Analysis

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Biomedical Innovation and Access to Essential Medicines: Alternatives to a Broken Model

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This is the first report in the series "Innovation and Access"

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Executive Summary

The World Health Organisation (WHO) estimates that one of every three people in the world today does not have appropriate access to the medicines they need to treat preventable diseases and guarantee them a safe and decent life. The proportion of the population lacking access to medicines can be as much as twice as high in the poorest regions of Africa, Asia and Latin America, but the problem is not confined to the less developed countries or to tropical diseases. As the prevalence of noncommunicable diseases like cancer and diabetes increases and inequalities within countries becomes the factor that determines the vulnerability of patients, difficulties in accessing essential treatments are also found in emerging economies and even in the most developed countries.

There is something terribly wrong with a system of innovation and access to medicines that allows millions of people to die when the drug that would save their lives can be produced and sold at a price that would cover costs—including the R&D investment—and yield a reasonable, but not abusive, profit for the company. A debate that has been confined for far too long to expert and activist circles has been revitalized by the Ebola epidemic, the case of the new antiviral therapies for hepatitis C, and the growing concern about bacterial resistance to existing antibiotics. Today, patients and taxpayers in dozens of countries —wealthy, emerging and poor— not only wonder whether the drugs they need will be developed, but also where the money to pay for them will be found and why the prices they have to pay are exorbitant.

This paper represents the first public position taken by ISGlobal on this issue and is the first in a series of papers that will analyse the cases of specific diseases. It presents three main arguments. First, the current system of pharmaceutical innovation and access to medicines is governed by a broken model in which commercial interests take precedence over all others. Second, the high cost of medicines and the lack of effective incentives for research into neglected diseases mean that most of the world's poorest patients lack the treatments they need. Third, a joint effort of all of the stakeholders is needed to correct this fundamental imbalance by developing economic and scientific alternatives to the current model. Some alternative mechanisms have already been defined and could be implemented immediately.

01
Introduction

"Support the research and development of vaccines and medicines for the communicable and noncommunicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health…".

Sustainable Development Goals 2030

During the summer of 2000, negotiators worked frenetically to put the finishing touches on the UN Millennium Declaration, an agreement that would define the roadmap for development for the next 15 years. Despite the prominent place given to health matters in that new global agenda, the authors of the Declaration did not see the need to include targets relating to access to essential medicines except for a vague reference to antiretroviral drugs to combat the HIV/AIDS pandemic. It was not until a few months later in a South African court that the heavy-handed strategy of a handful of pharmaceutical multinationals set in motion the international movement that ended up putting the World Trade Organization (WTO) against the ropes. For the first time since the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) had been adopted in 1994, the general public worldwide became aware of the consequences of the rigid protection of intellectual property rights controlled by the WTO.

The scandal sparked by the high prices charged for the drugs needed to treat AIDS led to the Declaration on the TRIPS Agreement and Public Health (Doha, 2001), undeniably a step in the right direction but insufficient to make a real difference in the battle for access to essential medicines. This declaration questioned the absolute primacy of commercial interest over patients rights, opening the door to exceptions and flexibilities that could expedite the production of generic antiretrovirals and radically reduce the cost of treatment in many poor countries, especially in Africa. However, even at that time, many observers warned that the declaration was a flawed solution to a problem that would in due course reappear in other guises, involving other diseases and more developed regions than sub-Saharan Africa[1].

And that is precisely what has happened. This time the problem is hepatitis C, an infectious disease caused by the hepatitis C virus (HCV), which has come to symbolise everything that

1 World Trade Organization. Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health, Decision of the General Council of 30 August 2003. Geneva: WTO; 2003. https://www.wto.org/english/tratop_e/trips_e/implem_para6_e.htm

is wrong with the global model for pharmaceutical innovation and access to essential medicines. Although the issue of HCV therapy is just one of many related to access to medicines that have arisen in the last 15 years (a similar controversy arose over cancer treatments), the social and political impact of this debate has been amplified by the implications of the high cost of HCV therapy for the rights of patients in Europe and the United States.

The logic of the problem has a familiar ring: by paying out a large sum of money a pharmaceutical company acquires a drug that has been developed partly through public funding. The company hits the jackpot, recovers its investment in just one year, and gets ready to reap the benefits of the 20-year monopoly guaranteed by intellectual property laws by charging an exorbitant price for the drug. It is true that a policy of tiered pricing has been established under which different prices are set taking into account the country's purchasing power, but the lowest price offered by the company to a developing country is still 15 times higher than the cost of the generic alternative.

The outcome has been a series of negotiations and legal clashes that have given little satisfaction to either the patent holders or the countries facing the problem. Meanwhile, most of the nearly 150 million people affected by the disease worldwide are not receiving treatment.

There is something terribly wrong with a system of innovation and access to medicines that allows millions of people to die when the drug that would save their lives can be produced and sold at a price that would cover costs—including the R&D investment—and yield a reasonable, but not abusive, profit for the company. The debate confined for far too long to expert circles has been revitalised by the case of the new antiviral agents for the treatment of HCV infection and by the way the patent holder, Gilead, has managed to hold on to its market position on the basis of a patent system that effectively discourages innovation. Today, patients and taxpayers in dozens of countries—wealthy, emerging and poor—not only wonder whether the drugs they need will be developed, but also where the money to pay for them will be found and why the price they must pay is exorbitant.

The difficulty of ensuring access to treatments for chronic diseases is just the latest episode in a series that includes diseases historically considered neglected or forgotten (such as Chagas

disease and leishmaniasis) and other cases in which there are no incentives to motivate innovators to look for and develop essential treatments. One of the most worrying examples of this situation today is the failure to develop a new generation of antibiotics.

Opinions about the best alternative to this broken model are as numerous as the public, business and civil society stakeholders involved in the debate. However, there is growing consensus on one point: the need to solve the problem. And, for the first time in years, we have an opportunity to consider the limitations of the current model of innovation and access to medicines and to propose alternatives.

