended. Therefore, all reasonable measures should be taken to prevent such diversion in accordance with the relevant paragraphs of the Decision. In this regard, the provisions of paragraph 2(b)(ii) apply not only to formulated pharmaceuticals produced and supplied under the system but also to active ingredients produced and supplied under the system and to finished products produced using such active ingredients. It is the understanding of Members that in general special packaging and/or special colouring or shaping should not have a significant impact on the price of pharmaceuticals.

In the past, companies have developed procedures to prevent diversion

of products that are, for example, provided through donor programmes. “Best practices” guidelines that draw upon the experiences of companies are attached to this statement for illustrative purposes. Members and producers are encouraged to draw from and use these practices, and to share information on their experiences in preventing diversion.

Third, it is important that Members seek to resolve any issues arising from the use and implementation of the Decision expeditiously and amicably:

- To promote transparency and avoid controversy, notifications under paragraph 2(a)(ii) of the Decision would include information on how the Member in question had established, in accordance with the Annex, that it has insufficient or no manufacturing capacities in the pharmaceutical sector.
- In accordance with the normal practice of the TRIPS Council, notifications made under the system shall be brought to the attention of its next meeting.
- Any Member may bring any matter related to the interpretation or implementation of the Decision, including issues related to diversion, to the TRIPS Council for expeditious review, with a view to taking appropriate action.
- If any Member has concerns that the terms of the Decision have not been fully complied with, the Member may also utilise the good offices of the Director General or Chair of the TRIPS Council, with a view to finding a mutually acceptable solution.

Fourth, all information gathered on the implementation of the Decision shall be brought to the attention of the TRIPS Council in its annual review as set out in paragraph 8 of the Decision.

In addition, as stated in footnote 3 to paragraph 1(b) of the Decision, the following Members have agreed to opt out of using the system as importers: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom and United States of America.

Until their accession to the European Union, Czech Republic, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia agree that they would only use the system as importers in situations of national emergency or other circumstances of extreme urgency. These countries further agree that upon their accession to the European Union, they will opt out of using the system as importers.

As we have heard today, and as the Secretariat has been informed in certain communications, some other Members have agreed that they would only use the system as importers in situations of national emergency or other circumstances of extreme urgency: Hong Kong China, Israel, Korea, Kuwait, Macao China, Mexico, Qatar, Singapore, Chinese Taipei, Turkey, United Arab Emirates.

“BEST PRACTICES” GUIDELINES

Companies have often used special labelling, colouring, shaping, sizing, etc. to differentiate products supplied through donor or discounted pricing programmes from products supplied to other markets. Examples of such measures include the following:

Bristol Myers Squibb used different markings/imprints on capsules supplied to sub Saharan Africa.

Novartis has used different trademark names, one (Riamet®) for an anti-malarial drug provided to developed countries, the other (Coartem®) for the same products supplied to developing countries. Novartis further differentiated the products through distinctive packaging.

GlaxoSmithKline (GSK) used different outer packaging for its HIV/AIDS medications Combivir, Epivir and Trizivir supplied to developing countries. GSK further differentiated the products by embossing the tablets with a different number than tablets supplied to developed countries, and plans to further differentiate the products by using different colours.

Merck differentiated its HIV/AIDS antiretroviral medicine CRIXIVAN through special packaging and labelling, i.e., gold-ink printing on the capsule, dark green bottle cap and a bottle label with a light-green background.

Pfizer used different colouring and shaping for Diflucan pills supplied to South Africa.

Producers have further minimized diversion by entering into contractual arrangements with importers/distributors to ensure delivery of products to the intended markets.

To help ensure use of the most effective anti-diversion measures, Members may share their experiences and practices in preventing diversion either informally or through the TRIPS Council. It would be beneficial for Members and industry to work together to further refine anti-diversion practices and enhance the sharing of information related to identifying, remedying or preventing specific occurrences of diversion.

