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Pharmaceutical Patent Analyst

Learning from practice: compulsory licensing cases and access to medicines

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In March 2012, India issued its first compulsory license for a kidney cancer drug. India is one of several countries that have applied the flexibility incorporated in the Agreement on Trade-related Aspects of IP rights. It is expected that the importance of compulsory licenses may grow in the future due to the loss of generic drugs sources after the introduction of pharmaceutical product patents in India, the continuing high prevalence of epidemics, such as of HIV/AIDS, in developing countries and the increase in noncommunicable diseases in these nations. This article analyses the effectiveness and feasibility of compulsory licenses to ameliorate access to medicines based on the historical, factual and legal backgrounds of case examples, such as in Thailand, Canada/Rwanda and India. It addresses challenges and controversial questions, such as the interpretation of the compulsory licensing conditions, the questions surrounding a systematic use of compulsory licenses and the lack of economic incentives for generic pharmaceutical companies' participation to export drugs to countries without manufacturing capacities. Lessons from the cases discussed and implications for policymakers are outlined.

Pharmaceutical products offer a simple and cost-effective solution to many major illnesses today. Access to these health technologies has significantly increased worldwide over the past few decades and has contributed to the well-being and cure of many patients affected by communicable or noncommunicable diseases. As a relevant body of the UN infrastructure, the WHO has considerably contributed to the emergence of drug use in all parts of the world, including the developing regions, particularly by the introduction of its Action Programme on Essential Drugs in 1981 (now **Essential Medicines** and Pharmaceutical Policies). Despite these significant improvements, a large part of the world's population, predominately in low-income countries in the sub-Saharan and South Asian regions, lacks regular access to effective pharmaceutical products. According to the WHO nearly 30,000 children are dying every day from diseases that would be easily treatable if they had access to a basic range of essential medicines. In many least-developed and developing countries (DCs), the average availability of essential medicines in the public sector remains below 40%. This deficit is a direct contradiction to the fundamental human right to the highest attainable standard of health that entitles people access to good-quality medicinal products and technologies.

The principal reasons for the lack of access to essential medicines are poverty and constrained resources of individuals and governments in the countries concerned. The factors influencing access to pharmaceuticals are manifold and include global inequities arising from multiple market failures in the pharmaceutical sector, weak basic public health infrastructures in the least developed countries and DCs, lack of skilled health professionals and of functioning delivery structures, the consequences of trade agreements, and high prices for pharmaceutical products.

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Key terms

Essential medicines: Products that serve the priority healthcare needs of the population, which are selected based on factors such as public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness; and which are desired to be available anytime in assured quality, adequate amounts, appropriate dosage formulations, and at affordable prices (WHO).

The Doha Declaration on the TRIPS Agreement and Public Health: Adopted during WTO's Fourth Ministerial Conference in Doha, Qatar (2001) to respond to concerns about the possible implications of the TRIPS Agreement on access to medicines. It emphasizes the importance of the implementation and interpretation of the treaty in a way supportive to public health by promoting both access to existing medicines and the creation of new products. It clarifies some of the forms of flexibilities of the TRIPS Agreement, for example, compulsory licenses.

With the emergence of the HIV/AIDS crisis particularly on the Africa continent, health issues in DCs have become prominent topics at an international level. The impact of ill health on the development of resource-poor countries has been widely recognized. The international community committed in the UN Millennium Declaration to address the public health issues, such as HIV/AIDS, malaria and other illnesses, in these regions. This time period has also seen the establishment of various global health initiatives, such as the global fund to fight AIDS, tuberculosis and Malaria (Global Fund) and nonprofit product development partnership organizations, such as the Medicines for Malaria Venture. One current example of international initiatives is the adoption of the World Health Assembly Global Strategy and Plan of Action on public health, innovation and IP (GSPA) in 2008. The GSPA addresses the health needs in DCs and provides a global policy and specific actions for various stakeholders to be implemented in order to increase R&D for diseases predominately affecting developing nations, and

access to developed and existing health products.

Health as topic has also found its way into the World Trade Organization (WTO) and the trade negotiations of its Member states. The WTO Agreement on Trade-Related Aspects of IP Rights (TRIPS) of 1995 [1] requires WTO members to implement and enforce minimum standards of IP rights (IPRs). The incorporation of IPRs into the multilateral trading system was highly disputed during the Uruguay Round establishing the WTO. DCs particularly feared the implications of stronger IPRs for their economic and social development and for transfer of technology. Moreover, the tense relationship, particularly of patents, with diverse key public policy areas, such as health, had been of growing concern over its impact on individuals and on society in general. The exclusivity right conferred by a patent enables the inventors to set higher prices above marginal costs and to recoup their R&D expenditures, and to gain some profits. While it preserves incentives for future R&D, it also causes a threat to access to products for consumers with

limited financial resources. It was of general concern in DCs that the grant of pharmaceutical patents and their enforcement could have a strong negative impact on the availability of generic substitutions of the patented medicines. In consequence, this would reduce the health status of DCs populations, the countries' power of price and health budget control. The manufacture of pharmaceuticals that were not protected by patents in countries, such as India or Brazil before the implementation of the TRIPS requirements resulted in lower price competition particularly for HIV antiretrovirals (ARVs).

With the adoption of the **Doha Declaration on the TRIPS Agreement and Public Health** (2001)[2] the WTO members underlined the importance in finding the right balance between IPRs and the broader policy objective of public health by affirming that the TRIPS Agreement, can and should be interpreted and implemented in a manner supportive of WTO members' rights to protect public health and, in particular to promote access to medicines for all, while reiterating the members' commitment to the TRIPS agreement (Paragraph 4 Doha Declaration). The declaration emphasizes the right of WTO members to fully use the 'flexibilities' provided in the TRIPS Agreement to address the effects of patents on access to pharmaceutical products. Compulsory licensing is one of these safeguards. Governments may grant such license to allow the use of the patented innovation without the authorization of the right holder, according to Article 31 TRIPS [1]. The provision has been used several times in DCs to increase access particularly to treatments for HIV/AIDS.

On 30 August 2003, the WTO General Council adopted the decision on the implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health (the decision) [3] in order to improve access to affordable pharmaceutical products for DCs. The decision regulates the conditions under which WTO members may issue compulsory licenses, with a view to exporting patented medicines to countries with no or insufficient manufacturing capacity in the pharmaceutical sector. It tries to close the loophole inherent in Article 31 of the TRIPS Agreement on the use of a patented product without the authorization of the right holder. Article 31(f) TRIPS establishes that generic products produced under a compulsory license should predominately supply the domestic market, having the practical effect of limiting the exports of generic medicines to countries that are lacking a significant pharmaceutical industry [1]. The decision will be permanently included in form of an Amendment to the TRIPS Agreement as Article 31 *bis* (the amendment), after ratification by two-thirds of the WTO members [4].

So far, the framework set out in the amendment has been used only once for the shipment of ARVs from Canada to Rwanda. The reasons for the slow start are not only widely discussed in public and academic literature, but were also a prominent topic at the WTO TRIPS Council meeting in March 2010 [101]. For some DCs members, the limited application proves that the Amendment mechanism might be an ineffective solution. Industrialized countries' members referred to other measures to increase access to needed pharmaceutical products in DCs, with compulsory licensing and the Amendment's system being only two of many.

There are various effective policy interventions that contribute to improved access to pharmaceutical products in DCs. They include increased international funding sources for the procurement of drugs; initiatives of the innovating pharmaceutical industry, such as the application of differential pricing schemes or voluntary licensing programs with DC focus; compulsory licensing as measure for governments to address their domestic public health need by authorizing the import or manufacture of generic versions of patented medicines. This article focuses on the latter. It intends to examine the effectiveness and functionality of the TRIPS flexibility to ameliorate access to medicines in DCs through the analysis of selected cases of nonvoluntary license grants in low- and middle-income DCs. The first section gives a brief overview on the access to pharmaceuticals and to some of the current measures employed to address the issue. The second part provides an introduction to the relation between patents, pharmaceutical products and compulsory licenses. It is followed by an analysis of selected compulsory license cases in low- and middle-income countries, run under the mechanism of Article 31 TRIPS in the form of compulsory license for national emergencies or noncommercial public use [1]. The third section examines the newer nonvoluntary license mechanism that allows the export of generic medicine to DCs with insufficient pharmaceutical manufacturing capacities as established under the TRIPS amendment. It also gives an overview of national implementations of the legal mechanism. The two known cases involving a Canadian generic manufacturer and Rwanda on the one hand, and an Indian generic company and Nepal on the other hand, are analyzed in detail, and first implications on the effectiveness of the recent compulsory license system are given. The fourth section discusses the most recent use of a compulsory license in India. The last chapter offers a conclusion on nonvoluntary licensing as an instrument to ensure or increase access to pharmaceutical products in DCs and provides policy implication future perspectives on the development of compulsory license uses.