To be fair, not all the problems of the model are related to the patent system or the attitude of pharmaceutical companies. Succumbing to the temptation of turning the equation on its head and excluding pharmaceutical companies from the model altogether would be just as misguided as insisting on maintaining the status quo based solely on the private sector. A fair and effective system of incentives would make it possible to retain the important contribution that the private sector makes to scientific innovation and the distribution of medicines. At the same time, the public interest needs to be protected through legislation that can prevent abuses of power, safeguard public resources, and ensure innovative research into possible treatments for less profitable diseases.

As is the case in any complex matter of public interest, the solution will involve a combination of economic, political and institutional elements depending on a host of public and private stakeholders. **The first step is to recognise that the status quo is unsustainable and to accurately identify the dilemmas that have to be resolved while respecting the rights and interests of all the parties involved.** The extreme positions adopted by some pharmaceutical companies and activist groups have not only failed to overcome barriers to access but have in fact had the opposite effect. The aim of the Barcelona Institute for Global Health (ISGlobal) in writing this paper is to help identify the crucial elements of the problem and to stimulate the dialogue that should form the basis of any constructive public debate. In this task, we have been encouraged by our own experience in the sphere of scientific research and knowledge transfer and by our ongoing collaboration with public, social, and business organisations.

This paper is ISGlobal's first public position on this issue. Our aim is not to offer prescriptive solutions but to try to ask the right questions and create the framework necessary for an informed public debate. It is the first of a series of papers that will be published over the coming months. The next one will discuss the problem of access to medicines specifically in the context of antiviral therapies for the treatment of HCV infection. A third report will briefly explore the need to develop new antibiotics, a problem of a different kind but one with similar effects. The fourth paper in the series will deal with the problems affecting access to medicines for Chagas diasease. In the final report in the series, we will present some of the key arguments for a real change.

02
Barriers to Access

Over the last 18 months, people all over the world have watched the events unfolding in West Africa during the Ebola epidemic as if it were happening to them. Initially overlooked as just another minor outbreak like the dozen or so that have occurred in the region since 1976, the epidemic that swept through Liberia, Guinea and Sierra Leone has already taken over 10 000 lives and put the health systems of half the world on high alert. What is equally worrying is that this medical and humanitarian emergency revealed the weaknesses of a model of pharmaceutical innovation that failed to provide incentives to complete the development of treatments and vaccines for Ebola and may now overburden both victims and donors with a disproportionately high cost for the response to the epidemic.

The Ebola crisis perfectly illustrates the global problem of access to essential medicines, a problem that also affects many other diseases. The World Health Organisation (WHO) estimates that one of every three people in the world today does not have appropriate access to the medicines they need to treat preventable diseases and guarantee them a safe and decent life[2]. The proportion of the population lacking access to medicines can be as much as twice as high in the poorest regions of Africa, Asia and Latin America, but the problem is not confined to the less developed countries or to tropical diseases. As the prevalence of noncommunicable diseases like cancer and diabetes increases and inequalities within countries become the factor that determines the vulnerability of patients, difficulties in accessing essential treatments are also found in emerging economies and even in the most developed countries (see Table 1).

2 World Health Organisation. Trade, foreign policy, diplomacy and health: access to medicines. http://www.who.int/trade/glossary/story002/en/

Table 1
Standardised Mortality Rate (per 100 000 Inhabitants)

REGIONS	COMMUNICABLE	NONCOMMUNICABLE	INJURIES
Africa	686	652	116
The Americas	63	437	62
South-East Asia	232	656	99
Europe	45	496	49
Eastern Mediterranean	214	654	91
Western Pacific	56	499	50
INCOME GROUPS			
Low income	502	625	104
Lower-middle income	272	673	99
Upper-middle income	75	558	59
High income	34	397	44

Source World Health Report 2013, WHO.

Caught in the 10-90 Gap

The reasons for the shocking disparities in mortality are complex. First, the treatments for some diseases are simply not available, while in other cases the composition and format of the available drugs are ineffective. The 10/90 gap (the fact that 90% of worldwide resources devoted to health research are focused on the diseases that affect only 10% of the world's patients) is a concept that first gained currency a decade ago in descriptions of the phenomenon of neglected diseases. The logic is that any system in which the initiative for developing new products is delegated to a profit-driven private sector will inevitably focus on innovations of interest to those who can pay for them. And this is exactly what has happened: a shocking article published in 2002 reported that of the 1 450 new chemical compounds approved between 1972 and 1999, only 13 (0.8%) were indicated in the treatment of tropical diseases[3]. The Harvard School of Public Health warned in 2001 that only two of the twenty companies interviewed in the course of a survey on this subject reported having a project related to either Chagas disease or leishmaniasis[4].

This picture has been transformed in recent years due, in part, to the emergence of public-private initiatives that have rescued diseases that were forgotten or neglected in the budgetary priorities for pharmaceutical innovation. Organisations involved in basic research (such as TI Pharma and the Innovative Medicines Initiatives) or product development (such as the Medicines for Malaria Venture and the Drugs for Neglected Diseases imitative) and others working to improve systems (such as the Malaria Eradication Scientific Alliance) offer possibilities that were unthinkable just two decades ago[5].

Despite these advances, some diseases that are closely linked to poverty but have a very low impact on overall levels of mortality—such as Chagas disease, leishmaniasis and trypanosomiasis—continue to be sidelined[6]. Other issues are neglected because of the paradoxical nature of an innovation model that does not offer effective incentives, such as the case of bacterial resistance to existing antibiotics or the appearance of emerging infectious diseases.