ANNEX 2

THE DOHA DECLARATION ON THE TRIPS AGREEMENT AND PUBLIC HEALTH

WORLD TRADE ORGANIZATION

WT/MIN(01)/DEC/2

20 November 2001

(01-5860)

MINISTERIAL CONFERENCE

Fourth Session

Doha, 9 - 14 November 2001

DECLARATION ON THE TRIPS AGREEMENT

AND PUBLIC HEALTH

Adopted on 14 November 2001

1. We recognize the gravity of the public health problems afflicting many developing and least-developed countries, especially those resulting from HIV/AIDS, tuberculosis, malaria and other epidemics.
2. We stress the need for the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) to be part of the wider national and international action to address these problems.
3. We recognize that intellectual property protection is important for the development of new medicines. We also recognize the concerns about its effects on prices.
4. 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. In this connection, we reaffirm the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.
5. Accordingly and in the light of paragraph 4 above, while maintaining our commitments in the TRIPS Agreement, we recognize that these flexibilities include:
 - (a) In applying the customary rules of interpretation of public international law, each provision of the TRIPS Agreement shall be read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles.

(b) Each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.

(c) Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

(d) The effect of the provisions in the TRIPS Agreement that are relevant to the exhaustion of intellectual property rights is to leave each Member free to establish its own regime for such exhaustion without challenge, subject to the MFN and national treatment provisions of Articles 3 and 4.

6. We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002.
7. We reaffirm the commitment of developed-country Members to provide incentives to their enterprises and institutions to promote and encourage technology transfer to least-developed country Members pursuant to Article 66.2. We also agree that the least-developed country Members will not be obliged, with respect to pharmaceutical products, to implement or apply Sections 5 and 7 of Part II of the TRIPS Agreement or to enforce rights provided for under these Sections until 1 January 2016, without prejudice to the right of least-developed country Members to seek other extensions of the transition periods as provided for in Article 66.1 of the TRIPS Agreement. We instruct the Council for TRIPS to take the necessary action to give effect to this pursuant to Article 66.1 of the TRIPS Agreement.

ANNEX 3

LIST OF ACRONYMS USED

AU	African Union
API	Active Pharmaceutical Ingredient
AIDS	Acquired Immune Deficiency Syndrome
ARIPO	African Regional Industrial Property Organization (ARIPO)
ARV/ART	Antiretroviral/Antiretroviral Therapy
BI	Boehringer Ingelheim
BMS	Bristol-Myers Squibb
CEWG	Consultative Expert Working Group on Research and Development
CIPIH	Commission on Intellectual Property Rights, Innovation and Public Health
CML	Chronic Myelogenous/Myeloid Leukaemia
COMESA	Common Market for Eastern and Southern Africa
CPTech	Consumer Project on Technology (now KEI)
DC	Developing Country
DNDi	Drugs for Neglected Diseases Initiative
EAC	East African Community
EU	European Union
GATT	General Agreement on Tariffs and Trade
GSK	GlaxoSmithKline
GSPOA	The Global Strategy on Public Health, Innovation and Intellectual Property at the WHO
HAART	Highly Active Antiretroviral Therapy
HAI	Health Action International
HIC	High-income Country
HITAP	Health Intervention and Technology Assessment Program
HIV	Human Immunodeficiency Virus
IDA	International Dispensary Association
IGWG	Intergovernmental Working Group on Public Health, Innovation and Intellectual Property
IP	Intellectual Property
KEI	Knowledge Ecology International
LDC	Least Developed Country
LMICs	Low- and Middle-Income Countries
MFN	Most Favoured Nation

MMSA	Military Medical Supply Agency
MPP	Medicines Patent Pool
MSD	Merck Sharp and Dohme
MSF	Médecins sans Frontières
NCE	New Chemical Entity
NGO	Non-governmental organisation
NHS	National Health Service
OAPI	Organisation Africaine de la Propriété Intellectuelle
PEPFAR	The Presidents Emergency Plan for AIDS Relief
PQP	The WHO's Prequalification of Medicines Programme
QALY	Quality Adjusted Life-Year
R&D	Research & Development
SACU	Southern African Customs Union
SADC	Southern African Development Community
TAC	Treatment Action Campaign
TB	Tuberculosis
TPP	Trans-Pacific Partnership Agreement
TRIPS	The Trade-Related Aspects of Intellectual Property Rights Agreement
UNDP	United Nations Development Programme
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

ANNEX 4

GLOSSARY

ACTIVE PHARMACEUTICAL INGREDIENT (API): The part of a pill that provides the medical benefit. Other parts of the pill are inactive and may include the material in which the API is encased (e.g., a gel capsule) or suspended (e.g., a liquid).

ANTIRETROVIRAL (ARV) AND ANTIRETROVIRAL TREATMENT (ART): A medicine for the treatment of HIV. There are several classes of ARVs, which all target a different phase in the reproductive cycle of the virus. ART is a treatment regimen composed of several ARVs (usually three).

