# Seeking Remedies for Access to Medicines and Intellectual Property

**Recent Developments** 



# Germán Velásquez



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#### PREFACE

This book is a collection of research papers published by the South Centre between 2015 and 2019 on recent international deliberations, including in the context of the United Nations (UN), on access to medicines and its relationship with international trade and intellectual property regimes. The book addresses, among other issues, the development of guidelines on the patentability of pharmaceutical products, the international debate on generic medicines of biological origin and access to Hepatitis C treatment.

The South Centre is an intergovernmental research organization of developing countries that focuses on critical development issues for the South. It is an observer to the governing bodies of the World Health Organization (WHO) and other UN agencies. The collection of papers presented in this book is illustrative of the work undertaken by the Centre to provide policy makers, researchers and other stakeholders information and analyses on critical issues pertaining to public health and access to medicines.

Chapter 1 provides an analysis on the link between the examination of patent applications carried out by national patent offices and the right of citizens to get access to medicines. There is now greater understanding that the examination of patent applications and the role played by patent examiners are key elements that could contribute to or obstruct access to medicines. A review of the vast literature on intellectual property and access to medicines, suggests, however, that the analysis of the key role played by patent offices in shaping the market dynamics in pharmaceuticals has often been overlooked. Patentability requirements are not defined in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) and the Member States of the World Trade Organization (WTO) are free to define these three criteria in a manner consistent with the public health objectives defined by each country. Given the impact of pharmaceutical patents, patent offices should draw up policies and strategies that are integrated with and respond to public policies regarding access to medicines.

Chapter 2 provides an analysis on the debate on generic medicines of biological origin. The debate on generic medicines is not new; what makes it different today is that attacks levelled against biological generic products are couched in ever more "technical" and abstruse language that confuses the public and competent authorities. Innovative biological drugs introduced on the market in the few past decades (human insulin was first introduced on the market by Eli Lilly in 1982) make up, in terms of units, no more than 2 per cent (eleven products, compared to thousands of chemically synthesized products that flood world markets) of the WHO Model List of Essential Medicines but, in terms of cost, they account for 15 to 20 per cent of national drug expenditures. The high price of biological drugs stems mainly from two new factors: first, a change in the pharmaceutical industry's approach to price-setting and, secondly, the introduction of additional barriers to the entry of biogenerics into the market. In any debate on this issue, it should be made it clear that what is at stake is not whether "identical" products can be made available, but whether they are therapeutically equivalent. What matters to the patient, after all, is whether or not the drug can prevent, cure or mitigate the effects of a particular disease, and not the abstract concept of identity.

Chapter 3 addresses five items: 1) General context and background of the debate over access to medicines. 2) The problem of the Hepatitis C virus (HCV). 3) Access to new direct-acting antiviral (DAA) treatments for Hepatitis C. 4) How to overcome barriers to access: using the flexibilities of the TRIPS Agreement. 5) Some examples of countries that have launched the new HCV treatment.

Chapter 4 describes and analyses the mandate, programmes, strategies, and activities that different international organizations such as the World Health Organization, the World Trade Organization, the World Intellectual Property Organization (WIPO), the United Nations Conference on Trade and Development (UNCTAD), the United Nations Development Programme (UNDP), the Joint United Nations Programme on HIV and AIDS (UNAIDS), the United Nations Human Rights Council, and the United Nations Secretary-General's High-Level Panel (UNHLP) have undertaken on the subject of access to medicines, intellectual property, international trade rules and human rights. This chapter also analyses two cases of existing inter-agency cooperation: the

WHO-WTO-WIPO tripartite partnership and the WHO, UNDP and UNCTAD collaboration for developing guidelines for the examination of pharmaceutical patents from a public health perspective.

Chapter 5 is co-authored by Carlos M. Correa and Germán Velásquez. It discusses first, the limitations of the current research and development (R&D) model and its implications for access to medicines. Second, it considers the tensions between intellectual property rights applied to medicines and States' implementation of the fundamental right to health. Third, it examines the case of access to medicines for the treatment of Hepatitis C, and illustrates the barriers to access created by intellectual property and the high prices normally associated with its exercise. Fourth, it presents the main obstacles to the achievement of the objectives that led to the approval, in 2001, of the Doha Declaration on the TRIPS Agreement and Public Health. Against this background, this chapter examines in three sections the grant of compulsory licenses and the government use of patents to produce or import medicines and improve access for the population, and the experiences in Latin America (in particular, Ecuador, Peru and Colombia) and in other countries, including the role of civil society.

Carlos Correa Executive Director South Centre Geneva

# CHAPTER 1 GUIDELINES ON PATENTABILITY AND ACCESS TO MEDICINES

Germán Velásquez<sup>1</sup>

#### I. INTRODUCTION

Until recently, the link between the examination of patents carried out by national patent offices and the right of citizens to access to medicines was not at all clear. They were two functions or responsibilities of the State that apparently had nothing to do with each other. Examining the growing literature on intellectual property and access to medicines, it seems that the analysis of one actor has been left out: the patent offices. And the reason is clear: patent offices are administrative institutions. Patentability requirements are not defined by patent offices, but frequently by the courts, tribunals, legislation or treaty negotiators.<sup>2</sup> There is now greater understanding that the examination of patents and the role played by patent examiners are key elements that could contribute to or obstruct access to medicines. Given the impact of pharmaceutical patents on access to medicines, patent offices should draw up public policies and strategies that respond to national health and medicine policies.

In 1994, the creation of the World Trade Organization (WTO) resulted in the establishment of a new treaty, the broadest on intellectual property rights: the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement). This Agreement links issues of intellectual property and trade for the first time and provides a multilateral mechanism to resolve disputes between States. The TRIPS Agreement requires all WTO Member States to incorporate into their legislation universal minimum standards for almost all rights in this

<sup>&</sup>lt;sup>1</sup> Germán Velásquez is Special Advisor, Policy and Health at the South Centre.

<sup>&</sup>lt;sup>2</sup> Cf. Drahos, Peter "Trust me: Patent offices in developing countries", Centre for governance of knowledge and development, working paper, November 2007.

domain: copyright, patents and trademarks.<sup>3</sup> In addition, the Agreement has considerably limited the freedom previously enjoyed by countries to develop and apply their own intellectual property systems.<sup>4</sup> Such an obligation did not exist within the framework of previous international agreements. In the past, it was considered that each nation had the right to legislate in this respect. International agreements prior to the TRIPS Agreement did not specify minimum standards on intellectual property. Before the TRIPS Agreement, over 50 countries did not provide patent protection for pharmaceutical products; many provided patent protection for the processes but not the products and in a large number of countries, the duration was less than 20 years.<sup>5</sup>

A patent is "a title granted by the public authorities conferring a temporary monopoly for the exploitation of an invention upon the person who reveals it, furnishes a sufficiently clear and full description of it, and claims this monopoly."<sup>6</sup> Monopolies generally lead to high prices that, in many cases, restrict access. The structure, patent – monopoly – high price – restricted access, does not present a problem when related to a patent for simple merchandise, such as a perfume or musical equipment. The problem arises when monopolies are granted for public goods or essential products used to prevent illness, improve health or prevent death.

According to the TRIPS Agreement, the patentability requirements used by national intellectual property offices require a product or manufacturing process to meet the conditions necessary to grant patent protection, namely: novelty, inventive step and industrial applicability (utility). These three elements, however, are not defined in the TRIPS Agreement and WTO Member States are free to define these three criteria in a manner consistent with the public health objectives defined by each country.

<sup>&</sup>lt;sup>3</sup> See Velásquez G. and Boulet P., "Essential drugs in the new international environment" *Bulletin of the World Health Organization* 1999, vol. 77, No. 3.

<sup>&</sup>lt;sup>4</sup> See Correa, C., "Health and Intellectual Property rights", Bulletin of the World Health Organization, 2001, vol. 79, No. 5.

<sup>&</sup>lt;sup>5</sup> See Correa, C., "Guidelines for the examination of pharmaceutical patents: Developing a public health perspective" WHO - ICTSD - UNCTAD, January 2007.

<sup>&</sup>lt;sup>6</sup> Velasquez, G., and Boulet P., Globalization and Access to Drugs. Perspectives on the WTO/TRIPS Agreement, WHO/DAP/98.9, Geneva 1998.

According to the report of the United Nations High Commissioner for Human Rights "The requirements under the TRIPS Agreement for the grant of patents – novelty, inventive step and industrial applicability – are open to interpretation under national legislation and each country can decide according to local conditions. Consequently, the High Commissioner encourages interpretations of these requirements that do not lose sight of the public interest in the wide dissemination of knowledge..."<sup>7</sup>

The world has never had at its disposal such a wide arsenal of treatments to fight the diseases that afflict humanity. At the same time many people die owing to a lack of certain medicines and/or vaccines. This applies to illnesses such as AIDS, malaria, tuberculosis, cancer, diabetes, hepatitis C, bacterial meningitis and pneumonia, among many others.

The growing concerns about the way international trade agreements, and particularly the TRIPS Agreement, could limit access to medicines led to the adoption of the Doha Declaration on the TRIPS Agreement and Public Health in 2001 (Doha Declaration). The Doha Declaration marked an important milestone in the discussions on intellectual property rights and access to medicines by affirming that the TRIPS Agreement should be interpreted and applied in a way that supports the right of WTO Member States to protect public health and, in particular, promote access to medicines for all. In this respect, the Doha Declaration contains the principles that the World Health Organization (WHO) has defended and promoted since the end of the 1990s, namely the reaffirmation of the rights of Members of WTO to fully apply the safeguarding provisions contained in the TRIPS Agreement in order to protect public health and promote access to medicines.

It is generally believed that patents are granted to protect new medications, but the number of patents obtained annually to protect truly new pharmaceutical products is very small and is decreasing. Every year, thousands of patents are granted for pharmaceutical products, however only a few are for new molecular entities (NMEs).

<sup>&</sup>lt;sup>7</sup> The impact of the Agreement on Trade-Related Aspects of Intellectual Property Rights on human rights: Report of the High Commissioner, E/CN.4/Sub.2/2001/13, 27 June 2001, para 62.

In a well-known and quoted article from 2002, P. Trouiller et al. found that of all of the pharmaceutical products developed in the world between 1975 and 1999, only 1.1 per cent were for neglected diseases, which should really be called ignored diseases. The same study was repeated recently<sup>8</sup> and the results were not significantly better. Of the 850 products brought to market around the world between 2000 and 2011, only 4 per cent (exactly 37) were related to neglected diseases, which mainly exist in developing countries and include malaria, tuberculosis, Chagas' disease, Leishmaniasis and diarrhoeal diseases.

The cumulative nature of innovations owing to low patentability standards and weaknesses in the patent granting procedure has significant repercussions on patent systems, limiting the diffusion of the innovations that the system seeks to promote and hindering access to vital medicines. "Patents on broad scientific principles are generally bad, because in the words of the United States Supreme Court, they may confer power to block off whole areas of scientific development, without compensating benefit to the public."<sup>9</sup>

All of the above led WHO, in collaboration with the United Nations Conference on Trade and Development (UNCTAD), the United Nations Development Programme (UNDP) and the International Centre for Trade and Sustainable Development (ICTSD), to develop, in 2007, guidelines for the examination of pharmaceutical patents from a public health perspective.

These guidelines or directives were intended to contribute to improving the transparency and efficacy of the patent system for pharmaceutical products, so that countries could pay more attention to patent examination and granting procedures in order to avoid the negative effects of non-inventive developments on access to medicines.<sup>10</sup>

<sup>&</sup>lt;sup>8</sup> Dr Belen Pedrique, Nathalie Strub-Wourgaft, Claudette Some, Piero Olliaro, Patrice Trouiller, Nathan Ford, Bernard Pécoul, Jean-Hervé Bradol, "The drug and vaccine landscape for neglected diseases (2000-11): a systematic assessment", *Lancet*, 24 October 2013.

<sup>&</sup>lt;sup>9</sup> John H. Barton, *Bulletin of the World Health Organization*, October 2004, vol. 82, No. 10. <sup>10</sup> C. Correa Op. cit.

The exercise to draft guidelines for patent examination sought a way to manage the pharmaceutical product patent system and, more specifically, the "strengthened patent system" arising from the TRIPS Agreement and current regional and bilateral trade and investment agreements. Patents are a social contract between the patent holder and society; therefore it is necessary to explore, identify and implement mechanisms to improve the functioning and transparency of the patent system in the interest of public health.

In order to develop a legal and normative framework to grant pharmaceutical products patent protection that ensures a balance between the producers and the users of technological knowledge (as required by Article 7 of the TRIPS Agreement), several issues need to be carefully examined at the national level so as to ensure access to medicines. In this context, the guidelines for the examination of patents are a contribution to tackle this significant challenge.

Three key questions that this document could address: 1) how to relate intellectual property and public health and what are the implications, particularly in terms of access to medicines; 2) how much room for manoeuvre and flexibility is permitted by new international trade rules, particularly the TRIPS Agreement; 3) third and central point of this reflection, what is the role of and, above all, the contribution that national patent offices could make to improving access to medicines, through guidelines for the examination of patents.

#### II. INTELLECTUAL PROPERTY, WHO AND MEDICINES

#### II.1 The Mandate of WHO

The issue of intellectual property first arose at WHO in 1996 and practically coincided with the end of the Uruguay Round and the creation of WTO. In 1995, the Charles III University of Madrid, together with the WHO Essential Medicines Programme, organized a conference at which Professor Carlos Correa<sup>11</sup> presented a piece of work

<sup>&</sup>lt;sup>11</sup> Negotiator of the TRIPS Agreement during the Uruguay Round, as Secretary of Industry of the Government of Argentina.

entitled "The Uruguay Round and Drugs".<sup>12</sup> The 40-odd page article analyses the possible implications of the TRIPS Agreement for access to medicines and describes the "room for manoeuvre" provided in the Agreement to protect public health. The article is the first document that specifically alerts the health sector to the possible implications of the TRIPS Agreement for public health and, more specifically, for access to medicines.

Even during the negotiations of the Uruguay Round (1986-1994) several negotiators from developing countries saw that the TRIPS Agreement would have significant implications for the pharmaceutical and health sectors. Shortly after its adoption, UNCTAD published a study on the TRIPS Agreement and developing countries.<sup>13</sup>

At the World Health Assembly (WHA) in 1996, a resolution was adopted on medicines,<sup>14</sup> which was the first mandate given by member States to the WHO Secretariat to work on the issue of intellectual property with regard to health (Resolution WHA 49.14).

The request made to the Director-General of WHO through resolution WHA 49.14 of 1996 to produce a study on the implications of the TRIPS Agreement was entrusted to the Action Programme on Essential Drugs, which would publish in November 1997 a document entitled "Globalization and Access to Drugs: Implications of the WTO/TRIPS Agreement".<sup>15</sup>

The executive summary of the document clearly states its objective: "The aim of this document is to inform people in the health sector with no particular legal background about the impact of globalization on access to drugs, and especially about the TRIPS Agreement that may have repercussions in the pharmaceutical field." Further on, the

<sup>&</sup>lt;sup>12</sup> Correa C., "The Uruguay Round and drugs" WHO/TFHE/97.1 Distr: General, Original: English, 1997, 40 pp.

<sup>&</sup>lt;sup>13</sup> United Nations Conference on Trade and Development (UNCTAD), The TRIPS Agreement and Developing Countries U.N. Pub. 96.II.D.10 (1996) (prepared for the UNCTAD Secretariat by Carlos Correa, Keith Maskus, J. H. Reichman, and Hanns Ullrich).

<sup>&</sup>lt;sup>14</sup> WHA 49.14 "Revised drug strategy", WHO, Geneva 1996.

<sup>&</sup>lt;sup>15</sup> Velásquez, G. and Boulet P., "Globalization and Access to Drugs: Implications of the WTO/TRIPS Agreement", WHO/DAP/98.9, Geneva, 1998, 58 pp.

document affirms that "The TRIPS standards derive from those of industrialized countries and are not necessarily appropriate for all countries' level of development. Public health concerns should therefore be considered when implementing the Agreement."<sup>16</sup>

This publication on globalization and access to drugs "anticipated what the Doha Declaration would eventually recognize: the right of the WTO Members to exploit as far as possible the flexibilities incorporated into the Agreement in order to protect public health".<sup>17</sup>

In the aforementioned UNCTAD document<sup>18</sup> C. Correa et al. refer to the "room for manoeuvre" in the TRIPS Agreement for the formulation of national public policies. According to one opinion, the expression "room for manoeuvre" was too harsh for the diplomatic environment of the United Nations and for this reason. WHO talked of "margins of freedom"<sup>19</sup> (1997). Subsequently, in March 2001, WHO adopted the term "safeguards" in a document widely distributed in the six official languages of WHO.<sup>20</sup>

In June 2001, the European Commission mentioned "a sufficiently wide margin of discretion<sup>321</sup> – referring to the implementation of the TRIPS Agreement. Some months later, in November 2001, the WTO Doha Declaration on the TRIPS Agreement and Public Health refers to "the provisions of the TRIPS Agreement, which provide flexibility."<sup>22</sup> It was only in June 2002 that WHO, in a document analysing the

<sup>&</sup>lt;sup>16</sup> Ibid p. 3 and 4.

<sup>&</sup>lt;sup>17</sup> Op. cit. p. 44.

<sup>&</sup>lt;sup>18</sup> United Nations Conference on Trade and Development (UNCTAD), The TRIPS Agreement and Developing Countries U.N. Pub. 96.II.D.10 (1996) (prepared for the UNCTAD Secretariat by Carlos Correa, Keith Maskus, J. H. Reichman and Hanns Ullrich).

<sup>&</sup>lt;sup>19</sup> Velásquez, G. Boulet P., "Globalization and Access to Drugs: Implications of the WTO/TRIPS Agreement", WHO/DAP/98.9, Geneva, 1998, p. 34.

<sup>&</sup>lt;sup>20</sup> WHO Policy Perspectives on Medicines, "Globalization, TRIPS and access to pharmaceuticals" No. 3 WHO, Geneva March 2001, p. 5. <sup>21</sup> Submission 0f 12 June of the European Commission: "a sufficiently wide margin of

discretion", (IP/C/W/280), 12 June 2001.

<sup>&</sup>lt;sup>22</sup> WTO "Doha declaration on the TRIPS Agreement and Public health", WT/MIN(01)/DEC/W/2, p. 1.

implications of the Doha Declaration, authored by Carlos Correa, referred to the "flexibilities" of the Agreement.<sup>23</sup>

Currently, there is broad consensus on the use of the term "flexibilities" to refer to the mechanisms and provisions of the TRIPS Agreement aimed at protecting public health. Flexibilities that are not, as some people try to suggest, exceptions for developing countries, but rather a right obtained through the negotiations that led to the adoption of the TRIPS Agreement.

Since 1999, in successive resolutions of the World Health Assembly, WHO has been requested to ensure that its pharmaceutical strategy addressed the important question of the effects of international trade agreements on public health and access to medicines. The World Health Assembly requested WHO to cooperate with Member States and international organizations to monitor and analyse the pharmaceutical and health consequences of international trade agreements, in order to help Member States to assess and develop policies and measures on health and pharmaceutical regulation that maximize the positive effects of these agreements and mitigate the negative effects. Overall, these resolutions have provided WHO with a mandate that can be broadly summarized as follows: 1) analyse and monitor the effects on public health caused by globalization, intellectual property rights and trade agreements and report on the issue; 2) assist Member States in the strengthening of their pharmaceutical practices and policies; and 3) provide support and technical assistance to Member States to fully apply the safeguards and flexibilities related to public health provided in the TRIPS Agreement.

# **II.2** Commission on Intellectual Property Rights, Innovation and Public Health

In 2003 via a World Health Assembly resolution,<sup>24</sup> the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) was

<sup>&</sup>lt;sup>23</sup> C. Correa "Implications of the Doha Declaration on the TRIPS Agreement and Public Health", WHO/EDM/PAR/2002.3, Geneva, 2012, see chapter titled Flexibility in TRIPS, p. 13.

p. 13.  $^{\rm 24}$  WHA Resolution, WHA56.26 Intellectual Property Rights, Innovation and Public Health.

established. WHO Member States requested the WHO Secretariat to produce a report by independent experts on the subject of intellectual property, innovation and public health, an exercise that would continue and go into further detail on aspects already addressed in the report of the British Commission on Intellectual Property Rights<sup>25</sup> in 2002 on the same issue.

In 2006, the report of the CIPIH on "Public Health, innovation and intellectual property rights" stated that "The TRIPS Agreement allows countries a considerable degree of freedom in how they implement their patent laws, (...) Thus developing countries may determine in their own ways the definition of an invention, patentability requirements, the rights conferred on patent owners and what exceptions to patentability are permitted (...)".<sup>26</sup>

The report of the CIPIH also suggests that the problem of access to medicines is not limited to developing countries. "This issue is important because even in developed countries, the rapidly rising costs of health care, including supplies of medicines, are a matter of intense public concern. In developing countries, and even in some developed countries, the cost of medicines, often not available through public health- care systems, can be a matter of life and death."<sup>27</sup>

The CIPIH report contains 60 recommendations. The majority refer to issues related to intellectual property, that were taken up by the Global strategy and plan of action on public health, innovation and intellectual property, resolution WHA 61.21 approved in 2009. It is in the context of the CIPIH recommendations and the mandate given by the World Health Assembly since 1999 that WHO drafted the "guidelines for examination of pharmaceutical patents", which are referred to specifically in chapter III of this document.

In the WHO guidelines, several mechanisms that could be adopted are suggested in order to incorporate a public health perspective into the procedures for granting patents for pharmaceutical products. The

<sup>&</sup>lt;sup>25</sup> Integrating intellectual property rights and development policy" Report of the Commission on Intellectual Property Rights, London, September 2002.

 <sup>&</sup>lt;sup>26</sup> WHO, "Public Health, innovation and intellectual property" Geneva 2006, Op. cit. p. 21.
 <sup>27</sup> Ibid. p. 177.

guidelines also propose a series of general measures to assess some of the common methods of granting pharmaceutical patents and suggest elements for the drafting of guidelines that take into account public health in the assessment and examination of patents for pharmaceutical products at the national level in developing countries.

In little more than 10 years, WHO has produced significant material in the area of public health and intellectual property, whether in the 17 resolutions<sup>28</sup> of the World Health Assembly, or in the numerous publications<sup>29</sup> providing analysis and guidance with the aim of protecting access to health in light of new international trade regulations required within the framework of WTO, and recently the free trade agreements (FTAs) and bilateral investment treaties (BITs) that contain more demanding clauses and conditions than the standards set by the TRIPS Agreement. The publication on "guidelines for the examination of pharmaceutical patents" is perhaps the most important guiding documents drafted by WHO to fulfil the mandate set by various resolutions of the World Health Assembly and the Doha Declaration to provide a public health perspective to the use of the patent system in the pharmaceutical sector.

# **II.3** Strategy on Intellectual Property and Public Health

During the WHO World Health Assembly in May 2008, the "Global Strategy and Plan of action on Public Health, Innovation and Intellectual Property" (hereafter, the Global Strategy) was approved. The Strategy was drafted by the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG). The Global Strategy gives WHO the mandate to "Provide (...), in collaboration with other competent international organizations, technical support (...) to countries that intend to make use of the provisions of the TRIPS Agreement, including the flexibilities recognized by the Doha Declaration on the TRIPS Agreement and Public Health (...)."<sup>30</sup>

Resolution WHA 61.21 on the Global Strategy recognized that intellectual property incentives did not respond to the needs of the

<sup>&</sup>lt;sup>28</sup> See list in Annex I.

<sup>&</sup>lt;sup>29</sup> See list in Annex II.

<sup>&</sup>lt;sup>30</sup> WHO resolution 61.21 paragraph 5.2 p. 17.

majority of people living in developing countries. The Global Strategy declared that it is necessary: "to encourage and support the application and management of intellectual property in a manner that maximizes health-related innovation and promotes access to health products and that is consistent with the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights and other WTO instruments related to that agreement and meets the specific research and development needs of developing countries."<sup>31</sup>

The focus of a strategy on intellectual property for health, and for medicines in particular, should be centred on access to essential medicines and technologies for all persons that need them.

The principles on which the strategy should be based upon are as follows:

- The right to health protection is a universal and inalienable right and it is the duty of governments to ensure ways to fulfil that right.
- The right to health takes precedence over commercial interests.
- The right to health means equitable access to medicines.
- The promotion of innovation and technology transfer is the right of all States and should not be restricted by intellectual property rights.
- Intellectual property rights should not become an obstacle to access to medicines or to the formulation of policies to ensure and protect public health. Intellectual property rights should guarantee economic and social well-being in a balanced manner.
- Countries have the right to apply all of the flexibilities contained in the TRIPS Agreement, which were reaffirmed in the Doha Declaration and other international resolutions in order to safeguard access to technology and medicines.
- International negotiations related to intellectual property and public health carried out in different organizations should be consistent with public health priorities.

<sup>&</sup>lt;sup>31</sup> WHA 61.21 "Global strategy and plan of action on public health, innovation and intellectual property" May 2008.

- Strengthening innovative capacity is essential to respond to health problems.
- Developing countries should have the capacity to cooperate on the basis of their common interests and economic and social needs if they want to benefit from global markets.

The components of this strategy on intellectual property for health and medicines, which should be well-defined in national intellectual property laws and regulations, will be the so-called TRIPS flexibilities, namely:

- Pre- and post-grant patent opposition
- Definition of patentability requirements from a public health perspective
- Research exception and "early working" exception (Bolar exception)
- Parallel imports
- Use of compulsory licenses
- Test data protection
- No to exclusive data protection as a way to extend monopolies
- Prior patent consent for the grant of the patent by health authorities (as in the case of Brazil and other countries)

### II.4 Pharmaceutical Policies and TRIPS Agreement

National pharmaceutical policies have drawn on political perspectives on trade agreements, public health and access to essential medicines. Political perspectives guide and ensure the coherence of national programmes to guarantee access to medicines for the entire population. However, implementation of these policies at the national level is often hindered by tensions between the different actors: health, trade, industry.

Political perspectives on issues related to the TRIPS Agreement, intellectual property rights and access to medicines can be summarized as follows:

- Essential medicines are a public good.
- Access to essential medicines is a human right and, as a result, a public health priority.

• Patents should be managed impartially, protecting the interests of the patent holder and preserving the principles of public health, meaning that it is essential to make appropriate use of the flexibilities and safeguards contained in the TRIPS Agreement.<sup>32</sup> WHO has been updating a guide for the development and implementation of national drugs policies.<sup>33</sup>

#### **II.5** Examination of Patents and Access to Medicines

The development of a public health perspective for the examination of pharmaceutical patent applications is one of the key elements of the work on access to medicines. In this context, WHO considered it important to train patent examiners of patent offices from developing countries. Therefore, between 2006 and 2010, workshops for national patent offices were carried out in more than 40 countries.

This technical assistance for patent offices was resumed by the South Centre, an intergovernmental organization, which is also continuing to analyse trends in the granting of patents for pharmaceutical products in order to respond to the growing concerns at the increase in the number of patents that protect variants of existing medicines or procedures while, as mentioned earlier, the number of patents for new molecular entities is limited and decreasing. Patent examiners and those responsible for health policy development should be aware that decisions relating to the granting of a patent (which is generally considered to be valid until otherwise demonstrated) can directly affect the health and life of the people in the country in which the patent is granted and used.

<sup>&</sup>lt;sup>32</sup> Owing to tensions between different national actors, the use of the flexibilities permitted by the TRIPS Agreement is not always found appropriately in drug legislation and policies.

<sup>&</sup>lt;sup>33</sup> World Health Organization, *How to Develop and Implement a National Drug Policy* (Geneva, 2001).

#### III. THE PATENT SYSTEM APPLIED TO MEDICINES

One third of the global population does not have regular access to essential medicines, and this proportion can reach more than half of the population in some developing countries. Of the 34 million people estimated by WHO, the United Nations International Children's Emergency Fund (UNICEF) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) in their report from 2012<sup>34</sup> to be living with the human immunodeficiency virus (HIV) and who should have been receiving treatment, only 8 million had access to treatment at the end of 2012.<sup>35</sup>

This situation, as stated by Eric Goemaere, is largely due to the high costs of medicines protected by patents. "How shocked am I to hear that patent rights do not constitute a barrier to treatment here in South Africa. I have seen young men and women die after experiencing unbearable headaches, victims of AIDS-related brain tumours. I have seen children covered in scars caused by AIDS-related dermatitis, unable to sleep because of the pain. I knew that antiretroviral therapy could help them, and that the only barrier that prevented this was the cost of patented medicine."<sup>36</sup>

The subject of patents for pharmaceutical products has been one of the most-debated issues related to access to essential medicines since the creation of WTO in 1995 and the signing of the TRIPS Agreement.

Patents are not the only barrier to access to medicines, but increasingly they can be a determining factor since patents grant a monopoly for a medication to the patent holder, who is then free to fix prices. This freedom to fix the prices of patented products has led to a large number of medicines not being available for the majority of the global population, that live in developing countries.

<sup>&</sup>lt;sup>34</sup> UNAIDS World AIDS day Report 2012.

<sup>&</sup>lt;sup>35</sup> Velásquez, G. in "Public Health and pharmaceutical patents" collection coordinated by Seuba, X. p. 24, Barcelona, 2008.

<sup>&</sup>lt;sup>36</sup> Goemaere, E. "Medicines patents in the spotlight. Sharing practical knowledge about pharmaceutical patents", MSF, Madrid, May 2003.

It is important to remember that a patent is a territorial right and that it is therefore possible to grant a patent for an invention in one country but that this can be legally rejected in another. At the same time, a patent that has been issued in one country can be revoked if it is demonstrated that the patent office ought not to have granted it.

It is also important to highlight that in the pharmaceutical sphere, the situation is not ONE product, ONE patent. An invention can be protected by numerous patents, the production process for the product can also be protected by one or numerous patents, and in many countries a combination or new clinical indication can be patented. As a result of this, a single medicine can be protected by a large number of patents.

The TRIPS Agreement contains provisions that require the amendment of patent legislation in the vast majority of developing countries in order to introduce, widen and strengthen intellectual property protection of pharmaceutical products.

It is important that in the adaptation of intellectual property legislation all of the provisions for protecting public health are included. In cases where the room for manoeuvre allowed by the TRIPS Agreement were not used, national legislation can always be revised, as done by countries such as China and India.

In principle, the patent system was conceived to ensure that the public benefited from inventions. Currently, not only do a large number of people that live in developing countries not benefit from inventions, but in many countries, patents represent a barrier to access to life-saving medicines simply because business logic overcomes the right to access to health care.

Almost 20 years after the adoption of the TRIPS Agreement, its impact, at least in terms of public health, raises more unanswered questions than solutions.

A few months after the creation of the WTO and the entry into force of the TRIPS Agreement, Carlos Correa stated that "The adoption of the Agreement has undoubtedly involved a major concession on the part of those countries which refused to grant patents for drugs in order to avoid the effects of market monopolies derived from exclusive rights. The information available (...) shows that the universalization of pharmaceutical patents will not lead to increased R&D on new drugs by large companies nor to the possibility that this will be carried out to any significant degree in developing countries. Neither will developing countries receive increased flows of direct foreign investment or transfer of technology."<sup>37</sup> Fifteen years later, as we will see, it was found that neither R&D nor technology transfer have increased and instead, the trend has been to decrease.

## III.1 The Problem

Four major problems can be identified in the current patent system used for medicines: reduction in pharmaceutical innovation, high prices of medicines, lack of transparency in research and development costs, and proliferation of patents.

## III.1.1 Reduction in pharmaceutical innovation

A study carried out by the journal *Prescrire* analysed the medicines that were introduced to the French market between 2006 and 2011 (six years), arriving at the conclusion that the number of molecules that produced significant therapeutic progress reduced drastically: 22 in 2006; 15, 10, 7, 4 in the following years up to 2011, which was a year in which *Prescrire* declared that only one medicine of significant therapeutic interest was brought to the market.<sup>38</sup> Given that France is one of the largest pharmaceutical markets in the world, where the State also pays the bills for medicines, it can be supposed that the large majority of medicines that were released in the world between 2006 and 2011 were introduced into the French market. In other words, the reduction in innovation confirmed in France is a good indicator of the global situation.

<sup>&</sup>lt;sup>37</sup> Correa, C., "The Uruguay Round and drugs" in Medicines and the New Economic Environment, Lobo, F. and Velásquez, G., Eds. (Madrid, Editorial Civitas, 1998).

<sup>&</sup>lt;sup>38</sup> Philippe EVEN, Bernard DEBRE, "Guide to the 4000 useful, useless and dangerous medicines" Ed. Cherche Midi, Paris, September 2012, p. 82.

## III.1.2 High prices of medicines

Another recent study demonstrated that, on average, medicines cost three times more in France than the same drugs in Italy.<sup>39</sup> It should be remembered that the medicines on the market are quite similar in both countries: the same laboratories, the same medicines and, most of the time, the same doses.

Oncologists from fifteen or so countries recently denounced the excessive prices of cancer treatments, which are necessary to save the lives of the patients, and urged that "moral implications" should prevail.<sup>40</sup> According to this group of oncologists, of the 12 cancer treatments approved in 2012 by the United States Food and Drug Administration (FDA), 11 cost more than US\$ 100,000 per patient per year.

In 2010, a group of English academics analysed the most prescribed drugs in the National Health Service (NHS) and calculated that approximately GBP 1 billion is wasted each year due to the prescription of patented "me too drugs", for which there is an equally effective out of patent equivalent.<sup>41</sup> What is considered to be a waste of State funds resulting from the use of patented medicines in the English system is the reality in developing countries simply because of the impossibility of accessing the medicine for the majority of the population.

During the summer of 2014, a number of European countries, including France and Spain, spent many months negotiating with the company Gilead on the price of a new medicine for hepatitis C (known as brand name "Sovaldi"). The price fixed by Gilead was EUR 56,000 per patient for a twelve-week treatment, that is to say EUR 666 per tablet. According the newspaper *Le Monde* the price of each tablet was 280 times more than the production cost.<sup>42</sup> In France, it is calculated that

<sup>&</sup>lt;sup>39</sup> Le Monde from 11 November 2013,

http://www.lemonde.fr/culture/article/2013/11/13/le-scandale-du-prix-des-medicaments\_3510819\_3246.html.

<sup>&</sup>lt;sup>40</sup> American journal *Blood*, publication of the American Society of Hematology (ASH) April, 2013.

<sup>&</sup>lt;sup>41</sup> B. Goldacre, Op. cit. p. 243.

<sup>&</sup>lt;sup>42</sup> Santi, P. "Hépatite C: le nouveau hold-up des labos", in *Le Monde* 8 July 2014.

250,000 patients should receive this medicine, the cost of which would represent 7 per cent of the annual State medicine budget.

#### III.1.3 Lack of transparency in R&D costs

Since the 1950s, there have been some references to the costs of R&D for pharmaceutical products. According to some sources (see box below) these figures have increased from US\$ 1 million to US\$ 1.3 billion for the development of a single product. While there continues to be no clarity and transparency in this sphere, the difficulty that can lead to the high prices of medicines continues to be unresolved.