The lack of resources allocated to research into the diseases associated with poverty is a serious problem. However, an even greater cause for concern is the fact that the development of

3 Trouiller P, Battistella C, Pinel J, Pecoul B. 1999 [2002]. Is orphan drug status beneficial to tropical disease control? Comparison of the American and future European orphan drug acts. TMIH. Vol. 4. (6): 412-420. http://onlinelibrary.wiley.com/doi/10.1046/j.1365-3156.1999.00420.x/full

4 Ibid.

5 Stolk P. Update on 2004 Background Paper, BP 8.1 Public Private Partnership. Utrecht. Priority Medicines for Europe and the World "A Public Health Approach to Innovation"; 2013. http://www.who.int/medicines/areas/priority_medicines/Ch8_1PPPs.pdf

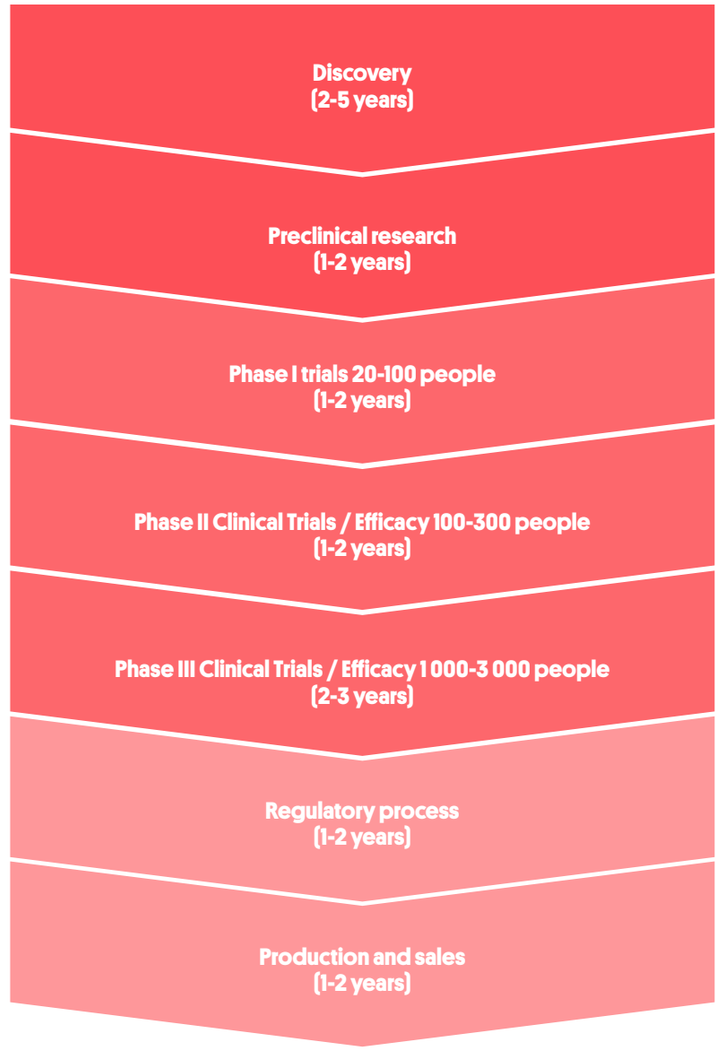
6 Stevens P. Diseases of poverty and the 10/90 Gap. London: International Policy Network; 2004. http://www.who.int/intellectualproperty/submissions/InternationalPolicyNetwork.pdf

many drugs that would save the lives of tens of thousands of children and adults all over the world every day may be abandoned in the early stages of the process because of a commercial strategy. Even worse, drugs that have been developed and are ready to be used remain completely outside the reach of the populations most in need of them. Difficulties affecting distribution (for example, medicines that require cold chain distribution) and the fragility and inequity of health systems in many developing countries are part of the problem, but very often the main obstacle is the high price that public and private buyers must pay for existing drugs. This barrier to access is a direct result of the fact that the model for innovation and the production and sale of pharmaceutical products is governed by the rigid protection of intellectual property rights and is subject to the regulatory mechanisms that administer such rights.

Do Pharmaceutical Companies Enjoy a Monopoly?

The discovery and development of new pharmaceutical products or new formulations that improve the administration or effectiveness of existing products depends on what could be described as a 'hyper-patented' environment in which each product is subject to numerous patents. These patents protect different components and formulations or an exclusive right to the data that gave rise to the discovery (see Figure). The ownership of an attractive patent can even play a decisive role in company mergers and acquisitions.

Figure
Drug Development Phases (approximately 15 years)



The logic of this model was enshrined in international law in 1994 when the recently established WTO introduced the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The pharmaceutical industry played a central role in the negotiation of the agreement, which was seen as a way to compensate investors for the risk they incurred financing research to make new discoveries. But the agreement—which requires member states to grant exclusive rights for 20 years for patents and for at least 8 years for data—is seen by many as a tool that affords an unreasonable level of protection for the rights of the patent holder while failing to protect those of the people who should benefit from the discovery.

This imbalance became very apparent in the late 1990s, when the cost of combination antiretroviral treatment for HIV/AIDS was in excess of $10 000 per person per year, an amount equivalent to 30 year's income for an average sub-Saharan African and way beyond the reach of the struggling health systems in Africa, where the pandemic was concentrated. However, WTO regulations prevented any competition from the numerous pharmaceutical companies in countries such as India or Brazil that could produce generic versions of the drugs for a price up to 140 times lower. Faced with a situation in which it was impossible to use an available treatment in a way that, in the poorer countries, did not even represent real competition for the patent holders (since the alternative to the high priced products was simply not buying the drug), the authorities were forced to resurrect a number of exceptions established in the Doha Declaration on TRIPS and Public Health (see below for more details).

Today, it is possible to distribute antiretroviral agents to treat HIV/AIDS for about $70 per patient per year, a change that has facilitated the access of millions of poor patients to the drugs that will protect their lives, despite the considerable limitations of the distribution system. It has been reported that, of the 20 million people who, according to the WHO and UNICEF, should have received antiretrovirals in 2009, only 5 million patients had access to treatment[7].

