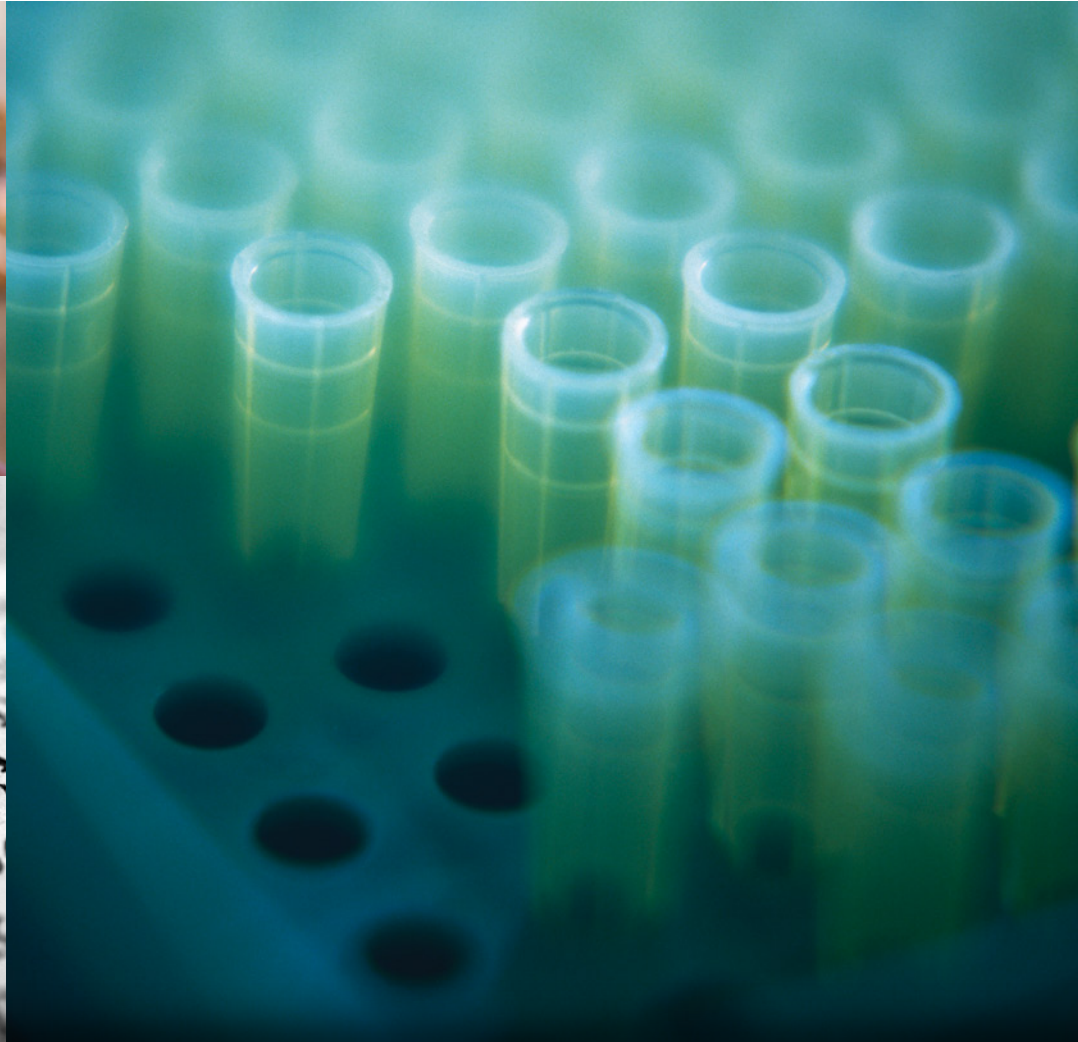




RESULTS FOR
DEVELOPMENT



Patent Pools

Assessing Their Value-Added
for Global Health Innovation and Access

Rebecca Goulding and Amrita Palriwala

Results for Development Institute

Results for Development Institute (R4D) is a non-profit organization whose mission is to unlock solutions to tough development challenges that prevent people in low- and middle-income countries from realizing their full potential. Using multiple approaches in multiple sectors, including Global Education, Global Health, Governance and Market Dynamics, R4D supports the discovery and implementation of new ideas for reducing poverty and improving lives around the world.

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Executive Summary

Background

A number of policy researchers and public health advocates have argued that the existing intellectual property (IP) regimes act to inhibit innovation and access to drugs for neglected diseases.¹ In response, several groups have proposed changes in IP rules and institutions, including the creation of various forms of joint IP management (JIPM)—known as *patent pools*—to address these alleged IP barriers.

Patent pools are not a new concept and have been successful in facilitating innovation for technologies ranging from aircraft to consumer electronics.² In these other fields, the pools are formed by two or more IP holders who license their individual patent rights to each other or to third parties, in return for royalties on sales of the resulting products. The formation and use of patent pools for global health technologies, which is not yet fully tested, appears to be different³ from these former approaches because it entails distinct groups of patent *donors* (mainly multinational biopharmaceutical companies or universities in the most affluent countries) and patent *users* (mainly generic drug companies and smaller biotechnology firms), instead of involving firms that both contribute and use the IP within the pools.

Will patent pools work in the field of global health, speeding up the development and delivery of new and affordable medicines to millions of people in low- and middle-income countries?

This study aims to answer this question through an in-depth analysis of IP barriers to innovation and access for neglected-disease drugs, plus case studies on two ongoing

initiatives: the Medicines Patent Pool (MPP)⁴ and the Pool for Open Innovation against Neglected Tropical Diseases.⁵ It reviews the design and progress to date for these pools, assesses their strengths and weaknesses, and considers whether they are likely to be successful.

The study draws upon on a literature review on IP and patent pools; interviews with IP experts, researchers, product development partnerships (PDPs), and industry; and analysis by the authors.

The two pools for global health IP

Even though both the MPP and the Pool for Open Innovation are examples of JIPM mechanisms, they are notably different in terms of disease focus, goals, and target stakeholders.

Based on an idea proposed by Knowledge Ecology International (KEI) and Médecins Sans Frontières (MSF) and then created by UNITAID in 2010, the MPP aims to foster generic manufacture of low-cost AIDS drugs (antiretrovirals, or ARVs) for low- and middle-income countries by securing from originator companies a range of voluntary licenses to patented AIDS medicines, which can then be used by generic drug firms. It is believed that this process will improve low-income patients' access to important ARVs and will also stimulate the "downstream" development of new, improved versions of these drugs, such as pediatric or heat-stable reformulations and fixed-dose combinations (FDCs) of drugs that better meet the needs of developing countries.

¹ Ellen 't Hoen et al., "Driving a Decade of Change: HIV/AIDS, Patents and Access to Medicines for All," *J Int AIDS Soc* 14.15 (2011), doi:10.1186/1758-2652-14-15; Michael Westerhaus and Arachu Castro, "How Do Intellectual Property Law and International Trade Agreements Affect Access to Antiretroviral Therapy?," *PLoS Med* 3.8 (2006): e332, doi:10.1371/journal.pmed.0030332; James Love and Tim Hubbard, "The Big Idea: Prizes to Stimulate R&D for New Medicines," *Chicago-Kent Law Review* 82.3 (2007): 1519–1554; Michael Heller and Rebecca Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science* 280.5364 (1998): 698–701 (see p. 698, n. 4); see also Rebecca S. Eisenberg, "Patents and Data-Sharing in Public Science," *Ind Corp Change* 15.6 (2006): 1013–1031.

² Toward the end of the 20th century the information technology and telecommunications industries initiated patent pools to promote the development and manufacture of consumer electronics (e.g., DVD, MPEG, and 3G patent pools). This type of patent pool had a goal of reducing transaction costs and inefficiencies resulting from multiple overlapping patents ("patent thickets") to provide a convenient, one-stop-shopping approach to patent licensing and create a standard for technology production.

³ Patent pools for global health technologies and those for other industries differ in several key ways, such as with respect to IP landscape, patent licensee types, and overall intent. For example, the need for incentives to encourage companies to join the pool is not as important in the case of traditional pools, where companies themselves, as opposed to a third party, have decided to form a patent pool.

⁴ See <http://www.medicinespatentpool.org/>.

⁵ See <http://www.ntdpool.org/>.

As of late 2011, the MPP was legally established, staffed, and operating as an independent nonprofit entity with funding from UNITAID. It had concluded agreements with the US National Institutes of Health (NIH) and the AIDS drug manufacturer Gilead Sciences and was in negotiations with a number of other patent holders. It had also brought on board its first two generic drug companies based in India.

The Pool for Open Innovation was conceived and created by GlaxoSmithKline (GSK) in 2009 and transferred to BIO Ventures for Global Health (BVGH) in 2010 (in late 2011, in a third recent move, the hub of the pool and its patent database were transferred to the United Nations World Intellectual Property Organization and renamed WIPO Re:Search). In contrast with the MPP, which is attempting to speed up the availability to generic companies of already patented inventions for AIDS drugs, the Pool for Open Innovation focuses on stimulating early, “upstream” scientific innovation of entirely new products—and for a different set of diseases: neglected tropical diseases (NTDs) such as malaria, tuberculosis, and kinetoplastid diseases (such as leishmaniasis and human African trypanosomiasis), which lack a large commercial market. The intent is to accelerate the discovery and development of novel drugs for NTDs by offering researchers and product developers access to small-molecule compounds, as well as associated data and know-how, held by GSK, other large pharmaceutical companies and product developers, and university-based and public-sector research institutions.

By mid-2011, BVGH had managed to build upon GSK’s contributions by bringing into the Pool for Open Innovation several biotechnology companies, one PDP, and more than half a dozen university research groups as well as the NIH. Some of these organizations had agreed to donate a number of their patents for NTDs, while others indicated their interest in being users of the pool. With no announced licensing agreement between organizations participating in the pool, however, there were few visible signs of uptake and use of these donated patents.

In late October 2011, BVGH announced a new partnership with WIPO and 5 pharmaceutical companies (Alnylam Pharmaceuticals, AstraZeneca, Merck, Pfizer, and Sanofi), plus a number of other nonprofit drug developers, recasting the Pool for Open Innovation as WIPO Re:Search.⁶ There appear to be several important changes in design, including expanding the scope of the pool to cover more diseases and to incorporate patents for vaccines and diagnostics as well as drugs. As with the

Pool for Open Innovation, WIPO Re:Search continues to offer royalty-free licenses on future product sales in least developed countries,⁷ but it also allows for the free use of IP for any research and development (R&D) globally. BVGH’s primary role will be to serve as a matchmaker between contributors and users of IP, data, and technical know-how.

Summary of our assessment findings

Overall, our analysis suggests that the value of establishing patent pools for global health technologies depends heavily on a small number of factors. The most important element is whether there is a strong commercial market for the products being pursued. Where the market prospects are robust, companies view patents as valuable assets and are reluctant to share the IP with others. Restrictions on use of patents and related know-how by others can become a barrier to faster access to more affordable products, and a pool that overcomes these barriers through one-stop licensing arrangements can potentially help to improve the situation. Where market prospects are poor, patent holders do not have strong incentives to withhold IP, so pooling patents may not add much value. However, it may still be challenging for some organizations seeking to develop new health technologies to create and deliver these products to patients without some kind of intermediary. Such an intermediary could help to make it easier for organizations committed to developing these “noncommercial” technologies to locate and work with holders of relevant IP, data, and know-how, thus overcoming information barriers (rather than IP barriers) and reducing transaction costs.

In this regard, the overarching answer to the question “will global health patent pools make a positive difference?” is “it depends”—on the nature of the products being pursued (high or low market potential), on the nature of the IP-related barrier being addressed, and of course, on the detailed design of the patent pool arrangement and its ability to overcome these barriers in an efficient manner.

The MPP. *Our findings suggest that the MPP could be useful in achieving its stated goals, if the pool can obtain participation from a critical mass of originator and generic companies.* There is a legitimate concern that vitally important first-line and second-line ARVs will become patented in India and other middle-income manufacturing countries in the next few years, and this could curtail

⁶ Interviews and analysis for this study were conducted prior to the change to WIPO Re:Search, and thus our findings primarily focus on IP barriers for NTD drugs. For more information, see http://www.wipo.int/pressroom/en/articles/2011/article_0026.html.

⁷ For more information on least developed countries as defined by the United Nations, see <http://www.unohrls.org/en/ldc/25/>.

generic manufacture of low-cost ARVs for developing countries, including sub-Saharan Africa, and keep prices for these drugs higher and less affordable. By providing licenses for several patents for ARVs, the MPP could also speed up development of FDCs that are easier to use (because they combine several medications in one pill), as well as pediatric and heat-stable formulations adapted to health systems conditions in low-income countries.

Already several of the major ARV patent holders have offered bilateral voluntary licenses to a number of generic drug companies for low or no royalties. The question is whether the MPP can go beyond this, by bringing into the voluntary licensing arena firms that have thus far been unwilling to offer voluntary licenses, widening the scope of these licenses, and making it faster and easier for both originators and generic companies to reach agreements on these licenses.

More time is needed to judge whether the MPP can demonstrate that it is more effective and efficient than the status quo of bilateral voluntary licensing currently being practiced by Gilead, Pfizer, GSK, and a few other ARV makers. As mentioned above, the recent agreements between the MPP and Gilead Sciences and between the pool and two Indian generic firms may suggest that momentum is building. But more originator companies and generic manufacturers must join the MPP to make it worthwhile. One strategy for the pool would be to focus on enlisting a critical mass of companies needed to make new FDCs for a select number of the most critically needed ARVs currently recommended by the World Health Organization.

The MPP may also be able to leverage its reputation as a neutral third-party intermediary pursuing global public health goals to negotiate more favorable licensing terms for generic firms and low-income countries. The MPP-Gilead agreement points in this direction, since it contains greater transparency, wider geographic scope, and stronger inclusion of flexibilities in relation to the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, as compared with the existing bilateral licenses between Gilead and its Indian generic partners. Critics of the MPP-Gilead agreement argue that the geographic scope of the voluntary licenses should be even wider, so that non-Indian generic companies are eligible and the resulting cheaper drugs can be sold in more middle-income countries.

As a one-stop licensing shop, the MPP could also reduce transaction costs for all parties, but it is too early to say whether this will be the case.

It is hard to predict whether more originator companies will join the pool, beyond Gilead. Of 10 target companies, 7 are currently in negotiations with the MPP, but it may be difficult for the MPP to engage some key companies, such as Abbott, which have until now been unwilling to offer bilateral voluntary licenses for their AIDS drugs. Firms are unlikely to be attracted to the MPP by financial incentives, since royalty rates are low. Furthermore, recent strong criticisms by advocacy organizations of both the MPP and Gilead over the terms of their agreement may dampen the enthusiasm of other companies to join the patent pool, if they anticipate that they may also be singled out and targeted for such criticism.

The Pool for Open Innovation. It is even earlier days for the Pool for Open Innovation (now WIPO Re:Search) as compared with the MPP, with the structure of the mechanism going through several important changes. This makes it difficult to assess its design ex ante and impossible to judge its actual implementation performance. The fact that the Pool for Open Innovation is trying to speed up the development of novel drugs (and now also vaccines and other technologies as WIPO Re:Search), which require many years to move from early concept to final product, means that it will be even more challenging to evaluate the pool's performance. A series of intermediate indicators will need to be used to track progress, since finished products will take many years to materialize.

The stated goal of the Pool for Open innovation (prior to its recent transfer to WIPO) was to "foster innovative and efficient drug discovery and development by opening access to intellectual property or know-how in neglected tropical disease research."

Our analysis suggests that the pool will have limited value in terms of facilitating access to IP for drug innovation, since IP for the NTDs with weak commercial markets is not a serious barrier to entry for additional scientific and product development organizations. The nonprofit PDPs consistently indicated to us that they can already access IP without assistance from the Pool for Open Innovation. At the margin, the pool could make it easier for university research organizations and some biotech companies in developing countries to identify and obtain the IP they need to create new drugs and other health technologies. This positive impact is as yet unproven and needs to be monitored.

Our analysis also highlights the fact that the pool may be more useful in bringing together large and small companies and nonprofit health technology organizations to form partnerships through which new product developers can more readily access scientific know-how and data related to the discovery of drugs, as well as the bioengineering know-how required to develop and eventually manufacture the new products. By creating a single, recognizable meeting place for health technology organizations from around the globe, and by supplementing this with active matchmaking by BVGH, the pool could promote the creation of partnerships that might not otherwise occur.

In that regard, the Pool for Open Innovation could be a positive component of a wider collaboration framework being pursued by some of the multinational companies like GSK, which also offers outside organizations and scientists access to its research center in Tres Cantos, Spain.

To make it easier for potential participants to decide whether to join the Pool for Open Innovation's successor WIPO Re:Search, it will be important for WIPO and BVGH to clarify exactly what functions and services the new entity can offer to researchers working in small and large companies, PDPs, and universities. Furthermore, it will be crucial that the IP-related contents of the WIPO Re:Search database, including patents and data in the form of trade secrets, be made more explicit and easier to search, so that potential participants can better judge the value of joining. The people we interviewed for this report generally felt that on both counts, the Pool for Open Innovation was hard to penetrate and understand.

It will be important to identify and promote key incentives for both contributors to and users of WIPO Re:Search to participate in it. It is unclear whether these incentives will be mainly nonfinancial (e.g., positive reputation as a socially responsible company) or might also include financial motives, such as developing platform technologies for other products with high returns or finding partners for other projects with large revenue potential. With the recent inclusion of drugs for Chagas disease in the pool, which has modest market potential in middle- and upper-income markets, WIPO Re:Search might now have an added boost.

As mentioned earlier, the managers of WIPO Re:Search will need to set performance targets that can be monitored over the next few years, in order to demonstrate its value-added. The number of participating organizations and the numbers of patents and datasets donated will be useful input indicators, but some output metrics will also be vital. Ideally these should be related to the number of collaborations formed through the initiative and evidence of meaningful exchange of IP and other data pointing to the development, in the lab and in the clinic, of new drugs, vaccines, and diagnostics.

Conclusion

For patent pools to have impact in global health, they need to solve specific key IP barriers and create adequate incentives for product developers to contribute and seek IP contained in the pools. To be worthwhile, the pools also need to add value relative to other competing approaches (e.g., the continued use of bilateral voluntary licenses) or relative to a counterfactual situation in which the pool does not exist. The ultimate test is whether these pools lead to a greater number of promising candidates that quickly result in licensable products needed for neglected diseases.

Our analysis suggests that IP and the rules governing it may be a significant barrier to the more rapid development and uptake of affordable health products for developing countries—but not in every case. Much depends on whether the specific health technology being pursued has a large commercial market opportunity. In that case, IP matters more, and patent pools that try to address this issue could make a positive difference. Seen in this light, the MPP has important potential to improve access to AIDS drugs if it can be organized and implemented effectively and efficiently.

In the case of the Pool for Open Innovation (now WIPO Re:Search), the argument for creating this mechanism to unlock existing IP for drug innovation is weaker. Some involved in the pool already acknowledge this fact. On the other hand, WIPO Re:Search is an interesting experiment in trying to create an effective meeting place for a diverse set of organizations from around the globe who have the common goal of discovering and developing new drugs and vaccines for neglected diseases with modest or minimal markets. It remains to be seen whether the opportunity to form partnerships in which IP, data, and know-how can be shared among two or more of these organizations will prove attractive enough to these parties to become actively involved in WIPO Re:Search. The answer to the question of whether such partnerships will ultimately lead to new and better health technologies that save lives in low-income settings in most cases lies many years in the future. Markers of intermediate progress toward that goal need to be established and tracked.

More generally, it will be critical for the managers and boards of the MPP and the Pool for Open Innovation / WIPO Re:Search to monitor closely and report on progress and performance so that they can continue to strengthen design and execution of these pools and change course, as necessary, to achieve their intended goals of accelerating innovation and access to life-saving medicines.

Chapter 1. Introduction

1.1 The challenge of creating new health technologies to combat neglected diseases

Neglected diseases (NDs) are a collection of infectious diseases that affect more than one billion people, mostly in developing countries.⁸ Appropriate treatments and medical interventions for these diseases often remain poorly researched and undeveloped, leading to a gap in ND research and development (R&D).⁹ Small and uncertain markets provide little incentive to pharmaceutical companies to invest in drug R&D for a number of neglected tropical diseases, such as human African trypanosomiasis or Chagas disease, which primarily affect developing countries.¹⁰ Other diseases, such as HIV/AIDS, affect both the developed and developing world. The existence of a large market for antiretroviral drugs (ARVs) in developed countries has led to significant investment in R&D for these drugs. However, the drugs that are developed do not always meet developing countries' needs, such as low-cost ARVs, including pediatric doses and formulations, and fixed-dose combinations (FDCs) for both adults and children. Moreover, even when appropriate products are developed, access is often still a problem. Medicines often do not reach patients in the developing world due to a number of factors, including lack of funding for medicine procurement, high prices of brand-name drugs, and deficient drug registration and manufacturing capacity, as well as systemic problems with infrastructure, distribution, and human resources within developing nations.¹¹

1.2 Intellectual property regimes and R&D incentives

A number of policy researchers have argued that intellectual property (IP) regimes exacerbate gaps in ND drug innovation and access in several ways. Patent exclusivity can hinder the production of affordable medicines for developing countries,¹² limiting access to existing drugs, vaccines, and diagnostics. A lack of access to patented inventions and other IP, such as know-how and data, may impede innovation,¹³ especially where IP holders are not incentivized to pursue innovation themselves.

Patents and trade secrets are legal mechanisms to protect man-made inventions. Government interest in safeguarding these forms of IP includes promoting patent disclosure¹⁴ and fostering investment in product development and further innovation in order to advance technical progress that in turn might improve social and economic well-being.

From the perspective of the pharmaceutical industry, the potential of market exclusivity conferred by a patent creates an incentive system that encourages companies to invest the capital and incur the risk of drug R&D, which typically takes a very long time from invention to market. Industry also benefits from the disclosure of competitors' patents. Patent rights give patent owners the exclusive rights for a period of time (usually 20 years) to exclude others from manufacturing, using, selling, and distributing an invention to consumers.

⁸ Our definition of neglected diseases comes from the G-FINDER survey and therefore includes HIV. See <https://studies.thegeorgeinstitute.org/g-finder/registered/docs/G-FINDER-disease-product-matrix.pdf>.

⁹ P. Trouiller et al., "Drug Development for Neglected Diseases: A Deficient Market and Public-Health Policy Failure," *Lancet* 359.9324 (2002): 2188–2194; M. Moran et al., "Neglected Disease Research and Development: How Much Are We Really Spending?" *PLoS Med* 6.2 (2009): e1000030.

¹⁰ P. Trouiller et al., "Drug Development for Neglected Diseases: A deficient market and public-health policy failure," *Lancet* 359.9324 (2002): 2188–2194.

¹¹ Laura J. Frost and Michael R. Reich, *Access: How Do Good Health Technologies Get to Poor People in Poor Countries?* (Cambridge: Harvard Center for Population and Development Studies, 2008).

¹² Ellen 't Hoen et al., "Driving a Decade of Change : HIV/AIDS, Patents and Access to Medicines for All," *J Int AIDS Soc* 14.15 (2011): doi:10.1186/1758-2652-14-15; Michael Westerhaus and Arachu Castro, "How Do Intellectual Property Law and International Trade Agreements Affect Access to Antiretroviral Therapy?," *PLoS Med* 3.8 (2006): e332.

¹³ James Love and Tim Hubbard, "The Big Idea: Prizes to Stimulate R&D for New Medicines," *Chicago-Kent Law Review*, 82.3 (2007): 1519–1554; Michael Heller and Rebecca Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science* 280.5364 (1998): 698–701; see also Rebecca S. Eisenberg, "Patents and Data-Sharing in Public Science," *Ind Corp Change* 15.6 (2006): 1013–1031.

¹⁴ *Disclosure* is defined here as publication of the patent in the public domain.

When a company wants to use the patent rights of another party, it must seek a license for the patent from the IP holder. A patent holder (“licensor”) can grant a license to another party (“licensee”) in order to authorize the licensee to manufacture, use, sell, and distribute the licensed material (e.g., a patented compound).

1.3 Neglected diseases—can changes in IP management make a difference?

Several groups have proposed IP reforms including the creation of various forms of joint IP management (JIPM)—known as *patent pools*—to address IP barriers in ND drug R&D and access. Patent pools are not a new concept and have been successful in facilitating innovation for technologies ranging from aircraft to consumer electronics.¹⁵ In these other fields, the pools are formed by two or more IP holders who license their individual patent rights to each other or to third parties, in return for royalties on sales of the resulting products. The formation and use of patent pools for global health technologies,¹⁶ which is not yet fully tested, appears to be different¹⁷ from these former approaches because it entails distinct groups of patent *donors* (mainly multinational biopharmaceutical companies or universities in the most affluent countries) and patent *users* (mainly generic drug companies and smaller biotechnology firms), instead of involving firms that both contribute and use the IP within the pools.¹⁸

Recent JIPM strategies for global health include the Medicines Patent Pool¹⁹ (MPP), founded by UNITAID, and the Pool for Open Innovation against Neglected Tropical Diseases,²⁰ created by GlaxoSmithKline (GSK) and now

managed by BIO Ventures for Global Health (BVGH).²¹ Such pools are in theory designed to address some IP barriers of ND drug R&D and access, by permitting broader access to relevant patents and know-how held by product developers, including pharmaceutical and biotechnology companies, product development partnerships (PDPs), and universities. Even though both the MPP and the Pool for Open Innovation are examples of JIPM mechanisms, they are notably different in terms of disease focus, goals, and target stakeholders.

The MPP aims to foster generic manufacture of low-cost AIDS drugs (ARVs) for low- and middle-income countries²² by securing a range of voluntary licenses to patented AIDS medicines from originator companies, which can then be used by generic drug firms. It is believed that this will improve low-income patients’ access to important ARVs and will also stimulate the “downstream” development of new, improved versions of these drugs, such as pediatric or heat-stable reformulations and FDCs, that better meet the needs of developing countries.

The Pool for Open Innovation against Neglected Tropical Diseases focuses on stimulating early, “upstream” scientific innovation of entirely new products—and for a different set of diseases: neglected tropical diseases (NTDs) such as malaria, tuberculosis, and kinetoplastid diseases (such as leishmaniasis and human African trypanosomiasis), which lack large commercial markets. The intent is to accelerate the discovery and development of novel drugs for NTDs by offering researchers and product developers access to small-molecule compounds, as well as associated data and know-how, held by GSK, other large pharmaceutical companies and product developers, and university-based and public-sector research institutions.

¹⁵ Toward the end of the 20th century the information technology and telecommunications industries initiated patent pools to promote the development and manufacture of consumer electronics (e.g., DVD, MPEG, and 3G patent pools). This type of patent pool had a goal of reducing transaction costs and inefficiencies resulting from multiple overlapping patents (“patent thickets”) to provide a convenient, one-stop-shopping approach to patent licensing and create a standard for technology production. See Appendix 1 for more details.

¹⁶ For example, the SARS patent pool, the genetic diagnostic patent pool.

¹⁷ Patent pools for global health technologies and those for other industries differ in several key ways, such as with respect to IP landscape, patent licensee types, and overall intent. For example, the need for incentives to encourage companies to join the pool is not as important in the case of traditional pools, where companies themselves, as opposed to a third party, have decided to form a patent pool.