Access to pharmaceutical products in least developed & DCs, & measures for improvement

Low availability and high costs of essential medicines remain a main challenge in the public health sector in many DCs. The average availability of selected generic pharmaceutical products at public health facilities in more than 70 mainly low- and middle-income countries was at 42 and 64%, respectively, in the private sector [5]. The average prices for pharmaceutical products in DCs are 2.7-times higher than the international reference price in the public health sector and 6.3-times higher in the private sector [6]. A study including 40 countries displayed that the availability of generic treatments for chronic noncommunicable diseases, such as cancer, cardiovascular diseases or diabetes, is substantially lower than that of drugs used for communicable diseases in the public (36 vs 53.5%) as well as the private sector (55 vs 66%) [7]. Originator brand products were rarely available in the public sector. The African region faces the most significant difference in the availability of drugs for communicable and chronic diseases in the public sector (~40%). Noncommunicable diseases were responsible for 63% of the deaths in 2008 (principally cardiovascular diseases, diabetes, cancer and chronic respiratory diseases) with 80% occurring in low- and middle-income countries [8]. DCs face an epidemiological transition from communicable diseases to noncommunicable diseases. For Africa, estimations propose that the prevalence of chronic illnesses is increasing rapidly and will cause *"almost three-quarters as many deaths as communicable, maternal, perinatal and nutritional diseases by 2020, and to exceed them as the most common causes of death by 2030"* [8].

For the most devastating epidemic HIV/AIDS access to pharmaceutical products has increased significantly over recent years. It is estimated that 6.6 million people in low- and middle-income countries are receiving ARVs, corresponding to 47% of the 14.2 million people infected by HIV [9]. Access to ARV therapy has contributed to a considerable decline in AIDS-related deaths, or to a reduction of mother-to-child transmission [9]. In 2009, the weighted average price of the six most widely prescribed first-line treatments was US\$137 per person per year in low-income countries, \$141 in lower middle-income countries and \$202 in upper middle-income countries. The weighted median price for the most common second-line therapy was respectively \$853, \$378 and \$3638 [10]. The Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR) are the main international funders of ARV programs in the low and middle income countries [10].

Major challenges remain in initiating more patients to treatment and sustaining existing ARV access

programs. In more than 50 low- and middle-income countries the coverage with ARV therapy remained below 40% of eligible people living with HIV. The 2010 WHO ARV therapy guidelines recommended an earlier initiation of infected persons to therapy, regardless of whether or not they have clinical symptoms [10]. Emerging drug resistance requires shifting to more sophisticated and costly second- and third-line therapies. Additionally, new scientific evidence proposes an important role of ARV treatment in the prevention of HIV transmission [11–13]. This calls for an extension of ARV access programs in DCs, which will require increased technical and financial resources. However, challenges are already faced in sustaining and managing existing ARV programs. The global financial crisis had a negative impact on the national budget of DCs, as well as the financial contributions to the Global Fund or the PEPFAR [14, 102]. Some DCs announced reduction of program budgets or downsized ARV coverage goals [103]. The Global Fund struggles with a shortfall of funds as a consequence of cuts in financial contributions from donor countries. This puts the continuation of existing ARV access programs at risk, and limits the possibilities to accept new applications for drug supply initiatives. At the same time, the PEPFAR could not expand any of its programs.

In order to address the need of improved access to affordable essential medicines in DCs, various innovative (political) initiatives are being explored, such as incentivizing the local production of ARVs [6] or pooled drug-procurement programs on a regional or international level to reduce costs [104,105]. Innovator pharmaceutical companies contribute to a large extent towards the increase in access to medicines through differential pricing schemes or drug donations. Other measures of the public or private sector focus on the intelligent use of IP. Pharmaceutical firms apply voluntary licensing programs or non-assert agreements for generic product manufacture with a geographical focus on DCs or forgo of patent enforcement in least-developed countries [106–108]. Universities develop socially responsible licensing and IP schemes for inventions related to DCs [109]. One of the latest initiatives is the Medicines Patent Pool, established in July 2010, in order to promote better access to improved first-line and second-line ARVs and to encourage the development of special formulations, such as for children. The geographic scope of the Pool is limited to DCs. The guiding principles are the non-exclusivity of licenses to enhance competition, royalty payments adjusted to a country's disease burden and its capacity to pay, and public availability of the terms and conditions of the negotiated licenses [110].

Generic competition is generally considered as a highly influential factor for improving access to and

the affordability of drugs [15,16]. In the field of ARVs, for example, it is suggested that only after the arrival of competing generic medicines the prices for the originator products decreased significantly. In 2001, an Indian generic manufacturer provided an HIV/AIDS triple-therapy for \$350 per patient and per year. The originator product was priced at \$10,000–15,000 per patient and years at that time. The lowest offer from originator pharmaceutical companies for DCs was at \$1000 [17]. Today, approximately 70–80% of the donor funded purchases of ARVs (e.g., the Clinton Foundation, the Global Fund or the UN Children's Fund [UNICEF]) are supplied by Indian generic companies [17]. The development of these generic and lower priced medicines was possible because of the lack of product patent protection in India until 2005. Many DCs did not provide comprehensive product or process protection on medicines prior to the adoption of the WTO TRIPS Agreement. With the introduction of the TRIPS Agreement all WTO member states, including DCs, are obliged to implement and enforce the minimum standards of patents. The Agreement attempts to establish a higher consistency in national IP laws. Variations in domestic legislations, however, still continue to exist. Countries with scarce innovative capacities tend to have weaker patent protection in order to facilitate reverse engineering processes and promote development of domestic technical skills. They may move to a process patent regime once the local industry has matured in the production of generics of existing products, and to a product patent policy after the development of innovation capacities. Contemplating these differences, the Agreement introduced transition periods for developing and least developed States to bring their national patent legislations in compliance with the TRIPS standards. For developing and transitional economies, such as Brazil or India, the period ended in January 2005, while least developed countries are not required to apply the TRIPS provisions on the protection and enforcement of patents on pharmaceutical products until 2016 (Article 65 para. 2, 3 and 4 TRIPS, Article 65 para. 1 TRIPS) [18,19].

Due to the introduction of product patents for pharmaceuticals in key manufacturing nations, such as India and Brazil, it is expected that the supply of lower priced generic reproductions of new drugs will be gradually reduced, and generic substitutions will be increasingly limited to older off-patent drugs. Medicine prices are expected to remain high due to lack of competition or alternative supply sources. Losing generic manufacture sources, DCs that are dependent on importations of pharmaceutical products may be confronted with the patent holding pharmaceutical company or its licensee as only suppliers of needed

medicines. For these nations the access to newer patented medicines will become more difficult as they may lack the financial power to afford the purchase of the original drugs.

Compulsory license for domestic supply of pharmaceutical products: Article 31 TRIPS

■ Patents & pharmaceutical products

Drug development is a highly regulated, risky and expensive process that can last 10–12 years on average. Only approximately 20% of initial candidate compounds get market approval of the regulatory authority [20]. The private pharmaceutical sector provides the main financial resources for health R&D. The European pharmaceutical industry invested approximately \$27.790 million in R&D in 2010 [21], compared with expenditures of \$49.4 billion in the USA [22], as reported by the relevant pharmaceutical industry associations. The public sector is the second largest contributor to the total health R&D expenditures. The average health related outlays of governments in the member states of the Organisation for Economic Co-operation and Development (OECD) was approximately 0.1% GDP in 2010 [11].

To encourage the high private sector investments in medicinal R&D it is widely accepted that patents play a principal role. Patent protection for pharmaceutical inventions is seen as critical, more than in other industry sectors, because of the high development costs and the low expenses for imitation once the original product has been developed [23]. A pharmaceutical company is likely to invest hundreds of millions of dollars for successful drug R&D [20,24,25] for screening activities, animal testing and clinical development, in order to prove efficacy, safety and quality of the molecules. The result of these long and costly efforts is the production of knowledge. Without patent protection, generic manufactures could use this knowledge to manufacture the medicine at modest production costs without having to invest the time and financial resources of the originator company.

Patents provide the right to exclude competitors from making use of the invention for a limited time. In the short term they reduce competition and elevate prices in the targeted market. In the long term they are expected to increase the R&D incentive through the opportunity to recoup R&D investments. Society's gains are access to the invention information through disclosure in the patent application, improved technology and better products. For innovating pharmaceutical companies patent provide the opportunity to charge higher initial prices for the innovation up to monopoly rents, thus providing the main investment incentive. The resulting profits are used to recoup the high R&D costs,

including those for the unsuccessful efforts, to distribute financial rewards to the company and the investors, and to fund future R&D activities. Too early competition may lead to price reductions on the product that may not allow the innovating company to recoup its investment. From the economic standpoint longer and stronger patents are more valuable and the longer lasting exclusivity provides greater incentives for innovation. Nevertheless, although pharmaceutical products receive a 20-year protection period like any inventions in other industry sectors, the actual term of protection will be reduced because of the long process of drug innovation. To protect investments and the innovation, pharmaceutical companies apply for a patent at an early stage of the R&D process, in generally before starting clinical development. Consequently, the average effective patent life can be diminished so far that it threatens the viability of innovative R&D. In order to compensate the pharmaceutical industry for the long authorization process for a medicinal product and to ensure amortization of investments, legislators worldwide have introduced the supplementary protection certificate. In Europe, for example, it can take effect for a maximum of 5 years after patent expiry and extend exclusivity conferred by a patent and the certificate for a drug to a maximum of 15 years (Article 13 of the European Council Regulation No. 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products [26]). Stimulated by the patent system and market forces in industrialized countries the private pharmaceutical sector mobilizes significant resources to develop disease treatments where considerable markets exist. Where there is no possibility to exclude competitors from exploiting innovations, private companies tend to reduce investments in R&D.

