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Intellectual Property and Access to Medicines: Patent Pooling as Access Enabler in Pharmaceutical Industry

(Master's Thesis)

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Declaration

I hereby declare that I am the sole author of the thesis entitled "Intellectual Property and Access to Medicines: Patent Pooling as Access Enabler in Pharmaceutical Industry". I duly marked out all quotations. The used literature and sources are stated in the attached list of references.

Prague, 20th April, 2015 .....

Renata Nemkyová

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List of Abbreviations

ART	Antiretroviral Therapy
ARV	Antiretroviral drug
CIPIH	WHO Commission on Intellectual Property Rights, Innovation and Public Health
CL	Compulsory License
DCs	Developing Countries
EAC	East Asia and Pacific
EECA	Eastern Europe and Central Asia
EU	European Union
FDC	Fixed Dose Combination
GATT	General Agreement on Tariffs and Trade
GDP	Gross Domestic Product
GPRM	Global Price Reporting Mechanism
HIC	High Income Countries
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
I-MAK	Initiative for Medicines, Access & Knowledge
IP	Intellectual Property
IPRs	Intellectual Property Rights
LDCs	Least-Developed Countries
LAC	Latin America and Caribbean
LMICs	Low and Middle Income Countries
MENA	Middle East and North Africa
MPP	Medicines Patent Pool
NCE	New Chemical Entity
PEPFAR	President's Emergency Plan for AIDS Relief
PCT	Patent Cooperation Treaty

PPY	Per Patient per Year
R&D	Research and Development
SA	South Asia
SPC	Supplementary Protection Certificate
SSA	Sub-Saharan Africa
TDF	Tenofovir Disoproxil Fumarate (one of the compounds used as ARV)
TNU	The smallest traceable unit of medicaments, such as pills
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
US	United States of America
USD	US Dollar
VL	Voluntary License
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Introduction

The role of intellectual property (IP), patents in particular, in access to medicines is currently one of the key policy issues discussed in many international fora. For example, World Health Organization (WHO) exhibits the high priority it attaches to this issue by having established the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) in 2003. Public health had also been at the forefront of revising the World Trade Organization's (WTO) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) that had resulted from the Doha Declaration on TRIPS and Public Health (hereafter referred to as "the Declaration") in 2001 and the August Decision of the General Council on the implementation of the Doha Declaration (hereafter referred to as "the Decision") in 2003. The World Intellectual Property Organization (WIPO) has within its structure a division designed to steer – through management of intellectual property – positive development in the area of pressing global challenges, such as access to green technologies, food security, and last but not the least, access to medicines for neglected diseases. The cross-cutting nature of this problem, elements of which touch upon public health policies as well as trade and IP policies, is reflected in the ongoing cooperation of the three aforementioned organizations in this regard.

The aim of this thesis is not to propose a new IP system that would bring about change in the access to medicines – such a debate would be purely theoretical – but to explore one of the possible ways to improve access within the current institutional and regulatory framework of IP protection. Its purpose is to evaluate whether patent pooling as an IP management strategy can be conductive to wider access to medicines in low and middle income countries (LMICs). To limit the scope of the presented thesis, for the most part only the medicines designed to treat human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), the so called antiretrovirals (ARVs) are subject to analysis.

Following the health-IP-trade axis, the first two chapters of this thesis focus on 1) IP-related Barriers to Access to Antiretroviral Therapy, and 2) trade in ARVs. The third chapter explores patent pooling as an IP management strategy. The fourth chapter comprises of a case study on the Medicines Patent Pool (MPP) initiative.

In order to clarify the links between development, access to medicines, IP and innovation, particularly with respect to HIV/AIDS, the first chapter is divided into three parts where the first one explains how access to medicines is relevant

to economic development and investigates what the barriers to access to medicines are in general, and in relation to IP. The second subchapter picks up on the first one, in that it reviews IP relevant to access, patents in particular, and examines their role in innovation. In the third subchapter, international framework for IP protection is reviewed, as well as the flexibilities in the WTO legal architecture in this area.

The second chapter focuses on trade in ARVs and the main characteristics of the market. Patent landscape in the area of ARVs is reviewed and the effect of proprietary rights on trade in these medicines is examined. The chapter provides an analysis of trade data retrieved from the UN Comtrade database and from the Global Price Reporting Mechanism (GPRM) managed by the WHO. These are analysed along the lines of the dichotomy between patent holders and generic companies. Patent holders develop and sell branded medicines and generic companies are those who produce their low-cost equivalents. For the reasons of availability of data, the analysis is oriented towards the markets of low and middle income countries (LMICs).

Patent pooling as an IP management strategy is examined in the third chapter. It is helpful in understanding the variety of purposes and managerial features of patent pools. History of patent pooling is briefly reviewed, which provides the grounds for finding the distinctive characteristics of patent pooling in the pharmaceutical industry.

The case study in chapter four explores pooling of pharmaceutical patents in practice, assessing the effects of activities of the MPP on procurement of ARVs in LMICs. MPP is an initiative that provides producers of generic drugs from developing countries (through pooling patents on branded drugs issued by multinational research oriented companies) with licenses to manufacture patented drugs in order to introduce them to the market and make them available to patients in resource-poor countries. Data from the GPRM database are used to analyze the development of prices and trade flows of ARVs with the emphasis on the output of one MPP licensor (Gilead Sciences) and one sub-licensee (Aurobindo).

Methods employed in this thesis are mainly description and comparison of theoretical approaches and their synthesis in the theoretical parts, collection and analysis of data, interviews with various stakeholders, and analysis of a licensing contract between the Medicines Patent Pool and a chosen sub-licensee in the practical part.

1 Intellectual Property-related Barriers to Access to Antiretroviral Therapy

The problem of access to medicines, mainly in relation to IP, has emerged as a widely discussed topic at the turn of the century after the entry of the WTO TRIPS Agreement into force in 1995. It sets the minimum standards for IP protection in all WTO Members. What is unprecedented about the agreement is the introduction of compulsory patent protection for all inventions, including product patents on medicines. Until then, the level of IP protection with respect to areas of public interest was purely in the hands of governments in their national authorities. In some countries, India for instance, product patents on pharmaceuticals were not deemed in public interest and had thus not been enforced (Cullet, 2003: 141). Although the existing WTO framework does provide for certain flexibilities, inasmuch as it leaves space for governments to prioritize public health considerations over the rights of IP holders as codified in the Doha Declaration, these flexibilities clash with the interest of pharmaceutical companies and have certain drawbacks, such as administrative difficulties, complex conditions for their lawfulness and others (Aginam, Harrington, Yu, 2013: 4).

One of the claimed advantages of the introduction of patents in developing countries (DCs) was the potential contribution to research and development (R&D) in new pharmaceuticals specific to the needs in resource-poor countries. Some studies suggest that the stronger IP rights protection introduced with the implementation of TRIPS has so far had a positive overall effect on the pharmaceutical industry in emerging economies like India (Kiran, Mishra, 2009). However, the link between stronger IP system and pharmaceutical innovation in the area of diseases that are predominantly present in DCs has not been confirmed. Another study reviewed by Kiran and Mishra (2009) points to the fact, that the IP system is a part of a broader policy framework and as such, its strength and enforcement are not sufficient to incite R&D in the area of neglected diseases.

1.1 Problem of Availability and Accessibility

This subchapter develops the following line of thought: It is aimed at finding the rationale for increased access to medicines in the context of economic development, followed by the introduction of the two main elements of access to medicines: accessibility and availability. It also provides an introduction into the specific features of HIV/AIDS in relation to the core topic.

1.1.1 Relevance of Access to Medicines to Development

Rationale for increased access to medicines is twofold. On one hand, there is the human rights and moral approach, discussed, for instance, by Cullet (2003). However, the moral dimension of the considered issue, one that refers to access to medicines as a basic human right, is not subject to polemics, analysis or discussion in this thesis.

As regards the economic point of view, access to medicines makes its case very clearly. There is a direct and an indirect economic impact of chronic diseases (PHAC, 2005: 51). The direct impact is represented by the loss of money one has to pay in order to obtain treatment. Internal redistribution in the form of health insurance does not exist in DCs[1] (Aginam, Harrington, Yu, 2013: 2). The budget of an individual, who is often the household breadwinner, is therefore directly limited by the cost of treatment.

The direct economic impact can be further strengthened indirectly, that is by decreased labour productivity, complete incapacity to work or even death of the actual or potential provider of income to the household. In addition to that, people in LMICs are far more susceptible to developing ill conditions (PHAC, 2005: 66). Poor people are more likely to acquire illnesses and in turn, chronic diseases contribute to the state of poverty. As demonstrated in a study conducted by Resch (2011), investment in HIV treatment, for instance, is far compensated by the economic returns stemming from increased employment and productivity and averted future expenses for medical services or care for orphans. Access to medicines is an indispensable part of health systems in DCs[2] and, in light of the above, contributes not only to the wellbeing of individuals, but also to the economic development in resource-poor countries. However, universal access to medicines that could improve the health of people in DCs can be, from the IP perspective, in conflict with interests of patent holders.

1.1.2 Specific Features of Treatment of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

Around 35.3 million people were estimated to be living with the virus in 2012, which should not be interpreted as a purely negative fact. This number has been

[1] Up to 90 % of the population in developing countries were purchasing medicines through out-of-pocket payments in the early 2000s, making medicines the largest family expenditure item after food (Cameron et al., 2008: 2).

[2] Expenditures on medicines take up a much larger part of total health care spending in developing countries than is the case in developed ones (Cameron et al., 2009: 2).

steadily increasing since 2001, to a certain extent as a result of the fact that development and scaling-up of antiretroviral treatment turned HIV, once a lethal syndrome, into a chronic condition. Despite the success in scaling up the provision of ART to HIV patients[3], there still are people with unmet needs (WHO, 2014).

People living with HIV can, supposed they have access to appropriate treatment, live a normal productive life today. This bears significant cost of long term treatment, since the retention of treatment for lifetime is necessary for it to be effective. 90 % of people with an unmet need[4] for ART live in 30 countries, 29 are DCs as per World Bank classification (UNAIDS 2013:46). Eligible patients not receiving treatment therefore live predominantly in DCs. Still, the problem is not prevalent in low-income countries only.

Even though the median price of WHO preferred first line ART regimens had dropped considerably over the period of the last ten years in DCs and cost less than USD 200 per patient per year (PPY) in 2013 (see Figure 1), the comparison with GDP per capita of USD 594 in low-income countries[5] points at the prohibitive nature of ART prices in some regions (WHO, 2014: 30).

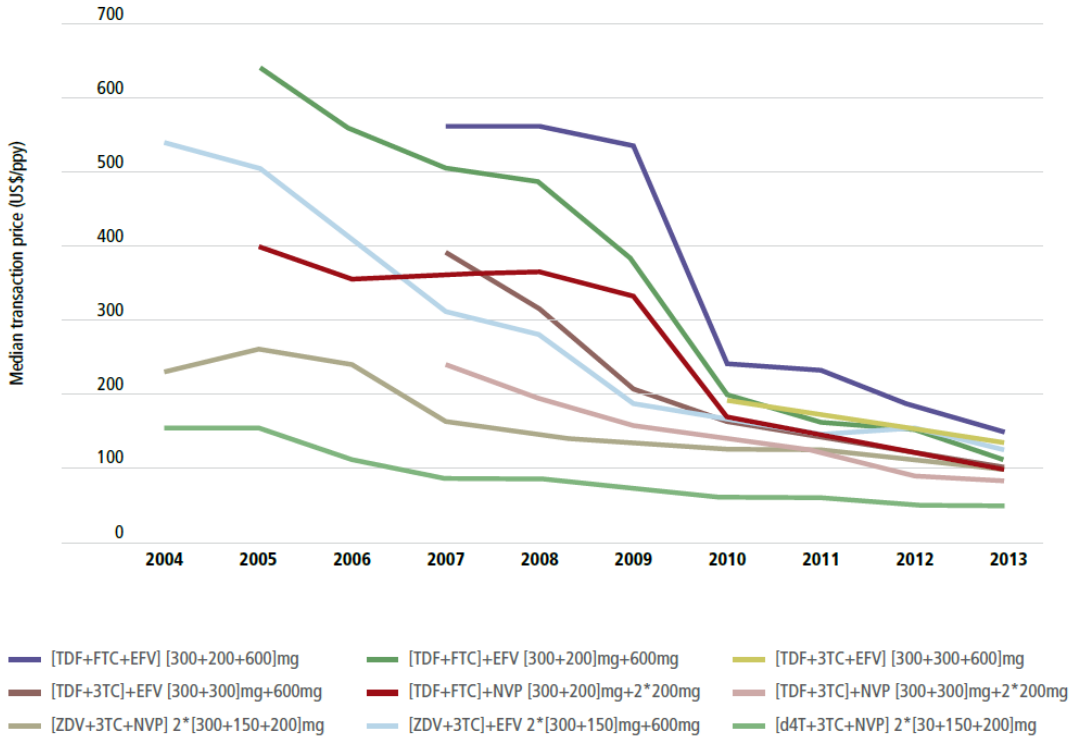
Retention of treatment requires a stable income of an individual or a stable provision of ARVs and related care by government or various non-state actors, as well as affordable prices. This is to demonstrate that bringing down prices through socially sound IPRs protection regimes is important, but not a stand-alone solution for delivering the drug to the patient on the individual level. National policies in areas other than IP, such as human resources in healthcare, infrastructure related to health facilities, internal redistribution in the form of health insurance, as well as willingness and capacity of patients to retain treatment are vital for fighting HIV epidemics and other health emergencies (Bigdeli, 2013).

[3] Between 1995 and 2012, 6.6 million AIDS-related deaths were averted thanks to scaling-up of ART, with the majority (5.5 million) in developing countries (UNAIDS, 2013: 6).

[4] Not all people living with HIV are eligible for treatment. Current statistics evaluating the success of ARV programs are therefore based on the assumption that out of 35.3 million people living with HIV, 28.6 million are in need of ART (UNAIDS, 2013: 6).

[5] World Bank classification is used.

Figure 1: Median prices of WHO preferred first-line regimens in USD PPY in LMICs, 2004-2013



Source: WHO (2014: 30)

Finally, what makes ARVs highly relevant for a patent related analysis is the fact that although most essential drugs[6] have expired patents or are not patented in DCs, ARVs form the majority of essential drugs with patent protection (Beall, Kuhn, Ford, 2012: 3),

1.1.3 Intellectual Property-related Barriers to Availability and Accessibility

Access to medicines has two dimensions related to IP. Availability can be thought of as having the right type of medicines available to those who need it (Peters et al., 2008: 165). The general assumption is that protection of IPRs serves as an incentive for innovation. However, where there is low or no purchasing power and thus little potential for profit, the IP system as an incentive for innovation proves to be failing (Singer, Schroeder, 2011). R&D in pharmaceuticals dealing with conditions occurring mainly in poor countries is not considered profitable by the private R&D subjects. In other words, these conditions are overlooked by the traditional research oriented pharmaceutical MNCs. The term neglected diseases was established as an overarching reference to those conditions. This constitutes a barrier in terms of availability (Peters et al., 2008: 162).

[6] Essentiality is based upon the WHO's List of Essential Medicines.

With regards to the HIV epidemics, insufficient innovation is observed in the area of paediatric formulations, and thus HIV in children is considered a neglected disease[7].

Supposing that the problem of lack of available products does not occur and suitable treatment is developed and marketed, the IP system provides for a monopoly position of the inventor who can commercialize the product exclusively. They therefore have an opportunity to recover the costs for R&D by setting the price at a level far higher than the level of marginal cost of production (Cullet, 2003: 140; Singer, Schroeder, 2011). This is the case for most of the ARVs for adults with still effective patents, since HIV in adults occurs in developed countries as well, where patent holders can capitalize on purchasing power of the population or government expenditures accruing from redistribution through social security systems (WHO, 2012).

Access to medicines is a vital part of public health policies. Public authorities play a vital role not only in setting the rules for trade – sometimes even in terms of price caps on medicines – but through public purchasing of medicines also as customers. The focal point of this thesis are the implications of global and national IP policies on competition between patent holders in the pharmaceutical industry and generic producers, who manufacture and sell drugs with expired or non-existing patents.

1.2 Intellectual Property System as an Incentive for Innovation in the Pharmaceutical Sector

In the centre of innovation stands an idea. In the economics of innovation and IP, knowledge and new ideas bear characteristics of public goods: 1) non-exclusivity and 2) non-rivalry. Once a piece of information is made public, it is not possible to 1) exclude others from making use of it, and at the same time, 2) if someone makes use of a piece of information, its amount or value available for the use of others is not restricted or diminished. The assumption is that without a regulatory tool that would prevent free sharing and replication of ideas, there would be little or no incentive for private entities to invest in developing new knowledge. Society could therefore not benefit from the creation of new ideas, since no protection at all would lead to underinvestment in innovation (Bartels, 2013: 86).

On the theoretical level, some authors question the notion of property in the context of ideas. Intellectual property does not constitute property *per se*, because

[7] For more detail on HIV as a neglected disease see Annex I.

it is inherently incapable to be so due to the aforementioned qualities of non-exclusivity and non-rivalry. The administrative design of IP as a legal privilege is unnatural and should not be in place (Braga 1989, Šíma 2004). This thesis, however, is not designed to investigate a theoretical or a philosophical discourse.

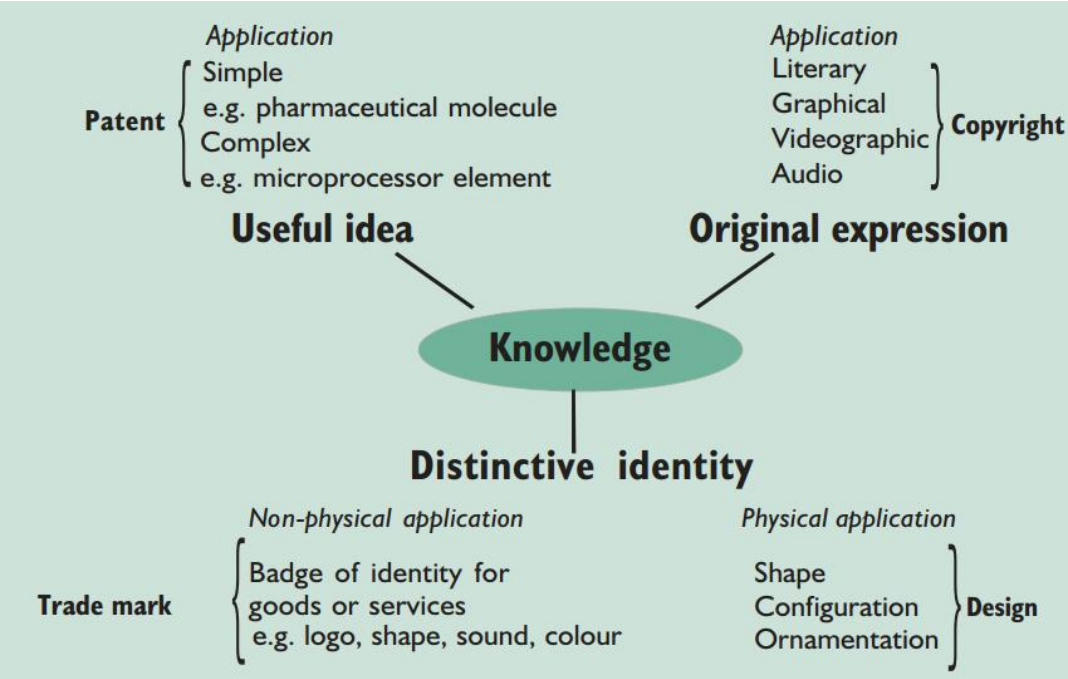
In practice, the debates about how to best incentivize innovation are focused on finding the right balance between the positive effects of IP rights protection on one hand, which is the incentive for innovation , and the negative ones, mainly the loss of consumer surplus due to the monopoly position of the IP rights holders, on the other (Braga, 1989). This translates into balancing between availability and accessibility. Weak IP rights protection might result in low investment in R&D and therefore a lack of availability, whereas on the other hand, too strong a system of protection, albeit conductive to promoting R&D, can render the outcomes of such R&D far too expensive for consumers with low income.