¹⁸ David Serafino, *Survey of Patent Pools Demonstrates Variety of Purposes and Management Structures*, KEI Research Note 2007:6 (Washington, DC: Knowledge Ecology International, 2007), <http://www.keionline.org/misc-docs/ds-patentpools.pdf>; Jeanne Clark et al., *Patent Pools: A Solution to the Problem of Access in Biotechnology Patents?* (Alexandria, VA: United States Patent and Trademark Office, 2000), <http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>.

¹⁹ <http://www.medicinespatentpool.org/>.

²⁰ <http://www.ntdpool.org/>; this pool addresses neglected tropical diseases (NTDs) as defined by the US FDA priority review voucher legislation in Section 524 of the Food Drug and Cosmetic Act, and as such excludes HIV/AIDS.

²¹ In late 2011, the pool moved for a third time; the hub of the pool and its patent database were transferred to the United Nations World Intellectual Property Organization and renamed WIPO Re:Search.

²² Unless otherwise noted, country income classifications conform to World Bank designations. See <http://data.worldbank.org/about/country-classifications/country-and-lending-groups>.

1.4 Study scope and methodology

The purpose of this paper is to provide a review and analysis of key dimensions of IP rights as potential barriers to neglected disease drug R&D and access. Further, this paper includes in-depth case studies on two ongoing initiatives, the MPP and Pool for Open Innovation against Neglected Tropical Diseases.²³ Specifically, the study addresses the following questions:

1. To what extent and in what ways is IP a barrier to drug R&D and access for neglected diseases?
2. Can the MPP and the Pool for Open Innovation address these barriers?
3. What incentives might these strategies provide to IP holders and users to drive product development and access, and to ultimately achieve intended public health goals?

We have addressed the questions above through literature and policy document review as well as through a series of interviews with IP experts, proponents of the JIPM strategies, and other stakeholders from a range of organizations including PDPs, university drug discovery centers, and nonprofit organizations.²⁴

For this study, we did not attempt to interview a representative group of pharmaceutical and biotechnology companies to better understand whether these mechanisms would influence them to contribute their IP to the pool. Rather, we consider the incentives for these product developers to participate in these mechanisms; therefore, a deeper investigation on the potential appeal of JIPM strategies for industry could be an important area for further work. In addition, we did not conduct extensive interviews with university NTD drug researchers to fully understand the barriers they encounter in upstream R&D and their reactions to either mechanism, which may be especially relevant for the Pool for Open Innovation.

In Chapter 2, we focus on HIV medicines and evaluate whether IP could pose significant barriers to ARV drug development and access. We also analyze the potential of the MPP to address these barriers and its value relative to direct voluntary licensing, an alternative mechanism. In Chapter 3, we review drug R&D and access for NTDs and similarly identify critical IP barriers affecting NTD researchers and product developers. We then discuss whether the Pool for Open Innovation against Neglected Tropical Diseases is designed to tackle these barriers. Finally, in Chapter 4, we provide overall conclusions and limitations of our study as well as suggestions for further work.

²³ This study does not aim to analyze how new patent pools for global health technologies compare to traditional pools for consumer electronic patent pools. Further, it does not evaluate whether the MPP and Pool for Open Innovation would technically be considered valid patent pools in the eyes of regulatory agencies in the United States. It is unclear to what degree previous experience and success with traditional pools offer lessons for new JIPMs for global health. This is in part because they differ in several key ways, such as with respect to IP landscape, patent licensee types and overall intent. For example, the need for incentives to encourage companies to join the pool is not as important in the case of traditional pools, where companies themselves have decided to form a patent pool as opposed to a third party.

²⁴ Appendix 2 lists the people interviewed for this study.

²⁵ David Serafino, *Survey of Patent Pools Demonstrates Variety of Purposes and Management Structures*, KEI Research Note 2007:6 (Washington, DC: Knowledge Ecology International, 2007), <http://www.keionline.org/misc-docs/ds-patentpools.pdf>.

Chapter 2. IP barriers for HIV/AIDS medicines and the Medicines Patent Pool

2.1 Background

According to the World Health Organization (WHO), there were nearly 33.3 million people living with HIV/AIDS at the end of 2009, including 2.5 million children.²⁶ Most people infected with HIV live in low- and middle-income countries, about 70 percent in sub-Saharan Africa. Between 1981 and 2006, approximately 25 million people died from AIDS-related illnesses, and nearly 2 million deaths occurred in 2009 alone.²⁷

Treatments for HIV/AIDS have been very successful over the last decade. Highly active antiretroviral (ARV) therapy has been shown to save lives and to reduce a patient's viral load and thereby reduce transmission. For example, there are virtually no children born with HIV in many developed countries, due to the success of treatment programs to prevent mother-to-child transmission.²⁸ The advent of fixed-dose combinations (FDCs) of ARVs, which combine up to three (and possibly more in the future) medicines in one pill, has revolutionized patient care, especially in developing countries.

Despite these achievements, by 2012 only 40 percent of people living with HIV (PLHIV) in developing countries who need treatment are expected to receive ARV therapy.²⁹ New, low-cost formulations and combinations of ARVs are required to treat PLHIV in developing countries for a number of reasons. HIV resistance to currently used ARVs is on the rise, requiring the use of combinations with

new, more expensive ARVs. Also, new ARVs are needed to replace old medicines that have poorly tolerated side effects. Finally, there are few dosages and formulations that are appropriate for children.

Global market and financing for antiretrovirals

Unlike most neglected-disease drugs, ARVs have a large global market, primarily driven by the existence of a profit-based market in developed nations. The global market for originator ARVs was estimated to be \$10.8 billion in 2008 and is expected to grow by 3.7 percent annually to \$13.9 billion in 2015.³⁰ Much of this projected growth is dominated by trends in the United States,³¹ including increasing numbers of prescriptions and use of new combination drugs like Atripla® (emtricitabine, tenofovir, and efavirenz).³²

At the same time, low- and middle-income countries³³ account for the majority of the global demand by volume for ARVs. While 13–14 million people in these countries were eligible for treatment in 2009 based on WHO 2009 ARV therapy guidelines,³⁴ a recent demand forecast estimates that only 7.9 million people will be receiving ARVs in 2012.³⁵ The demand for ARVs in low- and middle-income countries is also increasing due to a rise in the numbers of infections and because of a recent change in 2010 WHO treatment guidelines,³⁶ which recommend

²⁶ "Global Summary of the AIDS Epidemic," WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS), 2009, http://www.who.int/hiv/data/2009_global_summary.png.

²⁷ Ibid.

²⁸ State-of-the-art HIV treatment recommended for most people by US Department of Health and Human Services guidelines contain two nucleoside analog reverse transcriptase inhibitors (NRTIs)—emtricitabine (FTC) and tenofovir (TDF)—plus integrase inhibitor raltegravir (RAL), non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV/EFZ), or ritonavir-boosted protease inhibitors (PIs) atazanavir (ATZ) or darunavir (DRV); see <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.

²⁹ Karen Stanecki, "Impact of New ART Recommendations on Number of People in Need of ART," UNAIDS, 2010, http://www.who.int/entity/hiv/amds/un-aids_impact_new_art_recomm_k_stanecki.pdf; Françoise Renaud-Théry et al., "Utilization Patterns and Projected Demand of Antiretroviral Drugs in Low- and Middle-Income Countries," *AIDS Res Treat* 2011.749041 (2011), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3065871/>.

³⁰ GBI Research, "The Future of HIV Therapeutics—Market Forecasts to 2015, Competitive Benchmarking, Product Pipeline and Deals Analysis," December 2009, <http://www.docstoc.com/docs/64933501/The-Future-of-HIV-Therapeutics---Market-Forecasts-to-2015-Competitive-Benchmarking-Product-Pipeline-and-Deals-Analysis>.

³¹ "Research and Markets: Antivirals Market to 2016—Antiretroviral Agents and Combination Therapies to be Major Drivers HIV and Hepatitis C Markets," Business Wire, February 21, 2011, <http://www.businesswire.com/news/home/20110221005597/en/Research-Markets-Antivirals-Market-2016---Antiretroviral>.

³² This rate, however, represents a slower growth rate than that of previous years, and this is because a number of important ARV patents are due to expire, which will lead to increased competition by generic companies, thereby reducing profits brand-name companies can make from the sale of these drugs.

³³ Definitions according to WHO (see http://www.who.int/healthinfo/global_burden_disease/definition_regions/en/index.html).

³⁴ World Health Organization, "2009 ART Guidelines for Adults and Adolescents—Evidence Map," <http://www.who.int/hiv/topics/treatment/evidence3/en/index.html>.

³⁵ Karen Stanecki, "Impact of New ART Recommendations"; Françoise Renaud-Théry et al., "Utilization Patterns."

³⁶ This represents an increase in demand of 15 percent over 2011 numbers (6.9 million).

that antiretroviral therapy be started considerably earlier than is currently offered.³⁷ The demand for different ARVs is also likely to change over time, as first-line FDCs with stavudine are phased out in favor of FDCs based on less toxic ARVs such as tenofovir (TDF).³⁸ While there has been considerable reduction in prices for first-line treatments, the prices for second-line treatments have not declined as much. Most PLHIV and governments in low-income countries (LICs)³⁹ and many middle-income countries (MICs)⁴⁰ are unable to afford these originator medicines (at developed-world prices) and therefore this segment of the market does not provide sufficient profit incentive to firms. Some MICs, however, such as India and China, do offer significant commercial opportunity.

In 2008, \$15.6 billion was spent on AIDS programs in LICs and MICs.⁴¹ International financing sources, including the Global Fund to Fight AIDS, Tuberculosis and Malaria; the US President's Emergency Plan for AIDS Relief (PEPFAR); and other donors, have poured in substantial funding to procure ARVs for these countries.⁴² But such development assistance is widely considered to be unsustainable, especially since many donor governments in developed nations face financial constraints and competing priorities, while the number of PLHIV in need of ARVs increases. Modeling conducted by the aids2031 project suggests that funding required for developing countries to address the pandemic could reach \$35 billion annually by 2031—two and a half times the current level.⁴³

There are, however, important differences in current funding sources for HIV/AIDS between LICs and MICs, with high-prevalence LICs predominantly being funded by external donors and MICs largely financed by their own domestic public and private revenues.⁴⁴ For example, the government of South Africa, which has more than 970,000 PLHIV on treatment, financed on average 75 percent

of total AIDS expenditures in 2008 and 2009.⁴⁵ Recent economic growth in several MICs, including India, Brazil, and China, means that these countries have increasing fiscal capacity to contribute a larger share of, if not most, ARV costs, depending on the pricing of these medicines.

The advent of generic manufacture of low-cost ARVs has also made it more feasible for MICs to pay for treatments. Beyond resource mobilization, mechanisms to alleviate potential IP barriers for ARV development and supply by facilitating generic production could lead to further declines in ARV prices, thereby reducing the overall HIV/AIDS cost burden for both donors and countries.

India's role as "pharmacy of the developing world." The establishment of the Medicines Patent Pool (MPP) in part grew out of a legitimate and growing concern that vitally important first- and second-line ARVs will become patented in India—the "pharmacy of the developing world"⁴⁶—and other middle-income manufacturing countries in the next few years, and that this could curtail generic manufacture of low-cost ARVs for developing countries (more details in section 2.2).⁴⁷

Indian generic manufacturing of ARVs has made a significant contribution to increasing access to affordable ARVs in developing countries since the early days of the epidemic. In the late 1990s, the severe lack of access to ARVs in developing countries like South Africa was unsurprising given that the cost of treatment with originator drugs was in excess of \$10,000 per patient per year in some of these countries.⁴⁸ Generic production in India and drug price reduction through competition, increased donor funding, negotiation of volume discounts and improvements in transport, hospital, and clinic infrastructure in developing countries have all contributed to steadily increasing the number of people on treatment in the last

³⁷ Regardless of symptoms, new WHO 2010 guidelines recommend that treatment begin when patients have a CD4 count of 350 cells/ml or less, compared with previous guidelines of 200 cells/ml or less; see <http://www.who.int/hiv/pub/2010progressreport/en/>.

³⁸ TDF in combination with other ARVs, is now recommended as a first-line treatment by the WHO; see <http://www.who.int/hiv/pub/2010progressreport/en/>.

³⁹ Low-income countries according to World Bank country and lending group classification: http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Low_income;

⁴⁰ Middle-income countries (lower-middle and upper-middle) according to World Bank country and lending group classifications: http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Lower_middle_income; http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Upper_middle_income

⁴¹ Robert Hecht et al., "Critical Choices in Financing the Response to the Global HIV/AIDS Pandemic," *Health Affairs* 28.6 (2009): 1591–1605.

⁴² UNAIDS. *What Countries Need: Investments Needed for 2010 Targets* (Geneva: UNAIDS, 2009), http://www.unaidsrsta.org/sites/default/files/investments_needed_2010_en_0.pdf.

⁴³ Robert Hecht et al., "Critical Choices."

⁴⁴ Carlos Avila, "Financing ART in Low- and Middle-Income Countries," UNAIDS, http://www.who.int/entity/hiv/amds/p1_unaids_financing_art_c_avila.pdf.

⁴⁵ "Global Report: UNAIDS Report on the Global AIDS Epidemic 2010," UNAIDS, <http://www.unaids.org/globalreport/default.htm>.

⁴⁶ "Why India's Generic Medicines Industry is So Important," *Doctors without Borders*, November 5, 2010, https://www.doctorswithoutborders-usa.org/news/article_print.cfm?id=4837.

⁴⁷ "Who We Are: Background," Medicines Patent Pool, <http://www.medicinespatentpool.org/WHO-WE-ARE2/Background>.

⁴⁸ "AIDS, Drug Prices and Generic Drugs," AVERT, <http://www.avert.org/generic.htm>.

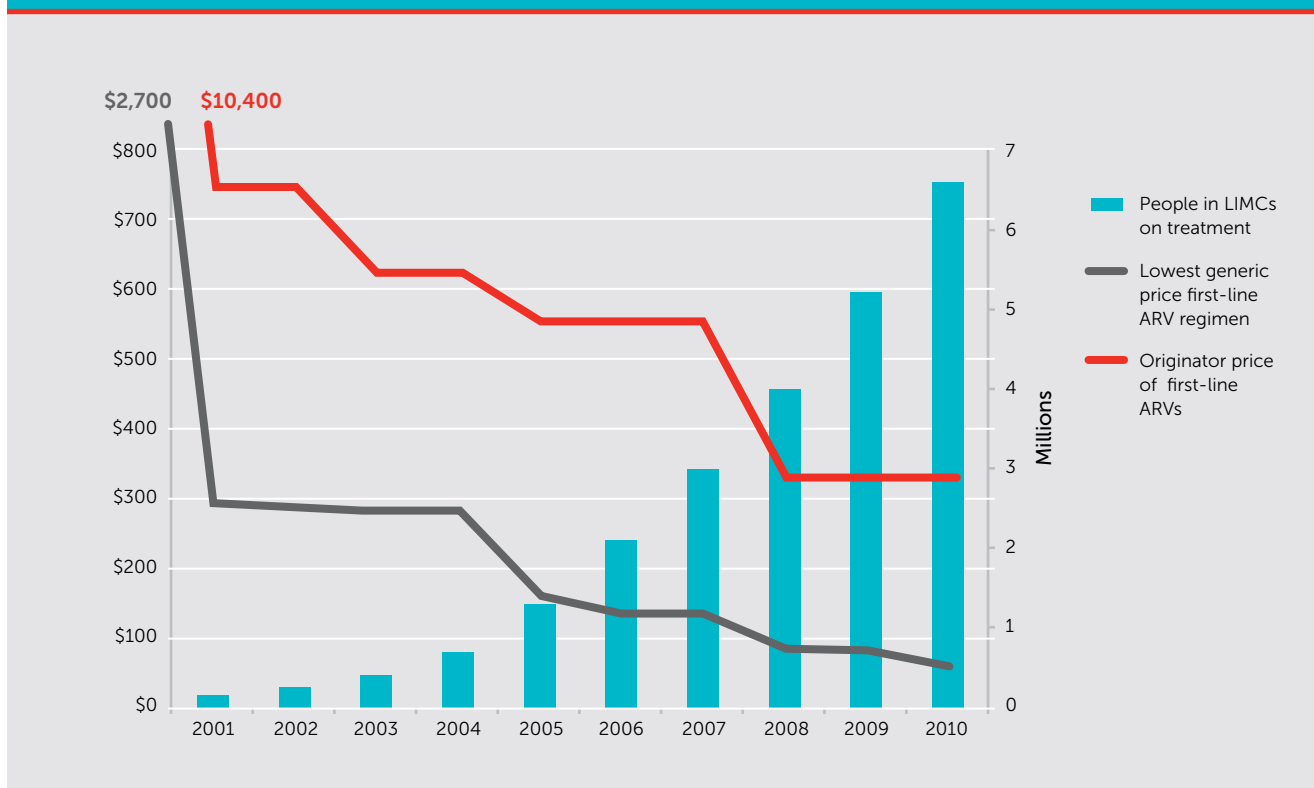
10 years.⁴⁹ In particular, prices started to fall dramatically in the early 2000s (see Figure 1), as competition between generic companies in India, Brazil, and Thailand took off and as originator companies became willing to negotiate prices under the threat of developing countries overriding their monopoly power by issuing compulsory licenses for patented drugs (see next section).

The development of India's generic manufacturing capability is in part attributable its permissive IP regime. Between 1970 and 2005, India did not have a patent law to grant product patents to originator companies, and this allowed Indian generic manufacturers to fill the growing demand for low-cost ARVs in developing countries, which themselves had no patent barriers preventing the importation of these drugs. The lack of ARV product patents in India also permitted generic companies to develop and produce FDCs and pediatric formulations and dosages of ARVs. As

a result, by 2009, 88 percent of all FDCs and 69 percent of all pediatric formulations approved by the US Food and Drug Administration (FDA) and WHO Prequalification Programme were from Indian generic firms.⁵⁰ Table 1 shows a comparison of originator versus generic (Indian company) prices for first- and second-line ARVs recommended by the WHO. As of 2010, Indian generic manufacturers supplied 80 percent of all donor-funded ARVs, including 91 percent of all pediatric formulations that were then available in developing countries.⁵¹

India's unique role as a low-cost manufacturer of ARVs is likely to change in the coming years, however, as the country navigates and fulfills its obligations under international trade agreements. India signed the World Trade Organization's (WTO's) Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement⁵² in 1994, along with other developing nations such as Brazil and

Figure 1. Generic competition and treatment scale-up



Source: Ellen 't Hoen, presentation at the UN High Level Meeting on HIV/AIDS, New York, June 11, 2011.

⁴⁹ WHO et al., *Towards Universal Access: Scaling Up Priority HIV/AIDS Interventions in the Health Sector; Progress Report 2010* (Geneva: WHO, 2010), http://whqlibdoc.who.int/publications/2010/9789241500395_eng.pdf.

⁵⁰ Brenda Waning, Ellen Diedrichsen, and Suerie Moon, "A Lifeline to Treatment: The Role of Indian Generic Manufacturers in Supplying Antiretroviral Medicines to Developing Countries," *J Int AIDS Soc* 13.35 (2010).

⁵¹ Ibid.

⁵² "Agreement on Trade-Related Aspects of Intellectual Property Rights," World Trade Organization, signed April 15, 1994, posted July 16, 2008, http://www.wto.org/english/docs_e/legal_e/27-trips.doc.

Table 1. Prices of WHO-recommended (2009) first- and second-line ARVs

WHO first line ART recommendations 2009 and examples of available medicines

AZT + 3TC + EFV

AZT/3TC 300/150mg	ViiV	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides	
\$US ppy	197*	110	111	115	110	110	131	
EFV 600 mg	Merck		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
\$US ppy	237*	657*	73	67	82	61	91	62

AZT + +3TC + NVP

AZT/3TC/NVP 300/150/200mg	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
\$US ppy	146	137	155	143	145	139

TDF + 3TC or FTC + EFV

TDF/PTC/EFV 300/200/600mg	Gilead/BMX/Merk		Cipla	Matrix
\$US ppy	613*	1033*	231	219
TDF/3TC/EFV 300/300/600mg	Cipla	Matrix		
\$US ppy	195	176		

TDF + 3TC or FTC + NVP

TDF/3TC 300/300mg	Cipla	Hetero	Matrix						
\$US ppy	110	128	100						
TDF/FTC 300/200mg	Gilead		Aurobindo	Matrix					
\$US ppy	315*	540*	155	244					
NVP 200mg	Boehringer Ingelheim	Aurobindo	Cipla	Hetro	Huahai	Matrix	Ranbaxy	Strides	
\$US ppy	219*	438*	37	34	37	34	39	39	37

WHO second-line ART recommendations 2009 and examples of available medicines

TDF + 3TC (or FTC) + LPV/r or ATZ/r

LPV/r 200/50mg tablet (heat-stable)	Abbott		Aurobindo	Cipla	Matrix
\$US ppy	440*	1000*	457	463	493

AZT + 3TC (or FTC) + LPV/r or ATZ/r

ATZ (ATV) 150mg capsule	Bristol-Meyers Squibb (BMS)	
\$US ppy	353*	431*
ATV 300mg capsule	Matrix	
\$US ppy	256	
RTV 100mg soft-gel capsule	Abbott	Cipla
\$US ppy	83*	323
RTV 100mg heat-stable capsule	Abbott	Matrix
\$US ppy	83*	180

Key to acronyms and abbreviations used above:

AZT—azidothymidine; 3TC—lamivudine; EFV—Efavirenz; NVP—nevirapine; AZT/r—azidothymidine/ritonavir; LPV/r—lopinavir/ritonavir

*Price available only to specific developing countries; generic company prices have no restrictions. See <http://utw.msfacecess.org/> for more detail.

Source: Data from Médecins sans Frontières (MSF) "Untangling the Web" database.⁵³

⁵³ "Untangling the Web of Antiretroviral Price Reductions," MSF Campaign for Access to Essential Medicines, <http://utw.msfacecess.org/>.

Thailand. TRIPS introduced IP rules into the multilateral trading system for the first time, and among other requirements, signatory countries agreed to grant patent protection in all fields of technology over time. Although most developing countries (excluding least-developed countries or LDCs)⁵⁴ had until 2000 to comply with TRIPS, there were some exceptions. Because India, Thailand, and Brazil did not have product patentability laws at the time of the TRIPS agreement, they were granted an additional 5 years (until 2005) to comply with TRIPS.⁵⁵ However, bilateral trade pressure from the United States induced Brazil and Thailand to give up this additional flexibility and instead change their patent laws to allow product patents very soon after signing.

Some experts argue that TRIPS compliance in Thailand and Brazil has stifled generic innovation and production of important FDCs,⁵⁶ and many advocates in the debate over access to medicines warn that the fallout from the amendment of India's patent law in 2005 is likely to have a similar effect. There are a number of specific terms of the law, however, that do mitigate the extent to which India's original role might change. First, since only drug compounds discovered after 1995 are eligible for patent application, many first-line and second-line ARVs (e.g., nevirapine, stavudine) discovered prior to January 1, 1995, and currently in use in developing countries, are not patentable in India.⁵⁷ Additionally, Sections 3(b) and 3(d) of Indian patent law restrict the patenting of improvements or reformulations (e.g., salts, polymorphs, solvates, isomers) of known chemical compounds if they are not shown to be more efficacious than the original form of the drug.⁵⁸ That said, there is some uncertainty even with improvements and reformulations since the standard for patentability according to these sections will depend on the interpretation of these sections of Indian patent law in the Indian courts.

What is clear, however, is that TRIPS affects new drugs discovered since 1995. As such, patents covering different forms (new compounds, new compositions, or new formulations) of the ARVs abacavir, maraviroc, rilpivirine, etravirine, saquinavir, and raltegravir have been granted in India since 2005. Patent applications for TDF,⁵⁹ darunavir, lopinavir/ritonavir combination and atazanavir⁶⁰ were rejected, however, as a result of legal opposition⁶¹ by civil society groups and generic companies who successfully argued that these patent applications did not qualify under Indian patent law.

Existing licensing mechanisms to facilitate ARV access

Before the MPP was established, there were already 2 mechanisms through which patented medicines could be licensed for generic manufacturing: compulsory licensing and voluntary licensing.

Compulsory licensing. The TRIPS agreement seeks to reward innovation by providing IP rights to the product developer. But in order to balance innovation and access, TRIPS also offers countries certain "flexibilities." One such flexibility is compulsory licensing, a mechanism whereby a government can override patent rights when it is in the interest of the state. In effect, compulsory licenses (CLs), established under Article 31⁶² of TRIPS, allow WTO member countries to grant the use of patent rights to generic manufacturers. Article 31(b) specifies that there need be no prior negotiation with patent rights holders in case of national emergency or some other circumstances (e.g., a public health emergency such as an epidemic). This means that if a patent holder refuses to reduce the price of a patented medicine to what is deemed reasonable by a government, the state can issue a license for the medicine's patent rights to a generic company that can

⁵⁴ Unless otherwise noted, country income classifications conform to World Bank designations. See <http://data.worldbank.org/about/country-classifications/country-and-lending-groups>.

⁵⁵ See TRIPS Article 65, Section 4, http://www.wto.org/english/tratop_e/trips_e/t_agm7_e.htm.

⁵⁶ For example, the nonprofit advocacy group AVERT claims that "TRIPS has stifled the generic competition that drove the price of first generation antiretrovirals down, causing huge disparities in the price of first- and second-line ARVs" ("AIDS, Drug Prices and Generic Drugs," AVERT, <http://www.avert.org/generic.htm>).

⁵⁷ Colleen V. Chien, "HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare?," *PLoS One* 2.3 (2007): e.278.

⁵⁸ See Appendix 3.

⁵⁹ In the case of TDF, the opposition claimed (a) that TDF was already known in the public domain through scientific publication to be useful for HIV treatment and (b) that the applicant had not shown any files to demonstrate that the fumarate salt of tenofovir disoproxil was an improvement over the soluble compound of tenofovir disoproxil and instead had only compared TDF with over another salt—citrate—which would not have improved efficacy compared with the soluble base compound tenofovir disoproxil.

⁶⁰ Declan Butler, "India Says No to HIV Drug Patents," *Nature*, September 3, 2009, <http://www.nature.com/news/2009/090903/full/news.2009.882.html>; "India Rejects Patents for Two Key AIDS Drugs," Doctors without Borders, January 7, 2011, <http://www.msf-me.org/en/news/news-media/news-press-releases/india-rejects-patents-for-two-key-aids-drugs.html>; "Our Cases," Initiative for Medicines, Access, & Knowledge, <http://www.i-mak.org/cases>.

⁶¹ Pre- and post-grant opposition against any patent application is allowed under Indian patent law.

⁶² In November 2001, the WTO Fourth Ministerial Conference of 2001 adopted the Doha declaration. Paragraphs 4 to 6 of the declaration reaffirm the ability of TRIPS member states to waive patent rights in order to achieve public health benefits under Article 31 of the TRIPS agreement. Specifically, Paragraph 5(b) restates the right of members to grant CLs for patented medicines. Many member countries also contain provisions in their patent laws that allow compulsory licensing in situations of national interest.

manufacture the drug at a lower cost. Article 31 does not stipulate a royalty rate for CLs,⁶³ but in general rates for ARVs have been between 0.5 percent and 5 percent.⁶⁴ Countries also have the right to issue such licenses for the manufacture of drugs for export to developing countries that do not have manufacturing capacity.