The granting of patents, based on which the inventor should recover the costs of their invention, when there is no clarity about the actual costs is something that States and society in general should examine. The duration of patents, for example, for a period of 20 years as arbitrarily required by the TRIPS Agreement, should be dependent on the R&D costs of the products.

Aver	age cost of research for a new pharmaceutical product*
1950:	US\$ 1 million
1970 &	1980: Between US\$ 48 million and US\$ 54 million
1991:	Tufts Center (Boston): US\$ 231 million
2000:	Tufts Center: US\$ 473 million
2002:	US\$ 802 million (double the cost in two years!)
2008:	IFPMA: US\$ 900 million
2012:	IFPMA: US\$ 1.3 billion
2014:	Tufts Center (Boston): US\$ 2.56 billion
*P	repared using diverse sources

An article from the journal *BioSocieties*<sup>43</sup> a publication of the London School of Economics, argues that the real cost of R&D is, in fact, a fraction of the commonly quoted estimates. According to the authors Light and Warburton, the average cost of R&D to develop a medicine varies between US\$13 million and US\$ 204 million depending on the type of product. The authors estimate an average cost of US\$

<sup>&</sup>lt;sup>43</sup> Donald W. Light and Rebecca Warburton, Demythologizing the high costs of pharmaceutical research" 2011 The London School of Economics and Political Science 1745-8552 *BioSocieties* 1-17. www.palgrave-journals.com/biosoc/.

43.4 million for R&D for each drug. And they conclude: "This is very far from the US\$ 802 million or US\$ 1.3 billion claimed by the industry."

The Drugs for Neglected Diseases initiative (DNDi), founded by the non-governmental organization Médecins Sans Frontières (MSF) in 2004, recently published its research costs after 10 years of experience.<sup>44</sup> Its figures are as follows:

- From EUR 6 million to 20 million to improve a treatment.
- From EUR 30 million to 40 million for a new chemical entity.

If this figure were to be adjusted as usually done for pharmaceutical R&D for infectious diseases to cover the risk of failure, the figures would be as follows:

- From EUR 10 million to 40 million to improve a treatment.
- From EUR 100 million to 150 million for a new chemical entity.

It is unfathomable that after 15 or more years of debate, there is still no consensus about the real costs of R&D for medicines. Until this issue is resolved, it will be difficult to advance constructive thinking that could determine the future of access to medicines. The differences in data between academia or non-profit initiatives, such as DNDi, and industry are between ONE and TEN. WHO has been silent on this issue, probably as a result of the growing influence of the pharmaceutical industry on policy development and decision-making within this organization.

This is how monopolies granted by patents will enable the obtaining of disproportionate benefits on the one hand, and on the other will block a large number of peoples' access to medicines, which in many cases are vital.

The problem with R&D costs is that there is no transparency about the real costs of R&D, as there is no pricing logic for medicines; rather

<sup>&</sup>lt;sup>44</sup> DNDi, "An Innovative Approach to R&D for Neglected Patients: Ten Years of Experience and Lessons Learned by DNDi", Geneva 2013.
the prices correspond to the maximum that each market can accept or pay.

# **III.1.4** Proliferation of patents

An investigation carried out by the European Union (EU) about the conduct and practices of the pharmaceutical industry between 2000 and 2007 found that a single medicine can be protected by up to 1300 patents or pending patent applications.<sup>45</sup> The number of lawsuits between originator companies and generic companies has increased four-fold in the EU. These lawsuits delay the entry of the generic product by between six months and six years. The study estimates that the savings resulting from the entry of generics could have been approximately EUR 3 billion, if the entry had occurred immediately after the loss of exclusivity.<sup>46</sup>

A policy and strategy change at the patent office level could lead to significant changes. In Argentina, for example, after the introduction of new guidelines for the examination of pharmaceutical patents in 2012, the number of patents granted was 54, while in Mexico, a similar-sized market to Argentina, the number of patents granted in 2012 for pharmaceutical products was 2500.

Other countries, as in the recent case of Ecuador, decided to raise rates for registering a new patent to more than US\$ 100,000 (with exceptions for example in the case of small companies and universities).

# **III.2** The International Context

In general, it is currently recognized that the existing protection regime using patents "globalized" by the TRIPS Agreement has significant repercussions on the pharmaceutical sector. In addition, there is a concern that the standards specified in the TRIPS Agreement are not necessarily suitable for countries fighting to meet their health and development needs. Since 2002, the Commission on Intellectual Property Rights (CIPR) of the United Kingdom published a report

<sup>&</sup>lt;sup>45</sup> Investigation by the European Union:

http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/index.html.

<sup>&</sup>lt;sup>46</sup> Investigation by the European Union, Op. cit.

recommending that countries ensure their intellectual property protection systems do not impact on their public health policies and are consistent with those policies.

Pharmaceutical R&D using the patent system as the main source of financing has not enabled the medicines to be accessible to the vast majority of people, especially those living in developing countries. On the one hand, there is limited investment in R&D for diseases prevalent in those countries, as large companies concentrate on the development of products to satisfy the demands of rich markets. On the other, products subject to patents and other methods of exclusive rights are usually marketed at unreachable prices for the majority of the population. Various reports and studies, together with the Global strategy and plan of action on public health, innovation and intellectual-property adopted by Member States of WHO (2003-2008),<sup>47</sup> have recognized these issues.

In April 2012, the WHO Consultative Expert Working Group on Research and Development (CEWG) recommended the start of international negotiations for a treaty on R&D for pharmaceutical products, within the scope of article 19 of the WHO Constitution, which states:

"The Health Assembly shall have authority to adopt conventions or agreements with respect to any matter within the competence of the Organization. A two-thirds vote of the Health Assembly shall be required for the adoption of such conventions or agreements, which shall come into force for each Member when accepted by it in accordance with its constitutional processes."

The only precedent in the history of WHO of the use of this article in a substantive area, was the Framework Convention on Tobacco Control (FCTC). New, effective and simultaneous mechanisms<sup>48</sup> that promote innovation and access to medicines are needed, particularly for diseases that chiefly affect developing countries. A binding international

<sup>&</sup>lt;sup>47</sup>World Health Organization, Global strategy and plan of action on public health, innovation and intellectual-property.WHA Resolution 61.21, (May 24, 2008).

<sup>&</sup>lt;sup>48</sup>World Health Assembly Global strategy and plan of action on public health, innovation and intellectual-property point 13.

instrument or international treaty on R&D, negotiated under the auspices of WHO could provide an adequate framework to guarantee the establishment of priorities, coordination and sustainable financing for medicines at affordable prices for developing countries.

Recently, in October 2014 in her speech opening the Sixth Conference of the Parties to the Framework Convention on Tobacco Control (COP6 of the FCTC) held in Moscow, the Director General of WHO said that:

"We have abundant evidence from multiple sources that implementation of the Framework Convention brings both immediate and long-term improvements for health. (...) As time has shown, the tobacco treaty is important for a second reason. It is a model of how multiple sectors of government, and multiple UN agencies, can work together seamlessly and in tandem, united by a most worthy shared goal. The importance of this model continues to grow as more and more of the century's biggest threats to health (...)."<sup>49</sup>

### **III.3 Human Rights and Intellectual Property**

When discussing international trade rules or questions related to public health, we are talking about two different regimes that are not at the same level. In the first case, it is a matter of trade and economic standards and regulations, and in the second case, we are referring to the right to health as part of human rights.

Medicines are a fundamental tool for society to prevent, treat and cure diseases and access to them is a fundamental right of citizens, an integral part of the right to health care as established in some international treaties and the constitutions of many countries.<sup>50</sup>

Access to medicines has to be considered as a fundamental human right, with full international and constitutional recognition. The

<sup>&</sup>lt;sup>49</sup> Speech of Margaret Chan, Director-General of WHO, opening of COP6 of the FCTC, Moscow, October 13 2014. FCTC/COP6/DIV/4.

<sup>&</sup>lt;sup>50</sup> Seuba, X. "The protection of health in light of international regulation of pharmaceutical products" Doctoral thesis p. 92 onwards, Barcelona 2008.

Universal Declaration of Human Rights (1948) refers to this in article 25: "Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services (...)"

"The areas of interaction between the patenting process for pharmaceutical products and human rights are numerous, given that the standards that a country adopts on patenting of inventions is linked to regulatory regimes that particularly protect legal rights. In reality, the impact on life, on science, on access to vital products that results from the application of standards in the patent process, including patentability requirements, leads to their interaction with a wide range of fundamental rights, such as the right of access to scientific and technological advances, the right to health care and the right to life itself. This is precisely the reason why courts, administrative bodies and ministries of health, among others, are paying increasing attention to the relationship between the patentability requirements that a country adopts and its human rights protection regime, particularly with regard to the right to health care "51

While, as stated by P. Drahos, the challenge is that patent offices have functioned, and many continue to function, as administrative institutions, the examination of patent applications "is much more than an administrative task. The basis on which such activity is carried out, and the activity itself, are closely related to the protection of the public domain and fundamental rights."52

In the context of the United Nations, the vast majority of countries have adopted international treaties, such as the International Covenant on Economic, Social and Cultural Rights (ICESCR), the Convention on the Rights of the Child or the Convention for the Elimination of All Forms of Racial Discrimination, which ratify, in different ways, the right to health care. The Committee on Economic, Social and Cultural Rights stated that "the right to health embraces a wide range of socioeconomic factors that promote conditions in which people can lead a

 <sup>&</sup>lt;sup>51</sup> X. Seuba, "The right to health care, national pharmaceutical policy and patentability guidelines", 2012 (unpublished work).
<sup>52</sup> X. Seuba Op. cit.

healthy life".<sup>53</sup> It is within this "wide range of socio-economic factors" related to health that patentability requirements can be linked to the right to access to health care.

In its General Comment No. 14 of May 2000,<sup>54</sup> the Committee on Economic, Social and Cultural Rights declared that the medical services referred to in Article 12.2.(d) of the Covenant include access to the essential medicines as defined by WHO. This is how the Committee on Economic, Social and Cultural Rights of the United Nations has included access to essential medicines among the key components of the right to health care.

The understanding that access to medicines is a right of citizens would change the debate and clarify the primacy of health over international trade regulations. This perspective of rights, as stated by Seuba, "simultaneously offers the tools to report violations and a framework to guide national drugs policies in this direction."<sup>55</sup>

### IV. GUIDELINES FOR THE EXAMINATION OF PHARMACEUTICAL PATENTS: DEVELOPING A PUBLIC HEALTH PERSPECTIVE<sup>56</sup>

### IV.1 A History of the Guidelines

As already mentioned, the fact that the TRIPS Agreement does not define novelty, inventive step and industrial applicability (utility) leaves countries significant room for manoeuvre; therefore patentability requirements represent the principal and most important flexibility allowed by the Agreement to protect public health and access to

<sup>&</sup>lt;sup>53</sup> Committee on Economic, Social and Cultural Rights, *General Comment no. 14, The right to the highest attainable standard of health* 2000, E/C.12/2000/4, paras. 4 and 9.

<sup>&</sup>lt;sup>54</sup> Committee on Economic, Social and Cultural Rights. The right to the highest attainable standard of health. 11/08/2000. E/.12/2000/4, CESCR General Comment 14, para 12(a).

<sup>&</sup>lt;sup>55</sup> Seuba X,. "A human rights approach to the WHO Model List of Essential Medicines", in World Health Organization Bulletin, vol. 84 No.5, Geneva May 2006.

<sup>&</sup>lt;sup>56</sup> Correa, C., "Guidelines for the examination of pharmaceutical patents: developing a public health perspective". WHO - ICTSD - UNCTAD, Geneva, January 2007.

medicines. "Politicians and legislators have broad room for manoeuvre to give legal effect to those flexibilities."<sup>57</sup>

Articles 7 and 8 of the TRIPS Agreement (1995) clearly stipulate that **all** of the provisions should be interpreted in light of their objectives and principles, which establish:

"Article 7. Objectives. The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.

Article 8. Principles.1. Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement."

The perspective of articles 7 and 8 of the TRIPS Agreement were ratified again by the Doha Declaration (2001), which:

- 1. recognizes "the gravity of the public health problems afflicting many developing and least-developed countries..."
- 2. stresses "the need for the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) to be part of the wider national and international action to address these problems"
- *3*. (...)
- 4. agrees "that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health (...) 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

<sup>&</sup>lt;sup>57</sup> Arias Eduardo, PPT on "Guidelines for the examination of patentability of chemicalpharmaceutical inventions, INPI, Argentina, 2014.

medicines for all. (...) we reaffirm the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose".

In 2005, with the mandate already granted by the World Health Assembly in different resolutions, the WHO Essential Medicines Programme decided to develop draft guidelines for the examination of pharmaceutical patents from a public health perspective. Based on the first working document drafted by Professor Carlos Correa, a series of international, regional and national consultations were started, the following of which are worth highlighting:

- 1. October 2005, in Bangkok, Thailand: consultations organized by Thailand's Food and Drug Administration and WHO and included: representatives of drug regulatory authorities and national patent offices of China, India, Malaysia and Thailand, representatives of schools of law, medicine and pharmacy in Thailand and representatives of the pharmaceutical industry.
- 2. In June 2006, comments and contributions were requested from experts in public health and patents from Australia, United Kingdom and WHO.
- 3. July 2006, in Buenos Aires, Argentina. This consultation included representatives of Argentina, Paraguay and Brazil from patent offices, Ministries of Health and schools of law and pharmacy from the three countries.
- 4. 14 September 2006, Geneva. This consultation included representatives of the Swiss patent office, the South Centre, WHO, UNCTAD, ICTSD, the Lausanne Polytechnic School, WIPO, WTO, MSF and Third World Network.
- 5. December 2006, in Beijing, China: the draft guidelines were discussed and analysed with 50 patent examiners from the China national patent office.
- 6. July 2007, Panama. This consultation included representatives of Costa Rica, Colombia, Cuba, Nicaragua, El Salvador, Guatemala, Honduras and Panama.
- 7. October 2007, Cairo, Egypt: consultation with patent examiners from the national intellectual property office of Egypt.
- 8. December 2007, New Delhi, India: review and discussion with the Indian patent office with the participation of representatives

of Thailand and Indian non-governmental organizations (NGOs) working on the issue.

In addition to the consultations mentioned, numerous comments were sent to the Director-General of WHO and the WHO Essential Medicines Programme. One example of this is the letter from the Minister of Health of Argentina dated 25 October 2007, which said:

"To DR MARGARET CHAN, DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION. By means of this letter, I wish to express my gratitude and appreciation for the document entitled "*Guidelines for the examination of pharmaceutical patents: developing a public health perspective*", recently published by WHO, ICTSD and UNCTAD. I consider the document to be of crucial importance for developing countries which, like Argentina, are compelled to ensure that the implementation of intellectual property rights related to medicines does not have a negative impact on the health of our society. In my position as health authority of Argentina, I recognize the hard work of WHO to follow up on and strengthen measures adopted by countries to protect public health, such as those established in the Doha Declaration, and I feel that the document is highly consistent with the timely recommendations made by the CIPIH."

Or the letter from the Secretary-General of Thailand's Food and Drug Administration on 10 September 2007:

"Your Excellency, Dr. Margaret Chan: The Food and Drug Administration, Thailand (FDA), has the honour of writing this letter to congratulate WHO for its successful contribution and commitment shown by the recent drafting and publication of a very useful document entitled, Guidelines for the examination of pharmaceutical patents: developing a public health perspective. (...)

The document addresses the vital need to take into account public health aspects in the examination of pharmaceutical patents in order to ensure that only high quality patents are granted to reward genuinely creative inventions. (...). The granting of low quality patents exacerbates the problem of people's access to essential medicines in developing countries. Therefore, the Guidelines have arrived at an opportune moment to help develop a public health perspective in the examination of pharmaceutical patents. (...). The publication of this document by WHO shows true and visionary leadership".

The letter from the Minister of Health of Brazil, dated 27 October of the same year, also sent to the Director-General of WHO, can be seen below:

"In the name of the Brazilian Government, I would like to congratulate you for the initiative of WHO to publish the document entitled "Guidelines for the examination of pharmaceutical patents: developing a public health perspective" written by Professor Carlos Correa.

The Brazilian Government believes (...) that the document is an indispensable tool to prevent abuse related to intellectual property rights, ensuring that only pharmaceutical products of processes that meet the criteria of novelty, inventive step and utility will have their patent applications granted."

In the comments made by the Swiss Patent Office, transmitted by the representative of Switzerland to WTO on 14 September 2006, the first paragraph included the following: "I think, the guidelines are carefully drawn up, very comprehensive and well-balanced in a lot of their points".

Lastly, it should be noted that approximately ten years after the publication of the document, no in-depth examination of the issue has taken place in the WTO. $^{58}$ 

<sup>&</sup>lt;sup>58</sup> The questions of some countries when the intellectual property legislation of Argentina was reviewed by WTO (March 2013) requested information but did not question the consistency of the legislation with the TRIPS Agreement.

# IV.2 What are the Guidelines for the Examination of Pharmaceutical Patents?

The Guidelines for the examination of pharmaceutical patents developed by WHO are a guide for the drafting of internal procedure manuals of national intellectual property offices for the examination of patentability of chemical-pharmaceutical inventions.

"It is the habitual practice of all patent offices in the world to instruct their examiners on the way to carry out the patentability assessment through so-called patentability guidelines that describe in detail the implementation of patent law in specific circumstances. (...). These guidelines generally include a chapter about patents in the chemical-pharmaceutical sector."<sup>59</sup>

It is also a habitual practice of all patent offices around the world to set the level of patentability requirements that the examiners use for the examination of patents through patentability instructions or guidelines, which describe in detail the implementation of patent rights in specific circumstances.

In the introduction of the guidelines it is stated that the pharmaceutical sector is a user of fundamental importance within the patent system. While each year only a small – and decreasing – number of new chemical entities are approved, thousands of requests are submitted to protect variations of existing products, manufacturing processes or, when permitted, second indications for known pharmaceutical products.

Given that patents grant exclusive rights for the production, sale and use of the patented material, they can be used to limit competition and fix higher prices than would have existed with competitive products and generic medicines.

Taking into account the underlying effects that patents can have on competition and, as a result, on prices and access to medicines, the

<sup>59</sup> Arias, E. Op. cit.

criteria used to examine and grant pharmaceutical patents are of significant importance for public health policies.

The purpose of the guidelines for the examination of pharmaceutical patents is to provide a series of general guidelines for the examination of some common types of pharmaceutical patents granted. They respond to the growing concerns emerging in different circles<sup>60</sup> about the proliferation of patents that protect minor variants, and in some obvious cases, existing medicines and processes (for example, changes to drug formulations and to salts, esters, ethers, isomers, polymorphs of existing molecules, and to combinations of known drugs with other known drugs), while the number of new chemical entities for pharmaceutical use is low and decreasing.<sup>61</sup> While those patents may be weak or –if subjected to strict scrutiny– invalid, in many cases they can be used to prevent generic competition and therefore, to reduce access to medicines.

While these guidelines recognize the importance of subsequent pharmaceutical innovations in certain cases,<sup>62</sup> their aim is to increase the capacity of patent offices, regulatory authorities for medicines and public health, and civil society to assess and adopt necessary measures, in accordance with national legislation, to protect public health in those cases in which patent requests and claims cover a material that does not merit the monopolistic reward that a patent grants. The purpose of the guidelines is to provide support to national patent offices and to try to contribute a rational analysis of pharmaceutical patents based on the rational implementation of patentability requirements.

<sup>&</sup>lt;sup>60</sup> See, for example, Federal Trade Commission (FTC) (2003); Jaffe and Lerner (2004); Correa, 2001a.

<sup>&</sup>lt;sup>61</sup> The number of new molecular entities approved by the United States Food and Drug Administration of the (FDA) has fallen drastically since the mid-1990s (from 53 in 1996 to a low of 17 in 2002). See "*CDER*, *NDAs approved in calendar years 1990-2004 by therapeutic potential and chemical type*". United States Food and Drug Administration, 22 March 2005 (http://www.fda.gov/cder/rdmt/pstable.htm accessed on 14 November 2005).

<sup>&</sup>lt;sup>62</sup> CIPIH, p. 17. However, in some cases, patents can hinder subsequent innovations, in particular when material from basic science is patented. See, for example, Commission on Intellectual Property Rights, 2002; Sampath, 2005, p. 29.

The guidelines do not suggest the implementation of a new condition for patentability, but the taking into account of specific considerations related to innovation in pharmaceutical products when the common requirements of novelty, inventive step and industrial applicability (utility) are applied.

# IV.3 Content of the Guidelines

The guidelines for the examination of patents analyse and discuss the most common claims in the pharmaceutical sector. They include observations on practices in a number of countries and analyses of 41 examples of individual cases of different claims considered. Transcribed below, for illustrative purposes, are the recommendations for each type of claim from a public health perspective that promote access to medicines.

# **IV.3.1** Formulations and compositions

Recommendation: New formulations and compositions, as well as processes for their preparation, should generally be deemed obvious in the light of the prior art, particularly when a single active ingredient is claimed in association with known or unspecified carriers or excipients. Exceptionally, claims of this type could be patentable if a truly unexpected or surprising effect is obtained, for instance, when a really difficult problem or a long standing need, such as a noticeable reduction in side effects, is solved in a non-obvious way, or when the solution found leads to a tremendous advantage compared to the state of the art.

### **IV.3.2** Combinations

Recommendation: Combinations of known active ingredients should be deemed non inventive. If, however, a new and non-obvious synergistic effect is considered a basis for patentability, it should be properly demonstrated by biological tests and appropriately disclosed in the patent specifications.

# IV.3.3 Dosage/dose

Recommendation: New doses of known products for the same or a different indication do not constitute inventions, particularly (but not only) in countries where methods of medical treatment are not patentable as such.

# IV.3.4 Salts, ethers and esters

Recommendation: New salts, ethers, esters and other forms (e.g. amides) of existing pharmaceutical products should not be deemed patentable. This may not apply, exceptionally, when tests, appropriately conducted and described in the specifications, demonstrate unexpected advantages in properties such as an important difference in efficacy or side effects as compared to what was in the prior art. Processes for obtaining salts, ethers, esters and other forms should be deemed as non-patentable.

# IV.3.5 Polymorphs

Recommendation: Polymorphism is an intrinsic property of matter in its solid state. Polymorphs are not created, but found. Patent offices should be aware of the possible unjustified extension of the term of protection arising from the successive patenting of the active ingredient and its polymorphs, including hydrates/solvates. Processes to obtain polymorphs may be patentable in some cases if they are novel and meet the inventive step standard.

### IV.3.6 Markush claims

Recommendation: Claims covering a large range of compounds should not be allowed. Patent offices should generally require patent applicants to provide sufficient information, such as fusion point, Infrared Absorption Spectrum (IR) or Nuclear Magnetic Resonance (NMR), obtained through true testing and experimentation to enable the reproduction by the disclosed method of each embodiment of the invention for which protection is sought. However, claims of limited scope could be granted if evidence is provided at least that, with the substitution of any member within the same family class, the same disclosed result would be obtained. The coverage of the patent should be limited to what is actually enabled by the disclosure in the specification.

### **IV.3.7** Selection patents

Recommendation: As a general rule, selection patents should not be granted if the selected components have already been disclosed or claimed and, hence, lack novelty. If an existing product were deemed patentable due to its unexpected advantages under the applicable law, the patentability of a selection could be considered when an inventive step is clearly present.

### IV.3.8 Analogy processes

Recommendation: Non-novel or obvious pharmaceutical processes, regardless of whether the starting materials, intermediaries or the end product are novel or inventive, should be considered not patentable as such.

### IV.3.9 Enantiomers

Recommendation: Single enantiomers should generally not be deemed patentable when the racemic mixture was known. However, processes for the obtention of enantiomers, if novel and inventive, may be patentable.

### IV.3.10 Active metabolites and prodrugs

Recommendation:

a) Active metabolites of drugs should generally not be deemed patentable separately from the active ingredient from which they are derived.

b) Patents over prodrugs, if granted, should disclaim the active ingredient as such, if previously disclosed or otherwise non-patentable. They should only be granted if the prodrug is specifically described and an unusual, non-predictable, effect was found. Like other subject matter claimed in a patent, a prodrug should be sufficiently supported by the

information provided in the specifications. In addition, evidence may be required that the prodrug is inactive or less active than the compound to be released, that the generation of the active compound ensures an effective level of the drug and that it minimizes the direct metabolism of the prodrug as well as the gradual inactivity of the drug.

# IV.3.11 Method of treatment

Recommendation: Methods of treatment, including for prevention, diagnosis or prophylaxis should be deemed non patentable where industrial applicability is required as a condition for patentability (including in cases where the patentability of such methods is not expressly excluded).

# IV.3.12 Use claims, including second indications

Recommendation: Claims relating to the use, including the second indication, of a known pharmaceutical product can be refused, inter alia, on grounds of lack of novelty and industrial applicability.

WHO has suspended the workshops for patent examiners, most likely because many countries have formally adopted the guidelines, as is the case for MERCOSUR countries, or informally, as is the case for Egypt, or the guidelines have inspired the development of their own guidelines, as in the case of India, Ecuador and a few others. Currently, the South Centre is continuing to provide this type of support to countries; most recently through seminars held in August 2014 in the four patent offices in India, in Mumbai, Chennai, Kolkata and New Delhi.

# IV.4 The Case of India

On 4 April 2005, the President of India gave his consent to the amendment of the patent law. This brought into force a law that should bring India into compliance with the TRIPS Agreement. India was one of the few developing country members of WTO that had opted to use a transition period of ten years (1995-2005), pursuant to the TRIPS Agreement, in order to delay the introduction of patents for pharmaceutical products.

As the TRIPS Agreement does not define the three patentability requirements – novelty, inventive step and industrial applicability – leaving a margin of flexibility for countries to define and interpret the meaning of these requirements, the new Indian Patent Act contains a series of provisions that try to define the patentability requirements, as follows:

Firstly, a definition of "inventive step" is provided as something that "involves technical advance compared to the existing knowledge or having economic significant, or both, and that makes the invention not obvious to a person skilled in the art." Secondly, there is a provision intended to hinder the "evergreening" of patents, by not allowing the simple discoveries of the following to be patentable: a new form of a known substance that does not improve the known efficacy of the substance; the mere discovery of a new property or new use of a known substance; or the mere use of a known process.

"India, considered the "pharmacy of the Third World", has since 2005, a legislation on Intellectual Property that from the public health standpoint can be considered as a model for other developing countries. For the first time ever, on 12 March 2012, the Indian Patent Office issued a compulsory license to the local company Natco Pharma for an anti-cancer medicine: 'sorafenibtosylate' (trade name Nexavar) patented by Bayer, thus creating the possibility to obtain this product at a lower cost so as to increase access to persons that need this medicine. In order to justify the high price of this medicine (USD 5,600 per patient, per month) Bayer attempted to put forward the high R&D cost involved in the creation of the medicine although it refused to present figures of the R&D for this product."<sup>63</sup>

After seven years of litigation, the Swiss pharmaceutical giant, Novartis, lost its case before the Supreme Court of India. On Monday, 1 April 2013, the Supreme Court rejected the patent application for a costly anti-cancer product with the Brand name Gleevec (or Glivec, depending on the country). Since 2006, Novartis has been fighting in different legal institutions in India to obtain a patent for Gleevec. In 2006 and then in 2009, India had rejected the patent on the basis that it

<sup>&</sup>lt;sup>63</sup> Velásquez, G., "India Compulsory license for anti-cancer medicine", South Bulletin Issue 62, 28 May 2012.

was not, according to the Indian Patent Act, related to a new medicine, and was rather a simple amendment of a known molecule. This medicine simply did not meet one of the requirements for patentability, that of novelty. Unhappy with the verdict, Novartis took the case to the Supreme Court to contest the article of Indian intellectual property law known as section 3(d), an article that was perfectly consistent with the requirements of the TRIPS Agreement of WTO.

With a certain amount of cynicism, when the law of India did not suit it, the Swiss company tried to change the law. According to MSF, stated by *Le Monde* on 1 April 2013, the price of Glivec in India is US\$ 4000 per person, per month (EUR 3122); while the generic version, Imatinib, is US\$ 73 per person per month (EUR 57). This, in a country where 40 per cent of the population live on less than US\$ 1.25 (EUR 0.97) per day.

When the case entered the Supreme Court to denounce the intellectual property law, it stopped being a case of Glivec versus India, and became a case of public health against the big pharmaceutical industry. India will continue to refuse to patent small changes (known as evergreening) and many countries may follow their example to enable low-resource populations to access medicines. Novartis' Glivec is patented in more than 40 countries, including the United States of America, Russia and China. The aforementioned article in *Le Monde* mentions that it is Novartis' most sold medicine, with sales in 2012 amounting to US\$ 4.6 billion (EUR 3.59 billion).

The generics industry of India could continue to produce and export this and many other medicines at prices at which people and health systems in many countries could access.<sup>64</sup>

Currently, in September 2014, the Indian Patent Office is completing the process of revising the guidelines for the examination of pharmaceutical products, which it is hoped will be approved at the end of 2014. As previously mentioned, in the guidelines currently being finalized by India, there are numerous elements in common with or similar to the guidelines proposed by WHO.

<sup>&</sup>lt;sup>64</sup> Velásquez, G., "David against Goliath" in *El País*, Spain. http://sociedad.elpais.com/sociedad/2013/04/01/actualidad/1364824227\_627519.html.

# IV.5 Experiences in the Implementation of Guidelines for the Examination of Pharmaceutical Patents

### IV.5.1 Argentina

Making use of the room for manoeuvre in the TRIPS Agreement regarding the definition of patentability requirements, the Ministry of Health, Ministry of Industry and the President of the INPI issued on 2 May 2012, joint resolution MI118/2012, MS 546/2012, and INPI 107/2012, through which the **Guidelines for the examination of patentability of patent applications for chemical-pharmaceutical inventions** were approved. The Guidelines have been applied to all pending patents since the date it entered into force.

"The Guidelines do not add new conditions for patentability. Patents are granted or denied on the basis of the consideration for each application of the conditions for patentability contained in patent legislation: novelty, inventive step and industrial applicability, as well as the rules pertaining to what are considered to be inventions and which inventions are excluded from patentability in accordance with that legislation."<sup>65</sup>

### IV.5.2 MERCOSUR

In the same vein, the Ministers of Health of the Common Market of the South (MERCOSUR) noted, on the occasion of the 27th Meeting of Ministers in Montevideo on 2 December 2009, that the coincidence of objectives between public policies and the intellectual property system, particularly compliance with and implementation of patentability requirements in the region, raises concerns about the proliferation of patent applications for materials that do not constitute an invention or marginal developments in their own right.

As a result, the Ministers took the opportunity to promote within MERCOSUR the adoption of criteria that protect public health in guidelines or guides on patentability.

<sup>65</sup> Arias E. Op. cit.

### IV.6 Compatibility with the TRIPS Agreement of WTO

During the fourth review of the trade policies of Argentina by WTO covering the period 2006-2011, carried out in 2013, a number of countries asked questions about the guidelines for the examination of pharmaceutical patents adopted by Argentina in 2012.

During the aforementioned review of trade policies, Japan, United States of America, Switzerland, Canada and the European Union asked very detailed questions about whether the new guidelines permitted the patenting of compositions, doses, esters and ethers, polymorphs, analogy processes, active metabolites and prodrugs, enantiomers, selection patents and Markush claims. The United States specifically asked if the new regulations added new patentability requirements other than novelty, inventive step and industrial applicability.

It is clear that the guidelines do not add new patentability requirements and only make use of the leeway allowed by the TRIPS Agreement in the definition and interpretation of patentability requirements.

Two developing countries, Chile and Costa Rica, expressed interest in the establishment by Argentina of guidelines on this issue.

Based on the provisions of the TRIPS Agreement, the response of Argentina to the long and detailed questions from the above-mentioned countries, limited itself to asserting that questions related to the guidelines for the examination of pharmaceutical products were not the subject of the review of the trade policies of Argentina as they are not a requirement of the TRIPS Agreement.

### V. CONCLUSIONS

National drugs policies, including matters related to intellectual property, are fundamental elements of a national health policy that endeavours to protect the right of all citizens to access to health care.

In order to develop new medicines, mechanisms promoting innovation and product development should be established, while at the same time it should be ensured that patients are able to quickly access the fruits of this research. In the context of essential medicines, innovation should be structurally linked to access. This means that the research costs and final product price should be separate.

The effect of the introduction of pharmaceutical patents on access to medicines largely depends on the way in which the TRIPS Agreement is interpreted and implemented. This is why it is particularly important that when incorporating the provisions of the TRIPS Agreement, countries consider, inter alia, the following measures:

- 1. The incorporation of the requirements of the TRIPS Agreement into national intellectual property legislation should take into account the principles of articles 7 and 8 in order to regulate intellectual property in a manner consistent with public health interests and minimize the economic and social costs that the changes can have on production, trade and access to medicines. These principles were ratified by the Doha Declaration (2001) on the TRIPS Agreement and public health;
- 2. Defining the three patentability requirements novelty, inventive step and industrial applicability (utility) in a manner consistent with public health objectives;
- 3. Integrating a mechanism to grant the compulsory licenses permitted by the Agreement into national legislation;
- 4. Ensuring the import of products that have been legitimately placed on the market, under the principle of international exhaustion;
- 5. Excluding naturally occurring substances from patentability (for not meeting the requirements for an "invention")
- 6. Limiting reversal of the burden of proof for process patents related to new chemical entities.

National intellectual property offices, through the examination of patents, play an important role in the access to medicines. The patentability requirements for public goods should be different from those for simple merchandise or luxury items. Therefore, the first and most important step is to use the freedom permitted by the TRIPS Agreement to define the patentability requirements: novelty, inventive step and industrial applicability (utility) in a way "that do[es] not lose sight of public interest in the wide dissemination of knowledge  $(...)^{366}$ 

Countries can interpret the criteria to assess patent applications in a manner consistent with their public policies. Patent regimes are generally part of national technological and industrial strategies, but it is also vital that they are designed in a manner consistent with public health strategies. In particular, it is important that the scope of patentability is consistent with public health policies, and that governments are aware that the undue expansion of patentability can distort competition and reduce access to medicines. Patents for minor developments can be used to effectively discourage and block competition, given that producers of generics, buying agents and consumers, particularly in developing countries, generally lack the essential financial and technical resources to oppose incorrectly granted patents or to defend themselves from infringement claims.

The purpose of the analysis and criteria contained in the guidelines for the examination of patents<sup>67</sup> is to provide general guidance to patent offices and other bodies that participate in the examination of pharmaceutical patents, so that such examinations are consistent with patent legislation and also with public health objectives, in particular with the right of all to access medicines. These guidelines can be perfected and adjusted to national legislation at a later date, where applicable.

As previously analysed, if these guidelines are implemented, it is unlikely that the following types of patent applications for pharmaceutical products will be admissible by a national patent office:

- A new salt, ester, ether or polymorph, including hydrates and solvates, of an existing chemical entity
- A single enantiomer of an existing chemical entity

<sup>&</sup>lt;sup>66</sup> Op. cit. The impact of the Agreement on Trade-Related Aspects of Intellectual Property Rights on human rights: Report of the High Commissioner, E/CN.4/Sub.2/2001/13, 27 June 2001, para 62.