AIDS is not the only disease that has highlighted the obvious conflict between the regulation of intellectual property and the rights of patients. A recent post published on The Lancet Global Health Blog by a representative of the consortium of Universities Allied for Essential Medicines, in response to a letter from

7 Velázquez G. Some critical issues related to access to medicines and intellectual property, p56. http://apps.who.int/medicinedocs/documents/s21542en/s21542en.pdf

the philanthropist Bill Gates, denounced the fact that the price of fully vaccinating a child is 70 times higher today than it was in 2001. The author puts her finger on the crux of the problem, the price of the vaccines:

> "The increase is mainly due to the soaring prices of newer vaccines such as the pneumococcal conjugate vaccine. This particular vaccine, which was the subject of Mr Gates' criticism of MSF, is singly responsible for approximately 45% of the price for the total vaccination package for a child living in a developing country. In the meantime, GSK and Pfizer—who are the only producers of the pneumococcal vaccine—have made over $19 billion dollars since it's arrival on the market in 2009. (…) Mr. Gates has accused advocacy groups of demanding that vaccines "cost zero". We are not calling for free vaccines. We are calling for sustainably-priced vaccines[8]."

In response to such arguments, pharmaceutical companies describe a business model complicated by the high cost of risky investment in research and in the development of new products, and contend that the only model that can guarantee innovation is one providing adequate protection for intellectual property rights[9]. However, at no time has the debate between these two opposing sides ever resolved the fundamental flaws inherent in the current model:

- **The risk that the public sector will have to pay twice.** The opponents of the current model argue that citizens are paying twice for the drugs they buy: first they pay for the basic research and development carried out in universities and public research bodies, which is financed by their taxes, and then they pay a second time when they buy the drugs through the public health system.

- **Lack of transparency.** The lack of transparency in the pharmaceutical industry is striking. First, the results of clinical trials are only made public in a very small proportion of cases, a practice which, in the words of the WHO, "engenders misinformation, leading to skewed priorities for both R&D and public health interventions[10]". Although some steps in the right direction have been taken in recent years, the system still cannot guar-

8 Sara Crager. Not free vaccines, Mr Gates, just sustainably-priced ones. The Lancet Global Health Blog. http://globalhealth.thelancet.com/2015/03/19/not-free-vaccines-mr-gates-just-sustainably-priced-ones MSF develops the arguments of the activists in this field: http://www.msfaccess.org/sites/default/files/MSF_assets/Vaccines/Docs/VAC_report_TheRightShot2ndEd_ENG_2015.pdf

9 A.T. Patents that kill. The Economist. Aug 8th 2014. http://www.economist.com/blogs/freeexchange/2014/08/innovation

10 World Health Organisation. WHO calls for increased transparency in medical research. Geneva: WHO Media centre; 2015. http://www.who.int/mediacentre/news/notes/2015/medical-research-transparency/en/

antee the disclosure of all the data generated by clinical trials. The European Medicines Agency has made publication of all such data mandatory starting in January 2016, but this directive only affects the trials that take place after it comes into effect, meaning that we will still not have access to all the trials that have been carried out before that date.[11] According to the All Trials campaign, clinical trials with negative results are twice as likely not to be published, despite the medical importance of knowing such results [12].

The other area clearly lacking transparency is the cost structure cited by the pharmaceutical companies to justify the final price of their products, including everything from the cost of the research to the development of the drug and the cost of producing, marketing and selling the final product. Given the huge discrepancy between the cost of production and the sale price of many products, this lack of transparency is often cited as a fundamental obstacle to finding solutions. In the case of HCV infection, the exact price the Spanish government paid for the antiviral sofosbuvir is not known even now.

• **Untapped Innovation.** The logic of the current innovation model also increases the risk that research findings that might be useful for the public interest may be neglected because they are difficult to patent or because of commercial considerations. This result is particularly egregious when the original research has been funded by public money.

• **Debatable innovation.** One of the effects associated with the phenomenon of 'hyper-patenting' is the tendency to treat something as an innovation when it is not, in fact, novel. A study carried out by the US National Institutes of Health concluded that only 15% of all the drugs approved during the period 1989 to 2000 were actually novel in this sense. To some extent, the root of this problem can be found in the desire to perpetuate or 'evergreen' patents by obtaining a new patent for an existing product on the basis of minor modifications.

11 European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. London: 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

12 AllTrials. All Trials Registered, All Results Reported. London: AllTrials; 2014. http://www.alltrials.net/find-out-more/why-this-matters/

Box 1
The Importance of Added Therapeutic Value (ATV)

A new drug can be only be approved when it has been shown to be both safe and more effective than placebo. However, European regulations do not require new compounds to be more effective than other drugs for the same indication already on the market. This results in a flawed market system that discourages pharmaceutical companies from developing more effective new treatments because the regulations allow them to develop products that are very similar to those already on the market even though there is an urgent need for innovative drugs, such as new antibiotics.

An analysis by the medical journal Prescrire revealed that **less than 25% of the new drugs launched on the French market in the last 10 years had any ATV;** over 50% had no ATV, and between 15% and 20% were more harmful than beneficial. A similar study in the Netherlands found that less than 1% of the medicinal products approved had any ATV over existing treatments. An analysis carried out in Germany in 2013 found that 55% of the new products approved in that country had no ATV, 24% had some added value, and 12% had considerable added value; none of the treatments approved were considered to have excellent added value. Thus, both citizens and the public health services are paying a high price for many treatments with no ATV and, at the same time, alarming public health problems, such as antibiotic resistance, are not prioritised by the innovation system.

Source
Wemos. Added therapeutic value: European citizens should get their money´s worth". September 2014. http://www.wemos.nl/files/Document-en%20Informatief/Bestanden%20voor%20'Medicijnen'/Position%20paper%20ATV%20Wemos%20SOMO%20EPHA%20ISDS.pdf

• **Uncertainty in the pharmaceutical industry.** The pharmaceutical industry enjoys a privileged market position that guarantees the companies fat profit margins (a mean of 18% in 2014, far higher than any other industrial sector)[13]. Nevertheless, the sector is also subject to considerable uncertainty because the pharmaceutical business model is determined by the unpredictable nature of the research process and by the pricing and reimbursement policies applied by different countries. Some observers have described this situation as a 'lottery' which must be faced by companies that have made a considerable effort to bring products to market without knowing what profit margin they can expect [14].