CLs for medicines had been used even before the advent of TRIPS and Article 31; until 1987, the Canadian government routinely issued CLs in order to allow generic companies to produce low-cost copies of patented medicines for the Canadian public. In recent years, some upper-middle- and lower-middle-income countries have argued that the tiered-pricing schemes for ARVs and other drugs offered by originator companies are still too high,⁶⁵ and these countries have moved to use or threaten to use compulsory mechanisms to gain access to cheaper versions of patented drugs. For example, Thailand and Brazil have both used CLs to manufacture or import cheaper versions of the ARV efavirenz (Merck) in 2006⁶⁶ and 2007,⁶⁷ respectively. Thailand also issued a CL for Abbott's branded product Kaletra (a combination of lopinavir and ritonavir) in 2007.⁶⁸ The response of patent holders to compulsory licensing or the threat of a CL has often been to lower drug prices.⁶⁹ However, as the case of the lopinavir/ritonavir CL illustrates, there may be serious consequences to countries who issue CLs, which may limit the utility of this mechanism in increasing access to low-cost ARVs. In response to Thailand's CL for the drug, Abbott took retaliatory action by declaring the company would no longer register new drugs for sale in the country for as long as the CL was in effect.⁷⁰ Subsequently, the US government responded by placing

Thailand on the Office of the US Trade Representative's Special 301 Priority Watch List.⁷¹

While India has not yet used compulsory licensing provisions, Natco, a generic drug company in India, has recently sought a voluntary license (VL) from ViiV Healthcare (a joint venture of GlaxoSmithKline and Pfizer) to make and sell the patented ARV maraviroc in India for one-fifth of its current cost (Pfizer sells it in India for \$1,431 per patient per year). This action is widely considered to be the first step toward the application for a CL,⁷² because in order to be eligible for a CL under Indian patent law, the generic company must demonstrate that it has attempted to secure a VL. If Natco proceeds to apply for a CL, it will test the strength of the compulsory licensing provisions in Indian patent law and may provide a mechanism to Indian generic companies to circumvent Indian ARV patents.

In addition to potential retaliation from the issuance of a CL, inertia can be an equally powerful barrier to countries making more widespread use of this mechanism. A number of organizations including the Joint United Nations Programme on HIV/AIDS (UNAIDS), the United Nations Development Programme (UNDP), and the WHO have expressed concern that very few developing countries have enacted IP reform legislation to take maximum advantage of TRIPS compliance flexibilities; these organizations have issued a statement encouraging use of such legal provisions to help improve scale-up and sustainability of HIV treatments.⁷³

⁶³ Article 2(a) Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health.

⁶⁴ Patent laws in some developed countries have a more stringent way of calculating what the royalty rate should be for a CL. The Canadian formula, for example, is based on guidelines that link the royalty rate paid on a contract to the importing country's ranking on the United Nations Development Programme's Human Development Index; the lower the importing country ranks on the index, the lower its royalty rate. See http://www.camr-rcam.gc.ca/compan-entrepris/applic-demande/royal_pay-verse_redev-eng.php. For further discussion on CL remuneration guidelines (royalties), see James Love, *Remuneration Guidelines for Non-Voluntary Use of a Patent on Medical Technologies*, Health Economics and Drugs TCM Series No. 18 (Geneva: WHO, 2005), http://www.who.int/medicines/areas/technical_cooperation/WHOTCM2005.1_OMS.pdf.

⁶⁵ Sangeeta Shashikant, "Brazil Moves on Compulsory License after Failed Talks with Drug Company," Third World Network, May 3, 2007, <http://www.twn-side.org.sg/title2/wto.info/twninfo050703.htm>.

⁶⁶ Tove I.S. Gerhardsen, "Thailand Compulsory License on AIDS Drug Prompts Policy Debate," Intellectual Property Watch, December 22, 2006, <http://www.ip-watch.org/weblog/2006/12/22/thailand-compulsory-license-on-aids-drug-prompts-policy-debate/>.

⁶⁷ Keith Alcorn, "Brazil Issues Compulsory License on Efavirenz," NAM AIDSmap, May 7, 2007, <http://www.aidsmap.com/Brazil-issues-compulsory-license-on-efavirenz/page/1427206/>.

⁶⁸ Thawach Sunrajarn, "Decree of Department of Disease Control, Ministry of Public Health, Regarding Exploitation of Patent on Drugs and Medical Supplies by the Government on Combination Drug Between Lopinavir and Ritonavir," Department of Disease Control, Thailand, January 29, 2007, http://www.cptech.org/ip/health/c/thailand/thai-cl-kaletra_en.pdf.

⁶⁹ Tove I.S. Gerhardsen, "Thailand Presents Reports on Compulsory Licensing Experiences," Intellectual Property Watch, March 12, 2007, <http://www.ip-watch.org/weblog/2007/03/12/thailand-presents-report-on-compulsory-licensing-experience/>; Jean-François Tremblay, "Abbott Drops AIDS Drug Price," Chemical & Engineering News, April 12, 2007, <http://pubs.acs.org/cen/news/85/i16/8516news6.html>.

⁷⁰ Amy Kazmin and Andrew Jack, "Abbott Pulls HIV Drug in Thai Patents Protest," *Financial Times*, March 14, 2007, <http://www.ft.com/cms/s/0/a2e81cc8-d1d1-11db-b921-000b5df10621.html#axzz1OXeDA2CI>.

⁷¹ "Priority Watch List," Office of the US Trade Representative, 2007, <http://www.ustr.gov/sites/default/files/2007-301-PRIORITY%20WATCH%20LIST.pdf>.

⁷² Khomba Singh, "Natco Seeks Pfizer Nod for Drug Clone," *The Economic Times*, January 5, 2011, <http://economictimes.indiatimes.com/news/news-by-industry/healthcare/biotech/pharmaceuticals/natco-seeks-pfizer-nod-for-drug-clone/articleshow/7220479.cms>. Should Pfizer refuse to grant a VL (a highly likely outcome), then NATCO can apply for a CL from the Indian government.

⁷³ See, for example, "UNAIDS/UNDP/WHO Concerned over Sustainability and Scale Up of HIV Treatment," press release, UNAIDS, March 15, 2011, <http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2011/march/20110315prtrips/>.

Direct voluntary licensing. Recognizing that strengthening IP protections is likely to negatively impact ARV access, some originator companies have “voluntarily” employed a number of strategies to make their drugs more accessible and affordable. For example, GlaxoSmithKline (GSK), Merck, Gilead Sciences, and other companies have access programs that include drug donations and tiered (or differential) pricing for products. While this paper does not cover these initiatives, there have been criticisms of drug donation programs because they do not increase market size and may deter generic companies from entering the ARV market.⁷⁴ Tiered pricing schemes that grant lower prices to some countries based on income could be an effective way to improve access to medicines for people living in LICs and MICs.⁷⁵ However, this approach does not encourage generic competition, which is likely to

be a more effective strategy at bringing down costs of production over the long run. Other companies, such as Bristol-Myers Squibb, have simply indicated that they do not intend to enforce patents in LDCs.⁷⁶ While this strategy would, in theory, allow for generic competition, in practice it has major limitations. This kind of informal arrangement makes it very difficult for generic companies to determine definitively whether they have the freedom to operate to sell drugs in these countries, likely dampening investment and limiting the scale of generic production.

Under direct voluntary licensing, originator companies negotiate licenses for their patented originator drugs with generic producers. A number of companies have negotiated VLs in recent years, resulting in more drugs and more countries that benefit from lower-cost generic

Table 2. Examples of voluntary licensing of ARVs to Indian generic companies

Licensors, product, date	Licensee	Geographic market scope
Gilead, TDF, 2006	Alkem Laboratories	95 developing countries including India, South Africa, and Thailand
	Aurobindo Pharma Limited	
	FDC	
	JB Chemicals & Pharmaceuticals	
	Matrix Laboratories	
	Medchem International	
	Ranbaxy International	
	Shasun Chemicals and Drugs	
	Emcure Pharmaceuticals	
	Hetero Drugs	
Strides Arcolab		
Bristol-Myers Squibb, atazanavir, 2006	Emcure Pharmaceuticals	Manufacture and sale in India and Africa
Bristol-Myers Squibb, didanosine, 2006	Aurobindo Pharma Limited	South Africa and 49 other developing countries
Tibotec, rilpivirine, 2011	Hetero Drugs	Sub-Saharan Africa, LDCs, and India
	Matrix Laboratories	

Source: Adapted from Tahir Amin, “Voluntary Licensing Practices in the Pharmaceutical Sector: An Acceptable Solution to Improving Access to Affordable Medicines?,” research paper for Oxfam, February 8, 2007, <http://www.docstoc.com/docs/23819033/Voluntary-licensing-practices-in-the-pharmaceutical-sector-An>.

⁷⁴ See, for example, Brook K. Baker and Eva Ombaka, “The Danger of In-Kind Drug Donations to the Global Fund,” *Lancet* 373.9670 (2009): 1218–1221. In other words, because a single company controls the supply, drug donations could have the effect of inhibiting the creation of a sustainable market supply.

⁷⁵ Prashant Yadav, *Differential Pricing for Pharmaceuticals: Review of Current Knowledge, New Findings and Ideas for Action* (London: UK Department for International Development, 2010), <http://www.dfid.gov.uk/Documents/publications1/prd/diff-pcing-pharma.pdf>.

⁷⁶ “Intellectual Property Rights and Pricing,” Bristol-Myers Squibb, http://www.bms.com/sustainability/issues/Pages/intellectual_property_rights_and_pricing.aspx.

manufacturing. In 2004, Boehringer Ingelheim signed VLs with generic manufacturers Cosmos Limited (Kenya) for the manufacture and sale of nevirapine in Burundi, Kenya, Rwanda, Tanzania, and Uganda, and with Memphis (Egypt) for the manufacture and sale of nevirapine in Egypt and neighboring countries. Roche voluntarily licensed (with free technology transfer) stavudine and saquinavir in 2006 for manufacture and sale in sub-Saharan African countries or countries defined as LDCs. Bristol-Myers Squibb signed VLs with Emcure Pharmaceuticals for manufacture and sale of atazanavir in India and Africa, and with Aurobindo for manufacture and sale of didanosine in South Africa and 49 other developing countries⁷⁷ (see Table 2).

In 2006, Gilead Sciences⁷⁸ granted nonexclusive VLs, for a 5 percent royalty fee, to 13 Indian generic companies⁷⁹ for the manufacture and sale of TDF products, covering a licensing territory of 95 developing countries (including India, South Africa, and Thailand but excluding Brazil, Russia, and China).⁸⁰ Some of these licensing deals were made at a time when the Indian courts were deciding the validity of the TDF patent application, which was subsequently rejected. Importantly, Gilead Sciences does not yet hold any Indian ARV product patents (it holds a process patent relating to TDF); therefore its voluntary licensing scheme has not been adequately tested in India as a means to avoid IP barriers. However, Gilead Sciences has a number of patent applications filed in India covering the new ARV drugs cobicistat (COBI) and elvitegravir (EVG) and has also filed divisional applications for TDF and improved formulations of TDF (after TDF patent applications were rejected) (see Appendix 5). Gilead Sciences' recent licensing agreement for TDF, COBI, EVG, and emtricitabine (FTC) with the MPP is discussed in detail in the next section.

Recently, ViiV Healthcare⁸¹ offered a royalty-free voluntary licensing scheme for its ARVs, including pipeline products.⁸² This is limited to manufacturers in LDCs.⁸³ A VL has also been extended to manufacturers in South Africa, and according to a verbal statement by ViiV, Indian generic manufacturers may also be able to seek a VL.⁸⁴ In response to Natco's action and a potential pursuit of a CL (discussed above), ViiV Healthcare announced that it is seeking local generic companies in India to produce maraviroc and also claimed to be open to a VL deal with Natco.⁸⁵

In January 2011, Tibotec announced a voluntary licensing scheme for generic manufacturers, including two Indian generic manufacturers and one South African⁸⁶ company, for the ARV rilpivirine, which is patented in both countries.⁸⁷ Under this agreement, the generic manufacturers will be entitled to manufacture a once-daily dose of rilpivirine as a single-agent medicine as well as an FDC product and sell them in sub-Saharan Africa, LDCs, and India. In return, they will pay royalties ranging from 2 to 5 percent to Tibotec. Tibotec will also provide the generic companies with technical information and knowledge to facilitate the manufacture of the single-agent product. This is the first time a VL has been offered for a drug patented in India to an Indian generic company. There is much discussion and interest in the possible expansion of voluntary licensing as a solution to potential IP barriers for research and development (R&D) and access, which we present in more detail in section 2.3.

⁷⁷ Tahir Amin, "Voluntary Licensing Practices in the Pharmaceutical Sector: An Acceptable Solution to Improving Access to Affordable Medicines?," research paper for Oxfam, February 8, 2007, <http://www.docstoc.com/docs/23819033/Voluntary-licensing-practices-in-the-pharmaceutical-sector-An>.

⁷⁸ "Originator Company Profiles: Gilead Sciences," Access to Medicine Index, June 2010, http://www.accesstomedicineindex.org/sites/www.accesstomedicineindex.org/files/publication/Final_Gilead_0.pdf.

⁷⁹ Not all generic companies signed on: Cipla, which manufactures TDF products, did not sign a VL with Gilead Sciences.

⁸⁰ "The Medicines Patent Pool / Gilead Licenses: Questions and Answers," Medicines Patent Pool, <<http://www.medicinespatentpool.org/content/download/490/2895/version/1/file/The+Medicines+Patent+Pool+Q%26A+Gilead+Licences+Final.pdf>>.

⁸¹ ViiV Healthcare is a for-profit company combining the HIV portfolios of GlaxoSmithKline and Pfizer.

⁸² "ViiV Healthcare Announces Further Initiatives to Improve Access to HIV Medications for People Living in the Least Developed Countries," ViiV Healthcare, July 16, 2010, <http://www.viivhealthcare.com/media-room/press-releases/2010-07-16.aspx>.

⁸³ For list of countries, see <http://www.viivhealthcare.com/media-room/press-releases/2010-07-16.aspx>.

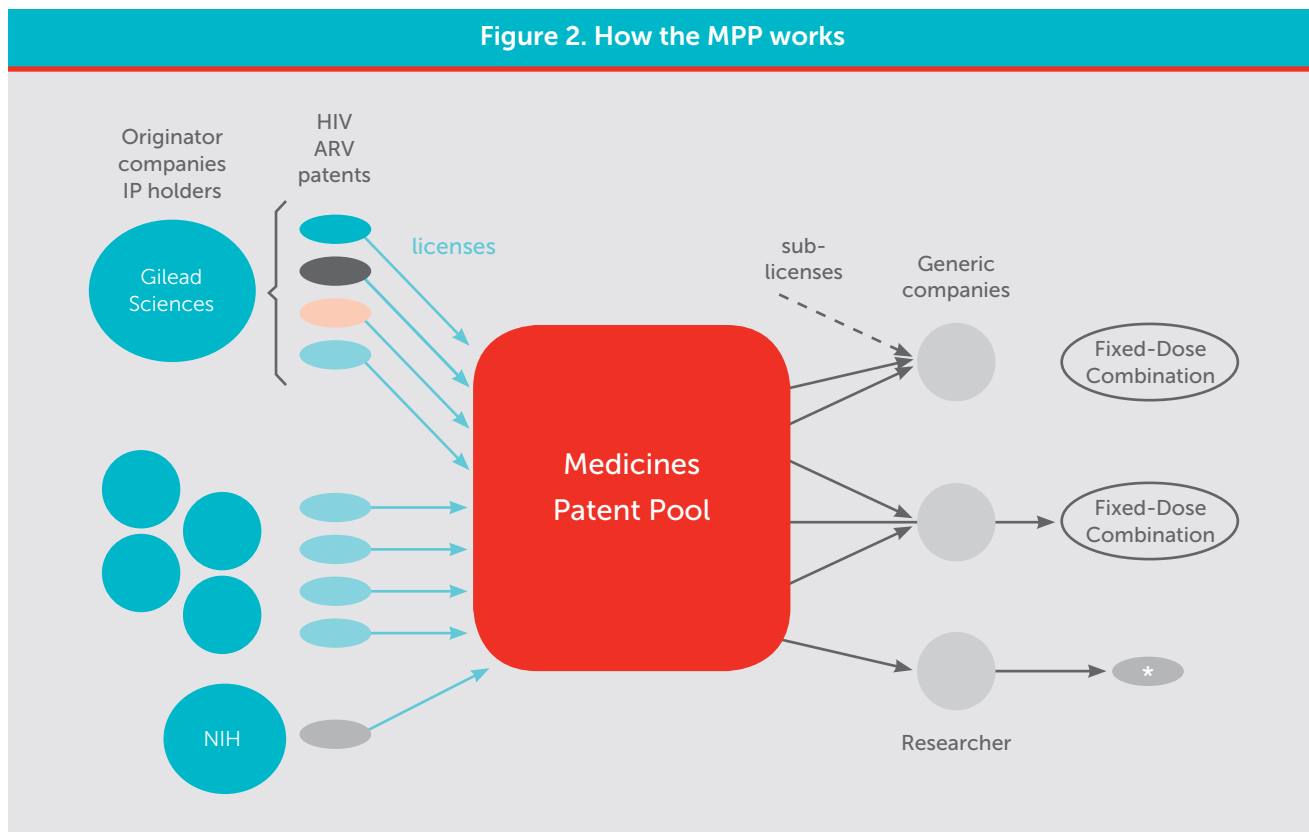
⁸⁴ Brook K. Baker, "ViiV Licenses vs. the Patent Pool: Unanswered Questions and Unwarranted Antipathy," Health Global Access Project, August 2, 2010, http://www.healthgap.org/trips/viiv_analysis.htm.

⁸⁵ Khomba Singh, "ViiV Healthcare Seeks Partners for HIV Drug in India," *The Economic Times*, January 18, 2011, http://articles.economictimes.indiatimes.com/2011-01-18/news/28428041_1_natco-pharma-low-cost-version-licence.

⁸⁶ Hetero Drugs Limited and Matrix Laboratories Limited (a Mylan company) of India, and Aspen Pharmacare of South Africa.

⁸⁷ "New Voluntary Licenses for Rilpivirine," Doctors without Borders, February 9, 2011, <http://msf-utw.tumblr.com/post/3199016548/new-voluntary-licences-for-rilpivirine>; "Tibotec Signs Multiple Agreements with Generic Manufacturers to Provide Access to New HIV Treatment," Johnson & Johnson, January 27, 2011, <http://www.jnj.com/connect/news/all/Tibotec-Signs-Multiple-Agreements-with-Generic-Manufacturers-to-Provide-Access-to-New-HIV-Treatment>.

Figure 2. How the MPP works



2.2 The Medicines Patent Pool as a solution to IP barriers

The Medicines Patent Pool (MPP), initially created by UNITAID and now independent, is a new mechanism to facilitate innovation for and access to ARVs by addressing IP and other economic barriers. In this section, we analyze the extent to which the MPP could reduce critical IP barriers for ARVs, in the absence of other interventions.

Pool motivation and structure

Médecins sans Frontières (MSF) and Knowledge Ecology International (KEI) first presented the concept of a patent pool for medicines to UNITAID in 2006.⁸⁸ At this time,

there was considerable uncertainty about the fate of several patent applications that had been filed in India for important ARVs (e.g., TDF, lopinavir/ritonavir). In July 2008, the UNITAID board decided to explore the feasibility of setting up a voluntary HIV/AIDS medicine patent pool, which received approval in December 2009. In July 2010, the MPP was legally created and established as an independent entity with the mission of improving access to HIV medicines in developing countries. The MPP became operational in November 2010.⁸⁹ As of mid-2011, the MPP is still in its infancy, with two organizations contributing to the pool (see “Support for the MPP,” below). UNITAID is funding the MPP for 5 years under a Memorandum of Understanding.⁹⁰

The MPP is a multilateral initiative that aims to collectively secure VLs for up to 19 existing ARVs, including first- and second-line ARVs, and to sublicense them to any competent generic manufacturing company in the

⁸⁸ See “IGWG Briefing Paper on Patent Pools: Collective Management of Intellectual Property—The Use of Patent Pools to Expand Access to Essential Medical Technologies,” Knowledge Ecology International Research Note 2007:3.1, January 23, 2007, <http://accessvector.org/oldkei/content/view/65/>; and “The Essential Medical Inventions Licensing Agency Working Plan,” Knowledge Ecology International, June 1, 2007, <http://keionline.org/content/view/64/1>.

⁸⁹ One MPP proponent indicated that the MPP could be used for other drugs beyond ARVs in the future.

⁹⁰ “Medicines Patent Pool Foundation Memorandum of Understanding,” UNITAID September 2010, <http://www.medicinespatentpool.org/content/download/208/1199/file/MemorandumOfUnderstanding_MedicinesPatentPoolFoundation_14Sept2010.pdf>.

world⁹¹ (see Figure 2). Patents in the pool that facilitate development of “adapted formulations,” such as FDCs, pediatric formulations, and heat-stable formulations, will also be made available to license. In other words, the pool is not simply aimed at promoting generic competition for existing ARVs but also supports the development of new formulations. Licenses from the pool will be made on a nonexclusive, nondiscriminatory basis to parties (such as generic producers) intending to manufacture the medications for sale in developing countries. Royalties will be used to compensate patent holders when there are sales of licensed products. Licenses may also contain provisions for tiered royalties that take into account different countries’ ability to pay (e.g., that of MICs) and will contain requirements to meet quality assurance (through, e.g., the WHO Prequalification Programme, FDA “tentative approval,” or European Medicines Agency approval under Article 58). The MPP will attempt to make core terms standardized, subject to negotiations, and has so far made all licenses public.

Proponents of the MPP argue that this IP management strategy would diversify supply sources and expand the global generic market size, leading to a reduction in ARV prices as well as promoting development of new ARVs. MPP advocates claim that the approach would create more legal and freedom-to-operate certainty for future generic manufacture in the post-2005 TRIPS era, in particular in the case of FDCs, where more than one license is needed. This approach would in theory allow generic producers to sign sublicenses for only those patents needed to develop or produce the desired product and would reduce transaction costs for those FDC producers who need to license more than one patent.⁹² The overall goal is that in the future all ARVs will automatically enter the pool once approved by the FDA or WHO Prequalification Programme.

Support for the MPP

In September 2010, the US National Institutes of Health (NIH) made the first contribution to the pool: a nonexclusive, royalty-free license for patents relating to the protease inhibitor darunavir.⁹³ This license agreement, however, does not allow a legal pathway for production and sale of darunavir. This is because Tibotec, a subsidiary of Johnson & Johnson, owns important patents in developed and developing countries (but not India) relating to the drug and its manufacture.⁹⁴ In addition, darunavir is only useful in combination with the booster ritonavir; the patent rights for ritonavir are owned by Abbott Pharmaceuticals, which is currently not a contributor to the MPP. The NIH licensed these patents to the pool to underline the US government’s commitment to the MPP and its goal of increasing the availability of HIV medicines in developing countries.⁹⁵

In July 2011, Gilead Sciences announced its participation in the MPP, making this the first pharmaceutical company to contribute licenses to the pool. Gilead Sciences signed multiple licenses with the MPP covering TDF, COBI, EVG, and a fixed-dose Quad pill combining these three ARVs plus FTC.⁹⁶ COBI and EVG are investigational drugs that have not yet received FDA approval. Gilead Sciences also issued a statement that it would not be enforcing patents on FTC⁹⁷ (for further details on the Gilead-MPP agreement see the next section).

The MPP aims to have all ARV patent holders join. Nevertheless, according to one proponent, the pool would be considered “successful” if three or four patent owners or companies (other than the NIH) agree to sign agreements with the pool within the year. In July 2011, the MPP announced that it was in negotiations with originator companies F. Hoffmann-La Roche,

⁹¹ “UNITAID Patent Pool Initiative, Implementation Plan—Executive Summary,” UNITAID, November 2009, http://www.medicinespatentpool.org/content/download/215/1231/version/1/file/ForWebsite_UNITAID_Patent_Pool_Implementation_Plan_-_Executive_Summary.pdf.

⁹² Another issue to highlight is the potential “hold-up” problem, whereby a patent holder has incentive to hold out licensing the third product needed to make an FDC for a period of time in order to make more money. The MPP is trying to mitigate this hold-up problem.

⁹³ “US National Institutes of Health (NIH) First to Share Patents with Medicines Patent Pool,” UNITAID, September 30, 2010, <http://www.unitaid.eu/fr/resources/actualites/290-us-national-institutes-of-health-nih-first-to-share-patents-with-medicines-patent-pool.html>; Thiru Balasubramaniam, “The NIH Patent License Agreement with UNITAID Supported Medicines Patent Pool for Patents on Darunavir,” Knowledge Ecology International, September 30, 2010, <http://keionline.org/node/956>; “Public Health Service: Non-Exclusive Patent License Agreement,” Medicines Patent Pool Foundation, September 20, 2010, <http://www.medicinespatentpool.org/content/download/214/1227/version/1/file/MPPF+Patent+License+Full+Executed+%28Sept+2010%29-NS.pdf>.

⁹⁴ “Questions and Answers: The US National Institutes of Health (NIH) License to the Medicines Patent Pool,” Medicines Patent Pool, September 2010, http://www.unitaid.eu/images/news/patentpool/20100930_nih_license_q%26a_en.pdf.

⁹⁵ Medicines Patent Pool et al., “US National Institutes of Health (NIH) First to Share Patents with Medicines Patent Pool as It Opens for Business,” September 30, 2010, <http://www.medicinespatentpool.org/content/download/310/2027/version/1/file/Medicines%2BPatent%2BPool%2BNIH%2Blicense%2BPR%2BEMB%2Bfor%2B30%2BSept%2B2010%2BFINAL-1.pdf>.

⁹⁶ “The Medicines Patent Pool / Gilead Licenses: Questions and Answers,” Medicines Patent Pool, <http://www.medicinespatentpool.org/content/download/490/2895/version/1/file/The+Medicines+Patent+Pool+Q%26A+Gilead+Licences+Final.pdf>. For license details see “The Medicines Patent Pool Announces First Licensing Agreement with Pharmaceutical Company,” Medicines Patent Pool, July 12, 2011, <http://www.medicinespatentpool.org/LICENSING/Current-Licences/Medicines-Patent-Pool-and-Gilead-Licence-Agreement>.

⁹⁷ “The Medicines Patent Pool / Gilead Licenses: Questions and Answers.”

Sequoia Pharmaceuticals, ViiV Healthcare, Boehringer-Ingelheim, and Bristol-Myers Squibb.⁹⁸ The MPP is also still in negotiations with the NIH regarding other patent licenses. With the exception of Gilead Sciences, originator companies have voiced support for the pool but have yet to join. But Tibotec, one of the patent holders that the MPP wishes to license from, announced its own voluntary licensing scheme outside of the pool,⁹⁹ which was seen by some as a rejection of the pool.¹⁰⁰ Both originator and generic companies surveyed by the MPP about their interest in the pool identified opportunities and threats in relation to joining the MPP.¹⁰¹

In July 2011, MedChem, a new player in the HIV field, became the pool's first generic company sublicensee. In October 2011, the Indian generic producer Aurobindo also signed an agreement that allows it to manufacture FTC and the pipeline products COBI, EVG, and the Quad combination of FTC, COBI, EVG, and TDF under the MPP-Gilead licenses.¹⁰² In 2006, Aurobindo had signed a deal with Gilead Sciences for a VL to manufacture TDF.

