

## **Standing Committee on the Law of Patents**

**Thirty-First Session**  
**Geneva, December 2 to 5, 2019**

### **REVIEW OF EXISTING RESEARCH ON PATENTS AND ACCESS TO MEDICAL PRODUCTS AND HEALTH TECHNOLOGIES**

*prepared by the Secretariat*

#### **INTRODUCTION**

1. The Standing Committee on the Law of Patents (SCP), at its twenty-ninth and thirtieth sessions, held in Geneva from December 3 to 6, 2018, and June 24 to 27, 2019, respectively, agreed that the Secretariat would submit, at the thirty-first session of the SCP, a review of existing research on patents and access to medical products and health technologies, as contained in document SCP/28/9 Rev. (see paragraph 22 of document SCP/29/7 and paragraph 23 of document SCP/30/10). Document SCP/28/9 Rev. is a proposal by the Delegations of Argentina, Brazil, Canada and Switzerland to conduct such a review for Committee's consideration under the agenda item "Patents and health".
2. Pursuant to the above SCP decisions, the Secretariat prepared the said review, which is contained in Annex I to this document for the Committee's discussions at its thirty-first session to be held in Geneva from December 2 to 5, 2019.
3. In line with the above SCP decisions, the review was conducted in accordance with the proposal contained in document SCP/28/9 Rev. Specifically, it was undertaken by the Secretariat in consultation with the WHO and WTO Secretariats and included studies prepared by these organizations as well as other relevant intergovernmental organizations (IGOs). The review also includes studies prepared by external researchers commissioned by these organizations, as well as peer-reviewed academic research.

4. As mandated by the Committee, in conducting the said review, the Secretariat primarily searched studies on the following topics:

- The relationship between patents and other related issues and the affordability and availability of medical products and health technologies;<sup>1</sup>
- The role of the patent system, including patent quality mechanisms, in incentivizing and promoting the development of new medicines and health technologies to address the global disease burden, facilitating access to medical products and health technologies, and ensuring the supply of quality products;
- The role of the intellectual property system in fostering knowledge spillovers and technology transfer in the medical products and health technologies sector;
- The role of compulsory and voluntary licensing mechanisms and patent pools in facilitating the affordability and availability of medical products and health technologies; and
- The availability of essential medicines in countries where those medicines are not under patent, taking into consideration the variety of other factors both on the supply and demand side that affect availability and affordability.

5. The review covered work produced over the time period of 2005 to 2018. Each study was summarized to provide, in about half a page, factual synopsis of the analysis, key conclusions and recommendations of the author(s) of the study. The list of studies included in the review is presented in Annex II to this document.

6. With regard to the works produced by the IGOs, in addition to the works of WIPO, WHO, WTO, and the works of external researchers commissioned by these organizations, the search was conducted on publications made by, *inter alia*, European Union, UNCTAD, UNAIDS, OECD, UNDP, ICTSD and South Centre.

7. The search of academic literature was conducted on more than 80 peer-reviewed journals, taking into account the relevance of their fields to the mandated topics. The readers should be mindful of the fact that while all identified peer-reviewed academic studies on the above topics have been included in this review, no quality assessment of their contents has been made by the Secretariat. Additionally, as mandated by the SCP, the review does not include working documents, drafts, blogs, commentaries and opinion pieces, etc. which are not considered to be peer-reviewed academic research.

8. Different number of studies have been identified in relation to each of the mandated topics above. Most of the economic and legal literature identified was relevant to the following topics: (i) the role of the patent system in incentivizing and promoting the development of new medicines and health technologies to address the global disease burden; (ii) the role of the patent system in fostering knowledge spillovers and technology transfer in the medical products and health technologies sector; (iii) the relationship between patents and the affordability and availability of medical products and health technologies; and (iv) the role of compulsory licensing mechanisms in facilitating the affordability and availability of medical products and health technologies. Less amount of literature has been found in relation to the topic of the

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<sup>1</sup> For the purposes of this review, “medical products and health technologies” refers to medicines, vaccines, diagnostics and medical devices.

availability of essential medicines in countries where those medicines are not under patent, taking into consideration the variety of other factors both on the supply and demand sides that affect availability and affordability. This reflects a lack of published research on that topic in economics, legal or other fields alike.

9. The paper is structured into three main sections: (i) Studies prepared by WIPO, the WHO, the WTO and other relevant intergovernmental organizations, including studies prepared by external researchers commissioned by these organizations; (ii) Peer-reviewed academic research (economic literature); and (iii) Peer-reviewed academic research (legal and general literature). While subsections are introduced to ease the reading of the document and to show the main focus of the studies included in the review, they are simply indicative.

[Annex I, follows]

## A REVIEW OF EXISTING RESEARCH ON PATENTS AND ACCESS TO MEDICAL PRODUCTS AND HEALTH TECHNOLOGIES

*Studies prepared by WIPO, the WHO, the WTO and other relevant intergovernmental organizations, including studies prepared by external researchers commissioned by these organizations*

### Incentivizing and promoting the development of new medicines and health technologies

10. Chapter II of the World Intellectual Property Report (WIPO, 2015) discusses the role IP played in the invention and development of antibiotics. The chapter discusses evidence that patents incentivized the development of sulfa drugs by pharmaceutical company Bayer in the 1930s. In contrast, patents appear to have played no significant role in the development of penicillin. However, patents appear to have played a significant role later on in the development of synthetic penicillin by the pharmaceutical company Beecham Group. Patents also played an important role again in the later development of new antibiotics, such as streptomycin. The streptomycin molecule was patented while the methods to generate the molecule were kept in the public domain. The chapter discusses evidence that suggests that this combination of free access to fundamental processes and the possibility of patenting the resulting products created strong incentives for follow-on research in antibiotics. The chapter also discusses the role that disclosure required by patenting played in drug development. On the one hand, some companies tried to delay and limit the disclosure of information, on the other the disclosure of information helped the Institut Pasteur in their development efforts. Patents appear to have also helped academia and private companies to engage in collaboration in drug development efforts. Antibiotics diffused quickly and widely which suggests that patents were not a barrier to diffusion of these new drugs, although some of that diffusion might have been helped by the absence of product patents on sulfa and penicillin. Finally, the chapter also describes how the development and marketing of antibiotics changed the patent system prompting a number of relatively fundamental changes such as the non-obviousness requirement introduced by the 1952 Patent Act in the U.S.

11. WIPO Global Challenges Report prepared by Jenner, A. et al. (2017) on antimicrobial resistance (AMR) and multidrug resistance (MDR), provides an overview of current approaches and consortia designed to meet the challenge of R&D investment for new antibiotics. It also examines patent applications by both the public and the private sectors as an indicator of innovative activity. With respect to the role of patents in incentivizing R&D for antibiotics, the report finds that pharmaceutical companies are reluctant to invest in antibiotic R&D because the returns are significantly lower than for other areas, leading to many companies exiting the market. The report lists specific problems relating to the development of next generation of antibiotics (such as limited use, low price, short lifespan, difficulty of conducting clinical trials) and suggests alternative mechanisms to help de-risk or de-link companies' initial investment. As regards the patent data on antibiotics, the data show that patenting activity of the last 10 years is relatively strong. However, this does not correlate to the number of new antibiotics produced over the same period and patenting tends to focus on existing classes of antibiotics, with more patent families directed towards the penicillin antibiotics than any other known class. In general, the report finds that there is a need to address the unique market challenges and specific uncertainties associated with the development of new diagnostics and treatments, where current approaches are not optimal. An effective global framework that achieves the necessary political support while ensuring effective local implementation is crucial. There is an opportunity to complement this work by formulating mechanisms that drive innovation for results to incentivize success, while feeding expertise and experience into stewardship and access efforts. As regards the role of IP specifically, the reports suggests that IP could be used in a

constructive manner as one element in any reward or prize system for AMR/MDR R&D – both in terms of providing an incentive and governance.

12. WHO, WIPO and WTO background paper for the Technical Symposium on Antimicrobial Resistance: How to Foster Innovation, Access and Appropriate Use of Antibiotics? (2016) provides general overview with regards to some questions, such as: what is antimicrobial resistance? what causes antimicrobial resistance? how does resistance develop? and why is antimicrobial resistance a problem? The paper notes that stewardship, innovation and access are three key objectives in addressing antimicrobial resistance. As regards innovation aspect, the paper states that there is a severe lack of investment in new medicines against microbes. The market-based innovation system has insufficient incentives because the return on investment in antibiotic research is too small to attract the required R&D investments. New innovative and comprehensive incentive initiatives are needed to complement the existing innovation model to foster the development of new antibiotics. This could include a mixture of push mechanisms (e.g. grants for basic research and clinical trials, product development partnerships), pull incentives (e.g. milestone prizes or market entry rewards) and regulatory measures (e.g. specific regulatory pathways). As regards access to antibiotics, the paper notes that antibiotics protected by patents will often have a higher price, which constrains access. One option to overcome this barrier is using delinkage in the development of new antibiotics. Voluntary licensing agreements have emerged as a tool that has helped improve affordable access to patented medicines for HIV/AIDS and hepatitis. The paper also notes that the TRIPS Agreement provides WTO Members with policy space within which they can put in place and apply a domestic IP regime that is responsive to their particular needs in the health sector, including using existing flexibilities to foster access to antibiotics. The paper adds that, in the long run, building strong health systems is the most sustainable approach to ensuring affordable access to good-quality essential medicines, including antimicrobial medicines and vaccines, as well as diagnostics and other vital interventions.

13. The paper “Patent issues related to influenza viruses and their genes” commissioned by the WHO was prepared by Life Sciences Program of WIPO (2007). It is a background paper on patent issues related to influenza viruses with a focus on the avian flu or H5N1 subtype. It was prepared in the context of a broad Resolution on pandemic influenza preparedness and access to vaccines. The aim of the paper is to provide neutral technical information and put the relevant patent issues in a practical context. The report contains extensive factual detail as to the various components of patentability for viruses, including reference to gene sequencing. The findings show that there has been a rapid and recent increase in the patenting activity referring to the H5N1 and not just in the context of vaccines but also in relation to diagnosis and treatment. The sudden growth of patenting activity is interpreted as signaling an intensive, broad based and diverse practical response to a potential health crisis. While the increase in research activity is found to be welcome, there is concern – in particular in relation to genetic material – about the accessibility of this research and potential obstacles this can create for the “freedom-to-operate”. However, the report emphasizes that it is rare for a single patent to correspond to a single vaccine or pharmaceutical treatment. Moreover, it is emphasized that genetic materials are not per se the direct subject of patent protection but rather certain inventive steps are required to earn a patent right. This determination of patentability criteria is said to be an area that health policymakers need to debate and resolve at the domestic level. The findings show that striking the right balance between positive incentives that promote research and development, while also providing safeguards for the effective dissemination of needed technologies, is challenging. The findings also show that the optimal response will vary according to the development status of a country, according to the nature of the technologies involved and according to where a specific patent lies along the pipeline of research. It is recommended that, where optimized and balanced, the patent system has a role to play for the future of influenza viruses, as it can clarify technology partnerships including freedom-to-operate, induce the investment of resources, leverage access to technology

packages such as public-private partnerships and patent pools, and permit transparency of trends in vaccine R&D.

14. The chapter “Intellectual property protection: impact on public health” in the WHO’s Drug Information Guide (2005) briefly considers the impact of intellectual property protections on public health, more specifically, in the context of access to medicines. Public health principles are noted as finding support in an array of international legal and policy instruments, including the Constitution of the WHO. However, there is concern that the TRIPS Agreement has introduced tension for these public health principles as the mandatory patent rules might restrict access to affordable medicines and thus the provision of public health care for populations in developing countries. A debate is thus identified, as to the impact and relevance of patents on access to medicines. The findings show that the patent system can provide R&D incentives for medicines developed for high-income countries but it does not provide an incentive for the R&D of medicines affecting public health that lack a commercially attractive market. The key provisions of TRIPS are then examined before looking to public health considerations, including compulsory licensing and parallel importation. The chapter concludes by recommending: the drafting of appropriate legislation and regulations on patentability to ensure the prompt introduction of generic drugs upon patent expiry; the use of exceptions to exclusive rights that permit early testing and approval of generic (including access to pre-registration test data); and compulsory licensing. It is also recommended that countries seek independent advice and technical assistance from WHO to developed informed approaches to address the health implications of trade and intellectual property devices.

15. The report of the Commission on Intellectual Property Rights, Innovation and Public Health (2006), was commissioned by the WHO Member States at the 2003 World Health Assembly. The Commission’s purpose was to, *inter alia*, consider the importance and effectiveness of intellectual property regimes and other incentive mechanisms to stimulate R&D for the creation of new medicines and other products, to analyze proposals for improvements to current incentive and funding regimes, including IP rights, and to produce concrete proposals for action by national and international stakeholders. While the mandate of the report was related to IP rights, authors place the issue in a broader perspective and examine other factors affecting the introduction of new and existing products into developing countries such as health delivery systems, regulation, pricing, policies to promote competition and issues such as the importance of political commitment. The findings were presented in six chapters, presented in the same chronology as the R&D process: (1) The health innovation cycle; (2) The deep well of discovery: early stage research; (3) The long road from discovery to development; (4) Delivery: getting products to patients; (5) Fostering innovation in developing countries; (6) Towards a sustainable plan to promote innovation and access. Each chapter is followed by recommendations. In relation to IPRs, authors note that IP rights are important, but as a means not an end. The relevance of IP rights as an incentive for innovation depends on the context and circumstance. While intellectual property rights are found to be a necessary incentive in developed countries, in the absence of a profitable market they are found to have little stimulatory effect on innovation. The effects of IP rights on innovation may also differ at successive phases of the innovation cycle – from basic research to a new pharmaceutical or vaccine. Authors considered the impact of TRIPS Agreement, the flexibilities contained in the Agreement, and also the impact of bilateral and regional trade agreements as they might affect public health objectives. Authors also suggest that other, non-intellectual property based, incentives and financing mechanisms are needed to stimulate R&D. Additionally, funding is identified as crucial, with more sustainable funding required. It is recommended that governments play a more proactive role and mobilize the funds necessary to promote financing and incentive mechanisms.