The lack of competition (during the patent term), generally associated with higher prices on the products that may impede access to important products, indicates a disadvantage of the patent system. Innovative pharmaceutical products are often more expensive than older medicines. In the HIV/AIDS field, for example, the price for second-line and third-line ARVs continue to be significantly higher than the prices for first-line treatments [15]. In industrialized countries this higher financial burden is generally carried by third-party payments of health insurances. In low- and middle-income DCs, drugs are in many cases provided at a high price in relation to the income level [27]. Here, a majority of people do not have health insurance coverage, and freely distributed medicines through a public sector program are often not available. In many cases the treatment is paid out-of-pocket by the patient [28]. Patents may also have the potential to deter the development of optional treatments. For example, a combination of

several patent-protected treatments may be required to receive a more convenient delivery form of the treatment that would be more effective and preferable for DCs' needs. If the patents on the different inventions related to the treatments are held by different owners it is rather unlikely that the combination will be developed and distributed. One case example is the triple combination ARV of the drugs zidovudine, lamivudine and nevirapine used in the HIV/AIDS treatment. The combination of the three products into one individual pill was considered as essential for the use in developing country settings in order to provide more effective life-saving HIV/AIDS treatment. The new fixed-dose combination, however, could not be manufactured due to differing patent holders, who themselves, limited the production of combinations only to drugs they owned. Eventually, the triple combination was developed by an Indian generic producer at a time when the relevant patents were not in force in India [29].

■ Compulsory license & its requirements according to Article 31 TRIPS

Compulsory licenses are one of the mechanisms to address undesired effects of the patent system without fully eliminating the rights of the patent owner. The nonvoluntary license allows a government to authorize a third party to perform activities on the patent-protected invention for the benefit of the public interest. While patents grant exclusivity rights, which may turn into the power to set monopoly prices, the system of IP also ensures that such rights are not abused by patent owners and the balance with the public interest of society is maintained. Compulsory licenses for pharmaceutical products are issued under the assumption that the beneficial health effect will outweigh the possible losses of innovation investments. Accordingly, regulations have been introduced worldwide in more than 100 national legislations. In international law the nonvoluntary license regime was first mentioned in the Paris Convention for the Protection of Industrial Property 1883, Article 5 A (2). The provision allows a partner to the Convention to adopt legislative measures (i.e. compulsory licenses) to prevent abuses of patent exclusive rights, such as the failure to work the invention within the patent-granting country (i.e., supplying the product thought importation instead of local production). In 1995, more than 100 years later, the TRIPS Agreement introduced Article 31 [1]. The regulation establishes strict safeguards under which a nonvoluntary license may be issued and further non-exhaustive grounds for the grant of such authorization, including national emergency or extreme urgency, public noncommercial use, and remedy to anticompetitive practices. The compulsory license provision is an important tool to

achieve and guarantee the social and economic functions of the patent system as specified in Articles 7 and 8 TRIPS [1]. These articles stipulate that IPR should contribute to the promotion of technological innovation and dissemination of technology in a manner conducive to social and economic welfare. Accordingly, IPRs aim at higher social goals. WTO members can establish national IP laws that respond to these superior objectives, and introduce IP-limiting measures that are necessary to, among other factors protect public health and nutrition, as well as other public interests.

Under Article 31 TRIPS a WTO member state may allow the use of a 'pharmaceutical' patent without the authorization of the right holder in certain, not exhaustively listed circumstances [30]. The grant of a compulsory license is subject to certain conditions, such as unsuccessful prior negotiations with the patent-holding company on reasonable commercial terms and conditions within a reasonable period of time; the payment of 'adequate remuneration' to the right holder; and the use of the nonvoluntary license to predominately supply the domestic market with the concerned generic version of the 'pharmaceutical' product for which it was issued [31]. The condition of previous negotiations is waived in the cases of 'national emergency' or other circumstances of 'extreme urgency', 'public noncommercial use' (often referred to as government use), and anticompetitive practices [31]. The authorization to use a patented invention has to be non-exclusive, nonassignable, and limited to the purpose, for which it is granted [31]. Furthermore, nonvoluntary licenses can only be granted on a case-by-case basis [31]. Automatic compulsory license eligibility for specific categories of inventions 'would seem' to infringe this condition [32]. Additional procedural safeguards of Article 31 TRIPS include the obligation of providing judicial or other independent review of the authorization of nonvoluntary use of the patent and the decision related to the remuneration provided for the use [31].

The Doha Declaration on the TRIPS Agreement and Public Health (2001) stipulates the freedom of each WTO member to determine the grounds for a compulsory license and the right to determine what constitutes a national emergency or circumstances of extreme urgency (paragraphs 5 (b) and (c) Doha Declaration) [2]. Furthermore, the Declaration affirmed that the TRIPS Agreement can and should be interpreted and implemented in a manner supportive to a members' right to protect public health and, in particular, to promote access to medicines for all (paragraphs 4 Doha Declaration).

Compulsory licenses have been issued in industrialized countries, particularly, to sanction anticompetitive practices of commercial enterprises in various industry

sectors. One example in the area of pharmaceutical products is the ruling of the Italian Competition Authority against a multinational pharmaceutical company to provide free, non-exclusive licenses to competitors for generic versions of an antibiotic combination medicine. The order was issued to remedy an alleged abuse of a dominant market position of the pharmaceutical firm [33]. In return, DCs in general used the nonvoluntary licensing mechanism for reasons of public health interest to improve access to needed pharmaceutical products for poor populations. The next section examines selected cases of compulsory licensing uses in low- and middle-income developing nations.

National use of compulsory license for domestic supply

Since its introduction, the flexibility provided under Article 31 TRIPS has been used in several low- and middle-income countries to ensure the supply of mainly lower-priced generic HIV/AIDS medicines [112]. The cases discussed below are limited to DCs with some or extensive domestic pharmaceutical industry, and include the middle-income DCs (Brazil and Thailand), and the low-income DCs (Zimbabwe, Zambia and Mozambique).

■ Selected case examples from middle-income DCs Brazil

Brazil employs a widely praised public HIV/AIDS program that provides all patients with access to free highly active ARV therapy. The country funds the large-scale program through domestic resources. The medicines distributed under the HIV/AIDS programs are in part generic copies of drugs that are not (anymore) patent protected. The drugs were developed before the introduction of pharmaceutical product patents in Brazil in 1997. They are produced locally in the country. Patented AIDS medicines, particularly second-line treatments, are procured from the innovating pharmaceutical manufacturers. The government is the biggest HIV/AIDS drug purchaser in Brazil. From 2001 to 2005, price negotiations with multiple firms resulted in sustained price reductions for five important patented ARVs [34]. The Ministry of Health used the threat of nonvoluntary licenses in order to pressure the companies. The expenditures for the ARV therapy program increased significantly since its introduction, from \$162 million in 2003 to \$414 million in 2005. The patented products constitute the largest share of drug costs (80% of the total costs in 2004 and 2005) [34]. Due to increasing resistance of patients to first-line treatments and improved side-effect profiles of the newer products, the demand for next-generation ARV treatments was expected to grow, as well as the burden on the public health budget.

In May 2007, after failed negotiations with the patent holder, the Brazilian government granted its first compulsory license for public noncommercial use of the drug efavirenz. The medicine was the most used ARV treatment in Brazil. The prior price negotiations with the patent-holding multinational pharmaceutical company started in 2006. The Brazilian government asked for price reductions comparable to those provided in Thailand as a reference country. The year's price for efavirenz in Brazil was \$580 per patient, while the costs for the drug in Thailand ranged at approximately \$245 per patient, and \$163 for the supply of the product by WHO prequalified laboratories. The company proposed a 2% price reduction and a technology-transfer agreement to the Health Ministry-owned pharmaceutical company Farmanguinhos after 2010, a date close to patent expiry. The government considered the proposal as insufficient [113]. It declared the drug efavirenz as being of public interest in April 2007 [114]. The following compulsory license [115] was issued in order to ensure universal access to the product and to meet the increasing demand under the national HIV/AIDS program for its 75,000 patients. The authorization is valid for five years. It constitutes a royalty rate of 1.5%. The Brazilian government estimated a cost-saving of \$30 million per year for its public health procurement budget [116]. In a first phase, Brazil imported generic reproductions from India, also for research on the product. Farmanguinhos had to further develop the local manufacturing production and perform its own research activities in order to rebuild the drug. The technical information disclosed in the patent description did not enable the generic company to reproduce the invention, and the patent holding firm refused any form of collaboration. The Brazilian government further established special work groups to guarantee the quality of the medicine and to accelerate the production [113].