<sup>&</sup>lt;sup>67</sup> Correa C. "Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective". WHO - ICTSD - UNCTAD, Geneva, January 2007.

- A new combination of two or more active ingredients that are already available as individual entities
- A new form of administration that enables a new administration route (for example, an injectable form when an oral tablet already exists)
- A new form of controlled release administration which already exists in uncontrolled release form
- A new route for an existing form of administration (for example intravenous administration of a drug when subcutaneous administration has already been approved)
- A change in formulation

An indispensable requirement when addressing the issue of patent applications from a public health perspective is, necessarily, to adequately train and retain qualified examiners in the patent offices. The training provided by patent offices from developed countries could increase the technical knowledge of the examiners, but can also pass on assessment standards that could lead to an undue expansion in the scope of patentability for pharmaceutical products.

Lastly, patent examiners should be aware that the decisions that they take, although they can seem of a technical nature, can have definite consequences on people's lives and health, since incorrectly granted patents can be used to unduly limit competition and restrict access to essential medicines.

# ANNEX I

# World Health Assembly Resolutions on Intellectual Property

1996 WHA49.14: Revised drug strategy

1999 WHA52.19: Revised drug strategy

2000 WHA53.14: HIV/AIDS: confronting the epidemic

2001 WHA54.10: Scaling up the response to HIV/AIDS

2001 WHA54.11: WHO medicines strategy

2002 WHA55.14: Ensuring accessibility of essential medicines

2003 WHA56.27: Intellectual property rights, innovation and public health

2003 WHA56.30: Global health sector strategy for HIV/AIDS

2004 WHA57.14: Scaling up treatment and care within a coordinated and comprehensive response to HIV/AIDS

2006 WHA59.24: Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action

2006 WHA59.26: International trade and health

2007 WHA60.30: Public health, innovation and intellectual property

2008 WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property

2009 WHA62.16: Global strategy and plan of action on public health, innovation and intellectual property

2011 WHA64.5: Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits

2011 WHA64.14: Global health sector strategy on HIV/AIDS, 2011-2015

2012 WHA65.22: Follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination

## ANNEX II

### WHO Publications on Intellectual Property and Public Health

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# CHAPTER 2 THE INTERNATIONAL DEBATE ON GENERIC MEDICINES OF BIOLOGICAL ORIGIN

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#### **EXECUTIVE SUMMARY**

The debate on generic medicines is not new. What makes it different today is that attacks levelled against biological products are couched in ever more "technical" and abstruse language that confuses even the World Health Organization.

Innovative biological drugs, which have been introduced on the market in the past 20 to 30 years,<sup>1</sup> make up, in terms of numbers, no more than 2 per cent<sup>2</sup> of the WHO Model List of Essential Medicines but, in terms of cost, account for 15 per cent to 20 per cent of national drug expenditure.

The high price of biological drugs stems mainly from two new factors: first, a change in the pharmaceutical industry's approach to price-setting and, secondly, the introduction of additional barriers to the entry of generics into the market. In any debate on the impossibility of producing "identical" drugs, it should be made clear that what is at stake is not identical products but therapeutic equivalents. What matters to the patient, after all, is whether or not the drug can prevent, cure or mitigate the effects of the illness.

#### I. INTRODUCTION

Over the past 40 years, transnational pharmaceutical companies have used specious arguments based on quality standards or intellectual

<sup>&</sup>lt;sup>1</sup> Human insulin was first introduced on the market by Eli Lilly in 1982.

 $<sup>^{\</sup>rm 2}$  Eleven products, compared to thousands of chemically synthesized products that flood world markets.

property rights to attack and disparage generic drugs in a bid to defend their highly lucrative monopolies. The pharmaceutical industry is currently waging a war against competition from generic biological drugs on the pretext of upholding "technical and scientific standards".

"Biological medicines are those in which **active protein substances** are extracted from living organisms, and are then purified and modified using advanced biotechnology. Because biological drugs derive from living organisms, they are characterized by more complex structures and functions, and higher molecular weight, than chemically synthesized drugs. There is no consensus on the difference in meaning between "biological" and "biotechnological", consequently these terms tend to be used interchangeably" [unofficial translation].<sup>3</sup>

Biological drugs, made from active protein substances that are reproduced through biotechnological methods, are increasingly used worldwide to treat arthritis, diabetes, cancer, haemophilia, multiple sclerosis, hepatitis and a number of rare diseases. By contrast, most drugs in use 20 years ago were either plant-derived or chemically synthesized. According to industry forecasts, pharmaceutical sales are expected to grow annually by 6.3 per cent between 2016 and 2022, when they should total US\$ 1.12 trillion in sales, with biological drugs making up 50 per cent of the market.<sup>4</sup>

Whether or not there is an adequate supply of generic biological drugs available will be crucial to ensuring the economic viability of health systems in both developing and developed countries.

### II. THE PROBLEM OF PATENTS AND DATA EXCLUSIVITY

As we know, the discovery of an innovative product entitles the originator company to take out a patent protecting the product for a minimum of 20 years after its release. At the end of that period, the

<sup>&</sup>lt;sup>3</sup> V. Vivancos, "¿Qué diferencias hay entre los medicamentos biológicos y los tradicionales?", INESEM online publication. https://revistadigital.inesem.es/biosanitario/medicamentos-biologicos-tradicionales/.

<sup>&</sup>lt;sup>4</sup> C. Lindgren, "World preview 2016: Outlook to 2022", EvaluatePharma. http://info.evaluategroup.com/rs/607-YGS-364/images/wp16.pdf.

product falls into the public domain and may be marketed by other companies. When a patent is registered, the data on the product becomes public knowledge but the originator may deny any other company the right to market the product for the duration of the patent in a specified territory.

Once the patent on a medicine expires, other companies are entitled to market products containing the same active principle. These drugs are known as "generics". Prior to the marketing of a generic, studies must be carried out to demonstrate that it is equivalent to the innovative product.

Since most biological drugs remain under patent protection for at least 20 years, laboratories are able to establish monopolies, frequently setting very high prices, as is the case with many recent cancer drugs.<sup>5</sup> Previously, when most drugs were chemically synthesized, the pharmaceutical industry set prices based on the estimated cost of research and development (R&D). Today, prices are no longer determined by production costs but by the supposed "value" of the medicine or its effects on or benefits to society. This new price-setting trend threatens the economic viability of our health systems.

Another way to extend monopolies is via "data exclusivity" (or "data protection"), a concept that certain governments, especially those of the United States and the European Union (EU), have included in bilateral trade agreements.

Data exclusivity is a practice whereby national drug regulatory authorities deny access to the registration files of an innovative product to any company seeking to market a therapeutically equivalent generic version, for a fixed period of time (five, eight or more years). Data exclusivity, which is different from a patent, can have a major impact in countries where the product is not protected by a patent, giving rise to the same type of monopolies as patents do.

The type of data covered by exclusivity clauses includes reports on clinical trials and all the other information that pharmaceutical

<sup>&</sup>lt;sup>5</sup> Where treatment can cost over US\$ 100,000.

companies must submit to national regulatory authorities in order to register a new medicine that they wish to introduce on the market.<sup>6</sup>

Multinationals have been pushing to obtain exclusive rights over data on their clinical trials in order to delay the entry into the market of competitor generics. In addition to patents and data exclusivity, various legislation exists, for instance in the United States and the EU, granting further market protection in the form of an extra period of time during which authorization to sell a generic is denied.

Chemically synthesized generics have played, and will continue to play, an important role in providing access to medicines in markets dominated by patent-protected drugs that are often priced beyond the means of individuals or health systems. Many countries are striving to ensure broader access to medicines by marketing generics since a sufficient supply of both chemically synthesized and biological products is fundamental to the survival of health systems in both developed and developing countries.

It is estimated that by 2020, half of the biological drugs that currently generate multimillion-dollar profits for transnational corporations will go off patent.<sup>7</sup> Some patents have already expired, which means that the drugs in question may be reproduced freely unless regulatory barriers are introduced that block or limit their marketing. There is an ongoing debate leading to much confusion over how national regulatory authorities should set standards for the approval of "biosimilars", "bioequivalents", "biogenerics" or simply biological generics.

### III. WHY ARE GENERIC DRUGS THE "SAME" AND BIOSIMILARS ONLY "SIMILAR" TO THEIR CORRESPONDING REFERENCE PRODUCTS?

The World Health Organization refers to "similar biotherapeutic products", whereas the EU and the European Medicines Agency (EMA) refer to "biosimilars" or "similar biological medicinal products". In the

<sup>&</sup>lt;sup>6</sup> MSF Technical Brief: "Data exclusivity in international trade agreements: What consequences for access to medicines?" May 2004.

<sup>&</sup>lt;sup>7</sup> C. Lindgren, op. cit. http://info.evaluategroup.com/rs/607-YGS-364/images/wp16.pdf.

United States, the same medicines are known as "follow-on biologics" or "follow-on protein products".<sup>8</sup>

### **III.1** Chemically Synthesized versus Biological Medicines

Biological drugs are characterized by a more complex structure and a higher molecular weight than chemically synthesized ones. Thus, their design, characterization, production, storage and conservation can all be more complicated. Most chemically synthesized medicines are administered orally, whereas biological drugs are always administered via injection or infusion in a hospital environment.

The regulations governing biological products also seem more complex than those applicable to smaller molecules of chemical origin. This is in large part because WHO has not set global standards and countries like the United States have adopted their own norms for both types of product.<sup>9</sup>

According to Marie A. Vodicka, biological drugs were not included in the "Hatch-Waxman" (1984) norms applicable to generics simply because, at the time, the science for these products was not sufficiently advanced.<sup>10</sup> In the past 30 years, however, biotechnology has made considerable progress and there is now more evidence supporting the possibility of reproducing biological products.<sup>11</sup>

<sup>&</sup>lt;sup>8</sup> V. Vivancos, op. cit. https://revistadigital.inesem.es/biosanitario/medicamentosbiologicos-tradicionales/.

<sup>&</sup>lt;sup>9</sup> Regulations on biological products: "Public Health Services Act (PHSA) 351". Regulations on chemically synthesized products: "Food, Drug, and Cosmetic Act (FDCA) 505".

<sup>&</sup>lt;sup>10</sup> Marie A. Vodicka, "Why are generic drugs the 'same' and biosimilars only 'similar' to their corresponding reference products?" http://www.biosimilarslawblog.com/2012/01/25/why-are-generic-drugs-the-same-and-biosimilars-only-similar-to-their-corresponding-reference-products/. <sup>11</sup> Ibid.

Schematic list of the main characteristics differentiating conventional (chemically synthesized) medicines from those of biological origin<sup>12</sup>

Conventional medicines	<b>Biological medicines</b>
Not very complex structure	Very complex structure
Low molecular weight < 1 kD	High molecular weight > 50 kD
Organic synthesis (semi-synthesis)	Synthesis from live cells/organisms
Well characterized structure	Not well characterized
Few critical stages in synthesis	Many critical stages in synthesis
Homogeneous active principles	Complex heterogeneous combinations
Maximum tolerated dose	Optimal biological dose
Linear dose response curve	Non-linear dose response curve
Known action mechanisms	Unknown action mechanisms
Elimination via metabolism	Elimination via degradation

### **III.2** Position of the Pharmaceutical Industry

According to the Swiss corporation Hoffmann La Roche:

"The production of monoclonal antibodies involves a highly complex process that relies on an exclusive bank of master cells to which the originator holds the property rights. It also involves procedures that are controlled by the originator. Such antibodies cannot therefore be reproduced by another company (...) It is impossible to create an identical monoclonal antibody since the process uses a different cell line, and the antibody's final characteristics depends entirely on that process."

By comparison, products made from small molecules can be reproduced relatively easily by chemical synthesis. These copies are known as generics. A complex biological product such as a monoclonal antibody cannot be copied. Biogenerics do not exist.

<sup>&</sup>lt;sup>12</sup> L. Cuñetti, "Generalidades de los medicamentos biológicos", *Boletin farmacológico*. September 2014. Available from:

http://www.boletinfarmacologia.hc.edu.uy/index.php?option=com\_content&task=view&i d=104&Itemid=66.

This term leads to confusion, is scientifically incorrect and should not be used. Copies of monoclonal antibodies are as similar as possible to the originator product and are called biosimilar antibodies" [unofficial translation].<sup>13</sup>

It is on the basis of this position taken by the pharmaceutical industry that WHO justifies the adoption of a biological qualifier scheme, which may well serve as a "technical barrier" to calling these drugs "generic biological medicines".

### **III.3** Scientists and Academics Hold a Different Opinion

Alexander Caleb of the Bloomberg School of Public Health at Johns Hopkins University (USA) analyzed a broad array of scientific literature comparing the use of biosimilars and reference products in treating rheumatoid arthritis, psoriasis and inflammatory bowel disease, such as Crohn's disease or ulcerative colitis. This class of drugs suppresses the activity of a key protein in the immune system known as tumour necrosis factor. The literature includes phase 1 clinical trials, to determine safety, and phase 3 trials, carried out prior to marketing. It also includes studies of patients who were first treated with the original medicine and then with the biosimilar.

According to the *Annals of Internal Medicine*, all the clinical trials that were analyzed, whether phase 1 or phase 3, found biosimilars to be within the equivalence margin of 80 per cent to 125 per cent, compared with the reference products. Although these percentages cannot be interpreted as direct evidence that some biosimilars are superior to the originals, Caleb notes that this equivalence margin represents the thresholds of efficacy between products.<sup>14</sup>

<sup>&</sup>lt;sup>13</sup> ROCHE website, "No puede realizarse copias de los anticuerpos monoclonales". http://www.roche.com.co/home/investigacion-y-desarrollo/innovacion-ytecnologia/biotecnologia/productos-biologicos.html.

<sup>&</sup>lt;sup>14</sup> Francine Chingcuanco, MHS; Jodi B. Segal, MD, MPH; Seoyoung C. Kim, MD, ScD, MSCE; G. Caleb Alexander, MD, "Bioequivalence of biosimilar tumor necrosis factor-α inhibitors compared with their reference biologics: A systematic review". http://annals.org/aim/article/2540851/bioequivalence-biosimilar-tumor-necrosis-factor-inhibitors-compared-reference-biologics-systematic.
Caleb concludes that "based on the available evidence, the products we studied appear comparable, and they will definitely be cheaper".<sup>15</sup>

"The biosimilar market is setting the stage for a veritable war", according to Professor Miguel del Fresno of Spain's National Distance Education University (UNED), who has spent years studying strategies used to hold up the marketing first of generics and now of biosimilars. And this war will be waged on many fronts, with battles fought over a clear definition of biosimilars, who is authorized to prescribe them, and the choice of name (brand name or name of active principle), as in the case of generics.

Fresno points out that "it will be crucial for public health officials to draw a distinction between public and private interests", adding that "while patents protect private property, access to reasonably priced medicines protects public welfare" [unofficial translation].<sup>16</sup>

#### III.4 Industry Strategies Aimed at Blocking Access to Generics

Whether the price of drugs, especially cancer drugs, remains high depends largely on the availability or absence of generics. The pharmaceutical industry therefore resorts to various strategies to delay the entry of affordable generic drugs into markets in the United States and worldwide.

Strategies and practices for delaying or blocking the marketing of generics include:<sup>17</sup>

### • Reverse payment or pay-for-delay patent settlements

In "pay-for-delay" settlements, patent holders agree to pay potential generic competitors that challenge the patent of the brand company to delay entry into the market. "Reverse payment" refers to the fact that the patent company pays the

<sup>&</sup>lt;sup>15</sup> Ibid.

<sup>&</sup>lt;sup>16</sup> M.A. Criado, "Los fármacos biológicos y sus 'genéricos' son igual de buenos", *El Pais*, Spain, 3 August 2016.

<sup>&</sup>lt;sup>17</sup> Gregory H. Jones, Michael A. Carrier, Richard T. Silver, Hagop Kantarjian, "Strategies that delay or prevent the timely availability of affordable generic drugs in the United States", *American Society of Hematology*, 2016.

generic company, with the payment moving in the opposite direction than what would be ordinarily expected in patent litigation (with a potential infringer typically paying the patent holder to enter the market).

In the past decade, it has become increasingly common for pharmaceutical companies to pay would-be competitors to delay entering the market, thereby securing a longer period of exclusivity. In return for lucrative payments that may even exceed the profits the generic competitor would have earned if it had entered the market, the generic firm agrees to delay entry and not contest the patent (...). These settlements have been criticized as anticompetitive and contrary to the public interest.<sup>\*18</sup>

#### • Authorized generics

"Authorized generic drugs" (AGs) are drugs that are produced by a brand pharmaceutical company or in collaboration with other companies and that are marketed under separate labels at "generic prices". Patent holders either produce their own AGs or grant their property rights to generic companies under confidential trade agreements that allow them to enter the market before their competitors. This practice is clearly contrary to the principle of free competition that should apply once a patent has expired.<sup>19</sup>

### • Measures blocking the importation of medicines

Several studies<sup>20</sup> have shown that the price of same-brand drugs sold outside the United States can be as much as 20 per cent to 50 per cent lower than the price charged inside the country. Moreover, owing to various strategies and lobbying efforts,

<sup>19</sup> Federal Trade Commission, "Authorized generic drugs: Short-term effects and longterm impact", 2011, accessed online August 13, 2015. http://www.ftc.gov/sites/default/files/documents/reports/authorized-generic-drugs-

short-term-effects-and-Iong-term-impact-report-federal-trade-commission/authorized-generic-drugs-short-term-effects-and-Iong-term-impact-report-federal-tradecommission.pdf.

<sup>&</sup>lt;sup>18</sup> Swati Shah, Matthew A Silva, & Michael J Malloy, "Are reverse payments and payfor-delay settlements business as usual or an anticompetitive practice?", *Nature Biotechnology*, 34, pp. 716–719 (2016), doi:10.1038/nbt.3627. Published online 12 July 2016.

<sup>&</sup>lt;sup>20</sup> Gregory H. Jones et al, op. cit.

certain generic drugs are available outside the United States much sooner than inside the country. For instance, in 2014 the brandname medicine Imatinib cost US\$ 132,000 for a year's supply in the United States and only US\$ 38.000 in Canada.

In order to obtain drugs at affordable prices, some patients attempt to import them from abroad for their personal use. However, Section 708 of the Food and Drug Administration's Safety and Innovation Act (FDASIA) permits the destruction of legal drugs imported for personal use and valued at US\$ 2,500 or less "in the interests of public safety". This discourages patients from seeking to obtain the same drugs in more affordable markets.

Strategies aimed at delaying the availability of affordable generic drugs constitute a worldwide problem. To cite but one example, the European Commission published a study on the pharmaceutical sector in 2009 that focused on practices engaged in by companies to block or delay the development and marketing of competitor generic products. The study found that 22 per cent of the settlements reached between 2000 and 2008 included payments by originator companies to generic manufacturers and restrictions on the marketing of generics.<sup>21</sup>

# IV. CLASSIFICATION OF BIOLOGICAL PRODUCTS BY THERAPEUTIC USE

Biological medicines account for a growing share of national drug expenditure and, as we have seen, are expected to represent 50 per cent of the cost of all drugs sold on world markets by 2022. Nevertheless, they make up a much smaller percentage of markets in terms of the number of products sold. In the most recent WHO List of Essential Medicines, they account for only 2.5 per cent of the total.

The 2017 revised WHO List of Essential Medicines comprises 433 products, 11 of which are biological:<sup>22</sup>

<sup>&</sup>lt;sup>21</sup> European Commission, "Pharmaceutical Sector Inquiry: Final Report 4", 268-85 (EU, 2009).

<sup>&</sup>lt;sup>22</sup> Email from Nicola Magrini and Lorenzo Moja, in charge of WHO List of Essential Medicines, June 2017.

- Bevacizumab (eye)
- Erythropoietin(s) [epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and their respective biosimilars]
- Pegylated interferon alfa (2a [patent expired], or 2b [patent expired])
- Insulins, Insulin(s)
- Filgrastim
- Factor VIII
- Factor IX
- Heparins [enoxaparin, nadroparin, dalteparin]
- Rituximab
- Trastuzumab
- Surfactant

The fact that a relatively small percentage of the drugs needed by a country's population accounts for over 50 per cent of national drug expenditure constitutes a major problem for the viability of our health systems. R&D costs for biological products do not appear to be the source of the problem. The fact is that the pharmaceutical industry has propelled us into a new era in which prices no longer reflect R&D costs plus a reasonable profit margin, but are based instead on a product's supposed "value" in terms of days of life "gained", labour force recovered, or – as argued in the case of Sofosbuvir, a drug used to treat hepatitis C – a liver transplant. To accept this type of logic is tantamount to agreeing that the purpose of the pharmaceutical industry is to speculate on financial markets, not to serve public health interests.

# **IV.1** Classification of Biological Medicines<sup>23</sup> by Therapeutic Use

### 1. Products used for active immunization

- Bacterial vaccines
- Vaccines prepared with Rickettsias
- Viral vaccines
- Toxoid vaccines

<sup>&</sup>lt;sup>23</sup> European Commission, "Pharmaceutical Sector Inquiry: Final Report 4", op. cit.

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#### 2. Products used for passive immunization

- Monoclonal and polyclonal antibodies
- Antivenins / antitoxins
- Immune globulin

#### 3. Agents used for diagnostic purposes

- Toxins
- Tuberculin

#### 4. Human blood and blood derivatives

5. Allergens

#### V. BASIC PRINCIPLES AND CONCEPTS GOVERNING THE APPROVAL OF GENERIC BIOLOGICAL MEDICINES

As already mentioned, the structure and composition of biological drugs are far more complex than those of conventional, chemically synthesized drugs. Biological drugs are those "in which **active protein substances** are produced from living organisms".<sup>24</sup> It is their biological nature and, consequently, their structural and functional complexity, that distinguishes them from chemically synthesized drugs (or "small molecules"). The relatively recent expiry of patents protecting the first biological medicines to arrive on the market has paved the way for the development and marketing of "biosimilars, generics or bioequivalents".<sup>25</sup>

#### V.1 EU 2006 Guidelines for the Evaluation of Competitor Therapeutic Proteins

The EU has been at forefront of efforts to adopt legislation governing the marketing of biosimilars. In 2006, the EMA adopted Guidelines for

<sup>&</sup>lt;sup>24</sup> V. Vivancos, op. cit. https://revistadigital.inesem.es/biosanitario/medicamentosbiologicos-tradicionales/.

<sup>&</sup>lt;sup>25</sup> Fundación Azierta, Science to business, Madrid 2016. http://azierta.eu/2016/06/02/biologicos-biosimilares-1/.

the evaluation of competitor therapeutic proteins (biosimilars). According to a recent study, these Guidelines, which establish requirements for biosimilars based on a comparability demonstration, confirm the impossibility of showing that two proteins are identical but acknowledge the possibility of showing their similarity through a stepwise exercise comparing the biosimilar competitor to the reference product, from the characterization stage to the clinical stage (comparative clinical study of equivalence or non-inferiority).

The EMA first approved a biosimilar in 2006 (a recombinant protein) and has to date approved a total of 28 biosimilars (see Annex I).

The concept of a biosimilar was introduced into European legislation through Commission Directives 2003/63/EC and 2004/27/EC, which define biosimilars as biological drugs that are similar in relation to previously approved innovator biological drugs (reference products). A biosimilar (or similar biological medicine) is a biological drug that contains the same active principle as the original reference biological drug.

The ultimate aim of a "biosimilarity" evaluation is to demonstrate that the biosimilar or generic product has a comparable or equivalent therapeutic effect on the patient to that of the reference drug. Countries outside the EU may adopt legislation and standards different from those of the EMA to evaluate biosimilarity or biological generics.

The comparability requirements set out in the EMA Guidelines have been the subject of major criticism.<sup>26</sup> Indeed, the debate over whether two chemical substances or two proteins are, or can be identical is of little interest in evaluating their biosimilarity from the perspective of public health since the aim is to establish therapeutic equivalency. The only purpose of insisting on the need to demonstrate that two proteins are identical is to block or delay the entry of generic products into the market since comparability is not required to demonstrate the therapeutic efficacy and safety of a biosimilar or a generic.

<sup>&</sup>lt;sup>26</sup> H. Schellekens, E. Moors, "Clinical comparability and European biosimilar regulations", available from: http://www.biosimilars-nederland.nl/wpcontent/uploads/2015/09/SchellekensMoorsClinicalcomparabilityandEuropeanbiosimilarreg ulationsNBT2010.pdf.

Experience over the past 10 years has highlighted the limitations of clinical comparability exercises as introduced by the EU, which are time-consuming and costly, thereby delaying the entry of biosimilar products into the market.

It is certainly true that developing biosimilars is a process that can take over five years and is more expensive (between 100 and 200 million dollars, depending on the source) than developing generics. This fact is put forward to explain the slow entry into the European market of challengers to drugs no longer under patent and the relatively small savings in cost as compared with chemically synthesized generics.<sup>27</sup>

In addition, it is difficult to carry out comparative clinical trials requiring large numbers of patients for rare diseases or for cancers with low incidence rates.

According to Gaviria et al., some countries have therefore considered devising pathways to approval other than comparativity exercises. In order to use such a pathway (individuality, simplified or fast-track), a company must first demonstrate a high degree of similarity between the competitor drug and the reference product in terms of quality and it must make sufficient clinical information available to the public.<sup>28</sup>

#### V.2 Colombian Decree on Biological Medicines

In 2014, Colombia issued Decree 1782 setting the standards that biological medicines must meet in order to be registered in the country.

The decree, which allowed the entry of new laboratories and products to the closed world of biotechnological drugs, was celebrated as a courageous decision taken in defiance of the pressure exerted by the transnational pharmaceutical industry. The industry is so powerful that it succeeded in convincing the vice-president of the United States, Joe Biden, several United States Senators and the Swiss Government to send letters urging Colombia not to adopt the decree.

<sup>&</sup>lt;sup>27</sup> A. Gaviria, C.P. Vaca Gonzalez, C. Gomez Muños, A. A. Morales. "El debate de la regulación de los medicamentos biológicos: Colombia en el contexto internacional", Rev Panam Salud Pública 40(1), 2016.

<sup>&</sup>lt;sup>28</sup> Ibid.

Decree 1782 marks an important step forward in defining the conditions governing access to generic biological products. It sets the standards and requirements applicable to new products. Through the decree, the government has opted to prioritize health needs rather than accept the technical barriers that multinationals wanted to impose in a bid to extend their monopolies. The battle is being, and will continue to be waged over whether or not to place public health concerns ahead of profit motives.

A key concept set out in the decree is that of an "abbreviated route", an unfortunate term that has lent itself to misinterpretation. This route, far from being a shortcut, includes all the requirements, clinical proof or trials involved in obtaining a license for a new drug in most countries. Its purpose is merely to avoid unnecessary delays associated with the repeated technical requirements that multinationals seek to impose.

As explained in section V.3 below, WHO has not yet issued any regulations in this field. Resolution 67.21 adopted by the 2014 World Health Assembly simply requested WHO to update its Guidelines on Evaluation of Similar Biotherapeutic Products. We are therefore at the beginning of a complicated process that will take several years.

#### V.3 WHO 2009 Guidelines

It was in 2009 that the WHO Expert Committee on Biological Standardization published its Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs),<sup>29</sup> which promote strict evaluation of the quality, safety and efficacy of biological products along the same lines as the standards set out by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH was created in 1990 on the initiative of the pharmaceutical industries of the United States, Europe and Japan, which promote and fund it, in a bid to influence the standards adopted by national drug regulatory authorities and WHO. During the 2015 World Health Assembly, a number of industrialized countries pushed – albeit

<sup>&</sup>lt;sup>29</sup> WHO, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), Expert Committee on Biological Standardization, Geneva, 2009, available from: http://www.who.int/biologicals/areas/biological\_therapeutics/BIOTHERAPEUTICS\_FO R\_WEB\_22APRIL2010.pdf.

unsuccessfully – for the adoption of a resolution approving ICH standards. WHO Guidelines do not, for example, provide for the same exemption from comparative clinical trials for biological drugs as is granted to chemically synthesized generics.

The pharmaceutical industry's main argument, which WHO seems to have accepted, is that it is impossible to make an identical replica of a biological medicine since biological substances, such as proteins, cannot be reproduced exactly. This argument underpins both the 2006 EMA Guidelines and WHO's 2009 Guidelines on Evaluation of Similar Biotherapeutic Products, which require that comparative clinical trials be carried out to demonstrate that a drug is similar but not identical to the reference product. However, as already mentioned, such trials are not always necessary since, from the medical perspective, the aim is not to make an identical product but one that has an equivalent therapeutic effect. If the product has the desired effect, there is no need for it to be identical. The patients who take the medicine are not identical either. The object of the exercise is to obtain equivalent clinical results.

WHO principle of precaution, which requires clinical trials, amounts to an extension of the principle of data exclusivity, and that in turn keeps prices high and ultimately restricts access. It is crucial to draw a clear distinction between measures designed to ensure patient safety and barriers intended to boost monopolies.

It is a well-known fact that many of the standards promoted by ICH are aimed at protecting markets rather than patients: "Under the pretext of harmonizing regulatory requirements for marketing authorization of new drugs, the drug regulatory agencies of the world's wealthiest countries and three pharmaceutical industry trade associations, joined together since 1990 in the ICH, are promoting their own interests by imposing their criteria for evaluating drugs on the whole world. The toxicity standards advocated by ICH sometimes promote faster, cheaper drug development over patient protection. The drug quality standards advocated by ICH sometimes increase manufacturing costs without providing any public health benefit."<sup>30</sup>

<sup>&</sup>lt;sup>30</sup> "ICH: An exclusive club of drug regulatory agencies and drug companies imposing its rules on the rest of the world", Prescrire International, August 2010; 19(108):183-6.

# In the French journal *Prescrire*, ICH is described as **"an exclusive** club of drug regulatory agencies and drug companies".<sup>31</sup>

It is against this backdrop that in 2014, a number of South-American countries noted that the WHO 2009 Guidelines had never been submitted for discussion or approval by the organization's governing bodies. A group of countries, led by Colombia and Argentina, therefore promoted the adoption of Resolution WHA 67.21,<sup>32</sup> which urges Member States and WHO "to work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to quality, safe, efficacious and affordable biotherapeutic products, including similar biotherapeutic products;"<sup>33</sup> The Resolution also recognizes that "pharmaceutical regulation should contribute to the performance and sustainability of health systems and the general welfare of society."<sup>34</sup> Lastly, the Resolution requests the Director-General to update the 2009 Guidelines on Evaluation of Similar Biotherapeutic Products – which is essentially what the countries that promoted Resolution 67.21 were seeking.

C. Vaca and C. Gómez identified at least three types of technical barriers set out in the WHO 2009 Guidelines: (i) "those associated with the general requirement for sophisticated confirmatory clinical trials prior to registration, (ii) those corresponding to the differentiation and designation of the active principle (differential nomenclature) in relation

<sup>&</sup>lt;sup>31</sup> Ibid. From its founding, the ICH Management Committee has comprised six members with voting rights, representing Europe, Japan and the United States, respectively: the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA); the Japanese Ministry of Health, Labour and Welfare and the Japan Pharmaceutical Manufacturers Association (JPMA); the US Food and Drug Administration and Pharmaceutical Research and Manufacturers of America, (PhRMA) [1]. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), a group of pharmaceutical corporations with its headquarters in Geneva, Switzerland, serves as the ICH Secretariat.

<sup>&</sup>lt;sup>32</sup> World Health Assembly Resolution WHA67.21: "Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy." http://apps.who.int/medicinedocs/documents/s21459en/s21459en.pdf.

<sup>&</sup>lt;sup>33</sup> İbid.

<sup>&</sup>lt;sup>34</sup> Ibid.

to prescribing and marketing, and (iii) those tied to restrictions on substitution and interchangeability" [unofficial English translation].<sup>35</sup>

Let us look at the second type of barrier identified by Vaca and Gómez, namely the differentiation and designation of the active ingredient (differential nomenclature), since WHO is currently trying to impose a scheme<sup>36</sup> over which there is no consensus and, as we shall see, may further block access to generic biological drugs.

#### VI. INTERNATIONAL NONPROPRIETARY NAMES (INNS) ASSIGNED BY WHO TO BIOLOGICAL MEDICINES

#### VI.1 International Nonproprietary Names

"Nonproprietary names, also called generic or common names, are intended to be used as public property without restraint, i.e. nobody owns any rights on their usage."<sup>37</sup>

Today's INN system was established in 1950 pursuant to World Health Assembly Resolution WHA3.11 and came into use in 1953, with the publication of the first list of INNs for pharmaceutical substances.<sup>38</sup> The current cumulative list includes some 10,000 INNs.<sup>39</sup>

The purpose of introducing the INN system was to provide health professionals with a unique and universally recognized number to identify each pharmaceutical substance. "The existence of an international nomenclature for pharmaceutical substances, in the form of INNs, is important for the clear and unambiguous identification, safe prescription and dispensing of medicines to patients, and for

<sup>&</sup>lt;sup>35</sup> C. Vaca and C. Gomez, "Barreras técnicas innecesarias a la competencia y la inequidad en el acceso: El caso de los medicamentos biotecnológicos".

<sup>&</sup>lt;sup>36</sup> WHO, Biological Qualifier (BQ): A Global initiative and consequences for not implementing BG, Geneva 1 March. INN Working Doc. 17.411.

<sup>&</sup>lt;sup>37</sup> S. Kopp-Kubel, "International Nonproprietary Names (INN) for pharmaceutical substances", *WHO Bulletin*, vol. 73, No. 3, 1995, pp. 275-279, 1995.

<sup>&</sup>lt;sup>38</sup> WHO, "Guidance on INN".

http://www.who.int/medicines/services/inn/innguidance/en/#.

<sup>&</sup>lt;sup>39</sup> WHO Report. Sixty-ninth World Health Assembly A69/43 (2016). http://apps.who.int/gb/ebwha/pdf\_files/WHA69/A69\_43-en.pdf.

communication and exchange of information among health professionals and scientists, worldwide."<sup>40</sup> All generic products reproduced from the first pharmaceutical substance registered and in circulation today have been assigned the same INN.

According to WHO, "INNs are intended to be used globally for the identification of a specific pharmaceutical substance. So as to ensure the universal availability of INNs for their intended purpose, they should be free from any protection by proprietary rights – hence, the designation nonproprietary."<sup>41</sup>

Every INN is a unique name, also known as a generic name that is recognized worldwide and is considered public property.<sup>42</sup>

# VI.2 International Nonproprietary Names "Biological Qualifier" (BQ)

Over the past five years, manufacturers of biological products have pressured WHO to disregard the principle underlying INNs, namely that they "are intended to be used as public property without restraint". Arguing that it is impossible to produce an "identical copy", manufacturers have supported the idea of assigning a biological qualifier (BQ) to each product, whether it is biosimilar or bioequivalent or generic.

According to certain documents issued by the WHO Secretariat,<sup>43</sup> the BQ concept was put forward by the Secretariat itself, in line with the practice followed in Japan, Australia and the United States.<sup>44</sup> One Secretariat document, however, indicates that the BQ concept was proposed at the request of "several countries" (it does not specify which ones).<sup>45</sup>

<sup>42</sup> Ibid.

