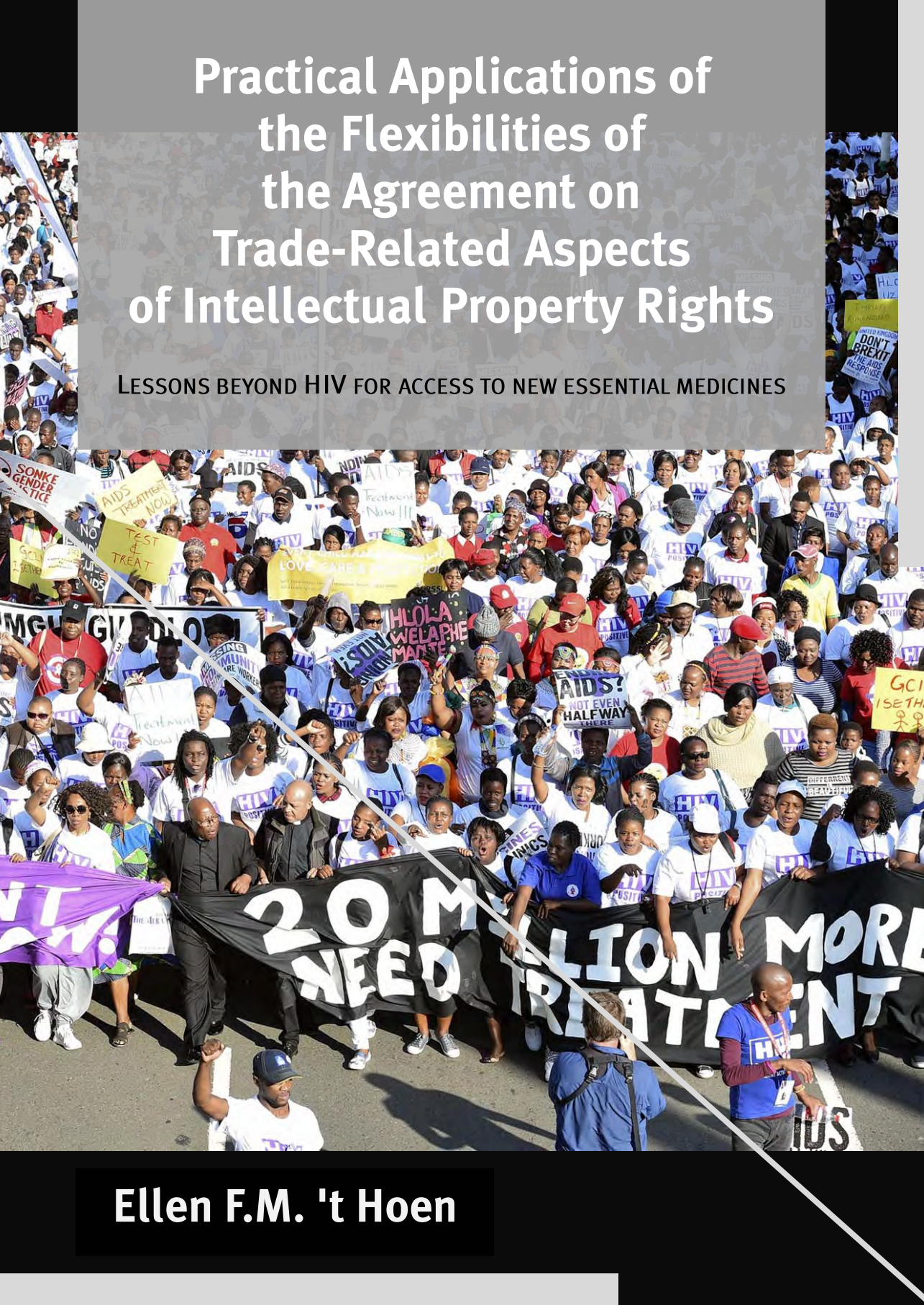


Practical Applications of the Flexibilities of the Agreement on Trade-Related Aspects of Intellectual Property Rights

LESSONS BEYOND HIV FOR ACCESS TO NEW ESSENTIAL MEDICINES

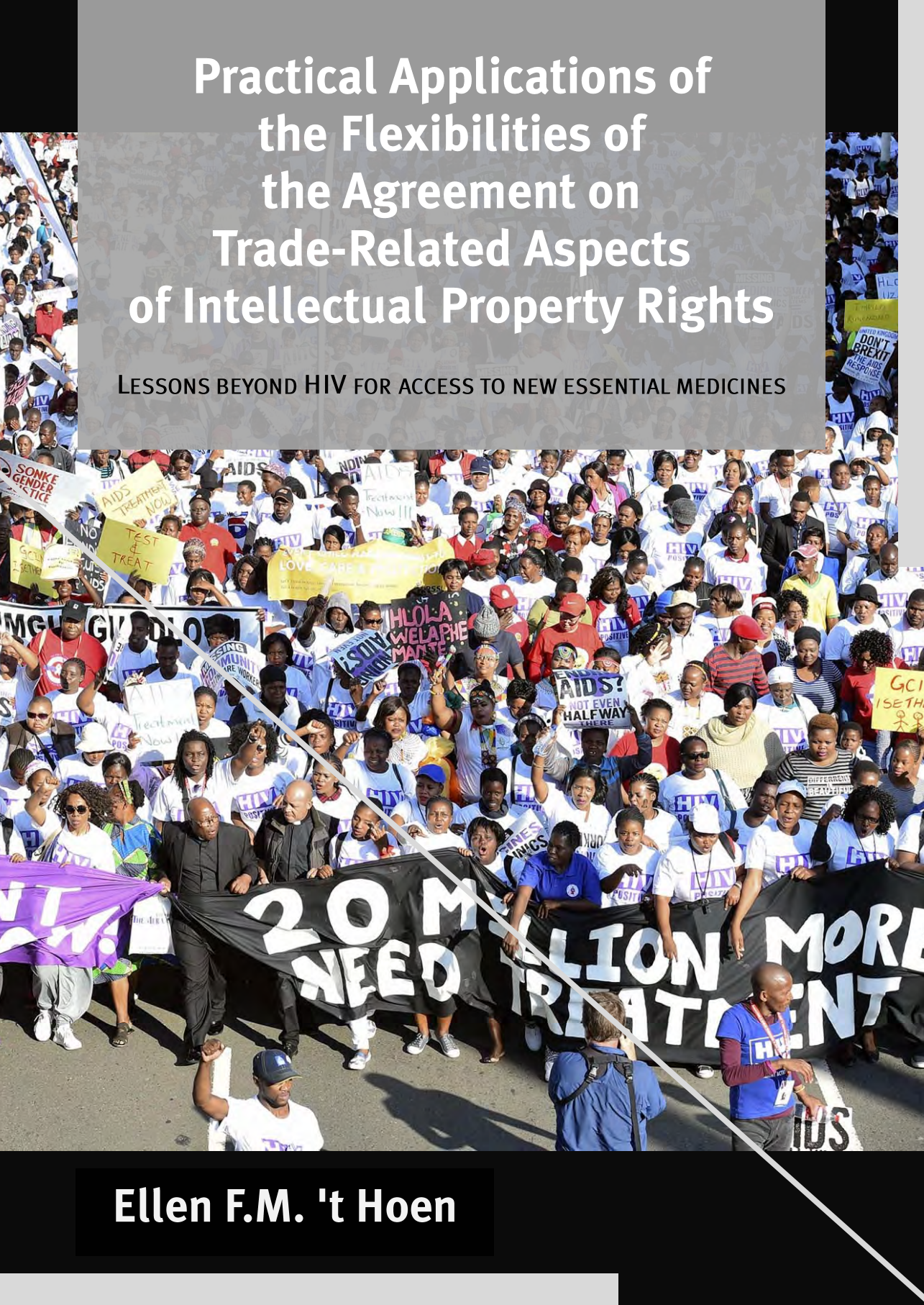
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Ellen F.M. 't Hoen

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Doctoral Dissertation, University of Groningen, The Netherlands

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university of
 groningen

Practical Applications of the Flexibilities of the Agreement on Trade-Related Aspects of Intellectual Property Rights

Lessons beyond HIV for access to new essential medicines

PhD thesis

to obtain the degree of PhD
at the University of Groningen
on the authority of
the Rector Magnificus Prof. E. Sterken
and in accordance with the decision
by the College of Deans.

This thesis will be defended in public on
Monday 9 April 2018 at 12.45 hours

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Introduction

The HIV/AIDS crisis of the late nineties, and the lack of affordable antiretroviral medicines (ARVs) in low and middle-income countries, showed that the pharmaceutical patent system was out of balance. The public health impact was staggering: 40 million people were infected with HIV in the developing world; 24.5 million of them lived in sub-Saharan Africa¹—and only one in a thousand had access to antiretroviral medicines (ARVs). In the developing world, every day over 8,000 people died of HIV/AIDS.

In 1996, effective ARVs had become available in high-income countries. However, these ARVs were not, or very sparsely, available in developing countries, and then only at very high prices from patent holding companies.² Even when low priced ARVs became available from Indian generic companies in the late nineties, many people living with HIV could not access them. In many countries, medicines patents restricted procurement agencies such as UNICEF, the International Dispensary Association (IDA), and non-governmental organisations (NGOs) such as Médecins sans Frontières (MSF) from distributing generic ARVs. Developing countries that tried to improve access to lower priced ARVs and or generic ARVs were confronted with trade retaliation by high-income nations, or legal actions by patent holding companies.^{3 4}

The HIV/AIDS crisis brought the international community together in formulating a response to facilitate access to diagnostics, medicines and other tools needed for prevention, treatment, and care for people living with HIV. The clear need to make treatments available on a large scale drove important policy processes at the international level, leading to greater flexibility in the implementation of intellectual property law related to medicines, changes to the World Health Organization (WHO) Model List of Essential Medicines, and new global approaches to assuring the quality of medicines that were needed to treat HIV/AIDS. Countries, together with international organisations, also established new international health funding mechanisms, such as the Global Fund to fight AIDS, Tuberculosis (TB) and Malaria, the United States President's Emergency Plan for AIDS Relief (PEPFAR), and UNITAID.⁵ As a result, by 2016 19.5 million of the

36.7 million people living with HIV had access to ARVs.⁶ The scale up of ARV treatment between 2005-2016 has led to a 48% decline in AIDS-related deaths.⁷ This progress in access to HIV treatment would not have been possible without the availability of low-priced generic medicines.

This thesis describes the solutions that the international community has developed to overcome intellectual property barriers to produce and disseminate generic medicines for the treatment of HIV/AIDS; and aims to respond to the question whether the solutions developed to address the HIV/AIDS crisis can also be deployed to improve access to other, new and expensive essential medicines, for example, those needed to provide treatment for non-communicable diseases (NCDs) such as cancer, diabetes and cardiovascular disease.

The research question of this thesis is:

Can intellectual property solutions developed to address the HIV/AIDS crisis also be deployed to increase access to other, new and expensive essential medicines?

I. Data sources and methods

This thesis presents the results of an interdisciplinary research project combining law and health science. Much of the data presented in this thesis, including historical data and political analyses, were collected over a period of seventeen years while working on advancing access to essential medicines for non-governmental organisations, governments, and the United Nations, often in settings that allowed for direct observation of and participation in international policy and legal processes.⁸ The selection of the research subjects was largely driven by the need to understand problems related to IP and access to medicines, and formulate practical legal and policy solutions. This thesis uses the so-called 'AAAQ' human rights framework, which identifies availability, accessibility, acceptability and quality as essential elements of the right to health, of which access to essential medicines is an integral part.⁹ While legal research is at the heart of the research project, the investigations from the health science perspective significantly contributed to the overall research, and thus were instrumental in identifying legal and policy insights for effective access to medicines.

II. Research questions

The thesis particularly aims to answer the overarching question:

Can intellectual property solutions developed to address the HIV/AIDS crisis also be deployed to increase access to other, new and expensive essential medicines?

This question is particularly pertinent in the context of expanding treatment to non-communicable diseases,¹⁰ and infectious diseases beyond HIV, TB and malaria, which require access to expensive and patented new essential medicines, such as hepatitis C.^{11 12}

The overall research question can be studied through five more specific research questions. These are systematically addressed in chapters 2-7, using the human rights framework for essential medicines that describes States as primary duty holders to ensure that essential medicines are available, accessible, acceptable and of good quality ('AAAQ' framework).¹³ Each chapter examines a different piece of the international response to the HIV crises: legal and policy developments at the international level, the use of those legal and policy changes at the national level, developments to ensure medicine quality, and access to data on medicines. Finally, this thesis ties all these pieces together and analyses possible public health approaches to pharmaceutical innovation with the aim of proposing approaches to innovation that avoid the development of unaffordable essential medicines in the future.

Those five research questions are:

II. a. How did HIV/AIDS lead to changes in intellectual property law and policy?

The availability of low-priced generic medicines is a cornerstone of policies designed to secure access to essential medicines. Intellectual property protection of medicines can impede access to lower priced generic medicines. The World Trade Organization Doha Declaration on TRIPS and Public Health (Doha Declaration) was adopted in 2001 to rebalance the rights of patent holders with the rights and duties of countries to protect public health and in particular to promote access to medicines for all.¹⁴ The Doha Declaration describes practical legal tools countries can use, known as TRIPS Flexibilities, and signalled international political support to take

measures to overcome patent barriers that impeded access to medicines. Chapter 2 describes the legal and policy developments that drove the changes in the approach to IP and public health.

II. b. How did the UN guarantee the quality of generic medicines for HIV?

Quality assurance of medicines is an inherent part of availability and accessibility of medicines. ARVs that were produced and that countries were willing to purchase could not be made available by the UN and other organisations when the quality of the medicines was unknown. The use of ARVs of unknown quality can also increase the risk of accelerating the development of resistance to HIV treatments, ultimately leading to a situation where the medical profession runs out of treatment options. Quality assurance of medicines, in accordance with international standards, therefore became a requirement of large donors of treatment programs such as the Global Fund for AIDS, TB and malaria.¹⁵ For this reason lifting intellectual property barriers to accessing medicines alone was not sufficient to ensure availability of generic antiretroviral medicines. Quality assurance of the products was a second and crucial condition for the large-scale supply and procurement of generic ARVs.

Chapter 3 addresses the question: How did the United Nations (UN) guarantee the quality of generic medicines for HIV? It examines the developments that led to the establishment of the WHO Prequalification of Medicines Program (PQP) as well as the achievements of the programme.

II.c. To what extent have governments used the TRIPS flexibilities in practice to access lower priced medicines?

When patents form a barrier to the procurement and use of lower priced generic medicines, the implementation and use of TRIPS flexibilities may be required to produce and access these medicines. Chapter 4 studies the question to what extent governments have used the TRIPS flexibilities in practice to access lower priced medicines. The purpose of this chapter is to document the actual use of TRIPS flexibilities by countries in promoting access to medicines during 2001 – 2016 specifically in the procurement of medicines. The chapter offers a more comprehensive overview of the use of TRIPS flexibilities than has previously been reported in the literature.¹⁶

II. d. How does data exclusivity form a barrier to the use of TRIPS flexibilities?

Data exclusivity can create additional hurdles, beyond patents, to access to medicines. In particular, it may hamper the effective use of TRIPS flexibilities which, as is shown in chapter 4, have been important in increasing access to HIV medicines. Data exclusivity prohibits a medicines regulatory agency from registering a generic equivalent product (to an originator product) using the clinical studies submitted by the originator, for a certain period of time. This implies that during this period generic applicants have to provide their own clinical efficacy and safety data. Doing so creates a serious ethical issue because it would require a placebo-controlled drug trial and thus withholding the proven effective treatment from certain patients; in reality such “repeat” studies are never approved. As a result, data exclusivity can be a strong barrier to the effective use of TRIPS flexibilities. Chapter 5 examines how data exclusivity is regulated in the European Union (EU), how it restricts the effective use of TRIPS flexibilities, specifically compulsory licensing, and what can be done about it.

II. e. How to achieve a public health approach to innovation and access?

A public health approach to innovation of and access to new medicines assures that pharmaceutical research and development (R&D) priorities match health needs, that new medicines are adapted and available to the populations who need them, and that the new products are priced at a level the population can afford. A public health approach to R&D is different from a commercial approach to R&D, which focuses on developing products with the greatest return on investment. Chapter 6 addresses the question how to achieve a public health approach to pharmaceutical innovation. It describes the shortcomings of innovation incentive mechanisms based on market exclusivity (high prices), and concludes with recommendations for alternative priority setting and financing models for pharmaceutical innovation.

II. f. Summary Conclusion and Reflection on the Future

The final chapter (Chapter 7) presents a general discussion of the findings and recommendations, and elaborates on the overarching question: will the practical application of TRIPS flexibilities remain confined to HIV or can

the TRIPS flexibilities serve to increase access to pharmaceutical treatment for a wider range of diseases, as part of the progressive realisation of the human right to health? It also offers further reflections on the future of pharmaceutical innovation and access, and the need for further research.

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TRIPS, Pharmaceutical Patents, and Access to Essential Medicines: A Long way from Seattle to Doha

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Introduction

Infectious diseases kill over 10 million people each year, more than 90 percent of whom are in the developing world.¹ The leading causes of illness and death in Africa, Asia, and South America—regions that account for four-fifths of the world's population—are HIV/AIDS, respiratory infections, malaria, and tuberculosis.

In particular, the magnitude of the AIDS crisis has drawn attention to the fact that millions of people in the developing world do not have access to the medicines that are needed to treat disease or alleviate suffering. Each day, close to eight thousand people die of AIDS in the developing world.² The reasons for the lack of access to essential medicines are manifold, but in many cases the high prices of drugs are a barrier to needed treatments. Prohibitive drug prices are often the result of strong intellectual property protection. Governments in developing countries that attempt to bring the price of medicines down have come under pressure from industrialized countries and the multinational pharmaceutical industry.

The World Trade Organization ("WTO") Trade-Related Aspects of Intellectual Property Rights Agreement ("TRIPS" or "Agreement"), which sets out the minimum standards for the protection of intellectual property, including patents for pharmaceuticals, has come under fierce criticism because of the effects that increased levels of patent protection will have on

drug prices. While TRIPS does offer safeguards to remedy negative effects of patent protection or patent abuse, in practice it is unclear whether and how countries can make use of these safeguards when patents increasingly present barriers to medicine access.

The Fourth WTO Ministerial Conference, held in 2001 in Doha, Qatar, adopted a Declaration on TRIPS and Public Health (“Doha Declaration” or “Declaration”) which affirmed the sovereign right of governments to take measures to protect public health. Public health advocates welcomed the Doha Declaration as an important achievement because it gave primacy to public health over private intellectual property, and clarified WTO Members’ rights to use TRIPS safeguards. Although the Doha Declaration broke new ground in guaranteeing Members’ access to medical products, it did not solve all of the problems associated with intellectual property protection and public health.

1 The access problem and intellectual property

A number of new medicines that are vital for the survival of millions are already too costly for the vast majority of people in poor countries. In addition, investment in research and development (“R&D”) towards the health needs of people in developing countries has almost come to a standstill. Developing countries, where three-quarters of the world population lives, account for less than 10 percent of the global pharmaceutical market. The implementation of TRIPS is expected to have a further upward effect on drug prices, while increased R&D investment, despite higher levels of intellectual property protection, is not expected.³

One-third of the world population lacks access to the most basic essential drugs and, in the poorest parts of Africa and Asia, this figure climbs to one-half. Access to treatment for diseases in developing countries is problematic either because the medicines are unaffordable, have become ineffective due to resistance, or are not sufficiently adapted to specific local conditions and constraints.

Many factors contribute to the problem of limited access to essential medicines. Unavailability can be caused by logistical supply and storage problems, substandard drug quality, inappropriate selection of drugs, wasteful prescription and inappropriate use, inadequate production, and prohibitive prices. Despite the enormous burden of disease, drug discovery and development targeted at infectious and parasitic diseases in poor countries has virtually ground to a standstill because drug companies in developed and developing nations simply cannot recoup the cost of R&D

for products to treat diseases that abound in developing countries.⁴ Of the 1,223 new drugs approved between 1975 and 1997, approximately 1 percent (13 drugs) specifically treat tropical diseases.⁵

TRIPS sets out minimum standards and requirements for the protection of intellectual property rights, including trademarks, copyrights, and patents. The implementation of TRIPS, initially scheduled for 2006 by all WTO Members, is expected to impact the possibility of obtaining new essential medicines at affordable prices.

Médecins sans Frontières (“MSF”), together with other non-governmental organizations (“NGOs”), formulated the following concerns related to TRIPS:

Increased patent protection leads to higher drug prices.⁶ The number of new essential drugs under patent protection will increase, but the drugs will remain out of reach to people in developing countries because of high prices. As a result, the access gap between developed and developing countries will widen.

Enforcement of WTO rules will have a negative effect on local manufacturing capacity and will remove a source of generic, innovative, quality drugs on which developing countries depend.

It is unlikely that TRIPS will encourage adequate R&D in developing countries for diseases such as malaria and tuberculosis, because poor countries often do not provide sufficient profit potential to motivate R&D investment by the pharmaceutical industry.

Developing countries are under pressure from industrialized countries and the pharmaceutical industry to implement patent legislation that goes beyond the obligations of TRIPS. This is often referred to as “TRIPS plus.” TRIPS plus is a non-technical term which refers to efforts to extend patent life beyond the twenty-year TRIPS minimum, to tighten patent protection, to limit compulsory licensing in ways not required by TRIPS, or to limit exceptions which facilitate prompt introduction of generics.⁷

Industrialized countries and World Intellectual Property Organization (“WIPO”) offer expert assistance to help countries become TRIPS-compliant. This technical assistance, however, does not take into account the health needs of the populations of developing countries. Both of these institutions are under strong pressure to advance the interests of large companies that own patents and other intellectual property rights.

2. Important developments in the debate on access to drugs and intellectual property

A number of factors have shaped the debate on TRIPS and access to medicines, directly or indirectly impacting the content of the Doha Declaration.

A. Big Pharma vs. Nelson Mandela: Trade dispute in South Africa

In February 1998, the South African Pharmaceutical Manufacturers Association and forty (later thirty-nine, as a result of a merger) mostly multinational pharmaceutical manufacturers brought suit against the government of South Africa, alleging that the Medicines and Related Substances Control Amendment Act, No. 90 of 1997 (“Amendment Act”) violated TRIPS and the South African constitution.⁸

The Amendment Act introduces a legal framework to increase the availability of affordable medicines in South Africa. Provisions included in the Amendment Act are generic substitution of off-patent medicines, transparent pricing for all medicines, and the parallel importation of patented medicines.⁹

At the start of the litigation, the drug companies could rely on the support of their home governments. For its part, the US had put pressure on South Africa by withholding trade benefits and threatening further trade sanctions, aiming to force the South African government to repeal the Amendment Act.¹⁰ In 1998, the European Commission joined the US in pressuring South Africa to repeal the legislation.¹¹ AIDS activists effectively highlighted these policies, profoundly embarrassing then-presidential candidate Al Gore. Confronted at election campaign rallies about his personal involvement in the dispute, demonstrators accused him of killing babies in Africa.¹² As a result of increasing public pressure, the US changed its policies at the end of 1999. By the time the case finally reached the courtroom in May 2000, the drug companies could no longer count on the support of their home governments.

Demonstrators in major cities asked the companies to drop the case; several governments and parliaments around the world, including the European Parliament, demanded that the companies withdraw from the case. The legal action turned into a public relations disaster for the drug companies.¹³

During the course of the trial it became clear that the most contentious section of the Amendment Act was based on a draft legal text produced by

the WIPO Committee of Experts,¹⁴ a fact that made it difficult for the drug companies to maintain the position that the Amendment Act violated South Africa's obligations under international law. Eventually, the strong international public outrage over the companies' legal challenge of a developing country's medicines law and the companies' weak legal position caused the companies to unconditionally drop the case in April 2001.

The widely publicized South African court case brought two key issues out into the international arena. First, the interpretation of the flexibilities of TRIPS and their use for public health purposes needed clarification to ensure that developing countries could use its provisions without the threat of legal or political challenge. Second, it became clear that industrialized countries that exercised trade pressures to defend the interest of their multinational industries could no longer exert pressure without repercussions at home.

B. US vs. Brazil: The Brazilian AIDS program

Since the mid-1990s, Brazil has offered comprehensive AIDS care, including universal access to antiretroviral ("ARV") treatment. An estimated 536,000 people are infected with HIV in Brazil, with 203,353 cases of AIDS reported to the Ministry of Health from 1980 through December 2000. In 2001, 105,000 people with HIV/AIDS received ARV treatment. The Brazilian AIDS program has reduced AIDS-related mortality by more than 50 percent between 1996 and 1999.¹⁵ In two years, Brazil saved \$472 million in hospital costs and treatment costs for AIDS-related infections.

At the core of the success of Brazil's AIDS program is the ability to produce medicines locally. In Brazil, the price of AIDS drugs fell by 82 percent over five years as a result of generic competition.¹⁶ The price of drugs that had no generic competitor remained relatively stable, falling only 9 percent over the same period. Brazil has also been able to negotiate lower prices for patented drugs by using the threat of production under a compulsory license.¹⁷ Article 68 of the Brazilian patent law allows for compulsory licensing, which allows a patent to be used without the consent of the patent holder.¹⁸ The Brazil AIDS program serves as a model for some developing countries that are able to produce medicines locally, and Brazil has offered a cooperation agreement, including technology transfer, to developing countries for the production of generic ARV drugs.¹⁹

In February 2001, the US took action against Brazil at the WTO Dispute Settlement Body ("DSB") over Article 68 of the Brazilian intellectual

property law. Under that provision, Brazil requires holders of Brazilian patents to manufacture the product in question within Brazil—a so-called “local working” requirement. If the company does not fulfill this requirement, the patent shall be subject to compulsory licensing after three years, unless the patent holder can show that it is not economically feasible to produce in Brazil or can otherwise show that the requirement to produce locally is not reasonable. If the company is allowed to work its patent by importation instead of manufacturing in Brazil, parallel import by others will be permitted.

The US argued that the Brazilian law discriminated against US owners of Brazilian patents and that it curtailed patent holders’ rights. The US claimed that the Brazilian law violated Article 27.1 and Article 28.1 of TRIPS.²⁰ Brazil argued that Article 68 was in line with the text and the spirit of TRIPS, including Article 5.4 of the Paris Convention, which allows for compulsory licensing if there is a failure to work a patent. Article 2.1 of TRIPS incorporates relevant articles of the Paris Convention.

The US action came under fierce pressure from the international NGO community, which feared it would have a detrimental effect on Brazil’s successful AIDS program.²¹ Brazil has been vocal internationally in the debates on access to medicines, and on several occasions, including the G-8, the Roundtable of the European Commission, and WHO meetings, Brazil has offered support to developing countries to help them increase manufacturing capacity by transferring technology and know-how. NGOs feared that the US action could have a negative effect on other countries’ ability to accept Brazil’s offer of assistance. On June 25, 2001, in a joint statement with Brazil, the US announced that it would withdraw the WTO panel against Brazil.²²

C. *The role of NGOs*

NGOs have played a key role in drawing attention to provisions of TRIPS that can be used to increase access to medicines. One such provision pertains to compulsory licensing, which enables a competent government authority to license the use of an invention to a third-party or government agency without the consent of the patent-holder. The patent holder, however, according to Article 31 of TRIPS, retains intellectual property rights and “shall be paid adequate remuneration” according to the circumstances of the case. The first international meeting specifically on the use of compulsory licensing to increase access to AIDS medicines took place in March 1999 at the Palais de Nations in Geneva and was organized

by Consumer Project on Technology, Health Action International, and MSF. Later that year, the same group of NGOs organized the Amsterdam Conference on Increasing Access to Essential Drugs in a Globalized Economy, which brought together 350 participants from 50 countries on the eve of the Seattle WTO ministerial conference. The statement drawn up at this conference ("Amsterdam Statement") focused on establishing a working group in the WTO on TRIPS and access to medicines, considering the impact of trade policies on people in developing and least-developed countries, and providing a public health framework for the interpretation of key features of WTO agreements. The working group was to address questions related to the use of compulsory licensing to increase access to medicines, mechanisms to allow production of medicines for export markets to a country with no or insufficient production capacity, patent barriers to research, and overly restrictive and anti-competitive interpretations of TRIPS rules regarding protections of health registration data. In addition, the working group was to examine "burden sharing" approaches for R&D that permit countries to consider a wider range of policy instruments to promote R&D and to consider the practical burdens on poor countries of administering patent systems. The Amsterdam Statement also urged national governments to develop new and innovative mechanisms to ensure funding for R&D for neglected diseases.

The Amsterdam Statement has served as a guide for the work of NGOs and other advocates on TRIPS and public health. Many international and national NGOs, such as the OXFAM campaign, "Cut the Cost," the South African Treatment Action Campaign, and Act Up, are now involved in campaigning for access to medicines.

D. The WTO Ministerial 1999 in Seattle

Though public health and access to medicines did not form part of the official agenda in Seattle in the way it would two years later in Doha, the issue did receive attention for a number of reasons. First, in Seattle a Common Working Paper section on TRIPS contained the following proposal: "to issue . . . compulsory licenses for drugs appearing on the list of essential drugs of the World Health Organization."²³ Since only about 11 of the 306 products on the WHO Model List of Essential Drugs are patented drugs in certain countries,²⁴ this proposal could have limited the use of compulsory licensing, rather than making sure it became a useful tool to overcome access barriers, such as prohibitive pricing, caused by patent abuse.