Brazil may be seen as a model example for determined and coherent compulsory-licensing strategy. For several years the Brazilian government has used the threat of issuing a nonvoluntary license to negotiate significant price reduction from the innovating pharmaceutical companies that served the public health interest. Brazil's success in negotiations may be attributed to several important factors, including the strong political will of its government to maintain the national universal access program for HIV/AIDS treatment, the high capacities for local production, and the strong market power that provides sufficient incentive for pharmaceutical companies to continue to invest in the country even after the use of the TRIPS safeguard. Only after failed agreement with one firm the country finally made use of the TRIPS flexibility. The actual

issue of a compulsory license demonstrated the country's seriousness in negotiations and only strengthened its future bargaining position.

Thailand

Thailand employs a public health policy that provides universal access to medicines for a large part of its population. Beneficiaries under the publicly funded universal health coverage scheme are entitled to at least the medicines on the National Essential Drug lists. Similar to Brazil, the Thai public health policy also includes a HIV/AIDS program with universal coverage for ARV treatment for HIV/AIDS patients free of charge (since 2003). Generic first-line treatment is produced by government laboratories. The country covers the costs of these ARV therapy programs largely through domestic funds. Thailand's overall public health budget expenditures significantly increased over the few last years, as well as the costs for the national HIV/AIDS program, constituting now almost 10% of the government budget [35]. The establishment of the universal access program for HIV/AIDS treatments triggered the demand for cheaper medicines. The number of HIV/AIDS treatment recipients rose from 20,000 in 2003 to approximately 120,000 in 2007. It was estimated that the country's health system could not manage to ensure the free access to the medicines for all people in need because of the high product prices associated with their patent protection. Moreover, the government anticipated a rising demand for second-line ARV treatments in the public sector (because of drug resistance). For example, in 2007, it was estimated that the need for (second-line) lopinavir- and ritonavir-based patented ARV would grow from 13,000 to 50,000 patients in the near future.

Between 2004 and 2005 the Thai government had unsuccessfully tried to directly negotiate price reduction for the ARVs for the public health programs from the patent-holding pharmaceutical companies. This included official communications and several negotiation meetings, also conducted by a specifically established *ad hoc* working group to address the issues caused by high priced essential drugs. The price cuts proposed by the firms were considered insufficient since the generic versions remained much cheaper than the original products. The failed negotiations induced the working group to suggest the introduction of compulsory license as a measure to strengthen the position of negotiation. Additionally, the national nongovernmental organizations and patient groups strongly advocated the use of nonvoluntary licensing as a mechanism to endorse the sustainability of the public health programs [36]. The Thai government established sub-committees that determined the

conditions for the implementation of government use orders and the criteria for the selection of medicines. Based on the illnesses with the highest burden of diseases in Thailand, including HIV/AIDS, cardiovascular diseases and cancer, the committees set up a list of related important medicines. The drugs were chosen according to factors, such as inadequate access, unaffordable costs, patent protection, necessity to solve public health problems and quality and availability of generic products. After several discussions on the pharmaceutical products that should become subject to a government use order, the grant of the first compulsory license was decided in 2006 [36]. Shortly before the grant of the first nonvoluntary license in Thailand, a World Bank report indicated the importance of the TRIPS flexibility as a mechanism to sustain the public HIV/AIDS programs. The authors estimated that Thailand could reduce the costs of second-line therapy by 90% through the issue of compulsory license, which would result in future costs savings of \$3.2 billion dollars through 2025 [37].

Between 2006 and 2008, Thailand issued seven government use orders, including two for ARVs (efavirenz and, lopinavir and ritonavir), a cardiovascular drug (clopidogrel), and four anticancer drugs (imatinib, docetaxel, erlotinib and letrozole), for the importation or production of generic versions for noncommercial use in the public health sector. Eventually, the authorizations were used for the import of generic drugs from Indian producers.

The government-use license on the ARV efavirenz in 2006 was set up until 31 December 2011. The distribution of the drug is limited to 200,000 patients per year. In January 2007, the government announced the government use of the second ARV (lopinavir and ritonavir) and the heart disease drug (clopidogrel). The license was valid until 31 January 2012. The distribution of the ARV is limited to 250,000 patients per year, while the use of the cardiovascular drug is unlimited for patients under certain national health security schemes. All three licenses provide a royalty of 0.5% of the generic's total sale value. The Thai government did not engage in negotiations of voluntary licenses with the patent holders prior to the announcement of the government use as a procedural step. It based its decision on the Doha Declaration on TRIPS Agreement and Public Health, and Article 31 (b) TRIPS that waives the condition of prior negotiations with the patent owner in the case of compulsory license for non-commercial public use. The government-use processes continued parallel to the negotiations with the pharmaceutical companies. These discussions were pursued with the intention to achieve constructive agreements on the supply of good-quality products at a lowest

possible price. In early 2008, the Thai government announced the compulsory licenses for four cancer drugs (imatinib, docetaxel, erlotinib and letrozole) for the treatment of leukemia and, breast and lung cancers. Discussions with the patent owner were held prior to this notice. The negotiations, however, were not fulfilling in the view of the government since they did not allow universal access to the four drugs without undue financial burden. Following the government use notice by the Thai government, one concerned patent-holding company proposed to include all patients under the country's universal health coverage scheme into the firm's funded International Patient Access Program that offers free access to its cancer product (imatinib). Satisfied with this proposal, the Thai government refrained from the implementation of the government-use of patents in this case [117]. For the other three cancer medicines, no agreement could be reached and the Thai government continued with the government use procedure. In September 2010, an Indian generic manufacturer was contracted to supply the generic version of docetaxel [118].

Thailand's core motivation to issue its nonvoluntary licenses for the pharmaceutical products on HIV/AIDS, coronary disease and cancer was to maintain the country's universal health coverage initiative, and to increase access to essential medicines for patients under the public health insurance schemes. The use of cheaper generic versions of the patented drugs would result in significant cost savings that could be used for the treatment of more patients in need. Generic competition was pursued in order to open a new market for the majority of the HIV/AIDS, coronary heart disease, and cancer patients who did not have access to these drugs before, while preserving the small existing private out-of-pocket market for richer and foreign patients that could afford the high prices on the patented products (covering 15–20% of the population) [35,36].

The political determination of the government and the focus to uphold the public national health programs were decisive factors in Thailand, similar to Brazil. The actual introduction of the government use orders reinforced Thailand's negotiation position in post grant discussions with the originator pharmaceutical companies. It has turned the TRIPS flexibility into a bargaining mechanism for more affordable price reductions for drugs considered as essential to treat the most prevalent diseases in the country. While Thailand has not used the compulsory licenses to manufacture the medicines locally, the fact that it has already proved the capacity to produce ARVs gave weight to its political commitment and negotiation position.

Reported results & effects of the compulsory license uses in Brazil & Thailand

In both the Thai and the Brazilian case the use of a compulsory license either as a negotiation instrument or a mechanism to import or manufacture lower priced medicines had the immediate visible consequences of substantial price reductions of originator products [36]; a high reduction of the average costs of ARV treatment per patient in the national public health schemes due to the use of lower cost medicines; and an increased number of patients receiving treatment. In Thailand, for example, the price for the original ARV efavirenz dropped to approximately 19% after first negotiations with the patent holder, and by approximately 45% following the announcement of the compulsory license. For the second ARV lopinavir and ritonavir the patent owning company proposed a price cut of more than 50% under the condition that the Thai government will not pursue the government use order.

As of June 2008, Thailand imported approximately 8 million tablets (each 600 mg) of the generic efavirenz and 900,000 capsules (each 200 mg) under the compulsory license. The price ranged between 571 and 684 baht, in comparison to the price for the original drug of 1400 baht. The distribution of the drug after the importation of the first generic substitutes increased from 5000 bottles (containing 30 tablets) per month in 2006 to 12,500–20,000 bottles per month in May 2007. In addition, 960,000 tablets of generic lopinavir and ritonavir, and 2 million tablets of generic clopidogrel were supplied to Thailand. Health providers acknowledged the changes in the national ARV policy and the better and more constant accessibility to the second-line treatments [36].

An increased use of drugs with therapeutic benefits obviously leads to sustained improved health outcomes in both Brazil and Thailand. Additionally, it can be assumed that the local capacities for pharmaceutical production have been strengthened through the reverse engineering processes in Brazil. Further research on the health economics, and on the associated health and economic benefits for the patients and the countries recommended, in order to have a better understanding and empirical evidence for future policy implications [36].