<sup>&</sup>lt;sup>40</sup> Ibid.

<sup>&</sup>lt;sup>41</sup> WHO, "International Nonproprietary Names: Revised procedure". EB110/3, 2002. http://apps.who.int/gb/archive/pdf\_files/EB110/eeb1103.pdf.

 <sup>&</sup>lt;sup>43</sup> WHO, "Biological qualifier: An INN Proposal", INN Working Doc. 14.342, October 2015. http://www.who.int/medicines/services/inn/WHO\_INN\_BQ\_proposal\_2015.pdf.
<sup>44</sup> Op. cit., p. 2.

<sup>&</sup>lt;sup>45</sup> WHO, "Biological qualifier: Frequently Asked Questions", INN Working Doc. 15.382, October 2015.

In the document "Biological Qualifier: An INN proposal", the WHO Secretariat states the following: "A scheme is proposed in which a unique identification code named a 'Biological Qualifier' (BQ) is assigned to all biological substances having (or eligible to have) INNs. The BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance (...) The BQ is a code formed of four random consonants in two 2-letter blocks separated by a 2-digit checksum."<sup>46</sup>

The BQ scheme proposed by WHO would only complicate the introduction of generic biological drugs, giving them an individual identity as if each were a distinct product. In addition to restricting the concept of generic biological drugs, the BQ scheme encourages a fragmentation of the market to the detriment of the principle of competition. The scheme may also cause confusion in the dispensing of drugs as it conveys the message that each drug is distinct.

According to a report presented by WHO Director-General to the 2016 World Health Assembly: $^{47}$ 

"66. The International Nonproprietary Names system administered by WHO provides pharmaceutical substances a unique and universally available designated name for the clear identification, safe prescription and dispensing of medicines, and for communication and exchange of information among health professionals and scientists worldwide. The cumulative list contains approximately 10 000 names. (...)

67. Following requests from some drug regulatory authorities, the International Nonproprietary Names Expert Group considered how WHO might develop a system for assigning biological qualifiers. Following discussions among interested parties, including through a web consultation, the Expert Group at the 61st Consultation on

http://www.who.int/medicines/services/inn/WHO\_INN\_BQ\_proposal\_FAQ\_2015.pdf?ua =1.

<sup>&</sup>lt;sup>46</sup> WHO, "Biological Qualifier. An INN Proposal", op. cit. http://www.who.int/medicines/services/inn/WHO\_INN\_BQ\_proposal\_2015.pdf, p. 2.

<sup>&</sup>lt;sup>47</sup> See full report in Annex I. WHO, Sixty-ninth World Health Assembly A69/43 (2016), op. cit. http://apps.who.int/gb/ebwha/pdf\_files/WHA69/A69\_43-en.pdf.

International Nonproprietary Names (Geneva, 13–16 October 2015) recommended a voluntary scheme whereby application for a biological qualifier could be made to the International Nonproprietary Names Secretariat. The biological qualifier code would not be a constituent part of the International Nonproprietary Names, but an additional and independent element used in conjunction with it. The Secretariat subsequently initiated an impact assessment study, to report to the International Nonproprietary Names Expert Group in 2016, on whether introducing such biological qualifiers would influence access or affect other aspects of public health."

In the working document 17.411 "Biological Qualifier (BQ): A global initiative and consequences for not implementing BQ" presented in March 2017,<sup>48</sup> the WHO Secretariat refers to a "global initiative". An initiative taken where and by whom? The document confines itself to listing the consequences of non-implementation of the BQ scheme without analyzing or even mentioning the consequences of actually implementing the scheme. The title of the document alone suggests that WHO has already decided to introduce the BQ scheme. Yet, to give each biosimilar an individual identity by assigning it a different BQ contradicts the very philosophy and raison d'être of the INN system.

In June 2017, the following information appeared on the website of the WHO Department of Essential Medicines:

"Following requests from some drug regulatory authorities, the INN Expert Group recommended that WHO develop a system for assignment of Biological Qualifiers to similar biotherapeutic products (SBPs).

After discussions among interested parties and approval by the INN Expert Group, a voluntary scheme is proposed by which an application can be made to the INN Secretariat for a Biological Qualifier (BQ).<sup>\*\*49</sup>

<sup>&</sup>lt;sup>48</sup> WHO, "Biological Qualifier (BQ): A global initiative and consequences for not implementing BQ", Geneva, INN Working doc. 17.411, March 2017.

<sup>&</sup>lt;sup>49</sup> WHO website, July 2017, http://www.who.int/medicines/services/inn/inn\_bio\_bq/en/.

The proposed BQ scheme, however voluntary it may be, could compromise the entire INN system and further delay the marketing of generic biological drugs. For this reason, it should be rejected by WHO governing bodies.

WHO has delayed issuing clear and universal guidelines while tolerating a situation in which countries may use whatever name they wish,<sup>50</sup> as some have already started to do. Allowing countries to decide on an individual basis which INN applies to a particular biological product is tantamount to condoning a confusing state of affairs that contradicts the very purpose of the INN system.

#### VII. CONCLUSIONS

The debate on generic medicines is not new. What makes it different today is that attacks levelled against biological products are couched in ever more "technical" and abstruse language that confuses even the World Health Organization.

Innovative biological drugs which have been introduced on the market in the past 20 to 30 years<sup>51</sup> make up, in terms of numbers, no more than 2.5 per cent<sup>52</sup> of the WHO Model List of Essential Medicines, but in terms of cost, account for 15 per cent to 20 per cent of national drug expenditure.

The high price of biological drugs stems mainly from two new factors: first, a change in the pharmaceutical industry's approach to price-setting, whereby prices no longer reflect the true costs of research and development plus a reasonable profit margin. They are now based on the product's supposed "value" to the pharmaceutical industry in terms of financial speculation, not on its role in promoting public health. Secondly, high prices are the result of the unjustified strengthening of

<sup>&</sup>lt;sup>50</sup> Document A69/43 (2016), cited in footnote 40, states: "Acknowledging that national authorities may use different terminologies when referring to similar biotherapeutic products".

 $_{1}^{51}$  Human insulin was introduced on the market by Eli Lilly in 1982.

<sup>&</sup>lt;sup>52</sup> Eleven products as compared with thousands of chemically synthesized products that flood world markets.

intellectual property rights and the introduction of additional barriers to the entry of generic drugs into the market. Instead of clarifying the situation, WHO has created a further obstacle by introducing a biological qualifier (BQ) that unnecessarily assigns a unique code to each generic biological medicine.

It is a source of major concern that WHO has not issued international guidelines based on the principle underlying the INN system, namely that: "International Nonproprietary Names, also known as generic names, are intended to be used as public property without restraint, i.e. nobody owns any rights on their usage".

In any debate on the impossibility of producing "identical" drugs, it should be made clear that what is at stake is not identical products but therapeutic equivalents. What matters to the patient, as we have said, is whether or not a drug can prevent, cure or mitigate the effects of the illness.

Certain biological drugs have revolutionized the treatment of cancer, arthritis and inflammatory bowel disease. Meanwhile, health-care costs have skyrocketed, with huge profits accruing to pharmaceutical companies.<sup>53</sup>

There are obviously differences between the reproduction of biological products and that of chemically synthesized ones. However, there is no reason why biological products cannot be reproduced under a clear set of rules that protect patients while ensuring affordable access to all those who need them.

Instead of biosimilars, interchangeable biosimilars or bioequivalents, why not simply opt for biological generics?

We hope that WHO will succeed in issuing clear guidelines prioritizing patient protection over the financial interests of pharmaceutical companies.

<sup>&</sup>lt;sup>53</sup> IMS Health, "The global use of medicines: Outlook through 2017", available from: http://www.quotidianosanita.it/allegati/allegato1501906.pdf.

### ANNEX I Biosimilars Approved by the European Medicines Agency (EMA)

MEDICINE NAME	ACTIVE SUBSTANCE	COMMON NAME	STATUS	BIOSIMILAR
Abasaglar (previously		insulin		
Abasria)	insulin glargine	glargine	Authorised	Yes
Abseamed	epoetin alfa	epoetin alfa	Authorised	Yes
Accofil	Filgrastim	Filgrastim	Authorised	Yes
Amgevita	Adalimumab	Adalimumab	Authorised	Yes
Bemfola	follitropin alfa	follitropin alfa	Authorised	Yes
Benepali	Etanercept	Etanercept	Authorised	Yes
Binocrit Epoetin Alfa	epoetin alfa	epoetin alfa	Authorised	Yes
Hexal Filgrastim	epoetin alfa	epoetin alfa	Authorised	Yes
Hexal	filgrastim	Filgrastim	Authorised	Yes
Flixabi	infliximab	Infliximab	Authorised	Yes
Grastofil	filgrastim	Filgrastim	Authorised	Yes
Inflectra	infliximab enoxaparin	Infliximab enoxaparin	Authorised	Yes
Inhixa	sodium	sodium insulin	Authorised	Yes
Lusduna	insulin glargine	glargine	Authorised	Yes
Movymia	teriparatide	Teriparatide	Authorised	Yes
Nivestim	filgrastim	Filgrastim	Authorised	Yes
Omnitrope	somatropin	Somatropin	Authorised	Yes
Ovaleap	follitropin alfa	follitropin alfa	Authorised	Yes
Ratiograstim	filgrastim	Filgrastim	Authorised	Yes
Remsima	infliximab	Infliximab	Authorised	Yes
Retacrit	epoetin zeta	epoetin zeta	Authorised	Yes
Silapo	epoetin zeta	epoetin zeta	Authorised	Yes
Solymbic	adalimumab	Adalimumab	Authorised	Yes
Terrosa	teriparatide	Teriparatide	Authorised	Yes
Tevagrastim	filgrastim enoxaparin	Filgrastim enoxaparin	Authorised	Yes
Thorinane	sodium	sodium	Authorised	Yes
Truxima	rituximab	Rituximab	Authorised	Yes
Zarzio	filgrastim	Filgrastim	Authorised	Yes

#### ANNEX II World Health Organization, World Health Assembly, Document A69/43, 1 April 2016: "Progress reports", Report by the Secretariat

#### H. ACCESS TO BIOTHERAPEUTIC PRODUCTS, INCLUDING SIMILAR BIOTHERAPEUTIC PRODUCTS,<sup>54</sup> AND ENSURING THEIR QUALITY, SAFETY AND EFFICACY (Resolution WHA67.21)

60. Pursuant to resolution WHA67.21 (2014), the Secretariat supported Member States in strengthening their capacity in the health regulation of biotherapeutic products, including similar biotherapeutic products. Ever more countries are building the necessary scientific expertise to facilitate the development of solid, science-based regulatory frameworks that promote access to quality, affordable, safe and efficacious biotherapeutic products, taking note of relevant WHO guidelines, which may be adapted to national contexts and capacities.

61. The 16th International Conference of Drug Regulatory Authorities gathered government officials and drug regulatory authorities in Rio de Janeiro in August 2014 to discuss global issues and ways to enhance collaboration among regulatory authorities regarding the quality, safety and efficacy of medicines. Experts from drug regulatory authorities, academia, international and nongovernmental organizations and the pharmaceutical industry participated in a pre-conference meeting on the theme "Ensuring Quality and Safety of Biosimilars for Patients Worldwide". The meetings encouraged and promoted cooperation and information exchange among Member States in this area and issued recommendations to Member States and WHO on the regulation of biotherapeutics and its impact on access to affordable, safe and efficacious biotherapeutics.<sup>55</sup>

62. WHO held an informal consultation with regulators, manufacturers and other experts in April 2015 to review draft WHO guidelines on the

<sup>&</sup>lt;sup>54</sup> Acknowledging that national authorities may use different terminologies when referring to similar biotherapeutic products.

<sup>55</sup> See

http://www.who.int/medicines/areas/quality\_safety/regulation\_legislation/icdra/16\_ICDR A\_Recommendations2014.pdf?ua=1, accessed 25 February 2016.

regulatory assessment of approved biotherapeutics. Following this, the WHO Expert Committee on Biological Standardization was able to finalize and adopt new WHO guidelines on regulatory assessment of approved rDNA-derived biotherapeutics. Addendum to: WHO TRS 987, Annex 4<sup>56</sup> in October 2015. Information on this work will be submitted to the Executive Board at its session in January 2017 as part of the reports of advisory bodies.

63. WHO held an informal consultation in April 2015 on the regulatory evaluation of monoclonal antibodies developed as similar biotherapeutic products. It was agreed to develop proposed WHO guidelines on the subject for submission to the 2016 Expert Committee on Biological Standardization. The public consultation phase for the document will begin in early 2016 with its posting to the WHO website<sup>57</sup> for comments, followed by a technical meeting hosted by the National Institutes for Food and Drug Control of China, a WHO Collaborating Centre, in April 2016.

64. The 2014 International Conference of Drug Regulatory Authorities meeting requested that WHO organize a workshop on implementing the 2009 WHO guidelines on evaluation of similar biotherapeutic products in the African Region, which it did in Accra in collaboration with the Food and Drug Authority of Ghana, in September 2015. The 40 experts participating, including 27 regulators from 16 countries in the African Region, recognized the WHO guidelines as a standard providing science-based principles in establishing national requirements for such products and requested strong, consistent support from WHO for their implementation.

65. WHO, through the Expert Committee on Biological Standardization, establishes international biological reference preparations, and convened an informal consultation in 2015 on reference preparations for biotherapeutic products. WHO reference preparations are used as benchmarks for biological activity, method development and system suitability assessment of biotherapeutic products, and, when linked with

<sup>&</sup>lt;sup>56</sup> See

http://www.who.int/biologicals/RA\_for\_BTP\_for\_WHO\_web\_editor\_2\_Nov\_2015(3).pd f?ua=1, accessed 29 February 2016.

<sup>&</sup>lt;sup>57</sup> See http://www.who.int/biologicals, accessed 29 February 2016.

a specific and well-validated national, pharmacopoeia or manufacturer's reference standard, facilitate the assessment of the potency of multisource products, support product surveillance, enable product lifecycle management and support the development of novel methods. The Expert Committee recommended that WHO enhance communication on the appropriate use of such standards and advocate for the continued provision by manufacturers of source materials as a public good for the development of WHO standards as public reference materials.

66. The International Nonproprietary Names system administered by WHO provides pharmaceutical substances a unique and universally available designated name for the clear identification, safe prescription and dispensing of medicines, and for communication and exchange of information among health professionals and scientists worldwide. The cumulative list contains approximately 10 000 names. Geneva hosted four consultations on International Nonproprietary Names during 2014 and 2015, where 552 name requests were discussed and 358 new proposed names published, 60 per cent of which were chemicals and 40 per cent biologicals, up from only 5 per cent in 2000. The proportion of International Nonproprietary Names assigned to biologicals has increased from 5 per cent to 40 per cent since 2000.

67. Following requests from some drug regulatory authorities, the International Nonproprietary Names Expert Group considered how WHO might develop a system for assigning biological qualifiers. Following discussions among interested parties, including through a web consultation, the Expert Group at the 61st Consultation on International Nonproprietary Names (Geneva, 13–16 October 2015) recommended a voluntary scheme whereby application for a biological qualifier could be made to the International Nonproprietary Names Secretariat. The biological qualifier code would not be a constituent part of the International Nonproprietary Names, but an additional and independent element used in conjunction with it. The Secretariat subsequently initiated an impact assessment study, to report to the International Nonproprietary Names Expert Group in 2016, on whether introducing such biological qualifiers would influence access or affect other aspects of public health.

68. WHO collaborated with the International Pharmaceutical Regulators Forum in 2015 and agreed on three deliverables for joint work in 2016: information regarding the public assessment of biotherapeutics to ensure the consistency and transparency of the review process; a reflection paper on the extrapolation of biosimilar indications; and a training manual on the analytical comparability of monoclonal antibodies developed as similar biotherapeutic products.

# CHAPTER 3 ACCESS TO HEPATITIS C TREATMENT: A GLOBAL PROBLEM

Germán Velásquez

"Viral hepatitis is an international public health challenge, comparable to other major communicable diseases, including HIV, tuberculosis and malaria. Despite the significant burden it places on communities across all global regions, hepatitis has been largely ignored as a health and development priority until recently."<sup>1</sup>

# I. GENERAL CONTEXT AND BACKGROUND OF THE DEBATE ON ACCESS TO MEDICINES

The problem of access to medicines until 2014 was concentrated in developing countries where one third of the world's population had no access to medicines, while industrial countries, thanks to public (Europe) and private (the USA) insurances managed to pay the cost of medicines. Currently the situation in developing countries remains the same but the great novelty, unprecedented, is that the industrialized countries are beginning to have difficulties in ensuring the supply of certain medicines to their citizens.

The debate and international negotiations on access to medicines began in 1995 with the creation of the World Trade Organization (WTO), at the end of the Uruguay Round, and the generalization of the

<sup>&</sup>lt;sup>1</sup> WHO, Global Health Sector Strategy on Viral Hepatitis 2016-2021: Towards ending viral hepatitis, June 2016. Available from: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf.

mandatory use of patents for pharmacological products for all WTO member countries (currently totalling 162).

During the 20 year period from 1996 to 2016, several important moments marked the progress of the debate:

- 1995 Creation of WTO and with it the mandatory adoption of the TRIPS Agreement.
- 1996 World Health Assembly Resolution 49.14 on "Revised Medicine Strategy".
- 1997 "The WHO Red Book" on Globalization and access to medicines.
- 2001 (April) the South-African case in which 39 pharmaceutical companies lost a suit that sought to denounce the medicine law developed by the Mandela government. (June) The African Group of the WTO requests a debate on access to medicines. (Nov.) The Doha declaration on Public Health and Intellectual Property.
- 2002 British Government Report on Intellectual Property and Development.
- 2006 WHO report on Intellectual Property and Public Health, known most widely by its English acronym CIPIH.
- 2008 Global Strategy on Medicines and Intellectual Property negotiated and approved by the WHO Member States.
- 2012 "CEWG", a WHO report, recommends an international treaty on R&D.
- 2013 (May) WHO demonstration projects: a distracting exercise?
- 2016 High-level Panel of the Secretary-General of the United Nations on Access to Medicines.

### I.1 Problems of the R&D Model

Let us recall that the current R&D model<sup>2</sup> for pharmaceutical products is based on the following scheme:

<sup>&</sup>lt;sup>2</sup> Model that must obligatorily follow all members of the World Trade Organization nowadays.

# **Research** (*private or public*) – **patent** – **monopoly** – **high price** – **restricted access**



This model contains several contradictions and problems that in the long run lead to a disarticulation between innovation and access. We will briefly refer here to three problems or faults of the current R&D model:

- Lack of transparency of R&D costs.
- Pharmacological innovation has effectively diminished in the last years.
- High prices restricting access.

#### I.1.1 Lack of transparency of R&D costs

The cost, reported in 2014 by a study of Boston Tufts Center, for the development of a new molecule was of **2.5 Billion US\$.**<sup>3</sup> This is the figure currently used by the so-called originator pharmaceutical industry (i.e. "big Pharma"). However, in a study carried out by the London School of Economics in 2011,<sup>4</sup> the authors claim that the average cost to develop a new product is only 43.4 million US\$.

<sup>&</sup>lt;sup>3</sup> Tufts Center for the Study of Drug Development, Briefing "Cost of developing a new drug" Boston, November 2014. Available from:

 $https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5ac66afc6d2a732e8\\3aae6bf/1522952963800/Tufts_CSDD_briefing_on_RD_cost_study_-$ 

\_Nov\_18%2C\_2014..pdf.

<sup>&</sup>lt;sup>4</sup> Donald W. Light and Rebecca Warburton "Demythologizing the high costs of pharmaceutical research",

The non-profit foundation DNDi (Drugs for Neglected Diseases initiative) reported in 2013 that the average cost for research and development (R&D) of the new chemical entities that it had developed in its last 10 years of existence was between 100 and 150 million Euros.5

As long as there is no clarity on the real cost of R&D, the problem of prices-and therefore of access to medicines-will continue to go unsolved. The massive difference between the estimates of 150 million US\$ or 2.5 Billion US\$ per molecule is significant, as the resulting price of the medicine would be significantly different.

#### I.1.2 Pharmaceutical innovation has significantly diminished in recent years

According to the data published by the French review Prescrire in recent years,<sup>6</sup> we find that the number of medicines that constant "an important therapeutic advance" introduced into the French market in the last 10 years are not more than 14 per year; furthermore, innovation appears to be diminishing, as the maximum number of 14 is significantly higher than the average number of yearly therapeutic advances over the past decade.

	2007:	14 products
-	2007.	14 product

- 6 products 2008:
- 3 products **2009**:
- 3 products •  $2010^{\circ}$
- **2011**: 3 products
- $2012^{\circ}$ 3 products
- 2013: 6 products
- 5 products •  $2014^{\cdot}$
- 2015: 5 products
- 5 products
- 2016:

http://www.pharmamyths.net/files/Biosocieties 2011 Myths of High Drug Research Costs.pdf.

<sup>&</sup>lt;sup>5</sup> DNDi, "Research & Development for Diseases of the Poor: A 10-Year Analysis of Impact of the DNDi Model", Geneva 2013.

<sup>&</sup>lt;sup>6</sup> Rev. Prescrire, "L'année 2016 du médicament: un système qui favorise l'imitation plutôt que la recherche de réels progrès." Paris, Page 136 Tome 37 No. 400.

#### I.1.3 High prices restricting access

In 2014, the American firm Gilead Sciences introduced the hepatitis C drug Sofosbuvir (brand name Sovaldi) at the eye-watering price in the USA of 84,000 US\$, 57,000 Euros, for a 12-week treatment.

A recent study in the United States of America indicates that out of the 71 anti-cancer medicines registered between 2002 and 2014 by the FDA, many of them cost more than 100 US\$ per treatment.<sup>7</sup>

Lack of transparency in the costs of R&D, a diminishing rate of pharmaceutical innovation in recent years and high prices all contribute to restrict access in both developing countries and developed ones. Collectively, these dynamics demonstrate a structural problem of the current R&D model for pharmaceutical products. Several documents discussed in the frame of WHO in the last 10 years, as well as a large number of studies and articles produced by scholars point to the existence of an incoherence in the R&D model.

At the end of 2015, the Secretary General of the United Nations issued a call for a High-Level Panel on Access to Medicines; the panel would be constituted by an array of international experts of demonstrated competence. The terms of reference set for the expert group called for a study on "The incoherence between the rights of inventors, international human rights legislation, trade rules and public health". In less than three months, more than 180 proposals were submitted by a wide range of stakeholders: governments, institutions, UN agencies, NGOs, universities, pharmaceutical industries and individuals.

The received proposals can be summarized into five categories:

- 1. Comments on the current R&D model. (40)
- 2. Proposals to strengthen Health Systems. (27)
- 3. Proposals to progressively modify the R&D model. (46)
- 4. Contributions proposing a significant reform of the model. (46)
- 5. Other.

<sup>&</sup>lt;sup>7</sup> Jama: http://jamanetwork.com/journals/jamaoncology/article-abstract/2497879.

Government proposals included submissions by Holland, Lesotho, Japan and Jordan.

Among the main points of the report by the United Nations Secretary-General (issued in September 2016), the following recommendations may be highlighted:

- Use the available room provided by article 27 of the TRIPS Agreement to apply rigorous definitions of invention and patentability.
- Adopt and implement legislations to support Compulsory Licenses (CL).
- Review the decision on paragraph 6 of the Doha Declaration
- Refrain (governments and private sector) from any threats that may hinder the right to use TRIPS flexibilities
- Initiate a process (conducted by the United Nations Secretary-General) to encourage governments to negotiate (...) a compulsory Convention for R&D.

### I.2 What Has Changed in the Last Few Years?

The main new development is that the problem has now become global, involving both developing and developed countries. The totality of WHO documents and resolutions had previously referred to "diseases disproportionately affecting developing countries". The distinction between communicable and non-communicable diseases, implied an understanding that only communicable diseases were affecting developing countries. However, nowadays, non-communicable diseases also represent a substantial source of morbidity and mortality for developing countries.

For the first time in history, there are medicines that industrialized countries cannot afford to pay; this is demonstrated by, to cite just two examples, their adoption of policies that effectively ration newer medicines against Hepatitis C and medicines against cancer.

The Human-Rights Commission of the United Nations tackles the issue from a human rights approach rather than a trade approach. In their 2015 deliberations, the Human-Rights Commission considered that access barriers to these medicines could be considered a human rights violation.  $^{\rm 8}$ 

# I.3 A Paradigm Shift in the Debate on Access to Medicines: 2014-2016

Three elements mark a paradigm shift in the debate on access to medicines: First: a medicine that heals... the efficacy of Sofosbuvir (and other direct-acting antivirals, known today under their English acronym. DAAs), stands in contrast to the vast majority of medicines that entered the market over the last 20 years. Second: the inaccessible **price** both for Northern and Southern countries has created a global pharmaceutical industries problem. Third important element: dissociate cost and price arguing that the price should be related to the paying capabilities of the country<sup>9</sup> or to the "value" of the medicine as compared to the potential cost of treating sequelae such as a liver transplant operations or liver cancer treatments, as was recently the case with the medicine against Hepatitis C: Sofosbuvir.

The pharmaceutical industry business model has changed. Previously, high R&D costs were being claimed (sometimes quite artificially) to establish high prices and increase profits. Nowadays the pharmaceutical industry, and this is precisely the case of Gilead, are, above all, financial industries whose first goal is to remunerate their shareholders and have managed what scholars and civil society organizations had been claiming for years, to de-link R&D costs from the final price of the product. However, the industry has attempted to coopt this term by twisting the meaning. As Ruth Dreifuss expressed in the Graduate Institute of Geneva on the 23rd of February, 2017, the industry's twist on the concept suggests a "malefic de-linkage" through which cost and final price are unrelated and no attempt is made to reconcile the two. Instead, the price is calculated by the estimated "value" as argued by the producer or by the buyer's purchasing power. As evidence of the latter, Gilead established a price of 84,000 US\$ in

<sup>&</sup>lt;sup>8</sup> HRC Resolution on "Access to medicines in the context of the right of every one to the enjoyment of the highest attainable standard of physical and mental health", Geneva, 2016.

<sup>&</sup>lt;sup>9</sup> Cf. Pratap Chatterjee, "Gilead Sciences Under Investigation for Over Charging for Hepatitis C Pil, http://www.corpwatch.org/article.php?id=15964.

the USA for a 12 week treatment, while charging 900 US\$ in Egypt for the same medicines.

### II. THE HEPATITIS C VIRUS: FIGURES AND DATA<sup>10,11</sup>

- Hepatitis C is a liver disease caused by the virus of the same name: the virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness that can cause death.
- According to the World Health Organization (WHO), it is estimated that globally approximately 130 million to 150 million<sup>12</sup> people live with a chronic hepatitis C virus (HCV) infection and it is estimated that 700,000 people die each year from hepatitis C-related liver diseases.
- The hepatitis C virus is a blood-borne virus and the most common modes of infection are through unsafe injection practices, inadequate sterilization of medical equipment, and the transfusion of unscreened blood and blood products.
- HCV can also be transmitted sexually and can be passed from an infected mother to her baby; however these modes of transmission are much less common.
- Hepatitis C is not spread through breast milk, food, water or by casual contact such as hugging, kissing and sharing food or drinks with an infected person.
- New types of treatment and oral therapeutic regimens named Direct Action Antivirals (DAAs) may heal more than 90 per cent of Hepatitis C infection cases.
- Currently there is no vaccine for hepatitis C.
- Hepatitis C virus (HCV) causes both acute and chronic infection. Acute HCV infection is usually asymptomatic, and is only very rarely associated with life-threatening disease. About 15–45 per cent of infected persons spontaneously clear the virus within 6 months of infection without any treatment.

<sup>&</sup>lt;sup>10</sup> WHO Facts sheet: http://www.who.int/mediacentre/factsheets/fs164/en/.

<sup>&</sup>lt;sup>11</sup> Ref. International Association of providers of Aids Care: http://www.aidsinfonet.org/fact\_sheets/view/674.

<sup>&</sup>lt;sup>12</sup> This data has been revised by WHO and the estimation is now 70 million.

- The remaining 55–85 per cent of persons will develop chronic HCV infection, and in these cases the risk of cirrhosis of the liver is between 15–30 per cent within 20 years. According to WHO, an estimated 2.9 millions of people living with HIV are infected with hepatitis C virus.<sup>13</sup>
- There are numerous HCV strains (or genotypes), variously distributed depending on the region.

### II.1 What are Hepatitis C Genotypes?

Genotypes of the hepatitis C virus are different strains of the virus. Each strain differs from each other and can be distinguished by laboratory tests. Different genotypes are more common in some parts of the world.

Globally, there are 6 HCV genotypes, although some others are being studied. They are identified by a number, for example genotypes 1 to 6. There are also subtypes, identified by a letter (for example, genotype 1a).

### II.2 Why do HCV Genotypes Matter?

The different HCV genotypes generally act similarly in how they infect people and cause disease; they are important for vaccine development, for the progression of hepatic fibrosis and to evaluate the response to antiviral treatments.<sup>14</sup>

### II.3 Where are the HCV Genotypes Found?

Genotypes 1, 2 and 3 are present all over the world. Subtypes 1a and 1b are the most common ones, representing approximately between 60 per cent and 70 per cent of global infections. Genotype 1a can be found primarily in North and South America, Europe and Australia, while type 1b is found in North America, Europe and parts of Asia.

<sup>&</sup>lt;sup>13</sup> WHO, Global Health Sector strategy on viral Hepatitis 2016-2021: Towards ending viral hepatitis. http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf, p. 11.

<sup>&</sup>lt;sup>14</sup> Lee CM, Hung CH, Lu SN, Changchien CS. Chang Gung Med J. "Hepatitis C virus genotypes: clinical relevance and therapeutic implications. Review" 2008 Jan-Feb, 31(1):16-25.

Genotype 2 occurs in most developed countries but is much less common than genotype 1. Genotype 3 is common in Southeast Asia but can also be found in other countries.

Genotype 4 can be found primarily in the Middle East, Egypt and Central Africa. Genotype 5 is found in South Africa and in local groups around the world, which, in general, results in a small number of infected individuals.

#### III. ACCESS TO HEPATITIS C TREATMENT

#### **III.1** The Direct-Acting Antiviral Treatments

Until the end of 2013, the standard treatment for Hepatitis C consisted of pegylated interferon injections over 24 to 48 weeks and complemented with ribavirin tablets twice a day. This treatment was costly, toxic, complicated to administer and with healing rates of less than 50 per cent.<sup>15</sup>

In late 2013, a new Hepatitis C treatment called direct-acting antivirals (or DAAs) was introduced in the market. In eight to twelve weeks of treatment these medicines could heal more than 90 per cent of persons with a chronic HCV infection.

The new DAAs treatments were introduced by the firms Gilead Sciences and Bristol Meyer Squib (BMS) in 2014. Gilead has patented or applied for patents for three DAA compounds: sofosbuvir, ledipasvir and velpatasvir.<sup>16</sup> BMS has patented or applied for a patent on daclatasvir in several countries.<sup>17</sup> As treatment in many cases must include both sofosbuvir and daclatasvir it means that there is a double barrier, two or more patents belonging to different firms. Other transnational firms such as AbbVie and Janssen have also put DAAs on

<sup>&</sup>lt;sup>15</sup> Manns MP, Wedemeyer H, Cornberg M. "Treating viral hepatitis C: efficacy, side effects, and complications". Gut 2006;55(9):1350-9.

<sup>&</sup>lt;sup>16</sup> Gilead Sciences, 2016 http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-irhome.

<sup>&</sup>lt;sup>17</sup> MSF Briefing Document, "Strategies to Secure Access to Generic Hepatitis C Medicines", May 2015. Available from: https://msfaccess.org/strategies-secure-access-generic-hepatitis-c-medicines.

the market, while additional products are in the "pipeline" of these and other firms. However, for the foreseeable future, sofosbuvir will likely remain the dominant DAA.

The first DAA launched by the North American firm Gilead Sciences, sofosbuvir, was put on the market at the exorbitant price of 84,000 US dollars for a twelve-week treatment.

According to WHO,<sup>18</sup> in 2015 (two years after the first DAAs came out), of the estimated 130 to 150 million people living with HCV only 275,000 persons received the new DAAs treatment, from which 170,000 were patients in Egypt, which is the country with the largest prevalence of Hepatitis C in the world. This was possible, as we shall see later, thanks to the huge price drop of the 12-week treatment from 900 US\$ to 153 US\$, instead of the 84,000 US\$ that Gilead originally demanded.

#### **III.2** Essential Medicines that Cure

As reported by Professor Philippe Even, there have only been a limited number of curative medicines launched by the pharmaceutical industry in the last 20 years.<sup>19</sup> The new orally-administered DAA medicines are effective and until now appear to be well tolerated. Cure rates, defined formally by spontaneous viral clearance or SVR figures after a 12-week treatment are greater than 90 per cent regardless of the patient's HIV status or prior history of HCV treatment.<sup>20</sup>

In April 2015, several DAAs were included in the WHO List of Essential Medicines, confirming once more that price is not an obstacle for a medicine to be considered an essential one. At the World Health Assembly in May 2016, WHO Member countries approved the Global Health Strategy for Viral Hepatitis for the period 2016-2021.<sup>21</sup> This strategy aims to eliminate Hepatitis B and C as a public health menace by 2030. Elimination is defined as a 90 per cent reduction in incidence

<sup>&</sup>lt;sup>18</sup> WHO Fact Sheet http://www.who.int/mediacentre/factsheets/fs164/en/, 2016 http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1.

<sup>&</sup>lt;sup>19</sup> Even Ph. "Le guide de médicaments utiles, inutiles ou dangereux" in *Le Nouvel Observateur*, September 2012, p. 81.

<sup>&</sup>lt;sup>20</sup> Pawlotsky JM. "New hepatitis C therapies: the toolbox, strategies, and challenges", *Gastroenterology* 2014:146(5):1176-92.

<sup>&</sup>lt;sup>21</sup> WHO/HIV/2016.06.

and a 65 per cent reduction in mortality. Achieving these goals implies extending treatment application to 80 per cent of the people living with chronic HBV and HCV diseases.

# III.3 Sofosbuvir: Between Financial Engineering and Public Health

According to the quarterly sales reports of Gilead Sciences, historical sales of Sofosbuvir, commercially sold as "Sovaldi & Harvoni", reached 40 billion US\$ by the first three quarters of 2016. Furthermore, Gilead's 2015 profits reached 18 billion US\$, most of which may be attributed to the company's Hepatitis C medicines. However, despite these massive profits, Gilead did not originally develop Sofosbuvir, as the product was developed by a small American company named "Pharmasset" that Gilead Sciences, realizing the potential of Sofosbuvir, acquired for 11 billion dollars in 2011.<sup>22</sup> This means that Gilead Sciences, in its first year of marketing sofosbuvir, fully recovered its investment. Such disproportionate returns—Gilead being but one example of many such cases—questions the justification of the 20 years of patent exclusivity provided by the WTO TRIPS Agreement.