Access to medicines, patent data and transparency

16. WIPO Global Challenges Report prepared by Krattiger A. et al. (2012) presents a “global access” freedom to operate (FTO) analysis of six vaccines under development against dengue hemorrhagic fever, a neglected tropical disease endemic to tropical regions. The goals of this FTO review are to: (i) understand how IPRs may affect access to dengue fever vaccines in developing countries; (ii) assess the ways in which some vaccine developers may be affected by IPRs and the extent of freedom they have to license their products to developing countries; and (iii) evaluate the freedom of vaccine developers in developing countries to market their vaccines outside their home countries. The results presented are based on a product deconstruction analysis as well as patent searches that were conducted using both open and subscription-based services. The analysis finds, *inter alia*, that some 10,800 patents and patent applications were found to have “dengue” in the abstract, title, text or claims, corresponding to 4,500 patent families. Of these, 700 families were found to be outside the scope. Of the remaining 3,800 patent families, 55 patents or patent families were deemed pertinent to the six vaccines discussed in the report. The number of patent families related to a given vaccine ranged from five to 22. Most of these were filed in developed countries with only a small number also filed in select developing countries. Each of the patent groups occupied a well-defined space in the patent landscape, with little overlap in the specific technological field implying that few, if any, cross-licensing deals may be required to bring any given vaccine to market. The results of this FTO analysis suggest that there are few major constraints related to patents that could complicate developing-country access to the vaccines under development. As analysis were limited to patent data and licensing information, market considerations such as economies of scale, pricing and regulatory approval, or efficacy of the vaccine itself were not part of the report.

17. Beall RF. and Attaran A. (2016) prepared the WIPO Global Challenges Report with an objective to identify which of the 375 items on the 2013 Model List of Essential Medicines (MLEM) of the WHO (18th edition) are patented and where. The field work was undertaken in 2014 and 2015. This study was completed in three phases: identifying which medicines from the 2013 MLEM could be considered “patented” using the United States Food and Drug Administration’s Orange Book (FDA 2015b), Health Canada’s Patent Register (Health Canada 2015), and previous studies; using these patent data to retrieve related patents abroad from international patent databases (INPADOC and Derwent) and to create a preliminary landscape report; and finally, approaching each medicine supplier with the preliminary data for confirmation or clarification of these data as needed. The report finds that 20 of the 375 items (or about 5 percent) listed on the 2013 MLEM as likely to be under patent protection in some developing countries. The remaining 20 drugs under patent protection are largely for antivirals (especially HIV), but also for non-communicable diseases and others. The percentage of developing countries covered by each of the 20 patent portfolios varies widely from less than one percent to 44 percent with a median of 15 percent. Where patents were filed, this appeared to be more common in countries where there was market and manufacturing opportunity, namely, middle-income nations with larger populations, higher health spending per capita and pharmaceutical manufacturing capacity. Given the relative scarcity of patented medicines appearing on the 2013 MLEM and of those patents typically being filed in developing countries, the report concludes that targeted and fit-for-purpose solutions, such as voluntary licensing agreements for patented medicines being added to the MLEM, should be considered. The report also discuss patent transparency as a more fundamental, yet promising policy intervention.

18. Beall, RF. (2016) prepared a Global Challenges Brief based on WIPO Global Challenges Report by Beall RF. and Attaran A. (2016). Focusing on key findings of that report, author suggests the following implications to be considered by the policymakers as starting points for reflection, to be adapted to specific needs and circumstances. First, most MLEM products are

off-patent in most lower income countries. For those countries, therefore, patent protection in major medicine-exporting countries is often a more important concern than patent protection domestically. Second, a pragmatic approach to improve access to essential medicines is to target interventions, such as licensing agreements authorizing generic manufacturing and/or procurement, squarely upon the specific cases where patenting poses a barrier to essential medicine access. Third, patent transparency on MLEM products is critical for proactively and correctly identifying these specific cases. Accurate patent information on MLEM products is not readily available in most countries, which may act as a deterrent to potential manufacturers and exporters of essential medicines, who may erroneously believe there is patent protection where there is none. Fourth, the need for patent transparency extends to generic manufacturers, as they sometimes hold patents on products commonly believed to be patent-free. Fifth, in the long-term, the proportion of patented products on the MLEM will likely increase and therefore there will be more opportunities to design and implement new inventive solutions for the changing essential medicine patent landscape.

### Technology transfer and local production of the medical products

19. The study by the WHO (2011) entitled “Increasing Access to Diagnostics Through Technology Transfer and Local Production” looks broadly at the issue of in vitro diagnostic (IVD) device technology transfer and local production of diagnostic tests in developing countries. The study identifies patents as one of the challenges for technology transfer and local production developing countries. Specifically, it recognizes the tension between on the one hand the need to protect inventions through patenting and on the other more restricted access to patented inventions due to the need to acquire licenses. The report suggests that smaller companies might not have the financial means and expertise to protect their novel IVDs through patents and therefore be apprehensive to collaborate with bigger firms for fear of losing the rights to their inventions. It also mentions that licensing costs might be a particular challenge for firms in developing countries.

20. The report by the International Center for Trade and Sustainable Development and World Health Organization (WHO) (2011) describes the current landscape on the local production of drugs and related technology transfer in developing countries. The use of voluntary and compulsory licensing initiatives is also explored. The report has three main methodological aims: (i) to provide a description of the landscape of local production of drugs, relevant investment promotion and related transfer of technology; (ii) to provide an outline of current and recent initiatives from the last 5-10 years; and (iii) to identify gaps and to provide a preliminary assessment on those initiatives. To accumulate the data, searches were conducted for a range of potential data sources from September to December 2009. However, in the absence of a uniform definition for the term “technology transfer” and no publicly uniform data source on initiatives for local production of drugs and relevant technology transfer, the landscape is fragmented. As such, one of the report’s recommendations is for the creation of a comprehensive and regularly updated and publicly accessible database of relevant initiatives. Overall, the evidence of the report shows a significant amount of activity taking place to support local production and induce the relevant transfer of technology, with an increase since the mid-1990s. However, the report finds that, without clearly articulated international goals, there is no objective way to measure whether these efforts are sufficient or whether greater efforts are needed. Some other findings include: the need to explore technology transfer on a broader spectrum of products; the potential systemic risks created by the concentration of API production in just two countries; renewed interest in the feasibility of local production in LDCs and the need for public policies and for mid- to long-term investment in capacity building. In addition, as regards to intellectual property specifically, the paper finds that patent barriers were found to be the largest barrier preventing local production in non-LDCs that were interested in producing newer medicines. By contrast, the extension of the TRIPS deadline for

LDC WTO Members to grant or enforce pharmaceutical patents until at least 2016 has created a renewed interest in the feasibility of pharmaceutical production in LDCs.

21. The study by Moon (2008) for UNCTAD – ICTSD addresses the question of whether technology transfer to the LDCs Members of the World Trade Organization has increased as a result of the TRIPS Agreement. Looking at reports submitted by countries to the TRIPS Council from 1999-2007, the study uses empirical analysis to determine whether the positive legal obligation pursuant to TRIPS Article 66.2 has led developed countries to increase incentives to enterprises and institutions in their territories for the purpose of promoting and encouraging technology transfer to LDCs. Since 2003, developed WTO Members have had an obligation to report to the TRIPS Council once every three years on the steps they have taken to comply with Article 66.2. The data for the study is extracted from these reports and therefore it is the actions taken (rather than the volume of actual technology transfers) by developed countries to establish technology transfer which forms the basis of the study. Problematically, however, “technology transfer” does not have a definition under TRIPS Article 66.2 and nor is there a standard definition of “technology transfer”. As a result, data showing evidence of a type “technology transfer” measure was given a broad scope in meaning. The results show that only 31 percent of the “technology transfer” policies and programs were specifically targeted towards LDC WTO Members. Of the 90 programs that were specifically targeted towards LDC WTO members, 64 qualified as a technology transfer. This evidence suggests that developed countries are over-reporting the measures they have taken to meet their Article 66.2 obligations. This can be interpreted as evidence that Article 66.2 has had a limited impact on the creation of incentives by developed country enterprises and institutions for the transfer of technology to LDCs. It is recommended that the TRIPS Council review Article 66.2 reporting mechanism. It is also recommended that WTO Members agree on a common definition of technology transfer and common, comparable metrics for measuring the extent to which the incentives have had their intended effect.

Affordability and availability of medical products, TRIPS safeguards (including compulsory licensing), voluntary licensing and patent pools

22. Perriens and Habiyambere’s WHO Technical Report (2014) explores the global trend in antiretroviral (ARV) prices to assess how WHO guidelines have influenced the uptake of different ARV formulations. The report examines the various constraints limiting the use of second- and third-line treatments and pediatric formulations. Considerations such as how to secure quality ARVs and how to improve in-country distribution are also assessed. The findings are generated using: country-level data reported to WHO on the procurement of ARV therapy via the Global Procurement Reporting Mechanism; WHO’s database on the regulatory status of ARV therapy; reports on the production capacity of several active product ingredients of ARVs; the annual WHO surveys on the use of ARV therapy; Global AIDS Response Progress Report data and other contributions. The findings show that the price of individual ARV formulations has decreased considerably over the last decade and treatment programs have used this as an opportunity to replace stavudine-based treatment with new and improved first-line medicines. However, the findings also reveal low uptake of second- and third-line treatments and pediatric formulations, as well as concerns over the regulatory control of quality ARVs in low- and middle-income countries (LMICs). In addition, a number of important ARVs are still under patent protection and thus limit the availability of cheaper generic medicines. However, voluntary licensing – in particular through the Medicines Patent Pool (MPP) – has been found to enhance access to newer patented ARVs in a large number of LMICs. The main challenge is now for upper-middle-income-countries who do not benefit from MPP licenses. With the demand for ARVs set to increase by 70 percent, it is recommended that manufacturers increase their production capacity and that national supply management systems are strengthened to ensure accurate stock forecasting, distribution and supply. In addition, there is a need for efficient regulatory approval processes without undue hurdles or ad hoc management.

23. The UNAIDS/WHO/UNDP policy brief (2011) reviews the ways in which countries can use TRIPS flexibilities to increase access to HIV treatment. The legal backdrop is set against the Millennium Goal for universal access to HIV/AIDS and the UNAIDS and WHO Treatment 2.0 platform to accelerate access by removing obstacles such as cost barriers to treatment. It is precisely the issue of pricing that forms the particular access issue and focus of the brief and while pricing is acknowledged as influenced by a variety of factors, intellectual property is identified as one such factor. The impact of intellectual property on the price of, and subsequent access to, antiretrovirals is thus examined in the following structure: first, by outlining TRIPS and its significance. Second, the brief looks at the importance of competition within a drug market before looking to selected examples and challenges in the use of TRIPS flexibilities, including a look at TRIPS-plus provisions. Finally, the brief examines what can be done for the better use of TRIPS flexibilities. The general findings show that despite substantial price reductions, price remains a key issue preventing access to HIV treatment in LMICs, particularly on second-line regimens, making it even more important for countries to take all available measures to reduce prices and increase treatment access. While the results promote the use of TRIPS flexibilities to improve access, the findings show that many countries have not yet amended their domestic laws to incorporate these flexibilities and thus, to permit their use. It is recommended that LMIC governments revise national legislation to ensure the flexibilities are incorporated, encourage regional cooperation and that LDCs take full advantage of the transition periods. It is recommended that high-income countries implement the "Paragraph 6" mechanism, comply with the principles of the Doha Declaration when entering into free-trade agreements, facilitate technology transfer and maintain global funding commitments to reach universal access goals. It is also recommended that international organizations have a role to play in ensuring the unencumbered use and protection of TRIPS flexibilities.

24. The South-East Asian Division of the WHO's publication (2014), prepared for the 23rd Meeting of the National AIDS Program Managers, explores the access to affordable medicines for HIV/AIDS landscape from the context of intellectual property rights. The publication begins by tracing historical intellectual property developments, such as the HIV/AIDS crisis in South Africa that led to the adoption of the Doha Declaration for Public Health in 2001 and the Doha Declaration Paragraph 6 Waiver. The publication then moves on to examine TRIPS flexibilities including compulsory licensing and voluntary licensing options. Higher patentability standards through a narrowing of the patentability criteria are also discussed as a measure that can prevent patent evergreening and ensure the novelty of patented medicines. Section 3(d) of Indian patent law – which prevents new patent grants on new uses of known substances – and the refusal of the US judiciary to grant patents on naturally occurring DNA sequences are provided as examples of domestic efforts that restrict patentability criteria in order to improve or to ensure access to medicines. The publication also briefly discusses the use of legal covenants and global health initiatives such as UNITAID and PEPFAR. Finally, the publication finishes by looking at new models of cooperation between pharmaceutical companies and governments, with Gilead's discount supply of sofosbuvir for Hepatitis C to Egypt considered one such example of cooperation. The publication concludes that these evolutions, at both the domestic and international level, have opened the field for newer options to more affordable medicines for HIV/AIDS.