An increased awareness of the public and various stakeholders on the issue of access to pharmaceutical products in DCs was an indirect effect of the use of compulsory license in Brazil and Thailand. According to some literature, the introduction of nonvoluntary licenses also fostered generic competition for ARVs and greater transparency about global ARV prices [34]. Moreover, the instances were also a test for the WHO's stance and leadership in providing support to

DCs that implement and use the TRIPS public health safeguards. Domestic and international nongovernmental organizations have been key players in both countries, not only in pressuring the governments to establish health programs, for example on HIV/AIDS, but also in the policy development, including the use of compulsory license to increase access to cheaper medicines in the countries for the majority of the poor population [36].

International reactions to the compulsory license policy in Brazil & Thailand

The compulsory license strategy employed by both Brazil and Thailand was highly welcomed by the national and international patient groups and public health-related civil-society organizations. At the same time it elicited a strong international reaction and high pressure from the patent-holding pharmaceutical companies, international pharmaceutical-industry associations, governments in some industrialized countries and the finance-related press. The Thai government also faced some domestic resistance from other industry sectors that feared the negative impact on trade relations and the reduction of foreign investments. The compulsory license concerned pharmaceutical companies that expressed strong disapproval of the nonvoluntary licenses on their products. Thailand's multiple compulsory licensing policy was particularly condemned. One firm reacted with the cancellation of several marketing applications of its medicines in Thailand, including for HIV infection, hypertension and arthritis, and the threat not to register any new drugs in the future in the country [119]. Both Brazil and Thailand were subject to pressing bilateral reactions. Since 2000 Brazil has been included in the yearly US Trade Representative (USTR) Special 301 report [38] that identifies those countries that deny adequate and effective protection for IPR. Brazilian patent law was also challenged by the USA in a WTO Dispute Settlement procedure in 2001. The reaction to the government-use orders in Thailand was divided in the USA. Despite acknowledging Thailand's right to use the public-health safeguards in accordance with the WTO rules, the administration in the USA continued to insist on

negotiations between the parties concerned in order to find an agreement respecting all interests, instead of introducing government use orders. The USA elevated Thailand to the Priority Watch list in its USTR 2007 Special 301 report due to concerns of an overall deterioration in the protection and enforcement of IPR in the country, amongst others, also based on the issue of the compulsory license introduction (Box 1) [120,121]. The USTR 2007 Special 301 Report states:

"[...]In addition to these longstanding concerns with deficient IPR protection in Thailand, in late 2006 and early 2007, there were further indications of a weakening of respect for patents, as the Thai Government announced decisions to issue compulsory licenses for several patented pharmaceutical products. While the USA acknowledges a country's ability to issue such licenses in accordance with WTO rules, the lack of transparency and due process exhibited in Thailand represents a serious concern. These actions have compounded previously expressed concerns such as delay in the granting of patents and weak protection against unfair commercial use for data generated to obtain marketing approval."

Trading partners identified on the list are the focus of increased bilateral attention in the problematic areas. It may already induce them to change or improve their IP policies, or to enter into related bilateral negotiations.

In Europe, an EU Trade Commissioner communicated the disagreement to an indicatively systematic use of compulsory licenses in Thailand whenever pharmaceutical products would surpass desired prices. This policy approach could not be justified by the TRIPS Agreement or the Doha Declaration and would undermine the patent system, as well its incentive effects for biomedical R&D. The EU Commissioner promoted the dialogue with the pharmaceutical companies as a constructive alternative and public-private partnerships to receive long-term solutions to the access to medicines issue [122]. Switzerland shared this opinion in a communication to the Thai authorities [123]. The WHO's position was commented of by the Director-General, Margaret Chan. Some reports cited

Box 1. The Priority Watch list.

A country is placed on the Priority Watch list if the US Trade Representative finds that particular problems exist in that nation with respect to IP rights protection, enforcement, or market access for persons relying on IP, and the market size of the country is of significant interest for the USA. Identified countries are "invited" to cooperate with the USA to develop a mutually agreed action plan designated to lead to the removal from the relevant list. The legislation in the USA does not require an actual infringement of international IP rights law. The Special 301 proceeding may be already initiated against and "unjustifiable" act of a foreign government that "burdens or restricts" U.S. commerce [65]. Critics to this system noted that a country may find itself on the list even if it is compliant with its international trade obligations. Trade issues between the USA and other World Trade Organization (WTO) members, such as Thailand, should be considered instead under the mechanisms provided by multilateral forums, such as the WTO.

her as being critical of the compulsory license policy of the Thai government and supportive of a mutual solution finding together with the pharmaceutical industry, for example, through prior negotiations, before the issue of government-use orders [124]. In an official letter, however, Chan declared the WHO's support of the right of the Thai government to grant compulsory licenses, indicating the misinterpretation of her initial disapproval [125].

Key criticisms of to the compulsory license policy in Brazil & Thailand

The main points of criticism of the nonvoluntary license uses in Brazil and Thailand included:

- The interpretation of the TRIPS compulsory license conditions;
- The loss of returns on the industry side with its negative impact on R&D investments;
- The fear of the establishment of systematic compulsory license use as policy intervention and its spill-over effects to other DCs.

The concerns of the innovating pharmaceutical companies were strongly related to the questions on the global implications of the compulsory license cases for the industry and on whether the compulsory authorizations would create disadvantageous legal principles that will guide future interpretations and applications of compulsory license rules.

■ Interpretation of the Article 31 TRIPS conditions

Controversy arose over the scope of diseases for which the public-health safeguard would be applicable. This issue has been a point of conflict since the introduction of the TRIPs Agreement. In the opinion of some debaters the compulsory license grant is limited to “*HIV/AIDS, tuberculosis and malaria and other epidemics*”, as stated in paragraph 1 or 5 (c) of the Doha Declaration. The expansion to noncommunicable diseases, such as cancer or heart diseases would erode the exceptional character of the TRIPS flexibility for public health problems of major impact in DCs as assumed for the three mentioned illnesses.

Paragraph 1 of the Doha Declaration, however, refers generally to ‘public health problems’ affecting many DCs, ‘especially’ those resulting from the listed diseases. These illnesses are used as illustrating examples that are understood to qualify as eligible diseases. The listing, however, does not constitute a limitation of the scope of diseases to the mentioned diseases [39]. Considering this language and the underlining purpose of the Doha Declaration to affirm the right of WTO members to interpret and implement IP protection in

a manner supportive to promote access to medicines for all, a limitation to certain diseases or group of illness, or epidemics, is not justified. The negotiation history of the Doha Declaration confirms this point of view. The request of the USA to include only the three devastating epidemics, or the later proposal for a list limited to 23 diseases [40], were not accepted and they are not reflected in the language of the final Doha Declaration. Moreover, DCs will face a significant increase in the burden of disease of NDCs. This group of illnesses is a leading global cause of death, reaching epidemic proportions and disproportionately affecting the low- and middle-income countries, where nearly 80% of the noncommunicable diseases deaths occur, according to the WHO. In African regions, noncommunicable diseases are rising rapidly and are estimated to surpass communicable, maternal, perinatal, and nutritional diseases as the major causes of death by 2030 [126]. A restriction of compulsory license use to “*HIV/AIDS, tuberculosis and malaria and other epidemics*” is contrary to DCs’ right to protect public health, as provided in the articles 7 and 8 TRIPS and paragraph 4 Doha Declaration [1,2]. In this regard, it is noteworthy that Thailand used the government order provisions for illnesses with the highest burden of disease in the country, which supports the presumption that the Thai government intended to address major national public-health issues by the government use orders. In summary, the wider interpretation of the scope of diseases eligible for compulsory license can be considered as justified under the provisions of the TRIPS Agreement and the Doha Declaration.

The dispute on the appropriate subject matter is linked to the misperception that a national emergency or situation of ‘extreme urgency’ is a mandatory condition for the compulsory license introduction [127]. According to paragraph 5 (c) Doha Declaration HIV/AIDS, malaria, tuberculosis and other epidemics “*can represent a national emergency or other circumstances of extreme urgency*”. Critics stated that the Thai nonvoluntary license on pharmaceutical products for cardiovascular disease and cancer would not fall under these terms and, thus, cannot be interpreted as cases of exceptional public health crisis. However, the Doha Declaration affirms that WTO members are free to determine what constitutes a national emergency or extreme urgency, a right that is often overlooked in discussions on the compulsory licensing conditions. In addition, the Thai license did not indicate the consideration of a national exceptional situation concerning cardiovascular disease or cancer. Instead, the country authorized the working of the patents for ‘public noncommercial use’. Article 31 TRIPS clearly states ‘public noncommercial use’ as possible grounds for a

nonvoluntary license. This term is not further defined. According to some commentators the expression 'public' may be interpreted in good faith, including broadly either the use by the government, or use that is for the public's benefit [41,42]. The 'noncommercial use' may be understood according to the purpose of the license to supply public institutions. It may also be interpreted as 'not-for-profit' use that allows the involvement of commercial enterprises as long as the licensed product is not provided for profit [33,41,42]. Thailand issued its government use orders to supply its national health programs with more affordable generic medicines. The country's action can be considered as use of the patents for public non-commercial purposes in the sense of Article 31 TRIPS. The authorization of a private sector company to fulfill the need of drugs would not have been contrary to the TRIPs Agreement as long as the firm would have operated on a nonprofit basis. This 'public non-commercial use' of the patent also qualified the Thai government for the waiver of prior negotiations with the patent-holding company, Article 31 (b) TRIPS.