1.2.1 Elements of the Intellectual Property System: Patents as Key Intellectual Property Rights in the Pharmaceutical Sector

IPRs are "*...a bundle of rights that protects applications of ideas and information that have commercial value*" (Gowers, 2006: 11). The IP system is formed by four elementary types of formal IP rights, namely patents, trademarks, industrial designs and copyrights, and these are briefly characterized in Figure 2. Patents are the core IP rights in the pharmaceutical industry and the main focus of this paper[8].

[8] Trademarks are often used for branding purposes in pharmaceutical industry. Given that protection of a trademark is not limited in terms of period of protection its usefulness grows when patents expire. The reason for that is that consumers develop loyalty towards the product and continue to purchase the branded drug even after the generic is available (Ho, 2011: 20).

Figure 2: Instruments of IP system



Source: Gowers (2006:13)

Patents are designed to create incentives for investing in knowledge. They provide exclusive rights to the inventor to exploit the invention commercially and as such, they constitute derogation from the principle of free trade. While patent is in force, others are banned from making use of the invention, including its making, using, selling offering to sell or importing, unless consent by the inventor is granted, usually in a form of a licence (Ho, 2011: 67). To counterweight the distortive nature of patents, the exclusivity is provided for a limited period of time and the inventor is forced to disclose the invention to an extent that others are capable of reproducing it and either commercialize or further build upon it when the patent expires (Cullet, 2003: 140).

Patents are statutory rights and are therefore enforceable in courts, but due to their territorial nature, they can only be protected within the country for which the patent has been granted (IPR Helpdesk, 2006). The management of patents can be costly[9], even more so if the owner operates in various markets. The decision concerning whether to make use of formal patent protection, as opposed to trade secret, lies mainly with the complexity of the invention and the expected return on its use (Brandt, Lohse: 2013). It is necessary to ensure that the patent becomes

[9] Costs in terms of legal and patent-office fees from drafting and application to post-issuance costs in one country can accrue up to 30 000 or even 50 000 USD (Viksnins, Mccrackin, 2006).

a commercial asset, not a liability (Viksnins, Mccrackin, 2006). IP management thus becomes a vital part of an innovation based company.

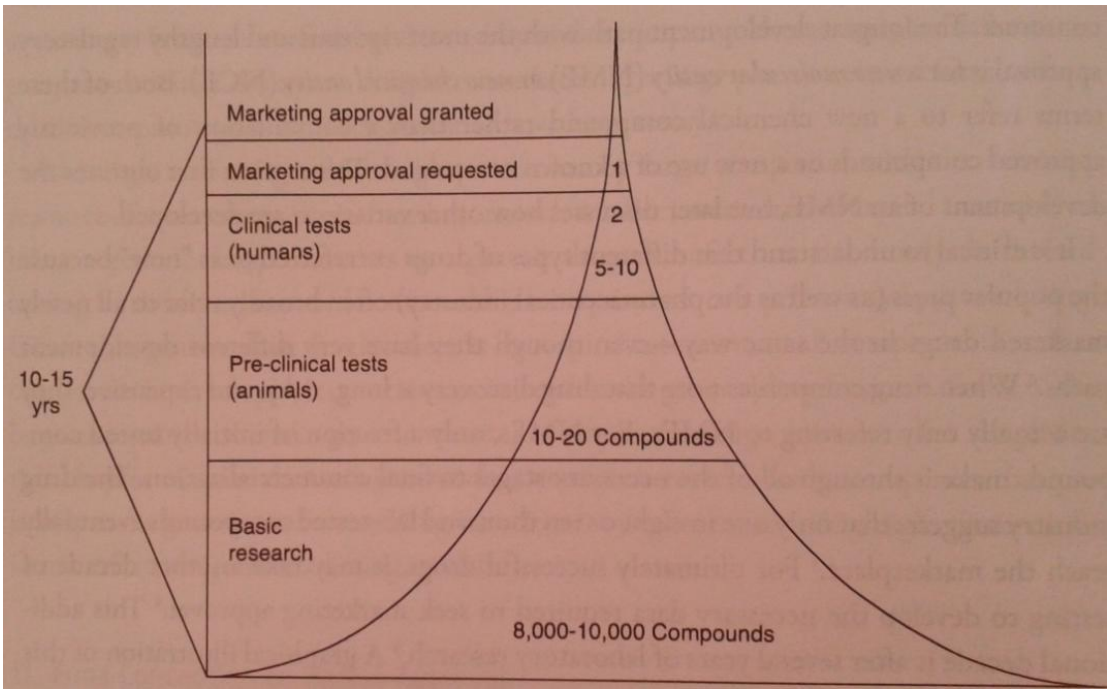
If the invention is easily reproducible[10] the inventor is more likely to patent it (Brandt, Lohse: 2013). The reasons why companies in the pharmaceutical industry revert to patent protection of their inventions more often than in other industries reflect two distinguishing features of pharmaceutical innovation and R&D: 1) The high cost of R&D and the concomitant high risk of failure and 2) The need for a rigorous regulatory framework to assess medical technologies in terms of their quality, safety, efficacy or effectiveness (Bartels, 2013: 102). The first feature is further strengthened by a complementary characteristic: a rather low marginal cost of production. This allows competitors that have not invested into R&D to copy and produce the product cheaply if patent protection and enforcement are not in place (Bartels, 2013: 86).

The second feature affects, among others, the length of the effective patent term. In general, there are two cardinal points in time when it comes to seeking patent protection. First is the filing of patent application. From that moment on runs the limited period of patent protection of 20 years as codified in the TRIPS agreement. If the application is successful, it is followed by the grant of the patent. The actual term of patent protection is thus the 20 years minus the amount of time needed for reviewing the application. On average, the actual patent term is around 17 years[11] (Ho, 2011: 22). In case of regulated areas of inventions, however, there is one extra requirement: regulatory market approval. New pharmaceutical inventions are usually patented at the pre-clinical stage, but regulatory approval is based on the outcomes of costly clinical trials. The time span of drug development is demonstrated in Figure 3.

[10] This is usually the case in the pharmaceutical industry with the exception of biomedicines.

[11] If a patented product is introduced to a market by a competitor between the filing and grant of patent, retroactive royalties can be sought upon the date of entry into force of the patent and in some jurisdictions, statutory ban on production by competitor can be applied (IP Handbook, 2006).

Figure 3: Drug development process



Source: Ho (2011: 8)

It is only after the regulatory market approval has been granted that the drug can be marketed. The period between the grant of the patent and obtaining market approval shortens the effective patent protection (Bartels, 2013: 87). Furthermore, by filing with a regulatory authority, the patent owner has to provide clinical data on safety and efficacy of the component[12]. To moderate the effect of the market approval process and compensate for the patent term loss, a sui generis IP right extending the patent protection is issued by some patent offices, including Supplementary Protection Certificates (SPCs) issued by national IP offices party to the European Patent Convention and patent term extensions in US, Japan, Israel, Australia, Taiwan, Korea and other countries (Leman Consulting, 2012). Other types of exclusivity include orphan drug protection or paediatric exclusivity. These tools provide inventors with exclusivity that can extend beyond the 20 year patent term, thus enabling them to capitalize on their inventions and recover costs incurred on R&D (Leman Consulting, 2012). Taking the example of the SPCs, an "8 + 2 + (1)" system has been in force since 2005. It constitutes an 8-year period[13] of data exclusivity with regards to disclosed clinical data that were provided to regulatory authorities by the inventor to obtain an approval. This prevents generic producers from filing an application for approval within this period. Another 2 years

[12] TRIPS imposes on Members to protect such undisclosed data against unfair commercial use without specifying what constitutes unfair commercial use or to what extent should the data be protected.

[13] This period starts on the day of market approval.

of marketing exclusivity are added to the data exclusivity and in course of this period, market approval for a generic version cannot be authorized. An extra one year of market exclusivity is granted supposing that in the 8-year period of data exclusivity new indication was filed that brings significant clinical benefit (GABI, 2011). These are legislative measures designed in favour of patent holders as opposed to flexibilities in TRIPS that can serve to the advantage of generic producers.

1.2.2 International Protection of Patents

As per the territorial nature of patents, inventors seeking protection beyond domestic markets are obliged to file applications abroad. This can be done nationally, regionally or internationally. The national regime requires filing applications separately in each of the target markets and the costs of such strategy grow significantly should the invention be commercialized in a range of markets. Regional filings are enabled through regional treaties. International applications are channelled through the WIPO administered Patent Cooperation Treaty (PCT). For inventions that are aimed for a broad range of markets, and pharmaceuticals do fall within this category[14], regional or international applications represent a cost-effective solution. Due to high competitiveness in the pharmaceutical industry, inventors are prone to filing applications in early stages of development, despite the uncertainty regarding the success of the compound. One of the benefits of filing with the PCT, apart from lower transaction costs, is that procedures set forth in the PCT allow applicants to obtain and/or preserve for 30 months, the priority date of the first-filed application in any of the PCT member countries, thus deferring the decision whether to proceed to the national phase or not[15] (Silverman, 2005).

In spite of the benefits and cost-effectiveness of the international filing, acquiring patent protection on a global scale is costly. The cost of filing for protection in countries that represent 99 % of global pharmaceutical market – including some that are not party to PCT and without incurring the post-grant maintenance expenditures – was estimated at USD 283,000 in a study published in 2005 (Silverman, 2005).

[14] For most pharmaceutical products there are potential sales in almost every country (Silverman, 2005).

[15] Within 30 months from the priority date, the patent seeker can decide whether to enter the national phase of the application. The PCT application usually claims priority to a national application filed one year earlier, the deadline for entering the PCT national stage is then eighteen months after filing the PCT application. The PCT national phase is among the largest expenses the applicant incurs; the period provided for the applicant to consider whether to enter the national phase or not is therefore often used by pharmaceutical innovators to the full extent (Silverman, 2005: 156).

In order to be able to recover these expenditures, strong protection and effective enforcement of patents is in the interest of research oriented companies.

1.2.3 Externalities of Research and Development in Areas of High Social Benefit but Low Market Incentives

Ideally, continuity of technology dissemination and social advancement are secured by the system of patents. Gowers (2006: 11) illustrates the continuity in innovation as follows:

> "…every creator 'stands on the shoulders of giants', it follows that the more knowledge that is available, the more others can develop and progress. Much of the value from the inventions and creativity protected by IP can only be realised if that knowledge is widely accessible to others. To secure an IP right, the idea must be made public, thereby adding to the common stock of knowledge available for progress."

This premise, however, is not universally applicable. Taking into account the fact that private patent holders are subjects that primarily seek profits, the patent system is an incentive for R&D in the private sphere in those instances, where companies can capitalize on their inventions[16]. The common stock of knowledge available or patent protection on its own does not suffice in promoting innovation where innovation produces external social benefits. By definition, positive externalities lead markets to produce a smaller quantity than is socially desirable. Producing innovation that incurs positive externalities in terms of the effect of a healthy population on economic and social development but one that does not present a direct economic potential for profit is not secured in current IP framework.

Another caveat in the principle proposed by proposed by Gowers relates to follow-up innovation. This can be particularly pressing in the area of pharmaceuticals, where there are complex patent landscapes of compounds or their indications (Thomson Reuters, 2011). Improving a substance so that it corresponds to the specific needs of patients in DCs, for instance, or creating a new drug while building upon previous research presents a challenge. The existence of too many IPRs on basic innovations impacts building upon these inventions. The barriers stem from expenses in terms of efforts in searching for owners of needed IP and, consequently, transaction costs incurred in negotiations of IP rights procurement (Jayadev, Stiglitz, 2008; Langinier, 2006). Problems stemming from fragmentation of property were identified by Heller (2008) as gridlock building on the doctrine of tragedy

[16] This can be exercised through marketing the patented invention, through licensing or sale of the patent.

of anticommons. The tragedy of anticommons draws on the Garrett Hardin's antithesis of 1968 – the tragedy of the commons. While lack of private property leads to overuse of resources in Hardin's theorem, underuse of resources is the outcome of the anticommons. The negative impact of anticommons was proved to exist in pharmaceutical innovation. As one of possible solutions to gridlock, albeit challenging in the pharmaceutical sector, Heller proposes patent pools (Heller, 2008: 72).

What can also hamper follow-up innovation is the excessive scope of patent protection. Broad patent claims are in the interest of patent holders. However, claims based on one substance that cover a whole genus of up to millions or even billions of compounds strengthen the gridlock problem as they can block other subjects from developing drugs in one whole area of therapy (Bai, 2008).

1.3 International Framework for Intellectual Property Protection

The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) came into force in 1995 as one of the multilateral trade agreements annexed to the Agreement establishing WTO. It was negotiated in the Uruguay round of GATT negotiations before the upswing of an active engagement of DCs in the multilateral trade debates and was therefore steered by the developed WTO Members. Opposition from India, for instance, was oppressed and avoided by unilateral sanctions from the part of the US[17] (Hoen, 2009: 12). The possible impact of the newly introduced minimum standards for patent protection on public health in DCs was first raised in an intergovernmental forum in the WHO in 1996. The 49th World Health Assembly adopted the first mandate of the WHO to work on the interface between public health and IP (Bartels, 2013: 21). It took more than 5 years from the entry into force of the TRIPS agreement before the issue found its way back to the WTO.

1.3.1 Flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights

Despite the diverse membership of the WTO in terms of level of development[18], the special and differential treatment provided for specifically to DCs was limited to transitional periods in the TRIPS Agreement, allowing developing

[17] This has been used as an offensive argument by civil society and DCs ever since.

[18] The status of developing countries in WTO is based of self-determination, however, as per WB classification, only 51 out of 160 Members are high-income countries, the rest is low- and middle-income countries.

and least developed country Members to delay its implementation, as stipulated in article 66.1 of the Agreement[19] (WTO, 1994). Other TRIPS flexibilities stem from the space TRIPS provisions leave to the discretion of governments as regards their implementation (Blouin, Heymann, Drager, 2007: 17).

As per article 27.1 of the TRIPS agreement (WTO, 1994), all inventions constitute a patentable subject matter "*...provided that they are new, involve an inventive step and are capable of industrial application."* Novelty and inventiveness are assessed with respect to what is known prior to the date of application, i.e. with respect to prior art[20]. If an invention is not identical with anything in prior art, it is new. Furthermore, if based on prior art, a person skilled in the art does not find the invention obvious, the requirement of inventive step is fulfilled (Ho, 2011: 16). However, terms such as "novelty", "prior art" or "inventive step" are not defined in the TRIPS agreement, leaving governments a manoeuvring space, thus allowing for flexibility in patentability requirements[21] (Blouin, Heymann, Drager, 2007: 17).

Another key flexibility is the freedom to determine a patent exhaustion regime. Within the domestic market, patent owners lose the ability to control resale of products that have been lawfully sold by either themselves or a license holder, while retaining the right to exclude duplication of the product. Such is the principle of domestic exhaustion of rights. While domestic exhaustion occurring with the first sale of patented goods restricts the patent owner from controlling the resale within one market, the international exhaustion doctrine limits the owner's ability to control resale anywhere in the world following the first global sale of the product. The doctrine builds upon the principle that the owner received remuneration with the first sale. International exhaustion allows for parallel imports, i.e. products imported into a country without the consent of the right-holder or its licensees from another country where they were marketed legitimately[22] (Blouin, Heymann, Drager, 2007: 17). Article 6 of the TRIPS Agreement reassures Members that exhaustion

[19] Developing countries were granted 5 years to put their legislation in line with TRIPS and 10 years to comply in areas that had previously been exempted from patentability. LDCs were originally obliged to become compliant with TRIPS by 2006. This term has since been extended twice. The first extension in 2005 stipulated that LDCs are not obliged to be TRIPS compliant until 2013 in general and until 2016 with regards to pharmaceutical patents (Blouin, Heymann, Drager, 2007: 13). In 2013, the implementation deadline for LDCs was further extended until 2021. However, most LDC WTO Members have implemented TRIPS before 2004 (Beall, Kuhn, Ford, 2012: 6).

[20] Countries have different definitions of what counts as prior art, but generally, what is publicly known before the application, be it patents or publications by someone else or even inventor himself, constitutes prior art (Ho, 2011: 16).

[21] This is particularly true in India, where a rather broad interpretation of TRIPS flexibilities was applied when translating the Agreement into national legislation (Mueller, 2006).

[22] Counterfeited products do not fall within the category of parallel imports.

regime shall not be subject to a dispute in WTO (WTO, 1994). The concern of patent holders is the effect of parallel imports on their tiered pricing policies. Tiered pricing stems from patent holders' ability to maximize their profits by selling the same product in different markets at the highest possible price attainable in those respective markets (Ho, 2011: 40).

Compulsory licensing allows governments and parties authorized by governments to use the patented subject matter without the authorization of right holders. CLs are embedded in article 31 of TRIPS and there are several rules to abide by. The proposed user must seek voluntary license (VL) prior to issuance of the compulsory one. This might however be waived by the government in case of "*national emergency or other instances of extreme urgency*" (WTO, 1994). Situations that constitute basis for national emergency are not specified, which created hesitance as to when fast-tracked CLs can be issued. Even in the cases of extreme urgency, patent holder shall be notified and receive adequate remuneration, and CLs shall be non-exclusive. According to article 31.f, goods manufactured under a CL shall be predominantly aimed for the supply of domestic markets.

Flexibilities arising from exemptions from patent rights are 1) the use of patented inventions for purposes of research as codified in paragraph 27, and 2) the early working (Bolar) provision. The Bolar provision allows generic producers to use the subject matter prior to expiration of patents in order for them to be able to swiftly introduce generic versions of medicines to the market. Another type of flexibility is the possibility to opt for a customized manner of protection of undisclosed data (Blouin, Heymann, Drager, 2007: 21).

Though flexibilities are tools for governments to promote public interests, they create business opportunities for generic producers. They create tensions between the research oriented companies and generic producers as they promote the interests of the latter to the detriment of the former.

1.3.2 Lead-up to Doha Declaration and the August Decision

The landmark event that induced the necessity to specify certain provisions in the TRIPS Agreement vis-à-vis public health was the lawsuit of the South African Pharmaceutical Manufacturers Association and 40 pharmaceutical manufacturers against the government of South Africa. It claimed that the Medicines and Related Substances Control Amendment Act No. 90 of 1997 did not abide by the provisions of the TRIPS agreement. The amendment contained, among others, an authorization of parallel imports of pharmaceuticals to solve the problem of pricing level applied

for drugs by the pharmaceutical companies – the South African government claimed these were higher than the prices in other countries[23] (Hoen, 2002).