Then-US President Clinton chose Seattle as the venue to declare a change in US policy with regard to intellectual property rights and access to medicines. The US government had come under fierce attack from AIDS activists because of its policies in South Africa. Under the new policy, the US Trade Representative and the Department of Health and Human Services would together establish a process to analyze health issues that arise in the application of US trade-related intellectual property law and policy. In his speech, President Clinton referred specifically to the situation in South Africa and the HIV/AIDS crisis, saying that “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.”²⁵

In May 2000, President Clinton confirmed the change in US policy by issuing an Executive Order on Access to HIV/AIDS Pharmaceuticals and Medical Technologies, supporting the use of compulsory licenses to increase access to HIV/AIDS medication in sub-Saharan Africa.²⁶ 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 WTO conference in Seattle.²⁷ However, outside the WTO, the debate on access to medicines, TRIPS, and compulsory licensing became more intense.

E. Changing attitudes among global players

A number of international institutions and UN agencies contributed to the debate on access to medicines and looked into the consequences of stronger intellectual property protection as a result of TRIPS for developing countries.

I. The World Health Organization

The public health community first raised concerns about the consequences of globalization and international trade agreements with respect to drug access during the 1996 World Health Assembly. A resolution on the Revised Drug Strategy (“RDS”) set out the WHO’s medicines policy.²⁸ The WHO resolution on the RDS requested the WHO in paragraph 2(10) “to report on the impact of the work of the World Trade Organization (WTO) with respect to national drug policies and essential drugs and make recommendations for collaboration between WTO and WHO, as appropriate.” This resolution gave the WHO the mandate to publish, in

1998, the first guide with recommendations to Member States for implementing TRIPS while limiting the negative effects of higher levels of patent protection on drug availability.²⁹ The US and a number of European countries unsuccessfully pressured the WHO in an attempt to prevent publication of the guide.³⁰

At that time, the WHO's involvement in trade issues was highly controversial. The emphasis on public health needs versus trade interest was seen as a threat to the commercial sector of the industrialized world. For example, in 1998, in response to the draft World Health Assembly's resolution on the RDS and in reference to "considerable concern among the pharmaceutical industry," the European Directorate General for Trade ("DG Trade") of the European Commission concluded: "No priority should be given to health over intellectual property considerations."³¹

However, subsequent resolutions of the World Health Assembly have strengthened the WHO's mandate in the trade arena. In 2001, the World Health Assembly adopted two resolutions in particular that had a bearing on the debate over TRIPS.³² The resolutions addressed 1) the need to strengthen policies to increase the availability of generic drugs, and 2) the need to evaluate the impact of TRIPS on access to drugs, local manufacturing capacity, and the development of new drugs. As a result, the WHO's work program on pharmaceuticals and trade now includes the provision of policy guidance and information on intellectual property and health to countries for monitoring and analyzing the effects of TRIPS on access to medicines.³³

II. The UN Sub-Commission for the Protection and Promotion of Human Rights

The UN Sub-Commission for the Protection and Promotion of Human Rights passed a resolution, pointing out the negative consequences for human rights to food, health, and self-determination if TRIPS is implemented in its current form. The resolution was an initial effort to monitor the implications of TRIPS on human rights concerns. Reminding governments of the primacy of human rights obligations over economic policies and programs, the resolution states that there are "apparent conflicts between the intellectual property rights regime embodied in TRIPS, on the one hand, and international human rights law, on the other."³⁴ Referring specifically to pharmaceutical patents, the resolution stresses the need for intellectual property rights to serve social welfare needs.

III. The United Nations Development Program

In 1999, the United Nations Development Program's ("UNDP's") Human Development Report made a plea for re-writing the rules of globalization to make them work "for people—not just profits."³⁵ The report, in particular, draws attention to the high cost of the patent system for developing countries compared to the unequal distribution of the system's benefits. 97 percent of the patents held worldwide are held by individuals and companies of industrialized countries, and 80 percent of the patents granted in developing countries belong to residents of industrial countries. UNDP called for a full and broad review of TRIPS and called upon countries not to create an unsustainable burden by adding new conditions to the intellectual property system. The report suggested that countries present frameworks for alternatives to the provisions of TRIPS and that the room for manoeuvring granted in TRIPS be respected in practice.

IV. The European Union

In February 2001, the EU adopted the Program for Action, a program which accelerates action on HIV/AIDS, malaria, and tuberculosis in the context of poverty reduction. The EU program recognized the potential problems of TRIPS and the need to rebalance its priorities. In addition, several European Parliament resolutions reflected a shift in support of a pro-public health approach to TRIPS.³⁶ As part of this approach, DG Trade changed its policy to acknowledge the concerns of developing countries. Reflecting this change, DG Trade dropped its objections to the use of compulsory licensing to overcome patent barriers to medicine access and became an advocate for a global tiered pricing system for pharmaceuticals.³⁷ These policy changes are in stark contrast to previous European Commission policies, which closely track the pharmaceutical industry's agenda.

V. Other Organizations

Other organizations, such as UNAIDS, the World Bank, the Group of 77, and regional organizations such as the Organization of African Unity, added their voice to the debate on TRIPS and access to medicines.

Unable to turn a deaf ear to the growing chorus of critics of TRIPS and its effects on access to medicines, the WTO changed course. In April 2001, when proposing a special TRIPS Council session on access to medicines,

Zimbabwe—chair of TRIPS Council—said that the WTO could no longer ignore the access to medicines issue, an issue that was being actively debated outside the WTO but not within it.³⁸ The voices had been heard; public health would be featured as a key subject at the Doha Conference.

3. A brief history of the Doha Declaration on TRIPS and Public Health

The Fourth Ministerial Conference of the WTO took place in Doha in 2001 and was a breakthrough in international discussions on TRIPS and access to medicines. The WTO Ministerial adopted a Declaration on TRIPS and Public Health, which put public health before commercial interests and offered much needed clarification in the field of TRIPS and public health.

A. The African proposal for a special TRIPS Council meeting in June

Zimbabwe's statement on behalf of the "African Group" about the need to confront the access to medicines issue initiated preparations for the Declaration. Just two months later, in June 2001, the TRIPS Council held its first session devoted to TRIPS and access to medicines. It was the first time that the TRIPS Council discussed intellectual property issues in the context of public health. At that meeting, the African Group proposed issuing separate declarations on access to medicines.³⁹ Referring to the devastating AIDS crisis in Africa and mounting public concern, Zimbabwe stated: "We propose that Members issue a special declaration on the TRIPS Agreement and access to medicines at the Ministerial Conference in Qatar, affirming that nothing in the TRIPS Agreement should prevent Members from taking measures to protect public health."⁴⁰

In September 2001, the TRIPS Council devoted another full day of discussion to the topic of access to medicines. At this meeting, the African Group, joined by nineteen other countries, presented a draft text for a ministerial declaration on TRIPS and Public Health. A comprehensive text, this proposal addressed political principles to ensure that TRIPS did not undermine the legitimate right of WTO Members to formulate their own public health policies. The text also provided practical clarifications for provisions related to compulsory licensing, parallel import, data protection, and production for export to a country with insufficient production capacity. In addition, the draft included a proposal for evaluating the effects of TRIPS on public health, with particular emphasis on access to medicines and R&D for the prevention and treatment of diseases predominantly affecting people in developing and least-developed countries.

At the meeting, the US, Japan, Switzerland, Australia, and Canada circulated an alternate draft, stressing the importance of intellectual property protection for R&D, arguing that intellectual property contributes to public health objectives globally. The text was aimed at limiting the flexibilities of TRIPS during crisis and emergency situations. The EU circulated its own draft, which proposed a solution to the problem of production for exports to fulfil a compulsory license in a country with insufficient or no production capacity by allowing production under the TRIPS Article 30 exception.

From the onset of the pre-Doha negotiations, the main point of contention was the text proposed by the developing countries: "Nothing in the TRIPS Agreement shall prevent Members from taking measures to protect public health."⁴¹ Some developed countries saw this wording as a new rule that would override the present rules of TRIPS, which do not allow for health exceptions that are inconsistent with TRIPS.⁴²

The text drafted by the chair of the WTO General Council, Mr. Stuart Harbinson, that was the basis for the negotiations in Doha left the issue unresolved and instead offered two options for Paragraph 4. The first option read:

Nothing in the TRIPS Agreement shall prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement shall be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to ensure 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.

Whereas the second option offered was:

We affirm a Member's ability to use, to the full, the provisions in the TRIPS Agreement which provide flexibility to address public health crises such as HIV/AIDS and other pandemics, and to that end, that a Member is able to take measures necessary to address these public health crises, in particular to secure affordable access to medicines. Further, we agree that this Declaration does not add to or diminish the rights and obligations of Members provided in the TRIPS Agreement. With a view to facilitating the use of this flexibility by providing greater certainty, we agree on the following clarifications.

In Doha, for three days the discussions on TRIPS and public health

dominated the trade talks. Early on in the meeting it became clear that a majority of Members preferred the first option of the Harbinson draft, making it the basis for further negotiation. The core supporters of the second option included the US, Japan, Australia, Switzerland, Canada, and Korea. The EU, at this stage, did not take a clear position and claimed it was playing the role of “honest broker.” After three days of negotiation among the participating Members, a compromise was reached. The compromise text, which resulted from negotiations primarily between Brazil and the US, read:

We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitments 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.⁴³

This text acknowledges the unmitigated right of countries to take measures to protect public health. Thus, if intellectual property rules should stand in the way of doing so (for example, in the case of high prices associated with patented medicines), countries are allowed to override the patent.

In Paragraph 5, the Declaration lays out the key measures and flexibilities within TRIPS that can be used to overcome intellectual property barriers to access to medicines. The discussions at Doha and the Doha Declaration itself make it unambiguously clear that the use of compulsory licenses is in no way confined to cases of emergency or urgency; in fact, the grounds for issuing a compulsory license are unlimited. Members who proposed language that would have limited measures like compulsory licensing to emergency situations, pandemics, or specified diseases such as HIV/AIDS were unsuccessful. In addition, the Declaration leaves Members free to determine for themselves what constitutes a national emergency or urgency, in which cases the procedure for issuing a compulsory license becomes easier and faster. The Declaration also resolves the question of whether TRIPS authorizes parallel trade once and for all by noting: “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.”⁴⁴

In addition, the Declaration grants least-developed country (“LDCs”) Members an extra ten-year extension—until 2016, instead of 2006—to the implementation deadline for pharmaceutical product patent protection.

The negotiating history illustrates that this outcome was not predetermined. Pre-Doha, the US proposed two operative paragraphs, which included this extension of transition periods until 2016 for patents on pharmaceutical products, as well as offering a moratorium on dispute settlement action to sub-Saharan African countries, which do not fall within the LDC grouping. The moratorium covered laws, regulations and other measures that improve access to patented medicines for HIV/AIDS and other pandemics. These proposals were viewed as a “divide and conquer” strategy employed by the US to break the cohesion of the developing countries⁴⁵ and the proposal for a moratorium on dispute settlement actions was rejected at Doha. The proposal to extend the deadlines for LDCs were accepted. The extended deadlines are important because they extend the timeframe (until 2016) in which countries may rethink the kind of pharmaceutical intellectual property law they want while still being able to import and produce generic medicines.

The Declaration also refers to the as-yet unfulfilled commitment of developed-country Members to provide incentives to their enterprises and institutions to promote technology transfer to LDCs pursuant to Article 66.2. The ten-year extension might be of limited value because only LDCs will be able to benefit from this provision. Of the 143 WTO members, only 30 are LDCs, representing 10 percent of the world’s population. The ten-year extension is also limited to Sections 5 (patents) and 7 (undisclosed information) of TRIPS; the extension does not apply to other provisions of the Agreement relevant to pharmaceuticals, notably Article 70 (“exclusive marketing rights”). Though there seemed to be an understanding among the negotiators in Doha that Paragraph 7 implied that LDCs are not required to provide “mail box” protection or “exclusive marketing rights,” this is not clear from the text of the declaration. Paragraph 7 of the declaration refers to pharmaceutical products, which means that LDCs still are under the obligation to provide process patents.

B. Other areas of debate

1. *Public Health*: Most of the language aimed at narrowing the scope of the Declaration to health crisis and pandemics⁴⁶ was replaced with language that referred generally to public health. Indeed, the title itself—Doha Declaration on Public Health— reflects this shift.

2. *Access for All*: Some countries objected to the text that countries have the right “to ensure access to medicines *for all*.”⁴⁷ In particular, Switzerland

objected to the wording, but had difficulty defending a position that advocated access to medicines for some but not for others.

3. *Scope:* A point of strong contention was how far-reaching the Declaration would be. Some WTO Members feared that the negotiations could lead to changes in TRIPS and wanted to include a confirmation that the Declaration was purely a clarifying exercise. They borrowed language from the WTO Dispute Settlement Process Rules to indicate that the Ministerial Declaration would have no formal legal effect to change the rights and obligations TRIPS established.

The text did not, however, make it into the final version of the Declaration. As a result, one could argue that the Declaration actually does go beyond clarifying the already existing rules. A Member can appeal to the Declaration and its negotiating history in the event that a Member's legislation, particularly relating to patents in the health field, is challenged on the grounds that it is incompatible with TRIPS.

C. Why Doha came to pass

Why was it possible to achieve a declaration on such a contentious issue considering that public health hardly played a part in the trade talks two years ago? Mike Moore, WTO Director-General, made it clear on the opening day of the conference that the TRIPS and health issue could be the deal-breaker for a new trade round. Observers point to a number of factors that contributed to the success of the negotiations.⁴⁸ First, the developing country Members were extremely well prepared and operated as one bloc. Second, the uncompromising positions of western countries such as the US and Canada were hard to maintain in light of the anthrax crisis and the threat that a shortage of Ciprofloxacin ("Cipro") might occur. Both the US and Canada rapidly expressed their willingness to set aside the patent held by the German company Bayer if other solutions could not be found.⁴⁹ The anthrax scare and the threatened shortage of Cipro forced all WTO Members to ask how much of a prisoner they want to be of their own patent systems. Third, a growing and active international NGO movement ensured the issue would be high profile, and that NGOs would monitor different countries' positions.

4. Drug industry response to the WTO Declaration on TRIPS and Public Health

The multinational pharmaceutical industry argued from the beginning that a declaration was not necessary because: a) patents are not a problem,⁵⁰ and b) weakening patent protection would have devastating effects on the R&D capabilities of the research-based industry. Although the International Federation of Pharmaceutical Manufacturers (“IFPMA”) officially welcomed the Declaration on TRIPS and Public Health, individuals in the industry expressed their concerns. Indeed, the US pharmaceutical companies asked the USTR to re-open the negotiations even after an agreement on the text of the Declaration was reached.

For more than two years, IFPMA has warned against the dangers of compulsory licensing—ever since NGOs started to propose compulsory licensing systems to overcome patent barriers. IFPMA’s position has not changed. “[C]ompulsory licensing is a threat to good public health by denying patients around the world the future benefits of R&D capabilities of the research-based industry from which new therapies come.”⁵¹

The generic drug industry welcomed the Declaration, in particular the freedom of countries to decide the grounds for compulsory licensing. The generic drug industry did express concern about possible unilateral pressure to influence countries not to make full use of the Declaration. The industry suggested that the advanced WTO Members should commit to the Declaration in practice by refraining from exerting unilateral pressure. The generic drug contingent expressed disappointment that there was no resolution of the issue that arises when a country with limited production capacity that issues a compulsory license for a medicine cannot find an efficient, affordable, and reliable source of medicines, due to TRIPS restrictions on production and export of medicines. After 2005, production of affordable medicine will increasingly become dependent on compulsory licensing. However production under a compulsory license is restricted to production “predominantly for the supply of the domestic market.”⁵² The problem is not the compulsory license itself, but the need to allow exports from a country where the drug is under patent to a country that has issued the compulsory license.

The generic drug industry expressed further disappointment that the Declaration did not offer an interpretation of the data protection issue addressed in Article 39.3 of TRIPS.⁵³ The concern here is that an overly restrictive interpretation of Article 39.3 will lead to delays in introduction of generic medicines, may provide exclusive marketing rights beyond the

patent protection term and increase barriers to the registration of generic medicines including those produced under a compulsory license.

5. The post-Doha agenda

A key issue that remained unresolved in Doha is how to ensure that production for export to a country that has issued a compulsory license, but does not have manufacturing capacity, can take place within a country that provides pharmaceutical patents. Since Article 31(f) of TRIPS limits compulsory licensing to uses which are predominantly for the supply of the domestic market, further clarification is necessary to ensure that countries without production capacity can make use of compulsory licensing provisions to the same extent that countries with manufacturing capacity can use these provisions. The Doha Declaration acknowledges the problem in Paragraph 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.

It is increasingly urgent that the production for export issue be resolved. Implementation deadlines for some important producing countries are quickly approaching, thus further limiting the possibilities of producing generic versions of medicines that are protected by patent elsewhere.

Another flaw of the Doha Declaration is that it does not resolve the problem of production for export from markets that provide patents to countries that do not grant pharmaceutical patents (and subsequently do not grant compulsory licenses). This is of particular importance now that the least-developed WTO Members can delay the granting of pharmaceutical product patents until 2016. These countries need to have access to sources of affordable medicines, which threaten to dry up as the 2005 deadline for TRIPS implementation is nearing for producing countries.

Another challenge will be to find ways to make the Doha Declaration on TRIPS and Public Health operational at the regional and national levels. A classic example is the Bangui Agreement, the regional intellectual property agreement for francophone Africa, which was adopted in 1977 and revised in 1999 to ensure TRIPS compatibility, but includes typical

TRIPS plus provisions that are not in line with the Doha Declaration.

At the national level, countries should be encouraged to make full use of the Doha Declaration in the process of adjusting national intellectual property laws to become compliant with TRIPS. This will require substantial advice and technical assistance from institutions like WIPO and WTO. While the spirit of the Doha Declaration is to go slowly and to tailor intellectual property laws to national needs, the practice has been to encourage developing countries to go beyond the minimum requirements and speed up the process to become TRIPS-compliant. It will require a “culture change” at WIPO and WTO to adjust the type of technical assistance to developing countries’ needs. In addition to increasing their interaction with countries, WIPO and WTO will have to increase their level of collaboration with the public health community, including the WHO, which has become heavily involved in trade discussions as a result of the process that led to the Doha Declaration.

6. Conclusion

The very fact that public health and access to medicines have been singled out as major issues needing special attention in TRIPS implementation indicates that health care and health care products need to be treated differently from other products. By giving countries broad discretion in deciding how to counter the negative effects of TRIPS, the Doha Declaration may stand for the proposition that public health concerns outweigh full protection of intellectual property.

In fact, the Doha Declaration takes a large step toward ensuring that intellectual property protection actually serves the public interest, an interest broader than that of the commercial sector. In the years to come, it will be important to scrutinize closely whether the results of intellectual property protection serve the poor as well as the rich. The Doha Declaration lays out the options countries have available when prices of existing patented drugs are too high for their populations. But Doha did not solve every problem: the lack of R&D investment in new drugs for the particular health needs of the poor remains to be addressed.⁵⁴

In the Doha process, developing countries and NGOs pointed to commercial and public sector neglect of the R&D needs of developing countries. Recent studies claim that the R&D cost of a commercial drug company per new pharmaceutical product is \$802 million.⁵⁵ The Global Alliance for Tuberculosis Drug Development, a non-profit entity for R&D of tuberculosis drugs, estimated that the total R&D cost for a new

tuberculosis drug, including the cost of failure, is between \$115 million and \$240 million.⁵⁶ These high R&D costs claimed by the commercial pharmaceutical sector pose some key questions that need to be resolved. Is the present system for funding R&D the most efficient, and is it sufficient to rely on the present intellectual property systems to fuel innovation? Clearly, in the area of neglected diseases, the answer is no.

In an increasingly globalized economy, additional international mechanisms need to be developed to address health needs in developing countries. MSF and others have proposed a radical shift in the way health R&D is financed in particular for drugs for neglected diseases. For example, health R&D could be financed based on burden sharing between countries, or obligating companies to complete essential medical research. Such a proposal might be incorporated into an international treaty on essential health R&D. In the end, the challenge for the coming years will be to encourage essential health R&D not only for the benefit of some, but for the benefit of all.

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Driving a decade of change: HIV/AIDS, patents and access to medicines for all

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Abstract

Since 2000, access to antiretroviral drugs to treat HIV infection has dramatically increased to reach more than five million people in developing countries. Essential to this achievement was the dramatic reduction in antiretroviral prices, a result of global political mobilization that cleared the way for competitive production of generic versions of widely patented medicines.

Global trade rules agreed upon in 1994 required many developing countries to begin offering patents on medicines for the first time. Government and civil society reaction to expected increases in drug prices precipitated a series of events challenging these rules, culminating in the 2001 World Trade Organization's Doha Declaration on the Agreement on Trade-Related Aspects of Intellectual Property Rights and Public Health. The Declaration affirmed that patent rules should be interpreted and implemented to protect public health and to promote access to medicines for all. Since Doha, more than 60 low- and middle-income countries have procured generic versions of patented medicines on a large scale.

Despite these changes, however, a "treatment timebomb" awaits. First, increasing numbers of people need access to newer antiretrovirals, but treatment costs are rising since new ARVs are likely to be more widely patented in developing countries. Second, policy space to produce or import generic versions of patented medicines is shrinking in some developing countries. Third, funding for medicines is falling far short of needs. Expanded use of the existing flexibilities in patent law and new models to address the second wave of the access to medicines crisis are required.

One promising new mechanism is the UNITAID-supported Medicines Patent Pool, which seeks to facilitate access to patents to enable

competitive generic medicines production and the development of improved products. Such innovative approaches are possible today due to the previous decade of AIDS activism. However, the Pool is just one of a broad set of policies needed to ensure access to medicines for all; other key measures include sufficient and reliable financing, research and development of new products targeted for use in resource-poor settings, and use of patent law flexibilities. Governments must live up to their obligations to protect access to medicines as a fundamental component of the human right to health.

Introduction

A decade ago, the world prepared to gather in Durban, South Africa, for the first International AIDS Conference to be held on the continent most devastated by HIV. At the time, the statistics were grim: only one in a thousand people living with HIV in Africa had access to AIDS treatment.¹ Antiretroviral (ARV) drugs were largely available only from the originator companies that controlled the patents on these medicines, and came with a paralysing price tag of US\$10,000 to \$15,000 per patient per year.²

With civil society at the forefront,^{3 4 5 6 7 8} a joint mobilization of people living with HIV/AIDS (PLHIV), doctors and nurses, ministries of health, developing country and donor governments,^{9 10 11 12} intergovernmental organizations, and pharmaceutical companies^{13 14} achieved today what most delegates at Durban thought impossible: access to ARVs for more than five million people in the developing world.¹⁵

This achievement required some essential ingredients: first, civil society had to put access to treatment for HIV/AIDS on the global political agenda; second, innovative healthcare providers had to demonstrate that delivering treatment was safe and effective and thus feasible in resource-poor settings; and third, the price of medicines had to come down. Once these ingredients were in place, increased funding for ARVs followed, and investment in strengthening health systems to deliver treatment and care for all - both HIV positive and HIV negative - was made possible. Civil society, alongside courageous leaders willing to take risks, made it happen.

While the achievements have been enormous, huge challenges remain to sustain the progress made to date and to meet future needs.

The past 10 years have shown how ARV treatment can reduce HIV/AIDS-related illness and death in developing countries. But in the current climate of wavering support for achieving universal access to treatment, prevention, care and support - a commitment that Member

States made at the UN General Assembly just five years ago,^{16 17} - it is necessary to look ahead to consider how to make an even greater impact.

Overall, ARVs are still underused relative to need, and they still reach people with too much delay. The latest World Health Organization (WHO) guidelines for HIV treatment in resource-poor settings recommend that people should start treatment when their CD4 cell counts are above 350 cells/mm³ rather than 200.^{18 19} Recent guidelines from wealthy countries recommend even earlier initiation of ARVs, at a CD4 cell count of 500 cells/mm³ or above.²⁰ The WHO recommendation is a critical step toward improving the efficacy of treatment in developing countries, and is also expected to help prevent transmission of the virus.²¹ However, it also means that over 14 million people are now in urgent need of treatment, with more than nine million still left empty handed in the waiting room.

In order to address this challenge, ARVs should be more affordable, meet current medical standards, and be developed or adapted for use in the contexts where they are needed: that is, in settings with minimal or no monitoring available (e.g., for toxicity, viral load, or resistance), where refrigeration may be scarce, and where health workers are in short supply.

Patents and access to medicines

What role do intellectual property rules and practices play in this equation? The AIDS crisis has radically changed conceptions of and policy approaches to patents on medicines. This shift is reflected in changes in international treaties, national law, public policies, and the business practices of pharmaceutical companies. In order to understand current thinking on HIV medicines patents, we need to look back at least to the 1990s.

In 1996, a group of health non-governmental organizations (NGOs) met in Bielefeld, Germany, to discuss the public health implications of new intellectual property rules created by the World Trade Organization (WTO). The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was part of the set of treaties that established the WTO in 1994, and had just come into force in 1995. The negotiations leading to TRIPS had been primarily driven by the trade and commercial interests of the industrialized nations.^{22 23} While developing country negotiators were able to preserve certain flexibilities in the agreement, such as transition periods for implementation in developing countries, overall, TRIPS was not focused on public health, and civil society organizations were not part of the negotiation process.

TRIPS required that all WTO Members, which today number 153, provide a minimum standard of intellectual property protection, and was enforceable through the WTO dispute settlement procedures. The standards for intellectual property protection that were globally harmonized through the TRIPS Agreement derived primarily from practices in the industrialized countries, where national patent systems had evolved over many years. While proponents argued that TRIPS would increase foreign direct investment, technology transfer and research in the developing countries, critics argued that it would retard industrialization, hamper technology transfer and increase the prices of essential goods, such as medicines and agricultural inputs.^{24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39}

Before TRIPS, pharmaceutical patent policies and practices were diverse. For example, many countries did not consider patents on such products as medicines and food to be in the public interest. Half of the 98 countries that were members of the 1883 Paris Convention on the Protection of Industrial Property (a major international patent treaty prior to TRIPS, now administered by the World Intellectual Property Organization) actively excluded pharmaceutical (product) patenting altogether.⁴⁰ Some countries reduced patent terms on medicines, or only made them available for manufacturing processes but not for the end product. Even among the wealthy countries, some did not grant product patents on medicines until relatively recently: for example, Italy and Sweden began granting pharmaceutical patents only in 1978 and Spain in 1992.⁴¹

TRIPS put an end to this diversity when it required all Members to introduce 20-year patents in all fields of technology; in practice, this requirement meant that many developing countries had to begin offering patents on pharmaceutical products for the first time. Because TRIPS was part of the WTO package, countries that wished to remain Members of the WTO could not opt out of TRIPS or make reservations to the treaty (unlike many other international agreements). The ensuing years saw a wave of intellectual property reforms in most developing countries in response to TRIPS obligations.⁴² The policy space that countries once enjoyed to design intellectual property systems in line with their development needs had been dramatically constrained.

In the late 1990s, the potential effect of these new intellectual property rules on access to medicines was little understood, and interest in intellectual property issues among the public health community was still rare. The tide begins to turn.

In early 1998, 41 drug companies and their representative body sued the new democratic post-apartheid government of South Africa over amendments made in 1997 to its Medicines Act, which aimed to make low-cost medicines more readily available. The companies asserted that it was neither constitutional nor in compliance with the TRIPS Agreement.⁴³

This lawsuit was brought against the backdrop of the growing AIDS crisis. It came two years after the 1996 International AIDS Conference in Vancouver, Canada, where the world had learned that highly active antiretroviral therapy could transform HIV infection from a disease with a certain death sentence into a chronic, manageable condition. However, while ARVs were becoming available in the industrialized countries, they remained far out of reach of most South Africans and others living in developing countries. At the time, South Africa was (and remains today) home to the largest estimated number of PLHIV in the world.

Big Pharma vs. Nelson Mandela shocked the world's conscience. It was a call to action that pulled many different actors onto the stage.

In 1999, at the United Nations in Geneva, a group of NGOs and AIDS activists held a conference on compulsory licensing for HIV medicines. A compulsory licence is a way to remedy problems caused by a patent, whereby a government body (such as a ministry, court or a statutory tribunal) grants a licence to an entity other than the patent holder, allowing them to produce the patented product in exchange for "adequate remuneration". It is allowed under the TRIPS Agreement, which sets out some procedural requirements but leaves countries free to determine the grounds for issuing a compulsory licence. Industrialized countries have repeatedly used compulsory licensing, including to purchase low-cost medicines. For example, from 1969 until 1992, when Canada changed its system as a requirement of the North American Free Trade Agreement, Canada granted 613 compulsory licences for the production or import of generic medicines, leading to some of the lowest medicines prices in the industrialized world.⁴⁴

(A generic drug is a pharmaceutical product, usually intended to be interchangeable with an innovator product.)

Today there is nothing revolutionary or newsworthy about holding a meeting about compulsory licensing and access to medicines, but in 1999, the situation was quite different. Discussing compulsory licensing was the exclusive domain of specialized intellectual property lawyers. The Geneva meeting gathered NGOs and health officials to discuss how flexibilities in intellectual property law, such as compulsory licences, could be used to increase the availability of low-cost HIV medicines in the developing

world. This caused a great deal of concern among patent holders.

The growing discontent with the public health implications of TRIPS culminated at the WTO ministerial conference in Seattle in 1999 with a call to “humanize the trade agreements”. Advocates from civil society and developing country governments began forming a strong coalition and pushed for the use of measures, such as compulsory licensing, to accelerate the production and availability of low-cost generic medicines for HIV/AIDS, without risk of trade retaliation. At the time, an editorial in the *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 (Gopal 2000).”