■ Discouragement of innovation

The discouragement of innovation was considered as main risk caused by compulsory license use. The prospect that returns obtained from the exploitation of a patent could be limited or lost reduces the incentive to invest in the expensive and lengthy pharmaceutical R&D. Firms might be rather stimulated to benefit from investments of a third party than performing R&D themselves. For innovative companies it reduces the incentive to patent inventions and to protect them instead as industrial secrets [43–47]. Empirical studies, however, have not confirmed the investment-reducing effect of compulsory license, particularly in the cases where the market is relatively insignificant compared with the global market of pharmaceutical products [43–48]. One example is Canada's experience with an extensive use of nonvoluntary licenses for pharmaceutical products. From 1969 to 1992, 613 compulsory licenses were granted, used mainly for the importation of active ingredients, and encapsulation and packaging activities in Canada. Changes in the Canadian patent legislation in 1969 meant that any person could apply for a compulsory license to import medicines or bulk active ingredients produced with patented processes. The Canadian policy resulted in a significant increase of market share of the generic pharmaceutical industry and a considerable drug price reduction. Despite the wide compulsory license regime the rather low R&D investments of the Canadian pharmaceutical industry did not experience a fluctuation, and foreign companies continued their business in the country, leaving leeway for the conclusion that the market in Canada

remained attractive for the pharmaceutical industry. It was suggested that the relative insignificance of the Canadian market when compared with the global pharmaceutical products market would make stronger patent protection less important. In 1993, under the pressure of the USA in the free-trade negotiations, the Canadian compulsory license regime was removed.

The market size of the DCs is large with 78% of world population and 85% of the world burden of disease [49]. However, there are only few viable economic markets in DCs and the pharmaceutical markets in these nations represent only a small share of profits for the pharmaceutical industry. Europe, Japan and the USA account for approximately 79% of the global sales in pharmaceutical products, while the other world regions and countries together contributed approximately 21% to the returns obtained by the pharmaceutical industry [50]. This percentage decreases even more if the market size of each individual developing nation is analyzed. The appropriate use of compulsory license to increase access to medicines in DCs is unlikely to have a considerable impact on pharmaceutical R&D investments. Economic research has demonstrated that investments in R&D of pharmaceutical products for diseases occurring in both the industrialized and the developing regions are greatly affected by incentives provided by the markets of industrialized countries [51]. Moreover, investigations into the relationship between pharmaceutical innovation and the burden of disease show that the amount of pharmaceutical innovation is positively related to the burden of disease in industrialized countries, but not to the burden of disease in DCs [49]. Where the pharmaceutical market is small due to the lack of purchasing power of patients, as for example assumed for the diseases predominately or exclusively affecting developing nations, investments in pharmaceutical innovation remain low, despite the existence of patent protection in most DCs. In these countries, pharmaceutical companies are also often reluctant to patent their products or enforce their IPR. The frequency of patenting in a country can be related to the market size of the country. The incentive for an inventor to seek patent protection is high where there are more consumers with disposable income [52]. In low-income countries the per capita spending for medicines remains insignificant and many pharmaceutical manufacturers decide to forgo patent protection in these regions. One may argue that if patents do not play a role in these markets than neither will there be an impact caused by the granting of a compulsory license on patents in these regions.

In summary, it is unlikely that the compulsory license uses in Brazil and Thailand will discourage pharmaceutical innovation in diseases fields that have their principal market in industrialized countries, such

as HIV/AIDS and cancer [43–47]. Figures presented by the pharmaceutical industry show that 56 ARVs are currently in development in the USA; furthermore, 98 drugs for lung cancer and 91 products for breast cancer. This provides some indications that America's research-based pharmaceutical companies are continuing to develop novel and effective medicines for HIV/AIDS and cancer [128,129]. The global IP issues in some countries, such as Brazil and Thailand, appear to have a less substantial impact on investments in pharmaceutical R&D than proclaimed by the pharmaceutical industry and other opponents.

■ Systematic use of compulsory license & its spill-over effect

The multiple compulsory license grants in Thailand, however, increased the concerns that this TRIPS flexibility might be turned into a policy instrument that will be used on a routine basis. In the opinion of the critics this would seriously weaken the IP system as principal incentive for pharmaceutical R&D investments. In direct correlation with this was the fear that the Thai compulsory license strategy might provide a model for other DCs.

Patent protection is a sensitive topic for the pharmaceutical industry due to its high value as investment incentive and protection. Selected nonvoluntary licenses create the benefits of addressing a lack in medicine supplies for certain diseases, or of forcing pharmaceutical companies into negotiations for price reductions. It may also result in a positive absorption of technologies that turns local manufacturing facilities into qualified production organizations. A more aggressive or general use of compulsory license, on the other hand, is expected to create social costs that risk to outweigh these benefits [53]. It may send a signal to companies with respect to the country's innovation, industrial and trade policy environment, demonstrating disrespect for their property rights and evoking market and investment uncertainty. For pharmaceutical companies that are subject to nonvoluntary licensing it might become unviable to pursue market approval for their products. Market registrations in emerging DCs require the performance of clinical trials on the domestic population. Recruiting personnel and sales forces adds to the cost. The loss of market advantages due to increased fear of compulsory license may lead the firm concerned and other companies to withdraw market approval processes or forgo them in the future. For the relevant developing country this would limit the access to new and better technologies.

It may also impede other possible routes of action for more sustainable solutions to the access to essential medicines issue, such as public–private cooperations

or investments of foreign or domestic pharmaceutical firms in local R&D and production facilities. Discouragement of foreign direct investments (FDI) and transfer of advanced technologies may make other countries more attractive for technology-exporting companies. So far, empirical studies have not been conclusive in demonstrating the conventionally assumed link between the level of IP protection and the attraction of foreign investment. FDI, investment and technology-transfer decisions of companies are influenced by many factors other than IPR, including particular, the potential economic growth of a country, or location advantages, such as market size, low wages, level of education and training of the local work force, the conditions of the financial sector, and transparency of governmental procedures. Important economic literature suggests that (the strength of) IP protection is an important variable for private investment decisions when two additional conditions are given, namely a strong local capacity to imitate foreign products and technologies; as well as a sufficiently large market that enables firms to capture the economies of scale. A recent study involving China confirmed this, and found a weak link between higher IP protection and increased FDI in the country. In fact, factors such as lower production costs, the country's strong imitative capacity, and the promise of an enormous emerging market were decisive for the substantial FDI increase, despite inadequate and ineffective IP protection [54]. The small markets and the locational disadvantages in low-income developing nations provide a far less economically profitable environment and only a minor threat to IP ownership advantages. This is different for large and economically much more viable markets, such as given in Brazil or China. Here, the threat of losing ownership over its intangible assets, and thus the possibility to optimally exploit the invention creates a much higher impact on pharmaceutical companies [55,56]. The pharmaceutical markets of leading emerging countries, such as Brazil, India or China, provide compelling growth perspectives. Estimates propose that these nations will account for 28% of global spending in 2015, in contrast to a decline in spending in the European and the US markets [57]. It can be expected that pharmaceutical companies would carefully weigh their decisions on whether withdraw investments and product launch in one of these markets in cases of increased compulsory license activities. On the other hand, DCs with emerging markets have already developed some innovative activities in the pharmaceutical sector. Accordingly they will be interested to support domestic and foreign R&D investments through stronger IP policies. A systematic use of compulsory license would have counter-productive effects.

The literature suggests that Brazil appears to have not suffered losses in FDI after the issue of the compulsory license on efavirenz [58]. The emerging market in the country remains a highly convincing incentive for further investments and business perspectives. The growth in the pharmaceutical market at double-digit rates continues to provide significant opportunities, and pharmaceutical companies are interested in ensuring their market presence, also by collaboration and technology-transfer arrangements with the government [130]. The effects on FDI in Thailand are not documented.