25. The report from the WHO's 23rd Meeting of Health Ministers of Countries of the South East Asia Region (SEAR) (2005) provides an overview of the TRIPS Agreement and Doha Declaration before looking directly at examples in which SEAR countries have employed the Doha Declaration in favor of public health. A detailed Annex 1 at the end of the report provides detailed information regarding regional implications of intellectual property protections as they specifically relate to access to vaccines within SEAR countries. Some of the SEAR country updates that have been included in the report include: Indonesia's use of a government license on two antiretroviral medicines (which is credited as being possible because Indonesia's patent

legislation has the necessary provisions for the grant of a government use decree); India's issues regarding increased drugs prices on the leukemia medicine imatinib after the 2005 requirements for patentability kicked in; the successful challenge of civil society organizations and the HIV/AIDS community in Thailand over the patent on didanosine; and the efforts by Sri Lanka to work towards the inclusion of the TRIPS flexibility of parallel importation into their national legislation. The negotiation between Thailand and the US of a free-trade agreement is also raised as a potential issue that could result in the raising of TRIPS minimum standards for a SEAR country. While the findings show that intellectual property protections have had an impact on the SEAR countries, the intensity is said to ultimately depend on the inclusion (or not) of public health safeguards into national legislation. It is recommended that countries make full use of the tools developed by WHO and technical assistance where available. It is also recommended that Ministries of Health be involved in discussions on trade that have an impact on health.

26. Part I of the WHO's Universal Health Care Technical Brief (2017) looks at in-country experiences using safeguards of the TRIPS Agreement to protect public health and access to medicines. Part I is focused on country experiences using compulsory licensing, as well as the application of strict patentability criteria for the purpose of preventing patent evergreening. It looks at the factual developments and outcome of developing countries Malaysia, Zimbabwe, Brazil and Ecuador in their use of compulsory licenses. The results show that in every instance the license resulted in a significant price reduction and improved public health access to the relevant drug. There is also reference to the use of compulsory licensing by developed countries pre-TRIPS and also post-TRIPS as a measure against antitrust violations. There is also discussion on the use of a compulsory license for export between Canada and Rwanda. The case study of India is examined regarding the legislative initiative against patent evergreening and mention is also made to similar measures adopted by the Philippines, Indonesia and Argentina. Four main conclusions are drawn from the case studies: (1) compulsory licensing can and has been used to protect public health in developed and developing countries; (2) while the number of instances of compulsory licensing by developing countries is relatively limited, those experiences show that compulsory licensing/ government use can be an effective mechanism; (3) a "credible threat" to issue a compulsory license can be instrumental in obtaining price reductions; and (4) various "pre-grant" flexibilities can play a complementary role in safeguarding access to medicines. However, the findings also show that even though compulsory licensing is permitted under the TRIPS Agreement, some countries experienced political pressure after issuing a license leading to the recommendation to safeguard the TRIPS safeguards.

27. Part II of the WHO's Universal Health Care Technical Brief (2017) is focused on the use of competition law and TRIPS safeguards that are specific to least-developed countries. The interface of competition law with intellectual property protections is recognized in TRIPS at Articles 8.2, 31, 40.1, and 40.2. In practice, despite variations between national competition laws, three main overarching areas of competition law are deemed relevant for the purpose of public health-related intellectual property protections: (1) anti-competitive arrangements (such as "pay-for-delay" deals to delay generic entry and restrictive licenses to generic companies); (2) abuse of dominant position (through excessive pricing, refusal to deal or license patents and other abuses of intellectual property rights such as sham litigation); and (3) mergers and acquisitions. South Africa, the USA and Italy provide the in-country case studies where competition law has been successfully used for public health purposes. Regarding the use of TRIPS safeguards that are specific to least-developed countries, the brief also looks at the incorporation of TRIPS transition periods in Cambodia, Uganda and Bangladesh. A legislative move at the national level that enables them to benefit from the extended period of exclusion for patents on pharmaceuticals. The brief argues that competition law can be used in both developed and developing countries to prevent the abuse of intellectual property rights but that it currently remains an under-used measure. It is recommended that civil society and health

groups play a role in filing competition complaints or investigations. Finally, it is recommended that any least-developed countries that have not already incorporated the transition periods into domestic legislation take the necessary steps to do so.

28. The WHO's progress report (2018) on access to hepatitis C treatment focuses on identifying and overcoming barriers in low- and middle-income countries. The report provides an update on the first edition (2016), by reviewing the progress that countries have made in expanding access to life-saving direct-acting antivirals (DAAs) to treat hepatitis C. The progress report is compiled using a WHO survey on the availability and use of DAAs in 23 low- and middle-income countries across six regions and a survey of innovator and generic companies, as well as interviews with key informants and stakeholders. The report reviews the main challenges countries face and describes recent developments in relation to five key factors that determine access to DAA medicines: affordability, quality assurance, regulatory approval, government commitment and financing. It highlights key areas of action by ministries of health and other government decision-makers, pharmaceutical manufacturers and technical partners. Some of the significant findings of the report show that: the uptake of DAAs is increasing slowly and unevenly; access to treatment – including more equitable access – needs to occur at a much quicker pace; increased competition has driven down treatment prices, with the issuing of voluntary licenses or absence of patents allowing generic production; costs still remain unaffordable for DAAs in many upper-middle and high-income countries; the coverage of screening and diagnostic services remains too low; and therapy treatment options continue to increase and improve. Overall, the report shows that different countries face different realities. While some are still struggling with price and patent barriers, others have been able to move on. These country experiences show that access to affordable DAA treatment requires a strong government response, national prevention, diagnosis and treatment plans and adequate financing. Stringent quality assurance of DAAs is also a necessity.

29. The WHO's Universal Health Care Technical Brief (2017) looks at selected provisions of patent laws which incorporate public health protections. While the brief provides samples of public health-inclusive legislative provisions, it is not intended to function as an intellectual property law drafting guide but rather as a guide for health officials who can raise the relevant issues during the drafting of intellectual property laws. The brief provides recommendations on a variety of public health measures using a "three-pronged strategy". The first-prong requires the provision of adequate safeguards under domestic law. To achieve this, it is recommended that countries incorporate the multitude of TRIPS-compliant safeguards such as "Bolar" exemption, parallel importation, compulsory licensing and government-use authorization provisions, and compulsory licenses exclusively or predominately for export. Furthermore, it is recommended that safeguards be workable in practice, for instance ensuring that appeal proceedings against a compulsory license will not suspend the license. The second-prong requires the wise use of exemptions and flexibilities. Predominately this is aimed at least-developed countries to ensure they take full advantage of the transition periods, while developing countries are encouraged to consider the use of patent opposition procedures and take legislative action to prevent patent-evergreening through a reformulation of the patentability criteria. Finally, the third-prong urges countries against the incorporation of TRIPS-plus provisions, such as data-exclusivity and patent-term extensions. The brief also errs against the use of criminal sanctions as a penalty for patent infringement. Importantly, all three-prongs are defined as cumulative rather than independent and thus, it is recommended that countries use them in combination.

30. The WHO Briefing Paper (2006) gives an overview of the TRIPS Agreement as it relates to access to medicines. Focusing on the "safeguard" provisions of the TRIPS Agreement, otherwise known as TRIPS flexibilities, the paper highlights some of the successful instances in which countries have used these flexibilities to improve access to antiretrovirals (ARVs). The paper also briefly examines the options available to countries interested in making use of TRIPS

flexibilities to increase access to HIV/AIDS drugs. The paper defines the access problem as a problem that is dependent on many factors, notably the rational selection and use of drugs, adequate and sustainable financing, affordable prices and reliable supply systems. While the paper acknowledges that price is merely one element of a larger access problem, the fact that 50-95% of drugs in developing countries are not publicly supplied but rather paid-for by the patients themselves means that prices still have direct implications on access to medicine. To mitigate the negative impact on drug prices and access to drugs, the following three TRIPS safeguards are flagged as being the most important: (i) compulsory licensing, (ii) parallel importation, and (iii) provisions for an early working exception. As the safeguards provided for in TRIPS can only be used when incorporated into national law, it is recommended that countries design and enact legislation permitting them to use these. Looking briefly at the compulsory licensing experiences of Thailand, Brazil, Malaysia and Indonesia, the paper recommends for countries that have local production capacity, to apply compulsory licensing or government use licenses to enable local production of generic versions of patented drugs. For countries where local production is not feasible- to look at options of parallel importation.

31. The WHO and Health Action International (HAI)'s second edition manual (2008) on medicine prices, availability, affordability and price components is a revised and updated manual providing a standardized methodological approach for the conducting of medicine price and availability surveys throughout the world. The bulk of the manual is dedicated to providing in-depth, step-by-step details as to how to conduct a survey, all the way from the pre-survey planning through to post-survey monitoring. Being a revision of the first edition, however, the introduction and foreword refer to the wealth of experience gained from four years of use, with more than 50 medicine price and availability surveys conducted using the WHO/HAI method. The results of which have generated reliable evidence demonstrating that for many low- and middle-income countries: medicine prices are high, especially in the private sector; availability can be low, particularly in the public sector; treatments are often unaffordable (requiring over 15 days of wages); government procurement can be inefficient; markups in the distribution chain can be excessive; and that numerous taxes and duties are being applied to medicines. High prices are found to be one of the biggest obstacles to access. The implementation and enforcement of patent rights at the country-level also has an impact on the price of medicine. From the aggregation of the results of previous surveys using the WHO/HAI survey tool, national policies, medicines pricing and procurement strategies are recommended to help ensure the improved affordability of medicines. As medicine price indicator guides do not show the price that patients pay in either the public or private sector due to their exclusion of new, essential patented medicines, it is recommended that prices continue to be monitored and cross-country comparisons made using a methodology such as the WHO/HAI method.

32. The European Commission's pharmaceutical sector inquiry (2009) analyzed potential obstacles to market entry of generic prescription drugs and competition between originator prescription drugs. The inquiry collected information on drugs associated with 219 molecules and data from 43 originator and 27 generic companies. The analysis focuses on the period 2000 to 2007. The inquiry found that around half of all drugs investigated faced generic entry within one year after patent expiration or loss of data exclusivity. On average, entry occurred seven months after loss of exclusivity and generic prices upon entry were on average around 25 percent lower than originator prices prior to loss of exclusivity. Prices declines further to around 40 percent below originator prices within two years of loss of exclusivity. Generic companies attained market shares of around 30 percent within one year and 45 percent within two years. The inquiry shows that originator companies have adopted a range of patenting strategies to extend the breadth and duration of patent protection of their drugs. They often file a large number of patents on the same drug creating uncertainty for generic entrants as to the scope and strength of patent protection. Uncertainty is also created through the strategic filing of divisional patent applications that can extend the examination period of the patent office. Patent litigation is also used by originator companies to deter in particular smaller generic

entrants and often ends with a settlement that restrict or delays generic entry. The inquiry also found that originator companies asserted mainly secondary patents in court. Concerning competition between originator companies, the inquiry suggests that originators engage in so-called defensive patent strategies to interfere with the development of a competing drug developed by another originator company. Overall, the results of the inquiry suggest that originator companies engage in a range of patent practices to prevent market entry by other originator companies as well as generics.

33. Watal and Dai (2019) use data on launches of 556 new molecular entities (which were approved by the U.S. FDA between 1987 and 2011 and consist of both innovative and non-innovative pharmaceuticals) over the period 1980-2017 in 70 markets to analyze whether the likelihood of new drug launches is affected by the introduction of product patents in pharmaceuticals as a consequence of the TRIPS Agreement. The study also uses price data for the period 2007-2017 to analyze whether prices for such new drugs are adjusted for lower income levels in developing countries. The results suggest that product patents increase the likelihood of a new, innovative product launch but the effect is very small for lower-income markets. The results also point to heterogeneity in the effect across different disease types and income levels. There is also evidence that both originators and generic drug producers price discriminate and set lower prices in low-income markets. Price differences are largest for pharmaceuticals that treat infectious diseases, in particular HIV/AIDS. The study also finds that within-molecule as well as within-therapeutic class competition drives prices down. The main findings are that product patents are associated with an increased likelihood of the launch of an innovative new drug, although this effect is small for lower-income countries. Drug prices are to some extent adjusted by income level.

34. The paper by Kampf (2015) surveys the domestic measures put in place by WTO Members to implement the “Paragraph 6 System” of the Protocol Amending the TRIPS Agreement, focusing on measures permitting export. The implementation of this additional flexibility is optional, not mandatory. As such, the adoption of such legislation is required at the domestic level in order to form part of the domestic law. Although, Paragraph 6 concerns a distinct new form of compulsory license expressly for export, countries intending to use it to import medicines are far less likely to implement specific legislation. Using a mix of information gathered from TRIPS Council notifications, TRIPS Council meeting minutes, WIPO Lex data and information collected from government websites, the paper provides a detailed overview of how and to what extent the key features of the Paragraph 6 System has been covered by WTO Members. The findings show that as of July 2015, 51 WTO Members (and Serbia) – almost a third of the WTO’s membership - have adopted specific, implementing measures, with varying degrees of detail and complexity. The predominant bulk of existing pharmaceutical exporters are included within those 51 Members. It is recommended that the Paragraph 6 System be used as an opportunity to aggregate the demand for a product in the form of regional procurement, thus, permitting an economically viable scale for the product and export of a pharmaceutical product. It is also advised that WTO Members continue an in-depth discussion of various issues, including the following: the use of the System as a procurement tool; how to more actively integrate Ministries of Health in the use of the Paragraph 6 System; how to make participation in the System more economically interesting, viable and sustainable; and how to simplify national measures implementing the System. It is also recommended that the international community support the Paragraph 6 System by encouraging the widespread use of this TRIPS flexibility.