In addition to companies, governments and international organizations have expressed their support for the MPP. In January 2011, the US government issued a statement putting pressure on the WHO to embrace the MPP at the WHO executive board meeting.¹⁰³ The UK government has also called for patent holders to join the pool.¹⁰⁴ In June 2011, the UN High Level Meeting on AIDS issued an official declaration supported by UN member states¹⁰⁵ that endorsed the MPP as a way to "help reduce treatment costs and encourage development of new HIV treatment formulations, including HIV medicines and point-of-care diagnostics, in particular for children." At this meeting,

Margaret Chan, Director-General of the WHO, also expressed the WHO's support and commended UNITAID for establishing the MPP. Others that have expressed support include UNAIDS and the Global Fund to Fight AIDS, Tuberculosis and Malaria, as well as the G8, the European Union, South Africa, Thailand, and Brazil.

IP barriers to ARV R&D and access

There is a significant potential for current and future patents to act as a barrier to the development and production of affordable ARVs. A number of ARVs have been patented in India, and new ARVs could be patented in the future. Alongside patent issues, new moves to shore-up data exclusivity laws are feared to potentially jeopardize generic production and development of ARVs, regardless of their patent status. Lack of technology transfer to manufacture ARVs and a possible increase in legal uncertainty concerning the scope and number of ARV patents over time, while also potential IP barriers, are considered to be less important than access to patents. The MPP-Gilead license is designed to address these barriers, and the MPP may have further impact if there is sufficient interest from other originator and generic companies in joining the pool. The extent of the impact of future agreements will depend on the details of each license.

The sections below will discuss some of these issues in detail, including the specific ways in which access to patents, data exclusivity, technology, and other IP barriers impact ARV R&D and access.

⁹⁸ "Patent Pool in Talks with the First Potential Contributors," Science and Development Network, February 15, 2011, <http://www.scidev.net/en/news/patent-pool-in-talks-with-first-potential-contributors.html>; "Medicines Patent Pool in Negotiations with Key HIV Medicines Patent Holders," Medicines Patent Pool, July 2011, <http://www.medicinespatentpool.org/LICENSING/Company-Engagement>; "The Medicines Patent Pool Announces Negotiations with Two Additional Pharmaceutical Companies for Patents on HIV Medicines," UNAIDS, July 18, 2011, <http://www.unaids.org/en/resources/presscentre/featurestories/2011/july/20110718aiaspentpool/>.

⁹⁹ "Tibotec Signs Multiple Agreements with Generic Manufacturers to Provide Access to New HIV Treatment," Johnson & Johnson, January 27, 2011, <http://www.jnj.com/connect/news/all/Tibotec-Signs-Multiple-Agreements-with-Generic-Manufacturers-to-Provide-Access-to-New-HIV-Treatment>.¹⁰⁰ "Birth Pangs of the Medicines Patent Pool," Generics and Biosimilars Initiative, February 25, 2011, <http://www.gabionline.net/Generics/General/Birth-pangs-of-the-Medicines-Patent-Pool>. Tibotec has signed agreements with a number of generic companies including Hetero Drugs Limited, Matrix Laboratories Limited (and also Aspen Pharmacare in South Africa), but critics of this strategy are concerned with the geographic scope of Tibotec's VL, which excludes Brazil. See Judit Ruis, "KEI Comments on Tibotec Voluntary Licenses of new HIV-AIDS Product," Knowledge Ecology International, January 27, 2011, <http://keionline.org/node/1068>.

¹⁰¹ "UNITAID Patent Pool Initiative, Implementation Plan—Executive Summary," UNITAID, November 2009, http://www.medicinespatentpool.org/content/download/215/1231/version/1/file/ForWebsite_UNITAID_Patent_Pool_Implementation_Plan_-_Executive_Summary.pdf (see pages 16–17); Appendix 4 provides details from this survey.

¹⁰² Due to the unbundled nature of the licensing agreement, Aurobindo and other generic manufacturers can sign up for licenses on a product-by-product basis.

¹⁰³ Ed Silverman, "US Tells the WHO to Support a Patent Pool," *Pharmalot*, January 20, 2011, <http://www.pharmalot.com/2011/01/us-tells-the-who-to-support-a-patent-pool/>; Thiru Balasubramaniam, "US Government Urges WHO to Support Medicines Patent Pool: Extract of US Intervention on Draft WHO HIV/AIDS Strategy 2011–2015," Knowledge Ecology International, January 18, 2011, <http://lists.keionline.org/pipermail/ip-health_lists.keionline.org/2011-January/000628.html>.

¹⁰⁴ All-Party Parliamentary Group on AIDS, *The Treatment Timebomb* (London: APPG, 2009), http://img.thebody.com/confs/ias2009/pdfs/MSF_07-10_APPG_Policy_Report_TheTreatmentTimeBomb.pdf.

¹⁰⁵ "Resounding Support for Medicines Patent Pool at UN High Level Meeting on AIDS," Medicines Patent Pool, June 10, 2011, <http://www.medicinespatentpool.org/NEWS-ROOM/News-from-the-Pool/UN-High-Level-Meeting>.

Access to patents. The majority of experts who were interviewed about IP barriers to ARV R&D and access stated that patents are and may continue to be a major barrier. Several of these experts raised specific concerns about new ARVs that have been recently patented in India because such patents threaten the availability of low-cost FDCs and pediatric formulations based on these ARVs.¹⁰⁶ In the case of FDCs, it takes only one patent to block the development of these new treatments.

Data from the MPP's patent database¹⁰⁷ shows that of the 19 ARVs (plus an additional 4) that are being sought by the MPP, six ARVs (and other forms) have been patented in India (see Appendix 5). None of the WHO-recommended first- and second-line drugs have been patented in India; however, some of these drugs have been patented in other developing countries like Brazil and Thailand, which have substantial manufacturing capacity (see Table 3).

In addition, there are at least 20 patent applications currently filed in India for 8 of the 13 ARVs that currently lack Indian patents (see Appendix 5), according to a search of the MPP patent database.¹⁰⁸ Importantly, there are a

number of patent applications filed in India, Brazil, and Thailand for first- and second-line ARVs recommended by the WHO (see Table 3). It is outside the scope of this paper to assess whether these applications will be successful in India. However, the existence of patent applications for these ARVs does constitute a potential threat to their continued generic manufacture, since India currently provides 80 percent of the ARV supply in sub-Saharan Africa.

So far, VLs have been granted to Indian generic manufacturers for only one of the ARVs patented in India (rilpivirine) (see Table 4). While there are also indications that ViiV Healthcare will pursue voluntary licensing of maraviroc in India, it is unclear whether VLs will be offered for other existing drugs patented in India (see Table 2). Furthermore, there has not been a substantial move by originator companies to offer VLs for patented ARVs to generic companies in countries like Brazil and Thailand, but South African generics have been recipients of a number of ARV VLs from different originator companies, including VLs for nevirapine and TDF.¹⁰⁹

Table 3. Patent applications filed and granted in India, Brazil, and Thailand for first- and second-line ARVs recommended by the WHO in 2009

ARV	Patent status in India	Patent status in Brazil	Patent status in Thailand
zidovudine (AZT)	No	No	No
lamivudine (3TC)	No	No	No
efavirenz (EFV)	No	Granted	Granted
nevirapine (NVP)	Patent application pending on extended-release formulation	No	No
tenofovir (TDF)	Divisional application pending for TDF, ester prodrug and combinations with LPV/FTC/EFV and EFV/FTC	Divisional application pending for TDF, patent application pending for combinations with LPV/FTC/EFV and EFV/FTC	Patent application pending for combinations with EFV/FTC
emtricitabine (FTC)	No	No	No
lopinavir (LPV) / ritonavir (RTV)	Divisional application pending for LPV/r tablet formulation	Patent granted for LPV + RTV soft-gel caps, patent application pending for LPV and two LPV + RTC tablet formulations	Patent granted for LPV, patent application pending for LPV + RTV soft-gel caps
atazanavir (ATV)	Divisional application pending	Granted	Patent application pending
ritonavir (RTV)	No	No	No

Source: Data from MPP Patent Status Database, <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs>

¹⁰⁶ In the case of triple-ARV FDCs (three medicines in one pill), a generic company may have to negotiate licenses with three different patent holders in order to manufacture one product.

¹⁰⁷ <http://www.medicinespatentpool.org/patent/search>.

¹⁰⁸ There could be more patents and applications than represented in the database; see the MPP's "Explanatory Notes on Patent Status Database for Selected HIV Medicines," which state, "The database provides information on the patents identified as the most important ones in relation to a specific medicine, but many other additional patents, possibly owned by different patent holders, related to new forms, new formulations or compositions, or to new manufacturing processes, may have been filed or granted" (Medicines Patent Pool, <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs/Explanatory-Notes>).

¹⁰⁹ Tahir Amin, "Voluntary Licensing Practices in the Pharmaceutical Sector: An Acceptable Solution to Improving Access to Affordable Medicines?," research paper for Oxfam, February 8, 2007, <http://www.docstoc.com/docs/23819033/Voluntary-licensing-practices-in-the-pharmaceutical-sector-An>.

Table 4. ARVs patented in India and potential for voluntary licensing

ARV patent in India	Originator	VL in India
abacavir (ABC)—pediatric composition	GlaxoWellcome	No
etravirine (ETV)	Tibotec	No
maraviroc (MVC)	ViiV (Pfizer)	ViiV indicates it is seeking manufacturing partners in India
MVC crystal form	ViiV (Pfizer)	ViiV indicates it is seeking manufacturing partners in India
raltegravir (RAL)	Merck & Co.	No
rilpivirine (RPV)	Tibotec	Yes: January 2011, to two manufacturing companies in India and one in South Africa
saquinavir (SQV) improved composition	Hoffmann-La Roche	No
saquinavir (SQV) oral dosage form	Hoffmann-La Roche	No

Source: Data from MPP Patent Status Database, <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs>.

As mentioned above, India permits patenting of novel therapeutics but not of drugs that show only incremental improvements compared to the original version. Of the first- and second-line ARVs on the MPP's patent search tool, 12 were discovered prior to 1995,¹¹⁰ and such versions of these ARVs are unlikely to be patented in India (no patent applications have been filed). However, in theory, new formulations (e.g., oral) or compositions (e.g., new chemical composition) of these drugs that show enhanced efficacy could be patented. For example, although saquinavir was originally patented in the UK in 1989 (and the original patent has since expired), patents on an improved composition and an oral-dosage form of saquinavir were granted in India in 2007 (see Appendix 5).

All of this suggests that the MPP could have a potential impact in eliminating barriers imposed by patents in the near term, depending on the importance of patented ARVs and the success of existing patent applications, and on whether the MPP adds value relative to direct voluntary licensing already under way (see section 2.3 for more discussion).

The MPP also proposes that all future manufacturers of ARVs make licenses available through the pool, so that new combinations and formulations can be quickly tested, developed, and manufactured by multiple generic companies (through nonexclusive licenses). There are several new, promising HIV drugs undergoing Phase II and III clinical trials (see Table 5). Of these, COBI and EVG have been licensed to the pool through the recent agreement with Gilead Sciences.

Specifically, the MPP's agreement with Gilead Sciences would allow for Indian manufacturers to produce TDF, COBI, EVG, and the fixed-dose Quad pill containing these three ARVs plus FTC. Through this license, these ARVs could then be exported and sold in many different LICs and some MICs (the *licensed territory*), depending on the drug in question.¹¹¹ Indian manufacturing licensees are not prohibited from supplying the ARVs covered under the license to other countries, outside of the licensed territory, that issue a compulsory license,¹¹² although according to the International Treatment Preparedness Coalition (ITPC) and the Initiative for Medicines, Treatment, and Knowledge (I-MAK),¹¹³ the license requires them to follow certain rules that are possibly onerous.¹¹⁴

¹¹⁰ See Medicines Patent Pool Patent Status Database: <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs>.

¹¹¹ "The Medicines Patent Pool / Gilead Licenses: Questions and Answers," question #13, Medicines Patent Pool, <http://www.medicinespatentpool.org/LICENSING/Current-Licences/Medicines-Patent-Pool-and-Gilead-Licence-Agreement/Q-and-A-Gilead-Licences#13>.

¹¹² James Love, "KEI Comment on the Medicines Patent Pool License with Gilead," Knowledge Ecology International, July 12, 2011, <http://keionline.org/node/1184> ("The new agreement between Gilead and the MPP contains some of the shortcomings of the earlier license, but not all of them. Most important, while the new licensing agreement excludes many countries in Asia and Latin America, it does not prevent licensees from serving these markets through production from countries outside of India, or from India when countries outside of the voluntary license issue a compulsory license. The licenses explicitly state that exports of medicines from India to other countries under compulsory licenses do not constitute a breach of the license."); also see questions #7 and #9 in "The Medicines Patent Pool / Gilead Licenses: Questions and Answers."

¹¹³ ITPC is a global network of community organizations, local nongovernmental organizations, researchers, and activists united to promote access to treatment for people living with HIV. I-MAK is a team of lawyers and scientists working to increase access to affordable medicines by challenging unmerited patents, increasing patent transparency, and reforming the patent system.

¹¹⁴ "ITPC and I-MAK Briefing Paper: The Implications of the Medicines Patent Pool and Gilead Licenses on Access to Treatment," International Treatment Preparedness Coalition and Initiative for Medicines, Access, and Knowledge, July 28, 2011, <http://www.i-mak.org/storage/ITPC%20-%20IMAK%20letter%20to%20MPP.pdf>.

Table 5. Selection of ARVs in Phase II and III clinical trials

Compound	Company	Class	Stage
Rilpivirine/TDF/FTC	Tibotec	FDC: non-nucleoside reverse transcriptase inhibitor (NNRTI) plus Truvada	Phase III
Elvitegravir (EVG)	Gilead	Integrase inhibitor	Phase III
Cobicistat (COBI)	Gilead	Pharmacokinetic enhancer	Phase III
Quad	Gilead	FDC: boosted integrase plus Truvada	Phase III
Dolutegravir (GSK1349572)	ViiV/ Shionogi	Integrase inhibitor	Phase IIb
GSK2248761 (IDX-12899)	ViiV	NNRTI	Phase II
UK-453061 (Iersivirine)	ViiV	NNRTI	Phase II
BMS-663068	BMS	Attachment inhibitor (gp120)	Phase II
Vicriviroc	Merck	CCR5 entry inhibitor	Phase II/3
Ibalizumab (TMB-355, was TNX-355)	TaiMed Biologics	CD4-specific humanized IgG4 monoclonal antibody	Phase IIb
Cenicriviroc (TBR-652)	Tobira	CCR5 entry inhibitor	Phase II
CMX157	Chimerix	NNRTI similar to TDF	Phase II

Note: May not be exhaustive.

Source: Polly Clayden et al., "2011 Pipeline Report," Treatment Action Group and i-Base, September 2011, <http://www.treatmentactiongroup.org/publication.aspx?id=4524>.

Licensees can license whichever drug they wish, irrespective of patent status, and pay 3 to 5 percent in royalties to Gilead.¹¹⁵ For example, although there are Indian patent applications pending, TDF currently remains unpatented in the country. Under the terms of the agreement, licensees do not have to license TDF to make the Quad pill¹¹⁶ but could do so in the future (at the lower 3 percent royalty rate) if the patent application goes through. Royalties are also waived for new pediatric formulations.¹¹⁷

While there are concerns about new ARV patents in India, Brazil, Thailand, and other developing countries with manufacturing capacity, the patent status of ARVs in LDCs may also impact access. A few experts raised concerns about new patent laws in LDCs, which are due to be enacted by 2016, as required by the TRIPS agreement.¹¹⁸ If LDCs do in fact grant patents to new ARVs after 2016, this could prevent the importation of generic versions of these ARVs from other countries. However, the date for TRIPS

compliance for LDCs may be extended, which could put off such concerns into the future. Some companies have clear policies to refrain from enforcing patents on LDCs, but other patent holders do not have such policies. The MPP could address these barriers if the voluntary licensing terms afford the manufacturer the rights to distribute ARV products in LDCs where the drug is patented.

Protection of data submitted for registration of pharmaceuticals—data exclusivity. Beyond patent protection, a few interviewees raised the concern that pressure from WTO members on India and other countries to enact so-called data exclusivity (DE) laws could result in an additional barrier to market entry for generic manufacturing companies. These laws generally seek to grant an additional level of IP protection to originator companies by preventing third-party access to clinical trial data submitted by originator companies during drug registration.¹¹⁹ In the absence of DE laws, or their

¹¹⁵ "Gilead Sciences–MPP License Agreement," Medicines Patent Pool, July 11, 2011, [http://www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+\(FINAL\)+08JUL11%5B2%5D.pdf](http://www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+(FINAL)+08JUL11%5B2%5D.pdf).

¹¹⁶ Krista Cox, "Medicines Patent Pool Agreement with Gilead Contains Flexibilities Including Termination Provisions and Severability of Licenses," Knowledge Ecology International, July 12, 2011, <http://keionline.org/node/1192>.

¹¹⁷ "The Medicines Patent Pool / Gilead Licenses: Questions and Answers."

¹¹⁸ Some already seem to enforce patents, and many have patent laws.

¹¹⁹ Joseph Alexander, "EU Still Pushing Data Exclusivity through FTA, India Stands Firm," Pharmabiz.com, 22 January 22, 2011, <http://safron.pharmabiz.com/article/detnews.asp?articleid=59448§ionid=44&Arch=a>.

enforcement, a generic company can seek authorization from the appropriate drug approval regulatory body by meeting its requirements.¹²⁰ With the enactment of DE laws, however, once an originator company has submitted original test data to a regulatory authority, no competing manufacturer is allowed to use this data for a period of time (5 years in the United States and 10 years in the European Union). In other words, generic companies would have to replicate clinical trials in order to gain product approval, unless the originator company waives DE rights. In practice, DE acts as a barrier to market entry (similar to monopoly protection) because of the high cost to generic companies of replicating trials. In addition to the financial burden of replication, rerunning a trial in which a control group would be withheld an effective treatment to “re-prove” its efficacy and effectiveness could pose ethical dilemmas as well.

The extent to which DE laws in developing countries will impact generic ARV development and production depends on a number of factors, including:

1. whether VLs or CLs would be able to override DE and
2. whether DE is extended beyond patent exclusivity (in the United States and Europe this is the case).

In recent years, there have been signs that the United States and the European Union have begun pushing for DE laws that would impact generic manufacturing of ARVs. Recent bilateral and regional free trade agreement (FTA) talks between the United States and developing countries¹²¹ have included negotiations of so-called TRIPS-plus provisions,¹²² which include both higher IP protection and adoption of DE. The EU is currently in bilateral trade talks with India and is likewise pushing for a number of measures, including an introduction of DE laws.¹²³ If DE provisions were used to block the registration of generically produced unpatented drugs that have already

received approval (licensure) from the Drugs Controller General of India (the Indian equivalent of the US FDA) or if DE extended the period of market exclusivity beyond the period under the patent, then their enactment would pose a new, additional barrier to ARV access.

However, a number of signs from the Indian government suggest that the more stringent DE provisions may not go into effect. A proposal by the Indian government for a 5-year DE, released in 2006, suggested a number of safeguards that could act to preserve generic ARV production in India, including an application to “new chemical entities only”; an exception for emergencies and public health crises; an exception for drugs of mass consumption, including those for HIV/AIDS, upon payment of a reasonable royalty; termination of exclusivity following a grant of a VL by the data originator; and termination of exclusivity upon patent term expiration.¹²⁴ If these safeguards are included and have terms that are defined appropriately (e.g., the meaning of the phrase “reasonable royalty”), then DE may not significantly impede the registration of generic ARVs in India. Moreover, the Indian government has recently announced that it is rejecting DE as part of the EU-India FTA negotiations.¹²⁵ This implies that the MPP may not need terms in its license to address a potential DE law in India.

Even if DE laws do not affect India, however, they may impact ARV product registration in other LICs and MICs. It is relatively safe to assume that if companies are willing to provide VLs, they are unlikely to enforce DE related to licensed products in licensed territories. But to avoid uncertainty on this issue, it would be beneficial for MPP licenses to directly grant rights that rely on or reference originator data for purposes of registration in the countries of export (e.g., India) and import.

The Gilead Sciences license agreement with the MPP deals with the issue of DE by legally requiring “Gilead to waive any data exclusivity rights that might apply, and prevent[ing]

¹²⁰ In other words, the generic company can rely on clinical trial data submitted to the drug approval regulatory body by the originator company as evidence that its own version of the drug is safe for human consumption.

¹²¹ The United States has concluded negotiations for FTAs with Australia, Bahrain, Chile, Central American countries, the Dominican Republic, Colombia, Jordan, Panama, Peru, Morocco, Oman, and Singapore. It is currently negotiating bilateral FTAs with South Korea, Thailand, Malaysia, the United Arab Emirates, and Ecuador, and attempted to pursue regional negotiations in southern Africa and the entire Western Hemisphere (Free Trade Area of the Americas).

¹²² Bryan C. Mercurio, “TRIPS-Plus Provisions in FTAs: Recent Trends,” in *Regional Trade Agreements and the TWO Legal System*, ed. Lorand Bartels and Federico Ortino (New York: Oxford University Press, 2006), 215–237.

¹²³ Vuyiseka Dubula and Nathan Geffen, “Concerns Regarding Indian Trade Negotiations with EU: Letter to the High Commissioner for India to South Africa,” Treatment Action Campaign and Section 27, June 30, 2011, <http://www.section27.org.za/2010/06/30/indian-trade-concerns/>.

¹²⁴ Brook Baker, “A Critical Analysis of India’s Probable Data Exclusivity / Data Compensation Provisions,” Health GAP, October 20, 2006, <http://www.health-gap.org/camp/novartis/India.doc>.

¹²⁵ “India Says ‘No’ to Policy that Would Block Access to Affordable Medicines,” Médecins Sans Frontières Access Campaign, June 22, 2011, <http://www.msfaccess.org/about-us/media-room/press-releases/india-says-no-policy-would-block-access-affordable-medicines>.

the licensee from applying for any such exclusivity.¹²⁶ Therefore, regardless of what emerges during negotiations between India and other countries on the issue of DE, such changes will not affect the ability of generic companies to produce ARVs sublicensed from the MPP under the MPP-Gilead agreement. Generic firms are also prohibited from enforcing DE.

Other potential barriers: Technology transfer and legal uncertainty. An additional potential barrier to the development and production of affordable ARVs is so-called technology transfer—the transfer of know-how related to manufacturing processes from the originator company to the generic manufacturer. Although the need for technology transfer varies widely by firm and country, as one expert pointed out: bare patent licensing is not sufficient for access. In order to manufacture a copy of an ARV, generic companies need to develop drug compound manufacturing processes and bioequivalence¹²⁷ testing (although this can be outsourced). Technology transfer for drug manufacturing is the process of transferring documentation and professional expertise (e.g., know-how and associated data) to another site capable of reproducing the process. Some generic companies have benefited from VLs granted by originator companies under which originator companies had an incentive to ensure that their licensees could actually produce the products. For example, Gilead Sciences has included technology transfer in its voluntary licensing agreements for TDF, enabling production of large volumes of high-quality generic versions of TDF.

Relative to other barriers, such as access to drug patents, lack of technology transfer may not be a major impediment in India since some generic manufacturers have routinely been able to reverse engineer ARVs without any transfer of knowledge from an originator company (e.g., Cipla manufactures TDF without technology transfer from Gilead Sciences). However, this could be a barrier to local production in some settings, such as in sub-Saharan Africa.

The importance of technology transfer may also vary depending on the drug or FDC in question. If the goal is to create the leanest, most efficient synthetic route possible for a drug, then technology transfer may be very important. Access to know-how and data could help reduce economic costs to generic production, as discussed in greater detail in section 2.3. The Gilead Sciences license agreement with the MPP allows for a one-time transfer of know-how related to the manufacture of TDF, EVG, COBI, and the Quad pill, addressing this potential barrier.

In addition to technology transfer, the current state of ambiguity about whether ARVs will be patented in India in the near future is itself a potential barrier for several reasons. Information on patent application status is very difficult to obtain in India, as the Indian patent database is still deficient. Even once patent information is available, freedom-to-operate (FTO) analysis can be costly.¹²⁸ A proponent of the MPP pointed out that it is often difficult to ascertain the patent status of new drug candidates during drug development. There may be hundreds of different patents around the world covering the drug candidate, and it would be an arduous process to determine whether the drug is patented in any given territory, since this information is neither disclosed by the company nor made readily available by the relevant LIC or MIC patent office. It is possible that without resources or expertise to determine their FTO, generic companies could abandon manufacturing ARVs simply because they do not want to risk infringement of a patent.

The MPP seeks to reduce uncertainty around patent status in several ways. First, it recently launched a patent search database, which attempts to make information on current and pending applications accessible and transparent (we used this database to construct the table in Appendix 5). Moreover, MPP licenses would make the terms of generic manufacturing clear at an uncertain time for the industry. Whereas Indian generic companies have reverse engineered and manufactured originator drugs with

¹²⁶ "The Medicines Patent Pool / Gilead Licenses: Questions and Answers," Medicines Patent Pool, <http://www.medicinespatentpool.org/LICENSING/Current-Licences/Medicines-Patent-Pool-and-Gilead-Licence-Agreement/Q-and-A-Gilead-Licences>. Further, "upon Gilead's or Licensee's request, Licensee or Gilead, as applicable, shall provide nonproprietary data that it perceives is reasonably necessary to obtain any such approvals, authorizations, permits or licenses. Licensee shall obtain, have and maintain all required registrations for its manufacturing facilities. Licensee shall allow appropriate regulatory authorities to inspect such facilities to the extent required by applicable law, rule or regulation. Gilead agrees to provide Licensee with NCE Exclusivity or other regulatory exclusivity waivers as may be required by the applicable regulatory authorities in order to manufacture or sell Product in the Territory, provided such manufacture and sale by Licensee is compliant with the terms and conditions of this Agreement" ("Gilead Sciences–MPP License Agreement," Medicines Patent Pool, July 11, 2011, [www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+\(FINAL\)+08JUL11%5B2%5D.pdf](http://www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+(FINAL)+08JUL11%5B2%5D.pdf), page 18).

¹²⁷ Center for Drug Evaluation and Research, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* (Rockville, MD: FDA, 2003), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>.

¹²⁸ An FTO analysis is carried out to determine whether a particular action, such as testing or commercializing a product, can be done without infringing valid intellectual property rights of others. An FTO search (also known as a clearance or infringement search) and associated clearance opinion or validity/enforceability opinion can cost upwards of \$100,000 in the United States.

relative impunity for many years, India's amended patent law changes this practice. Any originator company with a new drug can now apply for patent protection in India, and in fact, Gilead Sciences has applied for Indian patents for the pipeline drugs EVG and COBI (see Appendix 5). Although many critics may not agree with the specific licensing terms, the MPP agreement does clarify Gilead Sciences' intentions vis à vis the generic manufacturing of these drugs. In addition, the license agreement terms are publicly available,¹²⁹ which sets a precedent for transparency¹³⁰ and allows generic companies wishing to pursue production of the ARVs covered under the licenses to make plans and investment decisions based on the explicit terms of these licensing deals.

2.3 Comparison of MPP and direct voluntary licensing

In addition to analyzing whether the MPP can tackle key IP barriers to ARV innovation and access, it is important to understand the value of the MPP in light of other mechanisms that have similar goals. Notably, the use of direct voluntary licensing by several patent holders, including Gilead Sciences, ViiV Healthcare, and Tibotec (discussed earlier, in the background section), raises the question of whether there will be expanded support for VLs and whether the MPP would add value beyond what direct VLs already offer.

What is the future role of voluntary licensing?

Already several of the major ARV patent holders are offering bilateral VLs to a number of generic drug companies, for low or no royalties. But while there has been considerable uptake of VLs, only one originator company has granted VLs for a patented ARV to generic companies in India.¹³¹ There are some positive indications that suggest originator companies might become more inclined to use voluntary licensing in the future. Because some companies have had experience licensing to generic

companies, this may become a general business strategy for those who want to exploit emerging markets.