13 Anderson R. Pharmaceutical industry gets high on fat profits. BBC News. 6 November 2014. http://www.bbc.com/news/business-28212223

14 Cueni T. Can Europe afford innovation? Eurohealth; Vol 14 (2): 8-10. 2008. http://www.euro.who.int/__data/assets/pdf_file/0003/80445/Eurohealth14_2.pdf

In a context in which an unacceptably high proportion of patients have no access to essential medicines, these issues are important. How to resolve the problems associated with the model for innovation and access to medicines has for years been the subject of an intense public debate that revolves around a series of fundamental scientific, economic, political and, undoubtedly, ethical questions: *What does it cost to bring a drug to market? What incentives do pharmaceutical innovators need? What constitutes a patentable innovation? Who determines the priorities on the research agenda? What is the role of the public sector throughout the whole process? Who sets the rules that guarantee the rights of all parties?*

03
Current Mitigation Measures

There is no one simple answer to these questions. Academics, activists and industry representatives have all proposed differing prescriptions for solving the problems surrounding innovation and access to medicines. In practice, most of the strategies that have emerged fall into one of four categories: the TRIPS flexibilities, unilateral decisions made by companies that own patents, unilateral actions taken by governments, or funding from public and private donors. In this setting, it has been possible to explore the different solutions described below, which have been implemented with mixed results.

• **Differential pricing policies.** Pharmaceutical companies often set different prices in different countries or regions for the same product, taking into account the buying power of each market. This mechanism allows them to optimise sales and increase the number of patients with access to the drug. The mechanism for establishing such tiered pricing is, however, never transparent, and the results are questionable. In 2006, Honduras bought the Lopinavir/Ritonavir combination antiretroviral therapy for the treatment of HIV at a price six times higher than that paid by Brazil. The incidence of AIDS is similar in both countries (0.5%), but the per capita gross domestic product (GDP) of Honduras is one-quarter that of Brazil[15]. Brazil's skilful handling of negotiations, the attractiveness of its market and the possibility that the country might adopt unilateral measures to buy or produce generic drugs probably had more impact the final price they paid than the poverty of the Honduran people did on the price their government paid. Moreover, differential pricing based on a country's average income ignores the problem of the very significant inequalities that occur within countries and thereby penalizes the poorest sectors of the population in countries with emerging economies. This issue is a recurrent topic of debate, sometimes triggered by the public-private alliances whose role is to facilitate access to medicines, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria[16].

What happened in the case of HIV/AIDS clearly demonstrated that the best price offered by pharmaceutical companies through tiered pricing is always much higher than the prices set by their generic competitors. It was

15 Ford N, Wilson D, Chaves GC, Lotrowska M, Kijtiwatchakul K: Sustaining access to antiretroviral therapy in the less-developed world: Lessons from Brazil and Thailand. AIDS 2007, 21(Suppl 4):S21-S29.

16 Open Society Foundations. Undermining the global fight. OSF; 2014. http://www.opensocietyfoundations.org/sites/default/files/undermining-global-fight-20141201.pdf

this factor that justified the proposal made by the Global Fund and made possible the leap from 50 000 to 10 million patients treated in developing countries between 2001 and 2013.

• **Pooled procurement mechanisms.** Pooled purchasing strengthens the negotiating position of the members of the group, enabling them to obtain a lower final price. A number of successful joint purchasing mechanisms exist, including the Vaccines Alliance (GAVI) and the Pan American Health Organization's Revolving Fund For Vaccine Procurement. The latter makes group purchases of childhood vaccines to supply dozens of countries, obtaining more advantageous prices than those that could be secured through bilateral negotiation. Unfortunately, joint purchasing is a mechanism not used as often as it should be. In response to the influenza A pandemic in 2011, the members of the European Union expressed an interest in setting up a joint purchasing mechanism to acquire the appropriate vaccines, but the initiative was not successful[17]. The practice is, however very common in other sectors, such as defence and construction[18].

• **Advance market commitments.** Advance market commitments represent a guarantee of the investment in a new drug. This is achieved through binding commitments from governments and donors to purchase the product in large quantities.

• **Voluntary licensing.** Companies holding the patents for a drug can grant licences to third parties to manufacture and sell generic versions of the product in a specific country in exchange for a royalty, often around 5%[19]. This practice, known as voluntary licensing, allows the patent holder to retain control over the sale price of the generic product, but usually reduces the cost to the patient and increases the availability of the drug in the market[20]. In the past, this type of licence has been granted by patent holders to generic producers in countries like South Africa and India to reduce the cost of antiretroviral treatment for HIV/AIDS[21]. Medicines Patent Pool (MPP)—an initiative launched in 2010 to accelerate access to treatments for AIDS—used this

17 European Commission Health and Consumers Directorate-General. Explanatory Note on the Joint Procurement initiative. Public Health Threats. Luxembourg; 2014. http://ec.europa.eu/health/preparedness_response/docs/jpa_explanatory_en.pdf

18 Ibid.

19 Tahir A. Voluntary licensing practices in the pharmaceutical sector: An acceptable solution to improving access to affordable medicines?. Oxfam GB, 2007.

20 Heydari S, Kembabazi A, Monahan C, Ragins K. Ending an epidemic: overcoming the barriers to an HCV-free future (p. 28). Connecticut: Yale Global Health Justice Partnership; 2015. http://media.wix.com/ugd/148599_3746a108d074493d8fc18ed1f9c262c2.pdf

21 For more information on the history of voluntary licensing see: Voluntary licensing practices in the pharmaceutical sector: An acceptable solution to improving access to affordable medicines? Tahir Amin, Oxfam, United Kingdom, 2007. http://static1.1.sqspcdn.com/static/f/129694/1099999/1192729231567/Oxfam+-+Voluntary+Licensing+Research+IMAK+Website.pdf?token=GKJXv4VRmd%2BOFuIE9pq8gZFvlpw%3D

22 Medicines Patent Pool. Progress and achievements of the Medicines Patent Pool 2010-2015.http://www.medicinespatentpool.org/wp-content/uploads/WEB_Progress_Report_2015_EN.pdf

model, negotiating with pharmaceutical companies for voluntary licences and then granting sub-licenses to producers in the affected countries. To date, MPP has signed license agreements for 11 antiretroviral drugs[22]. The criticism that has been made of voluntary licensing—and differential pricing—is that it is not effective in reducing prices. The industry has been accused of a number of doubtful practices: waiting until the last moment to grant the voluntary licence, overloading the operations with restrictive terms, and using this mechanism to limit the use of TRIPS flexibilities, such as compulsory licensing[23]. To make matters worse, voluntary licensing operations often exclude middle income countries, which are home to a large proportion of the world's poor[24].