The legal actions taken against the government of South Africa were defended by the pharmaceutical companies on the grounds that parallel importation would undermine their tiered pricing policy, one that allows for subsidizing poor countries based on higher profit margins realized in developed markets (Fisher, Rigamonti, 2005: 6). It also questioned the compliance of such measures with TRIPS, notably as parallel imports breach the exclusive right of patent holder to import the subject matter.

Even though this case, later withdrawn due to the pressure from the side of civil society not only in South Africa but also in the US and other developed countries, was not brought to the multilateral instance, it reinforced the uncertainty in terms of the interpretation of the TRIPS flexibilities. For instance, some countries that made use of CLs were included in the United States Trade Representative (USTR) Special Section 301 list[24] as a form of unilateral pressure (Blouin, Heymann, Drager, 2007: 20).

Clarification regarding under what circumstances the use of flexibilities could constitute a basis for a dispute under WTO was discussed at the Special Discussion on Intellectual Property and Access to Medicines meeting in WTO in July 2001. The European Union stated that TRIPS "*...cannot be held responsible for the health crisis in developing countries, while it must not stand in the way for action to combat the crisis*" (WTO, 2001a). EU was ready to discuss the issue of compulsory licensing being issued *"predominantly for the supply of the domestic market of the Member authorizing such use*" as per article 31 of TRIPS or the possibility to use patented inventions for research, but did not at all touch upon the issue of parallel imports (WTO, 2001a). EU assured that the requirements for protection of undisclosed data under TRIPS did not undermine the fast-track option for issuance and effect of compulsory licenses. Much stronger position was presented from the part of the African Group and several like minded countries, who stated that "*nothing in the TRIPS Agreement should prevent Members from taking measures to protect public health"*, and *"nothing in the TRIPS Agreement limits the grounds for Governments to issue compulsory licenses"* (WTO, 2001b). They sought a more

[23] A large number of ARVs were patented in SA at the turn of the century resulting in the monopoly pricing position by pharmaceutical companies. IP holders claimed it was not their policies that rendered the medicines inaccessible, but inadequate health infrastructure in South Africa and thefts of medicines (Fisher, Rigamonti, 2005: 7). This was echoed by the United States in WTO meetings.

[24] The Special Section 301 lists countries that do not enforce IPRs enough and can be subject to unilateral retaliation measures from the US (Blouin, Heymann, Drager, 2007: 20).

formal clarification (preferably in a form of a decision of the General Council or a declaration on the ministerial level) on grey areas where further reflection was necessary to assure that public health interests were not overridden by trade considerations. They also stressed the freedom to determine the regime of exhaustion of rights to enable parallel imports. The United States made their case for the importance of IP as incentives for research and conveyed that provisions in TRIPS were sufficient to ensure public health needs. As regards parallel imports, USA reiterated how such imports can discourage producers from tiered pricing (WTO, 2001c).

Based on these discussions, the Ministerial Conference in Doha in 2001 adopted the Declaration on TRIPS and Public Health that has assured the WTO Members of the precedence of health considerations over trade interests. The impact of article 31.f on countries with limited or no manufacturing capacities was the major concern of DCs in the lead up to the Doha Ministerial, but nevertheless was not tackled in the Declaration. Revision of article 31.f was the subject of the Decision of 2003. The Decision (WTO, 2003) stipulates that Members planning on importing medicines under a CL shall notify the TRIPS Council, while demonstrating that they lack capacity to produce the drug themselves, and in cases where the subject matter is patented in the importing country, CL shall be issued. The Decision also limits the amount of drugs that can be manufactured under a CL in the exporting country to the extent that it fulfils the importing country's needs.

1.3.3 Effects of the Amendments to the Agreement on Trade-Related Aspects of Intellectual Property Rights on Enjoyment of Chosen Flexibilities for the Purposes of Public Health

What was expected from the amendments to TRIPS was an increased use of flexibilities, especially CLs and after the Decision of 2003, even for exports to countries without manufacturing capacities. The use of CLs, however, did not grow sharply. Several problems stood, and still stand, in the way. Excessive use of CLs could lead to producers withdrawing from or not entering the market as they would fear the loss of patent rights. Another barrier to use of flexibilities is existing legislation in DCs, which can require higher level of IPRs protection that TRIPS does[25]. This is true not only of CLs, but also of the determination of the regime of exhaustion of patent rights. Such TRIPS-plus legislation can stem from bilateral

[25] These are called TRIPS-plus.

and plurilateral trade agreements[26]. Last but not least, administrative burden can be too high for DCs to abide by the rules governing issuance CLs and CLs for exports. Taking the example of ARVs, the main contribution to scaling up access to ARVs can be attributed to the increased philanthropic activity, public private partnerships and bilateral aid; there is little evidence of the link between Doha Declaration and increased access (Beall, Kuhn, Ford, 2012). On the other hand, the mere threat of CLs can serve as leverage in the negotiations of VLs.

Flexibilities in TRIPS are not widely used even after the reassurance of their legality by the Declaration and the Decision. A study from 2011 identified only 24 CLs in 17 countries, covering 40 pharmaceutical product patents between 1995 and 2011 (Beall, Kuhn, Ford, 2012: 3). As regards the impact of the Decision, it is limited by the administrative burden of notifications, the *ad hoc* nature of the possible contracts and the requirement of specification of exact amount of exported drugs (WTO, 2003). So far only one importing country has notified of importing medicines under the Decision. It was Rwanda in 2007 and the medicines were imported from Canada (WTO, 2007).

[26] Most recently, the US has been striving for and defending robust IP protection in the negotiations of the Trans-Pacific Partnership (GIPC, 2014), whereas think tanks such as Knowledge Ecology International warn against loss of consumer rights and safeguards (Love, 2013).

2 Trade in Antiretroviral Medicines

There are generally two types of producers in the pharmaceutical sector – R&D based companies developing new medicines and consequently selling branded products on one hand, and, on the other, generic manufacturers who provide the market with cheaper versions of existing drugs based on a license, after the patent expired or in a country where the branded drug is not patented. Patents serve as a tool to postpone the market penetration by cheaper generic products. But a simple line cannot be drawn between generic and originator producers, as originator companies in some cases produce generic drugs and vice versa. This is further complicated by the fact that, in some cases, originator companies use manufacturing capacity of generic producers in developing countries for production[27]. Certain level of abstraction is thus applied in this analysis.

2.1 Pharmaceutical Patents

As explained in the previous chapter, patents are usually filed in an early stage of a discovery of potentially useful compounds, thus shortening the effective period of market exclusivity. Patenting alterations – even minor ones, in some cases – is a strategy used by patent holders to prolong the period of market exclusivity and generate higher profits. This strategy is called "evergreening", but it can prove to not always be successful[28]. The TRIPS agreement allows national authorities to determine what constitutes novelty, leaving a gap between the interpretation by pharmaceutical companies on one hand and governments on the other.

When there are a large number of patents expiring within a short period of time, the situation is referred to as a "patent cliff". It is measured by the loss in profits of research oriented companies to generic competition due to expiry of patents, often on so called "blockbuster" medicines[29] (Ishmael, 2014). Patent holders in the pharmaceutical sector faced a $49 billion loss to generic producers over the three-year patent cliff period between 2010 and 2013[30]. This can be viewed as a positive development in terms of accessibility resulting from lower prices. On the other hand, it might lead to large R&D oriented companies switching their focus to lucrative areas and losing interest in improving the availability in some key

[27] Merck uses manufacturing sites of a Chinese generic firm, Zhejiang Huahai (PEPFAR, 2014).

[28] A widely discussed was the case of Novartis' cancer drug Gleevec, an alteration of which was not accepted by the Indian Supreme Court as patentable due to negligible improvement of therapeutic efficacy (Chaudhuri, 2013).

[29] "Blockbuster" drugs generate annual revenue over 1 billion USD.

[30] This loss relates to the pharmaceutical industry in general, not specifically the ARV sector.

areas of therapy, ART included. However, this outcome has a positive aspect to it too; it can increase the willingness of patent owners in the less lucrative areas to share their existing know-how, patents included, with the public sector. An example of such trend in upstream IP sharing is the WIPO Re:Search initiative that will be further discussed in the third chapter.

2.1.1 Patent Landscape Specific to Antiretrovirals

The analysis in this subchapter draws on data from the MPP's ARV patent status database. There are 25 core compounds that are used in ART. First observation when looking into the database is that most compounds are protected with more than one patent. New mode of administration, difference in dosage, physical form, various combinations of the molecules (so called formulations) or processes that lead to the final product are patented on top of the chemical entity itself. That corresponds with the general practice in the pharmaceutical sector described above as "evergreening".

Out of the 25 core compounds, 14 are listed in the WHO List of Essential Medicines (WHO, 2013)[31]. Governments are encouraged to supply their health systems with these products in order to meet the "*minimum medicine needs for a basic health-care*" (WHO, 2013). These are among the cheapest ARVs, mostly with expired patents on the core compounds. Based on data retrieved from the Global Price Reporting Mechanism[32] (WHO, 2011), the median price for this group of ARVs in developing countries is USD 74 per patient per year (PPY) and ranges between USD 8 and 2002. The median cost of the total of off-patent ones is even lower – at USD 49 PPY. 11 primary patents out of the 14 phased out within the period between 2006 and 2014, the remaining ones will have expired by 2018[33] (MPP, 2015). This gives opportunity to generic producers to enter the market and force price reduction on the remaining drugs as well.

This does not mean, however, that access to ARVs will be secured after 2018. Valuable insights explaining why were summarized by MPP in their list of priority ARVs. The document serves as roadmap for MPPs future endeavours and it assesses

[31] It is a compilation of *"the most efficacious, safe and cost-effective medicines for priority conditions"* (WHO, 2013).

[32] The Global Price Reporting Mechanism (GPRM) is a database recording international transactions of HIV, tuberculosis and malaria commodities purchased by national programmes in low- and middle-income countries. The main data providers of GPRM are the Global Fund, PEPFAR, UNITAID, and the procurement organizations working with them.

[33] Among those still on-patent is a compound called Tenofovir (TDF), developed by Gilead Sciences for HIV/AIDS treatment based on a compound originally synthesised by Antonín Holý at the Czech Academy of Sciences in 1948, only a year after the discovery of the HIV virus. TDF serves as a basis for the case study in chapter four.

the importance of ARVs based on more than simply the existing clinical priorities. The list is more forward-looking than the WHO one in the sense that it assesses the future development of the patent landscape in combination with market potential and clinical need. MPP thus prioritizes even those compounds for which the need is currently limited, but that have a potential to grow significantly in importance in the coming years, such as third line treatments.

The MPP list contains 16 compounds, but the overlap with WHO list is only partial (see Annex II). Only five of these compounds are currently off-patent. The median price as per GPRM is USD 92, which might still appear low; however, there is a much larger span between the minimum price (USD 15 PPY) and the maximum price (USD 8468 PPY). What further weakens the accuracy of cost estimates of MPP priority ARVs as a group is that five of the compounds have no transactions registered with the GPRM system. Two are still in clinical trials, two are only used in formulations and the price in the consumer market is not tracked separately and one (Dougletavir) was only approved by the FDA in 2013 with the initial price at USD 14, 000 PPY.

The situation from the IP perspective becomes complicated when formulations are taken into consideration. Formulations, i.e. combinations of various compounds, can be patented as well. The patent landscape then becomes even more confusing. What that means for the producers is that obtaining a license for manufacturing an existing combination or developing a new one incurs considerable transaction costs. Some R&D based companies create joint ventures[34] in order share IP, knowledge, resources and thus also risks in order to, among others, surmount the problem that fragmented IP presents to development of new medicines.

2.2 Market Characteristics and Producers of Antiretrovirals

Study conducted by the Clinton Health Access Initiative (CHAI, 2014) estimated a growth between 2003 and 2013 of patients on ART from merely 400,000 patients to over 11.7 million, registering almost thirty fold growth in 10 years. The goal of the WHO is to further scale up the uptake of ART to 15 million people worldwide by the end of 201, and the growing variety of needs (ARVs for paediatric use, third line treatment etc.) enables deepening of product portfolios of pharmaceutical companies. The market potential becomes even more tempting if we consider these two facts: 1) HIV/AIDS becoming a chronic disease, meaning that

[34] For example Glaxo Smith Kline established a joint venture with Pfizer – ViiV Healthcare.

people have to be constantly on medication and 2) HIV/AIDS affects people both in developed and developing world. But as explained above, there is a threat that non-existence and/or lack of enforceability of patents will lead to lack of interest in research.

The size of the ARV market was calculated based on data from the GPRM database (WHO, 2011) administrated by the WHO. For better accuracy, data from 2013 were used, as the 2014 data are not as comprehensive at the time of writing this paper. The GPRM (WHO, 2011) collects information on various characteristics of ARV shipments to LMICs, such as target country, number of units, price per unit, price per year of treatment, manufacturers (with the indication of whether it is a generic or originator producer), year of order, type of ARV and others. Processing the data in excel showed that the transactions in 2013 were worth USD 1, 170, 746, 531. A study conducted in 2011 by the WHO concluded that transactions registered in the GPRM represent around 80 to 90 % of the total number of patients on ARV. If we consider 85 % accuracy of GPRM data, the estimate of the size of ARV market in low and middle income countries (LMICs) is USD 1, 377, 348, 860. CHAI (2014: 4) predicts the market to grow to USD 2 billion by 2018.

As prices differ between various LMICs, data exported from the GPRM database were processed also on a regional basis. The table below shows that ARVs are on average most expensive in the regions of Latin America and Caribbean (LAC), Eastern Europe and Central Asia (EECA) and East Asia and Pacific (EAP). The lowest prices are in South Asia (SA). Sub Saharan Africa (SSA) has the second lowest mean price for ARVs. The table also reveals that by far the biggest portion of ARVs is purchased in the SSA region[35].

Table 1: Pricing of ARVs in developing regions

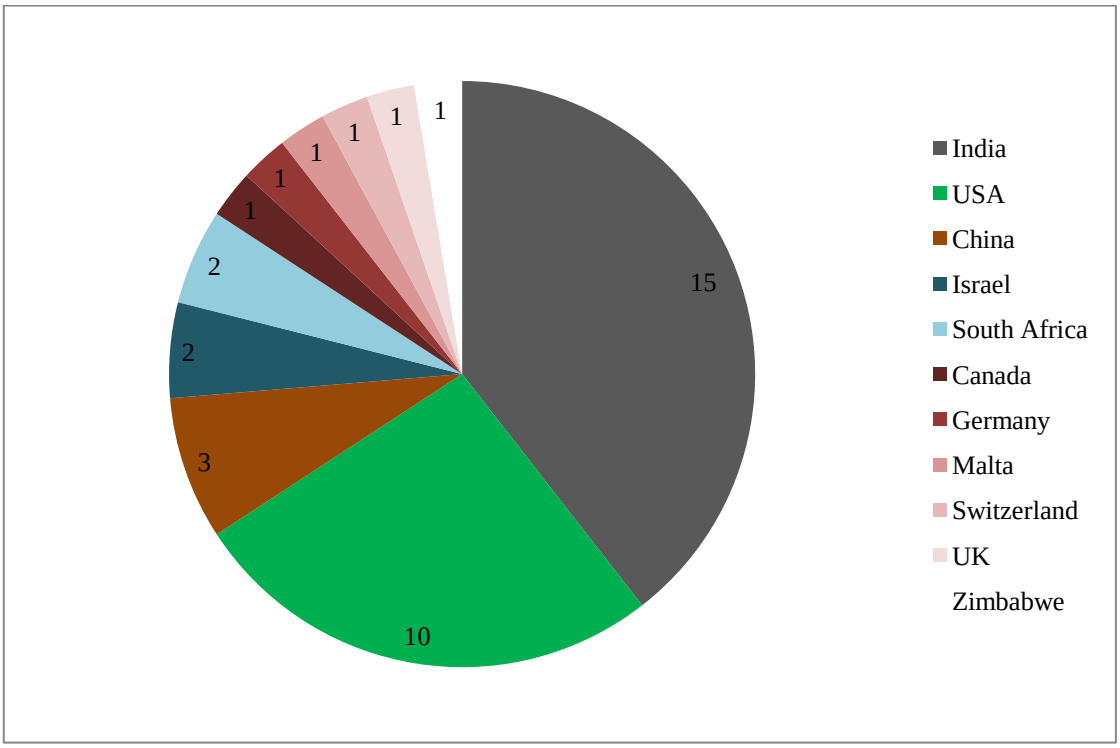
Regional Differences in ARV Pricing and Distribution							
	number of units	% of total units	total cost	% of total cost	mean price*	min price*	max price*
SSA	7269277914	90.06%	1044826683	89.24%	92	13	1510
EAP	283801500	3.52%	54216340	4.63%	131	7	4210
SA	262581830	3.25%	29360690	2.51%	69	16	2884
LAC	157330179	1.95%	26637489	2.28%	140	8	6721
EECA	73523860	0.91%	12031431	1.03%	136	14	8468
MENA	25403080	0.31%	3673898	0.31%	120	9	5360
total	**8071918363**	**100%**	**1170746531**	**100.00%**			
* price of treatment PPY							

Source: own configuration, based on data from the GPRM database (WHO, 2011)

[35] Unit is used here as the smallest traceable unit of medicaments, such as pills.

Combining data from the PEPFAR[36] Consolidated List of ARVs Eligible for Purchase (2014), the information from the MPP on its licensors and licensees (MPP, 2015a) and the data from the GPRM database (WHO, 2011), a territorial distribution of ARV producers was made.

Figure 4: Territorial distribution of ARV manufacturers[37]



Source: own configuration, based on data from the GPRM database (WHO, 2011), MPP (2015a), PEPFAR (2014)

The ARV market is dominated by Indian and American producers. All of the Indian companies selling ARV medicines are generic producers as opposed to three generic producers out of ten in the USA (PEPFAR, 2014; WHO, 2011). As per the data from GPRM (WHO, 2011), a generalization can be made that the USA represents the research oriented segment and India the generic one[38]. This is further validated in respective subchapters.

Looking into data on international trade, figures below demonstrate the export dynamics of the two key ARV players – USA and India. These are not restricted to ARVs but reflect the overall situation in the pharmaceutical retail industry[39].

[36] PEPFAR stands for President's Emergency Plan for AIDS Relief.