In general, originator companies seem to be more open to partnering with generic manufacturers than they were 10 years ago, since such partnerships provide certain advantages. Challenged by increasing financial constraints, these multinational companies are realizing that they can maximize profits by working with generic companies that have efficient manufacturing processes and lower production costs. In fact, more multinational companies are buying generic companies in India because of the profit potential of generic manufacturing. Indian generic manufacturers now represent a significant share of total pharmaceutical industry revenue—in some cases generic companies have a market capitalization of up to USD \$1 billion. One IP expert pointed out that firms seeking ARV drug approval from the FDA might also find it useful to work with generic companies. The US Pediatric Research Equity Act requires drug companies that are submitting a new drug application to conduct pediatric studies on the drug in question.¹³² Considering that generic companies have built up experience in developing and manufacturing FDCs for children, multinational companies may choose to partner with or license to generic companies and outsource some of this work required for drug approval in the United States.

During consultations, one IP expert suggested that the most reasonable solution to the problem of future patents would be for current and future Indian ARV patent holders to offer VLs to multiple Indian generic companies (and those of other MICs with manufacturing capacity) for the manufacture and sale of ARVs in India and other developing countries. Interestingly, this expert pointed out that, while Gilead Sciences and ViiV Healthcare are likely to continue to use VLs, and even potentially expand them, other companies that hold ARV patents (e.g., Abbott) are unlikely to do so because of differences in corporate culture.

It is also possible that VLs may be offered to deter governments from issuing CLs.¹³³ Yet some concerns remain that might deter companies from using VLs, which also presumably similarly affect their willingness to join the MPP. Patent holders are highly sensitive to problems with drug

¹²⁹ "The Medicines Patent Pool Announces First Licensing Agreement with Pharmaceutical Company," Medicines Patent Pool, July 12, 2011, <http://www.medicinespatentpool.org/LICENSING/Current-Licences/Medicines-Patent-Pool-and-Gilead-Licence-Agreement>.

¹³⁰ James Love, "KEI Comment on the Medicines Patent Pool License with Gilead," Knowledge Ecology International, July 12, 2011, <http://keionline.org/node/1184>.

¹³¹ Brook K. Baker, "ViiV Licenses vs. the Patent Pool: Unanswered Questions and Unwarranted Antipathy," Health Global Access Project, August 2, 2010, http://www.healthgap.org/trips/viiv_analysis.htm. ¹³² Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, "Guidance for Industry: How to Comply with the Pediatric Research Equity Act," draft, United States Food and Drug Administration, September 2005, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>.

¹³³ Tahir Amin, "Voluntary Licensing Practices in the Pharmaceutical Sector: An Acceptable Solution to Improving Access to Affordable Medicines?," research paper for Oxfam, February 8, 2007, <http://www.docstoc.com/docs/23819033/Voluntary-licensing-practices-in-the-pharmaceutical-sector-An>.

manufacture quality. Poor quality can lead to issues with drug safety and resistance, which are not only morally problematic but may also impact a company's brand image. Another concern patent holders have about voluntary licensing is the potential for unsanctioned reimportation of generic products from lower- or lower-middle-income markets into middle- or high-income markets. So far, however, this does not seem to be a major concern, as there is no evidence of widespread parallel importation of generic ARVs.

Overall, it seems likely that there will be an increase in uptake of direct VLs. Since the MPP in essence aims to combine several separate VLs into one pool, a number of these factors that foster a more enabling environment for VLs would likely also apply to the MPP. The question is whether the MPP can go beyond the status quo, by bringing into the voluntary licensing arena firms that have thus far been unwilling to do so, widening the scope of these licenses, and making it faster and easier for both originators and generic companies to reach agreements on these VLs.

ITPC and I-MAK also have concerns that through these licenses generic companies in India will have to pay royalties for unpatented medicines (e.g., TDF) (see Text Box 1). However, it should be emphasized that all four products licensed through this mechanism can be unbundled; in other words, they do not have to be licensed all together.¹³⁴ This means that generic companies can choose which ARVs to license and can continue to make unpatented ARVs without a license. Aurobindo, a recent

licensee of the MPP, is taking advantage of this unbundling feature of the MPP-Gilead licenses to manufacture the existing drug FTC as well as COBI, EVG, and the Quad pill. Generic companies also retain the right to be able to legally oppose any Gilead Sciences patent application in India (e.g., patent applications for TDF).

What are the incentives for originator and generic companies to join the MPP?

While the MPP and an independent VL are similar in many ways, key differences in regard to structure could make the MPP more or less attractive to originator and generic companies. What would be the advantage to patent holders to license to the MPP versus directly licensing to generic firms? And to what extent is the MPP a better approach for generic manufacturers?

This section deals with incentives for firms to join the pool, a requirement for the MPP to achieve its intended public health goals. The MPP's focus is to promote public health benefits, and while admirable, this intention is not sufficient: what matters is whether the MPP can make an important difference. A key determinant of the MPP's success and therefore its ability to achieve public health goals will be whether it offers advantages to both patent holders and generic suppliers over what they can achieve through bilateral deals.

Text Box 1. Objections to the MPP-Gilead agreement

The MPP has received strong criticism by civil society on the recent MPP-Gilead licenses. Notably, a recent response by ITPC and I-MAK made several strong objections to its licensing structure and governance in relation to achieving public health benefits. In particular ITPC and I-MAK took exception to the MPP's charging an administrative fee of 5 percent out of the 3–5 percent royalty rates paid to Gilead Sciences by generic companies (which equals 0.15–0.25 percent of the generic price).¹³⁵ There are concerns that this payment from Gilead to the MPP could undermine the credibility of the MPP to act as "negotiator for public health benefits"—but the total revenues to the MPP are quite small. The MPP calculated this fee to be in total about \$1,500 to \$30,000 in 2011–12, which is less than 1 percent of the MPP's annual budget.¹³⁶

The ITPC/I-MAK response also criticized the fact that the licenses for TDF are not restricted to HIV only but expand the field of use to hepatitis B. The civil society groups claim that this expansion promotes royalty revenue generation from fields of use that are currently unpatented, which they argue could inadvertently validate patents on new uses. According to the MPP, this move should be seen as positive because it expands the field of use, regardless of patent status. In addition, a VL for unpatented new uses cannot act to validate new-use patents, particularly in jurisdictions that have restrictions on such patents in the first place.

¹³⁴ Krista Cox, "Medicines Patent Pool Agreement with Gilead Contains Flexibilities Including Termination Provisions and Severability of Licenses," Knowledge Ecology International, July 25, 2011, <http://www.keionline.org/node/1192>.

¹³⁵ "The Implications of the Medicines Patent Pool and Gilead Licenses on Access to Treatment," I-MAK, July 25, 2011, <http://www.i-mak.org/storage/ITPC%20I-MAK%20-%20The%20Broader%20Implications%20of%20the%20MPP%20and%20Gilead%20Licenses%20on%20Access%20-%20FINAL%2025-7-2011.pdf>.

¹³⁶ Letter from the MPP to the boards of directors of ITPC and I-MAK, July 27, 2011 (MPP shared with the authors).

Geographic scope. In general, generic companies have shown enthusiasm for voluntary licensing. However, there are certain aspects of current direct voluntary licensing practices and the MPP that may be unattractive to generic companies. Generic companies make low margins on high volumes in the highly competitive ARV market. One IP expert interviewed for this study suggested that excessive competition within one country might make it difficult for some generic companies, and that they may need a broader geographic market scope, including middle-income market segments, in order to have a more sustainable business model. Multinational companies are interested in maintaining and expanding profits in emerging middle-income ARV markets in India and other MICs, and so they may want to preserve the geographic boundaries of their licenses. In other words, generic companies want a broad geographic scope for VLs, whereas originator companies want a limited scope.

Many of the VLs (described in section 2.1) restrict the geographic scope to LDCs and sub-Saharan Africa, with the exception of the original Gilead Sciences VL for TDF, Tibotec's VL for rilpivirine, and Bristol-Myers Squibb's VL for atazanavir, which included India. The ViiV Healthcare VL extends to 67 LDCs, which includes all of sub-Saharan Africa, but the company has unofficially indicated that India¹³⁷ is included in its geographic scope.

The previous Gilead Sciences VLs for TDF were for 95 developing countries (including India). The new MPP-Gilead licenses are for an additional 16 countries (a total of 111) for TDF and FTC, including MICs Indonesia and Thailand. Nine countries have been excluded from the MPP-Gilead license for COBI, and an additional 3 countries have been excluded from the EVG and Quad pill licenses.¹³⁸

The MPP-Gilead agreement is seen by some as an improvement over previous Gilead Sciences VLs in that it has a broader licensed territory and does not prohibit licensees in India from producing and selling final products and active pharmaceutical ingredients (APIs) to countries outside of the licensed territory that issue a CL. However, others argue that the geographic scope does not expand far enough and that it should be broadly extended to MICs with manufacturing capacity, such as Brazil and China.¹³⁹

Parallel to the MPP agreement, Gilead Sciences has granted additional "semi-exclusive" VLs for pipeline products (COBI and EVG) to preferred Indian generic partners with adjusted, higher royalty rates for a time-limited period in exchange for a pediatric development commitment. These licenses cover the sale of these ARVs in the nine developing countries that were excluded from pipeline products.¹⁴⁰ When deciding on the geographic scope for these additional licenses, Gilead Sciences operated on a country-by-country basis, considering both disease burden and income. The MPP could promote such conditional agreements to help to address the gap in geographic scope.

Access to active pharmaceutical ingredients. Another concern that was raised by one IP expert we interviewed is that restrictions in some VLs associated with buying the APIs for ARVs could affect the ability of the generic company (the licensee) to make affordable products. Some VLs, such as the previous Gilead Sciences VL, restricted licensees from purchasing APIs from a company not approved by Gilead Sciences. From the perspective of Gilead Sciences, this is to assure good-quality APIs, adequate volumes, and low-cost suppliers. From the perspective of the licensee, this may be an unnecessary restriction since the final ARV product will need to be approved for sale by FDA or WHO regulatory bodies, regardless of where the API is purchased.

The new MPP-Gilead agreement imposes similar restrictions, requiring the licensee to purchase APIs from a licensed Gilead supplier or another Indian licensee. In other words, Indian licensees cannot purchase APIs from other countries that have API manufacturing capabilities, such as China, Brazil, or Thailand. Public health advocates have raised concerns that this restriction on importing APIs could lower API manufacturing competition and in turn increase their cost. But Gilead has argued that, given the market dynamics for APIs, there is a threshold above which additional API manufacturers and more competition would not lead to reduced prices, so there is an advantage to encouraging a certain amount of volume from each supplier.¹⁴¹

Royalties. Royalty rates vary among VLs. Gilead Sciences' previous nonexclusive VL, for example, has a standard 5

¹³⁷ Brook Baker, "ViiV Licenses vs. the Patent Pool: Unanswered Questions and Unwarranted Antipathy," Essentialdrugs.org, August 2, 2010, <http://www.essentialdrugs.org/edrug/archive/201008/msg00001.php>.

¹³⁸ See the appendix of "The Medicines Patent Pool / Gilead Licenses: Questions and Answers," 7–8, <http://www.medicinespatentpool.org/content/download/490/2895/version/1/file/The+Medicines+Patent+Pool+Q%26A+Gilead+Licenses+Final.pdf>.

¹³⁹ "ITPC and I-MAK Briefing Paper: The Implications of the Medicines Patent Pool and Gilead Licenses on Access to Treatment," ITPC and I-MAK, July 28, 2011, <http://www.i-mak.org/storage/ITPC%20-%20IMAK%20letter%20to%20MPP.pdf>; James Love, "KEI Comment on the Medicines Patent Pool License with Gilead," Knowledge Ecology International, July 12, 2011, <http://keionline.org/node/1184>.

¹⁴⁰ See Question 16 of "The Medicines Patent Pool / Gilead Licenses: Questions and Answers."

¹⁴¹ At the Access to Essential Medicines in the Developing World meeting sponsored by Gilead Sciences, New York, August 23, 2011, Gregg Alton of Gilead Sciences noted that for every 50 percent increase in API volume, there is a 20 percent reduction in API cost.

percent royalty rate for the sale of TDF in LDCs and India. ViiV Healthcare has announced royalty-free VLs for the manufacture and sale of ARVs in LDCs, including sub-Saharan Africa, and possibly in India.

The MPP will negotiate rates with the individual patent holders. The MPP-Gilead license royalty rate is a range from 3 to 5 percent for TDF, COBI, and EVG in the licensed territories, whereas licenses are royalty free for pediatric medicines and the FTC component of any combination product.¹⁴² The NIH VL to the MPP for the rights to make, use, and have made, but not to sell, the ARV darunavir is a royalty-free, nonexclusive license.¹⁴³

The royalty rates offered through direct VLs and the MPP largely fall within a similar range. Since royalties are relatively low, firms are unlikely to be attracted to join the pool by its financial incentives. Direct VLs, however, might be more appealing since they may provide more flexibility for firms to negotiate and set royalty rates.

One way for companies to capture ARV profits in MICs while using voluntary licensing is through tiered royalties paid to originator companies by generic companies for the rights to sell ARVs in different countries and market segments. This is illustrated by Gilead's "semi-exclusive" VLs to certain MICs, outside the MPP agreement, in exchange for higher royalties. The MPP could consider tiered royalties for different geographic areas to incentivize other patent holders to join, while widening the overall geographic scope for generic companies.

Technology transfer. While lack of technology transfer is not a major barrier for the manufacture of generic ARVs (see section 2.2), the presence of technology transfer could provide an economic incentive to generic companies by lowering their manufacturing costs. As mentioned earlier, direct VLs can be beneficial to generic companies by facilitating technology transfer of knowledge associated with drug manufacture that otherwise might be proprietary. One expert we interviewed argued that one of the reasons why so many Indian generic manufacturers signed an agreement with Gilead Sciences, in the absence of an Indian TDF patent, was that the VL allowed for the transfer of knowledge associated with the manufacture of TDF.

Facilitating the development of fixed-dose combinations.

Often licenses for several patents are needed to develop an FDC.¹⁴⁴ Proponents of the MPP emphasize that the pool creates efficiencies as a one-stop licensing shop. They claim that the patent holder or the generic company interested in developing an FDC would have to negotiate with only one organization instead of multiple companies and would thereby reduce its transaction costs. According to MPP assumptions,¹⁴⁵ the pool could save an estimated \$195,000 per FDC (assuming 5 agreements for the same FDC and market rates for legal services) if the same FDC were sublicensed to 5 generic companies. These savings could increase to \$345,000 per FDC (per 5 agreements for the same FDC) if the pool receives pro bono legal services. While MPP proponents interviewed believe this would be a real saving to generic companies, these costs would only represent a small fraction of the potential Indian and global market earnings for such a generic product. It is also not clear how significant these savings will be in comparison with the overall costs the MPP incurs in negotiating confidentiality, liability, IP ownership, market segmentation, and the like among many partnerships. Moreover, it is possible that some generic companies would prefer to engage in bilateral negotiations and arrangements with patent holders rather than have the MPP act as an intermediary facility, especially if they are able to negotiate one-on-one agreements and find that the number of sublicenses the MPP offers creates a more competitive environment for them. On the other hand, the MPP could have greater negotiating power compared with one generic company alone.

Recognition. One expert interviewed claimed that originator companies are increasingly committed to improving their corporate social responsibility and therefore are more likely to engage in activities that promote their reputation in this regard. In joining the MPP, originator companies could benefit from positive public relations in ways that might trump direct voluntary licensing agreements. As noted earlier, the pool has received significant recognition and political attention compared with direct VLs, with endorsement from a number of organizations (e.g., the NIH, the WHO) and several government officials.¹⁴⁶

¹⁴² "Gilead Sciences–MPP License Agreement," Medicines Patent Pool, July 11, 2011, [http://www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+\(FINAL\)+08JUL11%5B2%5D.pdf](http://www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+(FINAL)+08JUL11%5B2%5D.pdf).

¹⁴³ "Public Health Service: Non-Exclusive Patent License Agreement," Medicines Patent Pool Foundation, September 20, 2010, <http://www.medicinespatentpool.org/content/download/214/1227/version/1/file/MPPF+Patent+License+Full+Executed+%28Sept+2010%29-NS.pdf>.

¹⁴⁴ Before drug patents were allowed in India, generic companies did not have to pay transaction costs to manufacture and sell ARVs because they did not need a license in the first place.

¹⁴⁵ The MPP would have 4 licenses to negotiate (3 with each patent holder and 1 with the generic company) for the first FDC. Subsequently it would have only 1 sub-license to negotiate for every additional generic company. Therefore if negotiating with 5 generic companies to make 5 of the same FDC, the MPP would have to negotiate 8 licenses instead of 15 (5 x 3).

¹⁴⁶ If the MPP does end up successfully increasing greater access to appropriate ARVs, membership in the pool could be used as a metric to calculate the access-to-medicine ranking of pharmaceutical companies. See Access to Medicine Index, <http://www.accessmedicineindex.org/>.

Other differences. The new MPP-Gilead agreement also establishes the right of the licensee (the generic company) to challenge Gilead patent applications—previous iterations of the Gilead license had included terms that precluded licensees from such action. This means that pre-grant opposition to ARV patent applications in India can be initiated or supported by generic companies. The MPP-Gilead agreement also allows the licensee to apply the patents listed in its appendixes to broader fields of use than previously allowed. For TDF, uses include both HIV and hepatitis B. For COBI and EVG, the field of use extends to uses consistent with labels approved by the FDA and other “applicable” regulatory authorities.

Will the MPP deliver better licensing terms?

Aside from incentives for generic and originator companies, a separate question is whether the MPP will be able to leverage its reputation as a neutral third-party intermediary pursuing public health goals to negotiate more favorable licensing terms for generic firms and LICs.

The mandate of the pool, as given by the board of UNITAID (a public health institution), is to negotiate licenses from a public health standpoint. Thus, issues like transparency, flexibilities in international IP agreements, expansion of geographic scope (a greater number of countries within the licensed territory than in other bilateral VLs), explicit waiver of any DE rights, the right of licensees to choose individual products through unbundling, and other such features of licenses negotiated by the pool are particularly important in evaluating its ability to make a real difference in terms of ARV access.

To illustrate, the MPP and generic firms differ in their interests for competitive supply. Generic manufacturers likely want fewer licensees to ensure some degree of market exclusivity—hence their desire to limit competition.¹⁴⁷ On the other hand, the MPP aims to sublicense ARV patents nondiscriminately to a number of generic companies in order to encourage competition and thus keep prices low. Under direct VLs, originator

companies have taken different approaches with respect to the number of licenses offered. Gilead Sciences broadly licensed TDF to 13 generic companies in India, whereas other originator companies have given VLs for their ARVs far more restrictively. Voluntary licensing to at least two companies is needed to foster competition,¹⁴⁸ but some ARVs and FDCs are produced by several generic manufacturers, suggesting that several VLs might need to be offered to realize significant ARV price declines via generic competition. For example, up to 7 companies in India are currently competing to make and sell generic versions of nevirapine.¹⁴⁹

A key difference between the MPP-Gilead agreement and previous VL agreements is the degree of transparency associated with the online publication of the full license terms.¹⁵⁰ Transparency helps with legitimacy and credibility of the pool, and this level of openness with respect to license terms is unprecedented. This move by the MPP and Gilead Sciences may promote a new era of VL transparency and scrutiny, leading to increased use of VL terms that promote public health objectives.

2.4 Discussion of the MPP

The MPP has acted as an amplifier of publicity and advocacy concerning the threat of future ARV patent barriers and has put significant public pressure on patent holders to join the pool. Of the 10 companies the MPP aims to recruit, 7 are already in formal licensing negotiations. While advocacy and pressure may work to convince them to join the pool, several experts claimed that it might be the threat of compulsory licensing that would provide more of an impetus to join.¹⁵¹ One expert consulted for this study suggested that the presence of the MPP could exert pressure on firms that have not considered voluntary licensing as of yet and could encourage them to engage in VLs. It is thus possible that a consequence of the MPP would be an expansion of direct voluntary licensing outside of, as well as inside of, the pool.

¹⁴⁷ In certain limited circumstances where there are very small markets with low-volume products (e.g., certain pediatric formulations), generic competition can paradoxically increase prices and the risk of supplier exit. Competition is a means to an end, not an end in itself, and in some circumstances the public sector may get a better deal by contracting with a single supplier.

¹⁴⁸ David Reiffen and Michael R. Ward, “Generic Drug Industry Dynamics,” *Rev Econ Statist* 87.1 (2005): 37–49; “Untangling the Web of Price Reductions: A Pricing Guide for the Purchase of ARVs for Developing Countries,” Doctors without Borders, July 2006, <http://www.doctorswithoutborders.org/news/hiv-aids/untangled.pdf>.

¹⁴⁹ “Untangling the Web of ARV Price Reductions: Drug Prices and Patent Status; Nevirapine,” Doctors without Borders, July 2011, <http://utw.msffaccess.org/drugs/nevirapine>.

¹⁵⁰ “Gilead Sciences–MPP License Agreement,” Medicines Patent Pool, July 11, 2011, [http://www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+\(FINAL\)+08JUL11%5B2%5D.pdf](http://www.medicinespatentpool.org/content/download/480/2847/version/1/file/Gilead-MPPF+Non-Excl+License+Agmt+(FINAL)+08JUL11%5B2%5D.pdf).

¹⁵¹ The MPP cannot apply for CLs, however.

Table 6. Potential advantages and disadvantages of the MPP (compared with direct voluntary licensing)

Advantages	Disadvantages
MPP could induce more originators to make their patents available to generic manufacturers via VLs.	Some originator companies may prefer to directly license as a way to explore other business opportunities with generic companies.
One-stop licensing shop could reduce transaction costs for both originators and generic manufacturers.	Originator companies resisting voluntary licensing may not join, limiting the number of patents available for generic manufacture of single and FDC ARVs.
MPP could lead to licenses that are more advantageous to generic companies (lower royalties, wider geographic scope, greater transparency of the licenses' terms and conditions).	MPP may not be able to negotiate licenses on behalf of generic companies that would lead to the development of important low-cost FDCs.
MPP could encourage lower prices by expanding voluntary licensing to additional generic manufacturers (e.g., those in MICs other than India).	
MPP may help manage large volumes of ARVs in MICs for originator companies by facilitating out-licensing.	
Publicity and recognition may appeal to some originator companies.	

Our analysis of the terms of the MPP and individual VLs suggests, however, that the MPP might not attract many additional originator companies to engage in voluntary licensing, beyond those like Gilead Sciences and Viiv who are already reaching VL agreements with generic manufacturers. Low or no royalty rates offered by both direct VLs and the MPP, according to its first two license agreements, imply that in terms of financial incentives originator companies will likely not find the MPP much more attractive than direct VLs. Furthermore, although Gilead will be in direct contact with the sublicensees under the recent MPP agreement, some companies may prefer to create and develop bilateral relationships with generic companies without an intermediary involved, allowing them to maintain control. While it may be transaction intensive to pursue direct conversations, one expert on drug manufacturing suggested that these companies may find other benefits such as possible business deals with generic manufacturers in emerging markets, potentially leading to other joint ventures and agreements. Under a direct relationship, the originators and their generic partners can also set the pace of licensing discussions and negotiations.

One proponent of the MPP noted that some multinational companies facing limited capacity to manage the large volume of ARVs needed in developing countries could benefit from the pool, which would facilitate out-licensing for them. The associated publicity and recognition from participating in the MPP could also be important to some originator companies, but there are some concerns that the recent criticism by civil society advocates in response

to the MPP-Gilead agreement could undermine this benefit and may even serve as a potential setback for ongoing negotiations.

The MPP has successfully enlisted its first two generic producers, Aurobindo and MedChem, but the pool has yet to clearly demonstrate that it is a more effective and efficient approach than the status quo for both originator and generic companies to reach agreements on VLs. Through the MPP, Aurobindo is able to leverage the unbundling feature to manufacture the existing drug FTC and the pipeline products COBI, EVG, and the Quad pill. But Aurobindo had already engaged in a previous bilateral VL with Gilead Sciences for TDF, so it may have been possible for Gilead to offer Aurobindo agreements for the other drugs through a future bilateral VL. While MedChem is new producer to the HIV field, its license agreement with the MPP is yet to be publicly disclosed.

From the perspective of generic manufacturers, the MPP could make it more efficient for them to develop FDCs, which require multiple licenses. At the same time, it remains unclear how important reduced transaction costs from a one-stop licensing shop, as proposed by the MPP, would be to these firms. Some generic firms that do not have the proper capacity and skill set to negotiate financial terms on their own may benefit from the MPP's acting as an intermediary, while others may prefer more control and flexibility to set their own terms. Technology transfer, which has been possible under current voluntary licensing initiatives, could lower the economic costs borne by generic manufacturers. By negotiating on behalf of

generic producers and leveraging its bargaining power, the MPP may need to push for an even wider geographic scope to attract additional generic producers.

From a public health perspective, too, the MPP could help drive down the cost of generic ARVs, singly and in FDCs, by bringing more generic manufacturers into the competitive space, as compared with the situation in which originator companies negotiate a series of individual VL agreements, as they have in recent years. The MPP has appropriately prioritized urgently needed ARVs for potential inclusion in the pool, such as the Quad pill, and COBI and EVG in single-drug form—all part of the MPP-Gilead agreement. Going forward, the MPP might focus its effort on recruiting other originator companies needed to

develop important FDCs, according to the WHO priority list for missing HIV/AIDS formulations.

Table 6 lists some of the potential advantages and disadvantages of the MPP. Further investigation on the relative importance of these factors and other business considerations to better assess the appeal of the MPP to both originator and generic firms and its potential success as an instrument to accelerate ARV access and innovation would be useful. At the same time, it is possible that some of these issues may be resolved on their own over the coming months as it becomes clear whether the MPP is able to garner support from several key originator companies as well as more generic companies.

Chapter 3. Barriers to Neglected Tropical Disease Drugs and the Pool for Open Innovation

In this chapter, we evaluate the potential for intellectual property (IP) barriers that might impede research and development (R&D) of and access to drugs for neglected tropical diseases (NTDs). In addition, we evaluate whether the Pool for Open Innovation against Neglected Tropical Diseases can address problems related to IP. For this part of the study we focus on a selection of NTDs, namely Chagas disease, leishmaniasis, human African trypanosomiasis (HAT), malaria, and tuberculosis (TB).

3.1 Background

Burden of disease and available drugs for NTDs

NTDs¹⁵² are a collection of bacterial, viral, and parasitic infections that are mostly endemic among poor populations in developing nations. About a billion people are infected with one or more of these diseases, leading to about 2.8 million deaths¹⁵³ and 140 million disability-adjusted life years¹⁵⁴ (DALYs) lost each year. The geographic distribution and burden of disease vary for each of these NTDs (see Table 7). While some therapeutic treatments for NTDs exist, they are often unavailable, ineffective, toxic, or inappropriately formulated. The rising concern over drug resistance among many of these NTDs intensifies the need for new drugs, formulations, and combination therapies.

Despite this need, R&D investment for NTD drugs has not been a priority for the private pharmaceutical industry, largely because these diseases lack an attractive market. Of the 1,556 new drugs marketed between 1975 and 2004, only 21 were indicated for NTDs.¹⁵⁵ According to the Global Funding of Innovation for Neglected Diseases (G-FINDER) report, only \$470 million was spent on drug R&D together for these diseases in 2009¹⁵⁶—a relatively small amount given the cost of drug development overall.¹⁵⁷ Of the NTDs, Chagas disease, leishmaniasis, HAT, malaria, and TB—the diseases of focus in this paper—received the lion's share, 92 percent of total drug R&D funding to NTDs, in 2009.¹⁵⁸ The share of funding going to drug R&D for kinetoplastids (leishmaniasis and HAT) was 15 percent, while malaria and TB each accounted for 38 percent.