The period between the failed Seattle WTO Ministerial conference in 1999 and the 2001 WTO meeting in Doha saw a number of developments that had a profound effect on intellectual property rules and access to medicines.

Developing countries that were at the forefront of providing ARV therapy began to experience the consequences of pharmaceutical patents on HIV/AIDS drugs. For example, in Thailand and Brazil, patents significantly limited the legal space to produce lower-cost generics, resulting in a heavy burden on public health budgets.

Brazil was the first developing country to provide widespread access to HIV/AIDS treatment through its national programme; the Brazilian programme demonstrated to the world that ARVs could be provided safely even with limited toxicity and efficacy monitoring.⁴⁵ Initially, Brazil’s programme heavily relied on the ability to produce lower-cost generic versions of ARVs that were not patented in the country. However, like many developing countries, in the 1990s, Brazil had come under strong pressure from wealthy nations to tighten patent protection, and had amended its national laws to begin granting pharmaceutical patents in 1996 (nine years before it was obligated to do so by TRIPS). The high price of patented drugs soon began to consume more and more of the ARV budget. At one point in Brazil, three patented medicines (out of a total of 17) took up 75% of the AIDS programme’s drug budget.^{46 47 48}

At the same time that awareness of the public health implications of TRIPS was growing, the AIDS crisis also began to attract greater political attention at the global level. In 2000, the Group of 8 countries paid unprecedented attention to health and the need for action to increase access

to medicines. At the International AIDS Conference in Durban, the Treatment Action Campaign and its partners organized the Global March for Treatment, squarely placing access to ARVs on the political agenda.

In December of that year, a three-day global summit in Okinawa, Japan, on infectious diseases outlined an agenda to prevent the spread of AIDS, provide treatment and care for those affected, and to enhance research and development (R&D) for international public goods, including new approaches to managing intellectual property. Most importantly, Okinawa witnessed the birth of the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), a result of extensive efforts by many advocates to create a new approach to financing the international response to HIV and other global health concerns.

Under increasing public pressure to support rather than hinder efforts to combat the epidemic, the patent-holding pharmaceutical industry began to respond. In May 2000, five pharmaceutical companies announced the Accelerating Access Initiative, offering price discounts on HIV-related medicines and diagnostics in developing countries.⁴⁹ However, even with the discounts, the prices offered through this initiative paled in comparison with the prices offered by generic producers.

Generic production of ARVs in India was possible because the Indian Patents Act did not provide for patents on pharmaceutical products until required by TRIPS to do so in 2005. Generic producers competed with each other to make medicines at prices far lower than the originators. Indian firms also combined two or more medicines into one pill in “fixed-dose combinations” (FDCs), a type of innovation facilitated by the absence of medicines product patents. FDCs are thought to facilitate patient adherence, reduce the risk of resistance and simplify supply chain management.^{50 51 52} Although Indian firms were not the only ones that produced three-in-one FDCs, they were the first to produce the FDC of stavudine, lamivudine and nevirapine, a first-line regimen recommended by WHO at the time.

The convenience for patients and relatively low price of this FDC has helped make it the mainstay of many treatment programmes in developing countries.

In high-income countries, the patents on these three medicines were controlled by three different companies (Bristol Myers Squibb, GlaxoSmithKline and Boehringer Ingelheim), which raised the transaction costs of developing this product. In high-income countries, the first three-in-one FDC comprised of medicines on which patents were controlled by different companies was the combination of tenofovir, emtricitabine and

efavirenz (brand name Atripla). First approved by the US Food and Drug Administration in 2006, this product has become the standard of care in recent recommendations in high-income countries.

In early 2001, the Indian generic medicines producer, Cipla, offered a triple-combination of ARVs for US\$350 per patient per year - or HIV/AIDS treatment for less than a dollar a day.⁵³ At the time, originator prices through the Accelerating Access Initiative were generally not publicly announced, and eligibility was restricted to a limited list of developing countries.⁵⁴ The lowest publicly announced originator price for the same combination of drugs offered by Cipla was about \$1000 at the time, but countries negotiated case-by-case with originator companies for price discounts, with wide variation in prices by country.^{55 56} In contrast, Cipla publicly offered its price to all countries. Cipla's dramatic price reduction, which received widespread media attention, hammered the message home that many of the multinational drug companies were abusing their market monopoly in the face of a catastrophic human disaster. It also drew attention to the effects of generic competition in bringing drug prices down. India quickly was becoming the "pharmacy of the developing world".

Also in 2001, controversy had broken out over the cost of the drug stavudine (also known as d4T), which came to a head on the Yale University campus in March. Stavudine was developed by researchers at Yale University, which held the patent on the drug. The price of the generic version of stavudine in South Africa was 34 times less than the price of the brand-name product from Bristol Myers Squibb, but the patent prevented its use in South Africa. Under pressure from researchers, students and access advocates, Yale renegotiated its licence with Bristol Myers Squibb to ensure the availability of generic stavudine in developing countries.^{57 58}

Meanwhile, the Medicines Act court case in South Africa was progressing. In early 2001, an amicus curiae brief filed by the AIDS Law Project on behalf of the Treatment Action Campaign put the spotlight on access to ARV treatment and brought the matter to the international stage. In April 2001, after a global public outcry that built on the Treatment Action Campaign's legal intervention and domestic advocacy campaign, the drug companies dropped their case against the South African Government. The landscape had dramatically changed.

Access to medicines and the need to revisit the patent rules that govern them had become part of a larger political agenda, and was no longer the exclusive domain of trade negotiators or intellectual property lawyers.

In November 2001, governments at the WTO Ministerial Conference, in

an unprecedented move, adopted the Doha Declaration on TRIPS and Public Health. The Doha Declaration made clear that the TRIPS 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.”⁵⁹

This landmark event represented the first significant push back to the relentless march to strengthen private intellectual property rights without regard for societal consequences in poor countries.

Implementing the Doha Declaration

The 500-word Doha Declaration on TRIPS and Public Health has been essential in making lower-cost generic versions of patented medicines available on a large scale.

In 2003, the WTO adopted the “August 30th decision” in an attempt to find a remedy for legal barriers to exporting sufficient amounts of medicines produced under a compulsory licence, and to ensure that countries that rely on import for their medicines supply could benefit from compulsory licences. Most developing countries do not have domestic manufacturing capacity for ARVs. Although some argued that the absence of ARV patents in a number of African countries meant that intellectual property did not pose a barrier to HIV treatment, this perspective did not take into account the industrial reality that patents in a few producing countries (such as India) could hinder access to generic medicines in scores of importing countries.^{60 61} While the solution that was adopted is deeply flawed and should be revised, the proposed TRIPS 31bis amendment, which has yet to come into force, is the sole amendment agreed since 1994 not only to TRIPS itself, but to the full set of WTO agreements. Public health concerns in general, and the AIDS crisis in particular, made this happen.

On 1 December 2003, WHO and the Joint United Nations Programme on HIV/AIDS declared the lack of HIV/AIDS treatment to be a global public health emergency and announced the launch of a drive to get three million people on ART by 2005; this was the “3 by 5” campaign. The political momentum of the campaign, combined with newly available funding from governments, the Global Fund and the US President’s Emergency Plan for AIDS Relief (PEPFAR), allowed countries to begin purchasing HIV/AIDS medicines in significant volumes.

By 2010, such purchases were predominantly generic drugs.⁶² For example, by 2008, 95% (by volume) of the global donor-funded ARV

market was comprised of generics, primarily from India.⁶³ The generic proportion of PEPFAR-purchased ARVs grew from 15% to 89% from 2005 to 2008, with estimated savings to PEPFAR totalling \$323 million over the four-year period.⁶⁴ How did countries manage the potential barriers posed by patents? While Thailand and Brazil's compulsory licences for ARVs in 2006 and 2007 have been widely publicized, it is perhaps less widely known that over 60 developing countries have procured lower-cost medicines on a large scale using TRIPS flexibilities.^{65 66 67} Of these, 17 low- and middle-income countries have issued compulsory licences or government use licences to gain access to generic ARVs, including, most recently, Ecuador in 2010. Twenty-six out of 32 least developed country WTO members authorized importation of generic ARVs with reference to Paragraph 7 of the Doha Declaration, which allowed them to delay granting or enforcing medicines patents until at least 2016.⁶⁸ However, some countries, such as South Africa, have yet to make use of such flexibilities.

In other cases, the policy space for countries to use such flexibilities is being constrained by stringent intellectual property requirements that exceed TRIPS and are contained in bilateral or regional free trade agreements, investment treaties and/or WTO accession agreements.⁶⁹ Middle-income developing countries that are seen as potentially lucrative emerging markets, in particular, have been subject to strong bilateral pressure from industrialized countries to refrain from using TRIPS flexibilities. Despite these persistent pressures, however, the use of TRIPS flexibilities to access generic medicines has been widespread and represents a major normative and policy shift from 2000.

Many countries could import generic ARVs, largely because India could produce and export them.⁷⁰ There was great concern in the public health community when India had to begin granting pharmaceutical patents in 2005 under its TRIPS obligations. However, the Indian Parliament incorporated public health safeguards in its Patents Act, including strict patentability criteria and the possibility for anyone to oppose the granting of patents. PLHIV supported by the Lawyers Collective used these safeguards successfully to oppose patents on HIV/AIDS medicines that did not fulfil the patentability criteria that India had adopted. A challenge to these provisions by one drug company (Novartis), which did not receive a patent for its cancer drug (Glivec), was rejected.^{71 72 73}

Companies have also responded to patent challenges by agreeing to voluntary licences to their patents. For example, GlaxoSmithKline and

Boehringer-Ingelheim expanded their voluntary licences in South Africa as part of a settlement reached after the AIDS Law Project, acting on behalf of the Treatment Action Campaign and others, had filed a successful complaint with the South African Competition Commission.^{74 75} Companies have also made voluntary licences available in response to the threat of non-voluntary measures, such as compulsory licences and patent oppositions.⁷⁶ Such licences are critical because they can encourage robust competition among drug manufacturers; competition drove down first-line regimen prices by 99% over the past decade, from \$10,000 to as low as \$67 per patient per year.⁷⁷

In short, the AIDS crisis has been an engine for change. These changes extend beyond the field of intellectual property and access to medicines, and also include:

- Increasing political attention for global health well beyond HIV and AIDS
- Strengthening the role of civil society in decision making in health policy
- Bringing about new financing mechanisms, such as the Global Fund, PEPFAR and UNITAID, whose beneficiaries go beyond HIV and AIDS Catalyzing other innovative approaches to financing development, such as the “Robin Hood tax”⁷⁸
- Expanding healthcare delivery through task shifting from doctors to nurses and/or community health workers^{79 80}
- Empowering patients through treatment literacy, and putting PLHIV at the centre of their own treatment
- Catalyzing the establishment of access strategies by the pharmaceutical industry
- Establishing the WHO Prequalification Programme, which helped create the market for low-cost generics by providing quality-assurance and a level playing field for competitors⁸¹
- Improving the standard of care for chronic conditions in resource-limited settings.

Changing approaches to R&D

The HIV/AIDS crisis and AIDS activists also impacted the way R&D for new medicines is carried out. Since the 1980s, when the US National Institutes of Health was investing in the development of the first AIDS drugs, PLHIV developed scientific expertise on the virus, clinical trials, research methods and promising candidates for drug development. For

example, activists demanded greater freedom to decide which risks they were willing or unwilling to take with experimental therapies, and challenged what they saw as the slow pace of regulatory decisions at the US Food and Drug Administration.⁸² In addition, by calling into question the legitimacy of global intellectual property rules and their impact on access to medicines in developing countries, the AIDS crisis also helped to spur new thinking on how to generate R&D that would meet the needs of the world's poor.

A patent can be understood as a type of social contract: in exchange for exclusive rights, patent holders are expected to provide benefits, such as innovation, to society. If, however, these benefits are not forthcoming or not widely available, the contract is not being fulfilled.⁸³ In the conventional model, R&D priorities are driven primarily by the potential profitability of the market for a medicine. This means that the health needs of those who do not comprise a sufficiently attractive market - because they are too poor or too few - will be neglected.

Between 1975 and 2004, of the 1556 new chemical entities marketed globally, only 20 (1.3%) new drugs were for tropical diseases and tuberculosis, diseases that account for 12% of the total disease burden.⁸⁴ In 2006, the WHO Commission on Intellectual Property, Innovation and Public Health concluded that "there is no evidence that the implementation of the TRIPS Agreement in developing countries will significantly boost R&D in pharmaceuticals on Type II and particularly Type III diseases. Insufficient market incentives are the decisive factor."⁸⁵ (Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries. Type III diseases are those that are overwhelmingly or exclusively incident in developing countries.)

A number of new initiatives have been launched to address the problem of insufficient research into the neglected diseases. These include more than two dozen public-private product development partnerships, such as the Drugs for Neglected Diseases initiative⁸⁶ and a "priority review voucher" from the US Food and Drug Administration, awarded for the development of a new pharmaceutical for a neglected tropical disease (the voucher can be applied to any new drug application to speed up regulatory review time).^{87 88} At the global level, two years of intergovernmental negotiations culminated in the 2008 Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, adopted at the 2008 World Health Assembly.⁸⁹

The search is on for new ways to generate needs-driven medical innovation that will meet the needs of both the world's rich and poor.

Indeed, the crisis in innovation is not limited to developing countries or neglected diseases alone. While globally, the level of patent protection has increased over the past 20 years, the rate of pharmaceutical innovation has fallen, with an increasing number of “me-too drugs” of little or no therapeutic gain. *Prescrire International* found that 68% of the 3096 new products approved in France between 1981 and 2004 offered “nothing new” over previously available medicines. Furthermore, an analysis of more than 1000 new drugs approved by the US FDA between 1989 and 2000 found that more than three-fourths have no therapeutic benefit over existing products.⁹⁰

While patents can provide incentives for innovation if sufficient market prospects exist, granting too many intellectual property rights may also impede rather than accelerate innovation by creating a “tragedy of the anti-commons.”^{91 92} At the same time, the high prices of medicines that result from the current innovation system raise ongoing access barriers and serious ethical concerns.

Furthermore, recent improvements in access to first-line ARVs should not mask the need for additional research in this field. The gold standard three-in-one FDC (of tenofovir, emtricitabine and efavirenz) still cannot be used during early pregnancy because of the potential first trimester teratogenicity of efavirenz. In addition, the current widely used regimen (which is nevirapine-based) is not suitable for treatment in the early stages of HIV infection due to increased toxicity.

While tuberculosis (TB) remains the most frequent opportunistic infection of HIV/AIDS, using ARVs in combination with TB drugs is still a challenge. Regimens for patients for whom first-line therapy is failing are still expensive, inconvenient and carry side effects and potential interactions with multiple other drugs, making their use impractical. Economic incentives are insufficient for the industry to develop child-friendly drug formulations. Finally, implementing WHO’s new recommendations for earlier initiation of ARV therapy in both children and adults will require an expanded drug formulary geared towards addressing a generalized epidemic. Products should ideally be heat stable, require minimal monitoring, and offer simplified dosing and other features that facilitate adherence.

How can we address these interrelated problems of market-driven R&D priority setting, declining innovation and high medicines prices? A number of new proposals have been put on the table, and are being debated and/ or pilot tested, including: rewarding innovation based on therapeutic value; prize funds to attract new “solvers” to a problem;

guaranteeing markets for end products; open-source collaborative drug discovery; and an R&D treaty.^{93 94 95 96 97 98 99} While a full discussion of these proposals is beyond the scope of this article, and many cannot be fully evaluated for years to come, it is worth pointing out several lessons from the experience of HIV/AIDS.

First, competitive production of medicines has consistently proven to be the most powerful and reliable way to reduce drug prices to their lowest sustainable levels.^{100 101} New innovation models that can “de-link” the market for medicines production from the market for R&D - such that R&D costs do not need to be recuperated through high prices but are rewarded through other mechanisms - hold the promise of helping to address affordability issues.¹⁰²

Second, public involvement in and funding for research plays a key role in accelerating scientific progress. Governments need to invest sufficiently in medical R&D. For example, additional funding is needed to conduct further research on promising tenofovir-containing vaginal microbicides to reduce the risk of HIV transmission - a product that offers the important benefit of being woman-initiated and controlled.¹⁰³

Third, PLHIV engagement played a central role in overcoming both innovation and access barriers with respect to treatment for HIV/AIDS. New approaches to generating innovation and ensuring widespread access to the fruits of scientific progress should prioritize the engagement of people directly affected by a disease.

The “treatment timebomb”

With all of the progress of the past decade in scaling up access to ARVs, what is the problem? Unfortunately, the challenges ahead are formidable and many.

First, the cost of treatment is increasing again because new ARVs are likely to be more widely patented in developing countries and thus more expensive. Even with the high patentability standards implemented in India and other countries, some of the new ARVs are likely to be patented. Without production sources, the countries that rely on importation will find it hard to source low-cost medicines. In addition, patents on individual medicines can make it more difficult to develop new FDCs.

Second, increasing numbers of people will need access to new-generation ARVs: an expanded drug formulary is urgently needed. In addition, about two-thirds of people in need of treatment still do not receive first-line medicines today. ARV prices, particularly in some middle-

income developing countries, can still put them out of reach of the people who need them. There is wide variation in the voluntary licensing practices of the patent-holding companies, and such licences too often come with limitations that hamper the full effect of generic competition and the ability to develop FDCs.

Third, advances in research on newer drugs and combinations need to be available worldwide. For example, tenofovir is a promising newer drug that is finally becoming available in resource-limited settings, but experience on how to use it without monitoring or in specific populations (e.g., people with renal damage) is lacking. To avert such situations, research should be carried out in the specific contexts, and taking into account the specific co-morbidities of the target populations where medicines are needed. Some drugs, such as raltegravir, elvitegravir or rilpivirine, are promising, but long-term follow up regarding adverse events is lacking, and the feasibility of their use for treating TB co-infected patients is unclear at this stage.

Fourth, the policy space to produce or import generic versions of patented medicines is shrinking in some developing countries. Stringent intellectual property provisions exceeding TRIPS requirements ("TRIPS-plus") have been negotiated into free trade agreements between industrialized and developing countries, and/or investment and WTO accession agreements. Measures, such as patent term extensions, data exclusivity, patent-registration linkage and border enforcement requirements, can all delay access to generics by lengthening, strengthening or broadening monopolies on medicines.^{104 105 106 107} In addition, some agreements contain measures that confuse legitimate generics with counterfeit medicines; such policies can undermine public health by restricting access to affordable, quality-assured generic medicines.^{108 109 110 111} ¹¹² Countries that enter into agreements that undermine access to medicines are arguably violating their international human rights obligations.^{113 114}

Fifth, we are faced with a serious financial crisis that risks setting back the treatment achievements of the past 10 years.

In July 2009, the United Kingdom All Party Parliamentary Group on AIDS called this situation a "treatment timebomb" and called for "political activism" to "ensure that the next generation of drugs is available to the world's poorest in future."¹¹⁵

New approaches to managing intellectual property: the Medicines Patent Pool

We need to go further than where we are today. We need expanded use of the existing flexibilities in patent law and new models to address the second wave of the access crisis. Without generic competition, prices for newer drugs will not come down the same way that they did for the first generation of medicines. One promising new mechanism is the Medicines Patent Pool, established with the support of UNITAID.

UNITAID is a new financing mechanism based on a small solidarity levy on airline tickets, and is supported by 29 countries, the Bill & Melinda Gates Foundation, NGOs and communities. Its mission is to increase access to treatment for HIV/AIDS, TB and malaria by making markets work better for health. UNITAID has raised approximately US\$1.5 billion, and seeks to be innovative in the way that it both raises and spends funds.^{116 117}

It is UNITAID's overarching principle to make markets work better for health that made it a natural birth-place for the Medicines Patent Pool Initiative, which became operational in mid-2010. The idea for an HIV medicines patent pool was first launched at the 2002 International AIDS Conference in Barcelona, Spain, by James Love from Knowledge Ecology International. He had studied the US airplane patent pool that was established in 1917 by the US Government to overcome patent barriers to the mass production of airplanes needed for the military.¹¹⁸ He suggested doing the same for HIV medicines patents.

The Medicines Patent Pool is a response to the changed global intellectual property environment in which medicines are being more widely patented in developing countries. It is built on the principle of relying on market competition to bring medicines prices down. However, robust competition is possible only if licences are available. The Pool is expected to work as follows:

Patent holders will make licences available through the Pool that will allow others to produce low-cost generic versions of patented ARVs for use in developing countries. It will be important that the licences cover as many developing countries as possible, both to maximize public health benefit and to ensure economies of scale in generic drug production. The licences are also intended to facilitate the development of FDCs and other formulations adapted for use in resource-poor settings, such as special formulations for treating children, by ensuring that patents do not block generic companies or product development initiatives from carrying out follow-on R&D.

Companies that receive licences from the pool will pay royalties on their sales to the patent holders. The Pool will be a systematic and predictable way of making voluntary licences available, offering legal certainty to all parties involved. No change in international or national law is required for the Pool to work; what is required is a change in mindset from the patent holders, without whose collaboration this initiative cannot succeed. In other words, the Patent Pool will work only if patent holders are willing to collaborate to make their intellectual property available to the Pool. Several major leading patent holders have expressed an interest and willingness to engage with the Pool.

In addition, companies have increasingly adopted voluntary licensing practices as part of their access policies; voluntary measures, such as the Pool, may provide an attractive alternative to non-voluntary measures for patent holders, and can be understood as one outcome of the decade-long evolution in approaches to managing intellectual property and access to medicines. In September 2010, the US National Institutes of Health became the first patent holder to licence its patents (related to a class of ARVs) to the newly established Medicines Patent Pool.¹¹⁹

Despite these recent developments, the Pool faces many challenges and many key factors have yet to be determined.^{120 121 122 123 124} Nevertheless, it provides a clear illustration of the considerable normative shift that has taken place regarding how intellectual property should be handled relative to access to medicines and the central role played by the AIDS crisis in driving forward these debates.

Conclusions

New approaches to achieving innovation and access to medicines are possible today because of the previous decade of activism that demanded a change in the way we approach intellectual property and public health. The political and civil society mobilization catalyzed by HIV/AIDS was at the forefront of these changes. But three warnings merit attention at this point. First, initiatives such as the Pool are only one approach to addressing access issues, and must be seen as complements to a broad set of other policies that are needed to ensure access to medicines for all. The Pool is not a panacea, and governments must live up to their responsibilities to protect the health of their populations.

Second, overcoming intellectual property barriers to innovation and competitive production is critical, but is only one piece of the complex machinery required to ensure that we achieve our shared objective of

universal access to treatment, care and prevention services for HIV/AIDS. Improving access to medicines also requires addressing regulatory issues, strengthening procurement and supply chains, and establishing pharmacovigilance systems, among other measures. In particular, sufficient levels of funding are critical. Without a market for even the lowest-cost medicines, we cannot expect that anyone will be ready to develop and produce these products.

Third, while there may be progress in key aspects of HIV treatment, needs for the development of new products (such as microbicides) and access to medicines for other diseases remain immense. For example, treatment is often unavailable in many developing countries for both acute infectious diseases and chronic diseases, such as diabetes and cancer.^{125 126 127} Progress against one disease should not allow us to be complacent, nor should it overshadow the scale of ongoing unmet needs.

The struggle for improved access to medicines has been and will be a continuous fight, sometimes an uphill battle, and not always easy to win. But the lessons of the past 10 years show what can be achieved if we mobilize.

We are at a crucial point in time: not only do we need to protect what has been achieved, but we also need to be ambitious and go further. It is feasible that with better-adapted, more affordable ARVs, we can double or triple the number of people on treatment without doubling or tripling the cost. We can also ensure that people have access to better and better-tolerated medicines.

High prices simply cannot be legitimate grounds for withholding lifesaving treatment from people. Access to medicines is a fundamental human right,^{128 129} which puts the obligation on all of us to do all we can to ensure that it is fully realized.

List of abbreviations

ARV: antiretroviral; **FDC:** fixed-dose combination; **NGO:** non-governmental organization; **PEPFAR:** US President's Emergency Plan for AIDS Relief; **PLHIV:** people living with HIV/AIDS; **R&D:** research and development; **TB:** tuberculosis; **The Global Fund:** The Global Fund to Fight AIDS, Tuberculosis and Malaria; **TRIPS:** Agreement on Trade-Related Aspects of Intellectual Property Rights; **WHO:** World Health Organization; **WTO:** World Trade Organization

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Authors' contributions

EtH was involved in the conception and design of the study, analysis and interpretation of data, drafting the manuscript, and revising it critically for important intellectual content. JB was involved in drafting the manuscript and revising it critically for important intellectual content. AC was involved in drafting the manuscript and revising it critically for important intellectual content. SM was involved in the conception and design of the study, analysis and interpretation of data, drafting the manuscript, and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Competing interests

EtH is the Executive Director of the Medicines Patent Pool and a former employee of UNITAID. SM is a consultant for the Medicines Patent Pool and has been a consultant for UNITAID.

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A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme

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Abstract

Problems with the quality of medicines abound in countries where regulatory and legal oversight are weak, where medicines are unaffordable to most, and where the official supply often fails to reach patients. Quality is important to ensure effective treatment, to maintain patient and health-care worker confidence in treatment, and to prevent the development of resistance. In 2001, the WHO established the Prequalification of Medicines Programme in response to the need to select good-quality medicines for UN procurement. Member States of the WHO had requested its assistance in assessing the quality of low-cost generic medicines that were becoming increasingly available especially in treatments for HIV/AIDS. From a public health perspective, WHO PQP's greatest achievement is improved quality of life-saving medicines used today by millions of people in developing countries. Prequalification has made it possible to believe that everyone in the world will have access to safe, effective, and affordable medicines. Yet despite its track record and recognized importance to health, funding for the programme remains uncertain.

Introduction

In 1977, the World Health Organization (WHO) published the first Model List of Essential Medicines (Essential Medicines List, EML). The EML assisted health authorities in selecting products for primary health care. It introduced the idea that some medicines are more important than others.

Many later considered the first EML ‘a revolution in public health’.¹ After 25 years, WHO made an equally important decision to prequalify medicines. WHO Prequalification of Medicines Programme (PQP)’s greatest achievement is sustained improved quality of life-saving medicines used today by millions of people in low- and middle-income countries. The historical background of this WHO programme, how it developed over the last 13 years, its main achievements, and some of the challenges ahead are the subject of this article. We conclude with recommendations for the programme’s future.

The quality of medicines can help ensure effective treatment, maintain patient confidence in treatment, and prevent development of resistance. These problems are particularly prevalent in countries where regulatory oversight is weak (in about one third of low- and middle-income countries), where prices make medicines largely unaffordable to patients, and where official supply channels fail to reach patients.² In 2001, so that United Nations (UN) procurement would select medicines of assured quality, WHO established the PQP. A review of the regulatory and procurement environment at that time helps one understand why such a programme was needed.

Most international procurers doubted that Indian drug regulatory authorities could verify the quality of medicines. Yet India produced most generic medicines used in developing countries. Moreover, fixed-dose combinations (FDCs) of antiretroviral (ARVs) medicines and paediatric ARV formulations from India had no originator equivalents (medicines made and regulated in high-income countries), constituting another regulatory assessment challenge. Often national and international procurement organizations could not guarantee quality because their quality-assurance systems were limited in scope. WHO Member States requested WHO to assist procurement organizations by assessing the quality of increasingly available low-cost generic medicines.

Given its mandate to set international pharmaceutical norms and standards, WHO was suited for this role. Initially WHO focused first on low-cost generic versions of medicines to treat HIV, tuberculosis (TB), and malaria. The programme evolved and expanded to increase the availability of safe and effective medicines of quality by covering:

- essential medicines for reproductive health, diarrhoea, and neglected tropical diseases (NTDs);
- quality control laboratories;
- active pharmaceutical ingredients (APIs);

- review of clinical research used to prove equivalence of generic medicines with their comparators; and
- capacity of medicines regulators and pharmaceutical manufacturers in developing countries of Africa and Asia;

The WHO PQP has prequalified over 200 products for treatment of HIV/AIDS.³ Of 8 million people receiving treatment for HIV in 2012, 6.5 million were receiving WHO-prequalified ARVs (Box 1).⁴

Box 1: Timeline: WHO PQP.

2001 (February): The Indian generic medicines manufacturer Cipla announces triple-ARV AIDS treatment for \$350 ppy

2001 (March): WHO establishes the PQP

2001 (November): WTO adopts the Doha Declaration on TRIPS and Public Health

2002 (January): Global Fund to fight AIDS, TB, and malaria created

2002 (April): WHO publishes first list of 41 approved formulations of ARVs and other medicines used in the treatment of HIV, and at the same point WHO includes for the first time 12 ARV medicines in its EML

2003 (January): US PEPFAR approved by Congress

2003 (December): the first triple FDC for HIV treatment prequalified

2003 (December): WHO and UNAIDS announce the 3 by 5 Campaign

2004 (January): US FDA's Tentative Approval mechanism established

2004 (April): WHO PQP expands to include testing sites

2004 (April): Scientific and technical principles for fixed dose combination drug products drawn up at the meeting of interested parties held in Botswana

2004 (May): WHO PQP delists an ARV for the first time

2005 (June): The WHO Expert Committee on Pharmaceutical Specifications adopts a regulatory guideline for assessment of fixed-dose combinations.