COMPULSORY LICENCE/GOVERNMENT USE: A compulsory licence is an authorisation by a competent government authority to use a patented invention by a third party without the consent of the patent holder, against a payment of “adequate remuneration.” A ‘government use’ is a particular form of compulsory licence issued by the government for its own use or for the use of a third party.

DATA EXCLUSIVITY: Data exclusivity is the prohibition of use of pharmaceutical test data submitted to a regulatory agency by an originator company for the purpose of registering a generic drug. Generic companies rely on this test data to demonstrate the safety and efficacy of their bioequivalent drug. Delayed use of the data will therefore delay the registration and marketing of generic medicines, regardless of the patent status of the product.

DELINKAGE: A concept in public health wherein the cost of research and development on a new medicine is ‘delinked’, or independent from, the medicine’s final market price. There have been several ways discussed to achieve delinkage, including pooled funding for research and development and cash prizes.

ESSENTIAL MEDICINES LIST (EML): The EML is a list maintained by the World Health Organization that contains the most important medicines that should be available and affordable to the communities and people that need them. The EML is a tool for governments and healthcare providers seeking to meet the health needs of their populations. The EML is updated periodically to detail the medicines a health system should seek to make available.

EVERGREENING: The practice of seeking secondary patents with the aim to extend market exclusivity beyond the patent term of the basic patent.

FIXED-DOSE COMBINATION (FDC): A treatment combined of several medicines in one pill (usually two or three). FDCs have been instrumental in scaling up HIV treatment by allowing for easier treatment, improved treatment compliance, and simplified distribution.

HAART: Highly Active Antiretroviral Therapy (HAART) is a combination, usually of three or more, ARVs to help suppress HIV. The drug combination is selected depending on the patient's viral load, previous experience with/resistance to other medicines, age, and other factors. The World Health Organization periodically releases guidelines on preferred treatment regimens for HIV.

INTELLECTUAL PROPERTY: Intellectual property (IP) refers to the legal rights that result from intellectual activity in the industrial, scientific, literary and artistic fields. IP has two branches: Industrial property (e.g., inventions (patents), trademarks, industrial designs, geographical indications) and copyright (and related rights).

LDC TRANSITION PERIOD/WAIVER: Least-developed countries (LDCs) have an extended transition period before they have to comply with the TRIPS agreement; that period is currently in force until 2021. A separate LDC pharmaceutical waiver allows LDCs not to grant or not to enforce existing IP rights on pharmaceutical products. This waiver will be in place until 2033.

MOST FAVOURED NATION (MFN) TREATMENT: One of the founding principles of the World Trade Organization, MFN Treatment says that all trading partners must be given equal advantages as the 'most favoured' trading partner. For example, a country may not grant tariff exemptions to only one trading partner unless it extends the same to all trading partners.

PARALLEL IMPORTATION: Parallel importation refers to the import and resale in a country, without the consent of the patent holder, of a patented product that has been legitimately put on the market of the exporting country. Parallel imports take place when there are significant price differences for the same good in different markets.

PATENT: A patent is a form of IP granted to an inventor for the creation of something new, non-obvious to a person who is knowledgeable in the field, and useful. Patents grant a temporary monopoly (usually 20 years), during which time the patent holder can prevent others from making, using, or selling their invention. A patent is national in nature, and inventors must apply under each country's patent laws in order to receive protection in that country. In international trade, however, a blocking patent in either the country of import or export could interfere. That

means a patent in a country that produces lots of generic medicines, such as India, can be enough to restrict access to those medicines in other countries relying on the first country's exports, regardless of whether or not there is a patent in the importing country.

PREQUALIFICATION OF MEDICINES PROGRAMME (PQP): Established by the World Health Organization in 2001, the PQP provides a stringent, straightforward way to validate the quality of generic medicines and formulations. It is relied upon by United Nations-based and several external medicines procurement bodies, and has been critically important in scaling up treatment. Initially focussing on medicines for HIV, tuberculosis and malaria, the PQP has been expanding to new disease areas and medical technologies.

THE TRADE-RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS AGREEMENT (TRIPS): Administered by the World Trade Organization, TRIPS sets out minimum standards for the protection of several forms of IP that all World Trade Organization member countries need to implement. TRIPS also contains several important flexibilities to preserve the rights of nations to protect the public interest.