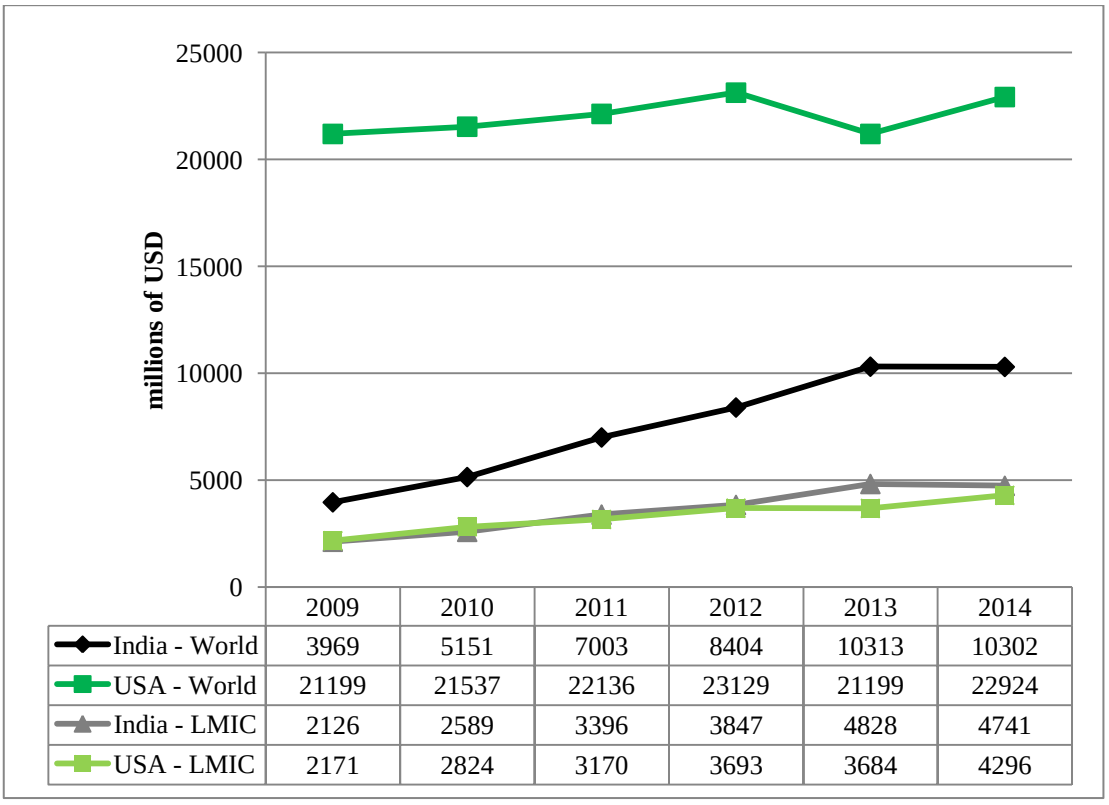
[37] See the detailed table of ARV manufacturers in Annex III.

[38] The author acknowledges that there are a number of important generic producers in the USA.

[39] UN Comtrade data (UN, 2012) were retrieved from the World Integrated Trade Solution (WITS) managed by the World Bank. The dataset reflects trade flows under the heading 3004 of the harmonized system, i.e. packaged medicaments for retail sale.

Both figures highlight the share of exports to low and middle-income countries (LMIC). The first figure shows the value of exports in thousands of USD. Worldwide, the exports from the USA in 2014 amounted to almost USD 23 billion. That is more than twice the value of Indian pharmaceutical exports. As for the dynamics, over the course of the reference period (from 2009 to 2014), the export of medicines from India more than doubled in value, while the value of exports from USA remained almost the same.

Figure 5: Value of exports of pharmaceutical under HS 3004 from India and USA

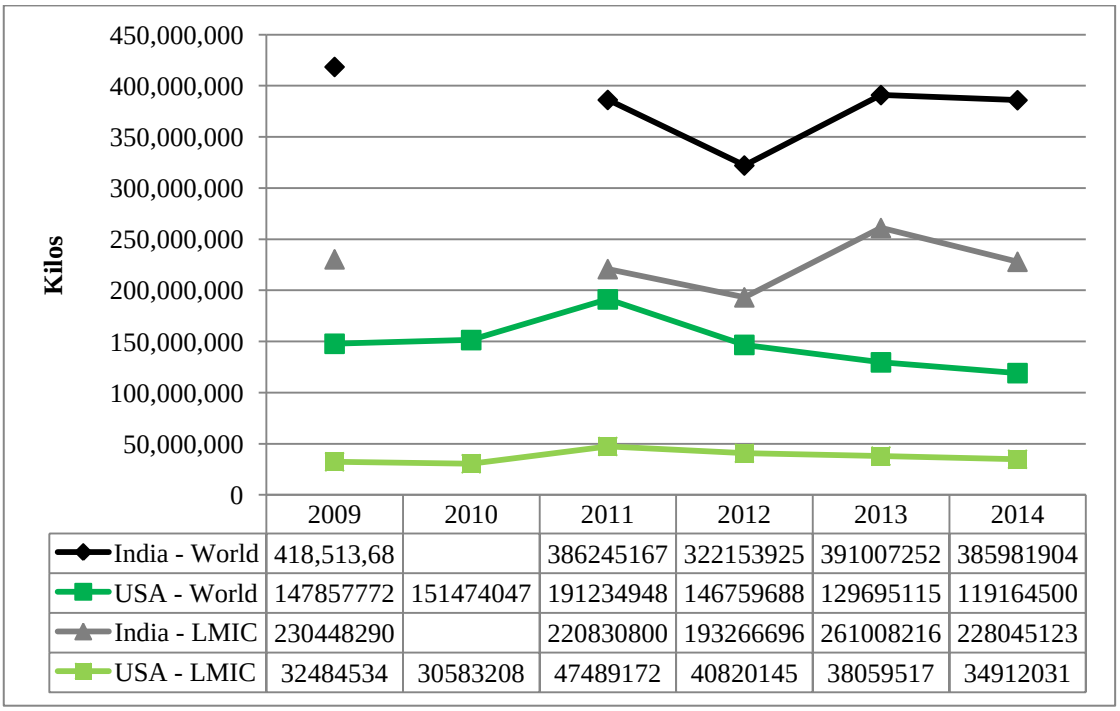


	2009	2010	2011	2012	2013	2014
India - World	3969	5151	7003	8404	10313	10302
USA - World	21199	21537	22136	23129	21199	22924
India - LMIC	2126	2589	3396	3847	4828	4741
USA - LMIC	2171	2824	3170	3693	3684	4296

Source: own configuration, based on data from the UN Comtrade Database (UN, 2012), and retrieved using the World Bank WITS tool

Figure 6 explores the export of pharmaceuticals from the perspective of quantity, in this case the net weight in kilos. This comparison reveals an important insight. While the exports by value are much higher in the USA, the volume of Indian export is more than three times that of the USA. Indian pharmaceutical industry can be referred to as a "low price – high value" market.

Figure 6: Volume of export of pharmaceuticals under HS 3004 from India and USA



	2009	2010	2011	2012	2013	2014
India - World	418,513,68		386245167	322153925	391007252	385981904
USA - World	147857772	151474047	191234948	146759688	129695115	119164500
India - LMIC	230448290		220830800	193266696	261008216	228045123
USA - LMIC	32484534	30583208	47489172	40820145	38059517	34912031

Source: own configuration, based on data from the UN Comtrade Database (UN, 2012), and retrieved using the World Bank WITS tool

However, a comparison of trends in the two figures shows that while the quantity of Indian exports slightly decreased over the reference period, the value grew considerably. That can be explained by the increasing acceptance and growing price of Indian medicines in developed markets. Growing value of Indian exports in developed markets is further validated by the following: the share of exports to LMIC by value shows a decreasing trend[40], the volume has been steadily growing[41]. Naturally then, the volume aiming at developed markets has been falling while simultaneously the value has been rising.

American exports display a slightly different trend. Both value and volume of exports to LMICs has been growing, but with the final forces being inversed relative to the case of India. In other words the prices of medicines exported to LMIC from the USA grow faster than the volume of these exports.

Moving the analysis forward to the ARV specific trade, using WITS for monitoring becomes restrictive. The data on international trade from Comtrade administrated by WITS are structured based on 2 digit, 4 digit or 6 digit HS codes. Firstly, HS sub-groups do not reflect indication, but the chemical composition

[40] From 54 % in 2009 to 46 % in 2014.
[41] From 55% in 2009 to 59 % in 2014.

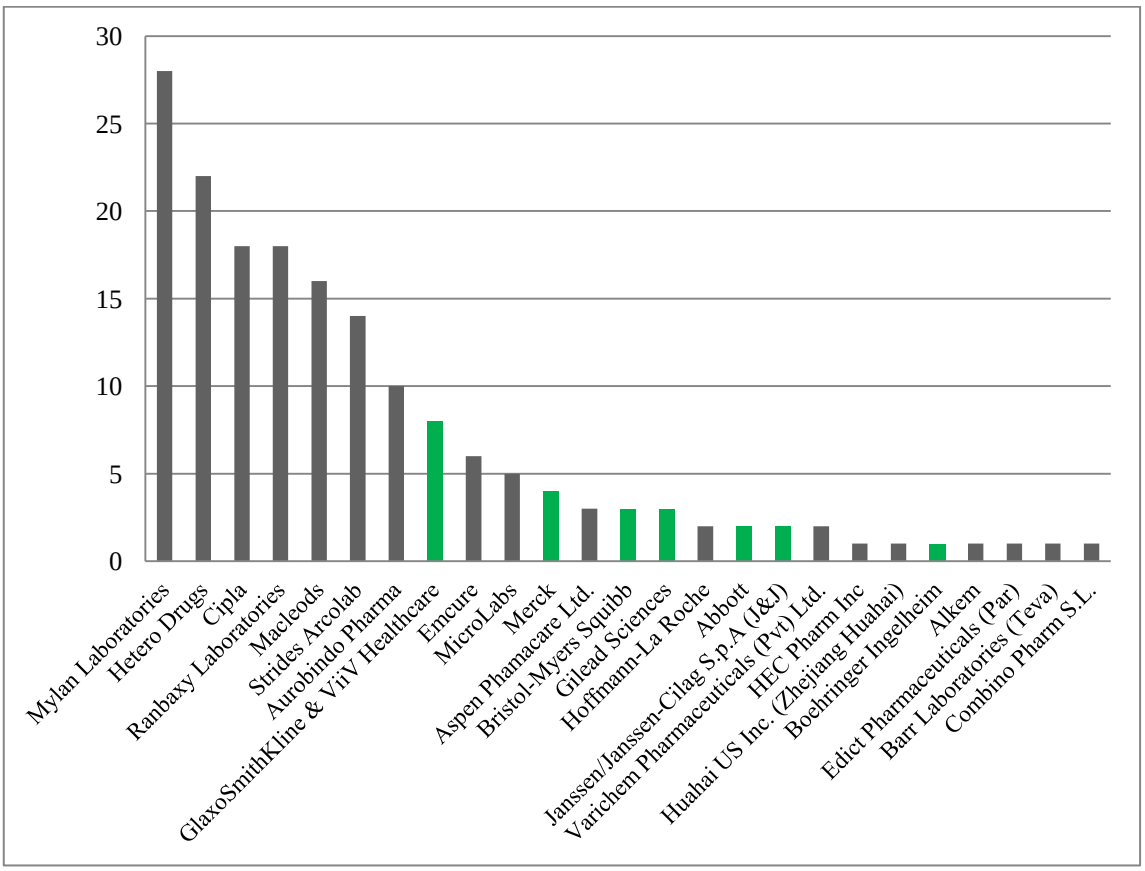
of substances, both in B2B and retail[42]. And secondly, it does not differentiate between originator and generic products. For the ARV specific analysis distinguishing between generic and originator manufacturers GPRM database is used as a source of data.

2.2.1 "Big Pharma" Companies

Research oriented companies tend to focus on production of a variety of dosages and modes of usage of one molecule – their proprietary one. They then develop various dosages and modes of administration in order to deepen their portfolio. An example of this can be seen in figure 7 below. Green columns indicate research oriented companies. The dependence on a single compound or a limited number of compounds influences the fierceness with which patent holders protect their patents.

[42]It is thus the case that within the international 6-digit codes, the most detailed level tracked by Comtrade, substances for use in humans and in animals can appear in the same group. Also, ARV formulations for retail are listed under the heading 3004 of the HS nomenclature (Cybex, 1997), "*Medicaments (excluding goods of heading 30.02, 30.05 or 30.06) consisting of mixed or unmixed products for therapeutic or prophylactic uses, put up in measured doses (including those in the form of transdermal administration systems) or in forms or packings for retail sale"*, sub-heading 300490, which is the "Other" or as well "not elsewhere specified" group of products – the same group of products as for instance Nizoral, the anti-dandruff shampoo belongs to (Kirschner, 1997).

Figure 7: Number of compounds and formulations sold by ARV manufacturers



Source: own configuration, based on data from PEPFAR (2014)

In 2013, originator producers catered for only a little over 3 % of the ARV market in LMICs, but collected 5.21 % of the total amount paid for ARVs. Measured by standard deviation, the scale of applied prices is considerably more dispersed than it is the case with generic producers. This demonstrates that originator companies are more likely to resort to tiered pricing.

Table 2: Characteristics of originator produce of ARVs in LMICs in 2013

Originator ARV Producers in 2013	
number of units sold	264858902
income in USD	61037903.38
weighted mean price per year of treatment in USD	288.3625227
% of total value of the market	5.21%
% of all units	3.28%
standard deviation (price per year of treatment)	1171.004486

Source: own configuration, based on the GPRM database (WHO, 2011)

96.7 % of the originator ARV units were sold by USA based companies, namely Abbot, AbbVie, Bristol Myers Squibb (BMS), Janssen and Merck[43]. The supremacy of the USA in this sector is undisputable. GSK and ViiV (a joint venture of GSK and Pfizer) represent the UK based companies and account for 2.6 %. The rest is distributed between the Boehringer Ingelheim (0.4 %, Germany) and Hoffmann-La Roche (0.3 %, Switzerland).

Table 3: Composition of the originator ARV market in 2013

	number of units	income in USD	% of total NoU	% of total income
AbbVie	123812992	28175258.79	46.75%	46.16%
Abbot	119328696	21170882.07	45.05%	34.68%
Gilead	10675230	7158696.431	4.03%	11.73%
GSK (ViiV)	6779710	1081968.719	2.56%	1.77%
Boehringer Ingelheim	1179060	130450.09	0.45%	0.21%
BMS	936839	181281.8311	0.35%	0.30%
Merck	890155	841246.6237	0.34%	1.38%
Hoffman la Roche	678480	994009.6342	0.26%	1.63%
Janssen	577740	1304109.195	0.22%	2.14%
Total	**264858902**	**61037903.38**	**100.00%**	**100.00%**

Source: own configuration, based on the GPRM database (WHO, 2011)

The sale of originator ARVs in LMIC is dominated by AbbVie and Abbott, which control over 90 % of the market. It has to be kept in mind, however, that originator drugs represent only a little over 3 % of the overall market in LMICs. There are two ways to increase originator companies' income: 1) applying disproportionally higher prices in developed countries, and 2) collecting royalties from licensing-out their IP.

2.2.2 Generic Producers

As opposed to the originator companies, large generic producers offer a number of molecules and formulations. Measured by standard deviation, they also apply much more even pricing policies.

[43] This does not mean they were manufactured in the USA. The production network is rather complicated with pharmaceutical MNCs, so instead of following a country of manufacture, the territorial division was made on the basis of the country of the mother company.

Table 4: Characteristics of generic produce of ARVs in LMICs in 2013

Generic ARV Manufacturers in 2013	
number of units sold	7807059461
income in USD	1109708627
weighted mean price per year of treatment in USD	87.60218677
% of total value of the market	94.79%
% of all units	96.72%
standard deviation (price per year of treatment)	80.12784774

Source: own configuration, based on the GPRM database (WHO, 2011)

84 % of the generic produce originates with Indian companies. 13.8 % is made by the company called Mylan Laboratories, technically an American company. According to the GPRM, however, all Mylan's medicines are manufactured in India. The remaining 2.2 % is supplied by the South African company called Aspen. Table 6 shows that 83 % of the generic ARV market is concentrated in the hands of top 5 generic producers. Taking into account that generic produce represents close to 97% of the entire ARV market in LMICs, these five companies control approximately 80 % of the ARV market in this as a whole. High market shares give these companies bargaining power in negotiations with the patent holders.

Table 5 Composition of the generic ARV market in 2013

	number of units	income in USD	% of total NoU	% of total income
Hetero	1871631370	282576435.9	23.97%	25.46%
Aurobindo	1737720480	181824190.9	22.26%	16.38%
Mylan	1077232166	237007018.8	13.80%	21.36%
Matrix	914638250	179196277.8	11.72%	16.15%
Cipla	866035220	105700007.4	11.09%	9.53%
Strides Acrolab	602008470	57235486.05	7.71%	5.16%
Ranbaxy	487545060	53972653.86	6.24%	4.86%
Aspen	174737730	6938341.466	2.24%	0.63%
MicroLabs	54306330	2864949.84	0.70%	0.26%
Macleods	11447190	1627619.824	0.15%	0.15%
Emcure	9757195	765645.4291	0.12%	0.07%
Total	**7807059461**	**1109708627**	**100.00%**	**100.00%**

Source: own configuration, based on data from the GPRM database (WHO, 2011)

The reason behind the success of the Indian generic industry dates back to 1970s. The Indian Patents Act 1970 introduced process patents on pharmaceuticals as opposed to the previous system of British law that favoured product patents. What that meant was that if manufacturers were able to produce the same compound using

different methods, they could produce and market the drug immediately. Moreover, the process patents in India were only valid for 5 to 7 years, after which the patented medicine could be copied freely. The IP system has played a crucial role in mastering reverse engineering by Indian pharmaceutical companies (Mueller, 2006).

Over the period of 35 years between 1970 and 2005[44] India established itself as a "pharmacy for the developing world". Even after the adoption of new the new WTO legislation, India managed to use as much of the flexibilities in the interpretation of TRIPS as possible. According to originator producers, some of the provisions are bordering with non-compliance with TRIPS. However, India remains firm in its stance towards pharmaceutical patents. The abovementioned ruling of the Supreme Court in the Novartis case set an important precedent for continuous process of formation and development of India's IP system. India is not willing to accept commitments beyond the TRIPS standards even in its free trade agreements (FTAs). That is true for the long negotiated India-EU FTA, where provisions on data exclusivity prevails a contentious issue (NITI Central, 2015).

The next chapter focuses on patent pooling. It introduces the main principles and focuses on its managerial aspects. It shows how the interests of both generic and originator companies can be taken into account when promoting access to medicines in both availability and accessibility through patent pooling.

[44] 2005 was the year when the TRIPS agreement was incorporated into India's legal infrastructure.

3 Pooling as a Viable Solution to the Intellectual Property Barriers to Access to Medicines

Shapiro (2007: 134) describes a patent pool as an arrangement that "*involves a single entity (either a new entity or one of the original patent holders) that licenses the patents of two or more companies to third parties as a package*". Literature concerning paten pools focuses mainly on its economic effects on competition. It balances pro-competitive and anti-competitive effects and some authors venture into modelling scenarios in order to show when positive pro-competitive effects outweigh the concerns linked to pooling.

In the first chapter, an important characteristic of positive externalities was discussed – they lead markets to produce a smaller quantity than is socially desirable. While there are models assessing economic effectiveness of pooling, literature on pooling in the pharmaceutical sector shows very little background in economics and is more oriented towards IP law and medicine. Throughout the research for this paper, no economic model was found that would extend the economic theory of pooling beyond traditional competitive analysis and would take into account the economic benefits that pooling can bring through positive externalities in terms of healthier population[45]. Such economic justification was identified as a potential area for further research, but ranges beyond the scope of this thesis.