2006 (September): UNITAID established as a new mechanism for the purchase of medicines for HIV, TB, and malaria financed by a tax on airline tickets

2006: WHO PQP includes medicines for reproductive health

2007: WHO PQP includes one medicine for use in pandemic influenza

2008: WHO PQP includes zinc for the management of acute diarrhoea

2008: UNITAID decides to fund the WHO PQP with a 5-year grant

2010: WHO PQP begins to prequalify APIs

2011: WHO and US FDA, also WHO and EDQM confirm confidentiality agreements that enable the exchange of confidential information and avoid repetition in assessments and inspections

2013: WHO prequalifies first medicine for treatment of a NTD (lymphatic filariasis)

2013: WHO merges its prequalification activities for diagnostics, medicines, and vaccines into one programme

The Global Health Environment Around the Turn of the Century

Neither national governments nor donors placed quality assurance of essential medicines high on their agendas. WHO estimated that only one third of regulatory agencies met standards; the rest lacked resources, procedures, and enforcement capacity. UNICEF, the International Dispensary Association (IDA), and Médecins Sans Frontières (MSF), were large international not-for-profit suppliers of essential medicines for national programmes and faith-based facilities. Their supplier selection and quality assurance mechanisms were generally considered adequate, and many bilateral donors and WHO programmes used their services.

In 2000, only one in a thousand people living with HIV in Africa had access to treatment.⁵ Highly active ARV treatment was available in wealthy countries. Thus AIDS changed from a death sentence into a manageable chronic disease. However, the drugs (ARVs) were available only from originator companies, who controlled the patents. They produced small quantities carrying paralysing price tags – US\$10 000–\$15 000 per person per year (ppy).⁶

Civil society and health professionals joined forces and campaigned for access to HIV treatment, adequate resources, and flexibility in patent rules – the last to enable production of generic ARVs. Controversies ensued over patents on ARVs following the introduction of new global rules on intellectual property (IP), international requirements to tighten national patent law. These patent restrictions largely prevented UNICEF, IDA, and MSF from distributing generic ARVs made in India.

In 1995, following creation of the World Trade Organization (WTO), the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) came into force. TRIPS is a WTO agreement and laid out minimum standards for IP protection, including an obligation to provide pharmaceutical product patents of at least 20 years.⁷ Such patent protection did not exist in most developing countries. In 2001, the WTO Ministerial Conference, to facilitate access to low-cost generic medicines, discussed making implementation of IP standards in developing countries flexible. In November 2001, the Ministerial Conference adopted the Doha Declaration on TRIPS and Public Health. Could TRIPS obligations be rebalanced with the need to protect public health, particularly with respect to affordable medicines?

The Doha Declaration affirmed the sovereign right of governments to take measures to protect public health, including the use of 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. The holder of the compulsory license pays a royalty (adequate remuneration) to the patent holder. Parallel imports are cross-border trade in a patented product, without the permission of the manufacturer or publisher. Parallel imports take place when there are significant price differences for the same item in different markets.

The Declaration also allowed least developed countries not to grant or enforce pharmaceutical product patents before 2016, taking away patent barriers to importing generic medicines from India. In 2002, this implementation deadline was extended to July 2021. These measures have become known as the 'TRIPS flexibilities'. When the Indian drug firm Cipla announced in 2001 that it could supply triple-therapy ARVs for less than a dollar a day, it was evident that the role of emerging generic medicines producers would grow and become a key element of the response to demand for greater access to HIV treatment.

In January 2002, the Global Fund to fight AIDS, TB, and Malaria was established after the endorsement of the G8 in 2001. It struggled to use its funds wisely. For new generic medicines, the Fund and other donors needed assurance that quality was acceptable. Although not yet a high-profile issue, Fund staff understood the dangers for their new organization if large sums were spent on medicines of unknown or substandard quality or used for expensive branded products only.

The case of TB medications was especially alarming. In 1999, WHO had received the disturbing results of a small pilot study by a research group in South Africa on the quality of FDCs for first-line (directly observed treatment, short-course, (DOTS)) treatment of TB (PB Fourie, personal communication 11 December 2013). Simple quality control tests had showed that the FDC tablets contained rifampicin, the key component of the combination, leading programme managers to believe that tablets met quality standards. Sophisticated testing, however, showed that in 6 out of the 10 samples, the rifampicin was not absorbed by the intestines of the patient, and was therefore clinically useless. If representative, the results suggested that more than half the world's TB patients were receiving DOTS treatment without its most important component. Poorer treatment outcomes and increased resistance would result. The results were never published but passed on under confidential cover to the relevant regulatory agencies to act upon. The studies convinced WHO staff that there were serious problems with the quality of TB drugs used in public programmes.

Better quality assurance was needed, although most donors and health workers were unaware of the problems. These findings underlay WHO's critical decision to start a quality assurance programme for essential combination medicines for TB.

The new fixed-dose combination AIDS tablets produced by generic companies in India needed quality assurance. Most regulators in generic drug manufacturing countries – India, South Africa, and China – and in potential recipient countries had no experience with these 'new' products. This problem demanded a quick solution as the originator medicines were extremely expensive and the recommended treatments were not available in patient-friendly combination tablets. In India, patents did not prevent generic companies from developing fixed-dose combination of ARV drugs from different originators. Could inexpensive and more convenient products from India be trusted and did they have the same efficacy and safety profile as the originator products? National regulators in recipient countries, UNICEF, and non-governmental organizations (NGOs) wanted to know. They requested WHO's expert opinion.

WHO could not immediately answer these questions. Thus WHO created a review process to apply assessment criteria used by stringent regulatory agencies to determine product safety, efficacy, and quality. The term 'prequalification' (PQ) refers to the outcome: after WHO approval, a product is deemed 'prequalified' to participate in UN procurement tenders. Products that have received approval by a stringent regulatory agency are already eligible for procurement.

The Development of the WHO PQP

Since 1996, the senior pharmaceutical advisers of all UN agencies – WHO, UNICEF, and World Bank – had met every 6 months in the 'Interagency Pharmaceutical Coordination' (IPC) group, to coordinate their medicine policies and to ensure that their agencies complement rather than duplicate each other in the medicines components of their country support programmes. A recurrent IPC discussion topic was the wide divergence between UN agencies in quality requirements.

The new prequalification programme fits this interagency environment. In 2001, the IPC accepted and endorsed the WHO/UN PQP as a UN interagency collaboration project. IPC wanted to streamline quality standards and policies on medicine procurement at WHO, UNICEF, World Bank, and later the Global Fund and UNFPA.

The medicine prequalification programme approach was not new. The

Expanded Programme on Immunization established proof of concept over 30 years. WHO tested and approved all children's vaccines supplied by UNICEF. Prequalification was new for medicines and new in that WHO decided to approve medicine products even from countries where regulatory agencies were not up to international standards. (For vaccines to be prequalified, the national regulatory agency had to be pre-qualified as well).

The new prequalification programme first took on fixed-dose combination medicines for TB, responding to the alarming rifampicin study. However, the global TB community and the Global Drug Facility that focuses on TB were slow to accept the study's results. They continued to procure medicines without sufficient quality assurance procedures. In the meantime, the Global Fund had been established and global attention shifted towards HIV/AIDS. WHO too decided to shift pre-qualification attention to medicines for HIV/AIDS (Box 2).

Verifying quality of medicines may appear a non-controversial activity, but early on the WHO PQP was criticized harshly, especially by high-income countries. Its principal critics maintained that WHO should not help commercial generic producers gain access to new markets, presumably at the expense of 'research-based companies'.

In 2002, WHO published its first list of 41 approved formulations of ARVs and other HIV medicines. The International Federation of Pharmaceutical Manufacturers, a trade organization 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.⁸

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 three million people on anti-retroviral treatment (ART) by 2005. The political momentum of the campaign, combined with new funding from governments, the Global Fund, and President's Emergency Plan for AIDS Relief (PEPFAR), and later from UNITAID, allowed countries to begin purchasing HIV/AIDS medicines in large volumes. Yet to optimize buying power and cover all patients needing treatment, the price of the ARVs would have to be lowered.

Everyone recognized FDCs as an important advance in HIV/AIDS treatment, particularly for resource-poor settings where the 'one pill twice a day' regimen would help increase adherence to treatment, reduce the risk of developing resistance, and simplify the supply chain.^{9 10} Indian firms

were the first to produce a FDC of a WHO-recommended first- line combination, although not the only ones to produce triple FDCs.¹¹ The price of the first generic triple combination by Cipla was less than \$140 ppy. The combination of lamivudine, stavudine, and nevirapine – compounds developed by three different originators – was sold under the name ‘Triomune’.

Box 2: WHO prequalification of medicines process

1. WHO lists for possible prequalification specific products with their recommended strength and presentation (tablet, injection, syrup). A product may be listed if it appears on the biennial WHO EML, or when a product is recommended in a new WHO treatment guideline and the maker has applied to put it on the next EML. (These are typically reviewed every 3–4 years).
2. WHO then includes the product on an Invitation to Manufacturers to Submit an Expression of Interest (EOI) List for Product Evaluation that it publishes on the WHO/PQP Website.
3. Any manufacturer of a product on that EOI may apply to have the product evaluated for inclusion in the WHO List of Prequalified Medicinal Products. To apply, each manufacturer must submit information to enable the international assessment teams convened by WHO to evaluate the product’s quality, safety, and efficacy. Submissions include comprehensive data on quality, safety, and efficacy, including details about the purity of all ingredients used in manufacture, stability of the finished products – tablets, capsules, oral liquids – in tropical climates, plus results of in vivo bioequivalence tests. These tests in healthy volunteers must prove that the product has the same absorption in the body as the originator product. The manufacturer must also open its manufacturing sites to inspection to assess compliance with WHO Good Manufacturing Practices (GMP). (To avoid duplication, WHO also recognizes recent inspections carried out by stringent regulatory bodies). The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopts standards and procedures for prequalification based on the principles and practices used by the world’s leading regulatory agencies.
4. A global team of assessors from developing and developed countries evaluates the data presented, and if satisfactory, dispatches a WHO inspection team of experts (also from developing and developed countries) to inspect the manufacturing site for compliance with GMP. If applicable, the team also examines the contract research organization that performed clinical testing relating to the product. The clinical testing must have been conducted in compliance with GCP and GLP. If the manufacturer’s product made at the inspected site meets all these standards, it may be added to the WHO List of Prequalified Medicinal Products.
(Source: <http://apps.who.int/prequal/>)

Brand-name companies set the price of a similar combination, using single tablets – six pills per day – at a minimum of \$562 ppy in developing countries. Because a three-in-one ARV product for first-line treatment, as recommended by WHO, was not manufactured by any research-based company, it had never been assessed or approved by any stringent regulator. Research-based companies were testing and producing only combinations of their own patent-protected products – not necessarily the best combinations from a medical perspective. The triple FDCs, produced only by generic companies, came to symbolize the great savings that generics could achieve. WHO's prequalification of Cipla's first generic FDC of three ARVs, a ground-breaking move, brought an important innovation to resource poor countries.

Prequalification of a first generic FDC provoked a global debate about WHO's role in making generic HIV/AIDS medicines accessible in developing countries. The new combination lacked an originator equivalent as a reference. Regulatory standards for FDCs, in general, were also lacking. WHO found itself in uncharted territory. A number of industry-based groups were quick to condemn the prequalification of triple FDCs, arguing that because triple FDCs did not exist as originator products, safety and efficacy comparisons could not be made and new clinical trials should be performed.^{12 13} As the three compounds in the FDC were still under patent in many countries, this provoked further criticism. Some questioned the legality of WHO's move.¹⁴

The US administration of George W. Bush insisted on buying only originator branded products for its programmes. It defended this policy by referring to concerns about the quality of generics approved by WHO.¹⁵ The head of the United States PEPFAR, Randall Tobias, a former CEO of Eli Lilly, publicly questioned the rigour of WHO's PQP. He told the Associated Press: 'Maybe [FDC] drugs are safe and effective. Maybe these drugs are, in fact, exact duplicates of the research-based drugs [sold in the United States]. Maybe they aren't. Nobody really knows'. He added that the United States does not want to contribute to an increase in ARV drug resistance because of 'widespread or inappropriate' use of the treatments.¹⁶ US refusal to accept WHO-prequalified AIDS medicines provoked responses from care providers dependent on access to lower-cost generic ARVs, as well as from politicians seeking to make life-saving medicines available in the developing world.^{17 18}

A breakthrough on the use of FDC ARVs came in March 2004 at a conference in Gaborone, Botswana. Co-sponsored by UNAIDS, WHO, the Southern African Development Community, and the US Department of

Health and Human Services, it focused on the safety, efficacy, and quality of FDCs, whether from innovator or generic sources. It tried to provide urgently needed guidance on the development, evaluation, and/or use of combination products for HIV, malaria, and TB. It also tried to encourage development of paediatric FDC formulations.¹⁹ Drug regulators of 23 countries, care providers, NGOs, government officials, industry, treatment advocacy groups of people living with HIV, and UN agencies, gathered to draw up this guidance.

In a great success for WHO, the conference's guidance for the future regulation of FDCs confirmed the regulatory principle, proposed by WHO, that if three separate medicines have successfully been used clinically in combination therapy, there is no need for new clinical trials of an FDC of the same medicines in the same dosages.²⁰ The only proof needed is that each of the compounds in the combination tablet achieves the same serum levels as did the original products when given separately. This principle, subsequently confirmed by WHO's expert committee, implied that establishing bio-equivalency (BE) in such cases would be sufficient to determine interchangeability with the originator products given separately. This agreement between the leading regulators of the world paved the way for rapid approval of ARV combinations based on product quality and BE grounds alone. Had new clinical trials been required, market entry of generic FDCs would have been delayed for several years, (or even a decade for TB, where the relapse rate is an essential measure of efficacy). The meeting also gave many stakeholders the opportunity to rally and secure US Government support of procurement and use of generic ARVs.^{21 22}

The July 2004 report of the United States General Accounting Office (GAO) helped change US policy on the use of generic ARVs. The GAO identified serious problems for PEPFAR funding recipients caused by a lack of procurement guidance. Thus GAO recommended that the US Global AIDS Coordinator explicitly specify what activities PEPFAR was permitted to fund in national treatment programmes that use ARV drugs not approved for purchase by the Office.²³ Unfortunately, the US Government was not yet ready to accept the WHO PQP and announced, with the support of the US Global AIDS Coordinator's Office, that it would establish its own review process for generic and other ARV drugs to be procured with PEPFAR money.

This 'United States Food and Drug Administration (US FDA) Tentative Approval mechanism' duplicated the WHO PQP. The global community quickly recognized it as a competitor to the WHO PQP that could undermine further development of WHO PQP.²⁴ For most developing

countries, however, WHO remained the only international agency with a global mandate to establish pharmaceutical standards for quality, efficacy, and safety, including the scientific justifications necessary to establish the bioequivalence of products. In 2004, supporters of WHO PQP sought to bolster the programme through a World Health Assembly resolution on HIV/AIDS that included a paragraph calling for strengthening of WHO's prequalification project. The resolution asked that inspection and assessment reports on the listed products, aside from proprietary and confidential information, be made publicly available.²⁵ Transparency of the WHO PQP has proved essential in creating and maintaining confidence among buyers, funders, and users of the approved medicines.

A Crisis of Confidence

Days after the heated debate in the Assembly, and while the WHO Executive Board was still meeting to discuss next steps, WHO was confronted with information that threatened to inflict severe damage on WHO PQP's credibility. Following an informal warning and a follow-up inspection at Cipla's manufacturing plant in India, inspectors reported to WHO's headquarters by telephone from India that the bioequivalence studies for a key prequalified ARV product were seriously deficient. The inspectors suspected them to be fraudulent. Inspectors had not found proven lack of bioequivalence, but there was simply no good evidence of bioequivalence. WHO's strict standards for bioequivalence studies, including inspection of the organizations that had performed the studies on the maker's behalf, tracked recently adopted European guidelines. At the time, these were stronger than those of any other regulatory body. The subtle difference between 'proof of lack' and 'lack of proof' later created confusion among regulators, health workers, and patients.

The information created a difficult situation for WHO. Only four originator and four generic ARV products had been prequalified. Besides pressure from some rich countries that objected to prequalified generic products, the activist community criticized WHO for having colluded with industrialized country interests to make the quality standards so high that generic products manufactured in low- and middle-income countries were largely excluded from prequalification.

Technically, it was clear that the Cipla product had to be delisted until its bioequivalence had been properly established. However, immediate publication by WHO, during the Board meeting, risked inflaming and derailing ongoing political discussions as the evidence appeared to show

that generic products might be inherently unreliable. Was the justification for the entire prequalification programme flawed? Not publishing the information immediately, and later being exposed as having withheld damaging knowledge to protect a generic product, despite lack of proof of its quality and efficacy, would support allegations that WHO promoted generic medicines without regard to quality problems.

WHO postponed publication of its findings until it received written confirmation from the inspectors. This gave WHO just enough time for the Executive Board to complete its meeting and for the delegates to travel home, avoiding an immediate and almost certainly acrimonious debate. Then, before publicly delisting the Cipla product, WHO informally told the treatment activist community and civil society organizations, asking them not to use the information to further attack the programme (see, for example, a message from Hogerzeil, H., Director of the Department of Essential Drugs and Medicines Policy at the WHO to Internet mailing lists: <http://lists.essential.org/pipermail/ip-health/2004-September/006896.html>, accessed 18 November 2013). The medical humanitarian organization MSF commented that being told about the flaws in the prequalification process demonstrated the programme's strength. 'MSF supports the WHO Prequalification Project and believes that on-going monitoring by the WHO is a sign of an efficient process. The rigour of this process ensures that companies are always striving to improve their assessment of quality'.²⁶ MSF's statement helped counteract those who saw the delisting as an opportunity to criticize the programme as a whole.

WHO described the decision to delist the Cipla product as 'short-time pain for long-term gain'. The public delisting sent a shockwave through the Indian generic industry, and gave a clear signal that quality standards would continue to be demanded of all products submitted for evaluation. In November 2004, insistent WHO requests for confirmation of the proper bioequivalence testing of its ARVs also led Ranbaxy Laboratories, another generic maker, to withdraw of several products from WHO's prequalified products list.

Very few prequalified generic products remained for the treatment of HIV. Cipla did not submit genuine bioequivalence studies for its products. (In later years, Cipla once again became an important supplier of quality-assured, low-cost ARVs.) Regulators, health workers, and patients found it difficult to understand why essential ARVs were withdrawn by WHO based on quality standards not yet applied to any other medicines in any jurisdiction. Many national AIDS programmes were seriously frustrated and confused by the withdrawal of essential products and struggled to find

alternative solutions. UNICEF refused a consignment of specially labelled ARV products that had already been shipped. An editorial in *The Lancet* though, hailed WHO's move, stating that '...it shows that this little known part of WHO is effective and has teeth that can bite rapidly'.²⁷

The strength and independence of WHO medicines prequalification seemed to gradually diminish political opposition to the programme. The only remaining opposition comes as occasional complaints from ministers of health that the WHO PQP is too slow or too strict, that it makes it hard for their national generic industries to meet requirements.

Ultimately, opposition to WHO PQP served to strengthen it. Yet two positive factors also helped it survive and grow: donor support and purchasing power. WHO began PQP with small amounts of donor funds not earmarked for a particular purpose. Then the Bill & Melinda Gates Foundation recognized the power of the prequalification concept and provided steady support for the programme. Since its inception in 2006, UNITAID has also supported the programme. Its generous 4-year commitment for 2009–2012, now extended into 2013 and perhaps further for 2014–2016, secured the programme when WHO's own resources were not equal to the demands from Member States and other stakeholders.

The most important factor in the survival and growth of the WHO PQP was the Global Fund's quality assurance policy for medicines procurement. Its policy restricts use of the Fund's immense purchasing power to products approved by stringent regulatory authorities or prequalified by WHO. This policy came out of the IPC process designed to harmonize international procurement quality standards among UN agencies. Later UNFPA adopted a similar policy. As a result, the public sector market for non-prequalified medicines for AIDS, malaria and, later, TB and reproductive health medicines shrank. Companies were obliged to get stringent regulatory approval or WHO prequalification to compete in the international market (Box 3).

Current Activities and Achievements of the WHO PQP

Since its establishment in 2001, the WHO PQP has prequalified more than 350 finished pharmaceutical products (FPPs). Only 20 products have been removed from the list, most upon request from the manufacturer. The original focus was prequalification of medicines for treating HIV/AIDS, TB, and malaria. In 2006, this range was expanded to cover medicines for reproductive health, in 2007 to cover a medicine for pandemic influenza, and in 2008 to cover zinc for the management of acute diarrhoea in

children.³⁰ More recently, the Programme has started to evaluate the quality of medicines for treating NTDs. (For the 17 diseases identified as NTDs by WHO see: http://www.who.int/neglected_diseases/diseases/en/).

Box 3: Relationship with the US FDA tentative approval programme.

Generic producers did not seek the approval of the US FDA for their ARVs because patents prevented them from marketing their products in the United States. Hence, the US rules that prevent it from spending PEPFAR money on medicines not approved by the US FDA were essentially a rejection of generic ARVs in favour of US companies' brand name products. However, some US politicians realized that PEPFAR's resources would not stretch far if they had to be spent on expensive branded medications.

In 2004, the US FDA, rather than providing expertise to the WHO PQP and in order to break through this deadlock, created its own mechanism for prequalifying medicines to be used for the treatment of HIV in developing countries and procured with US funds.²⁸ The so-called US FDA Tentative Approval System also assessed overseas generic products for use by US-funded programmes, and paved the way for PEPFAR procurement of generic medicines. No generic FDCs were approved until 2006, delaying by two years use of WHO recommended regimens by PEPFAR recipients.²⁹

US FDA Tentative Approval was for HIV medicines only. No similar approval process was established for products to treat other diseases. In the President's Malaria Initiative, WHO prequalification is relied upon. Now USAID has agreed to accept WHO/PQ as a quality standard, aligning itself with the Global Fund and UN interagency quality policies. In 2011 and after long discussions, WHO and US FDA reached an agreement that enabled them to exchange confidential information and thus avoid repeated assessments and inspections.

The time required for prequalification can vary enormously and depends on the quality of dossier and the manufacturer's experience with stringent evaluation. Today WHO prequalification of a medicine can take as little as 3 months, if the data presented are complete and demonstrate that the product meets all required standards. If a manufacturer responds quickly to questions from the assessment team, prequalification can be more rapid. WHO's fastest prequalification of a generic was 6 weeks.

In 2010, WHO started to prequalify APIs – the essential building blocks of medicines.³¹ In 2013, the WHO PQP approved 23 APIs.

Testing sites – medicine quality control laboratories and commercial contract research organizations that perform bioequivalence studies – have been inspected since 2004. These inspections ensure that sites meet standards for good laboratory practice (GLP) and good clinical practice (GCP).

A complete listing of prequalified products by disease category is available on the WHO Website <http://apps.who.int/prequal/query/ProductRegistry.aspx>). The programme's annual budget today is \$15 million.

The list of prequalified medicines has become a vital tool for any

agency or organization purchasing of medicines in bulk, whether at country or international level, as demonstrated by the Global Fund. The WHO PQP has prequalified 85–90 per cent of market of ARVs, malaria, and TB medicines for the Global Fund, UNICEF, and UNITAID. It is widely used by NGOs and others, such as national procurement agencies. It helps assure that scarce resources for health stretch further and are not spent on products of unknown quality, safety, and efficacy. (Table 1)

Table 1: WHO prequalified finished pharmaceutical products(FPPs) per year

WHO prequalified FPPs per year						
	2008	2009	2010	2011	2012	2013
<i>HIV</i>	29	18	22	23	18	27
<i>Tuberculosis</i>	5	7	5	7	19	17
<i>Malaria</i>	6	3	1	1	10	7
<i>Reproductive health</i>	0	3	5	3	0	10
<i>Influenza</i>	0	6	1	0	0	0
<i>NTD</i>	0	0	0	0	0	1
<i>Zinc</i>	0	0	0	0	1	0

WHO Prequalification and National Regulators

The programme promotes interaction and close collaboration with and between national drug regulatory agencies, in both developing and wealthy countries. The legitimacy of the WHO PQP's decisions derives in part from this collaboration, and from its solid and transparent procedures and standards. The standards come out of an international consensus process conducted with Member States. The process concludes with review and adoption by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Transparency builds confidence. The WHO PQP goes beyond the current information sharing practices of national drug regulators.

The Programme has raised the bar for quality assurance. Its standards are recognized and promoted by others, helping expand quality medicines production. Medicines Patent Pool (MPP) licenses, for example, oblige producers to play by the WHO PQP's rules.³²

WHO PQP assessments have always been managed and led by WHO, but they are executed by designated assessors and inspectors from WHO

Member States. The Programme also trains regulatory personnel and manufacturers from low- and middle-income countries. On-the-job involvement in dossier assessment and site inspections are offered each year to selected regulatory personnel from low-income countries. Training programmes for medicines regulators and manufacturers reach about 1300 participants annually, the most extensive in the world.³³

In 2011, WHO developed a procedure to promote accelerated approval by national regulatory authorities of products already prequalified by WHO, reducing duplication of regulatory effort. The procedure speeds up access to markets and patient access to treatment. In total, 15 countries are now testing the procedure on two products.³⁴ The East African Community (EAC) relies on the WHO PQP regulatory format and standards for regional regulatory harmonization. The EAC medicines regulatory harmonization project serves as a model for the continent-wide African Medicines Regulatory Harmonization Initiative spearheaded by the New Partnership for Africa's Development.

To build capacity, especially for regulators from developing countries, in 2007 WHO created a rotating position at the WHO headquarters in Geneva. National regulatory assessors and inspectors work for 3 months in Geneva getting first-hand experience with WHO PQP, also interacting with other WHO units and departments that have roles in medicines regulation.

Prequalification and Innovation

WHO promotes and supports a public health approach to innovation in several ways. Recent editions of the WHO EML,³⁵ and the two WHO reports on Priority Medicines for Europe and the World of 2004³⁶ and 2013,³⁷ identified missing essential medicines, medicines that should exist but do not, such as ARV combinations for children, zinc tablets for the treatment of diarrhoea, and injectable long-term contraceptives. These reports encourage innovation in neglected areas.

Early in product development, the WHO PQP can specify what regulatory requirements will ultimately be applied to the newly developed products – data on safety and product stability, for example – avoiding delays and conserving resources of not-for-profit drug development partnerships and others developing products.

Finally, WHO prequalification publishes an independent assessment of the product, making it eligible for procurement through international funding. It then supports rapid regulatory approval in recipient countries. Rapid uptake of a new product encourages innovation.

Saving Lives and Saving Money

From a public health perspective, WHO PQP's greatest achievement is improved quality of key medicines used by millions of people in developing countries. In a study of 12 958 ARV purchase transactions between 2002 and 2008, Brenda Waning concluded that five ARVs recommended by WHO in 2003 constituted 98 per cent of the ARVs purchased in 2004–2006. The price of the major FDCs decreased from \$484 per person in 2002 to \$88 in 2008. Purchases of new ARVs recommended by WHO in 2006 increased 16–20 times in the 2 following years. By 2008, 85–88 per cent of the ARVs procured by PEPFAR, the Global Fund, and UNITAID were prequalified.³⁸

The programme has saved money both directly and indirectly. In 2006, the Clinton Health Access Initiative and McKinsey estimated WHO PQP contribution to increased public access to low-cost quality generics. On the basis of the use of first-line ART in Africa since 2004, every dollar invested in the prequalification programme saved \$200 in public medicine procurement.³⁹ The programme has maintained this positive benefit/cost ratio: in 2009 the estimated return on investment was \$170 of savings for every dollar spent on prequalification.

Saving for PEPFAR from buying generics has also been sizeable. A report by PEPFAR, Supply Chain Management Systems (SCMS), and USAID concluded: '\$1.1 billion in taxpayer money [had been] saved [over six years] by procuring generics rather than branded ARVs'.⁴⁰

Use of generics effectively doubled the number of patients who could be treated for the same funds. PEPFAR's products were qualified through the US FDA fast track system. Would the US FDA system have been created without WHO PQP? Perhaps the indirect impact of the programme may be as great as its direct impact.

All global health donors would seem to favour WHO prequalification. Yet WHO PQP's funding continues to depend on the Bill & Melinda Gates Foundation and UNITAID. The two contributed 80–90 per cent of the WHO PQP budget in 2013. Money strapped WHO could not help pay for the WHO PQP. A narrow funding base brings risks, including donor-driven priority setting. UNITAID's mandate, for example, to focus on HIV, TB, and malaria⁴¹ is fine, but from a public health perspective, other priorities for prequalification exist, such as insulin and low-cost medicines for chronic diseases.

To establish financial sustainability for WHO PQP, WHO has introduced a fee-based system whereby companies applying for

prequalification of their products may be charged a fee. However, will this fee-based mechanism jeopardize WHO PQP's full independence?

The Future of the WHO Prequalification Programme

The recent revision of the WHO HIV treatment guidelines, recommending treatment initiation when CD4 cell count falls to 500 cells/mm³ or less (instead of 350 cells/mm³) means that 26 million people in low- and middle-income countries are eligible for ARV treatment compared with 10 million under the 2010 guidelines.⁴² Continued access to low-cost quality ARVs in FDC formulation remains critical.

How long will the prequalification programme be needed, and how long will it need public funding? The simple answer to that question is: as long as UN agencies procure medicines for low- and middle-income countries; or until the WHO PQP is no longer needed to provide assistance to national regulatory agencies that lack capacity to assess the quality of the medicines their countries produce or import. However, that day is still far in the future.⁴³

A more nuanced response is also possible. The WHO PQP has always improved both the quality of generic first-line ARVs produced in low- and middle-income countries, and the capacity of their national regulators to assess the quality of these products. A long list of internationally approved products indicates a mature market for these medicines. The WHO prequalification programme has become less urgent, as regulators in producing countries or in regional regulatory centres of excellence can now manage the assessment. This is where WHO PQP has taken us farthest. The situation is stable unless new domestic manufacturers enter the market or programmes recommend new first-line medicines.