TRIPLE THERAPY: The use of three different ARVs, of at least two different classes, in a treatment regimen in order to more effectively fight the virus. Different classes of ARVs act to inhibit different stages of the virus' life cycle. See also HAART, above.

TRIPS-PLUS/TRIPS+: These are measures that require more stringent IP standards than those contained in TRIPS or that limit flexibilities inherent in TRIPS. They are often contained in bilateral or regional trade agreements, and are a matter of concern for public health advocates.

URUGUAY ROUND: A round of multilateral trade negotiations that began in Punta del Este, Uruguay in 1986 and concluded in Marrakesh in 1994 with an agreement to establish the World Trade Organization on 1 January 1995.

WORLD HEALTH ASSEMBLY (WHA): Attended by health ministers from World Health Organization member states, the WHA is the most important World Health Organization governing body, setting the direction and priorities for the organisation at its annual meeting.

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CHAPTER 2

TURNING THE TIDE: THE WTO DOHA DECLARATION ON TRIPS & PUBLIC HEALTH

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- Colombia (7 August 2009)
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- Croatia (6 December 2010)
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- Egypt (18 April 2008)
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- Honduras (16 December 2011)
- Hong Kong, China (27 November 2007)
- Iceland (12 October 2015)
- India (26 March 2007)
- Indonesia (20 October 2011)
- Israel (10 August 2007)
- Japan (31 August 2007)
- Jordan (6 August 2008)
- Kenya (21 July 2015)
- Korea, Republic of (24 January 2007)
- Lao People’s Democratic Republic (29 September 2015)
- Macau, China (16 June 2009)
- Mauritius (16 April 2008)
- Mexico (23 May 2008)
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- Montenegro (9 September 2013)
- Morocco (2 December 2008)
- New Zealand (21 October 2011)
- Nicaragua (25 January 2010)
- Norway (5 February 2007)
- Pakistan (8 February 2010)
- Panama (24 November 2011)
- Philippines (30 March 2007)
- Rwanda (12 December 2011)
- Saint Kitts and Nevis (27 July 2015)
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- CHAPTER 3**
FROM DECLARATION TO APPLICATION: THE PRACTICAL USE OF THE DOHA DECLARATION SINCE 2001
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CHAPTER 6 FIXING THE BROKEN R&D SYSTEM: ENSURING ESSENTIAL INNOVATION AND ACCESS TO MEDICINES FOR ALL

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CHAPTER 7

RESTORING THE BALANCE: ACCESS TO ESSENTIAL MEDICINES IN A POST-TRIPS WORLD

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Millions of people around the world do not have access to the medicines they need to treat disease or alleviate suffering. Strict patent regimes introduced following the establishment of the World Trade Organization in 1995 interfere with widespread access to medicines by creating monopolies that keep medicines prices well out of reach for many.

The AIDS crisis in the late nineties brought access to medicines challenges to the public's attention, when millions of people in developing countries died from an illness for which medicines existed, but were not available or affordable. Faced with an unprecedented health crisis—8,000 people dying daily—the public health community launched an unprecedented global effort that eventually resulted in the large-scale availability of low-priced generic HIV medicines.

But now, high prices of new medicines—for example, for cancer, tuberculosis and hepatitis C—are limiting access to treatment in low-, middle- and high-income countries alike. Patent-based monopolies affect almost all medicines developed since 1995 in most countries, and global health policy is now at a critical juncture if the world is to avoid new access to medicines crises. This book discusses lessons learned from the HIV/AIDS crisis, and asks whether actions taken to extend access and save lives are exclusive to HIV or can be applied more broadly to new global access challenges.

“Ellen 't Hoen is a towering figure in the movement for access to medicines, and this book represents an outstanding, sorely-needed, impressively comprehensive overview of the dysfunctional system which creates deadly monopolies on essential, life-saving drugs.

Truly indispensable.”

– **Dylan Mohan Gray**, *Director of internationally-acclaimed 2013 film on access to medicines, Fire in the Blood*

“This is the definitive account of one of the most important social justice struggles of our times—by someone who not only knows it, but helped make it. Accessible, accurate and up-to-date, this book is a must-read for anyone interested in health policy, global justice, or global governance.”

– **Amy Kapczynski**, *Professor of Law at Yale Law School and Faculty Director of the Global Health Justice Partnership*