It is important to demonstrate the variety of existing managerial features of pooling to be able to identify the main traits of the MPP that correspond to the up-to-now theory and those that are unique to pooling in the pharmaceutical sector. As stated by Serafino (2007: 2): "*There is no single reason for creating a patent pool and no single way to manage a patent pool*. "

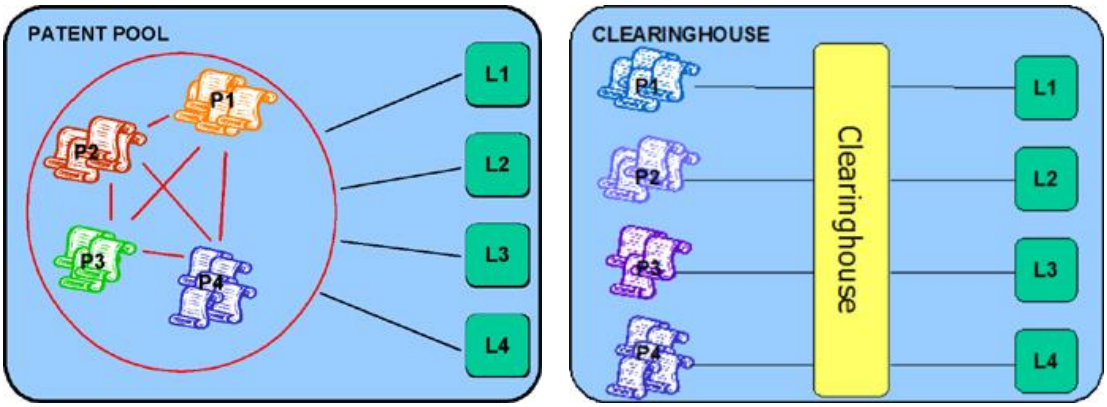
3.1 Managerial Aspects of Patent Pooling

At the outset, it is important to distinguish patent pooling as a concept from other forms of contractual sharing of IP. The closest and most resembling arrangement is cross-licensing. While pools offer a package of patents to third parties and all the patents are licensed simultaneously by one entity, cross-licensing involves two or more parties offering each other licenses so that both can produce their goods

[45] A paper called An Economic Justification for Open Access to Essential Medicine Patents in Developing Countries examines the potential positive effects of compulsory licensing, but does not expand on the possibilities of pooling in the area of open access (Flynn, Hollis, Palmedo, 2009).

without infringing on the other party's patents (Shapiro, 2007: 127, Simon et al., 2005: 708). Another form of joint IP management is through patent clearing houses. As depicted below, patent pools offer a bundle of patents to prospective licensees, while clearing houses serve as match-makers between specific needs of licensees and respective patent holders (Overwalle et al., 2007).

Figure 8: Patent pools versus clearing houses



Source: Overwalle et al. (2009)

Shapiro (2007: 120) examines pooling and cross-licensing of patents and finds these arrangements a useful tool to bypass patent thickets – a situation where so many patents are issued that a single new one will likely infringe on existing patents. In fields with complex patent landscape, another problem – patent holdup – can occur. It is a consequence of exploitation of patent's essentiality by the rights holder (Layne-Farrar, Lerner, 2010: 295).

The positive, pro-competitive effects of pooling are multiple. First of all, pools can help integrate complementary technologies and reduce transaction costs stemming from negotiating the licensing procedures with a large number of patent holders. (Kato, 2004: 257) In pharmaceutical sector, freedom-to-operate studies can incur significant costs to a company that seeks to test or commercialize a product without infringing on existing patents[46] (Palriwala, Goulding, 2012: 28). Furthermore, leveraged negotiation power of a pool is more likely to convince holders of essential patents to make their IP available for licensing, clearing the blocking positions in case of patent holdup. Pooling is also a form of *ex ante* protection against patent infringement, therefore can save considerable amounts of money on litigation (Kato, 2004: 257). Rodriguez (2010: 62) points out that patent pools also distribute risks among members and foster better exchange of information. And a study by WIPO (2014: 12) adds an overarching pro-competitive effect – promoting dissemination of technology.

[46] In USA, such costs can exceed USD 100,000.

Kato lists collective prices, output restraint and grant-back requirements among the possible anti-competitive effects of pooling (2004: 257). Grant-back clauses[47] are especially harming for follow-up innovation as they force the licensee to disclose and transfer all improvements made upon the licensed technology during the licensing period[48]. Collusion such as output restraint and price fixing has negative effects mainly on commercialization. Pools are not effective when anti-competitive factors outweigh the positive ones.

A study by WIPO (WIPO, 2014a: 6) sets forth guidelines for elimination of anti-competitive features of pooling:

> (i) Patents must be clearly identified and should be available for licensing individually as well as in a package as chosen by a potential licensee;
>
> (ii) The patents in the pool must be valid and must not have been expired;
>
> (iii) Limitation to patents that are technically essential which, by definition, are not competing, and use of an independent expert to assess whether a patent is essential;
>
> (iv) The patent pool should have limited duration;
>
> (v) The royalties proposed by the arrangements should be reasonable;
>
> (vi) Availability of worldwide non-exclusive licenses;
>
> (vii) Freedom of licensees to develop and use alternative patents;
>
> (viii) Requirement that licensees grant back non-exclusive, non-discriminatory licenses to use patents that are essential to comply with the technology; and
>
> (ix) The pool participants must not collude on prices outside the scope of the pool, e.g., on downstream products.

3.1.1 Relationships between Patents

When reviewing patent pooling, it is necessary to take into account the various relationships between patents. The basic distinction is between substitute, complementary and unrelated patents (Kato, 2004: 255). Unrelated patents do not have any significance for this thesis and are not debated any further.

Substitute patents cover alternative technologies that can be used in parallel without infringing on each other. Two products with substitute patents are competing

[47] Provision in a licensing agreement under which the licensee is required to disclose and transfer all improvements made (including related know-how acquired) in the licensed technology during the licensing period (WebFinance, 2015).

[48] One of the alternatives to patent pooling is independent voluntary licensing. Grant-back clauses are a practice used VLs as well.

products. These patents are therefore sometimes referred to as rival or competing patents. Shapiro (2007) presents a widely accepted point of view[49] that pooling of substitute patents presents a threat to fair competition and results in higher licensing fees. Kato (2004), however, challenges this view and presents an idea that patent holders determine not only licensing fees, but also the number of licenses they issue. In the environment of fierce competition among licensors, the fees might become so low that licensors would rather refrain from licensing to outside firms. In such cases, even pooling of substitute patents can promote social welfare – through broader commercialization of innovative products.

The reviewed literature (WIPO, 2014a; Shapiro, 2007; Kato, 2004) is united as regards pooling of complementary patents. Such patents have to be used together in order to manufacture specific products. Even without pools, competition would not exist between the rights holders, and the result of pooling such patents is not considered competition distorting. Pools are usually associated with complex technologies that require complementary patents to provide viable technological solutions. Thanks to pools, licensees can save transaction costs, and prevent themselves from purchasing a license without knowing whether they would manage to obtain a complementary one. Antitrust authorities both in the USA and Europe state that pooling of complementary patents is generally pro-competitive (WIPO, 2014a: 4). However, in its study, WIPO states that while pooling complementary patents does not have negative implications on price competition in the downstream market, it might have adverse effect on subsequent innovation. Outside firms might be discouraged from R&D by potential litigation from pool participants and redirect their efforts towards fields of technology not covered in the pool (WIPO, 2014a: 5).

An extreme case of complementary relationship between patents is that of blocking patents. Two mutually blocking patents are complementary from a legal point of view (WIPO, 2014a: 4). Mere usage of one patent leads to infringement of the other. Therefore none of the patented technologies can be marketed individually without breaching the rights of another subject, supposing that both technologies are patented in certain territory.

Patent pools are very relevant in fields that are subject to standard setting measures. The basic distinction in this area is between essential patents – those needed to be licensed in order to implement a standard - and non-essential patents.

[49] Same was the opinion of the US Department of Justice in the business letters concerning the DVD standardization patent pools.

Involvement of an independent entity that supervises the choice of patents to be included into the pool helps to avoid inclusion of substitute patents into a pool. As discussed below, global health pools bear resemblances to standard-setting pools. At MPP in particular, MPP itself serves as an independent supervisor that selects the priority medicines for the pool through analysing market potential, patent status and forecasts for clinical need of various compounds.

3.1.2 Incentives for Joining a Patent Pool

Rational behaviour of firms suggests that joining a pool is a decision based on the expectation of maximizing profits. That can happen through reaching out to a wider audience of potential users of the technology – prospective licensees – and increasing revenues through collecting royalties. Firms can also make use of complementary technologies in the pool and improve upon their own technologies. Or – in case of anti-competitive pools – maximizing profit is possible through the establishment of monopolistic position.

Economic literature examining incentives of firms for joining a pool does not contemplate a situation, where the administrator of the pool pursues its own objectives. It thus concentrates mostly on fee setting, royalty distribution and game theory where the main players are patent holders on the supply side of technologies and manufacturers on the demand side.

Layne-Farrar and Lerner (2010), for instance, examine the possible motivation of owners of essential patents outside the pool to join. They study the special case of standard-setting pools. They point out the findings of Aoki and Nagaoka (2004: 18) that for incentive analysis, it has to be distinguished between firms that conduct both R&D and downstream manufacturing, purely R&D oriented companies and manufacturers. Vertically integrated and manufacturing firms tend to push the licensing fee to as low as possible to lower their cost of production. To the contrary, R&D companies whose income constitutes solely of royalties have to rationalize between a fee too low to cover their expenses and a fee too high that would lower the demand for the licenses. This demonstrates that there is no one solution to managing a patent pool, because the members will never all have the same incentives to join.

There are various ways to distribute royalties that flow into the pool. As the patents are bundled and licensed-out as a package, the demand for a single technology cannot be tracked. The simplest distribution scheme is based on numeric proportional rules, whereby royalties are distributed according to licensor's numeric

share of the total number of pooled rights. This is a usual practice in standard-setting pools despite the fact that, according to theory, such pools tend to attract fewer joiners, because firms with high value patents are less likely to contribute to the portfolio. It also discourages genuine R&D as having several incremental patents repays better than contributing with one substantially progressive technology. Aoki and Nagaoka consider value proportional rules with extra distribution to R&D only firms a solution to this problem. Some pools offer royalty free licensing to members of the pool. As explained in the first chapter, patents are territorial rights. Royalties from each country should thus be divided based on the number of valid patents belonging to the pool in each territory. Formula for dividing the royalties can be a function of other factors, such as age of the patent or frequency of infringement (Aoki, Nagaoka, 2004; Layne-Farrar, Lerner, 2010).

Most modern pool agreements allow for independent licensing outside of the pool (Layne-Farrar, Lerner, 2010: 296). While conditions under independent licenses are negotiated bilaterally, the fee for the joint licences is typically set collectively by the members. The fees are can be set as percentage of the licensee's net sales of as a flat fee per unit sold and are collected by the administrator.

In a pool governed by the founding members, the rules for the pool to abide by are drafter by the first comers. However, this is not the case of the Medicines Patent Pool, since the incentive to start the pool did not originate with the licensors, but with a third party NGO.

3.2 Review of Patent Pools in History

Europe and the USA have been the centres of patent pooling, which is understandable as this region is also a cradle of the modern IP system. With the rise in Asian markets and their larger participation in development of sophisticated technologies, participation of companies from the region has been growing (WIPO, 2014a: 4).

Based on reviewed literature, four main objectives of pools were identified: 1) pools founded to pursue anti-copmetitive goals, 2) those that serve as tools to promote national interests, 3) standard-setting pools, and 4) those that pursue social benefits. It is possible to link these types of pools with various eras in history.

The early pools date back to the period between the second half of the 19th century and the beginning of the 20th and bore traits of cartel deals. They were present in a number of major industries that were moving the economy forward at the time, including textile, automobile, shoe-making, film, oil drilling or glass.

These pools were often designed to hinder expensive litigations or to form monopolies with the purpose to fix prices and limit competition (Serafino, 2007). In this period, foundations were built for current legal standards with regard to pooling.

Towards the end of the WWI, the US government used pooling to promote national policies. A classic example of such an arrangement is the establishment of the Manufacturers Aircraft Association. It was created with a view of faster implementation of warfare aircraft technologies after the entry of the USA in the World War I[50] (Serafino, 2007). After the WWI, US government interfered with private patent holders again in the case of Radio Corporation of America[51]. These policies have one aspect in common; interference with private rights holders in order to further urgent national priorities. These efforts are worth mentioning in the context of pooling in the pharmaceutical industry. They prove that even a country that ranks among the fiercest defenders of rights of patent holders on various international fora is able to mobilize the IP resources of private subjects in case of an emergency[52].

The emergence of modern patent pools dates back to the mid 1990s. These pools are often closely connected to standard-setting and revolve mostly around ITC technologies. Standard setting pools have been driven by the interests of the industry, i.e. the patent holders. The standards created by private entities can be either adopted by public standard setting organizations or can create a competitive edge that leads to the uptake of the pooled technology as opposed to a competing substitute (Aoki, Nagaoka, 2004:). Economic models examining pooling features such as incentives to join or justifications of royalties and their distribution among licensors are usually developed on the premises of standard-setting pools. The sample includes Aoki and Nagaoka with their study on consortium standard and patent pools (2004), Layne-Farrar's and Lerner's analysis concerning incentives to join pools (2010) or a study by Lerner and Tirole on efficiency of patent pools (2004). A standard setting pool is believed to be pro-competitive when it includes essential patents, i.e. complementary patents that are necessary for implementing a standard (WIPO, 2014a: 7). Private patent pools might take the form of a joint venture and technologies

[50] Prior to 1917, chaotic situation concerning validity and ownership of patents in the aircraft industry was prevalent in the USA. It stiffened the production of vital technologies at a time of a national emergency, as manufacturers would not deliver on orders by the US Government due to fear of IP related litigation.

[51] The Navy encouraged General Electric to buy out the U.S. branch of Marconi, and pool patents from Marconi, AT&T, Telefunken and Westinghouse into what became in 1919 the Radio Corporation of America (Serafino, 2007: 16).

[52] Government lead patent pooling initiatives are not the only channel whereby USA has been interfering with existing patents. It has been noted that USA had issued compulsory licenses covering 40 to 50 thousand patents by 1950 (Flynn, Hollis, Palmedo, 2009).

that have been widely adopted in the marketplace thanks to standardization and coordinated IP management include MPEG image formats, Bluetooth wireless transmission, DVD technologies or 3G mobile telecommunication technology and others.

Recent years have been marked by a new direction in pooling, one that reflects both economic and social interests. Parallels can be drawn with standard-setting pools, but the impetus to establish a standard and gather technologies in order to easily market certain products does not necessarily originate with the industry. The driving forces vary from public institutions through private entities to NGOs. Promoting wider uptake of the technologies is driven by the effort to further socially desirable outcomes. Increment of welfare reached by commercialization of pooled technologies is amplified by positive externalities resulting from their usage. Global health and agricultural technologies are the two main sectors where pools with social subtext have been established. The trend emerged in 2000 with the Golden Rice Pool designed to simplify licensing of patents related to a genetically engineered vitamin A enriched rice strain[53]. Pools in the pharmaceutical industry discussed below belong to this category as well. Even within this group of pools, however, various portfolio management styles and administrational structures were observed. The abovementioned Golden Rice Pool, for instance, provides licenses on a royalty-free basis to subsistence farmers that earn less than USD 10,000 per year. Some of the pools gather patents from non-profit institutions only[54] or do not allow for usage of the collected IP for commercial purposes[55]. But in general and contrary to traditional standard-setting pools, the incentives for owners of technologies to join the pool are not always easily reflected in fees. The incentives for MPP licensees are further discussed in the case study in chapter 4.

3.3 Existing Intellectual Property Pools in the Pharmaceutical Industry

In the presented paper, it has been established that patents can constitute a barrier to R&D ad access to medicines. Apart from pooling which is a rather recent strategy in the pharmaceutical sector, there are other existing licensing mechanisms to facilitate access – compulsory licensing, voluntary licensing and donations of medicines. Compulsory licensing is discussed in the first chapter. The general

[53] The social aspect lies with the fact that vitamin A deficiency in children can cause blindness and intensify viral infections such as HIV/AIDS, measles etc (Serafino, 2007).

[54] Public Intellectual Property Resource for Agriculture (PIPRA) – 2001.

[55] AvGFP (Green Florescent Protein) – 2001.

reservations towards VLs are for instance lack of transparency or uneven bargaining position between originator and generic companies. Donations do not increase market size and can discourage generic companies from entering the market. The case study presents the value-added of MPP vis-à-vis VLs and CLs.

Palriwala and Goulding (2012) observed that in areas where there is robust commercial market potential, it is difficult to pursue independent licensing as the rights holders view patents as valuable assets. Negotiating such patents for pooling is difficult. However, if reached, one-stop licensing agreements can make positive difference. Where market potential is poor, incentives to withhold patents are low and pooling might thus not add much value from the perspective of making patents accessible. The value-added of such pools lies rather with improving the logistics of research and commercialization.

There are two channels through which patent pools promote the two aspects of access to medicines as presented in the first chapter: availability and accessibility. One of them is enabling upstream innovation and thus improving availability of medicines. This is usually done by originator companies. The other channel is promoting downstream improvements and commercialization of existing medicines which contributes to wider accessibility. This is where low-cost manufacturing capacities of generic firms has the potential to make a difference. Two major health-oriented join IP management entities – the Medicines Patent Pool (MPP) and the Pool for Open Access Innovation that currently operates under the auspices of the WIPO as the Re:Search project – focus with different level of emphasis on both these streams of innovation/commercialization[56].

3.3.1 Medicines Patent Pool

The idea to create a pool of essential patents for generic manufacture of HIV/AIDS drugs was first presented by the Knowledge Ecology International (KEI), a think-tank based in Washington and Geneva, and Médecins Sans Frontières (MSF) in 2006. UNITAID implemented the concept by establishing the Medicines Patent Pool in 2010. MPP thus emerged based on the demand by international community and has always been driven by the non-profit sector (Palriwala, Goulding, 2012).

[56] Apart from these two initiatives, joint IP management was also proposed after the outbreak of SARS (Severe Acute Respiratory Syndrome) in 2002 (Simon et al., 2005). Global response spurred by the WHO led to a wide coverage of research on the SARS contra-virus genome, scattering the fragments of patented knowledge between various institutions – both private and public. Simon (2005) argues that without joint approach, developing new effective treatment in case of a new outbreak of the virus would be hindered by the fragmentation of the patent landscape. The SARS case touches upon a very controversial issue of patenting genomic sequences that stretches beyond the scope of this thesis.

The need for an impetus from an NGO is not surprising, as the ARV market is a robust one[57] and patens are therefore a valued asset of originator companies. Ideally, they can incur substantial income by marketing the products themselves, which does not incentivize them to start a pool by themselves.

MPP is a system of voluntary licenses, which enables generic manufacturers to produce and/or improve on existing patented ARVs. MPP focuses on commercialization and stimulates the downstream innovation processes. It is financed under a five year memorandum with the UNITAID mechanism[58] confirmed in 2011 (Palriwala, Goulding, 2012: 2). Apart from acting as an entity managing the pool of patents, MPP sets forth the guidelines according to which patents are chosen for the inclusion into the pool, negotiates the terms with the originator companies and provides legal support in drafting the licensing and sublicensing agreements. The fourth chapter expands on the functioning of MPP.