• **Compulsory licensing.** The intellectual property agreements establish a series of exemptions (flexibilities) that apply specifically to the needs of health care. These include parallel imports and a margin in the interpretation of patentability criteria. Another is compulsory licensing, which allows a government to issue licences authorising the production or import of generic drugs during the period covered by a patent. In many cases, a national emergency is declared before such a licence is issued, but the WTO does not consider this to be an essential prerequisite; in theory, "prompt notification" of the patent holder is sufficient[25]. The patent continues to belong to the original owner, but the financial remuneration paid is fixed by the national authority that issues the licence [26].

The possibility that a country might issue a compulsory licence has become a strong bargaining tool in negotiations, as demonstrated by the case of Brazil in 2001, when the country successfully reduced the price it paid for drugs to treat AIDS. In South Africa, GlaxoSmithKline and Boehringer Ingelheim agreed to grant voluntary licences for their antiretroviral therapy to generic companies in exchange for a royalty of 5% to avoid a situation governed by a compulsory licence [27].

23 Ending an epidemic: overcoming the barriers to an HCV-free future. 2015 (p. 29).

24 Médecins Sans Frontières Australia. Gilead licence expands access, but several countries left out. Excluded countries should be ready to issue compulsory licenses to access needed drugs. Geneva: MSF Press Release; 2011. http://www.msf.org.au/media-room/press-releases/press-release/article/gilead-licence-expands-access-but-several-countries-left-out.html

25 World Trade Organization. Compulsory licensing of pharmaceuticals and TRIPS. Geneva; WTO Secretariat; 2006. https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm

26 Ibíd.

27 Ending an epidemic: overcoming the barriers to an HCV-Free future. 2015 (p. 27).

Table 2
Applications for Compulsory Licences Between 2001 and 2010

Year	Country	Disease	No. of Drugs	Result
2001	Canada	Anthrax	1	Discount
2001-2007	Brazil	HIV/AIDS	2	CL
2001-2003	South Africa	HIV/AIDS	8	VL
2001	USA	Anthrax	1	Discount
2002	Egypt	Erectile dysfunction	1	CL
2003-2004	Malaysia	HIV/AIDS	3	CL
2003	Zimbabwe	HIV/AIDS	All ARV	CL
2004	Zambia	HIV/AIDS	3	CL
2005	Ghana	HIV/AIDS	All ARV	CL
2005	Indonesia	HIV/AIDS	2	CL
2005	Taiwan	Avian Flu	1	VL
2005-2006	Argentina	Avian Flu	1	VL
2006	India	Cancer	1	None
2006	Thailand	HIV/AIDS	1	CL
2007	Rwanda	HIV/AIDS	1	CL
2007-2008	Thailand	Cancer	1	Discount
2007-2008	Thailand	Cancer	3	CL
2010	Ecuador	HIV/AIDS		CL

Abbreviations:
CL, compulsory licensing;
VL, voluntary licensing;
ARV, antiretroviral therapy.

Source Trends in compulsory licensing of pharmaceuticals since the Doha Declaration: A database analysis, Plos Medicine, January 2012.

Table 2 shows the occasions when developing countries have made use of compulsory licensing to address the HIV/AIDS crisis, but such licences have also been issued for other diseases. Often, the decision to issue a compulsory licence is preceded and followed by political and commercial pressure brought to bear by the government of the patent holder's country, particularly when this is the USA[28]. Paradoxically, the USA has itself resorted to the use of compulsory licensing for all kinds of purposes, not just pharmaceutical, over 1000 times [29].

28 See, for example, the seizure by Dutch customs authorities of a shipment of antiretroviral drugs in transit from India to Nigeria. http://www.haiweb.org/06032009/6%20Mar%202009%20Press%20release%20More%20generic%20medicines%20intercepted%20in%20the%20Netherlands%20%28English%29.pdf

29 Rius J. Recent examples of compulsory licensing of patents. KEI; 2009.

• **Patent opposition.** TRIPS establishes three criteria for granting a patent: novelty, inventive activity and industrial application[30]. However, the agreement does not offer a precise definition of these criteria, leaving a margin of interpretation for the national legislatures in WTO member countries[31]. India, for example, has used the TRIPS flexibilities to strengthen the patentability criteria, thereby facilitating local production of generic drugs and increasing the population's access to essential medicines while at the same time complying with WTO regulations.

Article 3d of the Indian Patents Act clearly states that the following are not patentable inventions: "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process[32] results in a new product or employs at least one new reactant." Under this law, India has rejected patent applications made by large pharmaceutical companies for drugs that have been patented in other countries—including the application by Novartis for patent on the cancer drug Gleevec—because the drugs in question did not meet the patentability criteria established by the legislation. Other countries, including Thailand, the Philippines and Brazil, are following India's example and challenging patents in the courts. Brazil and Argentina are in the process of amending their patent guidelines to redefine a number of concepts more narrowly, including novelty and inventive activity[33].

This type of patentability criteria, which depends on legislative decisions made in each country, could bring the practice of 'hyper-patenting' to an end and facilitate access to medicines while protecting real innovation[34]. Ensuring appropriate use of the patent system is an approach that complements compulsory licensing. Unfortunately, the intellectual protection terms imposed by the new generation of trade agreements further complicate the use of the TRIP flexibilities (see Box 2).