35. Correa’s guide (2009) on the application and granting of compulsory licenses and authorization of government use of patent-protected pharmaceutical products is an attempt to foster a common approach in the use of TRIPS flexibilities for the procurement of medicines, vaccines and diagnostics kits. The aim of the guide is to provide practical, technical advice that can be used by governments, as well as procurement and non-governmental organizations,

about the modalities for the application of compulsory licenses and the utilization of government use provisions. The focus of which is centered upon the utilization of these mechanisms for the purchase and importation of patent-protected pharmaceutical products. The guide is split into two sections. The first looks at the application for and granting of a compulsory license. The second section considers the case of government use. When discussing what is contained in the guide, the author points out that it is meant to function as a guide only and that the concrete application of a grant of either a compulsory license or a government use license will depend on the relevant and applicable provisions of each country's individual national law. In trying to decide between which of the two mechanisms to use, the author recommends the government use license as in many cases it is the simplest and fastest way of purchasing patented medicines. This is because of a legal advantage whereby a government can issue a government use license without the need for a third-party request and, where issued for a public non-commercial purpose, without needing prior negotiation with the patent holder. The special rights of least-developed countries are also highlighted, with a reminder that paragraph 7 of the Doha Declaration removes the need to enforce patents or exclusive marketing rights on pharmaceutical product until the end of the transition periods.

#### Overarching studies relevant to patents and public health

36. The World Health Organization published a compilation of papers and perspectives on intellectual property and medicines (2010), with the aim of supporting efforts to build capacity in the application and management of intellectual property in a manner oriented toward the public health needs and priorities of developing countries. This was mandated by the Global Strategy and Plan of Action on public health, innovation and intellectual property, adopted by the World Health Assembly in 2008. In total, 17 papers are included on the following topics: (1) Trade agreements, intellectual property and access to medicines: an introduction; (2) Intellectual property right and public health: the general context and main TRIPS-compliant flexibilities; (3) Introduction to patent law; (4) Patentability standards: When is an invention patentable?; (5) Excerpts from "guidelines for the examination of pharmaceutical patents"; (6) TRIPS flexibilities: the case of India; (7) Implementation of the WTO decision on paragraph 6 of the Doha Declaration of the TRIPS Agreement and Public Health; (8) Patents, compulsory licenses and access to medicines: some recent experiences; (9) Challenging pharmaceutical patents: the case of India; (10) Monopolizing clinical trial data: implications and trends; (11) Protection of data submitted for the registration of pharmaceutical products: TRIPS requirements and TRIPS-Plus provisions; (12) IPR provisions in FTAs: Implications for access to medicines; (13) A few questions on health and human rights; (14) Excerpts from the report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health; (15) Protection of traditional medicine: lessons from India; (16) Using competition law and policy to increase access to a sustainable supply of affordable medicines; (17) Is Bayh-Dole good for developing countries: Lessons from the US experience. The papers thus, comprehensively explore the principal issues in intellectual property as it relates to health.

37. The trilateral study (2012) by the World Health Organization (WHO), World Intellectual Property Organization (WIPO) and World Trade Organization (WTO) provides a response to the increasing demand for strengthened capacity in informed policy-making between the intersecting areas of health, trade and IP, with a focus on access to and innovation of medicines and other medical technologies. The study is split into four chapters: (1) Medical technologies: the fundamentals; (2) The policy context for action on innovation and access; (3) Medical technologies: the innovation dimension; and (4) Medical technologies: the access dimension. Some of the findings and the main summary conclusions of the report includes the following: access to essential medicines is an element of the right to health; lack of access is rarely due to a single factor but is related to a multitude of factors; even lower-priced generic medicines are often unaffordable or unavailable in many low- and middle-income countries; regulatory

systems are important but at the same time too many regulatory barriers can delay access; the patent system, in principle, promotes innovation but this market-based innovation model fails to address neglected diseases; the impact of patents on access is complex but that the appropriate licensing of patent, including voluntary licenses, and the use of TRIPS flexibilities can help with the pursuit of public health objectives; competition policy can serve as a corrective tool, and that free-trade agreements are have an increasing impact on access issues. It is recommended, among other things, that governments must play a lead role and this must include their commitment to adequate and sustainable financing, effective procurement, the removal of tariffs and taxes and also the regulation of price mark-ups.

38. The World Health Organization's (WHO) Reference Guide on International Trade and Health (2009) is a collection of seven individual WHO Briefing Notes dating from 2001 until 2008 and selected WHO resolutions that have a bearing on public health, intellectual property and/ or international trade. This includes resolutions from WHO Regional South-East Asia as well as relevant resolutions from various World Health Assemblies. The intention of the guide, which also includes a basic dictionary of selected terms, is to help health professionals overcome the obscurity contained within the language of trade and health and to elaborate on some of the trade related public health issues through the amalgamation of informative briefing notes. The briefing notes which have been included are the following: Globalization, TRIPS and access to pharmaceuticals (2001); TRIPS, intellectual property rights and access to medicines (2006); data exclusivity and other "TRIPS-plus" measures (2006); innovation for diseases that mainly affect developing countries: issues and ideas (2007); Country experiences in using TRIPS safeguards (2008); Implications of bilateral free trade agreements on access to medicines; GATS and health related services (2006). It is recommended that this guide provide a starting point for health professionals who are interested in but not familiar with the trade and health domain.

*Peer-reviewed academic research (economic literature)*

#### Incentivizing and promoting the development of new medicines and health technologies

39. Gamba (2017) uses data on 74 developed and developing countries over the period 1977-1998 to study the impact of the strengthening of intellectual property protection on domestic innovation in the pharmaceutical sector. Domestic innovation is measured by citation-weighted pharmaceutical patent filings (according to the International Patent Classification) with the European Patent Office by inventors of a given country. The study considers two types of changes to a country's intellectual property system: a strengthening of intellectual property protection to achieve compliance with the TRIPS Agreement and the introduction of weaker forms of intellectual property protection pre-dating the TRIPS Agreement. The results show a large positive effect of a strengthening of IP protection on patent filings as a result of the TRIPS Agreement but there is also an equally strong positive effect on patent filings as a result of weaker forms of intellectual protection. Moreover, the effect associated with the TRIPS Agreement is significantly larger for developed than developing countries and is relatively short-lived. Overall these results suggest that the availability of patent protection is important; the strength of patent protection however appears to be less important.

40. Galasso and Schankerman (2015) assesses what happens when patents are invalidated by the U.S. Court of Appeals for the Federal Circuit (CAFC) over the period 1982-2008. The study does not focus only on pharmaceutical and medical device patents although the sample of patents litigated at the CAFC includes around 25 percent pharmaceutical and medical device patents. The results provide no evidence that follow-on research in pharmaceuticals is significantly affected by the invalidation of pharmaceutical patents, where follow-on research is measured by citations to the invalidated patent as well as new clinical trials. This result stands in stark contrast to the results for other technology areas, notably computers and

communications and medical instruments, where the study does find large effects on forward citations following the invalidation of a patent by the court. With respect to medical instruments, the study also uses FDA approval requests for new medical instruments as an alternative outcome measure and finds that approval requests increase following the invalidation of a relevant patent. The main conclusion from this study is that while patents appear to have a blocking effect on cumulative innovation in a number of technology fields including medical instruments, there is no evidence that this is also the case in pharmaceuticals i.e. pharmaceutical patents do not hinder the development of new drugs.

41. Kyle and McGahan (2012) analyze whether changes in the strength of patent protection brought about by the TRIPS Agreement have had any differential effect on R&D effort (measured as number of new clinical Phase I trials) between global and neglected diseases, i.e. diseases that are mainly prevalent in developing countries. The sample consists of 192 countries and covers 84 disease categories over the period 1990-2006. The study finds that stronger patent protection following the TRIPS Agreement increased R&D targeting global diseases but had no impact on R&D focused on diseases prevalent in developing countries (neglected diseases). That is stronger patent rights in developing countries did not lead to more investment in research on diseases relatively more prevalent in these countries. The main conclusion is that regardless of any static welfare losses in developing countries due to increased prices following a strengthening of the patent system, there is no evidence for any dynamic gains in the form of increased incentives for investment in R&D that tackles diseases prevalent in developing countries. In other words, if the static welfare losses are positive, there are no dynamic gains to balance them.

42. Panattoni (2011) analyzes stock market returns of originator companies following the decision by U.S. district courts on Paragraph IV related validity challenges on 39 branded drugs. More specifically, the paper analyzes cumulative abnormal returns in the stock market for originator companies following the decision in 37 district court cases on Paragraph IV challenges. Originators won 17 out of these 37 cases and experienced large positive cumulative abnormal returns as a result. In contrast, in the court cases that they lost, they experienced similarly large negative returns. The study interprets these findings to suggest that Paragraph IV related court litigation generates considerable risks for originators as a loss results in significant negative stock market returns. The study argues that the risk of losing patent protection generates uncertainty for companies which could affect their incentives to invest in R&D for the development of new drugs.

43. Ryan (2010) offers a case study in which he analyzes the impact of a strengthening of patent protection in Brazil in 1996 on the bio-medical industry in the Brazilian State of Sao Paulo. The article discusses five specific bio-medical projects which offer evidence that the strengthening of patent protection has led to an increase in innovative activity by established (generics producing) pharmaceutical companies as well as start-ups and to the launch of new patented bio-medical drugs in the Brazilian and potentially U.S. and European markets. The case studies also suggest an increase in collaboration between private generic companies and university researchers to develop new bio-medical technology as a result of stronger patent protection.

44. Athreye et al. (2009) offer several firm-specific case studies to argue that the pharmaceutical industry in India before the TRIPS Agreement was characterized by very low R&D intensity, a focus on reducing production costs of generics, and direct commercialization in countries that did not grant product patents, as well as licensing and contract-manufacturing agreements with foreign originator companies. The TRIPS Agreement (in combination with the Hatch-Waxmann Act in the U.S.) had a number of effects on the Indian pharmaceutical industry: Indian companies emphasized the focus of their R&D efforts on drugs, vaccines, and diagnostics where patent protection had already or was about to expire. Indian companies also

engaged in contract research and manufacturing and bioinformatics services, and conducted clinical trials for foreign originator companies. To a much smaller degree, Indian pharmaceutical companies also started to invest in the development of new drugs. Therefore, on the one hand the TRIPS Agreement strengthened patent protection and limited the ability of Indian generics producers to rely on reverse engineering, on the other the liberalization of the Indian economy and regulatory changes in the U.S. created new opportunities for Indian companies. The combination of these different factors led Indian generics producers to focus on the development of cheap, high-quality generic drugs and to insert themselves in the production chain of foreign originators by allowing originators to outsource at lower cost. That said, according to this study, there is little evidence for TRIPS Agreement to have encouraged domestic Indian new drug development.

45. Qian (2007) analyzes the effect of changes in pharmaceutical patent protection in 26 countries over the period 1978-2002 on different measures of innovation (measured as citation-weighted pharmaceutical patents granted by the U.S. Patent and Trademark Office and domestic R&D expenditures in pharmaceuticals) in these countries. The study analyzes the impact of changes in pharmaceutical patent protection by comparing the 26 countries that did experience a change to a set of matched comparable countries that did not undergo any changes either because they already granted pharmaceutical patent protection or because they continued not to do so throughout the relevant time period (for this matching approach, the 26 “treated” countries are allocated into 5-year time windows depending on when their patent laws changed). The results suggest on average no change in innovative activity as a result of changes in domestic pharmaceutical patent protection. However, stronger pharmaceutical patent protection is associated with more innovative activity among countries with higher GDP per capita and educational attainment. The main finding of this study is that there is no evidence that stronger patent protection of pharmaceuticals leads to an increase in domestic innovative activity in the pharmaceutical industry.

46. Dhar and Gopakumar (2006) assess the impact of the TRIPS Agreement on the Indian pharmaceutical industry. The study finds that the Indian pharmaceutical industry underwent consolidation and experienced an increase in R&D spending, driven mainly by the large players in the Indian market, Ranbaxy and Dr. Reddy’s. Indian generics producers also developed new generic drugs and novel drug delivery systems since the adoption of the TRIPS agreement. They have also increased the number of new market approvals in the U.S. and the UK. Indian generics producers also emerged as strong players in the global contract research and manufacturing markets. They are also increasingly engaged in collaborations and alliances with foreign originator companies. That said, despite increased R&D spending and patenting activities by Indian generics producers, so far there has been little success with the development of genuinely new drugs. The study also emphasizes that an important determinant of the success of the Indian pharmaceutical industry in the post-TRIPS period has been its ability to develop and grow under a weak pre-TRIPS patent regime that only granted limited protection to process patents.

47. Jack and Lanjouw (2005) present highly stylized theoretical analysis to explore optimal international price setting of pharmaceuticals in a global context. The model suggests that given the large disparity in income between developed and developing countries, prices in developing countries should not necessarily cover marginal cost of the production and distribution of pharmaceuticals. They should not contribute to the corresponding R&D expenses either. The main argument is that purchasing power in developing countries is low, so any increases in revenue for originator companies from stronger patent protection in developing countries are likely to be small. The exception to this are neglected diseases; for pharmaceuticals that target diseases mostly prevalent in developing countries stronger patent protection could increase incentives for drug development.

48. Sampath (2005) offers survey evidence collected from 103 Indian firms to suggest that product patent protection is likely to have a large effect on business strategies and R&D activities of generics producers in India. The survey suggests that Indian generics producers adopted competitive as well as cooperative strategies in response to the introduction of product patents. Competitive strategies included entry into regulated markets, a strengthening of product portfolios to cope with global competition, increased investment in R&D specifically to create innovation in generics through new products and processes and bulk drugs, supply of off-patent generics to semi-regulated and unregulated markets, by setting up manufacturing plants and marketing infrastructure outside India or strengthening supplier partnerships, and by offering specialized services in the contract research market. Collaborative strategies include in-licensing of foreign technology, collaborative R&D, contract research, and co-marketing alliances. The survey also provides evidence that Indian generics producers found it more difficult post-TRIPS to access new technologies because of the existence of often multiple patents on research input or high licensing fees. Finally, the evidence also suggests that Indian generics producers are increasingly patenting defensively to ensure their activities are not obstructed by others. Overall, the study indicates that the TRIPS Agreement has had a major impact on business strategies of Indian generics companies which are coping with the corresponding challenges while also grasping the opportunities.