3.3.2 World Intellectual Property Organization Re:Search Project

The Pool for Open Innovation, on the other hand, originated in the private for-profit sector. The pool was created by GSK in 2009 and after having been transferred to the BIO Ventures for Global Health (BVGH) in 2010, it was integrated into the WIPO structures and renamed WIPO Re:Search. It focuses on early stage research, promoting upstream innovation in developing neglected tropical diseases. The centre of its activities is promoting increased availability in areas of low market potential and high social benefits. There is not a wide market for such inventions; GSK thus did not renounce considerable earnings by offering their IP and know-how to the research community. The difference in market potential of ARVs (subjects to pooling in MPP) and drugs for neglected diseases (subject to pooling in Re:Search) is a possible explanation of the difference between the founding entities of these two pools (Palriwala, Goulding, 2012: 51).

The concept of Re:Search stretches far beyond a pool of patents. It is an open innovation platform offering patents, but also necessary technical know-how and associated research data. WIPO Re:Search offers royalty-free licenses to on future sales in LDCs. Subjects involved are big pharmaceutical companies and university based and public sector research institutions (WIPO, 2014b).

[57] This is true for HIV/AIDS in adults.

[58] More than a half of UNITAID's funds come from air ticket levies implemented by Cameroon, Chile, Congo, France, Madagascar, Mali, Mauritius, Niger and the Republic of Korea. Norway allocates part of its tax on CO2 emissions into the fund (WHO, 2015).

Assessing the effectiveness of Re:Search in pursuing its goals is difficult as those goals are long term ones. Development of novel drugs and bringing them to market will take years. Also, as the IP in question belongs to the category that offers low market potential, the value added might be hampered by the fact that obtaining such patents does not present considerable difficulties to research entities. Coordination of available trial data, however, may bring benefits in terms of easier access to information about ongoing research, thus avoiding duplicative efforts. Proving the concept requires further monitoring. Re:Search can also be beneficial in forming a global match-making platform where partnerships can be formed between entities that would otherwise not meet (Palriwala, Goulding, 2012). Paradoxically, the value added of this pool does not lie with IP as such, but with the associated data, know-how and potential for R&D cooperation on global scale.

What global health pools have in common differentiates them greatly from commercial pools. The financial incentive for drug developers is rather low and participants thus pursue other goals. Altruistic motives have to be examined carefully and with reservations and therefore other incentives have to be identified. Incentivizing R&D companies to join global health pools is the foremost challenge for the administrators, as royalties are an important but not sufficient condition for forming a pool.

4 Case study: Medicines Patent Pool

Accessibility presents a more pressing problem than availability in ARV access (see annex I for explanation). Commercialization of affordable medicines and downstream development, i.e. new formulations for paediatric use, heat resistant medicines etc., are vital in this area. For those reasons, MPP was selected for the case study as opposed to WIPO Re:Search. The MPP also has a longer history of existence and its goals are more short term based relative to the WIPO initiative. This helps to track the results of their operations. The MPP collects patents from private and public entities, but is not a for profit establishment.

In its purpose, MPP is an alternative to government issued CLs, donations of ARVs, and VLs by originator companies. As an umbrella tool for VLs, the most direct alternatives to MPP are bilateral VLs.

As an administrator and a third party NGO acting as access advocate, MPP uses its position and social pressure to negotiate the fees and terms with the prospective licensors. This is not to say that MPP is an involuntary arrangement, but it shows an important difference between commercial pools and the MPP. The administrator of the pool pursues its own goals, which means there are three types of entities with different objectives – the licensors, the licensees and the MPP itself.

The MPP "*...aims to lower the prices of HIV medicines and facilitate the development of better-adapted HIV medicines, such as simplified "fixed-dose combinations" (FDCs) and special formulations for children, through voluntary licensing and patent pooling* (MPP, 2015b)." In order to do so, the MPP strives to pool as many patented compounds as possible based on the aforementioned list of priority ARVs, and to engage as many generic companies as possible to produce the low-cost versions. This should in turn create a competitive environment and bring down the prices of priority ARVs at a time when the WTO TRIPS agreement is fully in force in countries that provide low-cost medicines to the developing world. At the same time, the MPP needs to motivate licensors to avail their rights and the generic companies to join the pool as sub-licensees.

While not denying the MPP's existing and prospective licensors' objective to maximize profit, the set of incentives for licensors in MPP differs in some ways from those of members of commercial pools. They are not easily calculable in royalties and reflect some specifics of the pharmaceutical market. One of these incentives is common for VLs and MPP – penetrating the LMICs' markets. As shown

in chapter two, it is difficult for originator companies to directly sell medicines in LMICs[59]. However, they can establish their presence in these markets indirectly through licensing out their patented products to generic manufacturers. Generic producers from developing countries are more suitable for low-cost, high-volume production necessary to cater for the LMICs market.

There are two obstacles that MPP needs to overcome in order to entice originator companies to pool their patents. Firstly, the rights holders have to be interested in licensing out their patents, and secondly, they have to choose the MPP over bilateral VLs. Originator companies have become more open to the former as increasing financial constraints make them realize the advantages of partnering with generic producers. A company willing to license its patents bilaterally will be more open to license to MPP and a growing number of transparent licenses brought in by the MPP can have a positive effect on patent owners' willingness to license out their IP, even if bilaterally (Palriwala, Goulding, 2012: 29). Technically, even bilateral VLs contribute to the MPP goals. Issues that contribute to hesitation of originator companies as to whether license out their patents or not are assurance of quality and safety, brand image and parallel imports. Although as for the latter, there is no evidence of widespread parallel importation of generic ARVs to MIC and HIC (Palriwala, Goulding, 2012: 30).

Palriwala and Goulding (2012: 62) present the following advantages of joining MPP vis-à-vis issuing VLs. Consequently, these are the incentives for originator companies to join the pool. Beyond royalty revenues, there is reduced licensing and administrational costs, improved knowledge of distribution and supplies in the LMIC markets, product quality assurance through MPP supervised licensing terms, risk sharing in developing new products and the geographical scope of the licenses which enable reserved production for higher margin markets. The MPP also has a reputation endorsed by the UN, the US National Institute of Health (NIH) and other well renowned institutions. That yields positive publicity and creates a space for patent owners to implements their corporate social responsibility (CSR) activities.

Incentives for generic producers are mainly legal certainty and avoidance of liability for patent infringement, equitable and transparent licensing conditions, broadening of product portfolio, wider geographical scope, larger volumes and consequently opportunity for sufficient economies of scale, and, last but not least, reduced licensing transaction and administration costs (Palriwala, Goulding,

[59] Originator companies supply circa 3 % of the total amount of ARVs in LMICs worth 5 % of the market.

2012: 62). The unprecedented transparency of the MPP's conduct is represented mainly by the fact, that all the licensing and sub-licensing agreements are freely available to the public on the MPP's website.

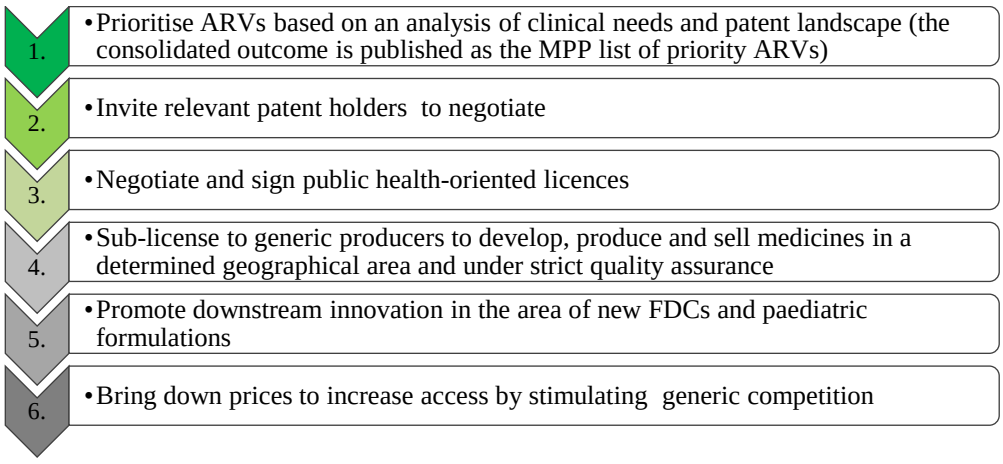
It needs to be kept in mind that the objective of generic producers is in its core the same as the goal of originator companies – to maximize profits. The only difference is that generic companies pursue a different strategy to accomplish this goal. The fact that activities of generic firms serve the purpose of the MPP does not mean that these subjects have the same motivation. While the MPP strives for as many generic producers as possible while assuring quality and safety of generics, it is not in manufacturers' best interest to increase the number of the generic companies involved.

Examining the MPP's modus operandi has shown that while it presents itself as a pool, it, in fact, bears certain traits of patent clearing houses. It does not bundle the licensed patents into one package and offers to generic producers the possibility to sub-license only a selected set of patents from the pool.

4.1 State of Play of Negotiations in the Medicines Patent Pool

To date, the MPP has managed to contract seven patent holders to join the initiative – six pharmaceutical companies and the US National Institute for Health (NIH). With regards to the generic manufacturers, MPP signed 23 sub-licensing agreements with 9 Indian producers[60]. The figure below represents a six-step summary of how the MPP operates.

Figure 9: Operations of the Medicines Patent Pool



Source: own configuration, based on MPP, 2014

[60] Mylan Labs is an Indian subsidiary of a USA based generic producer Mylan.

The initial phase of step 4, the so called Expression of Interest, is a procedure aimed at approaching prospective sub-licensees. In this phase, the MPP engages in a dialogue with the aspiring generic producer regarding manufacturing capacities, safety assurance or possible contributions to wider access to ARVs in developing countries.

4.1.1 Licensors, Sub-Licensees and Pooled Patents

The licenses in the MPP were negotiated individually with each company and are not identical in their content. They vary in geographic scope, target patients (adults/children), type of contribution (license for manufacturing/commitment to lower prices) or even stage of development of ARVs in question[61]. This also differentiates the MPP from commercial standard-setting pools where there is a set of rules for the group of licensors as a whole.

Negotiating with "pharma giants" requires a balanced approach that combines strong stance on one hand and the ability not to deter the originator companies from the joining the negotiating table on the other[62]. Compromises reached in such negotiations are sometimes a target of criticism by specialized access advocacy institutions such as Initiative for Medicines, Treatment and Knowledge (I-MAK) or International Treatment Preparedness Coalition (ITPC). While some of the concerns seem legitimate, it is important to take into account the benefits MPP brings compared to a situation where MPP does not exist.

[61] TAF for example, is still in phase II of clinical trials.

[62] One of the approached IP specialists claimed that in the first years of the MPP's existence, before the personnel changes on the executive level in 2012, the anti "big pharma" rhetoric might have discouraged some originator companies from joining. Looking at table 10, it is visible that most of the agreements were concluded after 2012. This might, however, be a result of intensive negotiations initiated before and concluded after the personnel changes.

Table 6: Current licenses in the Medicines Patent Pool

Patent Holder	Compounds	Joined the Pool	Additional Notes
US NIH	darunavir	09/2010	complementary licenses are necessary to allow for generic manufacturing
Gilead Sciences	tenofovir, emtricitabine, cobiscat, elvitegravir + Quad	07/2011	Quad is a formulation consisting of the four aforementioned compounds
ViiV Healthcare	abacavir	02/2013	for paediatric use
Roche	valganciclovir	07/2013	the subject matter of the agreement is a price reduction commitment, not a license for generic manufacturing
BMS	atazanavir	12/2013	
ViiV Healthcare	dougletavir	04/2014	
Gilead Sciences	tenofovir alafenamide (TAF)	07/2014	
AbbVie	lopinavir, ritonavir	12/2014	for paediatric use
MSD (Merck)	raltegravir	02/2015	for paediatric use

Source: own configuration, based on MPP (2015a)

Comparing patents currently licensed through the MPP with its list of priority ARVs shows that patents that have as of yet not been licensed to the pool belong to Merck (MSD) and two Johnson & Johnson (J&J) owned companies – Tibotec and Janssen. While Merck has already signed one licensing agreement with the pool[63], J&J has not entered into any negotiations with the pool. In 2011, J&J declared its decision to not license ARV patents for the use in developing countries through the pool[64] (MPP, 2011).

The J&J companies hold patents to two compounds essential for third line treatment, namely etravirine and darunavir. The new third line ARVs cause biggest

[63] This is the pool's latest agreement signed in February 2015 and the subject matter is Raltegravir for paediatric use.

[64] The reaction of the public was rather fierce, mainly coming from NGOs such as MSF. The rhetoric contained phrases like "*Johnson & Johnson Turns Its Back on AIDS Patients*" (MSF, 2011), or "*Pharmaceutical giant Johnson & Johnson is putting the lives of people living with HIV at stake by refusing to participate in the Medicines Patent Pool*" (MSF, 2011). Possibly as a reaction to this negative publicity, J&J announced a year later, that it would not enforce patents on its drug darunavir in SSA and LDCs. The geographical scope of 64 countries, however, is a step back in comparison with other companies' commitments to MPP (MPP, 2012). J&J's webpage that further states that "*...Johnson & Johnson has addressed the concerns in the Least Developed Countries by pledging not to enforce its patents, provided the generic versions of the drugs are of quality, medically acceptable and used only in the defined territory*." (Johnson & Johnson, 2015). Such commitments are commendable, but they do not have legal backing and might not create a clear and stable enough legal environment for manufacturers from LMICs that export to LDCs.

concerns for access advocates, as new compounds patented after 2005[65] cannot undergo the same sort of price reduction due to generic competition as the first wave of ARVs have over the last 15 years. As a "pharmacy for developing world", patent status of these drugs in India is a key factor for access in LMICs. Etravirine is patented in India and its follow-on patents for improved formulations are still under hearing with the Indian Patent Office. As regards darunair, although the patent was rejected due to pre-grant opposition, the divisional patent application is still pending. J&J maintains high prices of these compounds in their exports to LMICs; search and processing of GPRM data have shown that the weighted average price PPY is USD 2143; a price clearly prohibitive for a wide use in developing countries. The weighted mean price for darunavir only (produced by Janssen) is even higher – at USD 2806 PPY. Securing provision of such novel drugs at an affordable price presents a major challenge to the MPP's endeavour, but it is also an area, where MPP has the opportunity to make a positive change.

Moving on to the sub-licenses, Table 8 shows agreements with generic manufacturers. Generic companies can sign licenses for a selected number of patents with MPP and the owner[66]. That is allowed by the fact, that patents in the pool are not bundled. This characteristic stems from the territorial nature of patents – the sub-licensees can pick those patents that are in force in their country. Also, this points to the substitute nature of patents in the pool. Were all the patents in the pool complementary, it would not make sense to a producer to sub-license only a selected set of patents. Even though the patents are substitute, the role of the MPP as a third party policy maker and administrator ensures elimination of anti-competitive behaviour of licensors within the pool. MPP negotiates terms with licensors individually; antitrust concerns are therefore not well-founded since collusion would require the rights owners to communicate and set the rules together.

Seventeen out of the 23 sub-licensing agreements were concluded in 2014 – after a rather slow start, the MPP managed to attract a number of generic manufacturers that want to produce or improve upon the pooled compounds.

[65] This is the year of TRIPS implementation in developing countries, including India.

[66] With exception to early agreements for sub-licensing Gilead patents, where the contracting parties were the generic producers and MPP only.

Table 7: Sub-licensing agreements with generic producers in Medicines Patent Pool

Generic Producer	Parties to the Agreement	Sub-Licensed Compounds	Agreement Signed
Aurobindo	MPP, Aurobindo	FTC, COBI, EVG, and the Quad	09/2011
	MPP, Aurobindo	ABC (for paediatric use)	06/2014
	MPP, Aurobindo and Bristol-Myers Squibb	ATV	07/2014
	MPP, Aurobindo and Gilead Sciences	TAF	09/2014
Cipla	MPP, Cipla, ViiV Healthcare	DTG (for paediatric use)	07/2014
	MPP, Cipla, Gilead Sciences	TAF, COBI, FTC, EVG, Quad	09/2014
	MPP, Cipla, Bristol-Myers Squibb	ATV	11/2014
Desano	MPP, Desano, Bristol-Myers Squibb	ATV	05/2014
	MPP, Desano, Gilead Sciences	TAF, TDF, FTC, COBI	09/2014
	MPP, Desano, ViiV Healthcare	DTG (for paediatric use)	11/2014
Emcure	MPP, Emcure	FTC, COBI, EVG, and the Quad	01/2012
	MPP, Emcure, Bristol-Myers Squibb	ATV	07/2014
	MPP, Emcure, Gilead Sciences	TAF	09/2014
	MPP, Emcure, ViiV Healthcare	DTG (for paediatric and adult use)	10/2014
Hetero Labs	MPP, Hetero Labs, Gilead Sciences	FTC, COBI, EVG, and the Quad	07/2012
	MPP, Hetero Labs, ViiV Healthcare	DTG (for paediatric and adult use)	08/2014
	MPP, Hetero Labs, Gilead Sciences	TAF	09/2014
Laurus Labs	MPP, Laurus Labs	TDF, FTC, COBI, EVG, and the Quad	09/2012
	MPP, Laurus Labs, ViiV Healthcare	DTG (for paediatric and adult use)	07/2014
	MPP, Laurus Labs, Gilead Sciences	TAF	09/2014
Micro Labs	MPP, Mirco Labs, ViiV Healthcare	DTG (for paediatric and adult use)	07/2014
Mylan	MPP, Mylan, ViiV Healthcare	DTG (for paediatric and adult use)	07/2014
Shasun Pharma	MPP, Shasun, Gilead Sciences	TDF, FTC, COBI, EVG, and the Quad	02/2013
Shilpa Medicare	MPP, Shilpa, Gilead Sciences	TDF, FTC, COBI, EVG, and the Quad	06/2013

Source: own configuration, based on data collected from MPP (2015a)

4.2 Sale of Tenofovir Disoproxil Fumarate and Related Formulations under Medicine Patent Pool Licensing Agreements with Gilead and Aurobindo

Agreements analysed in this chapter were selected mainly due to the fact that they were concluded early on in the existence of the MPP. This allows for more insights as opposed to the later MPP contracts. The MPP-Gilead licensing agreement was signed in July 2011 and provided the MPP with the first private-owned patens. Two months later, Aurobindo signed a sub-licensing agreement with the MPP for production of FTC, COBI, EVG, and the Quad. Gilead's license to the pool included the patent for TDF as well, but as the patents in the pool are not bundled, Aurobindo had the opportunity to decide which patents to include in the sub-licensing agreement.

4.2.1 Situation Prior to the Medicines Patent Pool-Gilead License and Legal Provisions in the Contract

In the period during which the patent for TDF was under examination in India, the civil society along with generic producers and lawyers opposed the application and it was not certain, whether the patent would be granted. At that time, Gilead entered into VL agreements on manufacturing and sales of the compound with several Indian generic companies[67]. Even though the patent had not yet been granted then, the mere possibility of Gilead being granted a patent in India restrained generic producers from manufacturing the drug due to uncertainties stemming from the potential post-grant developments. Aurobindo was among those licensees (Amin, 2007:10).