As previously mentioned, in 2014 the American firm Gilead Sciences launched on the market—at a price of 84,000 US\$ for a 12-week treatment—the Hepatitis C medicine known as Sofosbuvir. A group of British academics<sup>23</sup> estimated that production costs for a twelve-week treatment could reach—in a figure that includes a profit margin of 50 per cent—a price of 62 US\$. Nevertheless, Gilead Sciences has managed to negotiate prices with several governments that reveal large price differences between countries and, above all, prices that have nothing to do with production costs. 50,426 Euros in Germany, 41,680 Euros in France,<sup>24</sup> 13,000 Euros in Spain, 6,000 Euros in Brazil, 3,465 Euros in Australia.<sup>25</sup>

<sup>&</sup>lt;sup>22</sup>FOSTER CITY, Calif. & PRINCETON, N.J., "Gilead Sciences to Acquire Pharmasset, Inc. for \$11 Billion", http://investors.gilead.com/phoenix.zhtml?c=69964&p=irolnewsArticle&ID=1632335.

<sup>&</sup>lt;sup>23</sup> Gotham D, Barber M, Fortunak J, Pozniak A, Hill A. Abstract number A-792-0516-01639, presented at AIDS2016, Durban.

<sup>&</sup>lt;sup>24</sup> On 17 March 2017, the French government announced a new reduction to 28,700 Euro for a 12-week treatment; a price which still remains larger than double of what Spain pays. "Soins: le prix des médicaments contre l'hépatite C va baisser".

Why 41,000 Euros in France and 13,000 Euros in Spain? Everything seems to depend on the negotiation ability of each country. Furthermore, Gilead's new business model reveals a philosophy of maximizing profits and ignoring any relationship between a medicine's profits and R&D costs. In short, Gilead goes in search of the highest price governments are willing to pay (even if governments are forced to pay prices that will make universal access impossible, as is the case of France or Spain).

To complete this almost cynical scenario in which a private company seems to be playing with society and governments, on 13 July 2016 the Washington Post published the news that Gilead, using Ireland as a tax haven, has evaded approximately 10 billion dollars of tax payments to the United States Government.<sup>26</sup>

It is worth remembering that Gilead was the company that sold "Tamiflu" for the H1N1 pandemic, giving exclusive exploitation to the Swiss company Roche. Many countries wasted large sums on precautionary procurement of a medicine that, in the end, scientists ultimately judged to be ineffective. Never in the history of modern medicine had "safety stocks" of such dimensions been made for a medicine whose efficacy was not proven.

#### **III.4 HCV Diagnosis**

HCV infection is diagnosed in two steps:<sup>27</sup>

- Detection of anti-HCV antibodies through a serological test revealing the infection.
- In case anti-HCV antibodies are positive, to confirm chronic infection a test detecting the ribonucleic acid (RNA) of the virus is required. As already mentioned about 15 per cent to 45 per cent of infected persons by HCV spontaneously clear the infection by a strong immune response, with no need for treatment.

http://www.leparisien.fr/laparisienne/sante/soins-le-prix-des-medicaments-contre-l-hepatite-c-va-baisser-31-03-2017-6812619.php.

<sup>&</sup>lt;sup>25</sup> Price for a 12-week treatment.

<sup>&</sup>lt;sup>26</sup> See http://www.corpwatch.org/article.php/article.php?id=16083.

<sup>&</sup>lt;sup>27</sup> WHO, Fact sheet, Hepatitis C, 2016.

http://www.who.int/mediacentre/factsheets/fs164/en/.

Once chronic hepatitis C has been diagnosed, the degree of liver damage (fibrosis or cirrhosis) should be assessed. This can be done by liver biopsy or other different non-invasive tests.

Furthermore, a laboratory test to identify the virus genotype should be carried out. Depending on the HCV genotype, treatment should differ. On the other hand, one single person may be infected by more than one genotype.

It is clear that the main barrier to access to treatment for the HCV is currently the price of treatment. Nevertheless, considering that we are dealing with an asymptomatic disease at the beginning, it is important to promote diagnosis, even though it has a certain complexity compared to other diseases with clearer symptoms. We must therefore become conscious of the problem, raise awareness, diagnose, and in many cases, refer the patient to other levels of care, evaluate the stage of the disease, complete the treatment and monitor the patient's progress. As WHO says, we are dealing with a cascade of steps:<sup>28</sup>



"Data is insufficient. Many countries do not understand correctly the true dimension and impact of the hepatitis epidemics from a Public Health perspective. Frequently there is no data at national or subnational levels or it is insufficient, and surveillance programs are poor, making difficult any planning of specific measures and the establishment of priorities in the assignation of resources."<sup>29</sup>

<sup>&</sup>lt;sup>28</sup> WHO, "Global report on access to hepatitis C treatment. Focus on overcoming barriers, Geneva, October 2016, available from http://www.who.int/hepatitis/publications/hep-caccess-report/en/, p. 9.

<sup>&</sup>lt;sup>29</sup> WHO, Global health sector strategy on viral hepatitis 2016–2021: Towards ending viral hepatitis, p. 14.

Early diagnosis of viral hepatitis is fundamental for effective treatment and care. According to WHO,<sup>30</sup> at a global level, less than 5 per cent of persons suffering chronic viral hepatitis know that they are infected. There is a lack of awareness both among the authorities and the general population.

HCV diagnosis is a challenge insofar as it is a process involving two stages. In countries with low resources, access to the test detecting the ribonucleic acid (RNA) of the virus is complex because there are few laboratories equipped to run the test, most of those laboratories are in big cities, and often patients must be referred to a different level of care (which are often in big cities too).<sup>31</sup>

Figures are overwhelming: 95 per cent of people infected with Hepatitis B or C virus are not aware of it. One of the reasons being that it is possible to live for many years without any symptoms, and when infected persons find out they are suffering hepatitis it is often too late for treatment to be fully effective. By then, hepatic damage may have developed into cirrhosis or liver cancer.

It is true that diagnosis of this "silent disease" is an added problem to that of the high cost of treatment, but there are already a good number of lessons learned from various countries that may, if adopted, help accelerate diagnosis and overcome this obstacle.

In a contest organized by WHO and MSF to promote and simplify diagnoses, initiatives have been rather diverse. "Among the initiatives, as well as national testing campaigns, approaches include testing in prisons, testing in the workplace and hospital emergency rooms, integrated HIV-hepatitis testing, as well as the use of Internet, social media, and electronic medical records to flag higher risk patients for testing in primary care."<sup>32</sup>

<sup>&</sup>lt;sup>30</sup> WHO, Global health sector strategy on viral hepatitis 2016–2021:Towards ending viral hepatitis. http://apps.who.int/iris/bitstream/10665/246178/1/WHO-HIV-2016.05-eng.pdf, p. 36.

<sup>&</sup>lt;sup>31</sup> WHO, "Global report on access to hepatitis C treatment: Focus on overcoming barriers", Geneva, October 2016, p. 10.

<sup>&</sup>lt;sup>32</sup> WHO, http://www.who.int/features/2016/access-hepatitis-testing/en/.
Experiences range from the realization of tests in Australian prisons to an internet-based risk self-assessment tool in the Netherlands, from community testing camps for drug users in India to testing in primary care facilities in Mongolia. In the Netherlands, thousands of red covers for bicycle seats were distributed with inscriptions targeting increased awareness of the need for hepatitis C testing.

The contest organized by WHO and MSF served to demonstrate a wide range of possibilities and showed that if we can develop initiatives for HCV diagnosis that suit different settings and cultures, then we will be able to increase effective hepatitis diagnosis in a greater number of countries and communities.<sup>33</sup>

### III.5 World Health Organization Standardized Treatment Guidelines

Recognizing the serious public health problem of HCV and the great promise represented by the new DAAs treatments, WHO developed in 2014<sup>34</sup> the first guidelines of standardized treatments. These guidelines were already reviewed in 2016 due to the fast evolution of treatments for the different genotypes. A new review is scheduled for 2017.<sup>35</sup>

### **III.6** The Sofosbuvir Patents

It is important to keep in mind that when talking of patents for pharmaceutical products we are talking of patents of diverse types, as for example:<sup>36</sup>

**Product patents**: claiming a chemic molecule/active pharmaceutical ingredient.

<sup>&</sup>lt;sup>33</sup> Ibid.

<sup>&</sup>lt;sup>34</sup> WHO, Guidelines for the screening, care and treatment of persons with hepatitis C infection. http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/.

<sup>&</sup>lt;sup>35</sup> WHO, "Global report on access to hepatitis C treatment. Focus on overcoming barriers, Geneva, October 2016, p. 22.

<sup>&</sup>lt;sup>36</sup> Carlos Correa, "Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective". WHO, ICTSD, PNUD, UNCTACD, Geneva, 2008.

**Process patents**: protecting the manufacture of a certain product. There are also many other types of patents, unaccepted by many countries as Argentina, Brazil or India, but among which we find hundreds and thousands of the current patents of pharmacological products, such as:

**Formulation patents**: of the dosage form, as, for example, on tablets of delayed release of the active ingredient.

**Combination patents**: claiming the combination of two or more existing active ingredients.

Patents on salts, ethers and esters: solid forms obtained by routine methods.

**Patents of polymorphic forms**: a polymorph is an intrinsic property of chemical products; polymorphs are not invented; instead they are only discovered and therefore should not be patented.

**Patents including a "Markush" claim**: very broad claims covering chemical structures that may include a family of thousands or millions of compounds.

Selection patents: claiming only a single element or segment of a Markush patent, for example, which was already included in the patented item.

**Patents on analogy processes**: covering an obvious method to produce a new compound.

**Patents on active metabolites and prodrugs**: metabolites are produced by the organism and cannot be considered an invented product. Prodrugs are inactive compounds that transform inside the organism into the therapeutically active principle, with which it shares the same active part of a molecule.

**Patents on treatment methods**: including prevention, diagnosis or prophylaxis methods; they do not protect a product itself but the way in

which the product is used and, therefore, may not be patented since they lack a key patenting requirements: namely industrial application.

**Patents on second uses**: second uses or second indications of a product, over which there are already a great number of patents, should not be patentable as this is not a case of invention but of a discovery; which in most cases, happens through medical practice and not in research laboratories of the pharmaceutical industries.

In the particular case of Sofosbuvir, a study conducted by WHO<sup>37</sup> revealed that this product is covered by 21 different types of patents: 2 Markush type patents that could give rise to dozens more, 4 process patents, 9 patents on salts and polymorphs, one patent on the combination of two products, and 3 patents on method of usage: "substance for the HCV treatment."

Several of these Sofosbuvir patents are now the subject of litigation or oppositions in different countries, showing the fragility and lack of evidence that it should be considered a true genuine innovation (Cf. 3.7.).

### **III.7** Oppositions to the Sofosbuvir Patent of Gilead

The Non-Governmental Organizations I-MAK (Initiative for Medicines, Access & Knowledge) and the Delhi Network of Positive People (DNP+) presented an opposition to Gilead's Sofosbuvir patent application in India. The lawyers of these two organizations claim that the medicine represents "old science" and therefore does not meet the patentability standards of India.<sup>38</sup>

Sofosbuvir patents have been rejected in Egypt, China and Ukraine and have met oppositions in Argentina, Brazil, Russia, Thailand and the European Union.<sup>39</sup>

<sup>&</sup>lt;sup>37</sup> WHO, Patent situation of key products for treatment of hepatitis C: Sofosbuvir, Geneva, March 2015.

<sup>&</sup>lt;sup>38</sup> MSF "Access: Patent challenge hearing on Gilead hepatitis C drug sofosbuvir starts in India", http://www.msf.org/en/article/access-patent-challenge-hearing-gilead-hepatitis-c-drug-sofosbuvir-starts-india.

<sup>&</sup>lt;sup>39</sup> Ibid.

Two of the challenged cases in India make reference to the crystalline form of sofosbuvir and daclatasvir that, in accordance to the Indian Patent Law, are not patentable unless evidencing a significant increase in therapeutic effect. There is a third opposition against velpatasvir (which combined with sofosbuvir is sold by Gilead under the brand name of "Epclusa") because it is considered as an obvious modification of the structure of a previous medicine for Hepatitis C "ledipasvir" (which combined with sofosbuvir is sold by Gilead under the brand name of Harvoni).<sup>40</sup>

A copy of the patent oppositions can be found with the following links:

https://www.patentoppositions.org/en/drugs/daclatasvir https://www.patentoppositions.org/en/drugs/sofosbuvir https://www.patentoppositions.org/en/drugs/velpatasvir

### **III.8** Voluntary Licenses Granted by Gilead

"In November 2013 and February 2014, public interest groups and generics companies filed the first patent oppositions against Gilead Sciences' patent applications in India. Within months, Gilead signed voluntary license agreements with eleven Indian generics pharmaceutical companies and API manufacturers for the HCV DAAs sofosbuvir, ledipasvir and velpatasvir".<sup>41</sup>

In 2014, Gilead issued voluntary licenses to 11 Indian manufacturers of medicine generics, giving them the possibility to market the product to a restricted list of 101 countries.<sup>42</sup> The prices of these Indian generic versions represent an important progress. (From September 2016 sofosbuvir "under the Gilead license" costs 750 US dollars and the other two medicines, Harvoni and Epclusa, cost 900 US dollars per

<sup>&</sup>lt;sup>40</sup> MSF, "Flawed patents on hepatitis C drugs latest to be challenged in global push for access" February 2017. https://msfaccess.org/about-us/media-room/pressreleases/flawed-patents-hepatitis-c-drugs-latest-be-challenged-global-push.

<sup>&</sup>lt;sup>41</sup> MSF Access Campaign, "Access to Sofosbuvir, Ledipasvir and Velpatasvir analysis & key recommendations on Gilead voluntary licence, March 2015.

<sup>&</sup>lt;sup>42</sup> MSF Briefing Document, "Strategies to Secure Access to Generic Hepatitis C Medicines", May 2015. Available from: https://msfaccess.org/strategies-secure-access-generic-hepatitis-c-medicines.

treatment,<sup>43</sup> instead of the 84,000 US dollars price in the United States.) However, its access is only allowed to the poorer countries of the restricted list.<sup>44</sup> In the other 94 countries excluded from the Gilead list, treatments are far from being accessible, and such rationing applies to many of the world's richest countries, including ones from Europe and North America.

Negotiations for the introduction of voluntary licenses between the patent holder and another actor in a given country, or operating in that country's market, may contribute to the reduction of prices. The benefits of voluntary licensing agreements depend largely on the conditions of the license itself.

Patent holders may, at their own discretion, issue to the other parties, with exclusive character or not, the rights to produce, import and/or distribute a pharmaceutical product. Depending on the terms of the license, the licensee may act completely or effectively as a representative of the patent holder, or be free to establish the conditions of sale and distribution of the product in a certain market or markets, in exchange for the payment of a royalty. Either of these options, or even intermediate agreements, can lead to a considerable reduction in prices. Nevertheless, the terms of a voluntary license may establish price margins or include clauses to keep prices at a similar price to that offered by the patent holder. At times, export possibilities are limited, or anti-diversion measures are required, as is the case with Gilead and the 11 licenses granted to manufacturers in India. Again, such issues will depend on the conditions of the license agreement, and such contracts are often confidential.

Voluntary licensing agreements, at the discretion of the patent holder, take place in general for strategic commercial reasons (as for example to penetrate a market) rather than as a mechanism to ensure access to the largest number of people.<sup>45</sup>

<sup>&</sup>lt;sup>43</sup>http://www.gilead.com/~/media/files/pdfs/other/chronic%20hepatitis%20c%20medicine s%20pricing%20-%20september%202016.pdf.

<sup>&</sup>lt;sup>44</sup> Access to the generics made under Indian voluntary licenses is restricted only to the poorer countries that comprise the license territory.

<sup>&</sup>lt;sup>45</sup> Velasquez, G., Correa C., Weisman R. "Cost-containment mechanisms for essential medicines, including antiretrovirals, in China" Health Economics and Drugs EDM Series No. 13, WHO/EDM/PAR/2003.6.

MSF expressed worries concerning the voluntary licenses granted by Gilead in India, and these worries can be summarized as follows:<sup>46</sup>

- Gilead licensing obligations and restrictions can undermine access and exclude millions of patients with HCV.
- There are approximately 49 million people living with HCV in developing counties excluded by this license.
- Gilead's license for DAAs lack transparency, and can be translated as an "evergreening" strategy.
- Gilead has provided no information on the type of applications being submitted in the excluded countries. Gilead has applied for secondary patents (crystallization forms, compositions, etc.) that, although weak and easy to reject in principle, will block competition from generic medicines in the countries where they are accepted.
- The definition of patents in voluntary licenses is too broad, (includes patents and patent applications), and refers to both primary and secondary patents as treatment method patents. This fact leads to a certain ambiguity, as for instance whether it would be possible to export or not to a country excluded from the Gilead licenses but issuing a compulsory license.
- Gilead has negotiated its voluntary licenses both for the end product and for the raw material (APIs) only with India but not with China or Brazil for example, and this is problematic in terms of the expansion of a global market of generics.
- Gilead has segmented the APIs market by means of the following strategies: firms licensed by Gilead may only obtain APIs through other licensees from India or from other Gilead suppliers, with its prior approval.
- Gilead does not authorize its licensees to import from potential Chinese manufacturers who would be able to produce much cheaper APIs and other intermediate substances.

# III.9 Anti-diversion Measures

Pharmaceutical companies have imposed what they call anti-diversion measures that both public programmes and private dealers have to

<sup>46</sup> Ibid.

comply with. The argument used to justify these measures is that developing countries have much cheaper products that may be reexported to developed countries. To this end, the industry is making use of a large list of measures, many of which are not ethically justifiable since they violate patient confidentiality.

A simple modification of packaging, or different brand names, or even a change in the colour of capsules or tablets would be enough. Much has been debated on electronic product tracking, a measure that would unnecessarily increase the cost of products, but there are other industry practices that go against patient confidentiality and should be simply rejected.

The measures required in the voluntary licenses granted by Gilead not only violate the rights of patients but also place a burden on health systems and providers of medicines.<sup>47</sup>

According to WHO,<sup>48</sup> reported anti-diversion practices include:

- Distribution of medicines with bar codes including information on the patients;
- Access to medicines being made contingent on the name of the patient and requiring identification;
- Demanding a proof of place of residence and nationality to deliver the medicines;
- Taking photographs of patients when delivering the medicines;
- Incomplete distribution of treatment requiring patients to return and show the first or most recent (empty) bottle;
- Require a negative viral load test if patients have lost the package.

These types of measures, in addition to violating patients' confidentiality rights, hinders the expansion of treatment and penalizes vulnerable populations such as peasants, migrants, prisoners or homeless people.

<sup>&</sup>lt;sup>47</sup> Ibid.

<sup>&</sup>lt;sup>48</sup> WHO, "Global report on access to hepatitis C treatment. Focus on overcoming barriers", Geneva, October 2016, p. 33.

Human rights violations, along with widespread stigma and discrimination, continue to hinder access to health services for populations that may be marginalized and perhaps criminalized and who are at higher risk of hepatitis infection.<sup>49</sup>

### IV. HOW TO OVERCOME THE BARRIERS TO ACCESS USING TRIPS FLEXIBILITIES

The voluntary license granted by Gilead to 11 generic manufacturers of India excludes, besides all developed countries, 41 middle-income countries.

Albania	Costa Rica	Kosovo	Saint Lucia
Argentina	Dominican Republic	Lebanon	Syria
Armenia	Ecuador	Macedonia	Thailand
Azerbaijan	Georgia	Malaysia	Turkey
Belarus	Grenada	Mexico	Ukraine
Belize	Hungary	Moldova	Venezuela
Bosnia and Herzegovina	Iran	Montenegro	West Bank and Gaza
Brazil	Iraq	Panama	Yemen
Bulgaria	Jamaica	Peru	
China	Jordan	Romania	
Colombia	Kazakhstan	Serbia	

# Middle-income countries excluded from the voluntary license of $\operatorname{Gilead}^{50}$

<sup>&</sup>lt;sup>49</sup> WHO, Global Health Sector strategy on viral Hepatitis 2016-2021: Towards ending viral hepatitis. http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06eng.pdf, p. 14.

<sup>&</sup>lt;sup>50</sup> MSF Briefing Paper, "MSF analysis of Gilead Hepatitis C license", March 2015. Available from: https://msfaccess.org/msf-analysis-gilead-hepatitis-c-license.

All countries excluded from the voluntary license of Gilead (or other companies arriving to similar agreements) do have legal options on which to lean to ensure supply of DAAs or any other essential medicine protected by a patent at inaccessible prices. Below we enumerate the different strategies and measures that countries can adopt to ensure universal access to the DAA treatments.

### **IV.1** Information on International Prices

Gilead Sciences has opted for a pricing strategy that reflects the negotiation capabilities of each country. Differences may be significant even between countries of similar economic and social development. 13,000 Euro for a 12-week treatment in Spain against 41,000 Euro for the same treatment in France or 900 dollars in Egypt against the 51,000 US\$ in Argentina.

Care must be taken during negotiation with the originating companies about the conditions eventually included in the contracts, such as renouncing to use some flexibilities of the TRIPS Agreement, or waiving parallel imports, or admitting import restrictions of raw material.

It is also advisable to know the prices of generics in the countries where the DAAs have not being patented, in order to evaluate whether it is needed or not to issue a compulsory license to ensure universal access.

# IV.2 Adoption of Patentability Criteria from a Public Health Perspective<sup>51</sup>

It is important to remember that a patent is a territorial right and that it is therefore possible that a patent is granted for an invention in one country but that the very same patent application could be legally rejected by another country. At the same time, a patent that has been issued in one country can be revoked if it is demonstrated that the patent office should not to have granted it.

<sup>&</sup>lt;sup>51</sup> Velásquez, G. "Guidelines on Patentability and Access to Medicines", *Research Paper* 61, South Centre, March, 2015.

It is also important to highlight that in the pharmaceutical sphere, the situation is not ONE product, ONE patent. An invention can be protected by numerous patents, just as the production process for the product can also be protected by one or numerous patents; therefore, in many countries there exist several types of patents that are applied to a single pharmaceutical product. (According to the previously mentioned WHO study,<sup>52</sup> Sofosbuvir is the subject of 21 types of patents, Cf. 3.6). As a result, a single medicine can be protected by a large number of patents.

In principle, the patent system was conceived to ensure that the public benefited from inventions. Currently, a large number of people living in developing countries not only do not benefit from inventions but, in many countries, patents represent a barrier to access to lifesaving medicines. These obstacles to life-saving medicine exist simply because business logic prevails over the right to health care access.

The patentability requirements used by national intellectual property offices, according to the TRIPS Agreement, require a product or manufacturing process to meet the conditions necessary to grant patent protection, namely: novelty, inventive step and industrial applicability (utility). These three elements, however, are not defined in the TRIPS Agreement and WTO Member States are free to define these three criteria in a manner consistent with the public health objectives defined by each country.

According to the report of the United Nations High Commissioner for Human Rights "the requirements under the TRIPS Agreement for the grant of patents – novelty, inventive step and industrial applicability – are open to interpretation under national legislation and each country can decide according to local conditions. Consequently, the High Commissioner encourages interpretations of these requirements that do not lose sight of the public interest in the wide dissemination of knowledge..."<sup>53</sup>

<sup>&</sup>lt;sup>52</sup> WHO, Patent situation of key products for treatment of hepatitis C: Sofosbuvir, Geneva, March 2015.

<sup>&</sup>lt;sup>53</sup> The impact of the Agreement on Trade-Related Aspects of Intellectual Property Rights on human rights: Report of the High Commissioner, E/CN.4/Sub.2/2001/13, 27 June 2001, paragraph 62.

The fact that the TRIPS Agreement does not define novelty, inventive step and industrial applicability (utility) leaves countries significant room for manoeuvre; therefore patentability requirements represent the principal and most important flexibility allowed by the Agreement to protect public health and access to medicines. "Politicians and legislators have broad room for manoeuvre to give legal effect to those flexibilities".<sup>54</sup>

### **IV.3** Compulsory Licenses – Aspects and Practical Procedures<sup>55</sup>

Article 31 of the WTO TRIPS Agreement explicitly allows the granting of compulsory licenses. The Agreement contains no limits on the grounds under which such licenses can be granted. Members' right to determine such grounds has been confirmed by the Doha Declaration on the TRIPS Agreement and Public Health (November 2001).

Article 31 makes particular, but not exhaustive reference to cases of national emergency or extreme urgency, dependency of patents, licenses for governmental non-commercial use, and licenses to remedy anticompetitive practices. National laws can, however, provide for the granting of such licenses whenever the titleholder refuses to grant a voluntary license "on reasonable commercial terms" (Article 31 (b)) and for other reasons, such as public health or broad considerations of public interest. The Agreement permits that compulsory licenses provide licensees the authority to exercise any of the rights conferred by a patent, including production or importation.

The granting of a compulsory license within the framework of national legislation (and in conformity with the TRIPS Agreement) requires a body of measures described here below.

<sup>&</sup>lt;sup>54</sup> Arias, Eduardo, Presentation on "Pautas para el examen de patentabilidad de invenciones químico-farmacéuticas, INPI, Argentina, 2014.

<sup>&</sup>lt;sup>55</sup> This point on the aspects and practical procedures for the granting of a Compulsory License is based on the article by Velasquez G., Correa C., Weisman R. "Cost-containment mechanisms for essential medicines, including antiretrovirals, in China", Health Economics and Drugs EDM Series No. 13, WHO/EDM/PAR/2003.6.

# IV.3.1 Identify relevant patents

It is often a true challenge for ministries of health to identify all primary and secondary patents around a given product. Historically, patent offices and health ministries have not developed strong links between them; however, countries such as Argentina, Brazil, Thailand, Ecuador or India have started to establish such links in order to make effective use of the flexibilities of the TRIPS Agreement, notably the granting of compulsory licenses. In 2015, WHO published – with the promise to keep it updated – a study of the landscape of the patents related to Hepatitis C, a very useful tool for countries wishing to issue a compulsory license or to make parallel imports. There is also a database, developed by the MPP, with the landscape of HCV patents.

In most cases, pharmaceutical products are protected by a patent for the active ingredient (primary patent) and by different (secondary) patents for formulations, production processes, new indications, etc. All these patents must be identified and included in the compulsory license, as appropriate, in order to be able to ensure the autonomy to develop the necessary product. Otherwise, the use of the invention targeted by the compulsory license may be disturbed or blocked by allegations of infringement of the secondary patents (as exemplified by the well documented case of the DDI product in Thailand).

### *IV.3.2* Explore possible sources of supply based on local production

The analysis to be undertaken should include:

- the availability of technical resources for reverse engineering
- the cost and duration of developing manufacturing processes and formulations
- the need for technology transfer
- GMP and quality of final products made by local producers, and
- estimates of the investment required and of the marginal cost of production.

# *IV.3.3 Identify possible sources of importation of the required medicines*

The analysis to be undertaken should include:

- compliance with GMP and product quality assurance by potential suppliers;
- prices of supply over time; and
- the sustainability of the exporter's supply.

# IV.3.4 Marketing approval

Registration requirements may represent an obstacle to rapid distribution of the necessary medicines, as could happen, for example, when the country has introduced a period of exclusivity for the protection of data coming from tests. When examining the possibility of issuing a compulsory license, all necessary measures should be taken to ensure that these obstacles will not be present or may be overcome.

# IV.3.5 Request for a compulsory license

The applicable conditions will depend on the alternatives and modalities chosen by each country according to its national legislation.

A request to the patent holder on reasonable commercial terms should be made, including:

- information about the requesting party;
- the expected volume of production;
- the royalty to be paid;
- the form of payment;
- the intended mode of use of the invention;
- quality controls;
- trademark to be used, if any;
- the duration of the license;
- the licensee's right to control sales for determination of royalties due;
- the applicable law and jurisdiction in case of disputes.

Some laws and regulations do not delimit a "reasonable period of time" for the patentee to accept or reject the offer, but a period of one to three months may be considered reasonable.

When dealing with governmental use, no prior negotiations are required; "public interest" constitutes a legitimate reason to grant a compulsory license.

Declaring a "national emergency" is not a requirement for a compulsory license to be granted. When choosing this option, it should be borne in mind that an "emergency" can be a long-term situation, as it happens with the HIV/AIDS pandemic, and not just a short-term problem.

In many cases a compulsory license for government use is preferable both because no prior negotiations are required and also because it will be clear from the start that the government's basic criterion for granting a compulsory license is public health. In this way, it is politically more difficult for patent holders, their trade associations and their respective governments to question the compulsory license.

# *IV.3.6 Granting of the compulsory license by the competent department*

The competent department will have to define the scope of the license and its duration. It would be advisable for the scope to include all commercial and non-commercial uses of the relevant invention, and for the license to last until the patents' expiry.

# *IV.3.7* Negotiation with patent holder about royalty rate

After the granting of the compulsory license, bona fide negotiations should be undertaken with the patent holder to establish the royalty rate for the exploitation of the patent. Generally, these royalties are determined as a percentage of the net sales price of the generic product made under the license (and not the patentee's own product), but other modalities can be adopted, for instance, a fixed sum per unit sold. The TRIPS Agreement requires that the compensation reflect the economic value of the license.

Commercial practice in voluntary licensing is to use royalties ranging between 2 per cent and 5 per cent, though they may be higher in certain cases. There is some evidence available on the royalties determined by national authorities in Canada, the USA, and other countries for the granting of compulsory licenses.<sup>56</sup>

Factors that may be considered to negotiate the royalties include: launch date of the product; possible substitutes; coverage and possible invalidity (total or partial) of the patent(s); pending challenges to the patent(s), if any; accumulated sales and recovery of R&D investment made by the patent holder; global market for the product (units and value); expected volume of production and price under the compulsory license; and royalties agreed upon in voluntary licenses on the same or similar products.

Of course, gathering this information will require considerable preparation and work by an inter-disciplinary team.

# *IV.3.8 Determination of royalty fee by the Patent Administration Department*

If the negotiations on the royalty fee fail, it will be set by the Patent Administration Department or the corresponding body charged with the relevant authority by law. For the sake of transparency and consistency, it would be advisable to make explicit the criteria used for this purpose and to design guidelines applicable to all such determinations of royalty fees.

### IV.3.9 Appeal

National legislations establish the modalities by which patent holders may file an appeal against a decision to grant a compulsory license; it is important that the appeal does not suspend the execution of the aforementioned compulsory license.

<sup>&</sup>lt;sup>56</sup> Niess, P. "Technology evaluation and pricing". Tech Monitor, November-December 1999, pp. 16-17.

#### IV.3.10 Other considerations

Patent holders (or their governments) may attempt to use legal measures, such as injunctions, to delay or prevent the execution of a compulsory license. It would also be useful to check for the possible application of other instruments, such as bilateral agreements on investment (or BITs), which often consider intellectual property as an "asset" subject to their rules.

#### V. SOME COUNTRIES HAVE LAUNCHED THE NEW HCV TREATMENT

In several countries the role of civil society organizations has been, and still remains, fundamental for the government to initiate diagnosis and treatment campaigns. In **Australia**, for example, in December 2015 the government announced an investment of more than 1 billion US dollars to enable universal access to HCV treatment. According to the statement from the Australian Government,<sup>57</sup> an estimated 230,000 Australians are living with HCV, and these people would have access to DAA treatment through the State Pharmaceutical Benefit Scheme (PBC).

In **France**, it is estimated that 500,000 people live with HCV; however, only 30,000 persons are currently (2016) following the DAAs treatment because the price negotiated with Gilead is approximately of 40,000 Euros for a twelve-week treatment. At this price, some observers wonder whether Minister Marisol Touraine's announcement of universal access to HCV treatment is possible.<sup>58</sup> The humanitarian organization "Médecins du Monde" has demanded that the government to issue a compulsory license to allow universal access to the treatment.<sup>59</sup>

In **Egypt**, the country with the highest rate of HCV infection in the world, the government managed to negotiate with Gilead a 12-week

<sup>&</sup>lt;sup>57</sup>http://www.health.gov.au/internet/ministers/publishing.nsf/Content/FAE2B6533145624 3CA257F20006D4C48/\$File/SL-154.pdf.

<sup>&</sup>lt;sup>58</sup> Vaugrente A. "Accès aux nouveaux traitements Hépatite C : l'annonce de Marisol Touraine saluée mais surveillée": http://www.pourquoidocteur.fr/Articles/Question-dactu/15845-Hepatite-C-l-annonce-de-Marisol-Touraine-saluee-mais-surveillee.
<sup>59</sup> Médecins du Monde.

https://issuu.com/medecinsdumonde/docs/mdm hep c brevet web.

treatment price of 900 US dollars. Following the announcement of this discount, the United States Senate addressed a letter to John Martin, President of the Gilead<sup>60</sup> and began an investigation into the reasons for the price differential of 900 US dollars in Egypt and the 84,000 US dollars in the US. In practice, the price of treatment is often higher (double), as patients with advanced HCV often need a 24-week treatment.

The Egyptian National Patent Office, applying more strict patent criteria than many other countries, rejected one of the Sofosbuvir patent applications, allowing the Egyptian firm "Pharco" to produce for less than 200 US\$ per 12-week treatment.

In 2015 alone, 170,000 people received treatment in Egypt and in 2016 more than 500,000 started DAAs treatment. More than 90 per cent of the HCV patients in this country are infected with genotype 4, something that simplifies treatment protocols.<sup>61</sup>

In **Morocco** the original patents on Sofosbuvir, Ledipasvir and Daclatasvir were never requested, and this has allowed importation and local production of generics. In Morocco as in other countries, civil society groups such as ITPC (International Treatment Preparedness Coalition) have played an important role on the path leading to the government's announcement of expanding treatment measures.

The cost of a twelve-week treatment with the generic Sofosbuvir, marketed as "SSB", is approximately 9,000 Dirhams (approximately 900 US dollars). The Health Ministry announced that Morocco will be free of Hepatitis C by 2030.<sup>62</sup>

<sup>&</sup>lt;sup>60</sup> Letter of the Senate of the United States to the CEO of Gilead Sciences: https://www.finance.senate.gov/imo/media/doc/Wyden-

Grassley%20Document%20Request%20to%20Gilead%207-11-141.pdf.

<sup>&</sup>lt;sup>61</sup> Plan of action for the prevention, care and treatment of viral hepatitis, Egypt 2014-2018. Ministry of Health and Population.

http://www.emro.who.int/images/stories/egypt/VH\_Plan\_of\_Action\_FINAL\_PRINT1.pdf. 62 Morocco World News:

https://www.moroccoworldnews.com/2015/11/173627/morocco-without-hepatitis-c-in-2020/.

**Pakistan** is a country with a high prevalence of HCV. Primary patents for Sofosbuvir were not filed and requests on some secondary patents are still pending. According to a survey conducted by WHO, the price for a twelve-week treatment with locally-manufactured generic Sofosbuvir is the cheapest in the world, at 45 US dollars per twelve-week treatment.<sup>63</sup>

In **Thailand**, following progress in antiviral access achieved by groups of patients living with HIV, the Treatment Action Group (TAG) has developed campaigns to raise awareness both on the government and the public opinion in order to accelerate programmes of treatment access to Hepatitis C.