Less far along are therapeutic groups for which very few products have been prequalified (for example, new first-line ARV combinations, second-line TB medicines, zinc, misoprostol, and oxytocin), or where un-assessed or substandard products are still widely procured (for example, contraceptives). Here prequalification can help stimulate a mature market of quality-assured products. As long as very few products are prequalified, the WHO Expert Review Process can help UN agencies select the least risky products, pending their prequalification.

Least far along are therapeutic areas where hardly any good-quality generic medicines are available in low- and middle-income countries, and whose national regulators lack experience in evaluating those products. Examples include insulin for diabetes and anti-snake venom. WHO

medicines prequalification has not begun, but could presumably make an important contribution. The same applies for 'new' products produced or marketed only in countries without stringent regulatory agencies, such as the dapivirine vaginal ring, a microbicide to prevent HIV transmission.

Creating a mature medicines market for first-line ARVs for use in developing countries took about 10 years of large-scale public procurement. The prequalification programme could continue for a long time, with a slowly changing range of essential medicines of great public interest, each in its own market development cycle. Future funding could then remain project-based and time-limited. Dedicated funds would be raised for certain medicines for the period necessary to create a mature market. Large-scale procurers and their funders could then contribute financially to the programme to assure the quality of the products and to work towards market sustainability.

Pressure on the Development of New Generics

The more widespread patenting of pharmaceuticals in countries traditionally suppliers of generic medicines may affect the work of the WHO PQP. Generic companies concerned about legal action by patent holders may find it too risky to develop generic versions of new medicines, slowing down availability of newer, second- and third-line ARVs. Will new results from the Medicines Patent Pool offer a solution? Patent licenses negotiated by the Patent Pool attempt to assure development of low-cost generic versions of new molecules. Similarly, generic medicines may be produced as a result of a compulsory license or a direct voluntary license agreement between the patent holder and a generic manufacturer.

Some of the first generic companies to have WHO prequalified their early products (Cipla Ltd., Ranbaxy Laboratories) have improved quality performance to the point where industrialized country markets are open to them. Good-quality generic manufacturers may then be tempted to shift to markets where prices are more attractive, to the detriment of production of cheap generics for Africa. There may be a continued need to prequalified products from other, newer companies.

Conclusion

The last 13 years have underscored the importance of the WHO PQP for public health. Without it, the goal of WHO's '3 by 5' programme or

reaching 10 million people with ARTs would not have been achieved as quickly and inexpensively or at all. Donor money would likely have been wasted on products of unknown quality with potentially devastating effects for public health. The Programme is a good example of far-sighted concerted international action by the UN system, supported by NGOs and donors.

Donors and buyers of medicines must still demand quality assurance in their procurement and resist the primitive temptation to procure only the cheapest medicines. Failure to do so paralyses the effectiveness of the WHO PQP. TB programmes, for example, continued too long purchasing medicines of uncertain quality – thereby removing an incentive for manufacturers to invest in better quality. Users of medicines in the reproductive health and family-planning domains continue to buy products of unknown quality.

The WHO PQP has become a global public good that has helped save millions of lives. Most international organizations and many governments that procure and supply medicines depend on the WHO PQP. Yet very few choose to contribute financially to its work. The Global Fund spends around \$610 million per year on medicines and other pharmaceutical products. (The Global Fund, 3 September 2013, personal communication). PEPFAR spent \$1.2 billion on medicines procurement over 5 years.⁴⁴ The \$15 million annual budget for the WHO PQP represents less than 2 per cent of the annual amount spent on medicines by these two organizations alone. Reliance on two donors is risky. It is time a consortium of public and private global health donors create a sustainable funding base. WHO PQP is essential to assure their products' quality. It is the strongest mechanism currently in place to create sustainable regulatory systems in low- and middle-income countries. This alone justifies investment in WHO PQP.

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The Poorly Understood Power of TRIPS Flexibilities:

A comprehensive overview of their use in the procurement and supply of medicines 2001–2016

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Abstract

Millions of people, particularly in low- and middle-income countries, lack access to effective pharmaceuticals for a number of reasons, including unaffordability. The World Trade Organization (WTO) Declaration on the TRIPS Agreement and Public Health adopted at the Doha Ministerial Conference in 2001 recognised the importance of intellectual property for the development of new medicines, as well as the concerns about its effects on medicines prices. It outlined a number of mechanisms WTO Members can use to promote access to medicines, which have become known as 'TRIPS flexibilities' and include compulsory licensing of medicines patents and the pharmaceutical transition for least-developed countries (LDCs). This study documents the use by countries of TRIPS flexibilities to access lower priced generic medicines. We compiled a database of instances of the use of TRIPS flexibilities by countries over the period 2001-2016. We found 176 instances of the use of or intention to use TRIPS flexibilities by 89 countries. Of the 176 instances, 100 (56.8%) concerned compulsory licences, including public non-commercial use licences, and 40 (22.7%) concerned instances of the use of the LDC pharmaceutical transition. The remaining cases concerned parallel import (1), patent exception (3), and non-patent-related measures (32). Of the instances documented, 152 (86.4%) were executed. The instances covered products to treat 14 different diseases. However, 137 (77.8%) of the instances concerned medicines for HIV/AIDS and/or related diseases. Our study shows that integrating the use of TRIPS flexibilities in medicines procurement provides a legal and practical pathway to access lower-cost generic versions of patented medicines.

Introduction

Challenges posed by the high prices of antiretroviral medicines in the late 1990's, coupled with the widespread patenting of these medicines, resulted in efforts to develop greater flexibility in the implementation of the World Trade Organization (WTO) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS).¹ In 2001, the Ministerial Conference of the WTO adopted the Doha Declaration on the TRIPS Agreement and Public Health (Doha Declaration).² The Doha Declaration, while recognising the importance of intellectual property in the development of new medicines, also recognised the concern of the effects of intellectual property on medicines pricing. The Doha Declaration lists a number of measures that countries can take to ensure access to medicines for all, including the use of compulsory licensing to produce or purchase lower-priced generic medicines. Paragraph 7 of the Doha Declaration lifted the obligation to grant and enforce medicines patents and data protection for LDC Members, initially until 1 January 2016. The TRIPS Council formally adopted a decision implementing paragraph 7 in 2002³ and later extended it until at least 2033.⁴ The UN designates 48 countries as LDCs, of which today 36 are WTO Members.⁵

Compulsory licensing (CL) is the right granted by a government authority to make use of a patent during the patent term without the consent of the patent holder, for instance, for the production or supply of generic medicines. The government can also grant the authorization for its *own use*, called 'public non-commercial use' in Article 31 of TRIPS, and is also known as 'government use' (GU). A public non-commercial use licence can be assigned to a state agency, department, or a private entity. Upon the issuance of a CL or GU, the patent holder is generally entitled to adequate remuneration for the use of the patent.⁶

The extent to which countries have deployed TRIPS flexibilities in the procurement of medicines remains underreported. Previous studies have documented well-known and widely publicized cases of compulsory licensing but did not take into account the usage of TRIPS flexibilities in procurement.^{7 8} There are several statements in the literature that perpetuate the belief that since 2001 the use of TRIPS flexibilities has been sporadic and limited.^{9 10 11}

While we recognize that the TRIPS Agreement offers a range of flexibilities that are relevant for pharmaceutical and patenting policies of countries, including the right of countries to define and apply patentability criteria and to refuse to grant patents for certain subject matter (e.g. plants or

animals), this study focuses on those measures that can be directly applied in procurement and supply of medicines. In that respect, compulsory licensing, the LDC pharmaceutical transition, parallel import and patent exceptions are the most relevant measures in efforts to increase access to medicines.

Methods

The research is based on a database of instances of the use of TRIPS flexibilities by countries over the period 2001-2016, identified and collected by one of the authors on an ongoing basis since 2007. For 164 of 176 instances identified, information from primary sources is available: patent letters held by procurement agencies (non-public documents); legal documents such as licenses; and legal notifications such as declarations to use the LDC pharmaceutical transition, which were obtained from governments or procurement agencies, court documents and country notifications to the WTO. Eight instances were found in secondary literature¹² and official reports.¹³ Additionally, two instances were identified through personal communication with an NGO representative directly involved in the case who could confirm their existence,¹⁴ and one was reported by a civil society organization.¹⁵ Of the 12 instances without primary sources, nine were not executed; this explains the absence of formal legal or government documentation. We made a final verification of our capture of all instances through a targeted search in Lexis Nexis, Medline and Web of Science, using the following search terms: 'compulsory license pharmaceutical' OR 'compulsory licence pharmaceutical' OR 'compulsory licensing pharmaceutical' OR 'government use pharmaceutical' OR 'non-commercial use pharmaceutical' and screening of specialised list servers.¹⁶ This search yielded one more instance for the database.

We use the term 'instances' to refer to the following events: the announced intention by government to invoke a TRIPS flexibility, a request or application to invoke a TRIPS flexibility by a third party, the executed use of a TRIPS flexibility, and the cases in which a government declared there to be no relevant patents in the territory.

We categorized the instances according to the disease for which the measure was invoked, along with the WTO country classification at the time the instance occurred: developed countries (DevC), developing countries (DCs), least-developed countries (LDCs); observers (countries in accession negotiation) and non-members. For each instance, we identified the relevant products and verified the patent status of the products concerned using the Medspal database (medspal.org), government

documentation, and other information in the public domain to determine whether the use of a TRIPS-flexibility measure was indeed required to access the generic products (for example, if no valid patent existed, the use of a TRIPS flexibility would not have been necessary). For the instances that were not executed, we collected and analysed information about the reasons for non-execution.

Results

We collected 176 instances between 2011–2016 of government actions to ensure access to patented medicines, of which 144 involved the use of one of the following TRIPS flexibilities: compulsory licensing including public non-commercial use, the LDC pharmaceutical transition, parallel import, and the research exception.

Out of the 176 instances, 100 concerned compulsory licensing or public non-commercial use. Of those, 81 instances were executed. 19 were not executed because the patent holder had offered a price reduction or a donation (six cases) or had agreed to a voluntary license (five cases); in one case, no relevant patent existed that warranted the pursuit of the measure; five cases were rejected on legal or procedural grounds; one application was withdrawn by the applicant; and one application was pending since 2005 without a response.

We found 40 instances of the use of the LDC pharmaceutical transition by a total of 28 countries of which two were developing countries that erroneously invoked the LDC transition, three were observers, and one was a non-WTO Member.

Table 1. Frequency per type of measure

<i>type of measure</i>	<i>frequency</i>	<i>percentage</i>
compulsory licence	48	27,3
public non-commercial use (government use)	52	29,5
LDC pharmaceutical transition	40	22,7
no patents	26	14,8
research exemption	3	1,7
parallel import	1	0,6
import authorisation	6	3,4
total	176	100,0

We found one instance of the use of parallel import and three instances of the use of the research exception for the supply of generic medicines used in a clinical study. In 26 instances countries informed the supplier that there were no relevant patents in the territory; however, this was only the case in 4 of the 26 instances.

Six instances concerned import authorizations for products without reference to the patent status of the products for which the authorization was granted. Of these six instances, four concerned the importation of a product for which patents existed in the territory, the other two concerned non-WTO Members

Table 2. Type of TRIPS Flexibility per country classification and disease

WTO CLASSIFICATION / DISEASE	CL/GU (ART 31)		LDC Pharm transition (ART 66)		EXCEPTION (ART 30)		IMPORT AUTH*		PARALLEL IMPORT		NO PATENT DECLARED		TOTAL	
DevC														
HIV**	2	1%	0	0%	0	0%	0	0%	0	0%	0	0%	2	1%
Cancer	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%
Other	6	3%	0	0%	0	0%	0	0%	0	0%	0	0%	6	3%
DC														
HIV	51	29%	1	1%	3	2%	4	2%	0	0%	17	10%	76	43%
Cancer	11	6%	0	0%	0	0%	0	0%	0	0%	0	0%	11	6%
Other	9	5%	1	1%	0	0%	0	0%	1	1%	1	1%	12	7%
LDC														
HIV	12	7%	26	15%	0	0%	0	0%	0	0%	0	0%	38	22%
Cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Other	0		8	5%	0	0%	0	0%	0	0%	0	0%	8	5%
NON-WTO MEMBER														
HIV	1	1%	1	1%	0	0%	0	0%	0	0%	2	1%	4	2%
Cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	
Other	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	
WTO OBSERVER														
HIV	7	4%	2	1%	0	0%	2	1%	0	0%	6	3%	17	10%
Cancer	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	
Other	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	1	1%
TOTAL	100	57%	40	23%	3	2%	6	3%	1	1%	26	15%	176	100%

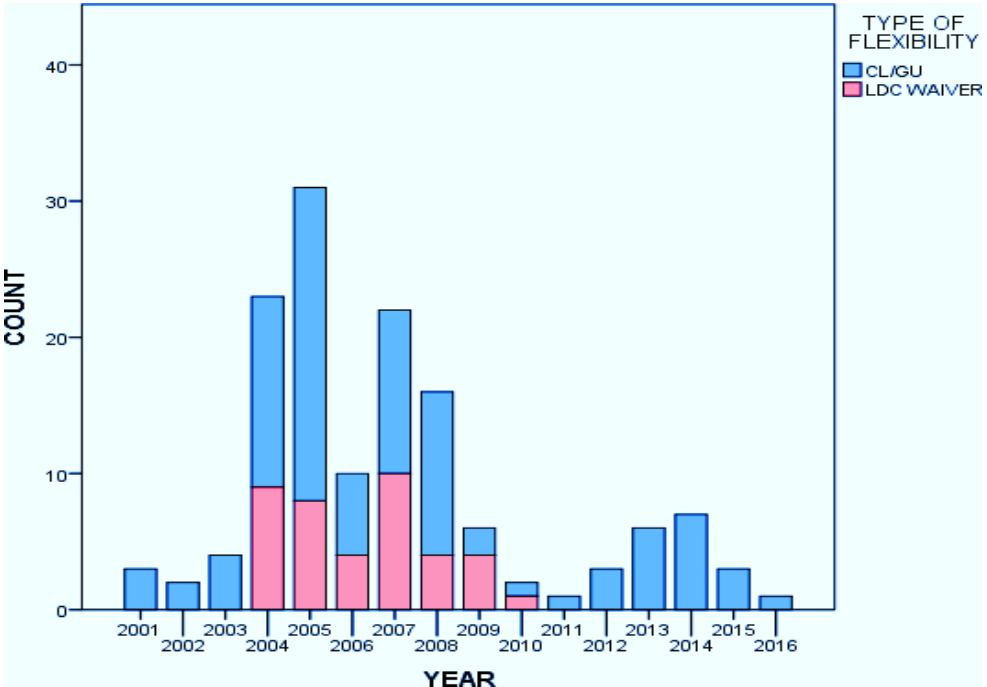
* import authorisation in case of patent but without reference to CL/GU or LDC transition

**HIV=HIV and related diseases

Table 2 presents the various diseases for which the flexibilities were used. As can be seen from the table, 74/140 (52.9%) instances of CL/GU and the LDC pharmaceutical transition were for HIV/AIDS and related diseases. 25% of LDCs instances (10/40) specified that the decision concerned all medicines. In 12/176 (6.8%) cases the flexibilities were used for cancer medication.

The use of flexibilities over time is presented in figure 1 which shows the use of CL/GU and LDC pharmaceutical transition peaking during the years 2004 -2008.

Figure 1. Compulsory licensing and LDC pharmaceutical transition 2001-2016



Discussion

Our study shows that during the period 2001–2016 countries have made extensive use of TRIPS flexibilities and reports previously unreported use. CL/GU and the LDC pharmaceutical transition were the most frequently used measures (79.5% of instances). The most comprehensive published database to date lists 34 potential CLs in 26 countries. We also documented 26 cases in which procurement of generic medicines took place after a statement of “no patent” was made. Strictly speaking this statement is not a

TRIPS flexibility. However, in only four of these 26 instances there were indeed no relevant patents; in 22/26 cases with a patent in force generic supply nevertheless took place. All these cases concerned HIV medications, which points to a more flexible attitude towards IP protection in the context of the global HIV response. In the vast majority of cases, the application of the TRIPS flexibilities was driven by the procurement of medicines for the treatment of HIV/AIDS and related diseases.

In 1998, the WHO published the first guide with recommendations to Member States on how to comply with TRIPS while limiting the negative effects of patent protection on medicines availability.¹⁷ The political momentum of the WHO “3 by 5” initiative for HIV treatment, combined with HIV treatment activism and new funding from governments, the Global Fund, and the US President's Emergency Plan for AIDS Relief (PEPFAR), allowed countries to scale up the procurement of antiretroviral medicines. The new global funding mechanisms provided procurement guidelines that encouraged countries to purchase low-priced medicines. The Global Fund, for example, encouraged its recipients ‘to attain and to use the lowest price of products through competitive purchasing from qualified manufacturers.’ The Fund also specifically encouraged ‘recipients in countries that are WTO Members to use the provisions of the TRIPS Agreement and interpreted in the Doha Declaration, including the flexibilities therein, to ensure the lowest possible price for products of assured quality.’¹⁸ World Bank guidelines for the procurement of HIV medicines provided practical guidance to governments on how to use various TRIPS flexibilities in the procurement of HIV medicines.¹⁹

Antiretroviral medicines (ARVs) were the first class of new essential medicines that were widely patented²⁰ and medicines procurement agencies did not have experience with the supply of such products. In the late nineties, concern about possible patent infringement suits was common among the suppliers of medicines. This concern was based on the fact that a number of legal disputes had broken out.²¹ Patent holders threatened procurement organizations that supplied generic HIV medicines in sub-Saharan Africa with legal action.^{22 23} Procurement agencies therefore sought assurance that they could supply ARVs without the risk of legal action by patent holders. The 2001 Doha Declaration offered a much-needed clarification on WTO Members’ legal rights regarding intellectual property and public health, that would become important in offering such assurances. It was also an important political statement of support to countries that were struggling to provide access to high priced medicines while complying with the TRIPS Agreement.²⁴

The increased funding for HIV treatment explains the increase of instances in the use of the TRIPS flexibilities after 2003 (see figure 1). The use of the flexibilities has helped create and sustain the generic competition that has brought HIV medicines prices down. By 2008, 95% (by volume) of the global donor-funded ARV market was comprised of generic medicines, primarily from India, where these medicines were not patented and offered fixed-dose combinations of ARVs that were not available elsewhere.²⁵ By 2008 certain companies had issued non-assert statements (commitments not to enforce their patents)²⁶ or engaged in voluntary licensing, often in response to the threat of a compulsory licence.

The employment of TRIPS flexibilities to treat HIV/AIDS decreased after 2008. By then voluntary licensing had become more common and in 2010, with the support of UNITAID, the Medicines Patent Pool (MPP) was founded. The MPP negotiated voluntary licenses to enable the production and supply of generic HIV medicines. Countries within the territorial scope of the MPP licenses therefore no longer need to invoke TRIPS flexibilities for HIV. The territorial scope of the MPP licences for adult formulations covers 87% to 91% of people living with HIV in developing countries and 99% for paediatrics.²⁷

Today 93% of people with HIV who have access to ARVs use generic products.²⁸ This would not be the case if the decrease in the use of TRIPS flexibilities had meant that countries were switching back to originator products. The MPP's disease scope now also includes hepatitis C and tuberculosis (TB). The Lancet Commission on Essential Medicines Policies recommends inclusion of all new essential medicines in the scope of the work of the MPP.²¹

It is interesting to note that most of the instances documented by this study were invoked and executed in day-to-day procurement practice and took place without much publicity. This procurement practice was very effective, especially for the supply of generic HIV medicines. This relatively unknown utilization of the TRIPS flexibilities in regular drug procurement is in stark contrast with the publicity attracted by some instances in middle-income countries. Compulsory licenses issued by Brazil,²⁹ Thailand,³⁰ and India,³¹ for example, became *causes célèbres* because of the harsh responses they provoked by the US and EU, which discourage the uptake of TRIPS flexibilities.³² For example, when India issued a compulsory licence in 2012 for a cancer medicine it provoked an out-of-cycle review by the US Trade Representative.³³ In 2016, Colombia sought support from the WHO to issue a compulsory license for the cancer drug imatinib, a medicine included in the WHO Model List of Essential Medicines.³⁴ The country had come under

strong pressure from the US and Switzerland to abandon its plans to issue this license, with the US officials threatening the withdrawal of financial support for Colombia's peace process.³⁵ These disputes show that effective use of TRIPS flexibilities remains politically sensitive. An important observation from our study is that the majority of the cases of TRIPS flexibilities were actually successfully executed.

There are, therefore, lessons to be learned from the procurement practices of ARVs for the future procurement of other new essential medicines when they are patented and highly priced. Due to the globalization of intellectual property norms through international trade law, new essential medicines for diseases such as cancer, tuberculosis, and hepatitis C will likely be widely patented.³⁶ In 2015, the WHO added a number of new, high-priced medicines to their Model List of Essential Medicines. Initiatives by pharmaceutical companies for the facilitation of access to medicines outside of the field of HIV are weak and predominantly based on donations or small-scale patient based price discounts.³⁷ Global funding for medicines outside HIV, TB, and malaria is lacking, which makes greater efficiency in the procurement of lower-cost medicines all the more important. Furthermore, in the face of increasingly widespread pharmaceutical patenting and hence nations' problems to provide access to high-priced medicines, the use of TRIPS flexibilities may become more relevant and urgent.

Our study shows that public non-commercial use of a patent and the LDC pharmaceutical transition have been applied effectively by governments in the procurement of medicines to offer the required legal assurances to suppliers of generic products. These mechanisms can also be legally used for medicines other than those for HIV/AIDS treatment. The procurement processes of generic medicines for new expensive medicines can be streamlined through the use of standard license models for this purpose.³⁸

The use of TRIPS flexibilities also remains important for countries that are excluded from voluntary licenses, including those of the MPP. The reason is that generic products produced under a voluntary license may be supplied to a country outside the scope of that licence if the importing country has issued a compulsory licence.³⁹ The flexibilities also remain important for disease areas in which voluntary licenses or other access initiatives do not exist, such as cancer and other non-communicable diseases.

Government non-commercial use of patents is not new. In the sixties and seventies of the last century, some European governments and the US

routinely used this method. The call to reinstate use of this measure in high-income countries to battle high medicines pricing is getting louder, as seen in France,⁴⁰ the UK,⁴¹ Ireland,⁴² The Netherlands,⁴³ Chile,⁴⁴ and the US.⁴⁵ With only a veiled reference to the high price of hepatitis C medicines, the Italian government recently gave its citizens the right to import more affordable generic versions of medicines for personal use.⁴⁶ In 2016 the German Federal Patent Court issued a compulsory license for the ARV medicine raltegravir, quoting urgent public interest of the patients and health risks of the non-availability of the ARV.⁴⁷

The use of TRIPS flexibilities therefore is an important tool for countries to fulfil their human rights obligations to provide access to essential medicines as part of the progressive realization of the right to health.⁴⁸ Alongside the legal obligation of states, pharmaceutical companies also have a responsibility to provide access to medicines, including through voluntary licensing.⁴⁹ The MPP could therefore expand to include all new essential medicines, so that these medicines can become available as generics well before the patents expire in low and middle-income countries. In the absence of such licenses, governments can use the TRIPS flexibilities as part of regular procurement.

Regrettably, while the need for government resolve and action to bring down the price of medicines of patented products is growing, the policy space to do so is narrowing because of TRIPS-plus provisions resulting from trade agreements.⁵⁰ TRIPS-plus provisions render the remedies in the TRIPS Agreement, such as compulsory licensing, less effective by putting restrictions on their use. An example is limiting the grounds for compulsory licensing to cases of emergency situations, which would make the use of compulsory licensing in regular procurement nearly impossible.³⁵ Further, the political response from high-income countries to the use of TRIPS flexibilities by certain middle-income countries is a significant obstacle to their routine use. The strong political responses to the plans of even a few countries to issue a compulsory licence for cancer medications are likely to have a chilling effect on others.

Conclusion

Our study shows that the use of TRIPS flexibilities has been effective in the procurement of generic essential medicines in particular those for HIV, and has been more widespread than is commonly assumed. In light of many countries' problems providing access to high-priced patented medicines, the employment of TRIPS flexibilities becomes even more relevant. TRIPS

flexibilities should not be regarded as a measure of last resort, but can routinely be considered in the procurement of generic versions of expensive new essential medicines, with adequate remuneration to the patent holder. This will help create and sustain the necessary generic competition that has proven effective in bringing medicines prices down and promoting universal access to essential medicines for all.

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Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union:

A proposal for greater coherence in European pharmaceutical legislation

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Abstract

The challenge of providing access to high-priced patented medicines is a global problem affecting all countries. A decade and a half ago the use of flexibilities contained in the World Trade Organization Agreement on Trade Related Aspects of Intellectual Property Rights, in particular compulsory licensing, was seen as a mechanism to respond to high-price medicines for the treatment of HIV/AIDS in low- and middle-income countries. Today a number of upper-income European Union (EU) Member States is contemplating the use of compulsory licensing in their efforts to reduce expenditure on pharmaceutical products. EU regulation of clinical test data protection and the granting of market exclusivity interfere with the effective use of compulsory licensing by EU Member States and can even prevent access to off-patent medicines because they prohibit registration of generic equivalents.

EU pharmaceutical legislation should be amended to allow waivers to data and market exclusivity in cases of public health need and when a compulsory or government use license has been issued. Such an amendment can be modelled after existing waivers in the *EU Regulation on compulsory licensing of patents for the manufacture of pharmaceutical products for export to countries with public health problems outside the EU*.

Allowing a public health/compulsory license exception to data and market exclusivity would bring greater coherence between EC regulation of medicinal products and national provisions on compulsory licensing and ensure that Member States can take measures to protect public health and promote access to medicines for all.

Protection of clinical test data, and exceptions to data exclusivity to allow registration of generic medicines

This paper addresses the issue of clinical test data regulation in the European Union which currently prohibits the use of the originator's pre-clinical and clinical test data in the processing of a marketing authorization for a generic medicine for a period of eight years. This is called the data exclusivity. After the eight years have passed the regulatory authorities can process the generic company's application for marketing authorization but the product may not be put on the market until ten years has passed after the initial marketing authorization of the originator product. This is called market exclusivity. Under certain circumstances, an additional one year of market exclusivity may be obtained, for example when the originator company is granted a marketing authorization for a significant new indication. This system of data and market exclusivity is also known as the 8+2+1 rule. The EU pharmaceutical legislation has no exception to this rule, which means that EU countries cannot register a generic product during the data/market exclusivity period, even when the medicine is needed for compelling public health reasons or emergencies or when a compulsory or government use license has been issued on a medicine patent. This paper will make recommendations for necessary changes to the EU pharmaceutical legislation to enable individual EU Member states to grant public health exceptions to data/market exclusivity and to make effective use of compulsory licenses.

Data exclusivity and TRIPS

Data exclusivity and market exclusivity are not requirements of international intellectual property law. While Article 39.3 of the TRIPS Agreement requires governments to *protect* undisclosed test data submitted for the registration of new chemical entities *against unfair commercial use*, it does not oblige countries to confer exclusive rights over data related to marketing approval to the originator company.¹ The scope of TRIPS Art. 39.3 is limited to the *protection* of undisclosed data required by a national

authority as a condition for obtaining marketing approval for a medicine, which ‘utilize new chemical entities,’ provided that the generation of the data involved a considerable effort.² Article 39.3 of TRIPS therefore leaves ample flexibility for a data protection regime that allows the marketing authorisation of generic medicines. It also leaves flexibility to deal with regimes, as in the EU, where TRIPS-plus data exclusivities are granted.

However, as discussed further below, the EU medicines legislation goes well beyond the requirements of the World Trade Organization (WTO) Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement Art.39.3 in granting exclusive rights that form an obstacle to the effective use of compulsory licensing by EU Member States regardless of the reasons for the licence and even in emergency situations.

In a 2006 letter to the European Generic Medicines Association, which was seeking clarification on whether data exclusivity would apply in case of an emergency compulsory licence for the flu medicine Tamiflu within the European Union, the European Commission acknowledged that the ‘Community pharmaceutical *acquis* does not currently contain any provision allowing a waiver of the rules on data exclusivity and marketing protection periods’.³ The European Commission, however, has yet to take any initiative to propose such a waiver in pharmaceutical legislation.