The biggest drawback of the Gilead VL was that it did not include a termination clause. I-MAK (2006) found that "*...should no product patent be granted in India, there is no clause for the Licensee to terminate the API/Product Licence on that basis*". Another problem was the geographical scope of the agreement that excluded countries such as Brazil, China, Indonesia or Argentina. Licensees were thus not able to supply API or the end product to these LMICs. Furthermore, the requirements as regards quality and safety compliance created uncertainties (I-MAK, 2006).

In the end, Gilead was not granted the patent for TDF and several Indian companies were in licensing agreements, paying 5 % royalties for a compound that

[67] Prior to the issuance of VLs, only Cipla and Hetero were producing the drug. Hetero opted for signing a license with Gilead. Cipla believed there was no ground for granting the patent to Gilead and continued producing TDF without a license (Amin, 2007: 10).

had no legal proprietary rights holder in the territory. The MPP-Aurobindo-Gilead agreement includes a notice of termination of the Gilead VL for TDF.

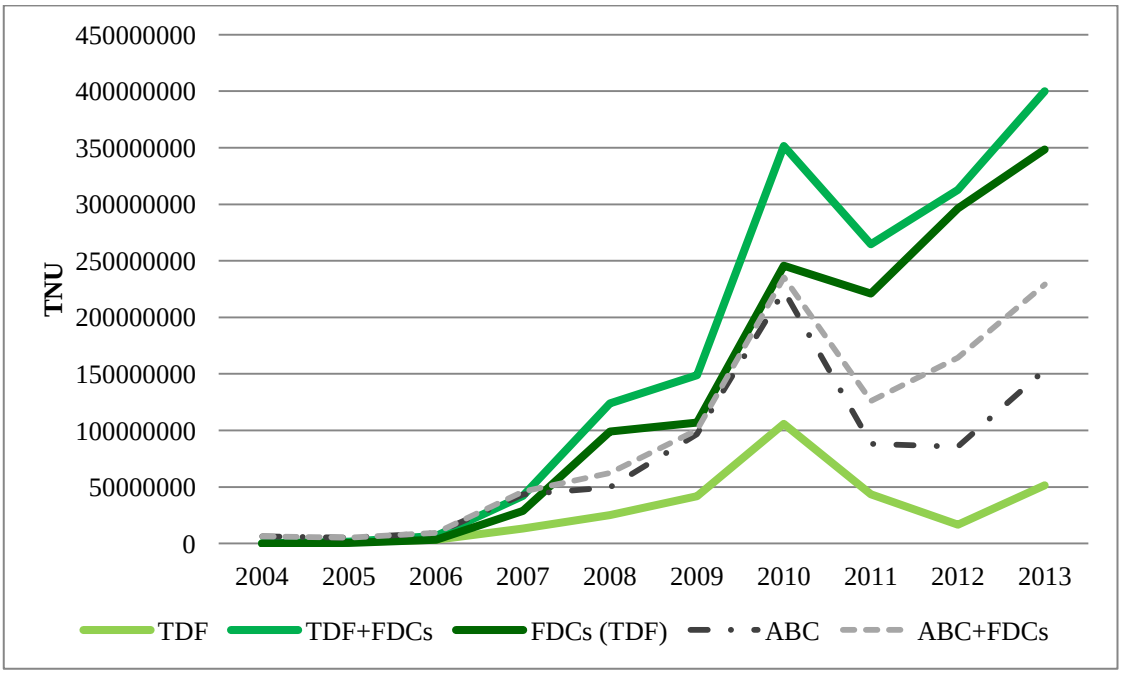
The MPP agreement did not bring along an unprecedented breakthrough in licensing TDF. It rather transformed the then existing agreements of Gilead into more transparent, wider reaching arrangements. For Aurobindo, entering into the MPP agreement brought benefits in terms of terminating the TDF VL and gaining rights for manufacturing of three additional compounds used in formulations with TDF and the one-pill FDC called Quad. Thanks to the termination of the previous VL, the geographical scope was not limited to 97 countries anymore. The MPP license also offered lower royalties to Gilead. As shown below in figure 11 FDCs far exceed TDF in volumes of sales, the ability to manufacture TDF in formulations with other compounds is an important competitive advantage.

4.2.2 Analysis of Trade in Tenofovir Disoproxil Fumarate

The figure below represents the volumes of sales of TDF and formulations thereof in LMICs[68]. While TDF is sold as a single compound as well, formulations are sold in much larger volumes. In 2013, formulations exceeded single compound sales of TDF almost seven times.

[68] When processing the data on TDF, a peak of the number of units sold was observed in 2010, followed by a sharp decline in 2011. In order to understand the circumstances of the decline, the sales of TDF were compared to the developments in 1) the aggregate sales of formulations containing TDF, 2) sales of abacavir (ABC) – the closest clinical substitute to TDF, and 3) in FDCs including ABC. The aim was to see whether the sales of these groups of products grew to detriment of TDF as a single compound, which was not confirmed. When data analysis showed similar trends for these products, the development of overall ARV sales was examined (See Annex IV). Similar trend was observed in overall ARV sales in LMICs, which proves that the sharp decline of sales in 2011 is not an extreme phenomenon that affected only the sales of TDF.

Figure 10: Volumes of sales of TDF and FDCs containing TDF in LMICs between 2004 and 2013

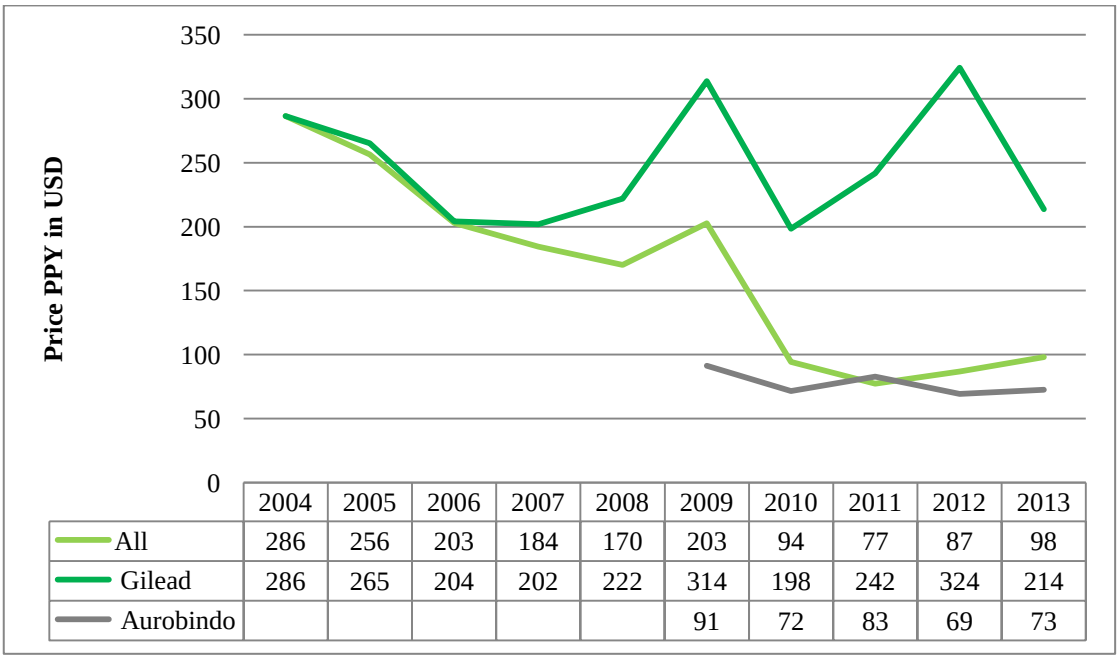


Source: own configuration, based on data from the GPRM database (WHO, 2011)

Following areas are explored using the GPRM database in the analysis of trade with TDF: supply of TDF and its formulations to LMICs by Gilead and Aurobindo and their share in overall transactions registered in GPRM, pricing exercised by the two companies and the value of their sales.

Before 2005, TDF was only supplied by Gilead. The figure representing the weighted mean price of TDF shows that prior to 2006, the price of overall supplies to LMICs was almost identical with Gilead's pricing. First competition appeared in 2005, when Cipla started manufacturing the product, was followed by Hetero Labs. In 2006, Gilead issued the aforementioned VLs for production and sale of TDF (I-MAK). While the price of TDF supplied by Gilead was decreasing before 2006, when generic competitors started selling TDF, bringing the overall price down, Gilead's prices grew. This can be explained by Gilead targeting those markets, where it can exercise higher prices. In 2013, for instance, Gilead's registered sales consisted by over 99 % of a large delivery of TDF at PPY of USD 218 to China.

Figure 11: Weighted mean price of TDF

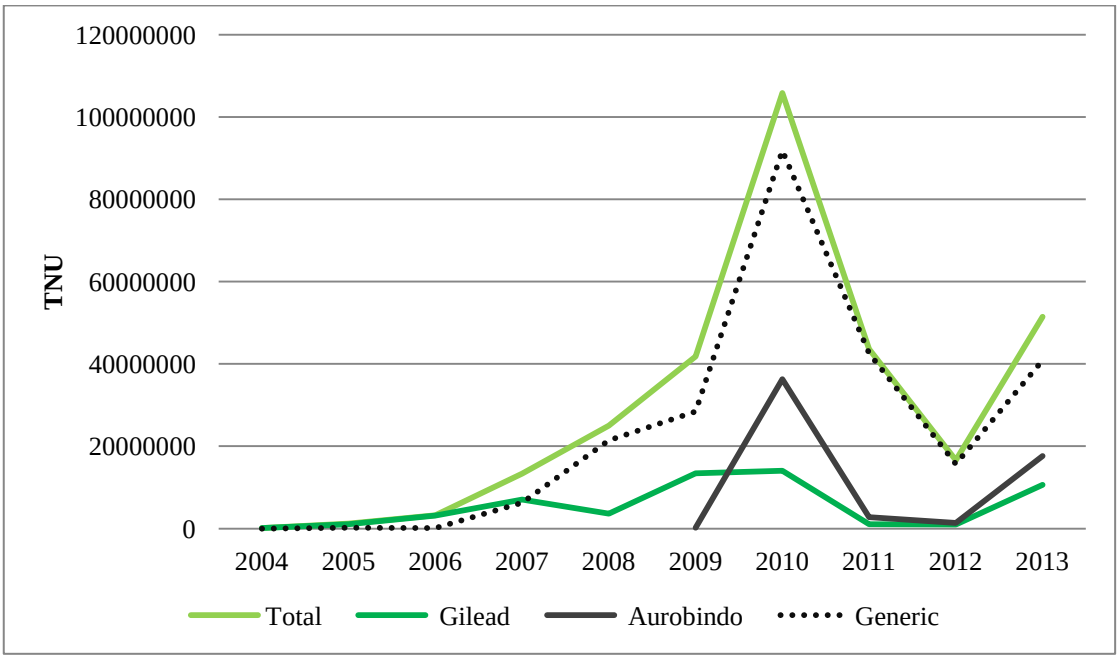


	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
All	286	256	203	184	170	203	94	77	87	98
Gilead	286	265	204	202	222	314	198	242	324	214
Aurobindo						91	72	83	69	73

Source: own configuration, based on data from the GPRM database (WHO, 2011)

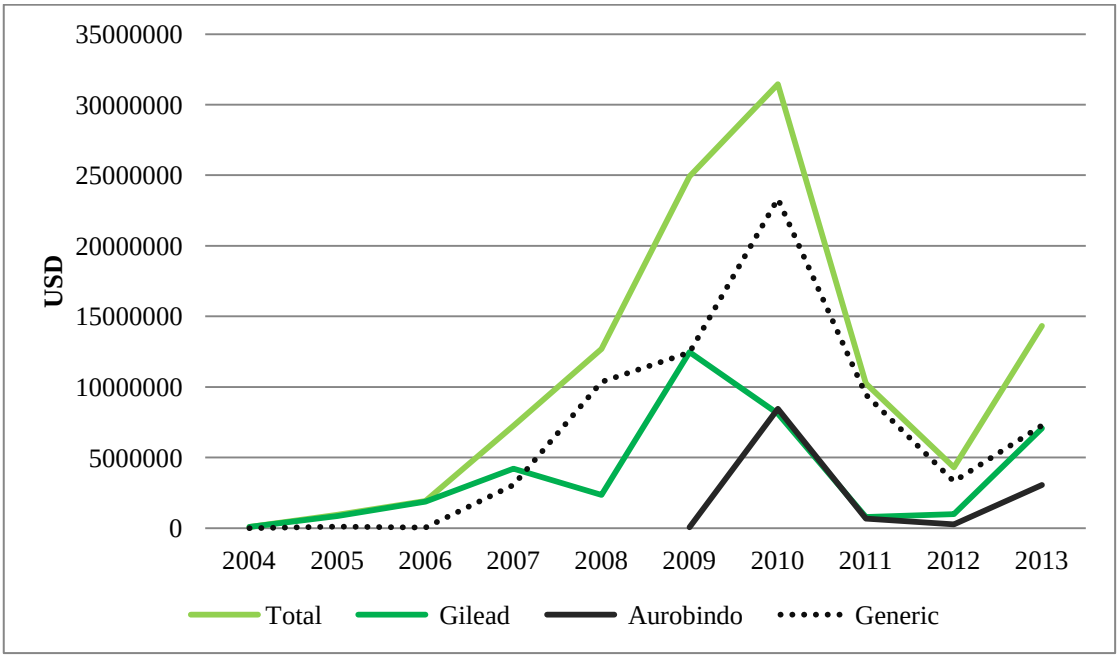
The insight into the volumes of sales of Gilead and Aurobindo shows the rapid penetration of the LMICs market by generic firms since 2006. This happened before the establishment of the MPP and even Aurobindo, the first sub-licensee, was manufacturing and selling TDF before joining the pool. However, despite the sharp fall both in volume and value of sales in 2011, Aurobindo's sales of TDF grew in both in absolute terms and relative to overall generic produce post 2012 and reached a 34 % market share in 2013. More time is needed to evaluate, whether this swift gain in market share can be credited to the MPP license.

Figure 12: Volumes of reported TDF sales (2004 - 2013)



Source: own configuration, based on data from the GPRM database (WHO, 2011)

Figure 13: Value of reported sales of TDF (2004 - 2013)



Source: own configuration, based on data from the GPRM database (WHO, 2011)

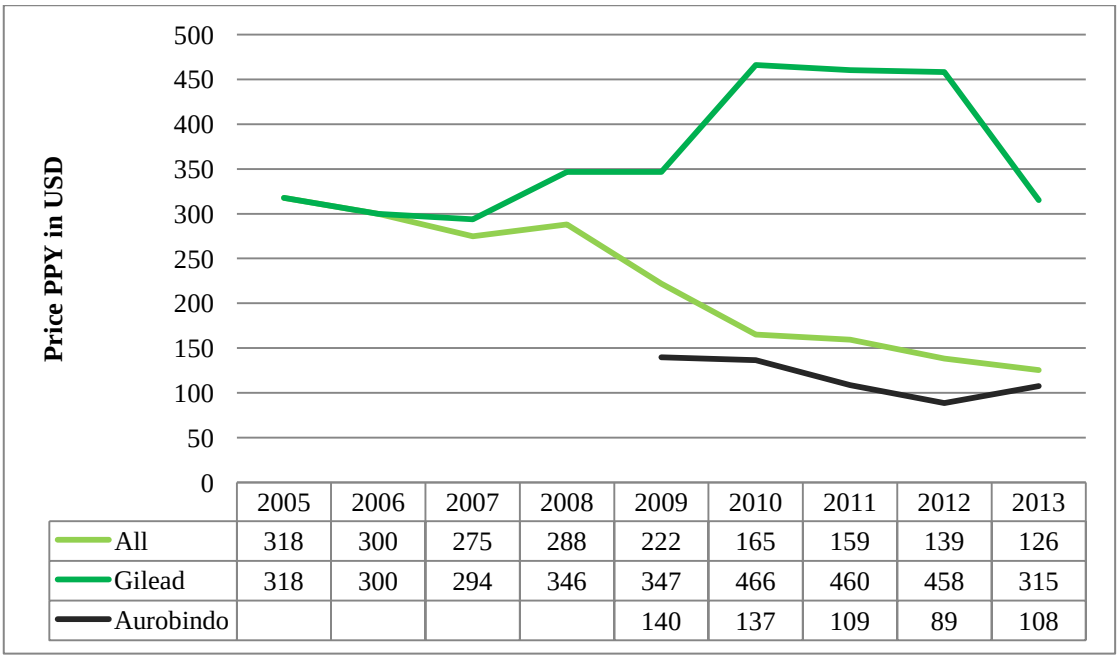
4.2.3 Analysis of Trade in Fixed Dose Combinations Containing Tenofovir Disoproxil Fumarate

As mentioned earlier in this chapter, the Aurobindo-MPP-Gilead license contained three compounds used in manufacturing FDCs, and the rights

to manufacture the Quad[69]. It has also been shown, that the trade in FDCs far exceeds the trade in the single TDF compound. Trade in these formulations is examined in this section[70] in order to see whether the rights attained in the MPP agreement are reflected in the development of Aurobindo's sales.

Development of prices follows a similar pattern as with the single compound TDF. Once generic competition appears, the patent owner withdraws to areas where higher prices can be charged. These are countries like China, Ukraine, Belarus or Brazil, which are not included in the geographical scope of neither bilateral VLs, nor the MPP licenses.

Figure 14: Weighted mean price of FDCs containing TDF (2005 - 2013)



	2005	2006	2007	2008	2009	2010	2011	2012	2013
All	318	300	275	288	222	165	159	139	126
Gilead	318	300	294	346	347	466	460	458	315
Aurobindo					140	137	109	89	108

Source: own configuration, based on data from the GPRM database (WHO, 2011)

The supremacy of generic producers over originator companies[71] in TDF procurement to LMICs is even more striking in the area of FDCs. This confirms once again that generic producers are struggling to operate directly on the LMICs markets. The chart below reveals that only about 0.04 % of these were procured by originator companies. In the fierce competition between generic producers, Aurobindo managed to attain an 18 % market share in the year of joining the MPP, but gradually had lost

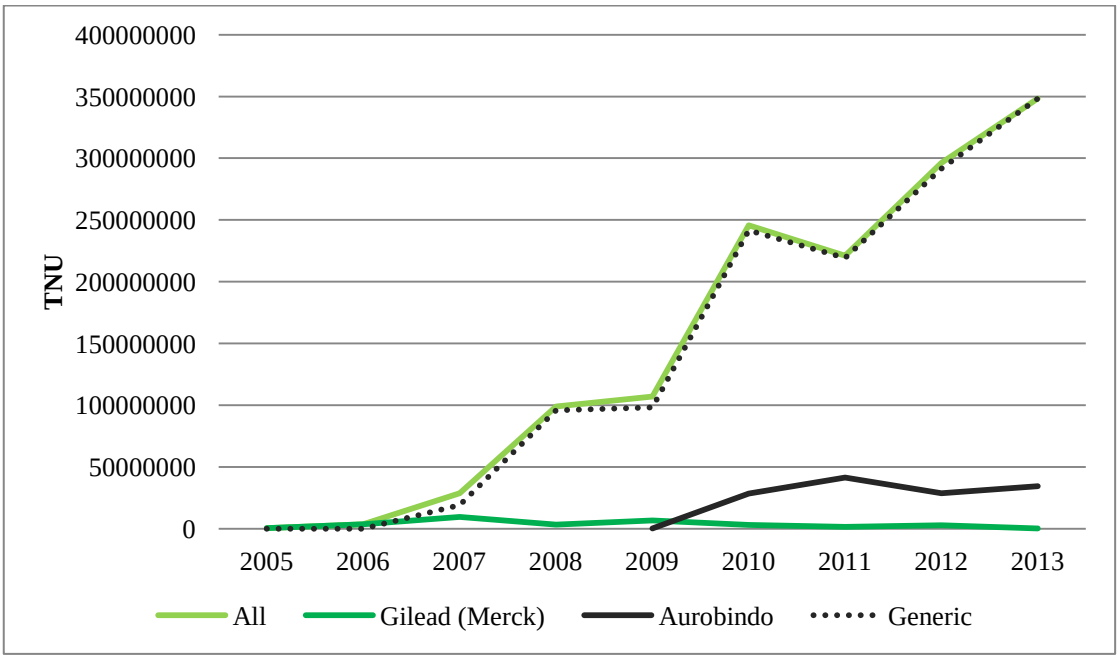
[69] Quad is a one-pill FDCs consisting of FDC, FTC, COBI, and EVG.