49. Williams (2013) analyzes the question of whether IP blocks subsequent research on genetic diseases and the development of genetic diagnostic tests. The study compares follow-on research and the subsequent development of gene-based diagnostic tests that build on human genomes that were sequenced by the public Human Genome Project or the private company Celera. This comparison is informative because the sequencing done by the Human Genome Project was made continuously available to the public domain for anyone to use free of charge. Celera instead treated its results as proprietary through contract-law based IP and charged commercial users data access and licensing fees. Eventually, the Human Genome Project also sequenced all the genes previously sequenced by Celera and placed the data in the public domain. The results suggest that IP protection by Celera had large negative effects (between 20 and 30 percent) on subsequent scientific research and the development of genetic diagnostic tests despite the fact that the genes protected by Celera's IP entered the public domain within two years after Celera started to market them. The main conclusion from this study is that IP, even when it is short-lived, can have lasting negative effects on medical research and the development of diagnostic tests.

Affordability and availability of medical products, TRIPS flexibilities (including compulsory licensing), voluntary licensing and patent pools

50. Cockburn et al. (2016) assesses the speed of diffusion of 642 new drugs in 76 countries between 1983 and 2002. The study asks to what extent the decision by pharmaceutical firms to launch new drugs in a given market depends on the patent regime and price regulation in place. The study finds that stronger patent regimes accelerate the launch of a new drug in a given country whereas price regulation delays it. The strength of patent protection is measured along four dimensions: duration of the patent term, coverage of pharmaceutical products, coverage of pharmaceutical manufacturing processes, and a patent strength index. These measures still contain substantial variation during the time period studied since not all countries had yet implemented the provisions of the TRIPS Agreement. The study finds that both product and process patents have an effect on the launch of a new drug, although the effect is stronger for product patents; process patents have no effect in countries that have a long patent term in place while product patents still have a large effect. Other important factors that accelerate launch include market size measured as population and GDP per capita, and the existence of national health policies that facilitate the distribution of drugs. The main conclusion from this study is that patent rights affect the diffusion of new drugs, which is a distinct effect from its impact on the development of new drugs.

51. Duggan et al. (2016) assess the impact of product patents available as a consequence of the TRIPS Agreement on prices of single-molecule pharmaceutical products in India. To do this, the study relies on some quasi-random variation in the timing of patent grants by the Indian patent office. The results suggest only modest price increases as a result of the granting of pharmaceutical product patents, on average only 3-6 percent after the grant of a patent. The modest effect appears to be largely driven by the continued existence of substitutes even after product patents were issued. Drugs without such substitutes experienced higher price increases, although an average increase of 20 percent is still relatively modest. The results do not suggest any significant effects on quantities sold and companies operating in the market. The main conclusion from this study is that the introduction of pharmaceutical product patents had only minor effects on prices. The interpretation of these results by the authors is that specific provisions under the TRIPS Agreement such as the threat of mandatory licensing, price regulation, the fact that generic producers that were manufacturing a drug before 2005 in India could continue to do so even if a patent was later granted (although they had to pay a licensing fee), as well as potential difficulties with patent enforcement may have limited the ability of patent owners to increase prices in practice.

52. Branstetter et al. (2016) analyze what happens when generic producers enter the U.S. market for hypertension drugs through a successful so-called Paragraph-IV challenge. Under this mechanism, a generics producer enters the market of a patented drug by claiming non-infringement or invalidity of the relevant patent(s). Using data on successful Paragraph IV challenges during the 2000-2008 period, the study suggests that consumer surplus increases by US\$42 billion as a result of entry before relevant patents would have expired while producer surplus drops by US\$32.5 billion. This means that generic entry before the relevant patent would have expired leads to a net social welfare gain of US\$9.5 billion. The welfare gain is not primarily driven by increased consumption of drugs where generic entry occurred but instead by an increase in the variety of drugs offered since when generic producers enter, they tend to offer new varieties of a drug. The study also shows that generic entry also leads to substantial cross-molecular substitution i.e. consumers switching from a branded patent-protected drug to the generic version of a different branded drug. This suggests that generic entry of one drug also affects prices of other drugs and therefore increases the benefits to consumers of generic entry (although the study highlights that it is not clear how much of that gain goes directly to consumers as opposed to for example pharmacies, insurance companies etc.). The conclusion from this study is that although generic entry has large effects on prices, the net welfare gain is relatively small. It mainly shifts surplus from originators to consumers. The study does not explore any effects this might have on incentives for new drug development by originators.

53. Danzon et al. (2015) analyze the determinants of differences in drug prices across countries. The study uses data on drug prices for HIV/AIDS, TB, and malaria in a large set of industrialized and developing economies for the period 2004-2008. The results show large differences between drugs patented by originators and generic drugs. While prices are sensitive to per capita income levels across countries, they are far from adjusting fully to the lower income levels in developing countries. This is in part explained by the skewed income distribution in developing countries. Moreover, price competition appears to be weak in developing countries due to uncertainty about the quality of generic competitors. The results suggest that promoting generic entry and competition might have little impact on access to drugs in low-income countries.

54. Berndt and Cockburn (2014) analyze the market launch lag of 184 molecular entities approved by the U.S. FDA between 2000 and 2009 in the U.S., Germany, and India. The study finds that out of these 184 drugs, 160 were available in Germany by 2010, but only 111 in India. Drugs were launched fastest in the United States of America followed by Germany: 93 percent of drugs were launched in the United States of America within three years of market approval

and 77 percent in Germany within the same time frame. In India, in contrast, only 30 percent were launched within three years and even within five years only 43 percent had been made available. Focusing on the subset of drugs that have been introduced in the market, the study finds that the median launch lag in the United States of America is less than two months, about a year in Germany, but around five years in India. An important factor determining launch lags is the market potential for a given drug where blockbuster drugs were introduced significantly faster even in India. Another explanation is relatively weaker patent protection in India: the data show that drugs introduced in India quickly faced generic competition while there is no evidence for similarly fast generic entry in the United States of America and Germany. The main take-away from this study is that relatively weaker patent protection and enforcement may lead to no or delayed launch of new drugs but conditional on launch, there is much faster entry of generic competition which presumably leads to lower prices.

55. Vandoros (2014) analyzes whether there is any substitution between molecules that lose patent protection and other molecules in the same therapeutic class that are still patent-protected. The study relies on data on 14 angiotensin-converting enzyme inhibitors and five proton pump inhibitors in six European countries over the period 1991-2006. The results suggest that when a molecule goes off-patent and there is generic entry, a switch occurs from the off-patent molecule to other molecules that are still patent protected within the same therapeutic class. These results suggest that the loss of patent protection affects also demand for molecules that are still patent protected. In the presence of such substitution patterns, generic entry will have a weaker effect on prices.

56. Bhaduri and Brenner (2013) look at a sample of 596 new drugs launched in the German market between 1990 and 2004 and ask which drugs are also introduced in India and the corresponding launch lag. The empirical analysis covers the pre-TRIPS Agreement period as well as the period after 1995 when India had signed the TRIPS Agreement but implementation was delayed due to a 10-year grace period until 2005. Therefore the analysis looks at new drug launch pre-TRIPS. The results show that around a third of the drugs launched in Germany were also launched in India. The main determinants of the launch delay are the expected commercial success of a drug, among blockbuster drugs, 42 out of 51 drugs launched in Germany were also launched in India. The analysis also shows that drugs were introduced significantly faster post-1995, presumably this is some type of TRIPS Agreement anticipation effect. There is also evidence that drugs for infectious diseases see longer launch delays, which may be explained by the small market size (in purchasing power terms) and lower prices due to generic competition.

57. Lakdawalla and Philipson (2012) analyze prices and demand for patent-protected pharmaceuticals in the U.S. after their patent protection expires. The sample consists of 101 molecules whose patent protection expired between 1992 and 2002. The results show that after a patent expires, drug sales contract on average by about 5 percent within 5 months after patent expiration instead of expanding as one would predict if high prices sustained by patent protection limit output prior to patent expiration. The study suggests that this pattern is explained by the fact that monopoly pricing enabled by patents provides incentives for originators to invest in advertising, measured as direct-to-physician marketing. Once patent protection expires, originators have fewer incentives to invest in advertising. In the short run, the reduced demand as a result of the decrease in advertising may offset any increase in demand from lower prices. In the long-run, however, the price effect dominates the advertising effect. Still, the results show that welfare gains from patent expiration to consumers are approximately 30 percent lower due to the decrease in advertising. The main conclusion from this study is that monopoly pricing due to patent protection creates valuable private incentives for companies to invest in marketing; if marketing creates value to consumers, such incentives can even offset the costs to consumers from monopoly pricing associated with patents.

58. Amin and Kesselheim (2012) show how an originator company used patenting strategically to extend the effective patent term and thereby delay generic competition for two antiretroviral drugs (Norvir and Kaletra). The study identified a total of 108 patents (including primary and secondary patents) that protect these two drugs and demonstrates how the use of secondary patents (i.e. patents that protect other aspects of a drug than the active ingredient, e.g. formulation patents) afforded the originator up to 12 years of additional patent protection counting from the expiration of the drugs' primary patents. The conclusion is that certain patent strategies allow originator companies to extend patent protection and therefore avoid generic entry and competition.

59. Ellison and Ellison (2011) analyze the behavior of the manufacturers of 63 drugs that lost patent protection in the U.S. between 1986 and 1992. The objective of the study is to test whether companies engage in entry deterring behavior prior to expiring patent protection. The results provide only weak evidence that firms behave strategically to deter entry in light of the looming loss of patent protection. The main conclusion from this study is that exclusivity through patent protection may provide strategic incentives for firms to deter entry of generic manufacturers even when patent protection has expired - here the mechanism through which entry is deterred is advertising - although the empirical evidence to support this hypothesis is relatively weak.

60. Mazzoleni (2011) analyzes the importance of patents and their exclusive licensing for collaboration agreements for the commercial development of drugs between academics that had received a National Institutes of Health (NIH) grant and private pharmaceutical companies between 1945 and 1965. The results show that before 1962, patents and their exclusive licensing to pharmaceutical companies played no significant role in promoting collaboration between academics and private companies and the commercial development of new drugs based on these collaborations. On the one hand, pharmaceutical companies were unlikely to obtain exclusive rights on any of the research by NIH grantees, on the other hand, they did not have to sign away any rights to patents that could result from the further development of that research. Regulatory reforms in 1962, in particular the Amendments to the Food, Drugs, and Cosmetics Act, changed this. After the reforms, patent protection and exclusive licensing became more important to pharmaceutical companies because costs of bringing new drugs to market had increased as a result of the reforms. At the same time, the government significantly increased public funding of biomedical research which increased the amount of publicly accessible biomedical knowledge. That increased the risk of competition by generating opportunities to enter the market especially for smaller firms that could not afford the R&D investment. In response to the increased cost of bringing drugs to market and the increased threat of competition based on government-funded research, pharmaceutical companies requested exclusive licensing agreements from academics which led to their increased use of patents on basic academic research.

61. Schweitzer and Comanor (2011) compare prices of the 30 top-selling drugs in the U.S. over the period 2000-2007 across 3 categories: drugs that are still patent protected, drugs for which there exists already generic competition, and WHO essential drugs. The study computes price indices for the drugs in each category and compares those between industrialized, middle-income, and developing economies. The results show that for patented drugs, middle-income countries pay on average 52 percent of the price charged in industrialized countries and developing countries pay 27 percent. For drugs for which there is generic competition, middle-income countries pay 71 percent and developing countries 41 percent of what industrialized countries pay. For WHO essential drugs, middle-income countries pay 28 percent and developing countries 6 percent. The results also suggest that the price of patented drugs is less sensitive to differences in per capita income across countries than off-patent and WHO essential drugs.

62. Berndt et al. (2011) examine availability of 156 new molecular entities that were launched in the U.S. between 2000 and 2009 in 8 other countries between 2004 and 2009. The results show that new drugs are significantly less likely to be launched in Brazil, China, and India, than countries that afford stronger pharmaceutical patent protection to pharmaceuticals including Germany and Spain. In addition, the study also finds that conditional on launch, drugs are much more likely to be offered by multiple firms in China and India, which indicates that weaker patent protection leads to generic entry and competition. The results therefore illustrate that weaker patent protection lessens incentives for originator companies to launch new drugs in a given market. At the same time, the results also suggest that conditional on launch, weaker patent protection leads to more generic competition and therefore lower prices.

63. Goldberg (2010) argues mainly based on the empirical evidence provided by Chaudhuri et al. (2006) that patents are unlikely to lead to higher prices on pharmaceuticals in developing countries because of lower purchasing power, existing price controls and other regulation. At the same time, the limited market size also makes it unlikely for foreign originators to have strong incentives to invest in the development of new drugs that target neglected diseases. Instead, the most important effect of patents on pharmaceuticals in developing countries concerns access. The main reason is that due to lower per capita income and therefore lower prices, originators launch new drugs in developing country markets with a delay or not at all. Even when access occurs, marketing and distribution may be constrained, effectively limiting access especially in more remote geographical areas. The paper argues that in order to ensure access, policies that focus on access in the short- and medium-run such as compulsory licensing are appropriate.

64. Ching (2010) analyzes market dynamics after a patent on an originator drug expires. Specifically, the study looks at how approval time by the U.S. FDA affects expected profits and therefore market entry by generics producers. The analysis relies on data for 4 high-blood pressure drugs in the U.S. between 1984 and 1990. The results suggest that if generics producers can enter faster, they are less likely to cover sunk entry costs and therefore in equilibrium fewer generics companies enter the market. However, on average generic options become available sooner in the market and there is less product differentiation among generics which leads to a lower price.