Compulsory licensing for public health

The WTO TRIPS⁴ includes provisions for compulsory licensing, a mechanism whereby a government grants third parties or itself the right to use a patent without the consent of the patent holder. When a government grants itself the right to make use of a patent, this is called ‘government use’, or ‘public non-commercial use’.⁵ Government use or public non-commercial use of a patent can be particularly useful in public procurement of medicines. A government may also authorise a third party to act on behalf of the government, for example, a medicines procurement agent, to perform certain acts that otherwise would have constituted a patent infringement. Payment of adequate remuneration – a reasonable royalty – to the patent holder is required when a compulsory licence is granted. In the case of government use, in case of a national emergency or other circumstances of extreme urgency, and in cases where a compulsory licence is issued to correct anti-competitive practices, there is no requirement to first seek a voluntary licence.⁶⁷

The government is free to determine the grounds for granting a compulsory licence. Some countries’ domestic law includes specific

grounds for issuing a compulsory licence such as ‘high prices’ of medicines, or a ‘lack of access to medicines’. For example, French patent law authorises government use upon request by the minister of health when medicines are ‘only available to the public in insufficient quantity or quality or at abnormally high prices’.⁸

In 2001 the WTO Doha Declaration on the TRIPS Agreement and Public Health⁹ provided a welcome clarification of the flexibilities^{10 11} contained in the TRIPS Agreement for the purpose of public health and specifically to promote ‘access to medicines for all’.¹² With the background of trade pressure on low- and middle-income countries that contemplated the use of compulsory licensing and other TRIPS-flexibilities, the Doha Declaration took away any doubts about the legality of such measures. Subsequently, low- and middle-income countries have used TRIPS flexibilities on a large scale to facilitate the supply of low-cost generic medicines used for the treatment of HIV.¹³

More recently, interest in the usage of TRIPS flexibilities for a broader range of health products has been growing. The UN High Level Panel on Access to Medicines recommended the use of TRIPS-flexibilities and the implementation of legislation that facilitates the issuance of compulsory licences ‘*designed to effectuate quick, fair, predictable and implementable compulsory licenses for legitimate public health needs*’.¹⁴ The Lancet Commission on Essential Medicines Policies recommended that national patent legislation allow for easy deployment of TRIPS flexibilities, effective automatic licensing of essential medicines in the absence of voluntary agreements, and regulatory test data protection rules that provide the necessary flexibility to register products submitted by licensees.¹⁵ These recommendations echo those from the Global Health Law Committee of the International Law Association.¹⁶ The European Parliament has adopted a resolution on options for the EU for improving access to medicines, which includes the use of compulsory licensing by EU Member States.¹⁷

High medicines prices, compulsory licensing and data exclusivity in the European Union

A decade and a half ago, the use of TRIPS flexibilities and in particular compulsory licensing was seen primarily as a mechanism to respond to the HIV/AIDS crisis in low- and middle- income countries. Today, a number of EU Member States, including high-income countries, struggle to formulate an effective response to high-priced patented medicines. In the UK, the National Institute for Health and Care Excellence (NICE) has

recommended against making the breast cancer medicine trastuzumab emtansine available through the National Health Service because of the high price, while recognising that the medicine is effective.¹⁸ In Italy the government has authorised the importation of generic direct-acting antiviral medicines for the treatment of hepatitis C on an individual basis to increase access to these medicines.¹⁹ In Switzerland, patients denied access to new hepatitis C treatment can receive reimbursement by some insurance companies when they source generic medicines for the treatment in India at a lower price.²⁰

Governments have signalled that they lack the negotiating power to obtain good results in price negotiations concerning patented products,^{21 22} despite the fact that production-cost data show that medicines can often be made for a fraction of the price demanded by the originator company. [Table 4] The Dutch ministers of health and international trade wrote in the *Lancet* about the challenges of negotiating with patent holders: “Patent and intellectual property exclusivities are the only cornerstone of the current model. Companies can ask the price they like. This will no longer do. We need to develop alternative business models.”²³

Table 4: Price of selected essential medicines and cost of production ^{30 31 32}

<i>medicine</i>	<i>originator price intro us</i>	<i>cost of production</i>
tuberculosis		
bedaquiline	\$ 30000 (6 month)	\$ 48–101
hepatitis C		
sofosbuvir (SOF)	\$ 84000 (12 week)	\$68–136
SOF+ledipasvir	\$ 95000 (12 weeks)	\$ 193
simeprevir	\$ 66360 (12 weeks)	\$130–270
daclatasvir	\$ 63000 (12 weeks)	\$10–30
cancer		
imatinib	\$ 30000–\$100000 (1y)	\$ 119–159
trastuzumab	\$54000 (1 y)	\$ 242

Patients and medical professionals and in some cases health authorities in high-income countries have become more vocal in asking their governments to address the patent barriers to accessing lower-priced medicines and to invoke compulsory licensing.^{24 25 26 27 28 29}

Referencing the lawful production or importation of affordable generic medicines through the use of compulsory licences will strengthen the hand of governments in price negotiations and is an effective remedy if price negotiations fail to deliver the desired result. There are lessons from the past when government use was routine in the procurement of medicines

for use in national health systems; for example, in the sixties and seventies in the UK, compulsory licensing had become common practice in government procurement by the NHS. Attempts by the industry to halt this practice at the time failed.³³

However, the ability of the EU to provide more affordable access to a patent-protected medicine through a compulsory licence may be hindered if the originator company's product simultaneously benefits from data exclusivity. Data exclusivity refers to exclusive rights granted to the original manufacturer of a medicine over the use of test data required for the registration of the product. These exclusive rights are distinct from patent rights in that they are granted by the medicines regulatory authority³⁴ in relation to safety and efficacy data submitted for the approval of originator medicines.

According to the EU Regulation for the authorisation and supervision of medicinal products,³⁵ a generic medicine may only be authorised with reference to the originator's registration file once eight years of data exclusivity has passed, and may only be placed on the market ten years after the initial marketing authorisation for the originator product has been granted. This marketing period may be extended to 11 years in cases of new indications that have a significant clinical benefit over existing indications.³⁶ This means that a generic applicant cannot submit a market authorization based solely on bioequivalence data before the expiration of eight years and instead would have to provide self-generated pre-clinical and clinical trial test data, which generic companies typically do not do. Additionally, such clinical trials would mean an unnecessary duplication of studies³⁷ and raise ethical questions. In the EU data and market exclusivity applies to both small molecules and biologics.

At present, EU pharmaceutical legislation does not provide for exceptions to the eight to ten years data and market exclusivity. Even in cases of national emergency or other situation of urgency, there are no explicit waivers foreseen in EU law to address the need to authorise the marketing of a generic product before the aforementioned exclusivity periods expire. Even though issuing a compulsory licence to overcome patents blocking the use of a generic medicine is a matter of national law, regulatory requirements for EU-wide marketing authorisation, including data exclusivity, are a matter of European pharmaceutical legislation. These concurrent legal systems lack coherence, both with regards to the effective use of compulsory licensing by EU Member States and with respect to public interest exceptions to data exclusivity more broadly.

Case of Romania

In 2016, the government of Romania contemplated issuing a compulsory licence for the hepatitis C medicine sofosbuvir, which, in Europe, was only available from the originator company at a price of around 50.000 euro for a 12-week treatment.³⁸ Since the registration of a generic version of sofosbuvir is not possible before the expiry of the data exclusivity in 2022,³⁹ Romania, like any other EU Member State, cannot give effect to a compulsory licence. Further, the EU market exclusivity for sofosbuvir expires at the earliest in 2024. The case of Romania reveals the obstacles to the effective use of compulsory licensing created by EU data exclusivity.

Use of DE waivers in voluntary licences aimed at ensuring access to medicines

The need to provide data exclusivity waivers to ensure effective availability of generic medicines is often acknowledged in voluntary licences. For example, all Medicines Patent Pool⁴⁰ (MPP) licences include a data exclusivity waiver to facilitate regulatory approval of generic medicines manufactured by MPP's licensees. These waivers are necessary to ensure that generic manufacturers that sign MPP licences are not prevented from registering their products in countries which are part of the licensed territory and which grant test data exclusivity. For instance, Guatemala is included in the territory of the MPP licences with ViiV Healthcare for paediatric formulations of dolutegravir (DTG) and for adult formulations of DTG and DTG/abacavir (ABC). The licences specifically state that:

ViiV shall provide any Sublicensee with NCE Exclusivity or other regulatory exclusivity waivers to the extent required by the applicable regulatory authorities in order to manufacture or sell Product in the Territory in accordance with the terms of the Sublicence. ViiV shall further provide to any Sublicensee such consents which it has the legal capacity to give as are necessary to enable such Sublicensee to perform its obligations.⁴¹

As indicated in the patent database Medspal,⁴² the formulations of DTG 50mg and ABC/DTG/3TC 600/50/300 mg are protected by test data exclusivity in Guatemala until 11 November 2020 and 29 November 2021 respectively. However, MPP licensees will nevertheless be able to register and market generic versions of these formulations in Guatemala before the expiration of these rights, based on the waiver included in the MPP licence agreements.

Gilead has also included the following waiver of data exclusivity in its licence agreements for sofosbuvir:

Gilead agrees to provide Licensee with NCE Exclusivity, or other regulatory exclusivity, waivers as may be required by the applicable regulatory authorities in order to manufacture or sell Product in the Territory, provided such manufacture and sale by Licensee is compliant with the terms and conditions of this Agreement. Licensee agrees not to pursue or obtain regulatory exclusivity on any Product in any country within the Territory.⁴³

Even though Gilead obtained test data exclusivity for sofosbuvir 400 mg until 14 July 2021 in Guatemala, for instance, Gilead licensees cannot not be barred from registering and selling generic versions of SOF 400mg during this data exclusivity period in Guatemala, which is included in the licensed territory. Governments, including in the EU, should be able to provide similar data exclusivity waivers.

Data exclusivity waivers in national legislation in other jurisdictions

Some middle- and high-income countries, all of them members of the WTO and thus subject to the TRIPS Agreement, provide for explicit data exclusivity waivers in medicines regulations or in relation to the use of compulsory licences in patent laws, with a view to facilitating generic medicines registration and sales where necessary to protect public health. For example, Section 5 of **Malaysia** 2011 Directive of Data Exclusivity,⁴⁴ entitled Non-Application of Data Exclusivity, provides that

Nothing in the Data Exclusivity shall:

- (i) apply to situations where compulsory licenses have been issued or the implementation of any other measures consistent with the need to protect public health and ensure access for all; or
- (ii) prevent the Government from taking any necessary action to protect public health, national security, non-commercial public use, national emergency, public health crisis or other extremely urgent circumstances declared by the Government.

In **Chile**, Article 91 of Law 19.996, as amended in 2012,⁴⁵ provides that test data exclusivity shall not be applied as follows:

- (b) Where, for reasons of public health, national security, public non-commercial use, national emergency or other circumstances of extreme urgency declared by the competent authority, it is justified to terminate the protection referred in Article 89 (e.g. on

test data exclusivity).

- (c) The pharmaceutical or agrochemical product is the subject of a compulsory license in conformity with the provisions of this law.

In **Colombia**, Article 4 of Decree 2085 of 2002 on data exclusivity provides that,

‘The protection referred to in this Decree does not apply in the following cases [...] c) where necessary to protect the public, as qualified by the Ministry of Health’.⁴⁶

Other exceptions in the US: trade agreements and the New Trade Policy exception

The US data/marketing exclusivity rule on previously unapproved chemical entities (new small molecule medicines) is that there are five years of marketing exclusivity and that a generic may not apply for tentative marketing approval until after the fourth year and may do so only if the applicant certifies that the underlying patent is invalid or that the medicine will be non-infringing. Final or tentative approval is not available until at least the end of the fifth year.^{47 48} If the original period of exclusivity is extended with three years because of new clinical trial data involving a previously approved chemical entity, e.g., for a new use or new formulation, an application for tentative approval is possible any time during the three years.⁴⁹ For biologics, the effective marketing exclusivity term provided by the *Biologics Price Competition and Innovation Act* is 12 years from the date the reference product was first licensed; there is data exclusivity preventing even applications for tentative approval for the first four years.⁵⁰

As with the EU, there is no express exception in US law to data/marketing exclusivity on medicines or biologics. However, the 10 May 2007 New Trade Policy⁵¹ in the US authorized an express public health exception to data/market exclusivity in the event of a compulsory licence or other public health need. Implementation flexibility to that effect was included in several US developing-country free-trade agreements (FTA), including FTAs with Colombia, Panama, and Peru:

For pharmaceutical products, Article 16.10.2(e)(i) provides an exception to the data exclusivity obligations for measures to protect public health in accordance with the Declaration on the TRIPS Agreement and Public Health (WT/MIN(01)/DEC/2) (the ‘Doha Declaration’). Thus, where a Party issues a compulsory licence in accordance with Article 31 of the TRIPS

Agreement and the Doha Declaration, the data exclusivity obligations in Chapter Sixteen will not prevent the adoption or implementation of such a public health measure. In addition, in a case in which there is no patent on the pharmaceutical product, and, therefore, no need to issue a compulsory licence, the data exclusivity obligations in Chapter Sixteen will not prevent the adoption or implementation of such a measure.⁵²

The advantage of the US New Trade Policy approach is that it allows countries to disregard data/marketing exclusivity if they take measures to protect public health, regardless of whether a compulsory licence needs to be issued or not – depending on the patent status of the medicine in question.

Existing EU legislation containing waivers or exceptions to data and market exclusivity

Waivers to data exclusivity and market exclusivity rules do exist in the *EU Regulation on compulsory licensing of patents for the manufacture of pharmaceutical products for export to countries with public health problems outside the EU*.⁵³ This regulation implements the WTO 'August 30 2003 decision', which provided a waiver to the TRIPS Article 31(f) requirement that production under a compulsory licence be predominantly for the domestic market. This restriction seriously hampered the use of compulsory licensing by countries that were dependent on the importation of medicines. The 30 August 2003 waiver recently became a permanent amendment of the TRIPS Agreement.⁵⁴ Article 18 of the EU Regulation addresses the situation in which the applicant for a compulsory licence for manufacture and export of a medicine outside the EU may use the scientific opinion procedure of the European Medicines Agency (EMA),⁵⁵ ⁵⁶ or any similar national procedures, to assess quality, safety, and efficacy of medicines intended exclusively for markets outside the EU. It provides waivers to exclusivity rules necessary to obtain such opinions from the EMA or national authorities.⁵⁷ ⁵⁸

Certain EU trade agreements establish, in regards to test data, that Member States may provide exceptions to exclusivity for reasons of public interest and for situations of national emergency or extreme urgency when it is necessary to allow access to certain data to third parties. Such a provision can be found, for instance, in Article 231(4) of the EU-Peru Agreement which reads: '[t]he Parties may regulate exceptions for reasons of public interest, situations of national emergency or extreme urgency, when it is necessary to allow access to those data to third parties.'⁵⁹ In practice, this means

that the EU and Peru, both party to this agreement, may provide and use data exclusivity waivers to ensure effective use of compulsory licence. The waiver may also be relevant for non-patented products that benefit from exclusivity in the market because of data exclusivity.

For example, in Peru, daclatasvir, used in the treatment of hepatitis C, is patented until 2027 and benefits from a five-year data exclusivity period set to expire in July 2019.⁶⁰ If the relevant Peruvian authority issues a compulsory licence to authorise the supply of generic daclatasvir, the medicines agency can ignore the data exclusivity and provide the necessary marketing authorisation for the generic product.

Peruvian law includes a specific exception to data exclusivity that allows the registration authority to authorise third parties to use pharmaceutical test data for reasons of public health and situations of national emergency or extreme urgency. In addition, the legislation specifically authorises third parties to use or refer to the test data in their application to obtain registration in case of a compulsory licence.⁶¹

The EU trade agreements create rights and obligations for all parties to the agreement, and therefore further strengthens the case for regulating explicit exceptions to data and market exclusivity in cases where a compulsory licence and/or other measures in the interest of public health are taken in the EU or by EU Member States.

Recommendation for greater legislative coherence in the EU

The right of governments to grant compulsory licences, including for public non-commercial use, is acknowledged in international law, including in TRIPS. Effective use of such licences requires a waiver of data exclusivity for the approval and marketing of licensed generic medicines. However, such waivers do not exist under EU law and as a result, an entity authorized to make use of the patent to supply a generic medicine under a compulsory licence still might not be able to do so because it cannot obtain a marketing authorisation from the relevant medicine regulatory authority. This lack of legal coherence within the EU renders national compulsory licensing provisions useless with respect to EMA approved medicines protected by data exclusivity.

Some patent holders recognise the need to address the barrier to market entry that data exclusivity can create. They therefore include relevant waivers in voluntary licence agreements, to ensure that licensed rights can be used effectively by licensees. For example, all licence agreements of the Medicines Patent Pool contain such waivers. The need

for data exclusivity waivers is also recognised in the US New Trade Policy of 2007 and certain bilateral trade agreements to which the EU is a party. Since a compulsory licence is a government remedy for the absence of a voluntary licence, the government should also be able to attach conditions to the licence including a waiver of data and market exclusivity.⁶² Further, data and market exclusivity waivers should also be available in situations where a needed medicine is not protected by a patent but a public health concern requires its availability.

The EU regulation on the grant of compulsory licensing for export does contain waivers for data and market exclusivity. These waivers allow European regulatory authorities to review dossiers of such licensed generic medicines to address third countries needs for affordable medicines. A similar waiver should be available to facilitate effective use of compulsory licensing or other measures needed for the advancement of public health within the European Union.

There is an urgent need to bring coherence to EU law now that Member States are under pressure to seek ways to ensure the availability of new essential medicines without undue burden on their health budgets. EU health ministers have recognised that steps need to be taken to address the effects of highly priced patented medicines on their budgets.⁶³ Legal coherence can be achieved by inserting the following provision into the EU legal framework governing medicinal products for human use:

‘The protection periods set out in article 14 (11) of Regulation 726/2004 shall not apply in cases where it is necessary to allow access to and the use of pharmaceutical test data to register a generic of a reference medicinal product, which is or has been authorised under article 6 of Directive 2001/83/EC, for reasons of public interest including public health, in case of compulsory licensing of patents, including for public non-commercial use, and in situations of national emergency or extreme urgency.’

In cases other than compulsory licensing and public non-commercial use of patents where adequate remuneration for the patent holder is required, payment of an adequate remuneration for the use of test data to the holder of the marketing authorisation of the reference medicinal product could be required. The adequacy of the remuneration could be determined based on an audited disclosure of direct drug development expenditure by the originator.⁶⁴ Alternatively, the royalty guidelines for non-voluntary use of a patent on medical technologies published by the UNDP and WHO could provide guidance for setting a remuneration rate.⁶⁵

Conclusion

Amending EU legislation to introduce waivers of data and market exclusivity requirements will ensure that European patients can benefit from flexibilities in patent law and that data and market exclusivities do not undermine EU Member States' ability to take measures needed to protect and promote public health. The proposed amendment would bring greater coherence between European regulation of medicinal products and national provisions on compulsory licensing in EU member States. The ability to effectively apply compulsory licensing will also strengthen the position of EU Member States in price negotiations with pharmaceutical companies. When such negotiations do not bring a satisfactory result, Member States can resort to compulsory licensing and produce or import lower-priced products without the consent of the patent owner.

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List of abbreviations

3TC: Lamivudine	MPP: Medicines Patent Pool
ABC: Abacavir	NCE: New Chemical Entity
DTG: Dolutegravir	NHS: National Health Service
EMA: European Medicines Agency	SOF: Sofosbuvir
EU: European Union	TRIPS: Agreement on Trade Related Aspects of Intellectual Property Rights
FTA: Free-trade agreement	UNDP: United Nations Development Program
HIV/AIDS: Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome	UK: United Kingdom
	US: United States
	UN: United Nations
	WTO: World Trade Organization

Developing Missing Essential Medicines

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A patient's experience

Bina is a single mother with three children. Just after the youngest was born, Bina tested positive for pulmonary tuberculosis. After a few months of treatment she felt better and stopped the treatment. A year later she began coughing again, and she was diagnosed with drug-resistant tuberculosis. Following this she needed daily injections for at least 6 months, as well as many pills. Bina was terrified: she was not sure how to keep up with the treatment and continue supporting her children at the same time. She begged the doctors for another medicine that was easier to use and less toxic. They told her that this medicine did not exist, and that she should consider herself lucky to live in an area with a hospital that could treat drug-resistant tuberculosis.

Introduction

The present system of developing new medicines is in crisis, as it largely fails to produce much-needed products to address the health needs of millions of people.¹ When new essential medicines are developed, market exclusivity, through patents or other mechanisms, allows for pricing that potentially makes them unaffordable, even in HICs.^{2 3}

In many cases missing essential medicines are not even developed at all. Even though the early stages of R&D of medicines has large public investment, the process of taking them to market is largely carried out by for-profit companies. Pharmaceutical companies and their shareholders are

typically reluctant to invest in developing medicines for patient populations that do not represent a profitable market or for diseases predominantly affecting LMICs.⁴

The problems of high prices and missing essential medicines are related, and both disproportionately affect people in LMICs. This section presents a summary of the complex and political problems ingrained in the current patent-based-innovation system.^{5–6} It examines the initiatives to address the system's deficiencies, and proposes concerted global actions and public policy interventions to lay the foundation for sustainable approaches to essential medicines development.

Key problems of the current innovation system

WHO,^{7–8} *The Lancet's* Commission on Global Health 2035,⁹ and the UN¹⁰ have all offered lists of missing essential medicines. Some important unmet public health needs include heat-stable insulin and oxytocin,¹¹ shorter treatments for latent and active tuberculosis, single-day treatments of malaria, and treatments for multidrug-resistant tuberculosis. Essential diagnostics are also needed, such as a point-of-care test to distinguish between bacterial and viral infections of the upper respiratory tract.¹² Some essential medicines do exist but have been abandoned—these are no longer produced in volumes that meet global demand because they are not sufficiently profitable. Examples include snake anti-venoms and benzathine benzylpenicillin.

A major category of missing essential medicines reflects a historic lack of attention to the specific needs of children. Between 1995 and 2005, 107 (44%) of the 243 medicines authorised in Europe by the European Medicines Agency (EMA) had a potential paediatric use, but no data on use in children were available at the time of authorisation.¹³ In 2007, WHO published the first Model List of Essential Medicines for Children⁷⁶ and launched the Make Medicines Child Size campaign.¹⁴ A key example is the gap in paediatric treatments for HIV—2.6 million children are living with HIV (88% of them in sub-Saharan Africa),¹⁵ but this statistic has not attracted sufficient commercial R&D investments.¹⁶

The alarming crisis in antimicrobial development is another example.¹⁷ A market-driven R&D system will not invest in new life-saving antimicrobials if their use will have to be rationed from the start to prevent resistance.¹⁸ The failure to respond to the 2014 Ebola virus outbreak showcases another example.¹⁹ Clinical testing of an Ebola virus vaccine has shown promising results,²⁰ but it took 11 000 deaths and extensive political

mobilisation to take the vaccine candidate off a shelf, where it had been sitting for 10 years after initial development by the Public Health Agency of Canada.²¹ Extensive R&D activity only started when the outbreak threatened richer populations. By October 2015, 31 molecules for Ebola virus treatment were under commercial development.

The issue of missing essential medicines has been discussed for decades. In 1990, only \$1.6 billion (5.3%) of \$30 billion spent annually on health research was oriented to the needs of LMICs.²² In a widely quoted study by Médecins Sans Frontières, only 15 (1.1%) of 1393 new medicines developed between 1975 and 1999 were for tropical diseases and tuberculosis, which account for 12% of the global disease burden.²³ Between 2000 and 2011, only 37 (4.4%) of 850 newly approved products were for neglected diseases, most of which were new formulations or combinations of existing medicines.²⁴ Similarly, in December, 2011, of nearly 150 000 registered clinical trials, only 1.0% were for neglected diseases. By October, 2015, only 167 (2.3%) of 7217 products in active development were for 19 of 64 listed neglected diseases (Commission's analysis of the data). Some work is being done, but it covers only part of the need.

The failures of market-driven R&D go beyond neglected diseases. An analysis of 1345 new medicine approvals in Europe revealed that no real breakthroughs occurred between 2000 and 2014; only 9% of new medicines offered an advance, and 20% were possibly helpful.²⁵ 51% of newly marketed medicines were modified versions of existing medicines, adding little to the treatment armamentarium. Nowadays, the R&D efforts therefore yield very few truly innovative products that respond to essential public health needs.

New essential medicines that are unaffordable to most people can also be considered as missing. High prices are a direct result of the reliance on the market monopoly granted by the patent system for the financing of R&D. High prices of new pharmaceutical products have long affected LMICs, but are increasingly being felt in HICs as well, and medical specialists in the USA²⁶ and the UK^{27 28 29 30} have started to protest.

Lessons learnt from initiatives to promote R&D of missing essential medicines

Not-for-profit R&D initiatives start to bear fruit

Several not-for profit Product Development Partnerships for neglected diseases have been established in recent years. In the Product Development Partnerships approach, R&D investments are funded up-front through

philanthropic and public financing, so companies do not need to recoup the full costs of R&D afterwards through high medicine prices. Examples include the Drugs for Neglected Diseases initiative (DNDi), the Medicines for Malaria Venture, the Global Alliance for TB Drug Development, the International AIDS Vaccine Initiative, the Foundation for Innovative New Diagnostics, Aeras Global TB Vaccine Foundation, and the Program for Appropriate Technology in Health. Some governments and major philanthropic actors, such as the Bill & Melinda Gates Foundation, have committed substantial funding to these initiatives. New industry R&D platforms have been created, and new incentives for industry involvement developed.^{31 32}

Table 5: Key achievements of not-for-profit Product Development Partnerships and their partners

	<i>disease</i>	<i>medicine</i>
<i>DNDi with Sanofi</i>	Malaria	Artesunate-amodiaquine
<i>DNDi with Farmanguinhos/Cipla</i>	Malaria	Artesunate-mefloquine
<i>DNDi with Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE)</i>	American trypanosomiasis (Chagas Disease)	Paediatric benznidazole
<i>Institute for OneWorld Health (iOWH)</i>	Leishmaniasis	Paromomycin
<i>MMV with Novartis</i>	Malaria	Artemether-lumefantrine dispersible tablets
<i>MMV with Guilin</i>	Malaria	Injectable artesunate
<i>MMV with Sigma-Tau</i>	Malaria	Dihydroartemisinin-piperazine
<i>MMV with Shin Poong</i>	Malaria	Pyronaridine-artesunate
<i>MMV with Guilin</i>	Paediatric malaria	Sulfadoxine-pyrimethamine and amodiaquine
<i>DNDi</i>	African trypanosomiasis (sleeping sickness)	Nifurtimox and eflornithine combination therapy
<i>DNDi</i>	Visceral leishmaniasis (East Africa)	Sodium stibogluconate and paromomycin combination therapy
<i>DNDi</i>	Visceral leishmaniasis (Asia)	Liposomal amphotericin B, miltefosine, and paromomycin combination therapy

Data from European Union Product Development Partnership Coalition. May 7, 2015.

DNDi=Drugs for Neglected Diseases initiative. MMV=Medicines for Malaria Venture

These initiatives are starting to bear fruit (table 5). For example, DNDi has developed six new treatments since 2003, and expects to complete 10–12 additional new treatments by 2023. DNDi is expanding its scope from

neglected diseases to HIV, hepatitis C, and antimicrobial resistance.³³ These initiatives have also provided important insights into the true cost of R&D (Box 4). Yet the research agenda of these initiatives largely follows the priorities of donor governments and foundations. A transparent priority-setting process is missing. As a result, some important therapeutic areas are hardly covered, such as diabetes, cancers and other NCDs, and mental disorders.

Box 4: Developing a new medicine: how much does it cost?

The real costs of pharmaceutical research and development (R&D) are often kept as trade secrets. In 2016, industry-supported estimates set the average cost for medicines developed between 1995 and 2007 at US\$2.5 billion per new product. In 2012, an industry-funded study by the Office of Health Economics came to an estimate of \$1.506 billion for development cost per new product. These figures are used by the pharmaceutical industry to justify high medicine prices, but have been challenged by others.^{34 35} Even some in the industry have expressed scepticism. GlaxoSmithKline's chief executive officer, Sir Andrew Witty, called the \$1 billion figure "one of the great myths of the industry."³⁶ Light and Warburton³⁷ estimated that the net investment by the industry to discover important new medicines amounts to 1.2% of sales. Table 6 summarises the R&D cost estimates published since 1991.

Table 6: Estimates of R&D cost from different sources and years

<i>Estimates of R&D costs in US\$</i>	
<i>DiMasi et al (1991)³⁸</i>	\$231 million (expressed in 1987 dollars)
<i>Office of Technology Assessment, US Congress (1993)³⁹</i>	\$140–194 million (expressed in 1990 dollars)
<i>DiMasi et al (2003)⁴⁰</i>	\$802 million
<i>Office of Health Economics (2012)⁴¹</i>	\$1.5 billion
<i>DiMasi et al (2016)⁴²</i>	\$2.5 billion

In 2001, the Global Alliance for Tuberculosis Drug Development estimated the costs of successfully developing a new chemical entity to treat tuberculosis to be approximately \$37–40 million (excluding the costs of failure). This cost covers preclinical development (\$4.9–5.3 million), pharmaceutical development (>\$5.3 million), and phases 1 to 3 of clinical development (\$26.6 million). Including the costs of unsuccessful projects would increase the total costs to \$76–115 million.⁴³

The Drugs for Neglected Diseases initiative estimated that R&D expenditure for an improved treatment (ie, a combination product using existing molecules) would be between \$10 and \$40 million. The Drugs for Neglected Diseases initiative's cost for the development of a new chemical entity is estimated at €100–150 million, on the basis of the real cost for products developed by the Product Development Partnership and including cost of failures.⁴⁴ These estimates do not include in-kind contributions by the industry.

The Commission concludes that international agreement should be sought on a global list of missing essential medicines with due regard of the needs of LMICs. R&D on the listed diseases should be supported by dedicated funds, and the list should be regularly updated.

Alternative incentives signal interest for change

In the past decade and a half, new push and pull incentive mechanisms have been established. Some new donors, such as UNITAID and the Japanese Global Health Innovative Technology Fund (which includes private companies, among others), have increased funding for R&D of missing essential medicines. The Longitude Prize established a prize fund of £10 million in 2014 for the development of a point-of-care diagnostic test to determine whether (and which) antibiotics are appropriate in a given case.⁴⁵ These initiatives are too new to show definitive results yet, but they signal public and private interest in new ways to incentivise innovation. The Commission supports the assessment of these alternate incentives.