Markets for NTD drugs

The limited ability of vulnerable populations in low- and middle-income countries (LMICs) to pay for NTD drugs creates significant barriers for private-industry investment. But some NTD drugs have the potential for a small, developed-world market that could provide incentives for pharmaceutical innovation. Chagas disease, for example, is prevalent in high-income countries (e.g., the United States) and upper-middle-income countries (e.g., Brazil, Mexico). In the case of TB, a small market for new first-line drugs exists in some developed countries, where TB affects marginalized populations. Travelers and military personnel from high-income countries that spend time in malaria-endemic settings are likely to be able to afford

¹⁵² For the purposes of this paper we are using the US Food and Drug Administration definition of NTDs, plus Chagas disease. See <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAActChapterVDrugsandDevices/ucm110316.htm>.

¹⁵³ Each year there are 1.7 million deaths from TB (12 percent associated with HIV infection), 1 million deaths from malaria, and 530,000 deaths from other NTDs combined.

¹⁵⁴ A DALY is the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. See http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/.

¹⁵⁵ Pierre Chirac and Els Torrelee, "Global Framework on Essential Health R&D," *Lancet* 367.9522 (2006): 1560–1561.

¹⁵⁶ Mary Moran et al., *G-FINDER 2010: Neglected Disease Research and Development; Is the Global Financial Crisis Changing R&D?* (London: Policy Cures, 2011), http://www.policycures.org/downloads/g-finder_2010.pdf; this amount does not include HIV drug R&D (\$28.5 million for developing country-specific drugs) and includes both public and private funding reported via the G-FINDER survey.

¹⁵⁷ There is significant debate concerning the actual costs of drug development. The cost of developing a drug in 2006 (using different methodology) has been estimated at \$98 million (Light and Warburton) to \$1.32 billion (inflation-adjusted estimate using \$802 million estimate by diMasi et al.). (Donald W. Light and Rebecca Warburton, "Demythologizing the High Costs of Pharmaceutical Research," *BioSocieties* 6 (2011): 34–50; Joseph A. DiMasia et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22.2 (2003): 151–185.) Further, the cost of drug development for NTDs is lower than most estimates since the cost of clinical trials in NTD-endemic settings is often lower than in developed countries.

¹⁵⁸ Mary Moran et al., G-FINDER 2010.

Table 7. NTD geographical distribution, treatment, and burden of disease

Disease/ parasite	Geographic distribution	Treatment options and issues	Estimated global prevalence and incidence (global burden) of disease
Chagas disease / <i>Trypanosoma cruzi</i>	Latin American countries (e.g., Brazil, Bolivia, Columbia). The United States also has an estimated 300,000 cases of the disease.	Benznidazole and nifurtimox: Both have severe yet temporary side effects and issues with drug resistance; are not effective for chronic symptomatic stages of disease.	Prevalence: 10 million ¹⁵⁹ Annual incidence: 40,000 Annual mortality: 11,000 (2004) DALYs: 0.7 million (2004) ¹⁶⁰
Visceral leishmaniasis / <i>Leishmania donovani</i>	60 countries. Of confirmed cases, 90% occur in India, Nepal, Bangladesh, Brazil, and Sudan.	Pentavalent antimonials: Still used despite toxicity and dramatic rates of drug resistance. Amphotericin B deoxycholate: Highly effective but toxic and must be delivered intravenously. Liposomal amphotericin B: Highly effective, less toxic than other drugs, but very expensive and must be administered intravenously. Miltefosine: First oral treatment available, highly effective, less toxic than other drugs, but results in teratogenicity in pregnant women. Paromomycin: Effective but must be administered intramuscularly.	Annual incidence: 0.5 million ¹⁶¹ Annual mortality: 50,000 ¹⁶² DALYs: 1.9 million (2004) ¹⁶³
Human African trypanosomiasis / <i>Trypanosoma brucei</i>	37 African countries. About 70% of infections occur in the Democratic Republic of the Congo.	NECT (nifurtimox- eflornithine combination therapy): Highly effective, but eflornithine must be delivered intravenously.	Reported number of cases annually: 10,000 (2009) ¹⁶⁴ Estimated number of cases: 30,000 (2009) ¹⁶⁵ DALYs: 1.7 million (2004) ¹⁶⁶
Malaria / <i>Plasmodium</i> species	Widespread in tropical and subtropical regions, including much of sub-Saharan Africa, Asia, and the Americas.	Artemisinin derivative combination therapies (ACTs): Recommended for treatment of malaria in most areas. Chloroquine: Still used in sub-Saharan Africa despite high rates of resistance.	Annual incidence: 247 million (2005) ¹⁶⁷ Annual mortality: 1 million (mostly children under five years old) ¹⁶⁸ DALYs: 34.0 million (2004) ¹⁶⁹
Tuberculosis / <i>Mycobacterium tuberculosis</i>	Widespread throughout developing countries: India and China bear one-third of the total TB burden.	DOTS (directly observed treatment, short-course), therapy: Isoniazid, rifampicin, pyrazinamide, and ethambutol (long treatment).	Prevalence: 14 million (2009) ¹⁷⁰ Annual incidence: 9.4 million (2009) Annual mortality: 1.7 million (2009) (An estimated 12% of incident cases occurred in patients who were HIV positive) DALYs: 34.2 million (2004) ¹⁷¹

¹⁵⁹ "Chagas Disease (American Trypanosomiasis): Fact Sheet No. 340," World Health Organization, June 2010, <http://www.who.int/mediacentre/factsheets/fs340/en/>.

¹⁶⁰ Peter J. Hotez et al., "Incorporating a Rapid-Impact Package for Neglected Tropical Diseases with Programs for HIV/AIDS, Tuberculosis, and Malaria," *PLoS Med* 3.5 (2006): e102, <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0030102>.

¹⁶¹ Philip Desjeux, "The Increase of Risk Factors in Leishmaniasis Worldwide," *Trans R Soc Trop Med Hyg* 95.3 (2001): 239–243.

¹⁶² *Control of the Leishmaniasis: Report of a Meeting of the WHO Expert Committee on the Control of Leishmaniasis, Geneva, 22-26 March 2010*, WHO Technical Report Series no. 949 (Geneva, WHO, 2010), http://whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf.

¹⁶³ WHO Regional Burden of Disease Estimates 2004. (Geneva, WHO, 2004), http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html.

¹⁶⁴ "African Trypanosomiasis (Sleeping Sickness): Fact Sheet No. 259," World Health Organization, October 2010, <http://www.who.int/mediacentre/factsheets/fs259/en/>.

¹⁶⁵ Ibid.

¹⁶⁶ WHO Regional Burden of Disease Estimates 2004. (Geneva, WHO, 2004), http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html.

¹⁶⁷ Roll Back Malaria, World Health Organization, and UNICEF, *World Malaria Report 2005* (Geneva: WHO, 2005), http://www.rbm.who.int/wmr2005/pdf/WMReport_lr.pdf.

¹⁶⁸ "Malaria: Fact Sheet No. 94," World Health Organization, October 2011, <http://www.who.int/mediacentre/factsheets/fs094/en/>.

¹⁶⁹ WHO Regional Burden of Disease Estimates 2004. (Geneva, WHO, 2004), http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html.

¹⁷⁰ "Tuberculosis: Fact Sheet No. 104," World Health Organization, November 2010, <http://www.who.int/mediacentre/factsheets/fs104/en/index.html>.

¹⁷¹ WHO Regional Burden of Disease Estimates 2004. (Geneva, WHO, 2004), http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html.

effective new antimalarial treatments such as artemisinin combination therapies, but these markets are relatively small and thus not very lucrative. Public-sector investment is therefore still needed to support product development efforts even for NTDs with some potential market return.

There are also dual-purpose drugs, which were developed for non-NTD diseases but turn out to have NTD indications. For example, amphotericin B, originally developed as an antifungal drug and sold in developed countries, is also useful for the treatment of leishmaniasis. Eflornithine was developed as an anti-facial hair treatment and has shown to be effective for HAT. Though the presence of profitable markets could help spur the development of these dual-purpose drugs, benefiting NTD patients, there is also a potential downside to this market pull; in order to protect their profits, companies may resist licensing their IP to another party to develop the NTD drug.

The NTD drug R&D landscape and the role of intellectual property

The NTD drug R&D landscape has evolved considerably in recent years and currently involves a number of different product developers working (in many cases together) on a large number of projects.

Traditionally, multinational pharmaceutical companies have carried out most NTD drug R&D. But their involvement in this area of R&D changed in the 1990s when many companies closed their infectious disease divisions. Looking to fill the gap in NTD drug R&D, new organizations known as product development partnerships (PDPs) have emerged over the last decade to develop products for neglected diseases. By 2005, five PDPs—Medicines for Malaria Venture (MMV), Global Alliance for TB Drug Development (TB Alliance), Drugs for Neglected Diseases Initiative (DNDi), Institute for OneWorld Health (iOWH), and the World Health Organization Special Programme

for Research and Training in Tropical Diseases (WHO/TDR)—accounted for 75 percent of all neglected disease drug R&D projects.¹⁷² These PDPs and another, Infectious Disease Research Institute (IDRI), were recipients of a total of \$177 million in drug R&D funding in 2009.¹⁷³

The treatment of patents and other forms of IP in NTD drug R&D has become complex in recent years. Pharmaceutical and biotechnology companies, universities, government institutes, and increasingly, PDPs own patents that cover NTD compounds, drug targets,¹⁷⁴ methods, processes, and “research tools,”¹⁷⁵ vital enabling technologies that support biomedical research. The classic business model for drug R&D consistently relies on a strong IP portfolio of compound and process patents, but with an increase in licensing and partnerships across NTD drug product developers, other forms of IP, such as trade secrets that may cover know-how,¹⁷⁶ data, and methods, have also become important.

Although PDPs typically partner with organizations that already have lead compounds or compound libraries (to screen for activity against NTDs), they are increasingly generating their own IP. PDPs have been effective in developing working agreements and relationships with partner organizations in TB, malaria, Chagas disease, leishmaniasis, and HAT R&D. Such agreements are likely to involve the transfer of IP associated with the development of NTD drugs. This suggests that for the most part they are able to negotiate access to patents needed to move forward with product development.

Smaller pharmaceutical and biotechnology companies are also pursuing the NTD drug R&D, both alone and in collaboration with PDPs. Some companies are sufficiently attracted to NTD markets for which there are strong commercial opportunities, while others are interested in parallel markets in developed countries that can support the NTD research. A number of other companies are contract research organizations. Biotechnology companies

¹⁷² Mary Moran, “A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need,” *PLoS Med* 2.9 (2005): e302, <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0020302>.

¹⁷³ Mary Moran et al., *G-FINDER 2010: Neglected Disease Research and Development; Is the Global Financial Crisis Changing R&D?* (London: Policy Cures, 2011), 81, http://www.policycures.org/downloads/g-finder_2010.pdf.

¹⁷⁴ A drug target is defined as a critically important molecule involved in a specific metabolic or signaling pathway of a disease condition or pathology.

¹⁷⁵ The US National Institutes of Health definition of research tools: “We use the term ‘research tool’ in its broadest sense to embrace the full range of resources that scientists use in the laboratory, while recognizing that from other perspectives the same resources may be viewed as ‘end products.’ For our purposes, the term may thus include cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software.” *Report of the National Institutes of Health Working Group on Research Tools* 3, NIH, <http://www.nih.gov/news/researchtools/>

¹⁷⁶ Know-how is the practical knowledge of how to do something, for example, how to do a specific experiment. It is tacit knowledge, which is difficult to transfer to another person by means of written instruction, or even through verbalization. One of the reasons for this is that sometimes researchers do not fully understand the value of the knowledge they possess, or even that they possess it at all. In the context of drug R&D, the transfer of know-how from one person to another is likely to require extensive periods of direct demonstration of the tacit knowledge, for example, demonstration of experimental intricacies of a compound screening method. On the other hand, data and methods associated with the drug R&D process (e.g., methods associated with a testing a compound library, or biochemical data for a particular compound) represent more explicit knowledge and are more codified compared with know-how.

typically have a different relationship to IP compared with large originator pharmaceutical companies and could be more protective of their IP, which is sometimes their most critical asset.

For large pharmaceutical companies, the traditional IP model has focused on internally derived IP, but in the last two decades the R&D model has switched to licensing a significant proportion of their IP portfolio from other organizations, especially for late-stage products.¹⁷⁷ Companies have reduced their R&D budgets¹⁷⁸ and have increasingly licensed IP from publicly funded researchers at universities to supply their R&D pipelines. This trend is largely due to the fact that under the US Bayh-Dole Act of 1980 universities were granted control of their inventions, thereby allowing them to generate considerable revenue from the licensing of their inventions to industry. Between 1988 and 2005, about 20 percent of priority¹⁷⁹ new molecular entity¹⁸⁰ applications evaluated by the US Food and Drug Administration (FDA) were associated with at least one academic patent,¹⁸¹ suggesting an increase in the numbers of patents granted to US universities following the Bayh-Dole Act.¹⁸² As a result of the rise in academic patenting, university technology transfer offices have been established to manage IP in ways that lead to revenue generation for both researchers and the university.

Closer ties with industry have also fostered new university-industry research partnerships,¹⁸³ and universities have begun to take on a more substantial role in drug discovery, in particular carrying out early “upstream” drug discovery research (target identification, lead discovery, and optimization). Sometimes universities contribute to preclinical research, while academic medical centers also play an important role in clinical trials during drug development. With increasing capacity to carry out early-stage R&D, universities and other public-sector institutions have become potential partners for PDPs. At the same time, other institutions have created robust NTD drug discovery centers or programs that operate independently.

3.2 The Pool for Open Innovation as a Solution to IP Barriers

The Pool for Open Innovation against Neglected Tropical Diseases, conceived and established by GlaxoSmithKline (GSK) and managed by BIO Ventures for Global Health (BVGH) since 2010, represents an open innovation initiative with the goal of increasing access to important NTD-relevant IP to facilitate drug discovery. In the following section, we consider whether those involved in NTD drug R&D experience issues with IP, and whether the pool is likely to counter potential IP barriers.

Pool origin and motivation

The Pool for Open Innovation against Neglected Tropical Diseases¹⁸⁴ aims to foster “innovative and efficient drug discovery and development by opening access to intellectual property or know-how in neglected tropical disease research.”¹⁸⁵ Andrew Witty, CEO of GSK, first announced the idea of a pool in February 2009 during a speech at Harvard Medical School. An official summary of the speech quotes him as follows:

IP’s primary objective is to incentivize and reward research. However, there are plenty of neglected tropical disease[s] where there is a severe lack of research. We need to see if we can use IP to help address that gap. One idea we are proposing is a Least Developed Country (LDC) Patent Pool for medicines for neglected tropical diseases. We would put our relevant small molecule compounds or process patents for neglected tropical diseases into the pool, allowing others access to develop and produce new products. The pool would be voluntary so as to encourage others to participate and any benefits from the pool must go in full and solely to LDCs.¹⁸⁶

¹⁷⁷ Deloitte and Thomson Reuters, *R&D Value Measurement: Is R&D Earning Its Investment?* (London: Deloitte, 2010), http://www.deloitte.com/assets/Dcom-UnitedKingdom/Local%20Assets/Documents/Industries/Life%20Sciences/UK_LS_RD_ROI.pdf.

¹⁷⁸ Daniel Cressey, “Pfizer Slashes R&D,” *Nature* 270 (2011): 154, <http://www.nature.com/news/2011/110209/full/470154a.html>.

¹⁷⁹ A Priority Review designation is given to drug applications to the FDA that offer major advances in treatment or provide a treatment where no adequate therapy exists. A Priority Review means that the time it takes the FDA to review a new drug application is reduced.

¹⁸⁰ A new molecular entity is, according to the FDA, a drug that contains no active moiety that has been approved by the FDA in any other application submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

¹⁸¹ Bhaven N. Sampat, “Academic Patents and Access to Medicines in Developing Countries,” *Am J Public Health*, 99.1 (2009): 9–17, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2636619/>.

¹⁸² David C. Mowery and Arvids A. Ziedonis, “Numbers, Quality, and Entry: How Has the Bayh-Dole Act Affected US University Patenting and Licensing?,” in *Innovation Policy and Economy*, ed. Adam B. Jaffe et al. (Cambridge: MIT Press, 2000), 1:187–220.

¹⁸³ Heidi Ledford, “Drug Buddies,” *Nature* 474 (2011): 433–434, <http://www.nature.com/news/2011/110622/full/474433a.html>.

¹⁸⁴ The pool uses the FDA’s definition of NTDs and therefore does not include Chagas disease. A proponent of the pool commented, however, that if an organization wanted to contribute Chagas disease patents to the pool, the pool’s administrators would be very interested in receiving them.

¹⁸⁵ “About the Pool: Project Mission,” Pool for Open Innovation against Neglected Tropical Diseases, BVGH, <http://ntdpool.org/pages/project-mission>.

¹⁸⁶ “Big Pharma as a Catalyst for Change: February 13, 2009, Speech to Harvard Medical School—Andrew Witty, CEO,” GlaxoSmithKline, <http://www.gsk.com/media/downloads/Witty-Harvard-Speech-Summary.pdf>.

During this speech, Witty called on other companies to add patents and make them available to researchers so that they could develop new drug products or formulations. He also acknowledged that the pool would be successful only if other firms joined.¹⁸⁷ GSK contributed 800 patents and patent applications on small molecules and their formulations, uses, and process of manufacture for NTDs (mostly malaria compounds).

GSK considers the pool as part of its three-pronged “open innovation” strategy to improve NTD drug R&D by increasing access to (a) patents, (b) compound data and know-how, and (c) research facilities. As a specific initiative, the pool is envisaged to provide access to patents and know-how but is also interconnected and synergistic with GSK’s other initiatives that promote this strategy. For example, to make compound data more available, GSK has released a large amount of data on 13,500 malaria compounds¹⁸⁸ to the public domain via the ChEMBL, Collaborative Drug Discovery (CDD), and PubChem databases. Of these compounds, 80 percent are proprietary, and proponents of the Pool for Open Innovation indicated these compounds would also be available via the pool. The Tres Cantos Medicines Development Campus located in Spain is an initiative addressing the third component of GSK’s NTD drug R&D strategy. It hopes to “provide a critical mass of knowledge and a drive for the discovery and development of desperately-needed new medicines for a number of neglected diseases, creating a truly world-leading facility that will stimulate research and collaboration in this critical area.”¹⁸⁹ The Pool for Open Innovation will help facilitate relationships with the Tres Cantos facility, bringing two components of the open innovation platform together. According to a spokesperson from GSK, any “open lab”¹⁹⁰ project with Tres Cantos must agree to the pool’s principles. Each open lab project at Tres Cantos disseminates some data into the public domain and any resulting patents arising from these projects will go into the pool. Tres Cantos can also play a role in facilitating partnerships that arise from the pool, by carrying out or assisting with product development (see below).

Interestingly, in an interview for *Inside Story*, Jon Pender, GSK’s head of government affairs, global access programs, intellectual property, and HIV, commented that the pool is not meant to be a panacea for NTD drug R&D and access, and that IP is not the main barrier to NTD drug R&D: “It’s not the reason that the research into neglected diseases wasn’t being done in the first place. The real reason is there are no commercial incentives to work in this area. What we hope is that by creating [the pool] and starting R&D, we can build momentum and attract financing and funding.”¹⁹¹

Pool structure and principles

The pool is governed by two core principles.¹⁹² The first is that therapeutics developed with pool patents and know-how must be those aimed at treating NTDs in humans, as defined by the FDA. According to this eligibility rule, the pool currently excludes R&D on HIV and Chagas disease drugs.¹⁹³ The second core principle is that resulting drugs will be licensed royalty free for sale in the world’s least developed countries (LDCs; as defined by the United Nations).¹⁹⁴ The territory of each license could extend to high- and middle-income countries, but at a minimum, sales in LDCs will be royalty free.

To become a pool contributor, an organization or individual must contribute IP to the pool. Pool contributors must ratify the two main principles above plus several others that govern the detailed workings of the pool. For example, the pool requires contributors to grant nonexclusive worldwide licenses to qualified participants “to research, develop, manufacture, and export therapeutics for NTDs for sales into LDCs under the patents that pool contributors chose to contribute (subject to the other limitations of the pool).”¹⁹⁵ In addition, contributors to the pool can “negotiate royalty rates beyond LDCs on a case-by-case basis.”¹⁹⁶ Contribution to the pool is to be voluntary, and pool contributors retain the ownership rights to their original IP. In an effort to create incentives for prospective pool licensees, improvements to inventions are owned by the innovator (as opposed to original IP holder).

¹⁸⁷ Mark Todoruk, “GlaxoSmithKline CEO Announces Price, Patent Initiatives for Poorest Countries,” *FirstWord*, February 13, 2009, <http://www.firstwordplus.com/Fws.do?articleid=5EF9B0BDC3954371AA6E3EDB4AFE5E8C>.

¹⁸⁸ A screen of 2 million compounds carried out at the GSK Tres Cantos Medicines Development Campus yielded 13,500 compound hits.

¹⁸⁹ “Tres Cantos Medicines Development Campus,” GlaxoSmithKline, <http://www.gsk.com/collaborations/tres-cantos.htm>.

¹⁹⁰ “GlaxoSmithKline’s Tres Cantos Open Lab for DDW R&D,” International Federation of Pharmaceutical Manufacturers and Associations, <http://www.ifpma.org/index.php?id=3855>.

¹⁹¹ Qudsiya Karrim, “Big Promises from Big Pharma,” *Inside Story*, January 9, 2010, <http://inside.org.au/big-promises-from-big-pharma/>.

¹⁹² “About the Pool: Core Principles,” Pool for Open Innovation against Neglected Tropical Diseases, BVGH, <http://ntdpool.org/pages/core-principles>.

¹⁹³ Don Joseph of BVGH indicated that BVGH is looking to include Chagas drugs as part of the pool (at the “Collaborative Innovation in Biomedicine” conference hosted by Cambridge Healthtech Institute in Philadelphia, April 4, 2011). Chagas disease was inadvertently omitted from the FDA list of NTDs for Priority Review Vouchers, which is the list that GSK originally chose to define the pool’s disease scope.

¹⁹⁴ See <http://www.unohrlls.org/>.

¹⁹⁵ See <http://ntdpool.org/pages/core-principles>.

¹⁹⁶ *Ibid.*

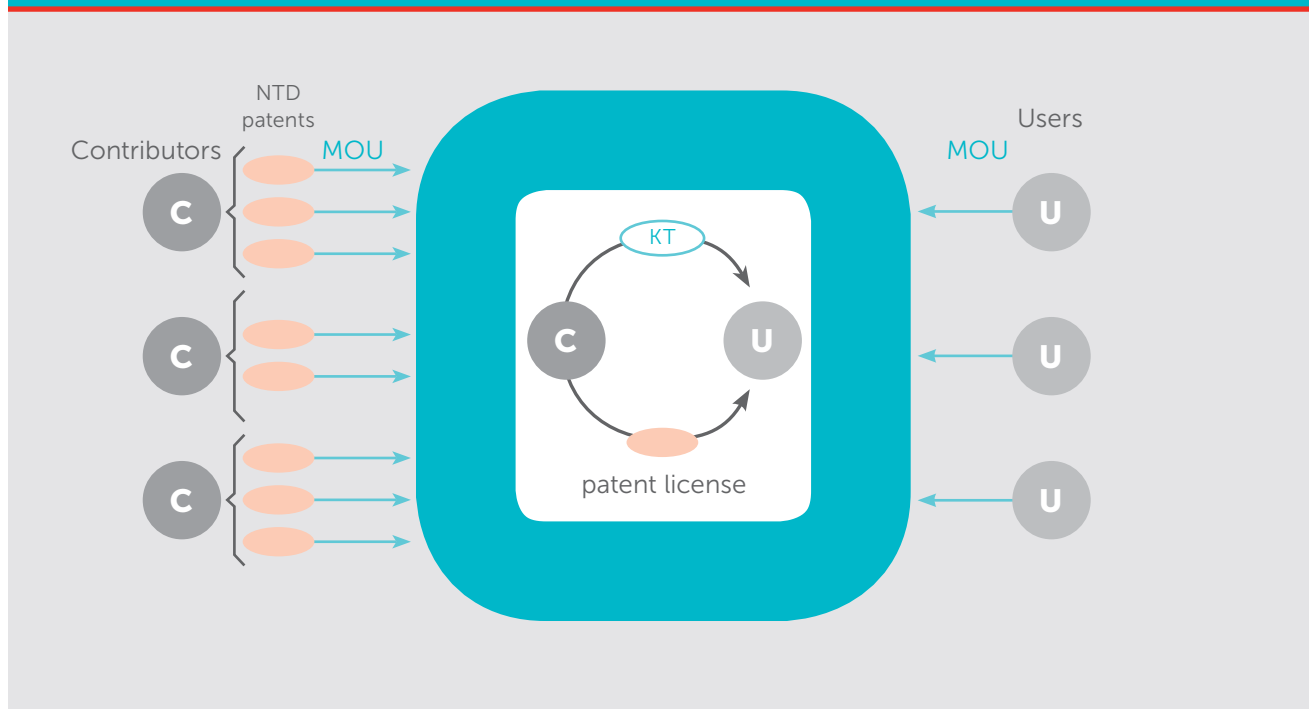
The pool requests contribution of IP related to compounds that have known activity against an NTD, technologies for drug target identification and validation, high-throughput screening, or complex dataset analysis and technologies for drug formulations or drug administration. So far, only patents have been contributed to the pool. In order to access or contribute patents and know-how in the pool, interested parties are requested to contact BVGH via an online registration form.¹⁹⁷ Most of the pool contributions are currently searchable¹⁹⁸ by keyword or patent number on the Pool for Open Innovation website.¹⁹⁹ For example, a search using the term “malaria”²⁰⁰ yielded 18 patents. Each patent citation links to a brief abstract and details of the countries in which patents have been filed and issued (although in some instances this information is not present because it was not provided to BVGH and therefore not contributed to the pool).

Users of the pool must sign a memorandum of understanding (MOU) that ratifies the core principles (see Figure 3). Other than this agreement, there are no

further requirements to define a user. Theoretically, a user interested in an IP contribution to the pool would sign a confidentiality agreement, indicating that the user is entering into a one-to-one relationship with the IP contributor. This might be followed by a material transfer agreement and an agreement that covers a research plan outline. Ultimately an agreement to license IP may be signed—according to BVGH this would be seen as one indicator of success of the pool. To date, there have been no license agreements reached on patents contributed to the pool.

The role of BVGH is to act as the nonprofit administrator of the pool; review and vet requests from potential users; and “assist in the smooth running of the pool,” which includes facilitating discussions of projects and licenses, handling inquiries from users and contributors, and administering the website and list of IP assets. In addition, BVGH is to “conduct extensive outreach to potential contributors and licensees of the pool” and will identify gaps in expertise and IP in NTD drug development.²⁰¹

Figure 3. How the Pool for Open Innovation works



¹⁹⁷ See <http://www.ntdpool.org/pages/search-register>.

¹⁹⁸ See <http://ntdpool.org/pages/search-the-pool>.