30 World Trade Organization. Geneva: WTO; c1994 [2015]. https://www.wto.org

31 Trade-Related Aspects of Intellectual Property Rights (TRIPS). Article 1.1. Marrakesh: WTO; 1994.

32 Intellectual Property India. The Patents Act, 1970 Chapter II, section 3(d). Updated to 2013. New Delhi: 1979. http://ipindia.nic.in/ipr/patent/patent_Act_1970_28012013_book.pdf

33 Ending an epidemic: overcoming the barriers to an HCV-Free Future. 2015 (p. 26)

34 WHO, UNAIDS, and UNDP. Using TRIPS flexibilities to improve access to HIV treatment. Geneva: World Health Organization; 2011.

Box 2
TRIPS Plus: When the WTO is Not the Biggest Problem

Low income countries and emerging economies won some battles over access to medicines in 2001, but the fight continues in the form of new bilateral and regional trade agreements that seek to make WTO conditions more restrictive, extend the effective term of patents and data exclusivity and invalidate the TRIPS flexibilities, in particular the possibility of issuing compulsory licenses.

Strongly influenced by the pharmaceutical and biotechnology companies, among others, the US Department of Commerce has become the champion of a model of agreement to which the European Union (EU) has acceded without complaint. These bilateral regional agreements limit the bargaining power of the weaker party by eliminating the possibility of alliances between poorer countries and other actors.

The American government has just signed the Trans-Pacific Partnership (TPP), a free trade agreement between various Pacific Rim countries, including Chile, Peru, Colombia, Malaysia and Vietnam. This agreement will legally prevent the signatories from benefitting from most of the TRIPS flexibilities and has been described by Doctors Without Borders (MSF) as the "worst trade agreement [in history] for access to medicines in developing countries[35]".

TPP is just one of a long list of US agreements, which also includes the Central America Free Trade Agreement (CAFTA), the South African Customs Union, and treaties with several countries in the Middle East and East Asia. All these agreements form part of a strategy aimed at building a critical mass of countries within the WTO that agree to more stringent TRIPS requirements. The EU has also done its part in negotiating such agreements, including ongoing discussions with India. More recently, the negotiations between the USA and the EU on a Transatlantic Trade and Investment Partnership (TTIP) have been criticised for their lack of transparency and the likelihood that the TTIP will limit the ability of states to ensure policies on pricing and access to medicines consistent with the public interest[37].

35 Rius J. Medecins Sans Frontieres. MSF statement on the conclusion of TPP negotiations in Atlanta. MSF Access Campaign; 2015. http://www.msfaccess.org/about-us/media-room/press-releases/statement-msf-conclusion-tpp-negotiations-atlanta

36 Devalière A, Tessel M. The EU-US trade deal could leave Europeans sick. Washington: EurActiv.com; 2015 http://www.euractiv.com/sections/health-consumers/eu-us-trade-deal-could-leave-europeans-sick-311829

The lack of options open to governments and patients under the current system have led to proposals for alternatives, ranging from partial reform of the status quo to openly questioning the intellectual property system. The WHO, in particular, has been a platform for an intense debate to which all the stakeholders have contributed their point of view. The Consultative Expert Working Group (CEWG) received more than 100 specific ideas, which eventually gave rise to a document outlining the proposals based on three main principles: de-linkage of the delivery price of medicines from research and development costs, the use of open knowledge innovation, and licensing for access. These principles should give rise to an international treaty or convention on research and development incorporating adequate and sustainable financing mechanisms and criteria for defining research priorities. Although progress is slow, this is still one of the few avenues of reform open at present.

Table 3 summarises the main proposals on the table, which can be grouped into two groups: those that plainly call into question the model of innovation based on monopolies and the patent system, and those that propose operating within that system but call for varying levels of reform. All the proposals call for increased transparency in both price setting and the role of operators in the market, which is seen as a necessary condition in all scenarios.

Table 3
Proposals for the Reform of the R&D Model for Medicines

	APPROACH	PROPOSAL	OBSTACLES
WITHIN THE TRIPS FRAMEWORK	**IMPROVE THE STATUS QUO**	Differential pricing	Countries with a higher GDP or larger population have a greater possibility of negotiating a lower price. Smaller countries lose.
		Voluntary licensing	It depends on industry's willingness. It does not ensure lower prices than the free competition between generic drugs would provide.
		Compulsory licensing	The conditions governing intellectual property (TRIPS+) in the free trade agreements currently under negotiation restrict the legal options open to countries who wish to issue compulsory licences.
		Advanced market commitment	Requires advance funding.
		Joint purchasing mechanisms	Strong **opposition from the pharmaceutical industry** is imposing constraints on the political will of governments.
	REFORM TRIPS AND EXPAND FLEXIBILITIES	Patent opposition	The terms relating to intellectual property (TRIPS+) in the **new free trade treaties currently being negotiated eliminate the TRIPS flexibilities** and limit the ways national authorities can promote generic competition and reject or challenge patents.
		Ensure generic competition	The countries with most weight in the world economy have more **influence in the negotiations** for reforms and can impose conditions that favour the pharmaceutical industries in their countries by limiting flexibilities.
		Price control (minimum and maximum)	Lack of **political will.** Industry opposition.
		Technology transfer to developing countries	**In developing countries, regulatory competence** is very limited. This shortcoming has a negative impact on the national capacity to develop a domestic industry and produce generic medicines.
		Public-private partnerships	National production capacity is limited in developing countries **The pharmaceutical industry is not interested in** investing in diseases that occur mainly in developing countries or those that do not, in their opinion, offer a good return on investment.
		Priority review voucher	The priority review voucher system lacks the criteria needed to ensure affordability and access. It is also affected by legal loopholes that allow the mechanism to be abused.
OUTSIDE OF THE TRIPS FRAMEWORK	**DE-LINKAGE OF R&D FUNDING AND PRODUCT SALES**	Innovation awards	**The financing of innovation awards depends primarily on public resources** and funding from philanthropic organisations, which means that strong political commitment, is needed to ensure that funding is **made available.** The difficulty in reaching an agreement on **research priorities.** Funding must be committed in advance, before it is possible to know whether the innovation will be effective. Awards are generally focused on **specific tools or diseases.**
		A biomedical fund for R&D	**Scientific capacity** for finding medical solutions Dependence on public or philanthropic resources.
		International treaty on research and development	Greater **negotiating power** of the wealthier countries when defining priorities and the resources to be allocated. Lack of specificity.
		Open research	The time taken to meet the medical needs of the population may be longer than necessary.
		Imposing criteria of interest on research financed with public funds	The agreements **are not binding.**