Nevertheless, the fear of losing foreign investments and the threat of trade sanctions by other countries remain the strongest arguments against the use of nonvoluntary licenses, and particularly their multiple or systematic grant for pharmaceutical patents. This accounts specifically for low- and middle-income countries that do not offer the same strong market opportunities as China or Brazil, nations that continue to encourage investments and remain attractive in terms of long-term business considerations. DCs are dependent on investments that come from outside the country and that support the growth of the domestic industry beyond what would be possible by local investments alone. Taking the example of Brazil, the country has the economic wealth to endure trade sanctions that, however, would much stronger impact other weaker DCs. Obviously, not every developing state has a strong political determination or can rely on economic power and technological infrastructure to withstand pressure or threats from the pharmaceutical industry, or withdrawal of investments by other industry sectors. Thus, it can be expected that DC governments will continue to carefully weigh the benefits and detriments of making use of the TRIPS flexibility before implementing a policy that foresees compulsory licenses as one principal instrument to ensure access to required medicines. The negative reactions of some industrialized countries on the compulsory license grants in Thailand reinforce this cautious attitude. Many DCs in Africa and South Asia may fear to upset donor nations that are strongly involved in development aid or finance the largest part of their HIV/AIDS programs. It is estimated that 88% of spending on HIV/AIDS in low-income countries comes from international funding. National HIV/AIDS programs of DCs largely depend on this international financial support with the majority of the money coming from bilateral donors such as the USA [131]. Additionally, some pharmaceutical companies have implemented treatment programs and drug-donation initiatives in some DCs that benefit impoverished parts of the population. Consequently, low-income countries might be more drawn to

the idea to sustain their relationships with donors and the pharmaceutical industry and their ability to attract them in the future, than to a compulsory license policy that endangers these dependencies.

Synthesis & implications of the compulsory license cases in Brazil & Thailand

Brazil and Thailand have both successfully introduced compulsory licensing to improve access to pharmaceutical products for their national public health programs either through the use as a negotiation instrument, or through the issue of the authorization for the import of generic substitutes or their local manufacture. Drawing on these two case examples there are several implications that emerge from these interventions.

Thailand is the first country that granted a compulsory license on noncommunicable disease. The demand for the drugs may be also explainable by the epidemiological transition in DCs from communicable diseases to noncommunicable diseases as becoming one leading cause of morbidity. The Thai example can be seen as the first and important test case for the application and interpretation of the Doha Declaration. The use of nonvoluntary licensing for medical treatments of illnesses outside the group of the three main epidemics HIV/AIDS, malaria, as well as tuberculosis is justifiable under the Doha Declaration in correlation with the Article 7 and 8 TRIPS. A more narrow interpretation of the TRIPS Agreement would diminish the hard negotiated public health benefits of the Doha Declaration for the developing nations. To issue a compulsory license under the conditions of TRIPS a country may employ the reason of a 'national emergency' in self-assessment, or the reason of 'public non-commercial use', which allows the unauthorized use of a pharmaceutical patent to supply, for example, public health institutions. The granting nation is exempted from prior negotiation in both cases.

Both the Brazilian and the Thai cases show that the actual grant of a compulsory license can reinforce the negotiation position of a country. A credible threat to issue a compulsory license can provide a very valuable tool to achieve price reductions, one that can be more effective than voluntary negotiations. The high value as a negotiation tool, however, depends on important factors such as existing national technological and manufacturing capacities and a strong political will of the government. Negotiation power additionally increases with the pharmaceutical market size of a country. Many least developed countries will lack these factors, which in consequence reduces the importance and effectiveness of compulsory license as a negotiation instrument.

The nonvoluntary licenses have resulted in temporary but significant increase of access to needed

medicines for the support of the national health programs. Long-term effects are the major decline in price of the originator products through generic competition, and the accessibility to lower-priced generic products.

The use of compulsory license can be a challenging solution. First, the Brazilian and the Thai licenses illustrate that countries using their rights under the TRIPS Agreement may be at risk of retaliation from the pharmaceutical industry and negative reactions of other (industrialized) nations. While the actions of foreign governments may be legally challenged under the WTO system, the retaliations of pharmaceutical firms can only be addressed through pressure from civil society. The use of compulsory license may require a strong political determination to endure threats and pressure. The fear of such reactions may prevent other nations, particularly those with a less strong economic position as Brazil and Thailand, from making use of the designated TRIPS safeguards that have been included to balance the impact of the patents on public health. In consequence these balancing rights would be practically reduced to their application in countries with stronger economies that may withstand such external pressure. In the light of the legality of the nonvoluntary license grants in Brazil and Thailand, the firms should refrain from actions with punitive character, such as a withdrawal of marketing of important drugs. Critical WTO states should also acknowledge the right of other members to implement public health protecting measures and should support their application. This includes, for example, expressing concerns on IP violations only in reference to clearly infringing activities of DCs, while avoiding disputes and retaliation threats or activities in the cases of TRIPS compliance. Second, as learned from the Brazilian case, the local production of more sophisticated drugs, such as second-line ARVs, will require a higher level of technological and production capabilities. This will challenge the reverse-engineering capacities of many DCs.

Pharmaceutical companies are concerned about the impact of compulsory licensing on innovation, the protection of their future R&D investments and ownership of the pharmaceutical inventions. Empirical evidence so far concludes that compulsory licenses granted in DCs with rather insignificant markets on pharmaceutical products with major market in industrialized countries will not be detrimental to innovation. Pharmaceutical markets in these nations are too small to impact business decisions related to disease areas and corresponding R&D ventures.

A systematic use of a compulsory license may have a negative social impact, such as limiting access to a new and better technology or the loss of domestic or

foreign investments in the granting country. However, decisions on investments and technology transfer depend highly on factors such as market size, potential economic growth of a country and other local advantages. These conditions may be compelling advantages for pharmaceutical companies that can outweigh the disadvantages of weaker IPR through compulsory license particularly in DCs with emerging economies. The fact that two middle-income DCs have issues compulsory licenses may encourage other nations with comparable economic development to consider the use of the TRIPS flexibility. DCs with increasing innovative activities will carefully weigh their compulsory licensing policy, being also inclined to protect R&D incentives and actions of domestic and foreign entities. DCs with weaker economies and high(er) dependency on foreign donors and funders of public health programs will be interested to maintain favorable relations to the provider, thus abstaining from compulsory license uses. However, the existence of international purchasing organizations, such as the Global Fund or the Clinton Foundation, and their strong performance in ameliorating access to needed medicines reduces the need for other mechanisms to ensure access to medicines. Donors and funders should continue to support organizations and programs that provide medicines to DCs, in order to sustain existing access schemes and to address the increased need of medicines in the area of HIV/AIDS. The medicines gap for noncommunicable diseases should also become topic on the agenda of international and bilateral funders and organizations.

Selected case examples from low-income DCs

Despite the above developed considerations related to the cautiousness of DCs in the use of compulsory rights, there have been several nations employing the TRIPS flexibility to increase access to HIV/AIDS medicines. The case examples, as discussed here, relate to the compulsory license use for the local production of HIV/AIDS medicines, as indicated for Zimbabwe, Mozambique and Zambia. Other DCs, such as Ghana or Eritrea have used the flexibility for the import of generic HIV/AIDS pharmaceutical products from India in 2005.

Zimbabwe, Mozambique & Zambia

Zimbabwe was one of the first low-income countries that granted a compulsory license for the local production of 'any' HIV/AIDS related drugs and the import of generic substitutes in May 2003 [132], after declaring a period of emergency on the infectious disease according to its national patent law. The declaration of emergency enables the government to authorize the use of patented inventions by any government

department or third party, including “to make, use, exercise and vend the invention for any purpose which appears to the Minister necessary or expedient” (Section 34 Patents Act) [59]. The authorization was granted to a Zimbabwe-registered pharmaceutical company that agreed to provide the generic pharmaceutical product at a price reduced by more than 50% [60]. Drugs manufactured under the authorization are subject to price controls, according to the conditions set out in the license. The local manufacturer provided the first generic substitutes in October 2003 (of a combination drug comprising zidovudine and lamivudine), and continues to supply the domestic public and private sector with several other ARVs. In addition, two further companies have been authorized to procure generic HIV/AIDS drugs under the emergency declaration from Indian manufacturers [61,62]. Detailed information on the procurement and concerned products are not readily available.

Zambia [133] and Mozambique [134] are further DCs that issued their first government orders in the year 2004. The authorizations enabled the local manufacture of a triple fixed-dose ARV combination of lamivudine, stavudine and nevirapine. The licensee was in both cases the same generic producer. The government use order in Mozambique did not indicate the time frame for its validity but stipulated that it remains valid until “the conditions of national emergency and extreme urgency created by the HIV/AIDS pandemic comes to an end” and the government has informed the concerned parties about the expiration of the nonvoluntary license. The royalty rate was limited to 2%. The government order was issued in reference to the gravity of the HIV/AIDS pandemic affecting more than 1.5 million infected persons in Mozambique in 2002, and the failure of the patent-holding companies to provide the medicines at an affordable price. The order further states that the needed triple combination therapy has proven to be one of the most effective and economic ARV treatment, but that “the three different international owners of such single drugs failed to reach an agreement to produce this combination” [134]. In contrast, the Zambian license provided a validity of 5 years and set the royalty payments to the patent holders at not higher than 2.5%. The Zambian compulsory license comprised similar language, referring to the national HIV/AIDS statistics and the unserved needs of the triple ARV combination. Zambia granted the nonvoluntary license after declaring a 5-year HIV/AIDS emergency. During a period of emergency, the Zambian government or an authorized person has the possibility to make, use, exercise and vend the invention “for any purpose which appears to the Minister necessary or expedient” (Section 41 Patent Act) [63].