[70] The examined period starts in 2005, because no shipments of FDCs were registered in GPRM in 2004.

[71] One of the FDCs was developed as a result of joint venture between Gilead and Merck, but Merck production is not explicitly shown in the chart. It is included in Gilead sales and was taken into account when calculating the aggregated generic produce.

almost half of its share to its competitors by 2013. It is worth noting that none of these competitors were MPP sub-licensees at the time[72].

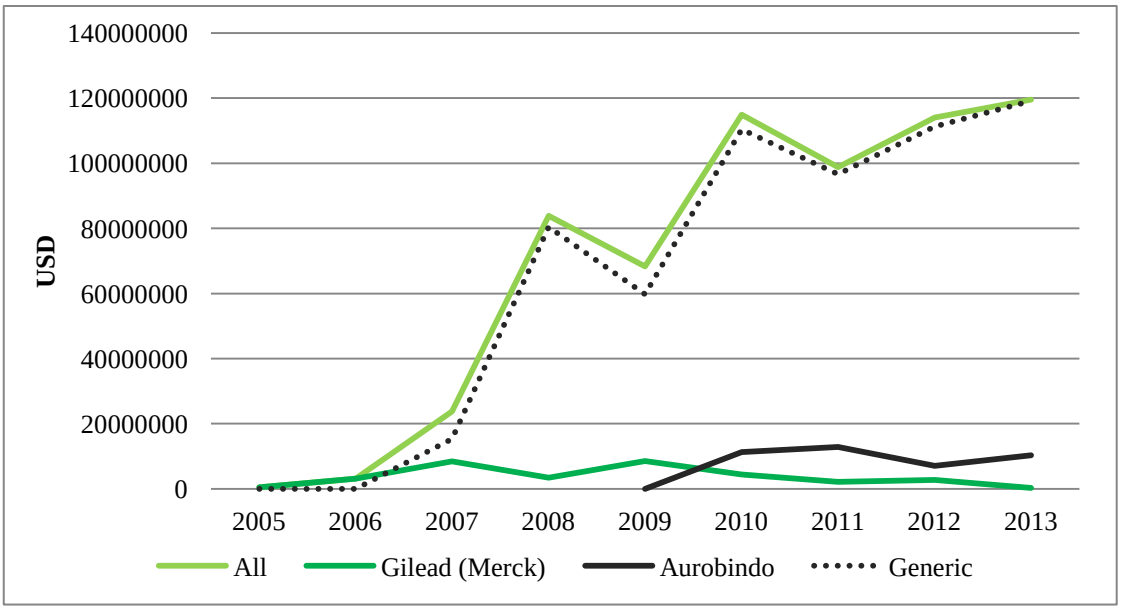
Figure 15: Volumes of sales of FDCs containing TDF (2005 - 2013)



Source: own configuration, based on data from the GPRM database (WHO, 2011)

The originator companies maintain higher prices, but the volumes are so low that the total value of their sales was at a negligible share of 0.2 % in 2013. Even though Aurobindo's absolute sales grew both in value and volume between 2012 and 2013, its share relative to other generic producers decreased.

Figure 16: Value of sales of FDCs containing TDF (2005 - 2013)



Source: own configuration, based on data from the GPRM database (WHO, 2011)

[72] The generic companies selling the FDCs in 2013 were Mylan, Matrix, Cipla and Aurobindo.

4.3 Lessons Learned

MPP's role in improving access to ARVs stretches beyond availing patented ARVs to generic producers. As with the example of TDF, some of the pooled compounds had already been produced by generic companies before the MPP was formed in 2010. Value-added of such MPP's licenses lies mainly with the ability of the MPP to leverage its reputation in negotiations with "big pharma" companies and incentivizing them to join the pool under more transparent and equitable licensing terms. As a result, a broader geographical scope can be reached, as well as reduction of the transaction costs linked with information exchange and license terms negotiations.

There are no traceable extreme developments in volumes or value of Aurobindo's sales of TDF – neither as a single compound, nor in FDCs – after joining the MPP. This demonstrates that the MPP's accomplishments are not yet traceable in the trade flows registered with the GPRM. While the prices of examined formulations had declined over the period in question, the analysis has not shown developments that would directly link this phenomenon to the Aurobindo-MPP agreement.

The improvements stemming directly from pooling novel patented compounds are yet to be validated in future.

It was clearly shown that there is little potential for originator companies in direct sale of branded products in LMICs. To mitigate the inability to compete with generic producers in the low-cost high-volume markets, originator companies can license out their IP and exploit these markets indirectly. Several benefits of the MPP as opposed to bilateral VLs were presented in this chapter.

Furthermore, an interesting strategy used by originator companies was revealed in the analysis. When generic competition starts to bring the prices down, the originator companies withdraw to areas where they can exercise higher prices. Such behaviour leads to elevated prices in some middle income countries that are not as much in the focus of the global access movement. The MPP-Aurobindo-Gilead agreement does not cover countries like China, Ukraine, Belarus or Brazil. Geographical scope of supply of generic produce to these countries should be an important feature of MPP licenses in future.

Pooling, MPP in particular, has the potential to improve access to ARVs in LMICs, yet it has not been in place for long enough to make definitive conclusions as to its effectiveness. The main challenge with respect to pooling licenses is to get on board companies that hold rights to recently patented promising ARVs and do not

have a track record of issuing low-royalty VLs to generic manufacturers from LMICs or had expressed their unwillingness to join the MPP initiative. Also MPP has to be able to offer advantages to both originator and generic companies over bilateral deals.

Conclusion

The proposed thesis aimed at examining the potential of patent pooling for surpassing IP barriers to access to medicines. It focused on antiretrovirals – medicines used for treatment of HIV/AIDS. The objective of the presented paper was not to propose a new IP system that would bring about change in the access to medicines – such a debate would be purely theoretical – but to explore one of the possible ways to improve access within the current institutional and regulatory framework of international IP protection set primarily by the WTO TRIPS agreement. It followed the health-IP-trade axis by focusing on health and IP in the first two chapters and then examined pooling as an IP strategy in chapter three. The fourth chapter consisted of a case study of an existing patent pool in the pharmaceutical sector called the Medicines Patent Pool.

At the outset, the first chapter provided an economic justification for wider access to medicines. It was established that IP does present a barrier to access and two main barriers to access were identified – lack of availability and accessibility. It was determined that, in the therapeutic area of ARVs for adults, accessibility, i.e. wider uptake of existing medicines, constitutes the key problem. The first chapter also pointed out the failures of current IP framework, as it does not inherently take into account the positive externalities in areas of high social benefits but low market incentives. Furthermore, the initial chapter outlined the following specific characteristics of IP management in the pharmaceutical sector: 1) the need to ascertain the safety and efficacy of medicines, which shortens effective period of patent protection, 2) high cost of R&D and the risk of failure, and 3) low marginal cost of production. Opposing views of various stakeholders on the international system of IP protection of medicines were reviewed, concluding that the international community recognized the need for a specific approach to IP in the area of medicines. However, TRIPS flexibilities aimed at promoting public health were found ineffective.

Chapter two focused on the trade in ARVs. The clash of interests between generic producers and originator companies was the underlining theme. It was unveiled that while a number of patents on currently essential ARVs are expired or about to expire in near future, concerns are raised as regards new medicines with a potential for third line therapy. These concerns are closely linked to the fact, that the first generation of ARVs underwent a major decrease in prices at a time when counties with robust generic industry, India, above all, did not recognize product patents

on medicines. Such situation cannot be predicted for medicines patented after the implementation of TRIPS in these countries. Analysis of the ARV market revealed the supremacy of two countries - USA and India - in the industry. While the USA is predominantly a home to originator companies, India was recognized a leader in the generic production catering for low-cost, high-volume markets. Indian companies played an important role in the decline of price of ARVs over the last 15 years and are currently catering for more than 90 % of the ARV market in LMICs.

In chapter three, distinctive traits of patent pooling in the pharmaceutical sector were recognized and compared to the up-to-now practice in pooling. A variety of purposes for establishing a pool were presented: from anticompetitive interests, through facilitating national policies, standard setting in areas with fragmented patent landscape to promotion of social welfare. The global health pools were classified as pools conductive to social welfare. As accessibility is the main problem in access to ARVs, the MPP is focused on downstream innovations and commercialization.

Voluntary licenses, compulsory licenses and donations of medicines were identified as alternatives to pooling in surpassing the IP barriers to access to medicines within the current IP framework. The case study has confirmed that originator companies struggle to directly penetrate developing markets. Licensing out IP in exchange for royalties can compensate for their inability to compete with generic producers in these markets.

Analysis of GPRM data related to the examined MPP licensing agreements has shown that additional time is needed to evaluate the impact of pooling on trade with ARVs. Pooling, MPP in particular, has the potential to improve access to ARVs in LMICs, yet it has not been in place for long enough to make definitive conclusions as to its effectiveness. However, when compared to its alternatives, notably the closes one – bilateral VLs – the MPP currently presents the best available tool for IP management conductive to better access to medicines. Furthermore, MPP's role in improving access to ARVs stretches beyond availing patented ARVs to generic producers. Value-added of MPP's licenses lies also with the ability of the MPP to leverage its reputation in negotiations with "big pharma" companies and incentivizing them to join the pool under transparent and equitable licensing terms. MPP needs to incentivize both generic and originator companies to join the initiative. The main challenge for the MPP is to get on board the owners of novel, third line treatment options, which will grow in importance as patients become resistant to the first and second generation of ARVs.

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List of Annexes

Annex I: HIV as a Neglected Disease

To assess whether HIV is a neglected disease or not, a background document prepared by the WHO Secretariat was used. The methodology combines the wealth of countries and the burden of disease by the incidence of the disease. It introduces three categories of diseases:

> **Type I diseases:** are incident in both rich and poor countries, with large numbers of vulnerable populations in each.
>
> **Type II diseases:** are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries.
>
> **Type III diseases:** are those that are overwhelmingly or exclusively incident in DCs.

According to this classification, HIV would fall within Type II. The methodology was taken one step further with the introduction of the Disability Adjusted Life Years (DALYs) indicator that takes into account also the size of the population affected by various diseases and thus allows for an estimate of the disease burden on national, regional or even global level. The ratio of a disease's DALY per 100,000 people in low- and middle-income countries vis-à-vis the same indicator in high income countries opens a door for a more thorough classification. What has to be taken into account as well is the R&D directed at the disease.

The verdict for HIV is that it both is and is not a neglected disease. According to the majority of burden, it is a Type II disease. According to R&D efforts the situation varies according to the type of HIV. Paediatric formulations, for example would be considered a type III. This distinction is crucial for assessing whether there is a need for action in terms of improved availability – paediatric formulations – or accessibility – HIV in adults (WHO, 2012).

Annex II: Patent landscape in the area of antiretrovirals

Compound	Branded product name	Primary patent holder, year of expiry	MPP priority ARVs	WHO essential	HIV-related patent expired
Abacavir sulfate (ABC)	Ziagen	Wellcome (GSK), 2010	Yes	Yes	Yes
Atazanavir (ATV)	Reyataz	Novartis (BMS), 2017	Yes	Yes	No
Cobicistat (GS-9350)*	Tybost	Gilead, 2027	Yes	No	No
Darunavir (DRV)	Prezista	Searle, Monsanto, 2013 (Tibotec, 2022)	Yes	No	No
Didanosine (ddI)	Videx	US Gov (BMS), 2006 (BMS, 2012)	No	Yes	Yes
Dolutegravir (DTG, S/GSK 572)*	Tivicay	ViiV, 2026	Yes	No	No
Efavirenz (EFV)	Stocrin/ Sustiva	Merck (MSD, BMS), 2013	Yes	Yes	Yes
Elvitegravir (EVG GS 9137)*	Vitekta	Japan Tobacco (Gilead), 2023	Yes	No	No
Emtricitabine (FTC)	Emtriva	IAF Biochem, 2010	Yes	Yes	Yes
Etravirine	Intelence	Janssen (Tibotec), 2019	Yes	No	No
Fosamprenavir (FPV)	Lexiva	Vertex (GSK), 2018	No	No	No
Indinavir (IDV)	Crixivan	Merck, 2014	No	Yes	Yes
Lamivudine (3TC)	Epivir	IAF Biochem GSK, 2010	No	Yes	Yes
Lopinavir (LPV)	Kaletra	Abbott, 2016	Yes	Yes	No
Maraviroc (MVC)	Selzentry	Pfizer, 2019	No	No	No
Nevirapine (NVP)	Viramune	Boehringer, 2010	Yes	Yes	Yes
Raltegravir (RAL)	Isentress	Institute for Research in Mol. Biology, Italy, MSD, 2022	Yes	No	No
Rilpivirine (TMC 278)*	Edurant	Janssen Pharmaceutica (Tibotec), 2022	Yes	No	No
Ritonavir (RTV)	Norvir	Abbott, 2014	Yes	Yes	Yes
Saquinavir (SQV)	Fortovase	Hoffmann-La Roche, 2010	No	Yes	Yes
SPI-452	Phase II clinical	Sequoia Pharmaceuticals, 2027	No	No	No
Stavudine (d4T)	Zerit	Yale Univ. (BMS), 2007	No	Yes	Yes
Tenofovir alafenamide fumarate (TAF)*	Phase II	Gilead, 2021	Yes	No	No
Tenofovir disoproxil fumarate (TDF)	Viread	Gilead, 2018	Yes	Yes	No
Zidovudine (AZT)	Retrovir	Glaxo Wellcome, 2006	No	Yes	Yes

*not available in the GPRM database

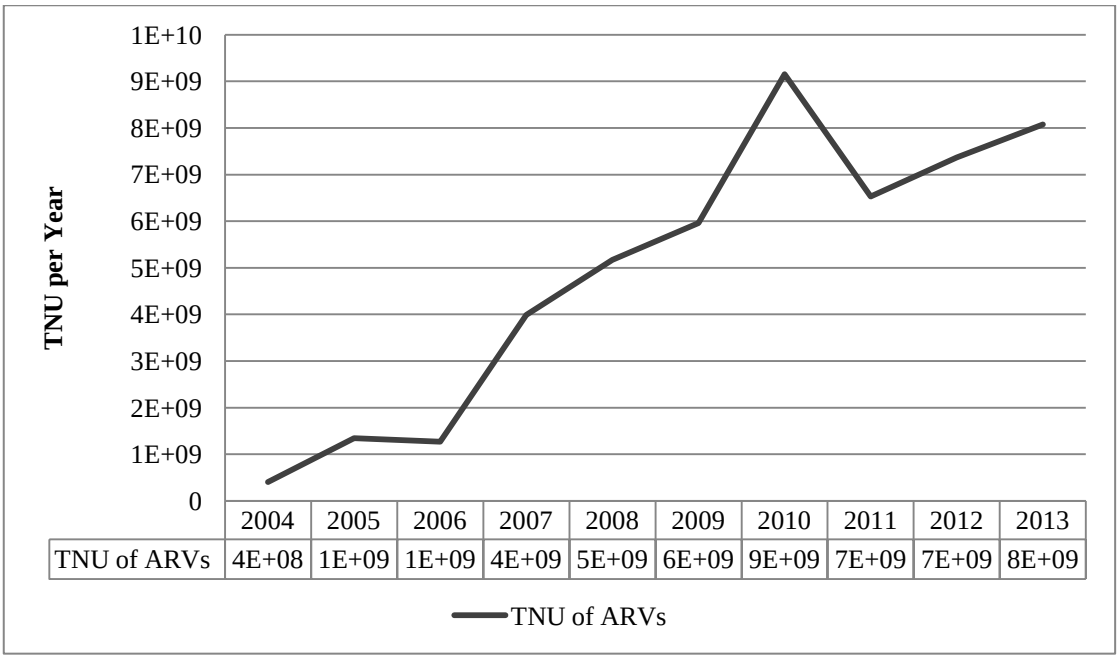
Source: own configuration, based on data from WHO (2013), MPP (2015a)

Annex III: List of Producers of Antiretrovirals

Name of the comapny	Country	Generic/ originator	Engagement in MPP
Abbott	USA	O	
AbbVie	USA	O	licensor
Actavis Pharma	USA	G	
Adcock Ingram Healthcare	South Africa	G	
Alkem	India	G	
Apotex Inc	Canada	G	
Aspen Phamacare	South Africa	G	
Aurobindo Pharma	India	G	sub-licensee
Barr Laboratories (Teva)	Israel	G	
Boehringer Ingelheim	Germany	O	
Bristol-Myers Squibb	USA	O	licensor
Cipla	India	G	sub-licensee
Combino Pharm	Malta	G	
Desano	China	G	sub-licensee
Edict Pharmaceuticals	India	G	
Emcure	India	G	sub-licensee
Gilead Sciences	USA	O	licensor
GlaxoSmithKline & ViiV Healthcare	UK	O	licensor
HEC Pharm Inc	China	G	
Hetero Drugs	India	G	sub-licensee
Hoffmann-La Roche	Switzerland	O	licensor
Huahai US Inc. (Zhejiang Huahai)	China	G	
Janssen (J&J)	USA	O	
Laurus Labs	India	G	
Macleods	India	G	
Matrix Laboratories	India	G	
Merck	USA	O	licensor
MicroLabs	India	G	sub-licensee
Mylan Laboratories	USA/India	G	sub-licensee
Ranbaxy Laboratories	India	G	
ScieGen Pharmaceuticals Inc	USA	G	
Shasun Pharma Solutions	India	G	
Shilpa Medicare	India	G	
Sonke Pharmaceuticals (Ranbaxy)	India	G	
Strides Arcolab	India	G	
Teva	Israel	G	
Tibotec (J&J)	USA	O	
Varichem Pharmaceuticals	Zimbabwe	G	

Source: own configuration, based on data from PEPFAR (2014)

Annex IV: Volumes of ARVs Sold between 2004 and 2013



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
TNU of ARVs	4E+08	1E+09	1E+09	4E+09	5E+09	6E+09	9E+09	7E+09	7E+09	8E+09

Source: own configuration, based on data from the GPRM database (WHO, 2011)