The non-governmental organization TAG filed with the patent office an opposition to the patent application for the Sofosbuvir by Gilead.<sup>64</sup>

# VI. CONCLUSIONS

- The eradication of the disease is only possible if medicines can be purchased at low prices within health budgets.
- New ways of delivering mass treatment programs for Hepatitis C are needed.
- It is necessary to become conscious of the problem, raise awareness, diagnose and, in many cases, refer the patient to another level of care, evaluate the stage of the disease, follow the treatment and monitor the patient's progress.
- Most medicines have low production costs; pharmaceutical companies could make high levels of profit if they would decide to sell large quantities at reasonable prices.

<sup>&</sup>lt;sup>63</sup> WHO, "Global report on access to hepatitis C treatment. Focus on overcoming barriers, Geneva, October 2016, p. 30.

<sup>&</sup>lt;sup>64</sup> TAG, "Gilead: Stop Blocking Access to Hepatitis C Treatment" http://www.treatmentactiongroup.org/hcv/2015/gilead-stop-blocking-HCV-access.

If pharmaceutical companies refuse to lower prices, it would be necessary to consider:

- Compulsory licenses.
- Parallel imports.
- Use of the money coming from their tax evasion to pay for treatments.
- Promotion of the manufacture of generics.
- Summoning them before Justice for a violation of Human Rights.

20 Years of "R"evolution				
1996		2016		
1.	27,000 patients with ARVs	1.	15-17 million, currently	
2.	2. Treatment cost: 12,000 US\$		Cost: Less than 100 US\$	
3.	. WHO, HM and some NGOs		The Whole UN, Ministries, NGOs	
4.	NDP: a question of health	4.	NDP: Health, Trade, Human	
			Rights, IP	
5.	A2M= political will or charity		A2M = A question of Rights	
6.	. CL for medicines = 0		More than 30 CL in 11 countries	
7.	R&D – IP model: ACCEPTED	7.	R&D model: QUESTIONED	
8.	Patients were patient	8.	Patients are impatient	
9.	Pharmaceutical Industry: impunity	9.	Phar. Ind. = Held accountable	
10.	Price of ARV 100 times its cost	10.	Hepatitis C price: 1,400 times its	
			cost	

# CHAPTER 4 INTELLECTUAL PROPERTY, PUBLIC HEALTH AND ACCESS TO MEDICINES IN INTERNATIONAL ORGANIZATIONS

Germán Velásquez

# I. THE WORLD HEALTH ORGANIZATION

# I.1 Background: First Mandate of the World Health Assembly

In 1996 the World Health Assembly (WHA) adopted a resolution on medicines<sup>1</sup> which constitutes the first mandate given by Member States to the Secretariat of the World Health Organization to work on intellectual property in relation to health.

The resolution (WHA49.14) on "Revised Drug Strategy" requested the WHO Director-General to undertake a study on the impact of the WTO, and particularly the TRIPS agreement, on access to health.

### I.2 The "Red Book"

Resolution WHA49.14 requested the Director-General to prepare a study on the implications of the TRIPS agreement. This study was entrusted to the Programme of Action on Essential Medicines (PAME). In November 1997, PAME published the study "Globalization and Access to Drugs: Perspectives on the WTO TRIPS Agreement,"<sup>2</sup> commonly known in the WHO as the "red book" on the TRIPS Agreement.

<sup>&</sup>lt;sup>1</sup> WHA 49.14 "Revised Drug Strategy", WHO, Geneva 1996.

<sup>&</sup>lt;sup>2</sup> Velásquez, G., Boulet P., "Globalization and Access to Drugs: Perspectives on the WTO TRIPS Agreement", WHO/DAP/98.9, Geneva, November 1997, p. 58.

#### I.3 TRIPS Flexibilities

The aforementioned UNCTAD document includes the "**room for manoeuvre**" for the creation of national public policies that the TRIPS agreement has. The WHO "red book" speaks about "**margins of freedom**" (1997).<sup>3</sup> Subsequently, in March 2001, WHO adopted the term "**safeguards**" in a widely distributed document available in the six WHO official languages.<sup>4</sup>

In June 2001, the European Commission talks about "a sufficiently wide margin of discretion" regarding the implementation of the TRIPS Agreement.<sup>5</sup> A few months later, in November 2001, the Doha Declaration on the TRIPS Agreement and Public Health refers to "the provisions of the TRIPS Agreement that provide flexibility."<sup>6</sup> It is only in June 2002 that WHO referred to TRIPS "flexibilities", in a paper analyzing the implications of the Doha declaration, authored by Carlos Correa.<sup>7</sup>

Currently, there is broad consensus on the use of the term "flexibilities" to refer to the mechanisms and provisions of the TRIPS agreement to protect public health.

### I.4 The Commission on Intellectual Property, Innovation and Public Health

The Commission on Intellectual Property, Innovation and Public Health (CIPIH) was created in 2003 by a resolution of the World Health

<sup>&</sup>lt;sup>3</sup> Velásquez, G., Boulet P., "Globalization and Access to Drugs: Perspectives on the WTO TRIPS Agreement", WHO/DAP/98.9, Geneva, November 1997, p. 34. Emphasis added.

<sup>&</sup>lt;sup>4</sup> WHO Policy Perspectives on Medicines, "Globalization, TRIPS and access to pharmaceuticals", no. 3 WHO, Geneva March 2001, p. 5. Emphasis added.

<sup>&</sup>lt;sup>5</sup> European Commission's submission on the 12th of June: "a sufficiently wide margin of discretion", (IP/C/W/280), June 12th, 2001. Emphasis added.

<sup>&</sup>lt;sup>6</sup> WTO "Doha declaration on the TRIPS Agreement and Public health, WT/MIN(01)/DEC/W/2, p. 1. Emphasis added.

<sup>&</sup>lt;sup>7</sup> C. Correa "Implications of the Doha Declaration on the TRIPS Agreement and Public Health", WHO/EDM/PAR/2002.3, Geneva, 20012, see chapter titles "TRIPS flexibilities", p. 13. Emphasis added.

Assembly.<sup>8</sup> WHO Member States requested the WHO Secretariat to produce a report by independent experts.

In 2006, the group of experts published a report entitled "Public Health, Innovation and Intellectual Property Rights."<sup>9</sup> It contains 60 recommendations, which have unfortunately not been fully adopted to date (ten years later).

#### I.5 Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property – Resolution WHA 61.21

This negotiation which was two years long, can be considered the most relevant and important in the almost 70 years of existence of WHO; second only to the negotiation and adoption of the convention against tobacco, FCTC.<sup>10</sup>

The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA) sought a substantial reform of the pharmaceutical research and development system in view of this system's failure to produce medicines for diseases affecting the majority of the world's population living in developing countries. The intellectual property rights required by the TRIPS Agreement and recent trade agreements could become one of the main obstacles to access to medicines. The GSPOA made a critical analysis of this reality and opened the door to the quest for new solutions to this problem.<sup>11</sup>

The Global Strategy and Action Plan on Public Health, Innovation and Intellectual Property (Resolution WHA 61.21), adopted by WHO Member States in 2008, became entangled in "UN-like" discussions and

<sup>&</sup>lt;sup>8</sup> WHA Resolution, WHA56.26 Intellectual Property Rights, Innovation and Public Health.

<sup>&</sup>lt;sup>9</sup> "Public Health, Innovation and Intellectual Property Rights", Report by the Commission on Intellectual Property, Innovation and Public Health, ISBN 92 4 356323 8, Geneva 2006, 204 pp.

<sup>&</sup>lt;sup>10</sup> FCTC: Framework Convention on Tobacco Control.

<sup>&</sup>lt;sup>11</sup> Velásquez, G., "The Right to Health and Medicines: The Case of Recent Negotiations on the Global Strategy on Public Health, Innovation and Intellectual Property" Research Paper 35, South Centre, Geneva, 2011.

procedures, and what was eventually achieved in this process was rather limited.

Analyzing the progress<sup>12</sup> made in implementing the "global strategy" and its action plan, the "progress" made so far is reduced to three points:

1. The Patent Pool,<sup>13</sup> a particular initiative, this is one of the many elements of the mandate given to the WHO by resolution 61.21. Patent pools can facilitate equitable access and make new HIV treatments more affordable. They can also facilitate the development of new fixed-dose combinations suitable to address developing countries' treatment needs. Patent pools may consist of compulsory licenses or licenses voluntarily granted by the patent holder, as is the case of the current Medicines Patent Pool (MPP) created with funds from the French initiative UNITAID. These patent pools are voluntary, and therefore they do not constitute a structural solution to the access to medicines problem. Unfortunately, in the case of the MPP, its existence has practically meant that the WHO has given up its work on advocacy and assistance to countries to implement the flexibilities of the TRIPS agreement.

2. The second activity that has been developed in the Americas region is the so-called "Platform on Innovation" promoted by the Pan American Health Organization (PAHO). It is a sort of "Facebook of medicines", a virtual network reporting on various activities in the pharmaceutical field.

3. The "Demonstration projects", an idea launched and promoted by the EU at the WHO. These demonstration projects, which were not part of the existing mandate in the various resolutions of the World Health Assembly, were used to delay the start of negotiations on a binding Convention. During 2012 and 2013, project selection took place in a process that involved the six WHO Regional Offices. This selection process was heavily criticized by non-governmental organizations and some observers. It confirmed the initial concern of

<sup>&</sup>lt;sup>12</sup> Currently a Canadian private firm contracted by WHO is conducting an evaluation of the global strategy. The results will say very little, since the terms of reference were poorly drafted.

<sup>&</sup>lt;sup>13</sup> http://www.medicinespatentpool.org/.

developing countries that these demonstration projects were only a distraction by industrialized countries to delay the start of negotiations on a binding Convention.

More than 4 years after the approval of the "demonstration" projects, the funding was still not there at the end of 2016 to start this exercise. The start of negotiations for a Convention was not formally contingent on the results of the demonstration projects, but in practice the debate on the demonstration projects took so much space that the start of negotiations was set aside. If the demonstration projects were only a pretext for delaying the subject of a treaty, as many suspected, they were certainly "successful" as the treaty was not only delayed but virtually removed from the WHO agenda.

Given the impasse to approve intellectual property issues within the global strategy the "Consultative Expert Working Group" was created.

# I.6 WHO Consultative Expert Working Group (CEWG)

At the beginning of 2011, the WHO Director-General established a WHO Consultative Expert Working Group (CEWG) to address the intellectual property issues that remained unaddressed in the "Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property". In July 2011, the CEWG coordinator announced that "the CEWG will recommend to the 2012 World Health Assembly the initiation of formal intergovernmental negotiations for the adoption of a comprehensive and binding instrument for health R&D, on the basis of Article 19 of the WHO Constitution." This recommendation has not yet been ratified by the Governing Bodies of the WHO.

# **1.7** The Collaboration of WHO with Other International Organizations

Interestingly, the United Nations agencies invited to participate in the debates on intellectual property and health, which took place in WHO between 2010 and 2015, were WIPO and WTO. This is despite the fact that there are other United Nations agencies that are much closer to the work of the WHO, such as UNDP, UNAIDS, UNCTAD, or the Commission on Human Rights. These were not invited by the WHO to

participate in the discussions on the subject of access to medicines. In the case of UNDP, its presence at the country level has been much more relevant in recent years than the rest of agencies mentioned above.

One of the main collaborative activities between WHO, WTO and WIPO has been the so-called tripartite report, entitled "Promoting Access to Medical Technologies and Innovation". Whereas the study could represent progress for WTO and WIPO given that it talks about the TRIPS flexibilities with no "taboos", it does not reflect the fact that the WHO was the International Organization that had until then led this issue. There are 17 World Health Assembly resolutions referring to intellectual property and public health, adopted between 1996 and 2012, and these are cited by the report in a table on page 44. These resolutions clearly have a prescriptive character for the WHO Secretariat and for countries on how to preserve public health from the potential negative impact of new international trade rules on public health. Numerous WHO publications<sup>14</sup> on this topic published over the past 15 years also point in this direction.

The disclaimer of the report states that "(...) the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the WHO, WIPO and the WTO be liable for any consequences whatsoever arising from its use." This type of "disclaimer" may give the reader the misleading impression that the WHO has no opinion as to whether a compulsory license may, in particular circumstances, promote access to medicines, or whether an international exhaustion regime that allows parallel imports from any country can reduce medicines costs and, therefore, contribute to access. The 17 resolutions mandate the WHO to engage, promote and defend mechanisms and policies in favour of access. This tripartite report has led the WHO to share the "neutral" and totally disengaged view of safeguarding health.

The trilateral report is weak, unambitious and does not reflect the work that WHO has carried out under its mandate. It is curious that the

<sup>&</sup>lt;sup>14</sup> See bibliography in Annex II of Chapter 1: Guidelines on Patentability and Access to Medicines.

251-page document does not have a single recommendation, not even a conclusion.

The dialogues or cooperation between the WHO, WIPO and the WTO from 2010 to 2015 have placed the international debate on access to medicines in a kind of "limbo". This was undoubtedly one of the reasons why UNDP sought to rescue the issue by suggesting to the UN Secretary-General to convene a high level panel on access to medicines by the end of 2015. The high level panel of the UN Secretary-General released its report on 14 September 2016, to which we will refer at the end of this chapter.

#### II. THE WORLD TRADE ORGANIZATION

#### II.1 Paragraph 6 of the Doha Declaration, or the Decision of 30th August 2003

In June 2001, the African Group requested the WTO TRIPS council to include in its agenda an item on "access to medicines", which eventually resulted in the Doha Declaration on TRIPS and Public Health. In the last 15 years, this has been the only contribution of the WTO to the access to medicines issue.

The so-called "Paragraph 6" mechanism of the Doha declaration, or the Decision of 30th August 2003, was a mandate of the WTO ministerial conference in Doha (2001) to solve, in an "ad hoc" manner, a problem that affected the poorest countries. The problem still lacks a solution 15 years later.

What was (is) the problem? In <u>section f</u>) of article 31 of the TRIPS Agreement, it is stated that any product manufactured under a compulsory license "shall be authorized predominantly to meet the supply of the domestic market". This can be applied to countries with the capacity to manufacture medicines and limits the volume of medicines that can be exported when their production has been enabled by a compulsory license. Such disposition affects mainly those countries that lack the manufacturing capacity to produce medicines, i.e. the least developed countries. This is the reason why Paragraph 6 of the Doha Declaration gives a mandate to find an expeditious solution to this problem.

After two years of negotiations, on 30th August 2003, WTO Member States reached an agreement on the regulatory modification that would allow countries to import generic medicines at a lower price and manufactured under compulsory licenses, in case they lack local manufacturing capacity. After reaching this Decision, the President of the General Council read a declaration to clarify the way in which this Decision should be interpreted and implemented by WTO members. The purpose of this statement was to ensure to industrialized countries that the Decision would not be abused, it was never clear whether the statement by the President of the Council was part of the decision or not.

The decision on Paragraph 6 contains a number of conditions, requested by industrialized countries, to ensure that beneficiary countries can import generic medicines without undermining the patent system. These include measures to prevent drugs from being diverted to inappropriate markets, and provisions requiring governments using this system to keep all other Members informed.

All WTO Member countries are allowed to import under this decision, but the decision lists 23 developed countries that voluntarily announced that they would not use the system as importing Members: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Iceland, Italy, Japan, Luxembourg, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

After joining the EU in 2004, 10 more countries have been added to the list: Cyprus, Slovenia, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, the Czech Republic and the Slovak Republic.

Subsequently, several potential exporting countries amended their laws and regulations with the aim of applying the exceptions and allow production exclusively for export: countries such as Norway, Canada, India and the EU among others. The 2003 exceptions are provisional in nature; the ultimate goal is to modify the TRIPS Agreement itself, which would enter into force when two-thirds of Members accept it. Thirteen years after the "expedited solution" agreed by WTO Member States, the mechanism has not been ratified, and only one country, Rwanda, has used it once, with an import of antiretroviral medicines from Canada. The manager of the Canadian generic firm stated, after export, that the system was so complicated that his firm had no intention of using it again.<sup>15</sup>

On 8 November 2016, the CIPLA representative at a "lunch seminar" organized by the South Centre at the WTO in Geneva stated that CIPLA would never use the paragraph 6 mechanism, and that this decision should be completely revised.

At the end of the aforementioned seminar, organized by the South Centre at the WTO, Suerie Moon, Research Director at the Global Health Centre of the Graduate Institute in Geneva, concluded by citing the recommendations of the UN High Level Panel: "WTO Member States should review the decision in Paragraph 6 to find a solution that would allow for a quick and convenient export of pharmaceutical products produced under a compulsory license. WTO Member States should, as appropriate, adopt an exception and a permanent reform of the TRIPS Agreement."

# **II.2** The WHO Proposal to Solve the Problem Exposed in Paragraph 6<sup>16</sup>

In 2002, WHO published a document on the implications of the Doha Declaration on TRIPS and Public Health, WHO/EDM/PAR/2002.3. This document describes possible solutions to the so-called "paragraph 6 problem" from a public health perspective. These characteristics include: a stable international legal framework; transparency and predictability of the rules to be applied in countries engaged in exportations and importations; simplicity and speed of legal proceedings

<sup>&</sup>lt;sup>15</sup> South Centre Policy Brief No. 7, "The Doha Declaration on TRIPS and Public Health: Ten years later – the state of implementation", Nov. 2011.

<sup>&</sup>lt;sup>16</sup> G. Velasquez, "El acceso a medicamentos y la propiedad intelectual: contribución de la OMS" in Revista jurídica de Buenos Aires, "Tendencias actuales en propiedad intelectual", coordinada por Sandra Negro, ed. Abeledoperrot, Buenos Aires 2013.

in exporting and importing countries; equal opportunities for countries in need of medicines, including for products patented in the importing country; multiplication of potential providers of needed medicine; and a wide coverage in terms of health issues and different drug types.

Thus, the basic public health principle is clear: people in a country that does not have the capacity for domestic production of a needed drug should not be less protected by the provisions of compulsory licenses (or other safeguards of the agreement on TRIPS), nor should they have more procedural obstacles compared to people living in countries with the capacity to produce the drug.

Among the solutions that have been proposed, the limited exception under **article 30** is the most consistent with these public health principles.<sup>17</sup> Under the mandate of the Doha Declaration, this solution would give WTO Member States expeditious authorization to enable third parties to manufacture, sell and export patented medicines and other health technologies to address public health needs.<sup>18</sup>

### III. THE WORLD INTELLECTUAL PROPERTY ORGANIZATION

According to Carolyn Deere,<sup>19</sup> WIPO is the largest donor providing training on intellectual property issues to developing countries. Between 1996 and 2006, WIPO spent more than US \$400 million on technical support. The problem is that this technical advice, according Carolyn Deere, was used to introduce stronger intellectual property management in developing countries, with the philosophy that "the more patents, the better". All of this is done through the provision of computers, computer equipment, salaries, invitations to conferences and consulting contracts, as a means of influencing decision-makers to strengthen the use of intellectual property.

When reviewing the agendas of the different WIPO training programs, published on their website, including online training courses,

<sup>&</sup>lt;sup>17</sup> Emphasis added by the author.

<sup>&</sup>lt;sup>18</sup> Extract from WHO intervention at the WTO TRIPS Council, 1 September 2003.

<sup>&</sup>lt;sup>19</sup> C. Deere, "The implementation Game: The TRIPS agreement and the global politics of IP reform in developing countries" Oxford University Press, 2009, p. 180.

none of those programmes include contents referring to the flexibilities of the TRIPS agreement. For those who have been following this debate for the last 15 years, it is clear that WIPO is more a part of the problem than the solution in terms of public health. WIPO is certainly responsible for the proliferation of patents on trivial innovations that result in expensive pharmaceutical products.

On the WIPO website, WIPO identifies its main activity in the field of medicines to be the fostering of a trilateral cooperation between WHO, WTO and WIPO. This point has been already mentioned and analyzed in the section referring to WHO.

The webpage concludes by saying: "The three organizations meet regularly, exchange information on their respective work programmes, discuss and plan, within the possibilities of their respective mandates and budgets, common activities. The trilateral cooperation is intended to contribute to enhancing the empirical and factual information basis for policy makers and supporting them in addressing public health in relation to intellectual property and trade."<sup>20</sup> There is no reference to what part of the work of the tripartite collaboration is devoted to supporting countries in the use of TRIPS flexibilities.

# IV. THE UNITED NATIONS CONFERENCE ON TRADE AND DEVELOPMENT

The United Nations Conference on Trade and Development (UNCTAD) has focused its access to medicines work on strengthening production capacity in developing countries.

In 2005, UNCTAD was mandated by the Commission on Investment, Technology and Financial Issues to carry out work related to the manufacture and supply of pharmaceuticals in the context of the Millennium Development Goal No. 8.

The Commission recommended that: "UNCTAD should, within its work programme on investment, technology transfer and intellectual

<sup>&</sup>lt;sup>20</sup> WIPO, http://www.wipo.int/policy/en/global\_health/trilateral\_cooperation.html.

property, assess ways in which developing countries can develop their domestic productive capability in the supply of essential drugs in cooperation with pharmaceutical companies."<sup>21</sup>

Within the framework of this mandate, UNCTAD established in 2006 a pilot programme on local pharmaceutical production and access to medicines, with the financial support of Germany and the United Kingdom.

The aim of the programme: "The overall objective of the programme ... is to assist developing countries – and least-developed countries (LDCs) in particular – to establish domestic intellectual property regimes that facilitate increased access to affordable medicines..."<sup>22</sup>

Within the activities foreseen by this programme, there are training courses on TRIPS flexibilities applied to local pharmaceutical production. Among the studies published by UNCTAD there are: "Role of competition in the pharmaceutical sector and its benefits for consumers" or "Enhancing productive capacities: the role of health".

# V. THE JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

The 2016-2021 Strategy of the UNAIDS Programme:

- To reaffirm the work of promoting innovation and continuous improvement of HIV-related medicines and technologies while ensuring their availability, quality and affordability.
- To support countries in the adoption and use of TRIPS-related flexibilities and in defending their ability to denounce the provisions of trade agreements that impede access to affordable medicines that go beyond international obligations under the TRIPS Agreement.

<sup>&</sup>lt;sup>21</sup> UNCTAD, https://unctad.org/en/pages/PublicationArchive.aspx?publicationid=437.

<sup>&</sup>lt;sup>22</sup> Ibid.

• Joins efforts to explore new systems of incentives for research and development where research and development costs are delinked from product prices.

# V.1 Some Examples of the Current Work of UNAIDS on Intellectual Property-related Issues

- Information papers on IP-related issues have been developed by the UNAIDS/UNDP Secretariats: the impact of intellectual property rights on access to medicines, the challenges of IP chapters in free trade agreements.
- In 2013, UNAIDS, UNITAID, WHO and the Brazilian Government organized a consultation on access to HIV medicines in middle-income countries. There were four blocks of recommendations: pricing; regulatory framework; IP and collaboration on local production; and R&D.
- In May 2014, UNAIDS co-sponsored a BRICS side event during the World Health Assembly to discuss access to medicines in the context of members of this group of countries. IP was an important item on the agenda.
- In May 2015, UNAIDS organized a reflection group on IP and access to medicines to inform the Secretariat on possible areas and actions that UNAIDS could undertake to improve access to medicines and address barriers to Intellectual property.
- In October 2015, UNAIDS, in collaboration with MSF, the Third World Network and the People's Health Movement, organized a session on TRIPS and access to medicines at the WTO Public Forum in Geneva.

Finally, it is worth mentioning that UNAIDS was part of the Secretariat of the United Nations Secretary-General's High-Level Panel that issued their report in September 2016.

# VI. THE HUMAN RIGHTS COUNCIL<sup>23</sup>

In 2016 the United Nations Human Rights Council approved a resolution reaffirming that access to medicines is a fundamental element to the full exercise of the right to health. Members also agreed to hold round tables on the issue of access to medicines during the next sessions, in 2017.<sup>24</sup>

Resolution 32/L.23 titled: "Access to medicines in the context of the right of everyone to the enjoyment of the highest attainable standard of physical and mental health" was submitted by Brazil, China, Egypt, Haiti, India, Indonesia, Paraguay, Peru, Senegal, Sri Lanka, South Africa and Thailand. The resolution was supported by 72 co-sponsors.

Many resolutions have been adopted in the last 15 years in the context of the WHO. There, the debate has fundamentally been between health and trade. What primes: health or trade? What were the possible contradictions and what were the mechanisms to protect health from the possible negative effects of the new rules governing international trade? On a number of occasions, developing countries attempted to introduce a reference to human rights as an argument for ensuring access to medicines. Unfortunately, all attempts failed because of opposition from the United States of America.

The great value of the Human Rights Council resolution 32/L.23 is to place the debate on access to medicines at another level, at the level of human rights. It may not be just by chance that in December 2015 the UN Secretary-General called for the High-Level Panel with the following terms of reference: to study the incoherence between inventors' rights, international human rights law, trade rules and public health.

The Human Rights Council confirms the primacy of human rights, such as the right to health over trade, intellectual property rights and other bilateral investment or trade agreements. "It is equally important that the resolution reaffirms the ability of countries to take advantage of

<sup>&</sup>lt;sup>23</sup> Human Rights Council, resolution (23/14 in 2013) Geneva, 2016.

<sup>&</sup>lt;sup>24</sup> Viviana Muñoz Tellez and Adriano José Timossi, "Human Rights Council adopts historic resolutions on access to medicines", South Bulletin, Issue 92, 4 August 2016.

the flexibilities envisaged by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) to promote access to medicines, recognizing that patents can be used to set high prices for medicines."<sup>25</sup>

The resolution reaffirms the importance of access to medicines for all human beings as one of the fundamental human rights and stresses that improved access could save millions of lives every year.

The resolution also refers to the Doha Declaration on intellectual property and public health which confirms that TRIPS does not prevent and should not prevent WTO members from taking measures to protect public health.

The adoption by consensus of the resolution coincided with the celebrations of the 30th anniversary of the Declaration on the Right to Development, which recognized both the right to health and access to medicines and public health as essential elements for the exercise of the right to development.<sup>26</sup>

# VII. THE UNITED NATIONS DEVELOPMENT PROGRAMME (UNDP)

The strategy of UNDP on intellectual property and access to medicines has been to frame all its work in the context of the fight against HIV. In other words, access to medicines for people living with HIV is a priority for UNDP. This is a very successful strategy since the drugs used to treat HIV are excellent examples of drugs marketed under conditions such as monopolies, high prices, unethical behaviour, and human rights violations. These issues are common to many other medicines to which many people lack regular access worldwide.

# VII.1 HIV and Health

The UNDP website states that "Globally, 35 million people are living with HIV. While new HIV infections have declined by 38 per cent since

<sup>&</sup>lt;sup>25</sup> Ibid.

<sup>&</sup>lt;sup>26</sup> Ibid.

2001, the HIV epidemic continues to outpace the response."<sup>27</sup> However, UNDP continues to state that: "There is a growing threat from noncommunicable diseases (NCDs) such as cardiovascular diseases, cancers, chronic respiratory diseases and diabetes - accounting for 60 per cent of premature deaths. Over the next twenty years, NCDs and mental health will cause a cumulative economic output loss of US\$ 47 trillion globally."28

The UNDP Strategic Plan 2014-2017 "Recognizes the broad range of social and economic impacts of HIV and the synergies between health and sustainable development. This plan addresses HIV as a cross-cutting issue and emphasizes the rights of people living with HIV; reducing associated discrimination and violence against women; empowering local governance and national capacities to achieve greater equity in access to services for those affected, and strengthening the rule of law and reform of legal systems."29

# VII.2 HIV and the Law: Risks, Rights, and Health<sup>30</sup>

The final report of the Global Commission on HIV and the Law is undoubtedly one of the most robust works produced by a UN agency in the field of health, access to medicines and in particular intellectual property. The legal environment – laws, repressive and judicial systems - has immense potential to improve the lives of people who do not have access to medicines and can save their lives. International laws and treaties can protect and improve access to healthcare and forbid discrimination stimulating the power of national laws to protect health and to ensure access to medicines as a right.

162-page report presents compelling evidence The and recommendations that can save lives, reduce costs, help eradicate the AIDS epidemic, and improve access to medicines in general.

<sup>&</sup>lt;sup>27</sup> http://www.undp.org/content/undp/en/home/ourwork/democratic-governance-andpeacebuilding/hiv-and-health/.

<sup>&</sup>lt;sup>29</sup>http://www.undp.org/content/undp/en/home/librarypage/corporate/Changing with the World UNDP Strategic Plan 2014 17/.

<sup>&</sup>lt;sup>30</sup> http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/hiv-and-the-law-risks--rights---health/.

Laws can prohibit or permit specific behaviours, and in doing so they shape policies economies, and society. Laws can be an excellent tool to protect and guarantee the health of citizens.

#### VIII. AN EXAMPLE OF COLLABORATION BETWEEN WHO, UNDP AND UNCTAD<sup>31</sup>

Under the TRIPS Agreement, for a product or a manufacturing process to be patentable it has to meet the patentability criteria. These criteria are required by national intellectual property offices and they are: novelty, inventiveness and industrial application (usefulness). However, these three elements are not defined in the TRIPS agreement; therefore WTO Member States are free to define these three elements in a manner that is coherent with the public health objectives defined by each country.

According to the report of the United Nations High Commissioner on Health:

"The requirements under the TRIPS Agreement for the grant of patents – novelty, inventive step and industrial applicability – are open to interpretation under national legislation and each country can decide according to local conditions. Consequently, the High Commissioner encourages interpretations of these requirements that do not lose sight of the public interest in the wide dissemination of knowledge (...).<sup>32</sup>

The world has never had at its disposal such a wide arsenal of treatments to fight the diseases that afflict humanity. At the same time, many people die owing to a lack of certain medicines and/or vaccines. This applies to illnesses such as AIDS, malaria, tuberculosis, cancer,

<sup>&</sup>lt;sup>31</sup> Velásquez, G., "Guidelines on Patentability and Access to Medicines" South Centre, Research Paper 61, 2015, p. 8.

<sup>&</sup>lt;sup>32</sup> The impact of the Agreement on Trade-Related Aspects of Intellectual Property Rights on human rights: Report of the High Commissioner, E/CN.4/Sub.2/2001/13, 27 June 2001, para 62.
diabetes, hepatitis C, bacterial meningitis and pneumonia, among many others."<sup>33</sup>

It is widely believed that patents are usually granted to protect new drugs, but the number of patents obtained annually to protect new compounds is actually very small and has been declining. Each year, thousands of pharmaceutical patents are awarded, although only a few are for new molecular entities (NMEs).

The cumulative nature of innovations, due to low patentability requirements and deficiencies in patent granting procedures, has important consequences on the patent system, which limits the dissemination of the innovations that the system seeks to promote: access to life-saving drugs. "Patents that are based on broad scientific principles are generally bad, because according to the United States Supreme Court, they may confer power to block off whole areas of scientific development, without a compensating benefit to the public."<sup>34</sup>

All of this led WHO, in collaboration with UNCTAD, UNDP and ICTSD, to develop, in 2007, a series of guidelines for the examination of pharmaceutical patents from a public health perspective.<sup>35</sup>

These guidelines were conceived as a contribution to improve the transparency and effectiveness of the patent system for pharmaceutical products. This would help countries to pay more attention to patent examination and grant procedures, in order to avoid the negative effects of patents on non-inventive developments on access to medicines.

"The exercise to draft guidelines for patent examination sought a way to manage the pharmaceutical product patent system and, more specifically, the 'strengthened patent system' arising from the TRIPS Agreement and current regional and bilateral trade and investment agreements. Patents are a social contract between the patent holder and

<sup>&</sup>lt;sup>33</sup> Velásquez, G., "Guidelines on Patentability and Access to Medicines" South Centre, Research Paper 61, 2015, p. 8.

<sup>&</sup>lt;sup>34</sup> Barton, John H., WHO Bulletin, October 2004, vol. 82, No. 10.

<sup>&</sup>lt;sup>35</sup> WHO – ICTSD – UNCTAD – UNDP "Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective", Working Paper by Correa, C. M., Geneva, 2007. Available at: http://ictsd.org/i/publications/11393/.

society; therefore it is necessary to explore, identify and implement mechanisms to improve the functioning and transparency of the patent system in the interest of public health."<sup>36</sup>

The report of the United Nations Secretary-General's high-level panel, to which we will refer next, recommends to "make use of the space available in Article 27 of TRIPS to adapt and apply rigorous definitions of invention and patentability."<sup>37</sup> The guidelines for the examination of pharmaceutical patents published by the three agencies WHO, UNDP and UNCTAD<sup>38</sup> are precisely the means to put into practice that recommendation.

#### IX. THE SECRETARY-GENERAL OF THE UNITED NATIONS

#### IX.1 The Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines

Towards the end of 2015, at the initiative of UNDP, the Secretary-General of the United Nations convened a High-Level Panel on Access to Medicines. This high-level panel published a report of their work on 14 September 2016.

The terms of reference of the UN Secretary General's call for the High-level panel (HLP) on Access to Medicines (December 2015) admitted a structural problem in the current medical R&D model. Members of the panel were asked to study the "Incoherence between the rights of inventors, international human rights law, trade rules and public health."<sup>39</sup>

In only 4 months, 180 proposals were received by the high level panel from countries, institutions, UN agencies, NGOs, universities, the

<sup>&</sup>lt;sup>36</sup> Velásquez, G., "Guidelines on Patentability and Access to Medicines" South Centre, Research Paper 61, 2015, p. 9.

<sup>&</sup>lt;sup>37</sup> Report of the United Nations Secretary-General's High-level Panel on Access to Medicines, September 2016, page 9.

<sup>&</sup>lt;sup>38</sup> In collaboration with the nongovernmental organization, ICTSD, Geneva.

<sup>&</sup>lt;sup>39</sup> Ibid., page 12.

pharmaceutical industry, and individuals. They can be classified into five categories:

- 1. Comments on the current R&D model (40)
- 2. Proposals to strengthen health systems (27)
- 3. Proposals to modify the R&D model progressively (46)
- 4. Contributions proposing a major reform of the model (46)
- 5. Other

Proposals were also received from the Governments of the Netherlands, Lesotho, Japan, and Jordan.

The main recommendations of the UNHLP report released in September 2016 can be summarized as follows:

- Make use of the available space in TRIPS Article 27 to adapt and apply stringent definitions of invention and patentability.
- Governments should adopt and implement legislation facilitating compulsory licenses.
- WTO members should review the paragraph 6 decision.
- Governments and the private sector must refrain from explicit or implicit threats, tactics or strategies that undermine the right to use TRIPS flexibilities.
- No to TRIPS-plus provisions.
- Universities and research institutions receiving public funding should prioritize public health objectives over financial profitability in their patent and licensing practices.
- All interested parties should test and implement new and additional models of research funding (R&D).
- The UN SG should initiate a process for governments to negotiate global agreements on the coordination, financing and development of health technologies, including negotiations for a binding R&D Convention to delink the cost of R&D from the final price of medicines, thus promoting access to good health for all. Governments should establish a working group to initiate the negotiation of a Code of Principles for Biomedical R&D.
- Governments should review the status of access to health technologies in their country through the lens of human rights principles.

- Governments should require manufacturers and distributors to disclose to drug regulatory and procurement authorities information regarding the cost of R&D, production, marketing and distribution of health technologies.
- Governments should make all clinical trial data publicly available.