¹⁹⁹ Except for the Alnylam Pharmaceuticals patents. This is because Alnylam has an RNAi-platform technology and has contributed its entire IP portfolio around this technology.

²⁰⁰ Search was done on June 29, 2011.

²⁰¹ “How the Pool Works: Contributor FAQs,” Pool for Open Innovation against Neglected Tropical Diseases, BVGH, <http://ntdpool.org/pages/for-contributors/faqs>.

Table 8. IP Contributors to the Pool for Open Innovation

Contributor	Patents or other IP
GSK	GSK contributed patent families that cover small molecules and their formulations, uses, and process for NTDs. Researchers are invited to turn to GSK for know-how on projects where GSK may have expertise.
Alnylam	Alnylam has contributed more than 1,500 issued or pending patents from its RNAi patent estate and know-how.
MIT	MIT has contributed several hundred patents in the biomedical and biotechnology fields—research, drug delivery, target validation tools
UC Berkeley	UC Berkeley has contributed some patents and is reviewing its portfolio for future contributions.
MMV	MMV contributed IP around trioxolane antimalarials.
Caltech	Caltech contributed 7 patents, including 4 related to the detection and treatment of duplex polynucleotides damage. ²⁰⁶
Stanford	Stanford’s IP contribution is still being determined.

Source: Don Joseph, “Breaking IP Barriers to Accelerate Drug R&D: The Pool for Open Innovation against Neglected Tropical Diseases,” presentation at “Collaborative Innovation in Biomedicine,” Cambridge Healthtech Institute, Philadelphia, April 5, 2011.

Support for the Pool for Open Innovation

Contributors to the pool. While GSK’s primary intent was to receive contributions from pharmaceutical companies, the pool aims to be “open” and attract a variety of product developers, including academics, nonprofit researchers, and small biotechnology companies. Since its inception, a number of organizations have joined. In July 2009, the RNAi company Alnylam joined the pool, contributing its portfolio of 1,500 RNAi²⁰² patents and patent applications, which cover therapeutic approaches to RNAi technology (see Table 8).

Following the announcement that BVGH would administer the NTD pool, several universities contributed to the pool, including the Massachusetts Institute of Technology (MIT)²⁰³, Caltech, Stanford University, and the University of California, Berkeley (UC Berkeley).

Medicines for Malaria Venture (MMV), a PDP, joined the pool and contributed patents in August 2010.²⁰⁴ In a press release

announcing MMV’s joining the pool, Professor Patrick Nef, executive vice president for business development of MMV, stated the organization’s motivations:

Our contribution to the pool is in line with MMV’s commitment to allow any patents and technologies resulting from our R&D work, developing new, effective and affordable medicines for malaria, to be used for public good.²⁰⁵

Users of the pool. Emory Institute for Drug Discovery (EIDD) also joined the pool primarily as a user to access know-how and patents but is not yet contributing IP. Through a partnership with Tres Cantos, EIDD will have access to scientists, research reports, and all relevant data for the project. James Curren, Dean of Emory’s Rollins School of Public Health, publicly stated:

We applaud GlaxoSmithKline for creating this innovative knowledge pool, and we look forward to this outstanding opportunity to continue our contributions to diminishing the burden of neglected diseases in developing countries.²⁰⁷

²⁰² RNA interference (RNAi) is the introduction of double-stranded RNA into a cell to inhibit the expression of a gene. RNAi is also known as RNA silencing, inhibitory RNA, and RNA inactivation.

²⁰³ “Massachusetts Institute of Technology (MIT) Joins Pool for Open Innovation against Neglected Tropical Diseases,” Pool for Open Innovation against Neglected Tropical Diseases, BVGH, May 5, 2010, <http://ntdpool.org/news/releases/massachusetts-institute-technology-mit-joins-pool->

²⁰⁴ “Medicines for Malaria Venture Becomes First Product Development Partnership to Contribute Patents to the Pool for Open Innovation against Neglected Tropical Diseases,” Pool for Open Innovation against Neglected Tropical Diseases, BVGH, August 16, 2010, <http://ntdpool.org/news/releases/medicines-for-malaria-venture-becomes-first-develo->

²⁰⁵ “MMV Becomes First PDP to Make Its IP Freely Available for Neglected Disease Research,” MMV, August 16, 2010, <http://www.mmv.org/newsroom/press-releases/mmv-becomes-first-pdp-make-its-ip-freely-available-neglected-diseases-resear->

²⁰⁶ Contribution determined by searching the pool using “Caltech” as search term, <http://ntdpool.org/pages/search-the-pool->

²⁰⁷ “Emory Will Partner with GlaxoSmithKline on Drug Research for Neglected Tropical Diseases,” Emory University, January 20, 2010, http://healthnewsdigest.com/news/Research_270/Emory_Will_Partner_with_GlaxoSmithKline_on_Drug_Research_for_Neglected_Tropical_Diseases.shtml.

Other partners²⁰⁸ that have joined the pool as users include the University of California, San Francisco; Stanford University; the South African Technology Innovation Agency (TIA); and the South African biotech company iThemba.²⁰⁹ iThemba Pharmaceuticals is working on some of its own compounds against TB and malaria and is interested in using GSK's expertise, through the pool, to help move forward with product development. iThemba is involved in a three-way partnership with EIDD and GSK to develop drugs for NTDs.²¹⁰ TIA plans to make use of the pool's IP and know-how to foster growth of the South African biotechnology sector and to work on neglected tropical diseases.

Proponents of the pool noted that while some interested parties considered licensing patents from the pool, they have instead decided to work with the Tres Cantos Campus facility directly. For example, pool members TIA and iThemba will use this campus for training while testing some of the pool compounds.²¹¹

In our interviews, contributors to and users of the pool expressed a range of motivations for joining and perceptions on what membership could offer. Two members of the pool that we interviewed said that they did not have a comprehensive knowledge of the actual IP value in the pool. In one case a representative for a contributing institution noted that the institution did not have many NTD small-molecule patents to contribute but may have some in the future. Another organization that joined the pool noted that access to the patents had initially attracted it to the pool, but access to know-how is what it is most interested in.

IP barriers to NTD R&D and access

Access to compounds and patented subject matter.

Interviews with representatives of PDPs,²¹² which carry out a significant proportion of drug R&D for NTDs, revealed that for the most part, patents have not greatly impeded their R&D programs. This is largely because they have fostered fruitful relationships with pharmaceutical companies, other PDPs, government institutes, and universities, facilitating their access (through license agreements) to compound libraries and individual compounds of interest. In fact, one PDP stakeholder stated

that the PDP had many leads to follow up on and that funding was more of a barrier than IP.

As mentioned earlier, most NTD drugs are different from drugs that pharmaceutical companies invest in because they have little or no market. Firms have, on the whole, little reason to protect IP associated with these drugs. Patents are therefore less likely to be an obstacle to either drug development or access. There are certain situations, however, in which firms may be reluctant to license patented compounds for NTD drug R&D, notably in the case where IP holders want to protect profits from the sale of the drug either because it is an NTD drug that has profit potential or because it can be used for a non-NTD indication with a large market.

A TB drug R&D PDP stakeholder we consulted described a biotechnology company's refusal to license an interesting compound, following a year of negotiations.²¹³ The reason given was that the company expected a greater financial return from the licensing agreement than the PDP was prepared to offer. The company wanted the ability to keep all profits from the sale of this drug for either NTD or non-NTD indication and wanted assurance that it would be the owner of all improvements. The biotechnology company may have viewed the PDP simply as an R&D investor as opposed to an organization that undertook product development. In addition, the compound was the only asset that it had at the time and it did not want to take on additional risk related to the development of an NTD product. In general in the NTD drug R&D area, small biotechnology companies are likely to be more reluctant than large companies to license products for financial reasons, resources, and opportunity costs, because the smaller companies are less flexible and largely dependent on one or two research investment projects to provide returns.

A PDP representative involved in Chagas disease R&D stated that the PDP had experienced a difficult time in trying to license a patented compound from a company that had developed the compound as a drug for a non-NTD indication. The company never refused to license outright, but the two parties never reached a deal. The representative speculated that the reason for the difficulties was the IP holder's fear that if it agreed to such a license, further clinical trials for the NTD indication could reveal

²⁰⁸ "About the Pool: Partners," Pool for Open Innovation against Neglected Tropical Diseases, BVGH, <http://ntdpool.org/news/partners>.

²⁰⁹ Rianna Stefanakis and Don Joseph, "Pooling Knowledge for Neglected Diseases," *Genetic Engineering & Biotechnology News*, November 1, 2010, <http://www.genengnews.com/gen-articles/pooling-knowledge-for-neglected-diseases/3469/>.

²¹⁰ "iThemba Pharmaceuticals (Pty) Ltd Will Partner with GlaxoSmithKline on Drug Research for Neglected Tropical Diseases," press release, iThemba Pharmaceuticals, January 20, 2010, http://www.ithembapharma.com/ithemba_gsk_partnership_release.doc.

²¹¹ Linda Nordling, "Patent Pool Starts to Attract Interest," *SciDev.Net*, May 20, 2010, <http://www.scidev.net/en/news/patent-pool-starts-to-attract-interest.html>.

²¹² Interviews were conducted with MMV, The Global Alliance for TB Drug Development (TB Alliance), the Institute of One World Health (iOWH), and the Drugs for Neglected Diseases Initiative (DNDI).

²¹³ We did not interview the biotechnology company and therefore we have not reflected the firm's perspective.

toxicities that could jeopardize profits made from original markets for the drug in the developed world. While Chagas may have a small market, the major concern in this case was putting at risk the other, non-NTD market returns.

The presence of a profitable market may not be the only reason why PDPs experience difficulties obtaining access to the necessary IP for developing a neglected disease product. Differences in the business culture or the structure of licensing arrangements between PDPs and other product developers could prevent a deal. For example, one PDP representative described a situation in which the PDP had been unable to license a particular patented compound from a university institute because it was unable to meet the financial conditions set by the university technology transfer office (TTO). The TTO had an inflexible position—requiring up-front royalties on an unproven compound. This may reflect a general trend in negotiation inefficiencies as a result of TTO bureaucracy.²¹⁴ One PDP expert claimed that university TTOs could also be difficult to negotiate with because they are typically unwilling to license exclusively to PDPs if they are required to pay for the patent application and maintenance. During consultations, experts noted that universities and biotechnology companies are likely to overvalue their IP, which could make negotiations with PDPs protracted and potentially unsuccessful.

A few stakeholders interviewed suggested that the formation of the Pool for Open Innovation in general was a positive and interesting approach initiated by GSK and that it should be encouraged, but they said they were unclear about the value of the pool since patents currently available through the pool are likely to be of little importance to most product developers, especially PDPs. As noted above, patents for NTD drugs, except for those related to drugs that have a potential profitable market, are not currently seen as barriers by PDPs. Notably, two PDPs stated that they had already gained access to the GSK compounds in the pool that were relevant to them through their own negotiations. If BVGH expands the pool to include Chagas disease, it is possible that patents for drugs for this disease would be of value. Proponents of the pool have acknowledged that patents themselves are currently not likely to impede drug R&D for NTDs and that the focus of the pool has shifted toward improving access to know-how, which is a more fundamental barrier (see next section). However, BVGH is still encouraging the contribution of relevant NTD patents into the pool because such a contribution could offer an entry point for know-how contribution. It is possible that there are unknown interesting compounds that have been patented

by large pharmaceutical companies, biotechnology companies, or universities that would be good assets for PDPs to access via the pool.

While PDPs may have access to important IP for their portfolios and therefore have little interest in using the pool, BVGH has highlighted NTD researchers, particularly those at drug discovery centers at universities, as targeted users of the pool. This class of users is less likely to have access, contacts, or the ability to comb various sources for needed access. For these stakeholders, the pool could serve as an intermediary that acts to leverage connections with IP holders and potentially industry partners. Thus, the pool may play a more important role in fostering collaborations in this regard. It was outside of the scope of this paper to conduct extensive interviews with NTD drug researchers and survey the obstacles they face with regard to both IP and drug discovery in general. As the pool matures and these users become more prominent players, BVGH may want to undertake further analysis in this area.

Based on our interviews, the general lack of interest in specific patents in the pool may reflect not only the fact that PDPs already have full pipelines and access to the patented compounds they need but also how the contents of pool are currently communicated to the NTD research community. Most PDP and university stakeholders interviewed, including some organizations that had joined the pool, did not have a very good understanding of whether the compound patents or other inventions in the pool had value and whether the pool and its contents would be useful. This problem might be addressed as knowledge of the contents of the pool increases throughout the NTD R&D community. In an effort to communicate the value of the patents in the pool, BVGH recently launched a page on the pool's website called "Potential Projects"²¹⁵ which is designed to illustrate R&D possibilities and features a family of patents in the pool covering DNA gyrase inhibitors for TB.

Access to know-how and compound data. Two interviewees suggested that the potential benefit of the pool would have less to do with access to the patents and more with access to compound data and know-how. Rights to patents in the pool and associated know-how and other data are available only through licensing agreements with IP holders. Information about the patents is available through the pool (patents are public documents), but it is not possible to reveal what know-how or data would be available until an agreement is decided upon, which is likely to include confidentiality clauses.

²¹⁴ Donald S. Siegal et al., "Assessing the Impact of Organizational Practices on the Relative Productivity of University Technology Transfer Offices: An Exploratory Study," *Research Policy* 32 (2003): 27–48, <http://www.rvm.gatech.edu/bozeman/rp/read/30303.pdf>.

²¹⁵ "Search the Pool: Potential Projects—DNA Gyrase Inhibitors," Pool for Open Innovation against Neglected Tropical Diseases, BVGH, <http://ntdpool.org/pages/potential-projects>.

Several NTD researchers and PDP representatives suggested that one of the most important features of drug discovery and development was access to compound data and know-how. As one PDP stakeholder noted, these are the most valuable assets to share. Compound libraries are collections of compounds for which information (data) is known concerning the chemical structure and the chemical and physiological characteristics. High-throughput screening of a compound library yields detailed information about compound pharmacological activity against a particular disease target. Access to compound data such as compound structure, chemistry, and pharmacological activity is critical for early stages of the drug discovery process, in order to determine which compound(s) should be tested further. Similarly, the acquisition of know-how to initially screen and further test compounds is required for successful drug discovery. Some PDP stakeholders we interviewed called for a more open-access approach to this type of information in the context of NTD drug R&D. On the other hand, one PDP expert claimed that the PDP was regularly able to access what it needed with respect to compound data and know-how from partner organizations (mostly universities and nonprofits). One university expert at a drug discovery center expressed concern that the center could not access important compounds for screening because companies that owned them were concerned about sharing compound structure data. As a result of this, center personnel carry out the screening blind; once they determine which compound(s) has (have) activity against an NTD, then they move forward with a legal process to have the structure(s) disclosed.

There is an increasing interest globally in utilizing large, open compound databases such as ChEMBL for dissemination of NTD compound information. GSK has recently contributed data (chemical structure,

pharmacological activity, etc.) on 13,500 potential antimalarial compounds to the ChEMBL, PubChem, and CDD databases.²¹⁶ Over time, access to NTD compound data and other knowledge may improve for all stakeholders. The Pool for Open Innovation is different from these open data collaborative approaches in drug discovery (see Table 9) because it is set up to involve the transfer of patent rights and industry or university know-how. In this way the pool could complement open data platforms by filling in important knowledge and expertise gaps in drug discovery and by providing the freedom to operate regarding NTD patents.

One university expert at a drug discovery center who joined the GSK pool commented that access to know-how (via contact with scientists and access to research reports) and data associated with compound research, through the pool-mediated partnership with Tres Cantos, represented a very large benefit to the organization and its mission to develop NTD drugs. This expert also pointed out that if the organization makes new compounds, the Tres Cantos facility will be used to evaluate them.

Legal uncertainty. Patents are difficult documents to understand—even legally trained experts find it challenging to determine what a patent covers. Given their reduced access to in-house legal resources (compared with researchers at for-profit companies and PDPs), university researchers could find this situation to be a potential barrier, leading to legal uncertainty about whether a researcher has the freedom to operate in a given research area and perhaps curtailing an avenue of scientific inquiry out of fear of patent infringement. However, it is difficult to assess the extent to which lack of legal knowledge deters researchers from pursuing drug R&D for NTDs.

Table 9. Other examples of open innovation projects in NTD research

Open innovation project	Description
Open Source Drug Discovery (OSDD)	The project's open-source collaborative hub allocates small pieces of work involving open datasets to contributing TB researchers that in aggregate complete larger tasks related to TB drug discovery. Through this strategy OSDD has produced a browser and annotated map of the TB genome.
Tropical Disease Initiative	Data on possible drug–drug target binding pairs for seven tropical disease pathogens have been released under an open-source license.
CDD	CDD is a platform for selective sharing of collaborative drug discovery data, which allows preclinical biological and chemical drug discovery data to be shared, analyzed, and collaborated upon through a Web interface.

²¹⁶ "GSK Deposits 13,500 Anti-Malaria Compounds in EBI's ChEMBL," Genomeweb, May 21, 2010, <http://www.genomeweb.com/informatics/gsk-deposits-13500-anti-malaria-compounds-ebis-chembl>.

As discussed above, valuable information about the patents in the pool could become more accessible to stakeholders. Also, the core principles of the pool establish some common standards for licensing arrangements such as royalty-free licenses for LDC products. While the pool may help to uncover what patents exist in the NTD drug R&D landscape, it is not designed to decipher what the patent claims are and therefore would not address the issue of legal uncertainty.

Availability and affordability of NTD medicines. All PDP representatives discussed the importance of ensuring access (availability, affordability, and adoption) to the products developed by their organizations. Ultimately, PDPs need the freedom to operate to develop and produce inexpensive drugs that can be sold or distributed to poor populations in affected countries. They currently have a lot of leverage in this respect and have set precedents for their licensing strategies. They have employed a number of different access strategies depending on the situation, including owning the IP for a compound, allowing the company to retain the IP provided the company bears the related patent costs, and gaining royalty-free license for a patent to develop and distribute the NTD product.²¹⁷ As a result, PDPs for the most part do not face large hurdles when negotiating access terms with companies for NTD products.

University representatives also noted the importance of global access licensing strategies; however, we did not consult universities broadly on this issue. Universities are increasingly adopting licensing policies that attempt to ensure access to technologies for developing countries.

In general, the pool offers licensing terms that allow for flexibility and align well with the strategies PDPs have successfully implemented in their bilateral relationships with firms. One concern with the pool, however, has been its geographic scope and market segmentation. One of the PDP stakeholders interviewed raised the issue that availability of drugs resulting from the pool's licensing efforts would be primarily focused toward LDCs and that PDPs would like broader ability to produce products for middle-income countries (MICs) where there are

significant mixed-payer markets. The principles of the pool may be able to address this concern: While it offers royalty-free licenses for the sale of drugs in LDCs, licenses with tiered royalties could be negotiated through the pool for the sale of drugs in MICs. Negotiations are discretionary between the contributor and the user of IP for MICs and developed-world markets, if applicable.

3.3 Discussion of the Pool for Open Innovation

Our analysis suggests that the NTD patents that currently exist in the pool would be of limited value to PDPs and possibly to other product developers. For the most part, this is because PDPs we interviewed generally said that they know the landscape of existing IP that is relevant and useful for their projects and that they have been able to work directly with other IP holders to gain access to IP. In addition, because most of the IP that would help the PDPs to create NTD drugs has little commercial value, IP holders are generally willing to donate it or license it on a royalty-free basis. Under such circumstances, it is unclear that the Pool for Open Innovation brings much direct benefit to NTD technology development.

There may be a few exceptional circumstances in which access to patents via the pool could be useful, however. One would be a case in which there is a profitable market for a patented compound or technology,²¹⁸ either for the NTD or for a non-NTD indication. An example of the latter situation is the Chagas drug for which there is some commercial market in middle- and high-income countries, but Chagas disease is currently not eligible under the pool's criteria for NTDs. In these conditions, the Pool for Open Innovation could help in promoting voluntary licenses that would allow for use of the IP for products in low-income markets while protecting the IP holder's rights to commercialize drugs in other parts of the world.

Another situation in which the pool could be beneficial is in making it easier for academic labs, which have less knowledge of the patent landscape, to access patents, know-how, and data (and to contact IP holders

²¹⁷ PDPs involved in NTD drug R&D typically have an approach to licensing that promotes an access-oriented mission. The TB Alliance's mission includes "an explicit commitment" to the "AAA" strategy of adoption, availability, and affordability (see <http://www.tballiance.org/access/our-commitment.php>). DNDi's approach is to "negotiate terms with partners to ensure that they will not use the acquired and/or held IP in a manner that impedes equitable and affordable access to the products of the research, or that impedes additional or follow-on research by DNDi, its partners and other researchers, especially those undertaking research on neglected diseases," according to DNDi's comment on the consultation draft of this paper (<http://healthresearchpolicy.org/assessments/patent-pools-assessing-their-value-added-global-health-innovation-and-access>). The International AIDS Vaccine Initiative (IAVI) "works simultaneously to use IP to draw in the expertise of the private sector and to ensure that we can influence access strategically to honor our commitment to make any future AIDS vaccine available to the people who need [it] most, wherever they may reside." As such, it uses a variety of licensing arrangements, depending on the development phase of a particular product or product component, and the respective capabilities and contributions of IAVI and its partners. For further details, see the Global Health R&D Policy Assessment Center blog post "Using IP to Accelerate Product Development and Ensure Access" by Margaret McGlynn (<http://healthresearchpolicy.org/blog/2011/oct/11/using-ip-accelerate-product-development-and-ensure-access>, October 11, 2011).

²¹⁸ For example, biologics-platform technologies, which are increasingly becoming important for drug development, could have some commercial value. Using field- or territory-restricted licenses, the technology could be made available via the pool.

themselves) for product design and preclinical activities. The pool could provide an opening to discuss other IP not in the pool, which may be of interest to the NTD researcher. Other potential benefits of the pool include providing a centralized source, easily searched, with visibility on contributions.

For most interviewees, the value of the pool's current contents remains unclear. This could be because the contents of the pool were not sufficiently communicated, because there is a lack of understanding of how the pool operates, or because the value of certain contents can only be revealed to users once they join the pool and enter into facilitated discussions. In particular, the latter situation may be problematic for prospective users interested in understanding the value of know-how and data in the pool. As BVGH improves the communication of the contents and as more partnerships involving the exchange of IP are established, the value-added of the pool may become easier to assess.

Several proponents of the Pool for Open Innovation expressed disappointment about the lack of a strong, sustained movement of IP holders to contribute. The pool has garnered some support but there remains to be any direct licensing agreement for any patent in it. The pool has been easily searchable only since mid-2010, when the website was launched. Thus, more time may be required before a greater level of participation is observed and results emerge. It is possible that as more organizations become involved and a critical mass is created, the pool could gain currency.

It is not clear if there are strong enough incentives for industry to join the Pool for Open Innovation, especially since companies perceive little value in the LDC setting. In general, there is a fear that such projects may be a potential distraction, or even risk, to other commercial programs, and the lack of commercial markets for NTDs deters interest in the area. The pool may need to offer some financial incentives to attract IP contributors. Potential advantages to industry could include positive publicity and a chance to contribute to a socially responsible effort to find new health technologies for diseases affecting the world's poorest citizens.

In late October 2011, BVGH announced a new partnership with the World Intellectual Property Organization (WIPO), a specialized agency of the United Nations

focused on IP, and five pharmaceutical companies (Alnylam Pharmaceuticals, AstraZeneca, Merck, Pfizer, and Sanofi), plus a number of other nonprofit drug developers, recasting the Pool for Open Innovation as WIPO Re:Search.²¹⁹ There appear to be several important changes in design, including expanded scope (more diseases, plus vaccines and diagnostics as well as drugs). As with the Pool for Open Innovation, WIPO Re:Search continues to offer royalty-free licenses on future product sales in LDCs,²²⁰ but it also allows for the free use of IP for any R&D globally. BVGH's primary role will be to serve as a matchmaker between contributors and users of IP, data, and technical know-how.

The Pool for Open Innovation is an interesting experiment in trying to create an effective meeting place for a diverse set of organizations from around the globe who have the common goal of discovering and developing new drugs and vaccines for neglected diseases with modest or minimal markets. But it remains to be seen whether the opportunity to form partnerships in which IP, data, and know-how could be shared among two or more of these organizations will prove attractive enough for these parties to become actively involved in the pool's successor, WIPO Re:Search.

Moving forward, it will also be important for WIPO Re:Search, which is primarily focused on discovery and early-stage product development, to demonstrate its impact and success. How the new initiative measures its early performance could be an important way forward to enhance this type of open innovation approach. Possible metrics to estimate how successful the pool's approach is in opening up access to IP and knowledge to the upstream NTD drug R&D community include number and type of patent licenses, data exchange agreements, types of terms in such agreements (e.g., those that relate to geographic scope or royalties) and an indicator to measure the transfer of tacit knowledge (know-how) from one researcher to another. Finally, product development milestones could serve as more tangible metrics of R&D success as a result of the initiative, even though in the long run an evaluation of product accessibility (e.g., availability, affordability, and adoption)²²¹ in developing countries will be the ultimate test of the pool's value-added.

²¹⁹ Interviews and analysis for this study were conducted prior to the Pool for Open Innovation's changing to WIPO Re:Search, and thus our findings primarily focus on IP barriers for NTD drugs. For more information, see "Leading Pharmaceutical Companies and Research Institutions Offer IP and Expertise for Use in Treating Neglected Tropical Diseases as Part of WIPO Re:Search," WIPO, October 26, 2011, http://www.wipo.int/pressroom/en/articles/2011/article_0026.html.

²²⁰ "Least Developed Countries: About LDCs," United Nations Office of the High Representative for the Least Developed Countries, Landlocked Developing Countries and the Small Island Developing States, <http://www.unohrls.org/en/about/>.

²²¹ Laura J. Frost and Michael R. Reich, *Access: How Do Good Health Technologies Get to Poor People in Poor Countries?* (Cambridge: Harvard Center for Population and Development Studies, 2008).

4. Overall Conclusions and Limitations

4.1 Conclusions

Joint intellectual property management (JIPM) strategies such as the Medicines Patent Pool (MPP) and the Pool for Open Innovation against Neglected Tropical Diseases (Pool for Open Innovation) are novel approaches to address intellectual property (IP) barriers that exist for global health research and development (R&D) and access. Recently implemented, these two mechanisms are similar in that they encourage product developers to make their IP available in a “pool” and license it to others, for modest or no royalty payments, with the goal of facilitating drug innovation and access for developing countries.

However, there are important differences in the focus and objectives behind these two patent pools. The MPP aims to encourage “downstream”²²² development and manufacture of affordable antiretrovirals (ARVs), especially in fixed-dose combinations (FDCs), by securing a number of voluntary licenses (VLs). On the other hand, the main purpose of the Pool for Open Innovation is to increase access to neglected tropical disease (NTD) drug-related IP, including patents, know-how, and data, and to promote collaboration and knowledge transfer, thereby stimulating innovation for NTD drugs at an earlier, “upstream” discovery stage.²²³

In order for these two JIPM mechanisms to have impact, we conclude that they need to be tailored to resolve specific, identifiable IP barriers; create adequate incentives for product developers to contribute and seek useful IP; and add value, in terms of the number of promising candidates, their quality, and speed to a licensable product, as compared with other possible approaches or a counterfactual situation in which the patent pool does not exist.

Our analysis further suggests that IP and the rules governing it may be a significant barrier to the more rapid development and uptake of affordable health products for developing countries—but not in every case. Much depends on whether the specific health technology being pursued has a large commercial market opportunity. In that case, IP matters more, and patent pools that try to address this issue could make a positive difference.