Regulatory incentives show mixed results

New initiatives such as the UN Prequalification Programme managed by the WHO and the EMA's Article 58⁴⁶ adapt regulatory activities to global health purposes. Under Article 58, the EMA provides scientific assessments, in coordination with WHO, of medicinal products for human use in markets outside the EU.⁴⁷

Since 2007, US federal legislation has allowed for priority review vouchers (PRVs). However, PRVs have been criticised because there is no provision that the product should be made available and affordable, and PRVs can also be used for products already registered outside of the USA or by a company that did not invest in the R&D.^{48 49} A marketed antituberculosis medicine, bedaquiline, was offered for prices of around \$3000 in MICs and \$900 in LICs. Yet in the USA it was marketed for \$30 000 per treatment, despite having received a PRV and fast-track approval by the US Food and Drug Administration. Efforts are underway to include access and novelty requirements into the legislation.⁵⁰

New regulations to encourage paediatric medicine development have been introduced by the USA⁵¹ and the EU.⁵² As of 2008, all new applications in the EU must include data for children (0–17 years) unless a specific waiver is approved. An increase in new paediatric formulations is possible,⁵³ yet the costs to society might become higher than the actual R&D

investment. Whether these innovations meet priority needs or are primarily used to extend the market exclusivity of products with predominantly adult indications remains unclear.^{54 55} In 2016, the EU initiated a review of R&D incentive mechanisms, including those for paediatric R&D, to strengthen the balance of pharmaceutical systems in Europe.⁵⁶

Regulatory approval of new essential medicines poses great challenges, for example with onerous studies needed for new paediatric formulations⁵⁷ or assessments of new medicines for neglected diseases not prevalent in countries with stringent regulatory authorities. The Commission asserts that assessments of new medicines for neglected diseases should be led by regulatory authorities in the affected areas. These institutions will probably need further strengthening to do such reviews, through enhanced collaboration with stringent regulatory authorities and the WHO/UN Prequalification Programme. Regional regulatory initiatives within zones with similar disease patterns should also be supported.

The costs of R&D are not transparent

High prices for medicines are justified by the pharmaceutical industry as compensation for the costs of R&D and the high failure rate. However, the real costs of R&D are not well known (Box 4). In 2014, industry-supported estimates set the average cost for medicines developed between 1995 and 2007 at \$2.5 billion per new product (table 6).⁵⁸ Although direct comparisons are not possible because of the lack of comparative datapoints, R&D cost data from not-for-profit developers show that substantial innovations are possible for much less, especially for small molecules. For example, DNDi's real cost for the development of a new chemical entity including the cost of failures is estimated at €100–150 million, or about 7% of the industry figure.⁵⁹ The Commission argues for transparency in the costs of R&D to enable effective dialogue and decision making on affordable pricing of new essential medicines, and a fair return on R&D investments.

Public funding of R&D: the public often pays twice

Initial pharmaceutical research is often largely funded from public funds, such as the US National Institutes of Health or the European Horizon 2020 programme. For childhood cancers, virtually all research funding comes from the National Cancer Institute, private foundations, and philanthropic sources.⁶⁰ However, the final commercialisation steps of the development

process are usually done by for-profit pharmaceutical companies, which obtain the intellectual property rights from publicly funded research institutes, thus controlling the technology, including decisions about commercialisation and pricing.⁶¹

Medicines should be priced such that the public does not pay twice for innovation: first through government-funded scientific research and then through high medicine prices. UN Special Rapporteur on the Right to Health Paul Hunt has noted that, “[b]ecause 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 R&D undertaken in publicly funded laboratories.”⁶² The student movement Universities Allied for Essential Medicines lobbies for responsible licensing by universities. The Commission recognises the need to actively manage and protect the public interest in the proceeds of state-funded research.

Patent pooling supports generic manufacturing

As a direct result of the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of 2008,⁶³ UNITAID established an MPP for HIV medicines in 2010. The MPP initially focused on patents related to HIV medicines to promote low-cost generic production and the development of fixed-dose combinations and paediatric formulations. The MPP has expanded its mandate to cover hepatitis C and tuberculosis. In November, 2015, the MPP signed an agreement with Bristol-Myers Squibb that allows supply of generic daclatasvir in 112 LMICs.⁶⁴ Separate from the MPP, Gilead Sciences Inc has licensed patents for its hepatitis C virus medicines for use in 101 LMICs.⁶⁵ Unfortunately, some MICs are excluded from these licences and must continue to rely on TRIPS flexibilities to access low-priced generics (appendix 5). Generics companies that produce hepatitis C virus and HIV medicines under a licence agreement with the MPP and Gilead Sciences Inc are mostly allowed to supply generic product to a country that makes use of TRIPS flexibilities.⁶⁶

After 5 years of operation of the MPP, millions of people have benefited and impressive financial savings have been achieved (Box 5). The Commission concludes that there is great potential for expanding access to other new essential medicines through licensing of patents through patent pooling.

Box 5: Achievements of the Medicines Patent Pool (MPP) between 2010 and 2015

Patent licences and agreements

- Patent licences signed on 12 priority antiretroviral medicines with six patent holders, and 59 sub-licences with 14 generic manufacturers.
- One licence on a treatment for hepatitis C virus infection for 112 low-income and middle-income countries.
- One agreement to increase access to treatment of cytomegalovirus retinitis.
- One agreement for antiretroviral medicines as nanomedicines, for all 135 low-income and middle-income countries and two high-income countries in Africa.

Effect on production and supply

- Generic companies with MPP licences have supplied more than 7 million patient-years of WHO-recommended antiretroviral drugs in 117 countries, including 41 countries that were previously unable to benefit from generic competition for such medicines.
- MPP licences enable manufacturing and sale of generic adult antiretroviral medicines to 87–93% of people with HIV in the developing world, which includes all 34 low-income countries and 55–80% of middle-income countries.
- MPP sublicensees supplied 4.3 million patient-years of tenofovir disoproxil fumarate in the first 6 months of 2012, shortly after the agreement was reached.

Financial savings

- In 2011–12, in Azerbaijan, Belarus, Egypt, El Salvador, Georgia, Iran, Iraq, and Tunisia the price of tenofovir-containing products dropped to a median of 13% of the price before the agreement (2010–11).⁶⁷
- MPP agreements have led to antiretroviral medicines procurement savings of US\$119.6 million between 2010 and 2015.
- The total direct global savings generated by the MPP⁶⁸ are estimated at \$2.2 billion by 2028, implying that for every dollar spent, the global community gains \$40.⁶⁹

TRIPS flexibilities have been used widely but are under threat

Patents present substantial challenges to medicines availability. However, flexibilities in patent law have been used by a number of countries to secure access to generic medicines. The most frequently deployed flexibilities are compulsory licensing of medicines, government use of patents, and the waiver that allows LDCs to postpone granting or enforcing medicines patents and test data protection until 2033.

These options have been used more widely than is usually assumed. New figures⁷⁰ show that since 2001, there have been 34 instances of compulsory licensing (CL) of medicines by 24 countries, 51 instances of government use of patents by 35 countries, and 32 of non-enforcement of

patents by 24 World Trade Organization LDC Members. The peak of these instances falls between 2004 and 2008, coinciding with increased global funding for HIV. Although originally focused on HIV, 23 out of 85 total instances of CL and government use have concerned non-HIV medicines, including seven instances for cancer medicines between 2008 and 2014, of which five were granted. These measures have improved access to medicines. For example, in Thailand, CLs for erlotinib, docetaxel, letrozole, and clopidogrel save the health-care system \$142 million per year.⁷¹

In the past decade and a half, some countries have amended their patent laws to reflect health concerns. For example, India rewards innovation⁷² but prevents trivial patents and so-called ever-greening of patents.⁷³ South Africa has proposed introducing patent examination to limit the number of inappropriate patents.⁷⁴ Rwanda, Uganda, and Cambodia have all excluded medicines from patentability, pursuant to Decisions of the Council for TRIPS of June 27, 2002 (IP/C/25), and of June 11, 2013 (IP/C/64).⁷⁵ In December, 2015, the Organisation Africaine De La Propriété Intellectuelle amended the Bangui Agreement to allow its LDC members to postpone granting of patents and protection of regulatory test data until 2033.⁷⁶

However, the plethora of trade agreements with TRIPS-plus provisions is a serious threat to the policy and legal space that TRIPS provides. Examples of such provisions are patent linkage, data exclusivity, extension of the patent terms and scope, and restrictions on grounds for compulsory licensing and parallel importation. Some or all of these provisions appear in various trade agreements,^{77 78 79} in World Trade Organization accession agreements such as those with China and Cambodia, and in the Trans Pacific Partnership Agreement. It's intellectual property chapter is promoted as the new standard for global trade rules.^{80 81}

The Commission believes that governments must make full use of all available TRIPS flexibilities and enable their efficient use through national legislation. Governments should stop making TRIPS-plus demands in trade agreements and resist any pressure to include TRIPS-plus provisions in their national laws. The Commission believes that the drive for ever-higher levels of intellectual-property protection through trade agreements should be stemmed and will probably require intervention at the multilateral level.

Many pharmaceutical companies neglect their social responsibility

Globalised norms for patent protection and very high prices for new products make for a very successful pharmaceutical business model, thus

satisfying the needs of investors. However, it is increasingly clear that this approach endangers the progressive realisation of global health equity objectives and human rights. The global community has laid out a vision of health care as a human right in treaties such as the 1966 International Covenant on Economic, Social and Cultural Rights, which enshrined the right to health and was ratified by more than 160 countries. The right to essential medicines is a key component of the right to health,^{82 83} and this also implies certain human rights obligations for pharmaceutical companies.⁸⁴

Some pharmaceutical companies fail to acknowledge their unique role in society as the providers of life-saving medicines. One assessment of five large pharmaceutical companies showed that their corporate social responsibility approaches were inconsistently applied.^{85 419} In some cases, official company credos are not in fact reflected in the company's actions. For example, Johnson & Johnson publicly commits to striving to reduce costs and maintain reasonable prices, yet the company does not license its HIV medicines patents to the MPP;⁸⁶ and one HIV medicine, darunavir, was priced at \$810 per patient per year in certain LMIC markets for both a 600 mg dose and only declined to \$663 by 2015.⁸⁷ In the USA, the price of Novartis' imatinib for the treatment of chronic myeloid leukaemia has tripled since 2001,⁸⁸ to \$92 000 per year, although the company received orphan drug incentives for its development and the number of users continues to rise.⁸⁹ It also vigorously defends its patents in LMICs that strive to have access to imatinib.^{90 91} AbbVie charges MICs \$740 per patient per year for lopinavir/ritonavir (more than twice the price of \$231 per patient per year in LDCs); this price has not changed since 2012. A price of more than \$3500 per patient per year was quoted for lopinavir/ ritonavir in 2014 in Malaysia. Investors' profit-seeking has been blamed when companies fail to arrange for access pricing.⁹²

Pharmaceutical manufacturers in LMICs are also expected to contribute to public health needs. However, many fail to produce essential medicines, or to produce them according to acceptable quality standards.⁹³ Academic institutions, when seeking to increase the commercial value of their research, also have an insufficient focus on developing missing essential medicines.⁹⁴

Towards a global R&D framework that assures access and innovation

The initial focus on R&D for neglected diseases in developing countries has driven many international policy developments in this area.⁹⁵ However, a

simplistic dichotomy between developed and developing countries is no longer appropriate. LMICs are experiencing an epidemiological transition, with increasing prevalence of NCDs. Certain neglected tropical diseases and emerging diseases also pose a threat to HICs, due to climate change and international travel.^{96 97 98} Therefore, high prices of patented newly developed essential medicines affect everyone in all settings.

Market failure or public policy failure?

The lack of private sector investment in developing medicines for diseases affecting people without purchasing power or for small patient populations is often described as market failure. The Commission disagrees. Relying on a profit-driven R&D model to respond to public health needs represents a public policy failure. As Nobel laureate Sir John Sulston said, “We have to recognize that the free market, as good a servant as it is, is a bad master. We cannot take important global decisions on the basis of the free market alone.”^{99 432} Inadequate regulation of the business sector to protect and promote human rights is also a public policy failure.⁴³³ The Commission concludes that government intervention, including at the international level, is needed to ensure markets respond to public health needs, and to hold private sector partners accountable, including with regards to their responsibility to protect and promote human rights.

Public spending, public policy—the urgent need for global action

The imperative for governments to act is pressing. The global market of pharmaceutical products was almost \$1 trillion in 2013, and is expected to have reached \$1.2 trillion by 2017.¹⁰⁰ The market share of LMICs, particularly those in Asia and Latin America, is growing at a rapid pace.¹⁰¹ The global medicines market represents money the public spends, either out of pocket, or through health insurance, social security schemes, or tax-based government-provided health care. Yet as previously described, industrial investment in R&D for neglected diseases remains very low. In 2013, public and private investment for R&D in 34 neglected diseases was \$3.2 billion, of which pharmaceutical corporations only contributed \$401 million. The latter amount represents only 0.8% of total industrial R&D spending of \$51.2 billion in 2014.¹⁰²

Not-for-profit R&D initiatives have compensated for some deficiencies of the current system, but they cannot provide a permanent solution to the

underlying fundamental problem of an innovation system relying on market exclusivity. The Commission believes that governments need to proactively set public health-based research priorities for so-called essential R&D and not leave these priorities to pharmaceutical manufacturers. Governments also need to finance new models of biomedical innovation that address access from the early stages of development, such as the Global Health Innovative Technology based in Japan. The massive spending on pharmaceuticals through increasingly higher pricing of medicines can be repurposed to shape a new R&D framework. As countries cannot do this on their own, it will require international agreement and regulation.

Delinking R&D costs from the price of medicines

The concept of delinking costs from prices is based on the premise that costs and risks associated with R&D should be rewarded, and incentives for R&D provided by means other than through the price of the product.¹⁰³ If the R&D cost of new medicines did not have to be recouped through high prices, those medicines would be free of market exclusivity and could be made more widely available and more affordably priced through better competition.

The Commission supports proposals to progressively delink the cost of R&D for priority medicines from the price of the products, and to develop new ways of sharing the cost burden of innovation internationally. As James Love suggested at the hearing of the UN High Level Panel on Access to Medicines in March 2016: “Let’s outcompete the patent-based innovation.” For example, countries could contribute to the development of missing essential medicines in amounts proportionate to their economic development. This contribution would reflect that R&D of essential medicines is a global public good, and would help to ensuring that the fruits of R&D efforts are accessible to all.

Public policy must be expressed in a global R&D framework

In 2006, WHO stated that “access to drugs cannot depend on the decisions of private companies, but is also a government responsibility.”¹⁰⁴ In 2008, after intense negotiations, WHO members adopted the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA).¹⁰⁵ The GSPA encourages needs-driven research rather than purely market-driven research and contains many practical recommendations.

Several proposals have been made for new policy frameworks and, in particular, new international agreements on medical R&D to achieve the two objectives of innovation and access.¹⁰⁶ The first proposal was made by Hubbard and Love in 2004.^{107 439} Over the years, their proposal has received support from an increasing number of governments, scientists, Nobel laureates, civil society organisations, and other experts.^{108 109 110} In 2015, representatives of research and international organisations also called for a Global Biomedical R&D Fund and Mechanism for Innovations of Public Health Importance.¹¹¹ Separate global financing mechanisms for innovation have been discussed for neglected diseases, antimicrobials, and Ebola virus, which all lack sufficient commercial market opportunities. As these are priorities for LICs, MICs, and HICs alike, the medical tools to address them should be considered as global public goods. All R&D needs should be reconciled within a global umbrella framework for funding and coordinating R&D that not only emphasises innovation but also secures access.

The need for new global approaches was reinforced by UN Secretary-General Ban Ki-moon's call for a new deal at the establishment of the High-Level Panel for Access to Medicines in November 2015.¹¹² The scope of this panel's investigation was "to review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies."¹¹³

WHO member states will continue to discuss the monitoring, coordination, and financing of health R&D, taking into account the report of the UN Panel¹¹⁴ and that of the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination,¹¹⁵ which recommended the establishment of a biomedical R&D treaty (Box 6). The talks about a new R&D framework are likely to be intensely political, as were the negotiations for the GSPA. It will be important for clear R&D priorities to inform this process.¹¹⁶

Box 6: An international agreement on research and development (R&D)¹¹⁷

Several proposals have been made for an international agreement on medical R&D to achieve the two objectives of financing needed innovations, and equitable access to those innovations.

Key features of such an agreement include:

- R&D priorities driven by health needs rather than commercial potential
- Binding obligations on governments to invest in R&D
- Equitable distribution of contributions across countries
- Measures to improve the regulatory environment
- Measures to ensure affordability of the end product
- Access-maximising licensing practices to deal with intellectual property issues
- Innovative approaches to promote R&D while delinking its cost from the ultimate sale price

Such an agreement could be crafted under the auspices of WHO, whose constitution allows for its 194 member states to negotiate formal international law.¹¹⁸ While both formal and informal norms (such as guidelines or global strategies) can influence the behaviour of states and other 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 agreement negotiated within WHO, which has contributed significantly to global tobacco control efforts.^{119 120}

The necessary practical details of a new medical R&D framework will need to be negotiated. These global discussions on R&D priorities provide opportunities for national governments, WHO, and the UN to fulfil their obligations to present a bold new global framework for achieving the dual objectives of health-need driven R&D and equitable access to its products.^{121 122}

Pooling patents of new essential medicines promotes universal access to innovation

On the basis of the positive outcomes of the MPP, the Commission concludes that there is a wide scope for patent pooling for other essential medicines (as defined by WHO or national committees). To this end, the current MPP could be expanded into an Essential MPP (or EMPP). This expansion would create an opportunity for companies to license patents for the purpose of creating a competitive generic market of essential medicines, in line with their responsibility to protect and promote human rights.¹²³ Patents of medicines developed under the new research agreement or new financing mechanisms could also be licensed. The EMPP should use a tiered royalty system to remunerate patent holders and to contribute to R&D expenditure at levels proportionate to the economies of the countries where the medicines are used.¹²⁴

The Commission notes that a patent owner's refusal to license an essential medicine to the EMPP would satisfy the condition for granting a compulsory licence under TRIPS Article 31, which requires the grantee to have made efforts to obtain authorisation from the right holder on reasonable commercial terms and conditions.¹²⁵ There is no such requirement in cases of national emergency, extreme urgency, or public non-commercial use.¹²⁶ Governments should also ensure that national patent legislation allows for easy deployment of TRIPS flexibilities, effective automatic licensing of essential medicines in the absence of voluntary agreements, and regulatory rules for protection of test data that provide the necessary flexibility to register products submitted by licensees.¹²⁷

The pharmaceutical industry should live up to its special responsibilities

Instances of important achievements when industry is open to collaboration are apparent. Examples have included the MPP, collaborative research for vaccines,¹²⁸ and neglected diseases research. In recent years, some firms have made listings of their patents available. In 2016, GlaxoSmithKline announced that it will not file or enforce patents in LICs, license its patents in LMICs, make its patent landscape more transparent, and commit its future oncology medicine patents to patent pooling.^{129 459} These hopeful developments might set important precedents. Yet the deep changes implied by a new global R&D framework will also require a general culture change in the industry and among its investors.

Detailed descriptions of what would be expected from the industry have been formulated since 2001. For example, the UN Special Rapporteur¹³⁰ and the Human Rights Council¹³¹ have defined the human rights responsibilities of pharmaceutical companies. These responsibilities include refraining from actions that limit accessibility, such as pursuing stronger intellectual property protection, and also taking all reasonable steps to make new medicines accessible to all those in need, within a viable business model. Company violations of these human rights principles give national governments a strong justification to impose corrective measures, such as compulsory licences for domestic production or importation.

The ATM Index is an independent review mechanism by which the policies and practices of large pharmaceutical companies with regard to LMICs are assessed every two years. The ATM Index is strongly based on human rights principles and has been refined over time in collaboration with the industry.

The Commission believes that moving away from an exclusively profit-oriented approach, towards a more patient-centred and public-centred, socially-responsive, open, and collaborative enterprise, would improve global health and the reputation of the pharmaceutical industry. As a result of the special nature of its products, the pharmaceutical industry has a unique role in society. It should now live up to this special responsibility, and be seen to do so.

Conclusion

Access to new essential medicines is a key component of UHC and of the progressive realisation of the right to health. Some of the developments described in this section represent real progress and will help bring new essential medicines to the market; and for certain diseases they will bring medicine prices down. Yet the recommended policies are often restricted to certain therapeutic areas (eg, HIV, neglected diseases, or paediatric formulations), and they are not sustainable when largely dependent on charitable contributions. While repairing some of its excesses, these partial solutions leave the existing system in place.

With the current patent-based innovation system, the feasibility of achieving or maintaining UHC is seriously at risk. The Commission therefore believes that business as usual will not resolve the problems with R&D, and that concerted global action is the only way forward. A new global R&D policy framework is needed to drastically adapt the current model and to reduce its reliance on market exclusivity as the main driver of innovation. The Commission concludes that a more public health-oriented R&D system is needed, but recognises that no country can tackle this issue on its own. International public policy should play a much greater role in setting R&D priorities and financing, and in coordinating new approaches to promote access to new essential medicines.

Practically, the Commission concludes that governments need to define a list of missing essential medicines to be provided under UHC schemes. Governments and non-governmental organisations need to make the necessary R&D financing mechanisms available for these identified needs. The price of new essential medicines can then be delinked from development costs and the products can be made widely available and affordable through non-exclusive licensing agreements. The resultant decrease in price can provide the financial space to more directly finance the identified priority R&D.

Recommendations

The Commission's analysis shows that challenges of access to new essential medicines are directly associated to the failure of the current R&D system to develop much needed new medicines. The Commission makes the following recommendations for stronger public policies on R&D, including at the international level.

1. Governments and WHO must take international public leadership for priority setting for essential R&D, with due regard for the public health needs of LMICs. This should include developing a list of missing essential medicines, within the context of the WHO Global Health R&D observatory and in close connection with the WHO Model List of Essential Medicines. The WHO mechanism to identify missing essential medicines should be further developed, with the involvement of all relevant stakeholders.
2. Governments must lead the process towards a global R&D policy framework and agreements, which include new financing mechanisms to ensure that missing essential medicines are developed and made affordable. Such mechanisms should be based on transparent estimates of the real cost of R&D; they might include a pooled fund for global health R&D, prize funds, targeted research partnerships and advance market agreements, and licensing of related patents, leading to an increasing number of new priority products with an affordable price which is delinked from R&D costs (known as progressive delinking).
3. The international community must create a general EMPP. Such a pool could be hosted and managed by the current MPP. Companies should license their patents related to essential medicines to the EMPP under a set of conditions. Patents of medicines developed under the new research agreement or any other new financing mechanism could also be licensed through the EMPP. The EMPP should use a tiered royalty system to remunerate the patent holder and to contribute to R&D expenditure.
4. Governments and national stakeholders must develop and implement comprehensive national action plans to guarantee equitable access to new essential medicines, including open knowledge innovation, fair licensing practices, support for a patent pool for essential medicines, full use of TRIPS flexibilities when needed, and rejecting TRIPS-plus provisions.

5. The pharmaceutical industry must better align its R&D priority setting with global health needs, and develop access strategies to make medically important innovations available to all in need. To this end the industry could determine a certain percentage of its profits to reinvest in R&D for medicines that are not commercially attractive, but are deemed essential from a public health perspective. Equitable access strategies should include broad licensing of patents and technology transfer to enable generic medicines production; and equitable pricing mechanisms. The policies and practices of pharmaceutical companies should be independently assessed by international mechanisms, such as the ATM Index.

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Conclusions and Reflections on the Future

This chapter presents the findings of the research project, and how they address the individual research questions described in chapters 2-6. It also comments on the methodology, and concludes with reflections on the future and suggestions for further research.

The HIV treatment crisis of the late nineties and early 2000s, and the civil society activism and political engagement it generated, drove a policy process that changed some of the international rules on intellectual property (IP) and the approach to their implementation. These policy processes introduced new flexibilities and strengthened existing flexibilities in IP law that have become known as TRIPS flexibilities. The global effort to improve access to treatment for HIV and other diseases also created new global health financing mechanisms, and new mechanisms to facilitate the availability of quality-assured generic medicines, such as the World Health Organization's Prequalification Program (PQP). These developments provided the conditions for the large-scale production, purchase, and use of generic low priced medicines for the treatment of HIV/AIDS. The widespread use of the TRIPS flexibilities has been pivotal to access lower-priced essential HIV medications in those countries where patents formed a barrier to making the medicines available.

Considering the growing burden of non-communicable diseases, including in low and middle-income countries, and the drive towards Universal Health Coverage (UHC), the key question this thesis addresses is: Can intellectual property solutions developed to address the HIV/AIDS crisis also be deployed to increase access to other, new and expensive essential medicines?

Main Findings

Chapter 2 documented the legal and policy developments that drove the change in the approach to IP and public health against the backdrop of the AIDS crisis of the late nineties. Policy processes at the World Trade Organization (WTO), and specifically the adoption of the Doha Declaration on the TRIPS Agreement and Public Health in 2001, offered important

clarification of the existing flexibilities contained in the TRIPS Agreement. These processes also created new legal options for LDCs that allow them to postpone granting and enforcing medicines patents and data protection until at least 2033, and new provisions for compulsory licensing for production and export of generic medicines.

The role of international organisations other than the WTO, including the Human Rights Council, the WHO, and civil society organisations, have been essential in moving the subject of IP out of the exclusive realm of trade negotiations. As a result, public health considerations, including the protection of the human right to health, became more central in multilateral discussions on IP at both the WTO and WIPO.¹ The Doha Declaration demonstrated international political support for the use of TRIPS flexibilities. This support was a significant signal that intellectual property protection serves the public interest, an interest beyond that of IP rights holders, which are mostly commercial companies.

We can conclude that the TRIPS Agreement and the Doha Declaration provide the necessary legal flexibility to address IP challenges to access to medicines in general and that this flexibility has been used for the supply of HIV medicines. However, our study could not determine whether political support will emerge for the use of the TRIPS flexibilities for other diseases than HIV.

Chapter 3 addressed the question how the UN guaranteed the quality of generic HIV medicines. Overcoming patent barriers to generic medicines is only one prerequisite to access; another essential condition is ensuring that the medicines are of acceptable quality. Quality assurance of medicines may sound like a purely technical endeavour but, in reality, it can be mired in political controversy, as described in chapter 3. The UN, through the WHO Prequalification of Medicines Program (PQP), succeeded in assuring the quality of HIV medicines at a global scale.

The following aspects played an essential role in the success of the PQP programme. The programme had rigorous review procedures and acted in a transparent manner, which helped instil confidence in its work. It was supported through resolutions of the World Health Assembly, which were important to garner political support, to regularly assess progress, and to strengthen its mandate. The PQP maintained its independence from industrial interests. It did not work in isolation, as it collaborated with national regulators from high, middle and low-income countries. In doing so it emphasised transfer of knowledge to and capacity building of regulators from less-resourced countries. An important aspect contributing

to the power and effectiveness of the PQP was the fact that global health donors demanded from their recipients that they buy prequalified medicines. This condition convinced manufacturers to collaborate with the PQP because it restricted the market for those manufacturers who did not wish to submit their dossiers to the WHO PQP. The PQP could also show its high economic value through its contributions to lowering the price of WHO recommended fixed-dose ARVs and other medicines. The economic value of the prequalification work helped in continued fundraising for the programme.

Our findings are relevant today because the PQP will continue to play an important role in quality assurance of new essential medicines beyond HIV, such as hepatitis C medicines and biologics. The PQP has become a global public good, which requires public financing to sustain it. The current pressure on the WHO to move to a partially self-financed model, which in reality means a user-financed model in which the manufacturers pay, carries significant dangers with regards to the sustainability and independence of the PQP Program. Global health donors that chose not to pay for the program directly now risk having to pay the price for the lack of quality assured affordable medicines later.

Chapter 4 presented the study of the practical use of the TRIPS flexibilities by governments in the procurement of medicines in the years 2001 – 2016. Prequalified generic antiretroviral medicines, including FDCs produced at a low price in India, could not be made available in countries where originator companies held patents. The use of the TRIPS flexibilities became important in lifting the barrier posed by these patents. However, the extent to which the flexibilities were used in practice was not really known until the development of the database of instances of the use of the TRIPS flexibilities that formed the basis for the study. The general belief was that its use was rather limited.

Our study identified 176 instances of the use of or intention to use TRIPS flexibilities by 89 countries, of which 81 were WTO Members. Of the 176 instances, 100 (56.8%) concerned compulsory licences, including public non-commercial use licences, and 40 (22.7%) concerned instances of the use of the LDC waiver. The remaining cases concerned parallel import (1), patent exception (3), and non-patent-related measures (32). Of the instances documented, 152 (86.4%) were executed. The instances covered products to treat 14 different diseases. However, 137 (77.8%) of the instances concerned medicines for HIV/AIDS and/or related diseases. In conclusion, the use of TRIPS flexibilities by countries in the procurement of generic medicines in

particular ARVs has been significant in lifting patent monopolies. The use of the flexibilities was initially driven by the procurement of medicines for the treatment of HIV/AIDS. However, it is noteworthy that out of the 176 instances 12 concerned cancer treatments. These instances, most of which occurred after 2010, may point at an increase in uptake of TRIPS flexibilities for non-communicable diseases, in particular in middle-income countries that have the medical infrastructure to provide cancer treatment and are confronted with growing demands from their populations for expensive patented medicines. All in all, our study therefore shows that the use of TRIPS Flexibilities has been effective in accessing lower-priced generic medicines; and could remain so in the future.

Availability of generic medicines requires registration by national regulatory authorities. Rules on clinical test data protection (data exclusivity), which prohibits regulatory authorities from registering a generic medicine for a certain period independent of its patent status, may, however, form an additional barrier to access.