Although discussions leading to the production of the report were not public, dissenting comments by some members of the panel at the end of the report clearly show that consensus was not reached on some of the recommendations, which would have otherwise significantly advanced the debate and achieved making substantive changes to the current R&D model to improve access to medicines.

The most significant progress made in the debate on access to medicines, through the UN Secretary-General's report, is undoubtedly the assertion that this is a global problem that affects both developing and developed countries. All documents produced in the WHO context stated that the problem encompassed some diseases that disproportionately affected developing countries. A report produced after the appearance of Sofosbuvir for Hepatitis C at a price of \$ 84,000 per 12-week treatment could not continue to claim that the problem was only limited to poor countries.

The second most important contribution of the report is the recommendation to "make use of the space available in TRIPS Article 27 to adapt and apply rigorous definitions of invention and patentability."<sup>40</sup> This is undoubtedly the most important flexibility of the TRIPS agreement, i.e. the freedom of each country to interpret and define the three requirements of the TRIPS agreement to grant patents: novelty, inventiveness and industrial application.

The third important point of the report is not new, but it is critical in that it rescues a recommendation that already exists in the WHO, that countries and the WHO Secretariat were unable to put into practice: "to begin negotiations on an binding R&D Convention that delinks research costs from final medicine prices to promote access to good health for

<sup>&</sup>lt;sup>40</sup> Ibid., page 9.

all.<sup>341</sup> In the 180 contributions from countries, institutions, UN agencies, NGOs, universities, pharmaceutical industry, and individuals from around the world; one-third alluded to some form of treaty or binding convention as an alternative or complementary model for R&D.

The fourth important point concerns the almost "symbolic" contribution that the WTO has made to the problem of access to medicines until now with the so-called "paragraph 6" a mandate given by the Doha Declaration, which has given no results yet after 13 years of existence. The report of the Secretary-General recommends that WTO members should review the paragraph 6 decision.

## X. CONCLUSIONS

In the last 15 years, a lot of material has been published in the area of public health and intellectual property. There have been World Health Assembly resolutions, 17 of them; and numerous WHO publications; and publications from academia and NGOs, that have analyzed and provided guidance on how to protect access to health vis a vis the new international trade rules required under the WTO. Also, important recently are the free trade agreements and bilateral investment agreements that contain clauses and conditions that are more stringent than the standards of the TRIPS agreement.

In terms of technical assistance to countries for their use of TRIPS flexibilities, the position of WHO seems to have had a turnaround in the last 3 years, due apparently to its alliance with WTO and WIPO. The collaboration between WHO, WTO and WIPO is a good thing, as long as the mandate given by the WHA resolutions is respected and implemented. In terms of international trade and investment agreements, WHO cannot have a "neutral position": its mandate is already biased by the perspective of public health and the mandate given by the different resolutions of the World Health Assembly in recent years. International trade rules and public health matters are two different regimes that should not be equated. In the first case, we are talking about norms and

<sup>&</sup>lt;sup>41</sup> Ibid., page 10.

rules of the economy and in the second case; we are dealing with the right to health as a fundamental human right.

In this regard, the pronouncements of the Commission on Human Rights and the UN Secretary-General's High-level panel are fundamental and can relaunch the debate that has been "dormant" in the WHO for the last 5 years.

In the future we will see whether the WHO Secretariat and Member States arrive at an understanding that working and supporting countries in the field of public health and intellectual property is an opportunity rather than a problem to be avoided. It is an opportunity, such as in the case of a possible international treaty to finance pharmaceutical R&D, which could help this United Nations specialized agency to rediscover its identity and a reason to be in the twenty-first century.

Finally, it is important to note that the international organizations are at the service of the Member States, which means that countries can always request an additional specific mandate, or demand that in the areas where there is a mandate, this mandate is actually executed.

## CHAPTER 5 ACCESS TO MEDICINES: EXPERIENCES WITH COMPULSORY LICENSES AND GOVERNMENT USE – THE CASE OF HEPATITIS C<sup>\*</sup>

Carlos M. Correa<sup>1</sup> and Germán Velásquez

#### I. INTRODUCTION

Access to medicines strongly relies on pricing and financing mechanisms that can be differently applied to each country. In developing countries, in the absence of broad health coverage systems, a large part of the expenditure comes from the patients' own pockets, provided, of course, that their level of income allows them to afford it. This does not happen, however, in many of the cases where medicine prices are inaccessible to various segments of the population. As medicines are financed by a third-party payer, high prices are the biggest source of pressure on the budget.

A determining factor regarding medicine pricing is the degree of competition in a particular therapeutic class, which in turn is influenced by the existence or nonexistence of intellectual property rights, such as invention patents. Patent rights grant exclusive rights over a medicine for at least 20 years, from the date that the patent application was filed. This allows the patent holder to act as a monopolist and to set the price that the market "can bear".

The restriction of the competition generated by intellectual property rights affects mainly patients from developing countries, especially after the adoption in 1995 – and the entry into force in those countries in the

<sup>\*</sup> Document prepared for the "International Congress on Policies and Strategies to Facilitate Access to Treatments for Hepatitis C", March 8 and 9, 2018, Bogotá, Colombia, organized by the Ministry of Health of Colombia, UNITAID, Coalition PLUS, and the South Centre. The authors are grateful to Francisco Rossi, Director of IFARMA, Colombia, for his contribution in the analyses of the cases from Colombia and Peru.

<sup>&</sup>lt;sup>1</sup> Carlos M. Correa is Executive Director of the South Centre, Geneva.

year 2000 – of the Agreement on Trade-Related Aspects of Intellectual Property Rights (the TRIPS Agreement) of the World Trade Organization (WTO). This agreement, actively promoted by the American and European pharmaceutical industry, forced all the member countries of this organization to grant patents on medicines. Consequently, for reasons of public health, many countries that excluded the patenting of pharmaceutical products had to adapt their legislation to this new international regulation. Failing to do so would expose themselves to commercial reprisals legitimized by the WTO dispute settlement mechanism.

First, this chapter discusses the limitations of the current research and development (R&D) model and its implications for access to medicines. Second, it considers the tension between intellectual property rights applied to medicines and the States' observance of the fundamental right to health. Third, it examines the case of access to medicines for the treatment of Hepatitis C, illustrating the barriers to access created by intellectual property and the high prices normally associated with its exercise. Fourth, it presents the background, main aspects and obstacles to the achievement of the objectives that led to the approval, in 2001, of the Doha Declaration on the TRIPS Agreement and Public Health. Having presented the above introductory sections, this chapter examines in three sections the concepts of compulsory licensing and government use of patents, experiences in Latin America (in particular, Ecuador, Peru and Colombia)<sup>2</sup> and in other countries, including the role of civil society and cases in which non-commercial government use was authorized in order to produce or import medicines and improve access for the population. Finally, the main conclusions are drawn

## II. HIGH PRICES, LOW PERFORMANCE OF RESEARCH AND DEVELOPMENT

A recent study in the United States found that many of their 71 cancer medicines registered by the Food and Drug Administration (FDA)

<sup>&</sup>lt;sup>2</sup> The authors are grateful for the contribution of Francisco Rossi, Director of IFARMA, Colombia, to the analysis of the cases from Colombia and Peru.

between 2002 and 2014 cost more than \$ 100,000 per treatment/year.<sup>3</sup> Another notable example of high prices, discussed below, is the treatment for hepatitis C based on sofosbuvir. The high price of such medicines – owing to the intellectual property system – is, as noted, especially burdensome for developing countries. It is estimated that one third of the world's population does not have regular access to medicines.<sup>4</sup> However, this problem increasingly affects the developed countries themselves where, thanks to state (in Europe) or private (in USA) health insurance, patients used to afford to buy the medicines they needed. This is no longer the case, because these countries have also begun to have difficulties to ensure the supply of certain medicines, excessively expensive ones, to all their citizens.

The argument traditionally used by the pharmaceutical industry to justify the high prices of medicines<sup>5</sup> has been high direct costs of R&D, as well as costs incurred in the development of products that, by not complying with health standards of efficacy or safety, never reach the market. In the last ten years, the estimates of R&D costs of the industry have increased dramatically. According to an estimate in November 2014 by the Tufts Medical Center in Boston, the development of a new molecule for medicinal use would require an investment of 2.5 billion US dollars.<sup>6</sup>

These estimates, which are based on data from the pharmaceutical industry, are not easily verifiable. In contrast, a study conducted in 2011 by independent researchers, published by the London School of Economics, estimated an average cost for the development of a new drug at only USD 43.4 million.<sup>7</sup> For its part, the non-profit foundation

<sup>&</sup>lt;sup>3</sup> Ariadna Tibau, MD, Alberto Ocana, MD, PhD et al., "Oncologic Drugs Advisory Committee Recommendations and Approval of Cancer Drugs by the US Food and Drug Administration", JAMA Oncol. 2016; 2(6):744-750. doi:10.1001/jamaoncol.2015.6479.

<sup>&</sup>lt;sup>4</sup> OMS, Accès équitable aux médicaments essentiels : cadre d'action collective, (Genève, Mars 2004). Available at http://apps.who.int/medicinedocs/pdf/s4963f/s4963f.pdf.

<sup>&</sup>lt;sup>5</sup> More recently, some pharmaceutical companies have justified their high prices for the therapeutic benefit of the product and the cost of alternative treatments.

<sup>&</sup>lt;sup>6</sup> Tufts Center for the Study of Drug Development, Cost of developing a new drug, (Boston, November 2014).

<sup>&</sup>lt;sup>7</sup> Donald W. Light and Rebecca Warburton, "Demythologizing the high costs of pharmaceutical research" (2011), Available from

http://www.pharmamyths.net/files/Biosocieties\_2011\_Myths\_of\_High\_Drug\_Research\_Costs.pdf.

Drugs for Neglected Diseases initiative (DNDi) disclosed in 2013 the R&D cost of the products it had worked on during its 10 years of existence, which amounted to USD 100-150 million per new chemical entity.<sup>8</sup>

While there is no transparency about what the real R&D costs are, the problem of pricing and, therefore, of access to medicines, will remain unresolved. Determining whether the cost of a new molecule is US\$ 40-150 million or US\$ 2,500 million is obviously critical to implement a medicines policy that ensures that therapeutic innovations reach those who need them and not only those who, by their own resources or the support of health systems, can afford them at the prices, sometimes exorbitant ones, imposed by the so-called "innovative" industry.

Paradoxically, the alleged increase in pharmaceutical R&D costs does not correspond to a parallel increase in the R&D efficiency of the industry. On the contrary, the R&D performance has lowered significantly in the last twenty years, not only measured by the number of new medicinal chemical entities approved for commercialization, but by the therapeutic usefulness of the new products introduced to the market. For example, according to Prescrire's<sup>9</sup> ratings of new drugs and new indications introduced in the French market, only one out of ten years (2007 - 2016) was rated as "Excellent", 10 rated as "Interesting" in that same period, and 14 rated as "Contributes something" in 2006 but only 5 in 2016. 524 products were rated as "Does not contribute anything new" in the ten years analyzed (see Table 1).

<sup>&</sup>lt;sup>8</sup> DNDi, "Research & Development for Diseases of the Poor: A 10-Year Analysis of Impact of the DNDi Model", (Geneva, 2013).

<sup>&</sup>lt;sup>9</sup> Rev. Prescrire, "L'année 2016 du médicament : un système qui favorise l'imitation plutôt que la recherche de réels progrès". Tome 37 No. 400 (Paris, février 2017), p. 136.

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2010										
YEARS	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Excellent	1	0	0	0	0	0	0	1	0	0
Interesting	2	0	0	1	0	1	0	2	3	1
Contributes something	14	6	3	3	3	3	6	5	5	5
Occasionally useful	27	25	14	22	13	14	12	15	15	9
Does not contribute anything new	79	57	62	49	53	42	48	35	43	56
Objected by the Journal	15	23	19	19	16	15	15	19	15	16
Without sufficient elements for evaluation by the Journal	3	9	6	3	7	7	9	10	6	5
Total	141	120	104	97	92	82	90	87	87	92

Table 1**Therapeutic value of medicines introduced in the market in 2007-2016** 

*Source*: Prescrire, "L'année 2016 du médicament : un système qui favorise l'imitation plutôt que la recherche de réels progrès", Tome 37 No. 400 (Paris, February 2017), p. 136.

Given the importance of the French pharmaceutical market, one can assume that the vast majority of medicines that came onto the world market between 2007 and 2016 were the same ones introduced in the French market. In other words, the limitations in the innovation of new pharmaceutical products found in France is a good indicator of the world's actual situation.

The opacity of R&D costs, the declining productivity in R&D activities of the "innovative" industry, and high prices are three aspects that characterize the current R&D model.

This has led civil society and groups of experts<sup>10</sup> to vast academic discussions and various initiatives pointing to a change in the R&D

<sup>&</sup>lt;sup>10</sup> See Velásquez, G., "Access to Hepatitis C Treatment: A Global Problem", South Centre Research Paper No. 77 (Geneva, May 2017), p. 4. In fact, 180 proposals were submitted to the United Nations Secretary General's High Level Panel on Access to

model that would allow generating more genuinely useful innovation from the point of view of public health, which would culminate in products accessible to those who need them, especially segments of society with fewer resources. These initiatives have included, in particular, the establishment of reward systems, advance purchase contracts, and the negotiation in the scope of the World Health Organization (WHO) of a binding instrument on R&D related to medicines.<sup>11</sup>

#### III. INTELLECTUAL PROPERTY AND HUMAN RIGHTS

The discussion of a new R&D model has faced the expected resistance of developed countries and the industry that benefits from the current model based on the scheme: R&D (private and public) – patent (monopoly)<sup>12</sup> – high price – high profitability – restricted access.

The application of the current R&D model leads, as discussed at the High Level Panel convened by the United Nations (UN) Secretary-General (SG) in late 2015,<sup>13</sup> to incoherence between the intellectual property system and the realization of human rights to health. The terms of reference set for the expert group called for a study on "The incoherence between the rights of inventors, international human rights legislation, trade rules and public health".<sup>14</sup> Among the main recommendations in the Report<sup>15</sup> of the Panel, the following stand out:

Medicines, 46 of which were proposals for a substantive modification of the current R & D model.

<sup>&</sup>lt;sup>11</sup> WHO, "Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG)", 2012. Available from http://www.who.int/phi/cewg\_report/en/.

<sup>&</sup>lt;sup>12</sup> In some countries, test data exclusivity is added to patent protection. See, e.g. Cortes M., et al., "Impacto de diez años de protección de datos para medicamentos en Colombia", IFARMA, Serie Buscando Remedio, No. 2 (Bogotá, 2014). Available from http://web.ifarma.org/images/files/buscandoremedio/BuscandoRemedio\_2.pdf.

<sup>&</sup>lt;sup>13</sup> The United Nations Secretary-General's High-Level Panel on Access to Medicines, "The Panel". Available from http://www.unsgaccessmeds.org/new-page/.

<sup>&</sup>lt;sup>14</sup> In less than three months, more than 180 proposals were received from countries, institutions, United Nations agencies, non-governmental organizations (NGOs), universities, the pharmaceutical industry, individuals.

<sup>&</sup>lt;sup>15</sup> Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines (2016). Available from http://www.unsgaccessmeds.org/final-report.

- Make full use of the policy space available in Article 27 of the TRIPS Agreement by adopting and applying rigorous definitions of invention and patentability
- Adopt and implement legislation that facilitates the issuance of compulsory licenses (CL)
- Revise the paragraph 6 decision of the Doha Declaration on the TRIPS Agreement and Public Health (hereinafter "Doha Declaration"<sup>16</sup>)
- Refrain (governments and the private sector) from explicit or implicit threats, tactics or strategies that undermine the right of WTO Members to use TRIPS flexibilities
- Initiate a process (led by the Secretary-General of the United Nations) for governments to negotiate a mandatory convention for R&D in the pharmaceutical area.

The aforementioned report suggests that although a change in the current R&D model is necessary, there are immediate measures that governments can adopt in order to mitigate the effect of intellectual property on access to medicines, within the framework of the TRIPS Agreement, in order to comply with human rights obligations and achieve the sustainable development goals set for the year 2030.<sup>17</sup> In particular, it is about the use of the so-called "flexibilities" that were confirmed in that agreement in 2001 by the Declaration discussed below.

Significantly, the Human Rights Council (HRC) of the United Nations considered, in its deliberations in 2015-2016, that barriers to access to medicines can be deemed as a violation of human rights.<sup>18</sup> The Council approved in 2016 a resolution that reaffirms that access to medicines is a fundamental element for the full exercise of the right to health.<sup>19</sup>

<sup>&</sup>lt;sup>16</sup> Declaration on the TRIPS Agreement and Public Health adopted on November 14, 2001, WT/MIN/(01)/DEC/2.

<sup>&</sup>lt;sup>17</sup> Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines (2016), p. 12. Available from http://www.unsgaccessmeds.org/final-report.

<sup>&</sup>lt;sup>18</sup> HRC Resolution 32/L.23 on "Access to Medicines in the Context of the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health", Geneva, 2016.

<sup>&</sup>lt;sup>19</sup> Viviana Muñoz-Tellez and Adriano José Timossi, "Human Rights Council adopts historic resolutions on access to medicines", South Bulletin No. 92 (4 August 2016).

Resolution 32/L.23 entitled "Access to Medicines in the Context of the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health", supported by 72 co-sponsors, was presented by Brazil, China, Egypt, Haiti, India, Indonesia, Paraguay, Peru, Senegal, Sri Lanka, South Africa and Thailand.

Many resolutions have been approved in the last 15 years in the context of the WHO. The debate was held fundamentally between health and trade. What comes first, health or trade? What were the possible contradictions and what were the mechanisms to protect health from the possible negative effects of the new rules governing international trade? On several occasions, developing countries attempted to introduce into these resolutions, and to approve by consensus, a reference to human rights as a basis to ensure access to medicines. Unfortunately, all the attempts were frustrated by opposition from some developed countries, particularly the USA.<sup>20</sup>

The importance of the aforementioned resolution 32/L.23 is mainly that the HRC confirmed the primacy of human rights, such as the right to health, over intellectual property rights and those derived from other investment or trade agreements. Equally important, the resolution reaffirms the ability of countries to take advantage of the flexibilities provided by the TRIPS Agreement to promote access to medicines, recognizing that patents can be used to set high prices to medicines.<sup>21</sup>

The resolution reiterates the importance of access to medicines for all as one of the fundamental human rights and emphasizes that the improvement of that access could save millions of lives each year. The resolution also refers to the Doha Declaration, which, as discussed below, confirms that the abovementioned Agreement does not and should not prevent WTO members from taking measures to protect public health.

<sup>&</sup>lt;sup>20</sup> During the negotiations of the Global Strategy on Public Health, Innovation and Intellectual Property in the WHO in 2006-2008, some developed countries, mainly the United States, refused to include the expression "human rights" in the text of the Strategy.

<sup>&</sup>lt;sup>21</sup> HRC Resolution 32/L.23 on "Access to Medicines in the Context of the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health", Geneva, 2016.

The approval by consensus of the resolution coincided with the celebrations of the 30th anniversary of the Declaration on the Right to Development in which both the right to health and access to medicines and public health are recognized as fundamental elements for the exercise of the right to development.<sup>22</sup>

## IV. THE CASE OF HEPATITIS C – TOWARDS A PARADIGM SHIFT?

A paradigmatic case evincing the incoherence between the exercise of intellectual property rights and the realization of the fundamental right to health is that which concerns the treatment against the hepatitis C virus.

Until late 2013, the standard treatment for hepatitis C consisted of injections of pegylated interferon for 24 to 48 weeks accompanied by ribavirin tablets. This treatment was expensive, toxic, poorly tolerated, complicated to administer and with cure rates of less than 50 per cent.<sup>23</sup>

At the end of 2013, a new type of treatment based on direct-acting antivirals (DAAs) was introduced into the market. With eight to twelve weeks of treatment, these medicines can cure more than 90 per cent of patients with chronic Hepatitis C infection.

The new treatments based on DAAs were introduced by the pharmaceutical companies Gilead Sciences and Bristol-Myers Squibb (BMS). Gilead has patented or applied for patents for sofosbuvir, ledipasvir and velpatasvir.<sup>24</sup> BMS has patented or applied for patents for daclatasvir.<sup>25</sup> As the treatment in many cases should include sofosbuvir and daclatasvir, a double barrier is generated when patents belong to

<sup>&</sup>lt;sup>22</sup> HRC Resolution 32/L.23 on "Access to Medicines in the Context of the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health", Geneva, 2016.

<sup>&</sup>lt;sup>23</sup> Manns MP, Wedemeyer H, Cornberg M., "Treating viral hepatitis C: efficacy, side effects, and complications". Gut 2006; 55(9):1350-9.

<sup>&</sup>lt;sup>24</sup> Gilead Sciences, 2016. Available from http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-irhome.

<sup>&</sup>lt;sup>25</sup> Médecins Sans Frontières (MSF) Briefing Document, May 2015. Available from http://hepcasia.com/wp-

content/uploads/2015/05/hcv\_overcomingbarrierstoaccess\_en\_may2015.pdf.

different companies. Other transnational companies such as AbbVie, Merck and Janssen have put other DAAs on the market, as new products are found in the pipeline of these and other firms. Gilead Sciences introduced sofosbuvir at the exorbitant price of US\$ 84,000 for a twelve-week treatment in the US.

According to a WHO<sup>26</sup> fact sheet published in 2015 (two years after the appearance of the first treatments), of the estimated  $130-150^{27}$ million people living with Hepatitis C, only 275,000 received the new treatment with DAAs, of which 170,000 lived in Egypt, the country with highest incidence of hepatitis C in the world. This was possible thanks to the dramatic drop in the treatment cost to US\$ 153 for 3 months (a product made by the Egyptian company PHARCO). The explanation for this situation is simple: Gilead could not obtain a patent on sofosbuvir in Egypt as the country's patent office applies strict patentability criteria.<sup>28</sup>

English scholars<sup>29</sup> have determined that the production cost for the twelve-week treatment with sofosbuvir is US\$ 62 (including a 50 per cent profit margin), but Gilead Sciences has managed to negotiate, with several governments, prices – with large differences from one country to another – completely unrelated to the probable costs of R&D and production: 50,426 euros in Germany, 41,680 euros in France,<sup>30</sup> 13,000 euros in Spain, 6,000 euros in Brazil, 3,465 euros in Australia.<sup>31</sup>

Why 41,000 euros in France and 13,000 euros in Spain? This seems to depend on the negotiating capacity of each country. Gilead's business strategy, in its new business model, is to obtain the maximum profits

<sup>&</sup>lt;sup>26</sup> Available from https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-c; https://apps.who.int/iris/bitstream/handle/10665/250625/WHO-HIV-2016.20-eng.pdf.

<sup>&</sup>lt;sup>27</sup> Figure recently reviewed by the WHO that now reports 70 million in the world.

<sup>&</sup>lt;sup>28</sup> Gilead offered Egypt a price of US \$ 900 per each 12-week treatment, an offer that was not put forward since the patent was not obtained, and a local firm offered a significantly better price.

<sup>&</sup>lt;sup>29</sup> Gotham D, Barber M, Fortunak J, Pozniak A, Hill A, Abstract number A-792-0516-01639, presented at AIDS 2016, Durban.

<sup>&</sup>lt;sup>30</sup> On March 17, 2017, the French Government announced a new reduction to 28,700 euros for the 12-week treatment, a price that is still more than double what Spain pays. "Soins: le prix des médicaments contre l'hépatite C va baisser". Available from http://www.leparisien.fr/laparisienne/sante/soins-le-prix-des-medicaments-contre-l-hepatite-c-va-baisser-31-03-2017-6812619.php.

<sup>&</sup>lt;sup>31</sup> Price of the 12-week treatment.

without any relation to the R&D costs – with the aim of setting the highest price that governments agree to pay (so in the end they realize that universal access will not be possible at the prices that were negotiated, as is the case of France or Spain).

This case brings forward three interesting elements that mark a change in the debate on access to medicines. First, they are medicines that heal, unlike the vast majority of drugs put on the market in the last 20 years that allow controlling a disease as chronic, without curing it. Second, unaffordable prices were set for both developed and developing countries. It is now a global problem. Third, the pharmaceutical industry de-links R&D costs from the final price, and argues that it must be related to the country's ability to pay<sup>32</sup> or to the "value" of the medicine compared to a possible cost of a liver transplant. With this approach, it is clear that the pharmaceutical industry's main objective is to remunerate its shareholders as much as possible, rather than as an instrument to serve public health. This industry has also achieved what academics and civil society organizations claimed several years ago: delink the R&D costs from the final price of the product. However, as stated by Ruth Dreifuss (former president of Switzerland) at the Graduate Institute<sup>33</sup> in Geneva, on 23 February 2017, it is a "malefic delinkage" because the cost of R&D and production has nothing to do with the final price of the medicine.

# V. THE USE OF THE TRIPS AGREEMENT'S FLEXIBILITIES AND THE DOHA DECLARATION

As aforementioned, to the same extent that a new R&D model has not been installed to simultaneously promote innovation and access to new medicines, governments must rely on the flexibilities of the TRIPS Agreement to favour such access. The Doha Declaration – adopted on 14 November 2001 by the Fourth WTO Ministerial Conference – played a key role in confirming these flexibilities.

<sup>&</sup>lt;sup>32</sup> Pratap Chatterjee, "Gilead Sciences Under Investigation for Over Charging for Hepatitis C Pill", July 21, 2014. Available from http://www.corpwatch.org/article.php?id=15964.

<sup>&</sup>lt;sup>33</sup> Seminar about the High Level Panel on Access to Medicines.

#### V.1 Background

In 1996, the World Health Assembly adopted Resolution WHA 49.14 regarding the Revised Drug Strategy in which it requested the World Health Organization (WHO) "to report on the impact of the work of the WTO with respect to national medicine policies and essential medicines, including making recommendations for collaboration with the WTO". With this resolution, the WHO was entrusted with the task of examining the new architecture of the multilateral trading system established by the WTO system in relation to public health.

In compliance with such a mandate, in 1998 the WHO Action Programme on Essential Drugs published a monograph entitled Globalization and Access to Drugs - Perspectives on the WTO/TRIPS Agreement.<sup>34</sup> This guide was made with the objective of informing professionals responsible for health policies, those who lack specific legal training, of the effect that the TRIPS Agreement could have on public health and pharmaceutical policies. Although the authors noted that the TRIPS Agreement imposed standards historically derived from industrialized countries, they also asserted that the Agreement provided considerable discretion to protect public health, now generally known as "the TRIPS flexibilities". The Agreement, in effect, gives countries the possibility of implementing measures such as granting compulsory licenses, admitting parallel imports, considering exceptions to patent rights, as well as rigorously defining patentability criteria. These flexibilities can be used with a view to striking a balance between patent rights and public health needs.<sup>35</sup>

However, in practice, the multinational pharmaceutical companies and the governments of some developed countries questioned, both legally and especially in the political sphere, the right of developing countries to make use of the aforementioned flexibilities.

<sup>&</sup>lt;sup>34</sup> Velásquez, Germán y Boulet, Pascale, "Globalización y acceso a los medicamentos: Implicaciones del Acuerdo de la OMC sobre los ADPIC", Serie: Economía de la salud y medicamentos, Serie del DAP Núm. 7 (WHO/DAP/98.9, Noviembre de 2007, Programa de Acción sobre Medicamentos Esenciales, Organización Mundial de la Salud, Ginebra).

<sup>&</sup>lt;sup>35</sup> In 1999, the 52nd World Health Assembly adopted resolution WHA 52.38 on the Revised Drug Strategy urging member countries to "ensure that the interests of public health be a priority in pharmaceutical and health policies".

In 1998, a lawsuit filed by 39 pharmaceutical companies against the South African Government to challenge the use of flexibilities (parallel imports, compulsory licenses), provided for in the TRIPS Agreement<sup>36</sup> in line with a correct interpretation of this Agreement and the recommendations of the WHO, provoked massive public protests. After an intense international campaign in support of the South African Government, the pharmaceutical industry was forced to withdraw the demand. As a result of this episode, the African Group proposed and obtained the necessary consensus to discuss the topic of intellectual property and access to medicines in special sessions of the WTO TRIPS Council. These discussions showed the need to confirm the legitimacy of the flexibilities allowed by the TRIPS Agreement, and ultimately led to the adoption of the Doha Declaration.

## V.2 Reaffirmation of the TRIPS Agreement's Flexibilities

The Doha Declaration recognized existing concerns about the effect of intellectual property rights on medicine prices (paragraph 3), which represented one of the greatest political achievements for developing countries in this area.

In addition, paragraph 4 of the Declaration provides a rule of interpretation to judge whether measures necessary to protect public health violate the provisions of the TRIPS Agreement. It declares that the Agreement "does not and should not prevent members from taking measures to protect public health" and that it "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".

The Declaration reaffirmed the right of WTO members to make maximum use of the flexibilities provided for in the TRIPS Agreement to protect public health and promote access to medicines. In paragraph 5, it confirms that its provisions must be interpreted in the light of its object and purpose, as expressed, especially in its objectives and principles (Articles 7 and 8 of the TRIPS Agreement). In the same

<sup>&</sup>lt;sup>36</sup> In 1997, South Africa introduced several amendments to its Medicines and Related Substances Control Act with a view, among other objectives, to authorizing "parallel imports" (i.e. imports without authorization from the patent holder) of pharmaceutical products.

paragraph, the Declaration identifies some of the flexibilities provided in the Agreement for public health and mentions, in particular, the right of Members to grant compulsory licenses and to determine the reasons why such licenses should be granted. These may include the lack of or insufficient exploitation of a patent; anti-competitive practices, exorbitant prices and, more generally, the public interest.

The Declaration also recognizes the right to determine what constitutes a national emergency, or other circumstances of extreme urgency, on the basis that public health crises, including those related to HIV/AIDS, tuberculosis, malaria and other epidemics can create those situations. This is a crucial element of the Declaration because, as discussed below. WTO Members can grant а compulsory license/government use without the obligation to previously negotiate a voluntary license with the patent holder (Article 31, subparagraph b, TRIPS Agreement). These measures can continue to be applied as long as the situation of national emergency or extreme urgency persists.<sup>37</sup>

Additionally, the Declaration confirms that members are free to apply the principle of international exhaustion of rights to allow parallel importation of a product protected by intellectual property rights legitimately marketed in any other country.

### V.3 Obstacles to the Implementation of the Doha Declaration

Even after sixteen years of the Doha Declaration adoption on TRIPS and Public Health, it still remains a historic achievement in terms of clarifying the relationship between intellectual property and public health. However, several developing countries have faced obstacles to implement it.

One of the biggest stumbling blocks that has been observed, after 16 years of the Declaration, is the lack of adequacy of national legislations. The use of flexibilities requires, in many cases, that national legislations be amended. The lack of appropriate national legislation for the full implementation of such flexibilities remains one of the greatest

<sup>&</sup>lt;sup>37</sup> Carlos M. Correa, "Implications of the Doha Declaration on the TRIPS Agreement and Public Health", (World Health Organization, June 2002). Available from http://www.who.int/medicines/areas/policy/WHO\_EDM\_PAR\_2002.3.pdf.

difficulties for some developing countries. At the international level, there is a need to improve the legal and technical assistance offered to these countries with respect to intellectual property and public health. In the 16 years since the Doha Declaration, technical assistance has been insufficient or inappropriate.

Although since the adoption of the Doha Declaration, the use of the TRIPS Agreement's flexibilities has been challenged on only two occasions in the face of the WTO Dispute Settlement Body (DSB). None of these cases resulted in a panel or report stating a violation of the Agreement. This situation is, perhaps, in itself a proof of the importance of the legitimation of these flexibilities to the developing countries by means of the Doha Declaration.

### VI. USES WITHOUT AUTHORIZATION FROM THE PATENT HOLDER

The possibility of authorizing the use of a patent without the consent of its holder is one of the main flexibilities of the TRIPS Agreement – confirmed, as could be seen, by the Doha Declaration – and a crucial element in a patent law that considers public health needs. These authorizations can serve to mitigate the monopoly rights conferred by a patent and, therefore, promote competition without denying the right of the patent holder to continue the exploitation of the invention (through importation or local production) or to receive remuneration for the use of the invention patented by third parties.

Two types of authorizations can be distinguished according to who their beneficiary is. On the one hand, "compulsory licenses" or "nonvoluntary licenses" are granted by the State (administratively or judicially) in favour of a natural or legal person that complies with the procedural and substantive requirements established by the applicable national legislation. The beneficiary is a person other than the State itself. On the other hand, the "authorization of government use", also called "non-commercial public use", can be dictated by the State for the use, by the very State, of a patented invention. In this case, unlike in compulsory licenses, the direct beneficiary is not a third party, although State contractors may intervene.

WTO Member countries can establish compulsory licenses for various reasons and arrange government use for non-commercial purposes in accordance with Article 31 of the TRIPS Agreement. Article 31 does not limit the reasons why compulsory licenses can be granted or non-commercial government use can be adopted. It leaves, in this sense, ample room for manoeuvre for countries to legislate and decide on the matter. This provision only establishes the conditions under which such authorizations may be issued, such as dictated on a case-by-case basis. prior negotiation with the patent holder (in some cases), payment of an adequate remuneration, and non-exclusivity of the licenses granted. In most countries, including developed countries, some form of compulsory licensing or government use is provided by law.<sup>38</sup> These instruments have been widely used, for example, in the USA in order to correct anti-competitive practices and as a part of the government's preeminent right to exploit any patented invention.<sup>39</sup> In that country, compulsory licenses can be articulated by the administration or by the judicial courts, through the file of authorizing a party in violation of a patent to continue with the use of the invention for reasons of "equity" against the payment of a royalty.<sup>40</sup>

Compulsory licenses have also been granted on patents in Italy and, more recently, Germany, specifically in relation to pharmaceutical products. In the latter country, for example, the court of appeal confirmed in July 2017 a compulsory license granted by a lower court for reasons of 'public interest' in relation to an antiretroviral drug.<sup>41</sup>

<sup>&</sup>lt;sup>38</sup> According to a World Intellectual Property Organization (WIPO) study, the laws of at least 84 countries contain provisions for the use of patents without the authorization from the holder. See WIPO Secretariat Report on Compulsory Licensing: SCP/21/4 REV., Nov. 3, 2014.

<sup>&</sup>lt;sup>39</sup> See JH Reichman, "Non-Voluntary Licensing of Patented Inventions: The Law and Practice of the United States" (UNCTAD-ICTSD, 2006).

<sup>&</sup>lt;sup>40</sup> See Supreme Court of the United States on eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388 (2006) and the decisions issued under the doctrine of this case, e.g. in Sue Ann Mota, "eBay v. MercExchange: Traditional Four-Factor Test for Injunctive Relief Applies to Patent Cases, According to the Supreme Court", Akron Law Review: Vol. 40:

Applies to Patent Cases, According to the Supreme Court", Akron Law Review: Vol. 40: Iss. 3, Article 4, available at

http://ideaexchange.uakron.edu/akronlawreview/vol40/iss3/4; Ryan T. Holte & Christopher B. Seaman, "Patent injunctions on appeal: An empirical study of the federal circuit's application of eBay", Washington Law Review, Vol. 92: 145, 2017, available at https://digital.law.washington.edu/dspace-

law/bitstream/handle/1773.1/1669/92WLR0145.pdf?sequence=1&isAllowed=y.