65. Chadha (2009) analyzes exports by a sample of 131 Indian pharmaceutical companies traded at the Bombay Stock Exchange over the period 1989-2004. The period coincides with a substantial strengthening patent protection in India to bring the country into compliance with the TRIPS Agreement. The results show that exports by Indian pharmaceutical companies increase if they have been granted patents at the USPTO or EPO. The study interprets these results as evidence that patents help Indian companies succeed in exporting.

66. Li (2008) compares China and India, where China had adopted patent protection for pharmaceutical products in 1993 while India adopted it only later as a result of the TRIPS Agreement and did not start granting pharmaceutical product patents until 2005. The study relies on secondary data sources to conclude that in China prices for a small selected set of drugs for which data was available were high compared to India while at the same time drug availability was in fact low in China. The study also suggests that R&D investment in drug development is lower in China than India. The main finding of this study is that China does not appear to have benefitted from its early adoption of pharmaceutical product patents compared to the late-adopter India.

67. Regan (2008) uses data on 18 oral solid prescription drugs in the U.S. that experience generic entry between 1998 and 2002 (where generic entry occurred because the end of the patent term or a Paragraph IV entry). The results suggest that price competition only occurs among generic drugs. Branded drugs are even able to raise prices, albeit only very moderately

by an average of two percent. Originators are able to charge these high prices to a price-insensitive segment of the market, which are consumers with some form of third party prescription drug coverage. Overall originators still experience a drastic decrease in market share following generic entry and revenue also drops due to overall decreased demand for originator drugs. The conclusion from this study is that patent protection allows originators to build brand recognition and customer loyalty that they are able to capitalize on when the patent expires. The evidence shows that when patents expire and generic entry occurs, it is possible that originators not only keep prices at the same level but even increase them slightly.

68. Chaudhuri (2006) analyze the impact of the TRIPS Agreement - specifically the introduction of product patents that cover pharmaceuticals - on prices of pharmaceuticals in India. More specifically, the study uses product-level data on monthly pharmaceutical prices and sales for the fluoroquinolones sub-segment of the systemic anti-bacterial segment in the Indian pharmaceuticals market over the period 1999-2000. The paper provides estimates for a counterfactual scenario where India had already been granting pharmaceutical product patents on these antibiotics to study what supply and prices would have been in the hypothetical situation. These simulations assume that the existence of patents would have limited the domestic supply of specific patented (by foreign pharmaceutical companies) antibiotics in the market. That is, instead of there being multiple essentially equivalent generic domestic products that compete with foreign products, only the patented foreign product(s) would have existed in the market. The study then estimates the resulting impact on prices and any resulting welfare loss for domestic producers and for consumers due to potentially higher prices. The results suggest that product patents would lead to significantly higher prices and a loss in domestic products on the market. The results suggest a price increase between 100 and 400 percent (in the absence of any accompanying price regulation). Domestic producers would suffer a significant loss for being excluded from the market, but the bulk of the welfare loss would be incurred by consumers due to these higher prices. In addition, the data suggest that consumers would also experience a welfare loss from the reduced supply of domestic products regardless of the price increase, i.e. domestic and foreign products are not regarded as perfect substitutes by consumers, presumably due to differences in marketing and distribution networks. The results also show an important effect of price increases of one type of antibiotic on other antibiotics within the same sub-segment. This means that the aggregate price increase and hence welfare loss when such interaction between markets is taken into account exceeds that of simply summing up welfare losses that would materialize if drugs were treated as separate, independent markets. The main conclusion from this study is that the introduction of patent protection in developing countries may lead to significant welfare losses due to increased prices and reduced variety available to consumers.

69. Reiffen and Ward (2006) analyze entry by generics and the evolution of corresponding drug prices. The study analyzes generic competition in the U.S. for 31 drugs that went off patent in the late 1980s and early 1990s. The results show that the first generics producer to enter the market for a given drug is able to charge significant mark-ups (20-30 percent). Mark-ups persist even when there are multiple entrants and only go to zero when there are 10 or more competitors. Markets with greater expected rents attract more entrants and entrants enter the market faster, bringing mark-ups down and dissipating rents for generics producers. This implies that larger markets tend to result in competitive pricing while smaller markets may retain positive price-cost margins as they do not attract sufficient entry by competitors. The main conclusion from this study is that the absence of patents in itself does not guarantee low price-cost margins. Instead, entry and ensuing competition brings price-cost margins down and the degree to which a market attracts entry depends on its size and hence expected profitability.

70. Stavropoulou and Valletti (2015) present theoretical analysis of the impact of compulsory licensing on access to drugs in developing countries and innovation by originator companies located in industrialized countries. In this model, compulsory licensing allows a developing

country to produce the originator drug and set its price equal to marginal cost. However, the developing country incurs fixed costs if it applies compulsory licensing. The analysis suggests that a developing country's ability to manufacture and distribute generic versions of an originator drug that is patent-protected is crucial in determining the welfare impact of compulsory licensing. If costs of manufacturing generics in the developing country are sufficiently low, compulsory licensing becomes a credible threat that leads originators to lower prices and therefore increase access. If costs are sufficiently low, compulsory licensing maximizes access to originator drugs. However, resulting lower prices have a negative effect on innovation by originator companies. On net, global welfare is higher if compulsory licensing is a credible bargaining tool that leads to lower prices and increased drug access in developing countries despite its negative effect on innovation.

71. Bond and Saggi (2014) analyze how a price control and the threat of compulsory licensing in a developing country in the South affect consumer access to a patented product in that country. In the model, the Southern government sets the level of the price control on a Northern patent holder who chooses between entry and voluntary licensing. While entry incurs a higher fixed cost, licensed production is of lower quality. If the patent holder does not work its patent locally, the South is free to use compulsory licensing. The analysis shows that the option to use compulsory licensing can benefit the South via three channels. First, compulsory licensing ensures that local consumers have access to the patented good (of a lower quality version) when the patent-holder finds it unprofitable to work its patent locally. Second, the threat of compulsory licensing improves the terms at which voluntary licensing occurs. Third, it can cause the patent-holder to switch from licensing to entry thereby leading to an improvement in the quality of the good available to local consumers. These benefits are somewhat offset by the possibility that compulsory license delays access to the product when it replaces voluntary licensing or entry as the market outcome (while also lowering quality when it replaces entry). The study also shows that a price control and compulsory licensing are mutually reinforcing instruments.

72. The paper by Flynn et al. (2009) uses theoretical economic modelling as justification for an open access license approach to patents on essential medicines in developing countries. Starting with the basic economic premise of patent law, the paper then uses this to make a distinction between the demand convex of a country with fairly equitable income distribution and a developing country, which typically has high-income inequality between the rich and the poor. Using the example of Norway versus South Africa, Flynn et al. demonstrate why there isn't an economic incentive for pharmaceutical companies to sell their patented invention to the majority of a population in a highly income disparate population, such as South Africa, when it can double its revenue by selling at a price that only the richest 10% can afford. On the other hand, in an egalitarian society like Norway, the demand convex means that profitability occurs with the greatest number of sales instead of the highest price. Therefore, the findings show that highly convex demand curves result in inequitable access to patent-protected essential medicines for all but the richest percentage of the population. To remedy this access problem created under by patent protection, it is recommended that developing countries use remedies such as compulsory licensing and look at the grant of open-licenses to permit competition by any qualified supplier for essential medicine patents. While the paper does not foresee the use of compulsory licensing as likely to affect the incentive to innovate in developing markets (as such incentives are presently negligible anyway), it is nevertheless recognized that the use of systematic compulsory licensing is unlikely to inspire the already negligible level of innovation for developing markets. Therefore, it is recommended that the incentivization of this innovation be encouraged through governmental and inter-governmental means.

Related literature: regulatory environment, market entry of new or generic drugs

73. Grabowski et al. (2017) analyze the behavior of originators and generics producers following important regulatory changes that occurred in the U.S. in 1998 and 2003. A court decision in 1998 changed the definition of a successful so-called Paragraph IV challenge to award 180-day exclusivity not only to the first generic market entrant through invalidation or a declaration of non-infringement by a court but also through a settlement with the patent owner. In 2003, the Medicare Modernization Act (MMA) provided for product-based 180-day exclusivity as opposed to exclusivity defined by on a patent-by-patent basis. Both changes increased incentives for generics companies to file a Paragraph IV challenge and to do so before competing generics companies did. The study uses data on 214 new molecular entities approved by the FDA and generic entry for the period 1994-2006 to show that in reaction to these changes generics producers filed more challenges and did so sooner after FDA approval of a new molecule in order to be first to enter the market. As a result, average market exclusivity for originators dropped from 14.5 years during the 1994-1998 period to 12.2 years during the 1999-2006 period. The analysis also shows that a large share of patent challenges in court are settled, potentially reflecting risk aversion by originators. Overall these results show that the regulatory environment can have strong effects on the effectiveness of patent protection for originators in preserving market exclusivity and hence their expected returns to R&D.

74. Gilchrist (2016) asks whether market exclusivity of a drug that is first in a given pharmacological class affects the number of other new drugs (not generics) that subsequently enter the same class. The data consists of 293 non-biologic drugs in 156 classes which includes new molecular entities first approved in the U.S. between 1987 and 2011 and subsequent entrants in the same pharmacological classes. The results suggest that the time lag between the approval of a drug that is the first in a given pharmacologic class and generic entry, i.e. market exclusivity, has a large positive effect on the number of other new drugs (not generics) that are launched later on in the same class. One additional year of market exclusivity leads to an increase of 25-30 percent in entry of new drugs in the same class. In other words, once generic entry occurs, there is significantly less entry of new drugs, presumably because the value of the market drops. Since subsequent new drugs are not perfect substitutes for the first-in-class drug, the results suggest that generic versions of the first-in-class drug nevertheless affect all drugs within the same class. That said, it appears that this effect is driven largely by some form of imitation within class rather than the development of genuinely new drugs. The main conclusion from this study is that patents protect rents that attract entrants, although the social value of such entry is unclear (since it appears to be driven by imitation, but entry could still lead to competition within classes and therefore lower prices even before generic entry, in addition different treatment options might be valuable to consumers).

75. Hemphill and Sampat (2011) analyze originator patent portfolios in the U.S. for new drugs approved by the FDA between 1985 and 2008 and study the determinants of Paragraph IV patent challenges targeting these new drugs. The study documents an increase in the number of patents filed for a given drug over time where growth is mainly driven by secondary patents. The increase in patent filings led to an increase in the nominal patent term i.e. the lag between a drug's approval date and the date of its last-expiring patent. At the same time, Paragraph IV challenges have also increased and generics producers target in particular drugs with secondary patents that extend the nominal patent term of a given drug. The evidence suggests that patent validity challenges counteract attempts by originators to extend the patent term through strategic use of the patent system.

76. Hemphill and Sampat (2012) analyze so-called Paragraph IV entry by generic manufacturers into the U.S. market by either invalidating existing patents or claiming non-infringement of the generic drugs. The analysis relies on data on 119 new molecular entities developed by originator companies that experienced first-time generic entry in form of a

Paragraph IV challenge in the U.S. between 2001 and 2010. The evidence shows that generic companies target high-sales drugs which also tend to rely on secondary patents to extend the effective patent term. This means that Paragraph IV challenges mainly serve to curtail attempts by originators to extend effective patent terms through secondary patenting. Paragraph IV challenges do not reduce the effective patent term afforded by the primary patent protecting a new molecular entity. The main finding from this study is that originator companies engage in strategic patenting in form of secondary patents to extent patent protection and in the U.S. Paragraph IV challenges allow generic companies to curb this behavior by successfully challenging the validity of these secondary patents.

*Peer-reviewed academic research (legal and general literature)*

#### Incentivizing and promoting the development of new medicines and health technologies

77. The article by Katz et al. (2006) searches for an explanation as to the decline in antibiotic research and patenting and offers some solutions to alleviate this problem. Using the statistics of other studies to establish the current antibiotic R&D and patent landscape, the article examines four potential areas that contribute towards this downward trend in antibiotic research. These include: a shifting of research priorities; a raised utility bar; and regulatory hurdles and lost profits. One reason identified for the decline of antibiotic R&D might stem from other healthcare advances which have reduced the occurrence of epidemics requiring new antibiotics. A result of which has been the shifting of R&D resources from antibiotics to other, more profitable, drugs. Another identified reason for the decline in the number of filed and issued patent applications stems from the USPTO's new guidelines, issued in 2001. Less liberal than the old guidelines, the new guidelines have more onerous patentability standards and thus, could explain part of the reason for the decline in the number of antibiotic patents. Other identified issues, such as increasing regulatory hurdles and the difficulty enforcing patents on new uses of an existing drug, are also raised as factors that contribute to the lack of commercial incentive to development new antibiotics. The extension of market exclusivity for a second use patent is recommended as one possible solution that could help to address this problem. Other recommendations include: a simplification of the FDA's approval process for antibiotics, an accelerated review process at the FDA for antibiotics, improved financial incentives for antibiotic R&D and the provision of longer patent term extensions to compensate the longer and costlier development of antibiotics.