Chapter 5 presented an analysis of the European Union regulation of clinical test data protection, and examined how it relates to the use of TRIPS flexibilities, specifically compulsory licensing of medicines in the EU. The main finding of our study is that EU regulation of clinical test data protection and the granting of market exclusivity interfere with the effective use of compulsory licensing (including public non-commercial use of patents by the government) by EU Member States, and can even prevent access to off-patent medicines as no remedies for such exclusivities are available. We recommend amendments to the EU pharmaceutical legislation to provide waivers to data- and market exclusivity in cases of public health need and when a compulsory licence or government use license has been issued. Such an amendment can be modelled after existing waivers in EU Regulation “on compulsory licensing of patents relating to the manufacture of pharmaceuticals for export to countries with public health problems”² outside the EU.

Many of the challenges of high medicines pricing described in this thesis have their roots in the financing model of pharmaceutical research and development, which is predominantly based on the granting of market exclusivities through patents or otherwise (see Chapter 5).

Chapter 6 therefore addresses the question how a public health approach to innovation and access can be achieved.³ A public health approach to innovation and access is based on the Availability, Accessibility, Acceptability and Quality (AAAQ) human rights framework,

and ensures that the R&D agenda reflects health needs, produces medicines that are adapted to the population they are meant for, and are affordable and accessible to that population. Our study describes the commercial approach to R&D, which is based on developing products that provide the highest return on investment and therefore leaves important health needs unmet. This is often described as a *market failure*. However, we conclude that relying on a profit-driven R&D model to respond to public health needs rather represents a *public policy* failure, and we therefore recommend public policy responses.

We formulated the following recommendations for action by governments, the WHO and the health care industry:

- 1) Governments and WHO must take international public leadership for priority setting for essential R&D, with due regard for the public health needs of low- and middle-income countries, including developing a list of missing essential medicines.
- 2) Governments must lead the process towards a global research and development policy framework and agreements, which include new financing mechanisms to ensure that missing essential medicines are developed and made affordable leading to an increasing number of new priority products with an affordable price that is de-linked from R&D costs (“progressive delinking”).
- 3) The international community must create a general Essential Medicines Patent Pool. It can do so by expanding the current Medicines Patent Pool's mandate. Companies should license their patents related to essential medicines to the EMPP under a set of conditions.
- 4) Governments and national stakeholders must develop and implement comprehensive national action plans to guarantee equitable access to new essential medicines, including open knowledge innovation, fair patent licensing practices, support for a patent pool for essential medicines, full use of TRIPS flexibilities when needed, and rejection of TRIPS-plus provisions.
- 5) The pharmaceutical industry must better align its R&D priority setting with global health needs and develop access strategies to make medically essential innovations available to all in need.

In summary, the public policy response to the R&D challenges must be expressed in a global response that includes new rules governing the sharing of benefits and cost of the innovation efforts. We conclude that the

necessary practical details of a new medical R&D framework will need to be negotiated by countries and that such negotiations are likely to be contentious. The global discussions on R&D priorities taking place at the WHO provide opportunities for national governments, WHO, and the UN to present a bold new global framework for achieving the dual objectives of health-need driven R&D and equitable access to its products consistent with human rights principles.

Reflections on methodology.

The selection and formulation of the research questions were driven by questions arising from my direct experience working on access to medicines for NGOs and governments over a period of 17 years. Therefore, the approach for selecting the topics was problem-based – rooted in practical experiences of barriers to accessing new essential medicines. While there are benefits of direct involvement in the research topic, there is also the risk of “insider” bias. I would not want to pretend that the perspectives I give in this work are not influenced by direct involvement in policy processes over a decade and a half. Neither do I pretend that the work represents the perspectives of all players involved in the policy processes. There is also value in being a participant observer in policy analysis, because of unique access to information and experts not readily available to the external researcher.⁴ I sought to remedy possible insider bias through collaboration with others, including researchers from other disciplines, and through the collection and presentation of robust empirical data on the use of TRIPS flexibilities (Chapter 4). A vital strength of the direct experience-based approach is that it allowed me to build an extensive database of instances of the use of TRIPS flexibilities over the years. While most cases included in the database are supported by original documents, or through cross-referencing with cases reported in the literature, or through consultation with colleagues, a few could not be fully verified at this stage. There is also a potential for missing cases, particularly those that have occurred but triggered a concession and were never made public. We intend to make the database public in the future, inviting others to contribute cases to it and keeping it updated as a useful tool for further research, including by others.

The fact that information and data were collected over a 17-year period made it possible to document and reflect on the political and legal developments over time, rather than presenting and analysing a single situation or event of a particular moment. The direct involvement in some

of the policy processes described in this thesis also offered direct access to data and information and access to experts in various fields, that otherwise would have been harder to obtain. The work experience strengthened the multidisciplinary character of the studies, which were often carried out in collaboration with medical, pharmaceutical and social science professionals from different regions of the world.

Reflections on Main Findings

So now we can return to our main research question: can the positive experiences of the last two decades to ensure equitable access to essential medicines for AIDS also be applied to other new essential medicines?

The deployment of TRIPS flexibilities has been effective in advancing the human right to access to essential medicines, particularly in the case for HIV, on a larger scale than is usually recognised in the literature or by policy makers. In addition, we can conclude that flexibilities in the TRIPS Agreement can indeed be lawfully deployed to access lower-priced medicines by countries that have made provisions for it in their national laws. The use of TRIPS flexibilities therefore plays an important role in advancing the availability, accessibility, and acceptability components of the AAAQ human rights framework. Are there reasons to believe that they would not work for other diseases?

The political responses from the US and the EU to the use of TRIPS flexibilities by certain middle-income countries is a significant obstacle to their routine use outside the realm of HIV.^{5,6} For example, when India issued a compulsory licence in 2012 for a cancer medicine it provoked an out-of-cycle review by the US Trade Representative.⁷ In 2016 Colombia came under pressure from Switzerland and a group of influential US senators for its plans to issue a compulsory licence for a leukaemia treatment, imatinib (Gleevec, marketed by Novartis).⁸ The price of Gleevec in Colombia was approximately USD 20,000 while the GNI per capita was USD 7,780. The US senators' response was particularly harsh because it linked the outcome of the compulsory licence process to the approval of US financing for the still fragile peace process in Colombia (the "Paz Colombia" Initiative).⁹ The patent holder, Novartis, threatened with an Investor-State dispute settlement (ISDS) procedure under the Swiss-Colombian bi-lateral investment agreement.¹⁰ Such strong political responses to the plans of one country to issue a compulsory licence are likely to have a chilling effect on others. To date, Colombia seems to have yielded to this political pressure and has not proceeded with the compulsory licence for imatinib.

Such strong negative responses from high income-countries to LDCs making use of the TRIPS transition periods and specifically the LDC pharmaceutical waiver may be exceptional. However, LDCs may also have capacity problems in making full use of the TRIPS flexibilities.¹¹ Many LDCs have not amended their laws to take full advantage of the options they have under the TRIPS Agreement.¹² On the other hand, this may not pose significant barriers in reality, as LDCs may leave their laws unchanged and simply declare that until the end of the transition period in 2033, they will not enforce legal provisions relating to pharmaceutical product patents and test data protection.¹³ Such declarations by LDCs have in practice helped the import of generic ARVs and are a powerful tool in the procurement of medicines. However, this solution is not open to other countries.

We conclude that the use of TRIPS flexibilities is possible, provided that countries make the necessary changes in their national policies and legislation, and resist external political pressure not to use them. LDCs are in a strong position to apply the pharmaceutical waiver until at least 2033.

With regards to safeguarding the quality of the medicines, the WHO prequalification programme, working with national governments and manufacturers, has performed an essential role. Since the mid-2000 the TRIPS-flexibilities have also been used to advance access to medicines for the treatment of non-communicable diseases, in particular cancer, but on a much smaller scale. It is too early to predict whether the PQP mechanisms will also be deployed for these medicines in the same routine manner than it was used in the procurement of HIV medications. An important reason for the slow uptake is the lack of global health funding for the purchase of essential medicines outside the areas of HIV, TB and malaria and lack of global funding for the PQP programme as a whole.

There are other options to consider, in support of a wider use of flexibilities. The Medicines Patent Pool has eased the need for the use of TRIPS flexibilities to access HIV and certain HCV medicines in the countries that are part of the licence territory. However, no such licensing mechanisms exist yet for other diseases, such as non-communicable diseases. We have recommended in the report of The Lancet Commission on Essential Medicines Policies (Chapter 6) that the MPP expands to include all new essential medicines, so that these medicines can become available as generics well before the patents expire in all low and middle-income countries. The MPP is currently studying the feasibility of this proposal.

Our research has shown that the political mobilisation around HIV

drove many of the policy and legal changes necessary to address the human right to access to medicines. These policy changes also included changes in WHO's approach to the Model List of Essential Medicines (EML) to allow for the inclusion of medicines that are not yet available at an affordable price. In the past, affordability – which in practice usually meant availability as a generic – was a prerequisite for inclusion of a product in the EML. Since 2002 the Model List also includes new essential medicines that are available from a single source only, are often widely patented and are expensive. Affordability is no longer a prerequisite for inclusion in the EML, but listing now implies that governments and other stakeholders should make efforts to make new essential medicines affordable and available. In other words, affordability has become a consequence of inclusion in the EML. Identifying and confirming the public health benefit of a new medicine can also help to call for a human rights approach to price and patent interventions, as the basis for further political support.

The national application of WHO's listing of highly-priced medicines on the EML (namely, to ensure equitable access at affordable price) faces numerous challenges. The patent status of an essential medicine can be an important impediment to achieving an affordable price and to a government's obligation to fulfil its population's right to essential medicines. This is the case when the patent holder refuses cooperation through fair pricing, or licensing of the relevant patents. It should be noted here that refusal to licence patents pertaining to an essential medicine to the MPP would satisfy the requirement under article 31 of TRIPS to have made efforts to reach a voluntary agreement.¹⁴ In such case the government has a valid reason and even the obligation under human rights law to intervene and to proceed with non-voluntary licensing, or to invoke other TRIPS flexibilities. The use by governments of TRIPS flexibilities when required is no longer “just an option” but a duty. Such interventions will be particularly important against the backdrop of the growing political momentum to address the lack of treatment of non-communicable diseases, the rising medicines prices, and the drive towards Universal Health Coverage as part of the Sustainable Development Goals.

Recently, the call for the use of TRIPS flexibilities can also be heard in high income countries. However, many high-income countries have self-imposed limits on the use of these measures. For example, many high-income countries including all member states of the European Union have opted out of the use of the WTO mechanism for compulsory licensing for

export as a beneficiary. This means that they can produce and export medicines under a compulsory licence but they cannot import medicines that can only be produced under a compulsory licence. This decision was taken in 2003 when the WTO adopted the waiver to the restrictions in TRIPS article 31 (f). Possibly, in 2003, countries were not as concerned about high medicines pricing in their own territories as they are today.

EU data exclusivity rules (Chapter 5) that interfere with the effective use of compulsory licensing constitute another example of limits to effective use of TRIPS flexibilities. In high-income countries including the UK, France, Switzerland, The Netherlands and the USA, the call on governments to issue a compulsory license for high priced medicines and to stop rationing of medicines is getting louder. And the growing burden of high medicines pricing on health budgets is an issue of considerable concern in all countries. It is therefore important, in low, middle and high-income countries alike, to halt the erosion of the TRIPS flexibilities and to ensure that regulations on medicines and IP allow for the effective use of TRIPS flexibilities when needed.

In addition to reasons of self-interest to protect efficacy of TRIPS flexibilities, there is a compelling human rights argument to dissuade high-income countries from the pursuit of TRIPS-plus norms in other countries. States are under an international human rights obligation to facilitate access to essential medicines in other countries, and to provide the necessary aid when required.¹⁵ They are to assist low and middle-income countries in realizing their core obligation to provide access to essential medicines to their population.¹⁶ Insisting on TRIPS-plus requirements such as those made in several trade agreements contravenes this human rights duty. In this context, it was significant that after the USA withdrew from the Trans-Pacific Partnership (TPP), the remaining negotiating parties suspended clauses from the draft agreement pertaining to TRIPS-plus requirements in the area of pharmaceuticals, such as data exclusivity and patent term extensions.¹⁷

Reflections on the Future

The use of the TRIPS flexibilities can offer immediate relief in a situation where an essential medicine is patented, is too highly priced, and the patent holder refuses to collaborate through lowering the price or licensing. But the flexibilities do not address the underlying reason of high medicines pricing.

The problem of high pricing is rooted in the financing mechanism for

pharmaceutical innovation, which is based on granting market monopolies through patents or regulatory exclusivities. A patent-based innovation system also neglects important health needs when profitability cannot be assured. This is, for example, the case in the area of antibiotics, neglected tropical diseases, diseases with a small patient population, and children's formulations. It will be important to explore new incentive mechanisms for pharmaceutical R&D that do not rely on high prices to finance pharmaceutical R&D. The need for fundamental change is increasingly recognised internationally. For example, the UNHLP recommends the initiation by the UN Secretary-General of "a process for governments to negotiate global agreements on the coordination, financing, and development of health technologies. This includes negotiations for a binding R&D Convention that delinks the costs of research and development from end prices to promote access to good health for all."¹⁸

This concept of delinking is based on the premise that costs and risks associated with the development of new essential medicines should be rewarded, and incentives for R&D provided, by other means than through the price of the product.

This recommendation is echoed by The Lancet Commission on Essential Medicines Policies which also recommends a new policy framework and agreements to ensure missing essential medicines are developed and marketed at an affordable price based on delinkage principles.

In June 2016, the European Council highlighted the need to address the shortcomings of the current innovation model in the *Council Conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States*.¹⁹ The European Council tasked the European Commission with evaluating the different incentive mechanisms and rewards for pharmaceutical innovation, and to analyse the current EU legislative instruments such as the marketing authorisation system, the supplementary protection certificate (patent), the orphan drug regulation,²⁰ and paediatric drug development incentives. These instruments aim at incentivising and encouraging investment in the development of new medicines but also lead to higher prices. It would be important that the studies currently being carried out by the Commission result in recommendations for changes in European legislation (Chapter 5).

The right to essential medicines is a key component of the right to health. The point could be made that the development of new essential medicines should then also be guided by human rights principles. This is currently not widely accepted, where commercial corporations set the

priorities for pharmaceutical drug development and make decisions on spending on new drug development. The Lancet Commission recommendations on delinkage could provide a practical application of human rights-based framework for pharmaceutical innovation.^{21,22}

The development of such a R&D framework requires international collaboration and a commitment to a multilateral approach. The current political climate is not conducive to international collaboration. However, the challenge of high medicines pricing, which is now a global problem, may bring likeminded countries together and start an international discussion. The development of new systems for sharing the cost and the benefits of pharmaceutical R&D will require that powerful industries, strongly attached to patent monopolies, and their home governments, be engaged. The policy failure to rely on the markets for medicine innovation can only be redressed with governments in the driver seat.

This study has documented the international processes that have led to important policy and legal changes in the field of intellectual property to improve access to expensive essential medicines. Additional research and analysis on how to foster changes in pharmaceutical innovation systems will be needed to inform the current policy debates from a public health and human rights perspective. Some suggestions for further research are presented in box 1.

Box 1: Suggestions for further research

The data base of the use of TRIPS Flexibilities which we developed as part of this Ph.D. project provides an important and unique source for further research involving other disciplines. For example:

- Economic analysis to estimate the savings in global health spending as a result of the use of TRIPS flexibilities.
- Further detailed legal analysis of the individual cases.
- Continue monitoring and documenting the use of TRIPS flexibilities, to determine over a longer period at what scale governments deploy the measures outside the field of HIV.

Other areas of further research are:

- The role of competition law, in conjunction with remedies, such as compulsory licencing and government use to investigate and address high pricing of patented products.
- A human rights approach to new models for pharmaceutical research and development.
- Implementation of policy recommendations, such as those made by the UN High-Level Panel on Access to Medicines.

Conclusion

The success of international efforts to secure access to affordable treatments for HIV has shown the potential of TRIPS flexibilities and of licensing of medicines patents. It is now both possible and necessary to translate these experiences in a wider uptake of TRIPS flexibilities for other diseases, including non-communicable diseases. To this end, countries should review and update their national legislation and resist international political pressure to refrain from using the TRIPS flexibilities. Countries should collaborate to develop new frameworks for health needs driven innovation and new innovation financing mechanisms that do not depend on market monopolies and high pricing.

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Summary

The issue of access to medicines has become an increasingly visible problem throughout the world. The HIV/AIDS crisis of the late nineties, when 8000 people a day died of AIDS in developing countries for lack of treatment, drew attention to intellectual property and specifically the effects of pharmaceutical patents on medicines. In 1996, antiretroviral medicines (ARVs) had become available in high-income nations, but the high price of ARVs made treatment unavailable to the vast majority of people living with HIV in low and middle-income countries. The HIV treatment crisis was a public health crisis but also had become a human rights crisis.

The HIV/AIDS crisis brought the international community together to formulate a response to facilitate access to HIV/AIDS prevention, treatment, and care. This response included: increased flexibility in the implementation of intellectual property protection related to medicines, changes in the World Health Organization Model List of Essential Medicines, the establishment of a new international approach to assuring the quality of the medicines and global health financing mechanisms. The global availability of ARVs increased thanks to a combination of lower priced generic medicines, and the new health financing mechanisms that funded the procurement of these medicines. The result was dramatic; millions of people gained access to effective treatment of their disease. Progress in treatment access would have been impossible without increased availability of low-priced generic medicines.

This thesis describes the solutions that the international community has developed to overcome intellectual property barriers to produce and disseminate low-priced generic medicines for the treatment of HIV/AIDS; and aims to respond to the question whether the solutions developed to address the HIV/AIDS crisis can also be deployed to improve access to other, new and expensive essential medicines, for example those needed to provide treatment for non-communicable diseases (NCDs).

This thesis addresses the question by examining the different approaches to intellectual property in the area of medicines and addresses the following specific research questions: 1) How did HIV/AIDS lead to changes in intellectual property law and policy? 2) How did the UN guarantee the quality of generic medicines for HIV? 3) To what extent have governments used the TRIPS flexibilities in practice to access lower priced medicines? 4) How does data exclusivity form a barrier to the

use of TRIPS flexibilities? 5) How to achieve a public health approach to innovation and access?

The HIV crisis led to changes in intellectual property law and policy through practical legal tools, known as TRIPS flexibilities, that can be used by countries to overcome patent barriers to access generic medicines. Effective treatment also requires that these medicines are of assured quality. The World Health Organization responded by developing the Prequalification of Medicines Program (PQP) and donors began to demand that only quality assured medicines were purchased. The PQP was essential in facilitating the international trade in lower priced generic medicines, in particular ARVs. Quality assurance and TRIPS flexibilities are important elements in advancing the availability, accessibility, and acceptability components of the human right to health framework.

This study provides data on the extent to which governments used TRIPS flexibilities in practice, particularly in the procurement of medicines. The study identifies 176 instances of the use of TRIPS flexibilities for the purpose of providing access to medicines during 2001-2016. The deployment of TRIPS flexibilities to deal with patents blocking access to generics has been effective in the procurement of generic medicines and has been more widespread than has been described so far.

Patents are not the only hurdle to access to generic medicines. Data exclusivity, for example, prohibits medicines regulatory agencies from registering an equivalent generic product for a certain period of time. The European Union implements data and other market exclusivities through the European Medicines Agency which affects all of its member states. Data and market exclusivity can hamper the effective use of compulsory licensing, a key TRIPS flexibility by EU member states. This problem is examined in this thesis which recommends amending the EU medicines regulation to introduce waivers of data and market exclusivities needed for the effective use of compulsory licensing by EU member states.

To reach sustainable solutions to innovation and access, a new approach to research and development (R&D) is needed. The pharmaceutical industry claims to depend on high drug prices and profits for funding of new drug development. This approach alone has led to many problems, including lack of attention to significant global health problems as well as the problem of high drug prices. A different approach to the development of new essential medicines requires alternative priority setting and financing models for R&D that do not rely on high medicines prices. This thesis concludes that governments need to define the priorities for R&D and make the necessary R&D financing mechanisms available. The price of new essential medicines could then be delinked from development costs and the products can be made widely available and affordable at generic prices through non-exclusive licensing agreements.

This thesis has documented the international processes that have led to important policy and legal changes in the field of intellectual property to improve access to medicines. Much of this change was driven by the need to formulate a response to the HIV crisis. There are no legal barriers to deploying the legal tools to access lower priced generic medicines more generally. HIV/AIDS offer, important lessons that can be applied for today's challenges in other diseases. However, the deployment of the TRIPS flexibilities, in particular by middle income countries, remains a political challenge because of the opposition by high income countries. Evolving approaches in intellectual property and financing of innovation consistent with the human right to health are necessary to assure access to essential medicines throughout the world. Additional research and analysis on how to foster changes in pharmaceutical innovation systems are needed to inform the policy debates and initiatives already underway.

Samenvatting

Toegang tot medicijnen is wereldwijd een steeds zichtbaarder en groter probleem geworden. Tijdens de hiv/aids-crisis van de late jaren negentig, stierven in ontwikkelingslanden elke dag 8000 mensen aan aids omdat voor hen geen behandeling beschikbaar was. Dit vestigde de aandacht op het intellectuele eigendomsrecht en vooral op de effecten van het geneesmiddelen octrooisysteem. In 1996 waren antiretrovirale geneesmiddelen (ARVs) beschikbaar gekomen in rijkere landen, maar de hoge prijzen die de octrooihoudende bedrijven vroegen voor de medicijnen, maakten toegang tot de behandeling erg moeilijk voor de overgrote meerderheid van de mensen met hiv in lage- en middeninkomenslanden. De hiv/aids-crisis was in eerste instantie een volksgezondheidscrisis maar bleek ook een mensenrechtencrisis te zijn.

De hiv/aids-crisis bracht de internationale gemeenschap bijeen op zoek naar een oplossing voor het probleem van de toegang tot (genees-)middelen die nodig zijn voor preventie, diagnostiek en behandeling van hiv/aids. De maatregelen die hieruit voortkwamen, omvatten onder meer: een grotere flexibiliteit in de (toepassing van) octrooiwetgeving met betrekking tot geneesmiddelen, aanpassingen van de lijst van essentiële geneesmiddelen van de Wereldgezondheidsorganisatie (WHO), een nieuwe internationale benadering om de kwaliteit van de geneesmiddelen te waarborgen en invoering van nieuwe financieringsmechanismen voor gezondheidszorg. De wereldwijde beschikbaarheid van ARVs is verbeterd dankzij een combinatie van lager geprijsde generieke geneesmiddelen en de nieuwe financieringsmogelijkheden voor de aankoop van deze geneesmiddelen. Het resultaat was indrukwekkend; miljoenen mensen hebben toegang gekregen tot een effectieve behandeling van hun ziekte. Deze vooruitgang zou niet mogelijk zijn geweest zonder de verbeteringen in de toegang tot laaggeprijsde generieke geneesmiddelen.

De oplossingen die de internationale gemeenschap ontwikkelde om de belemmeringen die voortkomen uit intellectuele eigendomsrechten te beperken, worden hier beschreven. Met name octrooien vormden een belemmering voor de productie en verstrekking van laaggeprijsde generieke geneesmiddelen voor de behandeling van hiv/aids. De centrale vraag van dit proefschrift is: kunnen vergelijkbare maatregelen de toegang tot andere, nieuwe en dure essentiële medicijnen ook verbeteren? Deze vraag is met name van belang in het licht van de groeiende prevalentie van niet-overdraagbare ziekten.

Het antwoord op die vraag wordt hier gezocht door de verschillende benaderingen te onderzoeken van intellectuele eigendom op het gebied van geneesmiddelen. De volgende onderzoeksvragen komen aan de orde. 1) Hoe leidde de hiv/aids-crisis tot aanpassingen in octrooirecht en beleid? 2) Hoe waarborgde de Verenigde Naties (UN) de kwaliteit van generieke geneesmiddelen voor hiv? 3) In welke mate hebben overheden in de praktijk gebruik gemaakt van de flexibiliteiten in het Trade Related-Aspects of Intellectual Property Rights (TRIPS) verdrag (TRIPS-flexibiliteiten) om de toegang tot lager geprijsde geneesmiddelen te verbeteren? 4) Hoe vormt data-exclusiviteit een belemmering voor het gebruik van TRIPS-flexibiliteiten? 5) Hoe te komen tot een 'Public Health' benadering voor innovatie en toegang tot behandeling?

De hiv-crisis leidde tot veranderingen in de octrooiwetgeving en het beleid door toepassing van juridische instrumenten die bekend staan als TRIPS-flexibiliteiten. Deze instrumenten kunnen landen gebruiken om octrooi-belemmeringen voor de toegang tot generieke geneesmiddelen weg te nemen. Effectieve behandeling vereist ook dat de kwaliteit van geneesmiddelen wordt gewaarborgd. De WHO ontwikkelde hiervoor het 'Prequalification of Medicines Program'(PQP). En donororganisaties gingen ertoe over om te eisen dat uitsluitend geneesmiddelen worden aangeschaft waarvan de kwaliteit kon worden vastgesteld. De PQP bleek essentieel voor het bevorderen van internationale handel in lager geprijsde generieke geneesmiddelen, met name ARVs. Kwaliteitsborging en TRIPS-flexibiliteiten zijn wezenlijke elementen voor het bevorderen van beschikbaarheid, toegankelijkheid en acceptatie, componenten die deel uitmaken van het raamwerk van mensenrechten met betrekking tot gezondheid.

Het hier beschreven onderzoek heeft gegevens opgeleverd over de mate waarin regeringen in de praktijk gebruik hebben gemaakt van TRIPS-flexibiliteiten, in het bijzonder waar het gaat om de aanschaf van geneesmiddelen. In de periode 2001 tot 2016 bleken in 176 gevallen TRIPS-flexibiliteiten te zijn toegepast om toegang tot geneesmiddelen te verschaffen. Het toepassen van deze juridische instrumenten voor het omzeilen van belemmeringen van de toegang tot generieke geneesmiddelen, is effectief gebleken. Het gebruik van deze instrumenten blijkt vaker voor te komen dan tot nu toe is beschreven.

Octrooien zijn niet de enige horde als het gaat om toegang tot generieke geneesmiddelen.

Zo is er bijvoorbeeld het mechanisme dat 'data-exclusivity' wordt genoemd. Dit mechanisme verbiedt de geneesmiddelenautoriteit om gedurende een zekere periode een gelijkwaardig generiek product te registreren (toe te laten tot de markt). De Europese Unie voert data- en marktexclusiviteitsbeleid uit via het Europees Geneesmiddelenbureau (EMA). Data- en marktexclusiviteit kan verhinderen dat een EU-lidstaat effectief gebruik maakt van dwanglicenties.

Dwanglicenties zijn een essentieel onderdeel van TRIPS-flexibiliteiten. Het is aan te bevelen om de Europese regelgeving zodanig aan te passen dat EU lidstaten toch dwanglicenties kunnen verstrekken waar strikt toegepast data- en marktexclusiviteitsbeleid dat zou verhinderen.

Om te komen tot duurzame oplossingen voor innovatie en beschikbaarheid, is een nieuwe aanpak nodig voor Onderzoek en Ontwikkeling (R&D). De farmaceutische industrie zegt dat ze de hoge prijzen en winsten nodig hebben om de ontwikkeling van nieuwe geneesmiddelen te kunnen bekostigen. Alleen al deze benadering heeft tot vele problemen geleid, waaronder onvoldoende aandacht voor belangrijke wereldwijde gezondheidsproblemen en de moeilijkheden die voortvloeien uit de hoge prijzen voor geneesmiddelen. Om los te komen van de hoge medicijnprijzen als bepalende factor voor de ontwikkeling van nieuwe, essentiële geneesmiddelen, is het nodig om op een andere manier prioriteiten te stellen en om andere een andere manier R&D te financieren. Overheden zouden de prioriteiten voor R&D moeten stellen en ook in de benodigde financieringsmechanismen moeten voorzien. De prijs van nieuwe essentiële geneesmiddelen kan dan worden losgekoppeld van de ontwikkelingskosten en de producten kunnen op grote schaal beschikbaar komen tegen generieke prijzen via niet-exclusieve licentieovereenkomsten.

In dit proefschrift is beschreven welke internationale processen hebben geleid tot belangrijke beleidswijzigingen en aanpassingen van wetgeving op het gebied van octrooirecht waarmee toegang tot belangrijke geneesmiddelen is verbeterd. Veel van deze veranderingen zijn ontstaan uit de noodzaak om de hiv-crisis het hoofd te bieden. Er zijn geen juridische obstakels om dezelfde instrumenten toe te passen voor de toegang tot andere laaggeprijsde generieke geneesmiddelen. Uit de hiv/aids-casus vallen belangrijke lessen te trekken voor uitdagingen waarvoor andere ziekten ons vandaag de dag stellen. Toch blijft de toepassing van TRIPS-flexibiliteiten door middeninkomens landen een politieke uitdaging omdat de rijkere landen daar weerstand tegen bieden. Om wereldwijd de mensenrechten met betrekking tot gezondheid zeker te stellen, in het bijzonder waar het gaat om de toegang tot essentiële geneesmiddelen, is het nodig om passende benaderingen te ontwikkelen voor intellectueel eigendom en financiering van innovatie. Om het beleidsdebat en de al lopende initiatieven van relevante informatie te voorzien, is aanvullend onderzoek en analyse nodig ten einde veranderingen in farmaceutische innovatiesystemen te kunnen bevorderen.

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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.

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.

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 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 transition period allows LDCs not to grant or not to enforce existing IP rights on pharmaceutical products. This is sometimes called the LDC waiver and will be in place until 2033.

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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