In both countries the patent status of the three ARV drugs was unclear making the need for granting a compulsory license questionable. Patenting behavior of pharmaceutical companies is inconsistent particularly in African DCs. Literature suggests that the patents on the three compulsory license concerned ARVs were mostly issued before or at the moment of the introduction of an IP legislation in Mozambique (1990), thus making the grant of patents on the earlier inventions related to the three ARVs contained in the fixed-dose combination rather unlikely [61]. ARVs, such as efavirenz and ritonavir or even stavudine were not yet patent protected in Mozambique or Zambia in 2000 [135]. Later issued patents on combinations and formulations of the ARVs are possible, through the regional patent system of the African Regional IPO of which both Zambia and Mozambique are members. The difficulties in obtaining relevant patent information on pharmaceutical products may be a common problem existing in DCs with limited IPO capacities to conduct comprehensive patent searches. This results in irregularities in the patent information provided. Notably, both countries are least developed countries and as such, are beneficiaries of the transition period until 2016 that allows them to refrain from implementation of protection and enforcement of pharmaceutical patents. To avoid the complexity of uncertain patent status both Mozambique and Zambia could have considered this pathway. Making use of this TRIPS flexibility would have enabled them to locally produce the ARV combination and without the obligation of remuneration to the patent-holding pharmaceutical companies [135]. This option, however, also depends on whether the countries already provide patent protection for pharmaceutical products, although not required under the TRIPS Agreement. In this case, they would have to suspend the operation of their patent legislation.

Implications

The impact of the compulsory license policy for local production and import of generic ARV substitutes in Zimbabwe, Zambia and Mozambique is not sufficiently documented and can hardly be assessed; detailed information on the effects of the use of the TRIPS flexibility is not available. It is also difficult to assess the cost-benefits of the locally produced HIV/AIDS drugs in comparison to generic copies from other countries, such as India, because of lack of related information. The three case examples may, nevertheless, permit some observations and conclusions.

The DCs concerned did not use the TRIPS flexibility for the import of generic copies of the patented drugs from other countries, but for the local production of substitutes. This may be attributed to the nations’

development objectives, including industrial policy and strategic economic interests in setting up and/or enhancing local pharmaceutical manufacturing capacities. There is an increasing interest in establishing domestic production in (African) DCs and with technical and financial support from other countries, including generic products exporting developing nations, such as India and Brazil, or their generic pharmaceutical manufacturers [64,136,137]. The threat of limited access to generic medicines because of the amendments in the Indian patent law to comply with the TRIPS Agreement can create an additional incentive for the developing nations to consider domestic manufacturing of required medicines as solution to address their public health needs. For foreign generic pharmaceutical companies (e.g., from India) joint ventures in African DCs may provide a valuable business strategy in the light of the possibilities provided by the TRIPS least developed countries' application extension until 2016.

Least developed countries should seriously consider making use of the advantages provided by the TRIPS transition period that allows the use of a pharmaceutical invention without the obligation to protect the innovation and enforce the relevant patent. This TRIPS flexibility provides a higher freedom to least developed nations that wish to improve access to medicines. On the one hand, it provides the opportunity to produce generic medicines without the obligation to pay royalties to the patent owner. On the other hand, it may also offer a valuable incentive to be used to attract foreign DCs' generic pharmaceutical companies to establish their business in these regions. After the introduction of TRIPS-compliant patent laws in the DCs in 2005, it may become economically and legally more feasible for generic manufacturers to produce in African least developed countries and supply the region with needed generic drugs rather than continuing the manufacturing in their home country.

Granting compulsory licenses in the low-income DCs has not evoked negative reactions from the patent-holding companies or pharmaceutical industry associations. This may be related to the negligible size of the pharmaceutical market in the concerned countries and Africa in general; furthermore, the awareness of the patent holding pharmaceutical firms of a harmful impact on their reputation if they confront a least developed country. For low-income DCs the fear of opposition from the pharmaceutical industry and the industrialized countries may be less justified than they perceive. The use of the TRIPS flexibilities in these nations has not been at the core of attention of the pharmaceutical companies or other states. This indicates a higher acceptance of compulsory license use by countries with small-market and limited-

technological capacities, contrary to the nonvoluntary license practice in middle-income countries with substantial pharmaceutical markets and a significant pharmaceutical industry.

There may be uncertainties about the conditions for compulsory license as set out in the TRIPS Agreement. The compliance of the license granted by Zimbabwe allowing the domestic production of 'any' HIV/AIDS drugs with the conditions of Article 31 TRIPS is questionable. Article 31 (a) TRIPS provides that a nonvoluntary license can be only granted on a case-by-case basis. This course of action has not been challenged by the pharmaceutical industry or other WTO members. However, to ensure better TRIPS compliance in the future, Zimbabwe may consider requesting technical assistance for the implementation and application of the TRIPS flexibilities according to Article 67 TRIPS.

Uncertain and unreliable information concerning the patents status of pharmaceutical products is a major issue in low-income countries. Patent offices in these states still lack the necessary technical skills and equipment to provide related data. Patent owners often hold several patents on the same pharmaceutical product in different forms, thus patent offices may have difficulties in recognizing what is patented. Moreover, some countries may not be aware of valid patents granted through the regional procedure of the African Regional IPO. However, more reliable data on the patent status of pharmaceutical products is essential to enable what is called 'the freedom to operate' where there is no patent protection. It allows to find information on health technologies and to use this information, among others, to assess the necessity of compulsory licensing, but also for R&D and generic manufacturing decisions, or for appropriate medicine procurement practices. To address this lack of capacities for patent search and more reliable patent information there is a continuous need for technical and policy support for DCs to further build and enhance efficiency of the national patent offices and the need for assistance in the application of the TRIPS flexibility, including the training of skilled personnel.

Conclusion

A compulsory license is a legal instrument included in the TRIPS Agreement to address the lack of pharmaceutical products in DCs and to balance the impact of the pharmaceutical patent exclusivity right with the domestic public health interests. It is one of many options that are employed and provided to address the problems of lacking access to essential medicines. The increasing patent protection of pharmaceutical products worldwide may enhance the importance of the TRIPS flexibility in the future. While diseases, such as

HIV/AIDS, malaria or tuberculosis receive high attention and the largest part of donor funding, the prevalence of noncommunicable illnesses, such as diabetes, cardiovascular diseases or cancer will grow in least developed and DCs and will require improved access to cheaper and effective treatment.

The analyzed cases show that the compulsory license mechanism can impact access to medicines in the short term through increased physical access for a limited period, and in a long-term perspective through the increased competition and subsequent price reductions. However, the various compulsory license uses also illustrate challenges that nations with the intent to apply the instrument for public health purposes may face. Themes that emerge from these experiences include, for example, the varying interpretations and understandings with respect to the TRIPS compulsory license conditions; the lack of operational capacities of IP offices in DCs including the issue to run a compulsory license

procedure, or the fear and risk of retaliation from other stakeholders when granting a nonvoluntary license. As will be further discussed in an article in preparation, some of these challenges addressed in this article are also likely to influence the application of the newer compulsory license system for the export of pharmaceutical products to DCs without or insufficient manufacturing capacities [B STIRNER, MANUSCRIPT IN PREPARATION].

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Executive summary

- The introduction of lower-priced Indian generic drugs was an important factor for increased access and affordability of medicines in developing countries (DCs).
- Low availability and high costs for essential drugs remain a problem in DCs, and the need of low-cost antiretrovirals (ARVs; first-, second- and third-line) and drugs for noncommunicable diseases (e.g., cancer and cardiovascular diseases) will increase.
- The introduction of pharmaceutical-product patent protection in India will impact availability of generic drug resources.
- Compulsory license can be a powerful instrument for the negotiation of price reductions for needed medicines.
- Its value as a negotiation tool depends on factors such as the political will and commitment of governments to address public health issues, local pharmaceutical market size and domestic manufacturing capacities.
- The uses of compulsory licenses in middle-income DCs have positively influenced prices on originator medicines and increased access to generic drugs for HIV/AIDS.
- It is not excluded under the TRIPS Agreement or the Doha Declaration to use compulsory licenses for diseases other than HIV/AIDS, malaria or tuberculosis, such as, for example, for noncommunicable diseases.
- The widely raised argument of compulsory license deterring pharmaceutical innovation of products with significant market in industrialized countries is not affirmed by empirical research.
- A systematic use of compulsory license can influence the investment and product marketing behavior of a pharmaceutical company in the granting DC.
- Depending on their development level countries may face different challenges when considering the granting of compulsory licenses.
- For least-developed countries difficulties in the uses of compulsory licenses may arise because of limited capacities and knowledge of local intellectual property offices; due to the lack of local manufacturing capacities; the fear of upsetting important donor relations and of negative reactions from various stakeholders on the use of the TRIPS flexibility.
- Governments in these countries should include the TRIPS flexibility into their wider policy strategy related to public health and access to medicines.
- Least DCs should consider continued training in the area of IP through the technical assistance programs of relevant international organizations, in order to enhance the capacities of their patent offices and personnel employed in the field of IP.

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