78. The paper by Quinn (2010) draws a contrast between present efforts to invigorate commercial participation in the development of new antibiotics and the collaborative approach that led to the development of penicillin during World War II. By reviewing the historical origins of the antibiotic industry, the paper shapes the imperative differences between "then" and "now". The historical analysis credits the U.S. government-coalition sponsorship of antibiotic R&D during World War II with the development of penicillin. The urgency of wartime demanded coordination and collaboration between government agencies and scientists and ultimately resulted in the development of an antibiotic without the need to develop entitlements for corporations. While not identical, the situation in the 1940s is said to have some similarity to now, in the 21st century. Namely, a heightened need for novel antibacterial drugs, corporate reluctance and concern about overwhelming infections in the face of national security concerns. Yet, unlike the World War II penicillin project – which prioritized scientific progress through extensive collaboration and the exchange of scientific resources – the current focus tends to center around patents and economic motivations to stimulate R&D for antibiotics. This is despite evidence showing that patents did not play a major role in the development of penicillin. Instead, it was the absence of restrictive patents and the ability to access to biological specimens that permitted the sharing of resources between government, scientists and major pharmaceutical companies during World War II, thus expediting the development of penicillin. While it is recognized that currently some large-scale scientific collaborations employ similar

exchanges such as that of the penicillin project, no such model has been proposed for antibiotic R&D. It is recommended that antibiotic research could benefit from following suit, with collaboration demonstrating how the absence of patents can actually increase scientific productivity and industrial growth simultaneously.

79. The report by Stevens et al. (2017) explores the innovation process of vaccines, looking at challenges within the field of vaccine development. Primarily, the report aims to put into perspective the debates around vaccine innovation and the availability of vaccines in developing countries, particularly in respect to intellectual property. Vaccines are studied because of their particular value in public health as one of the most cost-effective public health tools which increase productivity and reduce government spending. Nevertheless, three major global challenges are identified: namely sizeable gaps in vaccine coverage; no satisfactory vaccines for high-burden infectious diseases; and no satisfactory vaccines for chronic non-communicable diseases. Regarding the R&D side of vaccine innovation, the use of both “push” and “pull” mechanisms is discussed. Problematically for vaccines, the average vaccine candidate only has a 6 percent chance of market entry from the pre-clinical phase. Further difficulties arise for vaccine manufacture as vaccines are more sophisticated, more complicated products than small-molecule drugs. The result of which is more lengthy and costlier quality control requirements for vaccine manufacture. The report shows a range of factors preventing the delivery of vaccines and these include: supply chain issues; inaccurate demand forecasting; a lack of coordination between procurement and supply; inadequate infrastructure; insufficient storage, delivery capacity and trained staff; and underperforming national health systems, among other obstacles. While tiered pricing and parallel importation could improve access, there are also challenges associated with the use of these. Regarding intellectual property rights, patents can be found on the formulation and the device for administration. As vaccines consist of multiple technologies – often only some of which are patented – it is sometimes possible to “invent around” the patent. Improved patent transparency and better IP management between manufacturers could help overcome IP barriers. However, the restricted availability of vaccines is due to impediments at every stage of the process and IPRs are only one those obstacles.

80. The paper by Zhang et al. (2016) uses patent citations to establish a patent landscape that visualizes and analyses the technology flows of antibiotic development. Patent citations are used as they are broadly believed to be powerful tools representing the technology landscape. Using the IMS R&D Focus database, all original worldwide patents of antibiotic R&D projects were collected as part of the research sample, including patents of both successful and unsuccessful projects. In the end, 707 US patents related to antibiotic R&D were retrieved, collected, analyzed and organized into seven sub-classifications. The findings show that the overall trend for the active period of patents grants in the antibiotic domain has already passed. The proportion of granted patents on the mechanism of action of an antibiotic has also dropped and much time has passed since the introduction of a new mechanism. Almost all the chemical classes and modes of antibacterial action of the patents relevant to R&D pipeline have been discovered and developed for decades with only a few new chemical class antibiotics discovered since the late 1980s. The results show that most of the new antibiotics in pipelines are derivatives of existing structures which were reported over 30 years ago. The results also show that there are more patents against resistant Gram-positive bacteria than Gram-negative bacteria and multidrug-resistant bacteria. The paper urges for the development of new compounds belonging to novel classes or targeting new antibacterial actions in order to counter the decreasing efficacy of antibacterial drugs. The paper recommends the creation of a new antibiotic business model to counter the balance between market-oriented investment and public health. It also recognizes that large pharmaceutical companies are still the major players in the context of overall pharmaceutical development, with 81 percent of the leading developers in the R&D of antibiotics - according to patent citations - being large pharmaceutical companies.

This leads to the conclusion that patenting the discovery of antibiotics or related technologies remains a key commercial strategy for developers.

Affordability and availability of medical products, TRIPS flexibilities (including compulsory licensing), voluntary licensing and patent pools

81. The work by Abbas and Riaz (2013) explores the practical legal implications faced by least-developed and developing countries when using TRIPS flexibilities. The aim is to identify why the use of compulsory licensing remains low, despite the availability of this TRIPS flexibility in theory. Looking to the legal theory in practice, the paper identifies the impediments that prevent the use of TRIPS flexibilities whilst simultaneously exploring how to avoid those impediments. The main impediments are identified as the following: the loss of foreign-direct investment (FDI), the use of unilateral trade sanctions, TRIPS-plus provisions in free trade agreements, border measures such as the confiscation of imported drugs, the risk of retaliatory action, a failure to use the technology transfer provision under TRIPS Article 66 and paragraph 7 of the Doha Declaration, a lack of technical expertise when incorporating TRIPS flexibilities into domestic law, the high-cost of litigation for a compulsory license, the failure to achieve the fundamental objectives of the TRIPS transition period, the risk of counterfeit drugs and a reduced incentive to innovate. The authors recommend that developing countries experiencing similar problems when issuing a compulsory license collaborate to create a collective procurement. It is also recommended to make use of the WTO Dispute Settlement Body where necessary to ensure the unencumbered right to TRIPS flexibilities, without fear of unilateral or retaliatory action. This includes the use of WTO Settlement to ensure technology transfer pursuant to TRIPS Article 66.2. The use of technical expertise and capacity building work in the development of local laws is also advised. As regards the compulsory licensing specifically, the findings suggest that other options promoting access to medicines should be exhausted before resorting to such licenses. This is, in particular, because compulsory licensing can reduce R&D and FDI as pharmaceutical companies can elect to withdraw drugs from, or stop performing research on disease areas affecting, that country's market.

82. The paper by Adusei (2011) analyses twelve different patent regulatory flexibilities that are currently available for the developing and least-developed countries (LDCs) of Sub-Saharan Africa. Setting the scene with reference to the AIDS pandemic, the author raises the issue of patents preventing access to antiviral medicines before moving into a comparative review of the various legal mechanisms that could help to overcome those patent barriers. The twelve proposed mechanisms include: the use of negotiations (for voluntary licensing); compulsory licensing for domestic production; parallel imports; public-private sector partnerships and initiatives to promote the R&D for affordable essential medicines; patent pools such as the Medicines' Patent Pool and other collaborative initiatives; "taking the Doha Declaration seriously"; avoiding TRIPS-plus obligations that are often included in free-trade agreements; making use of competition law mechanisms; taking steps to prevent the "evergreening" of expired or old patents; creating more avenues for pre-court patent opposition proceedings; overcoming the pressure of patent litigation exerted by the patentee; and pushing for further differentiated treatment for LDCs under the TRIPS Agreement. The use of regional economic groups is also promoted as a measure that can strengthen the use of these pro-access mechanisms. The paper finds that, for Sub Saharan Africa, the best approach is an approach that exploits the full array of regulatory diversity: where negotiations, compulsory licensing, public-private partnerships, regional inter-governmental cooperation and competition law are better harnessed; where TRIPS-plus obligations are rejected and where patent protection is scrapped in LDCs. The study concludes that currently there is already an array of elaborate legal provisions and mechanisms that can overcome patent barriers that prevent access to affordable, essential patent-protected medicines and that the key issue for Sub-Saharan Africa lies in their lack of effective engagement with and their utilization of these available flexibilities.

83. The study by Beall and Kuhn (2012) explores the trends in compulsory licensing since the Doha Declaration. Being more than a decade since the adoption of Doha Declaration - which reaffirmed the right of WTO Members to use the legal flexibility of compulsory licensing - the study aims to confirm or reject some of theorized impacts that the Declaration was expected to have on compulsory licensing activity. While some expected an increase in compulsory licensing activity, others believed that the Doha Declaration would only have a negligible impact due to the limited production capacity of LDCs and the possibility of provoking retaliatory behavior. As such the study aims to provide the first measurement of Declaration's impact on the occurrence of compulsory licensing. To do this, the study assembled a database of all the episodes in which a compulsory license had been publicly entertained or announced by a WTO Member since 1995. Broad searches were conducted using media, academic and legal databases, resulting in a list of 34 potential compulsory licensing episodes in 26 countries. After conducting country and product specific searches to verify government participation, the final database contained 24 verified compulsory licenses from 17 nations, involving 40 pharmaceutical product patents on 22 unique pharmaceutical products. The results show that half of all of the announcements of a compulsory license resulted in some kind of price reduction, whether via a compulsory license, voluntary license or a discount. The findings also show that most of the compulsory licensing between 2003 and 2005, involved drugs for HIV/AIDS, and occurred in upper-middle-income-countries. Aside from HIV/AIDS, few licenses involved communicable disease, with none occurring in least-developed or low-middle-income countries. Despite the skepticism about the Doha Declaration's likely impact there has been a drop in compulsory licensing since 2006. It is recommended that future studies assess whether the Doha Declaration has had an impact on subsequent patenting behaviors of pharmaceutical companies.

84. The paper by Christie AF. et al. (2013) aims to contribute to the evidence base for understanding the potential misuse of the patent system by pharmaceutical companies to inappropriately extend their monopoly position by "evergreening" blockbuster drugs. The study analyzed all of the patents associated with 15 of the most expensive drugs in Australia over the last 20 years. Specifically, the study searched the patent register to identify all the granted patents that cover the active pharmaceutical ingredient of the high-cost drugs. Then, the patents classified by type, and identify their owners. The study finds a mean of 49 patents associated with each drug. Three-quarters of these patents are owned by companies other than the drug's originator. The majority of all patents are owned by companies that do not have a record of developing top-selling drugs. The findings show that a multitude of players seek monopoly control over innovations to blockbuster drugs. Consequently, the authors conclude that attempts to control drug costs by mitigating misuse of the patent system are likely to miss the mark if they focus only on the patenting activities of originators.

85. The article by T'Hoën et al. (2011) reviews a decade's worth of developments in terms of the creation of and access to HIV/AIDS treatments. With a historical overview of the international evolution of patent law, written in parallel to the historical developments of the HIV/AIDS crisis, the authors are able to draw attention to the impact that patent developments have had on access to HIV/AIDS treatment. The findings show that post-Doha there have been sixty uses of TRIPS flexibilities in low- and middle-income countries to access lower-cost, generic versions of patented medicines on a large scale. The AIDS crisis is accredited as the catalyst for this change and for also encouraging other improvements in the sphere of public health. One such "other", non-intellectual property improvement brought about by the HIV/AIDS crisis is identified as the changing approach to R&D. With the conventional model of R&D motivated by patent profits, R&D for non-profitable markets such as the HIV/AIDS market have demanded incentivization be offered through alternative methods. New initiatives such as the product-private partnership Drugs for Neglected Diseases Initiative and the creation of the Medicines Patent Pool provide examples of some of these alternative mechanisms. Yet, despite concluding that there has been an improvement in the scale-up of antiretroviral

treatment over the last decade, the authors raise concerns over a new treatment “timebomb” (in terms of access to newer and more suitable antiretroviral HIV/AIDS treatment). Five key issues are identified as creating this access barrier: the increased cost of newer antiretrovirals due to patenting; an increase in the number of persons requiring new-generation antiretrovirals; the lack of availability of advances in research on newer drugs and combination drugs on a worldwide scale; the shrinking policy space for importing generic versions of patented medicines; and the presentation of a serious worldwide financial crisis. The authors conclude that while a decade of activism has improved access to first-generation antiretroviral treatment, there are still challenges that remain unmet in terms of addressing the HIV/AIDS crisis.

86. The article by Baker (2018) analyses the use of voluntary licensing (VL) and the various legal technicalities involved under various types of VLs as a means of accelerating access to medicines. The article aims to: (1) increase understanding of the history and evolution of VLs, including key terms and conditions and their consequent impact on access to medicines; (2) to identify and assess best-practice licensing terms; and (3) to make policy recommendations that improve the terms and conditions of access to VLs. Using a human rights framework founded on the right to health, the article provides a brief history on the evolution of VLs before moving on to analyze the significance and impact of specific terms and conditions that are commonly contained in VLs, such as: patents rights and disclosure, license requirements and restrictions, territorial and sector coverage and restrictions, royalty rates, grant-back rights, licensees responsibilities concerning registration and supply, publication of licenses and transparency of patent landscapes, and opportunities to improve or amend existing VLs. The findings show that the impact of VLs – in terms of affordable access to medicines – is highly country specific. In addition, six harmful consequences of VLs are raised: (1) the possibility that VLs give a false assurance that the access crisis has been met; (2) too much expenditure on VL public health initiatives instead of other IP-related strategies; (3) difficulty in the “correct” timing of a VL (before a patent decision/ originator product registration); (4) equitable concerns about excluded countries; (5) the possibility of negatively impacting opposition strategies and opposition and (6) compulsory licensing strategies. It is nevertheless concluded that, the imperfection or incompleteness of an access strategy does not override the many benefits that exist from VLs. However, it leads to the recognition of the need for a complementarity of access approaches. It is recommended that more research be conducted to better establish the benefits and negative impacts of VLs.