<sup>&</sup>lt;sup>41</sup> See http://ipkitten.blogspot.co.za/2017/07/bgh-grants-compulsory-license-in.html.

Some developing countries have begun to make a more efficient use<sup>42</sup> of compulsory licenses/government use (see Table 2), despite the obstacles and pressures (from governments and the multinational pharmaceutical industry) that they have had to face. For example, in 1997, the USA threatened to impose sanctions on Thai exports if Thailand did not abandon its plan to use compulsory licenses. As mentioned, 39 pharmaceutical manufacturers filed in 1998 a lawsuit against the South African legislation on parallel imports, in which the legitimacy of compulsory licenses was also questioned.<sup>43</sup> The most recent case of Colombia referring to imatinib (discussed below) points out that the same obstacles persist twenty years later.

#### Table 2

## Compulsory licenses/authorizations for government use in developing countries

Zimbabwe, May 2002, compulsory license to produce seven generic versions of antiretroviral drugs (ARVs)

Malaysia, November 2003, compulsory license to import ARVs from India for 2 years from November 1, 2003

Mozambique, April 2004, compulsory license for the local manufacture of ARVs

Zambia, September 2004, compulsory license for the local manufacture of ARVs

Indonesia, October 2004, compulsory license for ARVs

Eritrea, June 2005, compulsory license to import generic ARVs

Ghana, October 2005, government use to import generic ARVs

Thailand, November 2006, government authorization for local production of efavirenz and importation of the same medication from India

<sup>&</sup>lt;sup>42</sup> See, for example, C. Oh, "Compulsory licenses: Recent experiences in developing countries", 1 Intl J of Intellectual Property Management no. 1-2 (2006): pp. 22-36.

<sup>&</sup>lt;sup>43</sup> J-F Morin, "Tripping Up: TRIPS Debates, IP and Health in Bilateral Agreements", International Journal of Intellectual Property Management 1, no. 1-2 (October 3, 2006): pp. 37-53; JC Nwobike, "Pharmaceutical corporations and access to drugs in developing countries: The way forward", Sur-Intl Journal on Human Rights 3, no. 4 (2006): pp. 126-143.

Thailand, January 2007, government authorization for the cardiovascular drug Plavix (clopidogrel)

Thailand, January 2007, government authorization for ARV Kaletra (lopinavir+ ritonavir)

Brazil, May 2007, government authorization for the importation of generic efavirenz from India

Thailand, 2008, government authorization for four anti-cancer drugs

India, 2012, license due to lack of Sorafenib (medicine for liver cancer) exploitation

Ecuador, 10 compulsory licenses between 2013 and 2014

Malaysia, 2017, government use for sofosbuvir

*Source*: Based on Carlos M. Correa, *Pharmaceutical Innovation*, *Incremental Patenting and Compulsory Licensing*, South Centre, Geneva, 2011.

While the majority of compulsory licenses/government use have referred to medicines for HIV/AIDS, the Doha Declaration confirmed that these measures can be adopted without being limited to particular ailments, such as HIV/AIDS, tuberculosis, and malaria. Thus, in 2008 Thailand authorized government use for four anti-cancer drugs. The same country had already granted in 2007 a compulsory license for a medicine for cardiac use (clopidogrel). India granted a compulsory license in relation to a medicine for liver cancer ("sorafenib") in 2012. These are compelling (albeit sparse) examples of the possible use of the flexibilities provided for in the TRIPS Agreement.

Some free trade agreements restrict the freedom of WTO members to determine the grounds for compulsory licensing, contrary to what was confirmed by the Doha Declaration on the TRIPS Agreement and Public Health. Thus, in free trade agreements of the United States with Jordan, Australia and Singapore, these causes are limited to cases of anticompetitive practices, non-commercial public use, national emergency or other circumstances of extreme urgency. This limitation, however, does not appear in other free trade agreements signed with developing countries (including those in Latin America) after the adoption of the aforementioned Doha Declaration. However, some provisions of free trade agreements, namely, data exclusivity and the patent protection/medicine registration link,<sup>44</sup> may in practice limit the use of patented inventions under compulsory licenses and for non-commercial governmental purposes.<sup>45</sup>

Finally, it should be noted that although from a public health perspective it is necessary that national legislation should provide for a system of compulsory licensing and governmental use, these instruments do not solve by themselves the problems that may arise from the granting of patents related to medicines, especially if lax or inappropriate examination standards are applied, which allow obtaining patents when the requirements of novelty, inventive step or industrial application have not been rigorously observed.

It is, therefore, crucial to ensure that patentability criteria be rigorously defined for the patent examination and the granting procedure, as is the case in a growing number of countries (Argentina, India, Egypt, Ecuador, Indonesia) and is what the European Parliament<sup>46</sup> has recently claimed.

<sup>&</sup>lt;sup>44</sup> The free trade agreements negotiated by the United States require a link between the registration of medicines and the protection of patents - not provided for in the TRIPS Agreement. As a result of this linkage, the national health authority may be required to refuse marketing approval of a generic version of a product if a patent on it is in force, unless it has the consent or acquiescence of the patent holder. In addition, such authority must inform the patent holder about the applications for approval of generic products. See, for example JR Sanjuan, "Patent-Registration Linkage" (Discussion Paper No. 2, Consumer Project on Technology, 3 April 2006). available at http://www.cptech.org/publications/CPTechDPNo2Linkage.pdf.

<sup>&</sup>lt;sup>45</sup> See C. M. Correa, "Bilateralism in Intellectual Property: Defeating the WTO System for Access to Medicines", Case Western Reserve J of Intl L 36, no. 1 (Winter, 2004).

<sup>&</sup>lt;sup>46</sup> European Parliament resolution of 2 March 2017 on European Union options for improving access to medicines (2016/2057(INI)), para. 48. '...emphasises that the European Patent Office (EPO) and the Member States should only grant patents on medicinal products that strictly fulfill the patentability requirements of novelty, inventive step and industrial applicability, as enshrined in the European Patent Convention'.

## VII. COMPULSORY LICENSES/GOVERNMENT USE IN LATIN AMERICA

The legislations of the Latin American countries provide for different foundations for the granting of compulsory licenses (see Table3).

Compulsory needses in Each Aint						
Reasons for the issuance of a	Countries					
compulsory license						
Lack of exploitation	Andean Community, Argentina,					
I	Brazil Dominican Republic					
	Honduras Mexico					
Dark line internet	Andrea Community Drazil					
Public Interest	Andean Community, Brazil,					
	Dominican, Republic, Honduras,					
	Mexico					
National emergency	Andean Community, Argentina,					
	Brazil, Dominican Republic,					
	Honduras Mexico					
To correct anti-competitive	Andean Community Argentina					
no correct anti-competitive	Prozil					
Unfair competition	Dominican Republic					
Reasonable conditions	Dominican Republic, Honduras					
If they are not produced locally	Brazil					
Dependent patents	Andean Community, Argentina,					
	Brazil, Dominican Republic,					
	Honduras					
Refusal to treat	Argentina Dominican Republic					
No monitor on complete	Donomo					
ino provision on compulsory	Fanama					
licenses						

**Compulsory licenses in Latin American legislation** 

Table 3

*Source*: Prepared based on Oliveira et al., "Has the implementation of the TRIPS Agreement in Latin America and the Caribbean produced industrial property legislation that favours public health policy?" Bull World Health Organ. 2004 Nov; 82 (11): 815-821.

In several Latin American countries, the lack of exploitation of a patent can be a valid reason for the granting of a compulsory license, but the importation of protected products is deemed as exploitation. Only Brazil has expressly provided for the possibility of granting compulsory licenses in cases of lack of local industrial use of the patent (Article 68 of the Industrial Property Code).<sup>47</sup>

Argentina and the Dominican Republic explicitly allow the granting of compulsory licenses in cases of "refusal to treat", that is, when the patent holder refuses to grant a voluntary license that has been requested under reasonable commercial terms.<sup>48</sup>

Brazil granted a compulsory license (in May 2007) after a failed agreement with the patent holder to reduce the price of an antiretroviral (efavirenz). Brazil had also announced the possible use of these licenses in 2001, but without granting them, since the prices of the patented medicines were considerably reduced as a consequence of the government threat.<sup>49</sup>

It should be noted that no country in Latin America has introduced changes to its legislation in order to implement the WTO Decision of August 30, 2003 (incorporated in January 2017 into the TRIPS Agreement as new Article 31bis), which establishes exemptions for the supply of pharmaceutical products to countries that do not have or have insufficient manufacturing capacity for pharmaceutical products. However, several countries in Latin America ratified the aforementioned amendment.

<sup>&</sup>lt;sup>47</sup> USA requested the constitution of a panel against Brazil in the WTO Dispute Settlement Understanding framework in relation to this provision, arguing that it was inconsistent with Article 27.1 of the TRIPS Agreement. The complaint was, however, withdrawn by the Government of the United States before the creation of the panel, upon reaching an agreement with the Government of Brazil according to which, before granting a compulsory license, the latter will report the alleged causes. See Brazil -Measures Affecting Patent Protection, Request for the Establishment of a Panel by the United States (WTO, WT/DS199/3, 9 January 2001).

<sup>&</sup>lt;sup>48</sup> See C. Correa, "Refusal to deal and access to an essential facility: balancing private and public interests in intellectual property law", in Mélanges Victor Nabhan, edited by Y Blais (Série Les cahiers de Proprieté Intellectuelle, 2004).

<sup>&</sup>lt;sup>49</sup> See "Public Health, Innovation and Intellectual Property Rights" (Report of the Commission on Intellectual Property Rights, Innovation and Public Health, World Health Organization, 2006), p. 135, available at http://www.who.int.

#### VII.1 The Case of Ecuador

From 2013 to 2017, the Ecuadorian Institute of Intellectual Property (IEPI) processed 33 applications for compulsory licenses,<sup>50</sup> some of which were denied, others were abandoned and ten of them were issued in relation to medicines.

The first three licenses were issued for antiretroviral drugs: Ritonavir+Lopinavir and Lamivudine+Abacavir, medicines that the Ministry of Public Health provides free of charge for the treatment of HIV/AIDS.<sup>51</sup>

In addition to the licenses issued for antiretroviral drugs, licenses were issued for Etoricoxib (Arcoxia® for the treatment of diseases with acute pains); Mycophenolate Sodium (MYFORTIC) used in the treatment of reception of kidney transplants; Sunitinib, an anticancer drug used for the treatment of carcinoma renal cells (CRC) and gastrointestinal stromal tumours (GISTs); and finally Certolizumab, used to counteract rheumatoid arthritis.<sup>52</sup>

According to Hernán Núñez Rocha, former president of the Ecuadorian Institute of Intellectual Property (IEPI), "with the compulsory licensing policy, prices can be reduced from 30 per cent and up to 90 per cent".<sup>53</sup>

The legal framework for compulsory licenses in Ecuador is composed of:

<sup>&</sup>lt;sup>50</sup> "Ecuador: Las 10 licencias obligatorias en el país bajarían el costo de medicinas hasta el 90%", Interview with Andres Icaza, Arsenal Terapéutico, 6 June 2015. Available from http://www.arsenalterapeutico.com/2015/06/06/las-10-licencias-obligatorias-en-el-pais-bajarian-el-costo-de-medicinas-hasta-el-90/.

<sup>&</sup>lt;sup>51</sup> Ketty Véliz, "Licencias obligatorias, mayor acceso a medicamentos en el Ecuador", 29 de septiembre de 2014.

<sup>52</sup> Ibid.

<sup>&</sup>lt;sup>53</sup> "Ecuador: Las 10 licencias obligatorias en el país bajarían el costo de medicinas hasta el 90%", Interview with Andres Icaza, Arsenal Terapéutico, 6 June 2015. Available from http://www.arsenalterapeutico.com/2015/06/06/las-10-licencias-obligatorias-en-el-paisbajarian-el-costo-de-medicinas-hasta-el-90/.

- **Republic Constitution, Article 3.1**: "It is the primary duty of the State to guarantee, without any discrimination, the effective enjoyment of the rights established in the Constitution and in international instruments, in particular, constitutionally recognized rights, such as health".
- Andean Decision 486, Article 65: "Prior to the declaration of a member country on the existence of reasons of public interest, emergency, or national security, and only while these reasons remain, at any time, the patent may be subject to compulsory license. In such case, the national office in charge will grant the licenses requested. The patent holder subject to the license will be notified when reasonably possible."

The national office in charge shall establish the scope or extension of the compulsory license, specifying in particular the period for which it is granted, the object of the compulsory license, the financial compensation amount and conditions.

The granting of a compulsory license for reasons of public interest does not diminish the right of the patent holder to continue to exploit it.  $^{54}$ 

- Ecuador's Intellectual Property Law of 1998, Article 154: requires the Republic President's Declaration of Public Interest to grant a compulsory license.
- Executive Decree 118 in October 2009, Article 1: "Declare of public interest access to medicines used for the treatment of diseases that affect the Ecuadorian population and that are priorities for public health, for which compulsory licenses may be granted on the patents of medicines for human use that are necessary for their treatments. Cosmetic, aesthetic, hygiene and, in general, those medicines that are not for the treatment of diseases will not be considered a priority for public health".<sup>55</sup>

<sup>&</sup>lt;sup>54</sup> Andean Decision 486, Art. 65 of the year 2000, http://www.wipo.int/edocs/lexdocs/laws/en/can/can012en.pdf.

<sup>&</sup>lt;sup>55</sup> Ycaza Mantilla, A., "LICENCIAS OBLIGATORIAS, EN ECUADOR", PPT presented in Havana, Cuba, 2017.

- **Resolution 10-4-P-IEPI 2010**: regulates the procedures for granting a compulsory license, including the following steps:
  - Interested Party Request (form).
  - Application Review.
  - Evidence that a voluntary license has been attempted with the holder and has not been achieved.
  - Notification to the patent holder.
  - Consultation with the Health Authority (Ministerio de Salud Pública – MSP) in order to indicate if the requested matter is considered as "of public interest" and if it is a medicine used in the treatment of diseases that affect the Ecuadorian population.
  - Determine the amount of royalties and the duration of the compulsory license.
  - Resolution for granting or denying.
  - According to Ycaza Mantilla, the results of the compulsory licenses granted in Ecuador can be summarized as follows:
  - Generation of competition with generic medicines
  - Improvements in the public procurement system
  - Reduction of medicine prices for reverse auctions.<sup>56</sup>

At a press conference in July 2014 in Quito, the Minister of Health of Ecuador, Carina Vance, referring to the compulsory licenses granted between 2013 and 2014, stated that: "In these nine processes, we have generated the potential for savings of 23 per cent to 99 per cent." As an example, she mentioned the case of Etoricoxib, a drug that could cost \$0.84 per tablet on the market, but with the license a saving of 99 per cent can be achieved, thus costing \$ 0.0084.<sup>57</sup>

A recent review by Ooms et al. evaluated the impacts of compulsory licenses granted in Ecuador.<sup>58</sup> The review noted that the procedure

<sup>&</sup>lt;sup>56</sup> "Ecuador: Las 10 licencias obligatorias en el país bajarían el costo de medicinas hasta el 90%", Interview with Andres Icaza, Arsenal Terapéutico, 6 June 2015. Available from http://www.arsenalterapeutico.com/2015/06/06/las-10-licencias-obligatorias-en-el-pais-bajarian-el-costo-de-medicinas-hasta-el-90/.

<sup>&</sup>lt;sup>57°</sup> Ministry of Public Health, "Ecuador concedió nueve licencias obligatorias para medicamentos estratégicos". Available from http://www.salud.gob.ec/ecuador-concedio-nueve-licencias-obligatorias-para-medicamentos-estrategicos/.

<sup>&</sup>lt;sup>58</sup> G., Ooms, C.M. Vargas-Peláez, H. van den Bosch, "A situation analysis of compulsory licensing in Colombia and Ecuador", Master Thesis, UV University, 2017.

requires the participation of an applicant, which has been interpreted as a potential producer or importer. Although compulsory licenses have been granted for reasons of "public interest" supported by the aforementioned presidential statement, the government has in no case been directly the applicant and receiver of those, nor have civil society organizations been so. It is not entirely clear if the requests could have been submitted by the Ministry of Health or an NGO, which may explain the difficulties in implementing some compulsory licenses, as happened to the one related to Kaletra.

Any compulsory license beneficiary must obtain the sanitary registration to enter the market; in addition, given that in the Ecuadorian case the main (if not only) buyer of medicines for HIV/AIDS is the Ministry of Health, the licensee must be part of the registered and qualified providers, which implies time and costs. For these reasons, according to WHO, the impact of compulsory licenses in Ecuador has been limited in certain cases in order to achieve price reductions and improvements in access with relevant and sustainable dimensions over time.<sup>59</sup> This situation may reflect a certain tension between the objectives of industrial policy (favouring the local production of medicines) and public health (obtaining medicines at the lowest possible price, whether by local production or importation) that governments must make compatible in the definition of their strategies in this matter.

The case of etoricoxib in which, as mentioned above, the price reduction was over 90 per cent, is illustrative of that tension. Etoricoxib is a "close relative" (a "me-too") of Rofecoxib (Vioxx® by Merck), a product that has gone down in history as one of the biggest scandals in the pharmaceutical industry.<sup>60</sup> Vioxx® was withdrawn from the market worldwide, but the large promotional investments that had been made benefited etoricoxib, arguing that it was a product with the benefits of rofecoxib but without its cardiac risks. However, etoricoxib has been little used in the vast majority of countries, precisely because of its

<sup>59</sup> Ibid.

<sup>&</sup>lt;sup>60</sup> The company received a heavy fine not so much for having caused serious side effects including deaths from cardiac causes, but because it was heavily promoted even though its risks were known. See Stéphane Horel, "Intoxication: Perturbateurs endocriniens, lobbyistes et eurocrates: une bataille d'influence contre la santé" (Ed. La Découverte, Paris, 2015).

proximity to rofecoxib, except in Ecuador, where the product opportunely patented by Merck became the best-selling antiinflammatory in a few years, thanks to a very effective promotional campaign with doctors. It was precisely because of this commercial success that a competing company decided to apply for a compulsory license. The Ministry of Health opposed this license because it was considered a product of little or no interest from a public health perspective.

#### VII.2 Experiences from Colombia and Peru

In the countries of the Andean Community, a compulsory license may be requested and obtained for reasons of public interest. An analysis of the concept of public interest made by the Ministry of Health of Colombia<sup>61</sup> comparing the decisions on compulsory licenses in 10 countries highlights that it is up to each country to define what is the public interest, according to its own criteria. The TRIPS Agreement, as mentioned, is limited to formulating flexibilities, but it gives a certain margin (certainly not unlimited) for different countries to adjust the relevant provisions, including compulsory licenses, to their needs. Additionally, the study notes that the concept is often associated with the social function of property and represents a means to address the tensions between human rights and commercial rights that have recently been examined by the High-Level Panel of the Secretary General of the United Nations.<sup>62</sup>

In cases where the public interest has been invoked for the granting of a compulsory license, it has been associated with epidemiological (Cancer, HIV), economic criteria (excessive prices derived from the existence of intellectual property protection), and budgetary restrictions (all applications have been filed in low- or middle-income countries). These three considerations are repeated, to a greater or lesser degree, in all the administrative acts of granting such licenses.<sup>63</sup>

<sup>&</sup>lt;sup>61</sup> Available from:

https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/interespublico-otorgamiento-licencias-medicamentos.pdf. <sup>62</sup> Report of the United Nations Secretary-General's High-Level Panel on Access to

<sup>&</sup>lt;sup>62</sup> Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines (2016). Available from http://www.unsgaccessmeds.org/final-report.

<sup>&</sup>lt;sup>63</sup> Ministry of Health of Colombia, Análisis del concepto de interés público para el otorgamiento de licencias en medicamentos (see citation 61).

In contrast to the Ecuadorian case, in which compulsory license applications were submitted by entities with the capacity to produce or distribute medicines, in Peru and Colombia (and more recently in Guatemala),<sup>64</sup> the applicants have been civil society organizations, which have formulated these requests based on the following considerations:

- existence of a problem that is considered "of public interest"
- derived from an abusive exercise of a patent right expressed at an excessive price
- in relation to medicines of high sanitary relevance (HIV, Cancer)
- in a context of budgetary limitations for health

The first application for a compulsory license was filed in Colombia in 2008 for the combination lopinavir+ritonavir, Kaletra® by Abbott Laboratories. It was presented by four civil society organizations: The Colombian Network of People Living with HIV (RECOLVIH), the NGO Working Group on HIV, the Misión Salud Foundation, and the IFARMA Foundation. The license request was based on "public interest" reasons. The request was rejected by the Ministry of Health based on the argument that, while the product was included in the Compulsory Health Plan, there were no access problems even though its price was very high as a result of a patent (the first granted to a combination of drugs in the history of the country's patent office).<sup>65</sup> The organizations involved appealed the decision of the Ministry before the judiciary and obtained a decision in their favour. After almost three years, access to that medicine was declared of public interest, and the judge in charge ordered a strong price control on the product, which resulted in a reduction of the final price of more than 90 per cent, an important result even when the compulsory license has not been granted.

<sup>&</sup>lt;sup>64</sup> In Guatemala, a compulsory license application has been submitted for the thermostable version of Kaletra®, a secondary patent of lopinavir-ritonavir. Kaletra® represents more than half of total HIV spending in that country. In Peru, a group of NGOs has requested compulsory licensing for atazanavir, which thanks to a patent is responsible for half of all HIV spending. The request is pending a decision, as is a compulsory license application for Antivirals of Direct Action for hepatitis C in Colombia.

<sup>&</sup>lt;sup>65</sup> This is an example of the granting of a "secondary" patent in the absence of a genuine invention, which would probably not have been granted if rigorous patentability criteria had been applied.

In Peru, a request was submitted by a coalition of civil society organizations led by International Action for Health (*Acción Internacional por la Salud* – AIS) to grant a compulsory license on atazanavir, patented in Peru as sulphate by BMS. Atazanavir came to represent more than half of the total cost of the Ministry of Health to treat HIV, with the highest prices in the region, precisely because a patent on a salt was obtained.<sup>66</sup> This request generated a national debate on prices and access to medicines that, although it did not result in a compulsory license, resulted in a price reduction of 30 per cent.<sup>67</sup>

In the cases of Peru and Colombia, strong disagreements between the Ministries of Health, on the one hand, and the trade sectors and the patent office, on the other, transpired to the public and the media. The latter managed to influence the procedure for processing compulsory license applications, turning these requests into a bilateral procedure in practice.

In Colombia, the procedure has been modified three times: by Decree 4302 of 2008, Decree 4966 of 2009, and, more recently, Decree 670 of 2016.

To understand the above most recent Decree, it is necessary to know in some detail what happened in the case of Imatinib. Novartis applied for a patent in 1998 for the beta crystal of imatinib mesylate salt (a typical "secondary" patent intended to extend the period of patent protection (a strategy commonly known as "evergreening"). This was how it was understood by the patent office of Colombia (the Superintendency of Industry and Commerce – SIC), which rejected the request arguing that it was the result of crystallization of the molecule and a particular salt of a product already known.

The response from the patent office was so strong that several companies registered and sold generic formulations of imatinib for many years, on the grounds that the denial of the application was *res* 

<sup>&</sup>lt;sup>66</sup> Another example of a "secondary" patent, granted for lack of rigorous application of patentability criteria.

<sup>&</sup>lt;sup>67</sup> Acción Internacional para la Salud (AIS Peru). Available from http://aisperu.org.pe/nuestro-trabajo/noticias/item/8-peru-continua-el-debate-sobre-lalicencia-obligatoria-para-atazanavir.

*judicata* (i.e., "a matter [already] judged"). In 2012, more than 60 per cent of the imatinib market was covered by a generic that had a price below 20 per cent of that of Novartis' Glivec®. However, Novartis successfully appealed to the State Council against the patent office's decision. In 2012, the State Council ordered the SIC to revoke its refusal and grant Novartis the requested patent.<sup>68</sup>

In 2014. Novartis asserted its intellectual property rights, excluding the main competitors of the market. The Ministry of Health, therefore, had to face a dramatic increase in spending on this product. Three civil society organizations - IFARMA, Misión Salud and the Drug Information Center of the National University of Colombia (CIMUN) requested a declaration of public interest on this product, so that a compulsory license was granted. The announced intention of the Ministry of Health to move towards the granting of a compulsory license unleashed strong commercial and political pressures (on the part of Novartis, the Swiss government, and the US government),<sup>69</sup> observed in the aforementioned High-Level Panel Report as an example of the unacceptable situation in which developing countries are often placed trying to legitimately use some of the TRIPS flexibilities.<sup>70</sup> The process, which ultimately led to a declaration of public interest that recommended the Minister of Health to carry out a price negotiation before resorting to a compulsory license, can be followed in detail on the website of the Ministry of Health.<sup>71</sup>

Consequently, the aforementioned Ministry requested the National Price Commission of Medicines and Medical Devices (CNPMDM)<sup>72</sup> to apply a novel method for "competition simulation",<sup>73</sup> which resulted in

<sup>&</sup>lt;sup>68</sup> This precedent compels us to insist once again on the need to apply rigorous criteria when examining patent applications. Many problems could have been avoided if patents had not been granted to combinations, salts or crystals of molecules that were already in the state of the art.

<sup>&</sup>lt;sup>69</sup> G. Ooms, C.M. Vargas-Peláez, H van den Bosch, "A situation analysis of compulsory licensing in Colombia and Ecuador", Master Thesis, UV University, 2017.

<sup>&</sup>lt;sup>70</sup> Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines (2016). Available from http://www.unsgaccessmeds.org/final-report.

<sup>&</sup>lt;sup>71</sup> See www.minsalud.gov.co/propiedadintelectual.

<sup>&</sup>lt;sup>72</sup> Composed of the Minister of Health, the Minister of Commerce, and a President of the Republic's delegate.

<sup>&</sup>lt;sup>73</sup> Circular 03 of 2016 of the CNPM.
the setting of a substantially lower price (a 44 per cent reduction) for the patented product.<sup>74</sup>

The industry's reaction to this decision led to the issuance of Decree 670 of 2016 which, in essence, requires that any sectorial technical committee in charge of determining if there are reasons to declare a "public interest" include a representative of the Ministry of Commerce and of the National Planning Department, and prohibits future pricing controls of products declared "of public interest".

## VIII. EXPERIENCES OF GOVERNMENT USE

Government use for non-commercial purposes of a patent, as noted, takes place when the government itself is the beneficiary of the authorization. This modality has two clear advantages, as regulated by the TRIPS Agreement, with respect to compulsory licenses.

On the one hand, it is not necessary to negotiate with the patent holder prior to government use. Moreover, one can start the use and then communicate to the patent holder (Article 31 (b) of the TRIPS Agreement). On the other hand, national laws may establish that governments may not be subject to an interdiction to use a patented invention; the only possible claim for a patent holder is a remuneration based on the "economic value" of the authorization (Article 44.2 of the Agreement).

In addition, the governmental and non-commercial nature of the authorization does not prevent the government from allowing a third party, including a commercial entity, to use the invention (for example, as a contractor) to satisfy the government's needs. This extends the possible use of this type of authorizations because – at least under the TRIPS Agreement – it is not necessary for the government itself to import or produce the product or use the patented process. As noted above, the United States has intensively used this modality;<sup>75</sup> any

<sup>&</sup>lt;sup>74</sup> Circular 04 of the CNPM of 2016.

<sup>&</sup>lt;sup>75</sup> See, for example, e.g., John R. Thomas, "Compulsory Licensing of Patented Inventions, Cong. Res. Serv., R43266, January 14, 2014; Colleen Chien, "Cheap Drugs at

ministry can decide on the use of a patented invention, at any time since its granting, even without previously communicating it to the patent holder, whose only recourse is to request judicial tribunals to determine the remuneration (28 USC section 1498).

The advantages of government use may explain why some of the socalled "compulsory licenses" granted in developing countries in the last two decades constitute, in fact, cases of government use.<sup>76</sup>

For example, in 2004 the Indonesian government authorized the Minister of Health to designate a "pharmaceutical manufacturer" to exploit a patent on behalf of the government. The authorization was based on Presidential Decree No. 83 of 2004 "Regarding Exploitation of Patent by the Government on Anti-retroviral Drugs".<sup>77</sup> According to the available literature; the government achieved substantial savings with such authorization.<sup>78</sup>

In 2005, the Government of Ghana issued a government use measure that allowed the importation of HIV/AIDS generic medicines from India. With this measure, costs were reduced by more than 50 per cent, from US\$ 495 to US\$ 235 per year/patient.<sup>79</sup>

Thailand decided in 2006 on the government use of an efavirenz patent until December 31, 2011 to import products from India and produce them locally. The amount should not exceed 200,000 patients per year covered under the National Health Security System Law. Merck marketed the product at 1,500 baht per month (USD\$ 41), while the government imported a generic version of the medicine from India at

What Price to Innovation: Does the Compulsory Licensing of Pharmaceuticals Hurt Innovation?", 18 Berkeley Tech. L. J. 853 (2003).

<sup>&</sup>lt;sup>76</sup> See Martin Khor, *Compulsory License and "Government Use" to Promote Access to Medicines: Some Examples* (TWN, Penang, 2014).

<sup>&</sup>lt;sup>77</sup> Ministry of Commerce, Trade and Industry letter, Compulsory Licence No.01/2004, signed by Minister Patel, 21 September 2004 and please see TWN website: http://www.twnside.org.sg/title2/par/TRIPS.flexibilities.30jan07.

<sup>&</sup>lt;sup>78</sup> See Padmashree Gehl Sampath, "Promoting Local Pharmaceutical Capacity in Developing Countries: A Discussion on Inventive Step and Compulsory Licensing", in Carlos Correa (editor), *Pharmaceutical Innovation, Incremental Patenting and Compulsory Licensing* (South Centre, Geneva, 2013).

<sup>&</sup>lt;sup>79</sup> See Martin Khor, *Compulsory License and "Government Use" to Promote Access to Medicines: Some Examples* (TWN, Penang, 2014).

an estimated cost of 800 baht.<sup>80</sup> In January 2007, Thailand decided on a new government use until the patent expires or there is no essential need, in relation to a medicine for cardiac treatment, "Plavix®" (clopidogrel bisulfate). The authorization allowed the supply of generic medicines for patients covered by the National Health Security Law B.E.2545, the Social Security Law B.E.2533, and the Medical Benefits Plan of Public Servants and Government Employees, subject to doctors' criteria. The cost of Plavix® was expected to decrease from 120 baht per pill to 6-12 baht per pill. On the same date, Thailand also decided on the government use until January 31, 2012 of the patent on the medicine against AIDS Kaletra® (LPV + RTV). The use of patent rights was limited to the provision of the medicines to no more than 50,000 patients per year, for those covered by the National Health Security System Law B.E. 2545, Social Security Law B.E. 2533, and the Medical Benefits Plan of Public Servants and Government Employees. In the face of 6000 baht per month or 72,000 baht per year per patient charged by Abbott, the government estimated to save 20 per cent with the generic version.

In May 2007, Brazil decided on government use after the negotiations with efavirenz's patent holder failed, in order to import the product from India at a cost of US 0.46 per pill instead of purchasing Stocrin $\mathbb{R}$  – the patented product from its US manufacturer Merck & Co.

Malaysia's recent intervention on the patent that protects sofosbuvir (for the treatment of hepatitis C) was also implemented through government use,<sup>81</sup> with the main intention of supplying the network of public hospitals.

## IX. CONCLUSIONS

The current R&D model for pharmaceutical products (characterized by a lack of transparency in R&D costs and high medicine prices) does not ensure desirable levels of innovation of genuine therapeutic value, nor universal accessibility to the new products that are introduced to the market. The implementation of this model (mainly through patents and

<sup>&</sup>lt;sup>80</sup> See CP Tech website: http://www.cptech.org/ip/health/c/thailand/.

<sup>&</sup>lt;sup>81</sup> https://www.ip-watch.org/2017/09/15/malaysia-grants-compulsory-licence-generic-sofosbuvir-despite-gilead-licence/.

other forms of exclusivity) generates inconsistencies in health policies and tensions with the States' obligations towards the realization of the fundamental right to health.

This situation seems to be aggravated by the new pricing policy of some companies, explicitly based on the **value** of the medicine (and the cost of alternative treatments), without connection to R&D costs. Significantly, as indicated in the High-Level Panel Report of the Secretary General of the United Nations, the problem of access to medicines has acquired a global dimension as it affects both developing countries and developed countries. Illustrative in this regard are the cases of new medicines for Hepatitis C and cancer, which even in industrialized countries are inaccessible to patients who need them. From a public health perspective, it is essential to continue with the search for global R&D models that guarantee, simultaneously, innovation and access.

In the current context, the use of the so-called flexibilities of the TRIPS Agreement, confirmed by the Doha Declaration, is one of the available ways to reconcile public and commercial health interests at stake. This Declaration, sixteen years after its adoption, remains a historic achievement in terms of clarifying the relationship between intellectual property and public health.

The analysis of compulsory licenses in Ecuador and requests in Colombia and Peru suggests that the feasibility of obtaining these licenses and their impact on access to medicines depend strongly on the applicable legal framework, including the possibility that these licenses are requested by non-governmental organizations (those that have had a leading role in the case of Colombia and Peru). There is a tension between the objectives of industrial policy and public health in the use of compulsory licenses. The extent to which these objectives are made compatible will depend on the extent to which a sustainable supply is ensured over time, price reductions and improvements in access to medicines with relevant dimensions.

Given the requirements that must be observed to obtain a compulsory license, to opt for government use may be a more direct and appropriate way (in particular, no prior negotiation with the patent holder is necessary) than the compulsory licenses requested by a third party. In fact, as the examples mentioned above have shown, in several cases governments have chosen the alternative of government use, which does not prevent them from subcontracting an entity (including commercial ones) for the non-commercial supply of the patented product. The precedent set by the Malaysian government is of particular interest as regards government use for sofosbuvir in response to the patent holder's high price and marketing strategy.

Finally, it should be noted that despite the unquestionable legitimacy of compulsory licenses/government use, the case of imatinib in Colombia demonstrates the persistence of political and commercial pressures to avoid the use of these instruments. It also points to the need to more effectively neutralize those practices that erode the national sovereignty and the right of every government to take the necessary measures to protect public health.

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This book is a collection of research papers by Germán Velásquez published by the South Centre, between 2015 and 2019 on the recent international deliberations and negotiations in the United Nations on access to medicines and their relationship with international trade and intellectual property regimes.

The books analyses, the patentability criteria of pharmaceutical products, the international debate on generic medicines of biological origin and the access to hepatitis C treatment, in particular. The South Centre is an intergovernmental research organization of developing countries on critical development issues for the South and is an observer to the governing bodies of World Health Organization (WHO) and other United Nations (UN) agencies. It is hoped that the collection of papers presented in this book will be useful for policy makers and researchers interested in the deliberations in UN and WHO in particular, on the critical issues pertaining to public health and access to medicines.



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