04
Conclusions

This document has presented two main arguments: **first, the current system of innovation and access to medicines is based on a broken model in which commercial interests take precedence over all others; second, most of the diseases that predominantly affect poor patients are still neglected.**

The current debate regarding access to the new hepatitis C therapies illustrates the nature of a problem that also affects patients with many other diseases—a problem that is primarily the result of commercial regulation and the disproportionate power of some of the parties involved. As was the case with HIV/AIDS at the end of the 1990s, patients, professionals and observers now see hepatitis C as a symbol of health inequities and a problem that is placing an overwhelming burden on our health system budgets.

In later reports in this series, when we analyse the situation regarding antibiotics, we will see that the regulatory framework governing intellectual property rights is only part of the problem. The market can fail patients for other reasons. But in any case, economic intervention and regulation of the public sector is a necessary precondition for a sustainable solution.

Furthermore, the category of vulnerable patients who lack access to essential medicines is no longer defined by the traditional boundaries between the rich world and the developing world. The alarming situation of millions of people in Europe and the United States is proof that the fundamental right to health is now determined by inequality and the shortcomings of our societies' protective systems and is no longer shaped by the old indicators or confined by the geographic borders of the developing world. Spanish society is experiencing the same situation that affects hundreds of millions of patients worldwide.

This community of interests opens the door to the possibility of **having a real global conversation that will take into account the rights and aspirations of all the parties involved.**

Our task today is to find a way to reframe a debate that has so far failed to achieve an acceptable balance capable of guaranteeing pharmaceutical innovation in line with the public interest and universal access to treatment. Fifteen years after the introduction of the WTO intellectual property agreements, the flexibilities they envisaged are still demonstrating limited effectiveness against the pressures brought to bear by pharmaceutical companies and the inability of governments to protect the common interest. To make matters worse, the latest generation of regional and bilateral trade agreements are even more restrictive than their predecessors and further limit the possibility that the conditions imposed by patents will be compatible with patients' rights.

In one sense, a set of conditions is necessary. Despite partial victories (for example, access to antiretrovirals) and their ability to attract public attention to these issues, activist groups have repeatedly come up against the wall of indifference erected by both governments and the private sector. Companies, on the other hand, make an indispensable contribution to the development of new drugs, but have generally adopted a short-term position oriented more towards milking the profits of the current model than towards laying the foundations of a sustainable system. Public-private initiatives involved in research and product development may be part of the solution, but the accumulated evidence of the political and financial constraints that limit their work shows that they can never provide a complete solution. The same can be said of the goal of reaching a binding multilateral agreement on R&D within the WHO, on which the General Assembly will have to state its opinion in May 2016.

As noted in the introduction, the aim of this paper is not to be prescriptive. Over the coming months, ISGlobal will publish a series of papers on this topic in which we will have the opportunity to make specific recommendations. The next three will address the specific cases of hepatitis C, antibiotic resistance, and Chagas diseases in greater detail, and the final report will be a more far-reaching work dealing with possible alternatives to the current model of innovation. The aim is to encourage a dialogue that will deal with the fundamental questions on the basis of the available scientific and economic evidence rather than one argued from the standpoint of ideological prejudices or financial interests.

The questions that still need to be answered are as numerous as they are important:

• **The process of research and creation.** How do we get from basic research to the development of new products? What are the

incentives? Is the path from public research to private development inevitable? What really constitutes an innovation worthy of patent protection? How is the research agenda defined? How do we stimulate research and how do we value different discoveries?

• **Economic considerations.** What is the real cost of innovation? How are prices set? Is it possible to establish a 'reasonable' profit? Who should bear the financial risks of innovation and how can this risk be compensated? How can we separate the creative and industrial processes to guarantee both profits and access?

• **Governance.** What is the financial, scientific, legal and ethical role of the public sector in this debate? What information should be freely available? What conditions should be attached to public investment in innovation? Who should be responsible for guaranteeing the minimum rights of patients? What institutions are needed to ensure that this happens?

Some progress has been made in the right direction. Many people believe that the coming years offer a unique opportunity to answer some of the important questions that have arisen in the open debate on the cost of treating HCV infection, Ebola and resistant bacteria. The first step is to achieve the transparency needed to allow public and private stakeholders to argue their respective positions on the basis of complete and accurate information. The measures needed to make this possible might include the following:

• **Financial transparency.** Public, business and non-profit organisations involved in research and in the development and sale of drugs should provide reliable data on their investment and profit margins as well as any public funds they receive. To achieve this goal, it would be useful if the institutions in the countries where these entities are located—particularly in the EU and the United States—could work towards getting their governments to enact legislation in this field similar to the US Dodd-Frank Act and the European Directive on Transparency and Accountability. These instruments require companies involved in extractive industries (mining, gas and oil) to disclose the payments they make, including taxes and royalties, and to report their profits and the subsidies they receive in each one of the countries where they operate.

• **Transparency in the negotiation of trade agreements.** Negotiations on trade, bilateral and regional treaties (which ultimately have an impact on the intellectual property rules) often take place behind closed doors and are never subjected to public scrutiny. It is imperative that such negotiations—starting with the free trade agreement currently being negotiating between the EU and the United States—should guarantee access to the draft treaties and open them up to public consultation before they are approved.

• **Transparency in public procurement mechanisms.** Negotiations between countries and pharmaceutical companies for the purchase of drugs with public money should be conducted in a framework of absolute transparency. Before making a purchase countries should conduct a cost-effectiveness analysis and a health technology assessment to determine whether the drug should be included in their national health system, and the results of such analyses should also be made public.

Even within the limits of the current model, the introduction of these measures would appreciably decrease the risk to the public interest and would facilitate the start of discussions on the reform of the model in the medium term.

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