When assessed against these criteria, we find that the MPP is designed to address real and significant IP barriers. Since there are substantial developed-world markets for AIDS drugs in the Organisation for Economic Co-operation and Development (OECD) and middle-income countries, the patent system in these countries has served as an incentive for the pharmaceutical industry to innovate ARVs but not necessarily at prices affordable to low- and middle-income countries. Less attention has also been given to the development of products that suit the specific needs of developing countries, such as pediatric doses and formulations, and FDCs of existing drugs. In the last decade, generic manufacturers have been able to fill this gap to a certain extent, but the new IP regime in India, which currently supplies the majority of generic ARVs, may be set to curtail these advances for new ARVs and may also lead to more expensive drugs. Through our consultations and research, we learned that there is a legitimate concern that patents granted in India and other countries with manufacturing capacity could block affordable development and production of new ARV treatments, in particular FDCs. We conclude that the MPP is appropriately designed to address key IP barriers related to ARV patents.

Since IP for HIV/AIDS drugs has considerable value for originator companies, a system in which such IP can be widely licensed to generic manufacturers for low-income and some middle-income markets, as soon as possible after the drug is registered in rich countries, would have significant public health benefits for the millions of people living with HIV in the developing world who need ARV therapy. In addition, such a system should make multiple ARVs available for generic manufacture so that FDCs can be produced. In this regard, the MPP has important potential, if it can be organized and implemented effectively and efficiently. But its success is by no means assured at this stage.

Under these circumstances, the question is whether the MPP can help to create such a system in ways that are significant improvements over the current situation in which several originator companies are already offering VLs, on a low- or no-royalty basis, to generic manufacturers in India and in some other developing countries. Our analysis suggests that the MPP could confer several potential advantages over the current practice

²²² In this case “downstream products” refers to combinations or formulations of already existing drugs. These products also need to receive approval from the appropriate regulatory authority; however, the approval process is not as lengthy as it is for new ARVs.

²²³ The MPP may move toward facilitating upstream drug discovery for new ARVs or also NTD drugs in the future.

with VLs, including: pressuring originator companies to contribute their IP to the MPP sooner than they would otherwise, reducing the transaction costs of licensing for both originators and generic manufacturers by serving as a one-stop shop, and lowering the price of generic ARVs by expanding the number of generic companies able to compete for single drugs and FDCs.

The MPP-Gilead license also points to the MPP's leverage in negotiating for better licensing terms from the public health perspective, including terms on issues such as transparency of licenses, use of flexibilities in international IP agreements, and expansion of geographic scope.

At the same time, the MPP may be challenged to live up to its promise due to several important factors. While recent agreements between the MPP and Gilead Sciences and two Indian generic producers may suggest that there is momentum building, it remains to be seen whether the MPP can obtain participation from a critical mass of originator and generic companies. One strategy for the pool would be to focus on enlisting a critical mass of companies needed to make new FDCs for several of the ARVs currently recommended by the World Health Organization (WHO).

Critics of the MPP-Gilead license argue that the geographic scope of the licensing agreement should be even wider, so that additional non-Indian generic producers are eligible and the resulting cheaper drugs can be sold in more middle-income countries.

It is also difficult to predict whether more originator companies will join the pool, beyond Gilead. Of the 10 target companies, 7 are currently in negotiations with the MPP. Similar to bilateral VLs, the MPP offers no or low royalties, thus making it difficult to attract companies based on financial incentives. Further, recent criticism by civil society organizations over the MPP-Gilead agreement may dampen interest from other companies, who were initially attracted to the public recognition benefit from participation but now anticipate that they could be at risk of criticism. In the end, the value of the MPP will also be diminished, particularly in the development of important FDCs, if some ARV patent holders, such as Abbot, who have hitherto been unwilling to do bilateral VL agreements also decide that they will not join the MPP.

In contrast, for NTDs, which typically lack a large market and require upstream scientific innovation for new drugs, patents appear to be less of a barrier, with a few exceptions. Our interviews with PDPs spearheading drug R&D for five NTDs, namely Chagas disease, leishmaniasis, human African trypanosomiasis (HAT), malaria, and tuberculosis, revealed that to a large extent patents have not impeded their pursuit of development activities. These organizations have been able to identify existing IP and

harness it, developing fruitful relationships, following up on leads, and successfully negotiating licenses with pharmaceutical and biotechnology companies and universities. For these PDPs, the main issue has *not* been the paucity of valuable IP for the drug candidates they are aiming to develop but rather the lack of funding. Thus, in the case of the Pool for Open Innovation, the argument for creating this mechanism to unlock existing IP for drug innovation is weaker, compared with the case for the MPP.

Our assessment of the Pool for Open Innovation suggests, however, that there may be special circumstances under which this strategy could be helpful in speeding innovation. Where there is a preexisting or potential commercial market for some NTD drugs, such as those for TB and Chagas, or for a dual-use drug (one that can be used to treat a disease that has a lucrative market and also an NTD), access to necessary patented compounds could be impeded, and the Pool for Open Innovation could therefore help to facilitate royalty-free or low-rate licensing, along the lines of what the MPP is trying to achieve. The pool may be more useful simply in bringing together large and small companies and nonprofit health technology organizations to form partnerships for licensing not only IP but also scientific know-how and data related to the discovery of drugs, as well as the bioengineering know-how required to develop and eventually manufacture new products.

The Pool for Open Innovation may also make it easier for academic labs dedicated to drug discovery to scan the landscape of IP, by providing a centralized source for IP, and to negotiate needed licenses for their work. This positive impact is yet unproven and needs to be monitored. In addition, through the pool, outside organizations and scientists may be able to use the GSK Tres Cantos "open lab" drug testing facility and access the expertise of GSK technical staff at Tres Cantos.

Interviewees engaging in upstream NTD drug discovery and development expressed the concern that the value of Pool for Open Innovation contents, such as patents and data, was unclear. This is something that the pool's new administrator, the UN's World Intellectual Property Organization (WIPO), could potentially address going forward if the costs of doing so are manageable. While there may be altruistic and public relations benefits that companies and nonprofit organizations can derive from donating IP to the Pool for Open Innovation, it is also difficult to envision any important economic incentives for them to participate, since the pool requires royalty-free licenses for LDCs.

In late October 2011, the Pool for Open Innovation underwent what seem to be important changes to its design and organization, resulting in WIPO Re:Search, a partnership between BIO Ventures for Global Health

(BVGH), WIPO, 5 pharmaceutical companies, and other nonprofit organizations. It is too early to assess whether this new initiative will be more successful than the original pool, but it may help to open the door for other forms of productive collaboration between nonprofit NTD researchers and pharmaceutical companies committed to some measure of philanthropic work in global public health. By creating a single, recognizable meeting place for health technology organizations from around the globe, and by supplementing this meeting place with active matchmaking by BVGH, WIPO Re:Search could promote the creation of partnerships that might not otherwise occur. The answer to the question of whether such partnerships will ultimately lead to new and better health technologies that save lives in low-income settings in most cases lies many years in the future.

Since both the MPP and the Pool for Open Innovation / WIPO Re:Search are relatively new, it will be important to closely monitor and measure the performance and impact of these two JIPM initiatives in the coming months and years. We hope that this paper can help to better explain the different goals behind seemingly similar “patent pool” proposals (e.g., the MPP’s goal of rapidly bringing down the cost of patented ARVs and spurring FDCs and new formulations, versus the Pool for Open Innovation’s goal of spurring innovation in novel drugs for neglected diseases with weak market demand); and that it can assist policymakers, R&D funders, and global health advocates in defining the criteria and the appropriate success metrics that should be used in judging prospectively and in real time the performance of proposed JIPM mechanisms.

4.2 Limitations and Further Research

We have identified a number of limitations of this study on IP barriers and JIPM strategies and have accordingly identified areas for further work. The study would benefit from more consultations with civil society organizations in developing countries. Further, consultations with generic and originator ARV companies were not carried out for this study, and a number of questions remain concerning their experience with IP barriers and their reactions toward the MPP.

Potential questions for generic companies and ARV access experts include:

- What are any drawbacks to joining the MPP compared with direct voluntary licensing?
- What specific objections would they have to the MPP-Gilead license?

- How would the geographic scope of the licensed territory affect their ability to sustainably supply ARVs to developing countries?
- How much of an economic difference would access to technology transfer make in the production of ARVs?
- How large of an economic benefit is the reduction in licensing costs associated with licensing components of an FDC from the MPP versus directly from each patent holder?
- Does the MPP negotiate terms on behalf of generic firms that would meet their needs to develop important FDCs?

Potential questions for originator companies include:

- What are the incentives to join the MPP compared with engaging in direct voluntary licensing?
- What are the drawbacks of the MPP?
- How geographically broad a licensed territory would they consider?
- What royalty rates do they consider reasonable for ARVs sold in developing countries?

We also did not carry out consultations with many university researchers, other nonprofit researchers, or biotechnology companies about their experiences with IP barriers and their attitudes toward the Pool for Open Innovation. In addition, it would be useful to interview large pharmaceutical companies to understand their interest in contributing IP to the pool and other strategies to improve NTD drug R&D.

Questions for universities, nonprofit researchers, and biotechnology companies about IP and NTD drug R&D include:

- Are there considerable patent or other IP barriers that impede their work and the development of NTD drugs?
- How important are know-how and data for their research or drug discovery and development strategy?
- What do they consider to be the main advantages of the Pool for Open Innovation against Neglected Tropical Diseases? How can the pool be improved to serve their needs?

Appendices

Appendix 1

Brief History of Patent Pools

An understanding of the history of patent pools, and what they set out to achieve, gives a sense of why joint intellectual property management approaches like the Medicines Patent Pool and the Pool for Open Innovation have been suggested in the first place. A conventional patent pool is formed by two or more patent holders who license their individual patent rights to each other, to third parties, or to an independent administrative agency.²²⁴ Although there are guidelines and significant litigation relating to patent pools in the United States (where most patent pools originated and where the majority are currently based), there is no formal definition of these arrangements, nor are there specific laws that govern them.²²⁵ The primary goals of patent pools in the 19th and early 20th centuries were to act as mechanisms to fix prices and create cartels;²²⁶ companies pooled their patents in order to reduce the possibility of competition from other companies.²²⁷ This led to heightened concerns about antitrust and anticompetitive conduct in the United States, and several court cases shut down these pools. Another very different kind of patent pool was set up during World War I by the US government to facilitate access to important intellectual property (IP) deemed necessary for the public interest. For example, in 1917 the US government created a patent pool by licensing groups of airplane technology patents from the Wright Company and the Curtiss Company, which would otherwise have blocked the production of affordable military airplanes. In order to acquire these groups of patents, the US government issued compulsory (mandatory) licenses that could not be refused by the IP holders.

Toward the end of the 20th century the information technology and telecommunications industries initiated a different type of patent pool, which was established with the goal of setting technology standards that would

promote the development and manufacture of consumer electronics (e.g., DVD, MPEG, and 3G patent pools). A larger number of patents, which were often overlapping and owned by many different patent holders, were often needed to develop these technologies. This type of patent pool had a goal of reducing transaction costs and inefficiencies resulting from multiple overlapping patents (patent thickets) to provide a convenient, one-stop-shopping approach to patent licensing and create a standard for technology production. All patents were placed in the pool voluntarily and an important feature of these pools was that they benefited all developers, which created an incentive to participate. In other words, the developers of these products came together to create a patent pool that was specifically designed for their needs but that also satisfied regulatory requirements.

In response to the rise of these new pools, the US government formed its antitrust regulatory position on these arrangements in a series of nonbinding guidelines.²²⁸ The Department of Justice (DOJ) and Federal Trade Commission (FTC) have developed an informal process to review any proposed patent pool before it is established to ensure that it does not raise antitrust concerns. According to the DOJ/FTC guidelines, in order to receive a positive review from the DOJ, patent pools must be procompetitive. To ensure competitiveness, all the patents in the pool must be valid (i.e., valid in the eyes of the US Patent and Trademark Office), essential (i.e., only patents required to make the product are allowed in the pool), and complementary (i.e., patents that achieve the same ends for technology production and are deemed highly similar are not allowed in the pool). In addition, patents in the pool must be licensed nonexclusively to third parties (i.e., not just to those who put licenses in the pool).

²²⁴ Jeanne Clark et al., *Patent Pools: A Solution to the Problem of Access in Biotechnology Patents?* (Alexandria, VA: US Patent and Trademark Office, 2000), <http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>.

²²⁵ Ed Levy et al., "Patent Pools and Genomics: Navigating a Course to Open Science?" *BU J Sci & Tech L* 16.1 (2010): 75–101, http://www.bu.edu/law/central/jd/organizations/journals/scitech/volume161/documents/Marden_WEB.pdf; David Serafino, *Survey of Patent Pools Demonstrates Variety of Purposes and Management Structures*, KEI Research Note 2007:6 (Washington, DC: Knowledge Ecology International, 2007), <http://www.keionline.org/misc-docs/ds-patentpools.pdf>.

²²⁶ David Serafino, *Survey of Patent Pools*.

²²⁷ By combining patents related to a particular technology, these companies created a patent thicket—a situation in which there are many overlapping patents. Imagine each patent is a piece of a fence; separately they do not block others from finding a way around the fence pieces. If the pieces of the fence are combined and overlap (meaning that certain claims may be shared by several patents), then they create an impenetrable barrier to anyone else interested in a particular technology sector. In this way, the combined intellectual property effectively blocks others from competing in the affected technology sector, meaning that the companies participating in the patent pool can also fix the prices of their products.

²²⁸ "Antitrust Guidelines for the Licensing of Intellectual Property," US Department of Justice and Federal Trade Commission, April 6, 1995, <http://www.justice.gov/atr/public/guidelines/0558.htm>.

Appendix 2

People interviewed for this study

Interviewee	Organization	Position
Gregg Alton	Gilead Sciences	Executive vice president, corporate and medical affairs
Tahir Amin	Initiative for Medicines, Access and Knowledge	Director of intellectual property
Sara Boettiger	Public Intellectual Property Resource for Agriculture	Managing Director
Pascale Boulet	Drugs for Neglected Diseases Initiative	IP & regulatory advisor
Tania Bubela	Department of Public Health Sciences, University of Alberta	Assistant Professor
Subhashini Chandrasekharan	Duke Genome Ethics, Law and Policy Center	Research Associate
Julie Cheng	Institute of OneWorld Health	General counsel & vice president business development
Charles Clift	Medicines Patent Pool	Chair of the board
Sylvie Fonteilles-Drabek	Medicines for Malaria Initiative	Business Development
Don Joseph	BIO Ventures for Global Health	COO
Dennis Liotta	Emory Institute of Drug Discovery	Director
Suerie Moon	Harvard School of Public Health	Instructor; Advisor to Medicines Patent Pool
Melinda Moree	BIO Ventures for Global Health	CEO
Lita Nelson	Massachusetts Institute of Technology, Technology Licensing Office	Director
Jean-Pierre Paccaud	Drugs for Neglected Diseases Initiative	Business development director
Jon Pender	GlaxoSmithKline	Director, government affairs, global access, IP & HIV/AIDS Issues
Molly Polen	BIO Ventures for Global Health	Communications Director
David Rosenberg	GlaxoSmithKline	Industry affairs manager
Inder Singh	Clinton HIV/AIDS Initiative	Executive vice president of access programs
Mel Spiegelman	The Global Alliance for TB Drug Development	CEO
Rianna Stefanakis	BIO Ventures for Global Health	Manager of research and policy
Mike Strange	GlaxoSmithKline	Research Scientist
Ellen 't Hoen	Medicines Patent Pool	Director
Geertrui van Overwalle	K.U. Leuven–Centre for Intellectual Property Rights	Professor
Richard Wilder	Bill and Melinda Gates Foundation	Associate general counsel
Paul Wyatt	Drug Discovery Unit, University of Dundee	CEO

Appendix 3

Indian Patent Law Section 3(b), 3(d)

The Patents Act 1970 Section 3(b)

Available online: <http://ipindia.nic.in/ipr/patent/patAct1970-3-99.html>

3(b) an invention the primary or intended use of which would be contrary to law or morality or injurious to public health;

The Patents (Amendments) Act 2005 Section 3(d)

Available online: http://ipindia.nic.in/ipr/patent/patent_2005.pdf

3. In section 3 of the principal Act, for clause (d), the following shall be substituted, namely:—

“(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation.—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;”.

Appendix 4

Pros and cons of the Medicines Patent Pool, from the perspectives of originator and generic companies

	Pros	Cons
Originator companies	<ul style="list-style-type: none"> • reputational benefits; • alignment with corporate social responsibility activities; • protection for patent holder’s intellectual property through agreement on standard terms & conditions of patent use; • collaborative middle ground to work together to scale up availability of essential medicines; • development of new products and potential risk sharing for new product development with third parties; • product quality assurance through license agreement terms; • royalty revenues from broader market reach through extended production and distribution; • reserved production capacity for higher-margin markets; • access to markets where marketing & distribution channels are limited; • voluntary licenses on equitable terms; • reduced licensing transaction & administration costs; • improved knowledge of distribution and supply channels in emerging markets. 	<ul style="list-style-type: none"> • the geographical scope of the licenses, in particular whether they will retain control of middle-income markets; • the scope of the licensed technology (e.g. diseases); • assurance of quality; • how clinical data would be dealt with; • parallel importation diversion; • grant-back for improvements; • whether the pool would be better than their current activities; • the pool could represent a “slippery slope” that would affect high-income market profits.
Generic companies	<ul style="list-style-type: none"> • legal certainty and avoidance of liability for patent infringement; • voluntary licenses on equitable terms and conditions; • potential access to new markets (products and geographic scope); • aggregated markets to ensure sufficient economies of scale; • facilitated access to patented technologies in a nondiscriminatory manner; • reduced licensing transaction & administration costs. 	<ul style="list-style-type: none"> • whether key patent holders would join the pool; • what the royalty terms would be; • what would be the extent of geographical scope of the licenses.

Source: “UNITAID Patent Pool Initiative, Implementation Plan—Executive Summary,” UNITAID, November 2009, http://www.medicinespatentpool.org/content/download/215/1231/version/1/file/ForWebsite_UNITAID_Patent_Pool_Implementation_Plan_-_Executive_Summary.pdf (see pages 16–17).

Appendix 5

Existing patents and patent applications for the 23 ARVs in the MPP Patent Search Tool

INN / Compound	Patent Holder	International patent application or patent of reference	Expected date of expiration	Brazil (last updated July 2010)	India (last updated Jan. 2011)	South Africa (last updated Dec. 2010)	Thailand (last updated March 2010)
Abacavir sulfate (ABC)	Wellcome (GSK)	WO9100282 EP0434450	2010	No	No	Yes	No
<i>New intermediates</i>	Wellcome (GSK)	WO9521161	2015	Granted	NA	Granted	Granted
Hemisulfate salt	Wellcome (GSK)	WO9852949	2018	Yes	Withdrawn	Granted	NA
<i>Composition for pediatric use</i>	Wellcome (GSK)	WO9939691	2019	Rejected— under appeal	Granted	Granted	NA
Atazanavir (ATV)	Novartis (BMS)	WO9740029	2017	Granted	Withdrawn but div. applic. pending	No	Yes
<i>Bisulfate salt</i>	BMS	WO9936404	2018	Rejected	NA	Granted	No
Use in HIV therapy	BMS	WO03020206	2022	Lapsed	NA	Granted	NA
<i>Process</i>	BMS	WO2005108349	2025	Yes	Rejected	Granted	Yes
Cobicistat (GS-9350)	Gilead	WO2008010921	2027	Designated in int. applic.	Yes	Designated in int. applic.	NA
<i>Cobicistat (GS-9350)</i>	Gilead	WO2008103949	2028	Designated in int. applic.	Yes	Designated in int. applic.	NA
Cobicistat (GS-9350)	Gilead	WO2009008989	2028	Designated in int. applic.	Yes	Designated in int. applic.	NA
Darunavir (DRV)	Searle, Monsanto	WO9404492	2013	No	No	No	NA
Specific	Searle	WO9628464 WO9628465	2016	Granted	NA	No	NA
<i>Method of use</i>	US Gov	WO9967417	2019	No	No	No	No
Combination with RTV	Tibotec	WO03049746	2022	Yes	Rejected but div. applic. pending	Granted	NA
<i>Pseudopolymorph</i>	Tibotec	WO03106461	2023	Yes	Rejected following pregrant opposition	Granted	NA
Prep. of key intermediates	Tibotec	WO2005095410	2025	Yes	Rejected following pregrant opposition	Granted	NA
<i>Combination with RTV & TDF</i>	Tibotec	WO2006005720	2025	Yes	Withdrawn	Granted	NA
Didanosine (ddl)	US Gov (BMS)	WO8701284	2006	No	No	No	No
<i>Improved oral formulation</i>	BMS	US5880106	2012	No	No	Granted	Withdrawn
Enteric-coated	BMS	WO9961002	2018	Granted	NA	Granted	Yes
Efavirenz (EFV)	Merck (MSD, BMS)	WO9403440	2013	Granted	No	Granted	Granted
Elvitegravir (EVG) (GS 9137)	Japan Tobacco (Gilead)	WO2004046115	2023	Yes	Yes	Granted	NA

INN / Compound	Patent Holder	International patent application or patent of reference	Expected date of expiration	Brazil (last updated July 2010)	India (last updated Jan. 2011)	South Africa (last updated Dec. 2010)	Thailand (last updated March 2010)
<i>Crystal form</i>	Japan Tobacco (Gilead)	WO2005113508	2025	Yes	Yes	Granted	Yes
Improved pharmacokinetics w/RTV	Gilead & Japan Tobacco	WO2007079260	2026	Yes	Yes	Granted	NA
Emtricitabine (FTC)	IAF Biochem	EP0382526	2010	No	No	Granted	No
Emtricitabine (FTC)	Emory Univ. (Gilead)	WO9111186	2011	Rejected—under appeal	No	Granted	No
Etravirine (ETV)	Janssen (Tibotec)	WO0027825	2019	Yes	Granted	Granted	NA
Novel series	Tibotec	WO2006094930	2026	Yes	Yes	No	NA
<i>New forms</i>	Tibotec	WO2006079656	2026	Yes	Yes	No	NA
Fosamprenavir (FPV)	Vertex (GSK)	WO9933815	2018	Rejected—under appeal	Yes	Granted	Yes
<i>Calcium salt</i>	GSK	WO0004033	2019	Rejected—under appeal	NA	Granted	NA
Indinavir (IDV)	Merck	WO9309096	2012	Rejected	No	Granted	Withdrawn
Lamivudine (3TC)	IAF Biochem GSK	EP0382526	2010	No	No	Granted	No
<i>Crystal form</i>	IAF Biochem GSK	WO9221676	2012	No	No	Granted	No
<i>New formulation</i>	IAF Biochem GSK	WO9842321	2018	Granted	Yes	Granted	NA
Lopinavir (LPV)	Abbott	WO9721685	2017	Yes	NA	Granted	Granted
<i>LPV + RTV soft-gel caps</i>	Abbott	WO9822106	2017	Granted	Withdrawn	Granted	Yes
<i>LPV + RTV tablet formulation</i>	Abbott	WO2005039551	2024	Yes	Rejected but div. applic. pending	Granted	NA
<i>LPV + RTV tablet formulation</i>	Abbott	WO2006091529	2026	Yes	Yes	Granted	NA
Maraviroc (MVC)	Pfizer	WO0038680	2019	Yes	Granted	Granted	NA
<i>Crystal form</i>	Pfizer	WO0190106	2021	Yes	Granted	Granted	Yes
Nevirapine (NVP)	Boehringer Ingelheim	EP0429987	2010	No	No	Granted	No
<i>Hemihydrate formulation</i>	Boehringer Ingelheim	WO9909990	2018	Rejected	Rejected	Granted	Yes
<i>Extended-release formulation</i>	Boehringer Ingelheim	WO2008154234	2028	NA	Yes	Granted	NA
Raltegravir (RAL)	Institute for Research in Mol. Biology, Italy, MSD	WO03035077	2022	Yes	Granted	Granted	No
Potassium salt	Institute for Research in Mol. Biology, Italy, MSD	WO2006060712 WO2006060730	2025	Yes	Yes	Granted	Yes
Rilpivirine (TMC 278)	Tibotec	WO03016306	2022	Yes	Granted	Granted	No
Ritonavir (RTV)	Abbott	WO9414436	2013/ 2014	No	No	No	No
<i>Crystalline polymorph</i>	Abbott	WO0004016	2019	Rejected—under appeal	Opposed	No	Yes
Saquinavir (SQV)	Hoffmann-La Roche	EP0432695	2010	Rejected	Expired	Granted	Expired

Appendix 5. (continued)

INN / Compound	Patent Holder	International patent application or patent of reference	Expected date of expiration	Brazil (last updated July 2010)	India (last updated Jan. 2011)	South Africa (last updated Dec. 2010)	Thailand (last updated March 2010)
<i>Improved composition</i>	Hoffmann-La Roche	WO9639142	2016	Granted	Granted	Granted	Granted
Oral dosage form	Hoffmann-La Roche	WO2005004836	2024	Yes	Granted	No	Yes
SPI-452	Sequoia Pharmaceuticals	WO2008022345	2027	Designated in int. applic.	Designated in int. applic.	Designated in int. applic.	NA
Stavudine (d4T)	Yale Univ. (BMS)	EP0273277	2007	No	No	Expired	No
Tenofovir (TDF)	Gilead	WO9905150	2018	Rejected but div. applic. pending	Rejected but div. applic. pending	No	No
Ester prodrug	Gilead	WO9804569	2017	No	Rejected but div. applic. pending	No	No
<i>Combination with LPV, FTC, EFV</i>	Gilead	WO2004064845	2024	Yes	Rejected but div. applic. pending	Granted	NA
Combination with EFV + FTC	Gilead & BMS	WO2006135933	2026	Yes	Yes	Granted	Yes
Zidovudine (AZT)	Glaxo Wellcome	US4724232	2006	No	No	Granted	Expired
AZT + 3TC	Glaxo Wellcome	WO9220344	2012	No	No	Granted	No
<i>AZT + 3TC tablet formulation</i>	Glaxo Wellcome	WO9818477	2017 (officially withdrawn)	Withdrawn	Withdrawn	Granted	Withdrawn

Notes	
INN	international nonproprietary name
Yes	A patent application has been filed in this country.
No	A patent application has not been filed in this country.
Designated in int. applic.	The country has been designated in the international application filed under the World Intellectual Property Organization (WIPO) Patent Cooperation Treaty (PCT).
Withdrawn	A patent application was filed in this country and then withdrawn.
Rejected	The patent application was rejected in this country.
Granted	The patent application was granted in this country.
Rejected but div. applic. pending	The original patent application was rejected, but another application based on the previous application is filed. The divisional application may retain its parent's filing date and will generally claim the same priority date.
Rejected—under appeal	The patent application was rejected, but the decision is being appealed by the company that submitted the application.
NA	No information was available.
Expected date of expiration	Except where otherwise specified, the table provides for the expected expiry date of the relevant patents, based on a 20-year term from the filing date of the related international patent application (filed in accordance with the provisions of the PCT). The international patent application and priority numbers are also provided to facilitate confirmation of the information at country or regional level and further search in additional countries. In cases where no international patent application was filed, the related US or European patent number and expected patent expiry date are provided.

Source: Data from Medicines Patent Pool Patent Status Database, <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs>.

See explanatory notes: <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs/Explanatory-Notes>.



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