87. The paper by Cohen-Kohler et al. (2008) explores the major legal and political constraints preventing coordinated global policy solutions that increase access to essential medicines in the developing world. After examining the status and causes of the global drug gap, which include elements such as poverty, insufficient infrastructure and government failures, the paper elects to focus on patent-related barriers under TRIPS. The authors also pay particular attention to the various case examples in which TRIPS flexibilities have been lost or narrowed in scope because of a bilateral or free-trade agreement or an early WTO accession process. The paper finds that, where TRIPS flexibilities have been exercised by developing countries, some developed countries have opposed their decision to exercise that right. As a result, the use of TRIPS flexibilities has declined or become limited in use. The results also suggest that the principal beneficiaries of IP protection are the pharmaceutical companies in OECD countries while there is little evidence to suggest that TRIPS has resulted in technology transfer to help the social and economic welfare of developing countries. To overcome the legal barriers to access, the authors recommend the adoption of the following policy options: the use of the TRIPS amendment (with the right of production for export under a compulsory license, as per paragraph 6 of the Doha Declaration) without all the red-tape and the leveraging for compulsory licenses on a regional rather than a per-country basis; the use of voluntary licensing agreements in advanced, developing countries that have domestic manufacturing capacity; promoting access to medicines as a fundamental human right; and research and advocacy that

focuses on proposing amendments to the TRIPS Agreement and/or that questions the legitimacy of TRIPS standards in developing countries and LDCs.

88. The article by Guennif and Chaisse (2007) explores the impact of the TRIPS Agreement both as it relates to, and as it has transformed, the Indian patent regime and domestic pharmaceutical industry. By adopting a historical approach to the legal and economic analysis, the authors chronologically map out three major evolutions that have occurred within the Indian intellectual property regime over the last decade. The historical evidence shows that the first stage of patent protections in Indian law (during the colonial period before the 1970s), which included patent protections on products and processes, prevented the evolution of a strong domestic pharmaceutical industry. After the 1970s and the weakening of the patent laws – particularly on pharmaceutical products – India’s pharmaceutical industry grew. Then in the third stage, after joining the WTO, India was required to re-strengthen domestic intellectual property laws and meet the requirements of TRIPS. After summarizing the major legal changes and challenges for India in her move towards implementing domestic, TRIPS compliant law, the authors then engage in a balancing exercise. Specifically, to determine whether developing countries have in fact benefited from stronger intellectual property regimes as required under the TRIPS Agreement. By comparing the experience of Thailand with India, the authors conclude that the system of weaker patent protections in India demonstrated more advantages in terms of access to affordable medicines than the stronger regime of Thailand. India’s efforts to limit the patentability criteria, as well as the strong political will of India’s authorities against the trade pressures of developed countries, are identified as providing important public health measures. Nevertheless, the article finds that developing countries could do more to ensure access to pharmaceuticals. For instance, it is recommended that institutional price control measures could provide a useful pricing measure given that the TRIPS Agreement does not prohibit WTO Members from using such measures.

89. The paper by Kuan (2009) explores the concerns that patent protection may be impeding access to affordable healthcare. Building upon pre-existing literature, including public health statistics, the author begins by identifying a global public health crisis before moving on to propose five avenues of more affordable access to patented medicines. The author approaches the legal problematic – patent barriers and high-prices – with two carveouts. First, that any use of patent flexibilities should maintain an appropriate balance with patent rights, so as not to stifle further innovation and access to medicines. Secondly, by admitting that the access problem is a much more complex web of additional, non-patent related obstacles and that such obstacles are beyond the scope of this particular paper. The findings demonstrate that, despite the majority of the essential medicines for HIV/AIDS, tuberculosis and malaria being off-patent, access to affordable patented medicines remains an issue by virtue of outbreak diseases such as SARS. The author then examines the following five avenues of access to patent protected medicines: generic competition, parallel importation, compulsory licensing, voluntary licensing, and the limitation of patentability criteria. The author recommends the exploration of a “Quota system” based on a percentage of global turn-over to ensure the appropriate balance between public interest and the legitimate private interest of patent holders when determining adequate remuneration under a compulsory license. The possibility of an industry framework of good practice is also proposed, among other recommendations. The findings also exhibit the existence of an R&D gap for neglected diseases. The main conclusion of the paper is of the need to reconcile and effectively manage competing interests in order to ensure better access to medicines in certain circumstances. This is said to require the striking of a balance between public interest and the legitimate interest of patent holders.

90. McKeith’s article (2014) examines the usefulness and the role of parallel importation on the public health outcomes of and accessibility to affordable, patent-protected medicines in developing countries. First, the parameters of patent exhaustion as per Article 6 of the TRIPS Agreement are established before the article moves on to identify the various legal possibilities

and flexibilities available at the domestic level. Next, the practical difficulties faced by those who engage in parallel importation as a public health policy tool are discussed. The findings demonstrate that the competition created through parallel importation has a downward effect on prices enhancing consumer welfare with price reductions. There is also evidence that patent exhaustion improves access to affordable antiretroviral medicines in developing countries. Nevertheless, the findings also evidence reduced R&D incentives for diseases common in those countries that engage in the practice of patent exhaustion. It also results in increased international pressure, the threat of trade sections and threatens schemes of price differentiation which are ordinarily offered by pharmaceutical companies in developing markets. To address these issues, it is recommended that regional organizations harmonize their patent laws by adopting a regional regime of exhaustion, coupled with certain complimentary regulatory and policy measures. One such complimentary policy measure is to prevent the re-exportation of the parallel import outside the regional group into a higher-priced market. The article finishes by acknowledging the existence of several theoretical and practical difficulties which could arise when adopting a regional approach and an additional section that discusses how those issues might best be resolved.

91. The paper by Pwasiri (2013) explores the effectiveness of pre- and post-grant patent opposition using Thailand as a case study. To make this assessment, the paper analyses the legal reasoning of the existing case law – both successful and unsuccessful – invoking Thailand's pre-opposition procedure. Patent opposition procedures are identified as an important TRIPS flexibility that can ensure the elimination and exclusion of low-quality patents, thus ensuring greater and more affordable access to products such as medicines. The paper is structured as follows: looking first at patents and patent quality in general, examining both the pros and cons of patent opposition system as a mechanism through which to regulate this. The historical evolution of the patent laws of Thailand's pre-grant patent opposition then provides the context for the case study analysis. Particular attention is devoted to the use of the Thailand's pre-grant opposition system for pharmaceutical products, as the most important type of patent opposition is defined as that involving medicine. The results show that, while Thailand's pre-grant opposition procedure has proven a success overall, it has not been as effective as a shield against low-quality drug patents. Nevertheless, there is still evidence of some instances in which the pre-grant opposition procedure led to the non-award of a patent for a medical product. The main reasons for failed pre-grant oppositions included: poor planning and insufficient evidence, inexperienced patent agents or lawyers, the unpredictable discretion of patent officers, evidence of foreign registered patents and the influence of large companies. In particular, the author found that Thailand could take further steps to improve the quality of examiners and officers within the patent examination office and to recruit more specialist. Overall, it is concluded that a pre-grant opposition system is better than a post-grant opposition system because it allows a patent office to control patent quality before a patent is even issued. In addition, the pre-patent opposition procedure is considered important for the defense of public interests.

#### Availability and affordability of off-patent medicines and other factors affecting availability

92. The study by Cameron et al. (2008) examines the price, availability and affordability of medicines in 36 developing and middle-income countries using secondary data. A 2001 Resolution of WHO called for the development of a standardized method for measuring medicine prices, resulting in the launch of the WHO/ HAI (Health Action International) Project on Medicine Prices and Availability. Using their methodology, this study examines the data of 45 national and subnational WHO/HAI surveys and makes a comparison with the international reference prices of generic products. The surveyed medicines are generally off-patent and thus the generic comparator can be used as the reference price for both the originator and generic products. Affordability is then estimated using the salary of the lowest-paid unskilled government worker. To increase the comparability of the findings, summary results are

presented for 15 medicines included in at least 80 percent of surveys, irrespective of their actual availability at individual facilities. The results show that, in the public sector, the availability of the 15 generic medicines was low, ranging from 9.7 percent in Yemen to 79.2 percent in Mongolia. Even in the private sector the availability of generics was low, with wide variations in availability according to regions. This low availability could be due to: product variations in national essential medicine lists, poor compliance with their recommendations, inadequate funding, lack of incentives for maintaining stocks, inability to forecast accurately, inefficient distribution systems, or leakage of medicines for private resale. The results also show that generics are more widely available than originator brands in the private sector in low-income and lower-middle income countries, whereas in upper-middle income countries the availability of brands and generics was similar. It is recommended that the most appropriate action will depend upon a country's individual survey results and local factors. Nevertheless, some general recommendations to address problems of availability include improved procurement efficiency and adequate, equitable and sustainable financing. It is also recommended that duties and taxes on medicines be eliminated and that the use of generic medicines be increased for affordability.

93. The article by Ho and Leisinger (2013) provides a commentary style analysis of the relationship between high prices and the accessibility of essential medicines. The authors also examine the role of intellectual property protections upon the two aforementioned access issues. Using the numerical data of other scholars, it is demonstrated that there is insubstantial evidence to prove that patent protections are the main factor limiting access to essential medicines. The findings demonstrate instead that essential medicines on WHO's Model List of Essential Medicines are rarely patented, with patented medicines accounting for only 1.4 percent of all medicines. Using this data, the authors advocate for a reorientation of the focus of the access to medicines debate to one centered around the non-patent barriers preventing access. These non-patent barriers are said to include poverty, lack of financial aid, issues of regulatory approval, out-of-pocket payments, insufficient health facilities and poor supply and distribution systems. The identification of these other non-patent barriers exposes the broadness to the accessibility problem; a problem much broader than high prices or patents. This leads the authors to their final question: one that explores the moral and corporate responsibility of the pharmaceutical industry to improve access to medicines. The authors conclude that, due to a lack of other societal actors working on the development of innovative medicines, the pharmaceutical industry has a certain degree of obligation to improve access to medicines. However, it is admitted that that it will require more – in the form of pooled resources and the establishment of multi-stakeholder teams (between national governments, the international community, NGOs, pharma and academics) – to facilitate the development of and access to essential medicines.

94. The study by Mackey and Liang (2012) examines the patent and data exclusivity status of essential medicines from the WHO's Model List of Essential Medicines (MLEM) used in the treatment of non-communicable disease (NCDs). The objective of the study is to assess whether intellectual property rights impede generic production and the availability and affordability of essential NCD medicines. Using statistics, which show that over two-thirds of deaths in 2008 were NCD-related, with almost 80 percent occurring in low- and middle-income countries (LMICs), the need to examine potential access barriers is thus justified. Using a two phase methodology, the study first identifies the medicines on the EML that treat diabetes, cancer, cardiovascular disease and respiratory diseases. Those particular NCDs were selected because of their status as major contributors to the global disease burden and mortality. Phase two of the study examines the patent and exclusivity status of the NCD medicines in those selected categories using the US Orange Book and the USPTO databases. The results show that 22 percent (79/395) of all medicines on the MLEM are medicines used to treat a targeted NCD. The results from phase two show that, of these 79 medicines, only eight required in depth patent/exclusivity assessment. Further review shows that none of the patent claims of those

eight patents would have impeded the generic manufacture of the active product ingredient (API), nor the MLEM-indicated route of administration or dosage. Furthermore, generic versions were commercially available for all eight of those drugs. As findings demonstrate that none of the targeted NCD medicines had applicable patent/exclusivity provisions which could hinder generic production of the API, or MLEM-indicated formulation or dosage, authors conclude that the availability, affordability and delivery of essential NCD medicines, particularly in LMICs, may be affected by other considerations. While in this paper findings are limited to a narrow working definition of supply-side factors of availability and affordability influenced by generic production, several additional factors may limit greater NCD drug access, production and uptake. These include demand-side aspects of availability including prescribing practices, lack of generic substitution/ procurement, acceptability of medicines for prescribers and users, greater public and private sector health financing, and better utilization of available medications.

95. The article by Mecurio (2007) examines barriers to the access of essential medicines in developing countries. Adopting a critical legal approach that analyses the broader range of issues, the author's aim is to expand upon the traditional literature in which patent barriers often feature as the centerpiece of the access problem. The author argues that this fixation upon patent barriers is both misguided and overstated regarding the access problem. Instead, the author's findings demonstrate that even if patent regulations did not exist, the developing world would still lack access to essential medicines. Moreover, more than 95 percent of the pharmaceutical products on the WHO Essential Drug List are off-patent and, due to the extension of the patent waiver for LDCs in relation to patent-protection of pharmaceutical products, most LDCs do not currently provide patent protection for pharmaceuticals. Starting with a review of the TRIPS Agreement and the Doha Declaration as they apply to public health, the author then uses data from pre-existing studies to demonstrate his point that, although patent protection has frequently been blamed for creating or worsening the public health crises in the developing world, patents and the TRIPS Agreement actually play a very small role. The author then moves on to review the various factors which actually contribute in a substantial way to the access problem before offering some implementable recommendations that could help developing nations. The findings show that these factors include poor living conditions, lack of medical facilities and proper infrastructure, lack of a means of distribution and administering medicine and corruption, among other things. To overcome these obstacles it is recommended that there be a greater financial commitment from the developed countries and a greater political commitment from the developing ones; better coordination between funding efforts and aid initiatives; the development of improved infrastructure in developing countries; the careful use of differential pricing conditioned upon the use of drugs for the health crisis and not for re-exportation; and finally, the use of an alternative system for the incentivization of R&D of diseases of neglect – such as through the use of public-private partnerships.

96. The paper by Zainol et al. (2011) assesses whether patent protection under the TRIPS Agreement inhibits access to essential medicines in Sub-Saharan Africa or whether access to medicine is instead inhibited by non-patent related factors. To answer this research question, a keyword search of electronic databases is conducted, alongside a review of the relevant literature from print sources. The paper is organized into three main sections. The first section provides an overview intellectual property rights and the evolution of the TRIPS Agreement. The second section proceeds to review the debate on pharmaceutical patents. Finally, the third-section analyses and compares the arguments with the Sub-Saharan situation. Two main arguments are polarized against one another regarding the impact of patents on access to essential medicines. However, both sides agree on one point that a range of non-patent factors contribute to the access problem. These non-patent factors are identified as stemming from a lack of effective political leadership, the low purchasing power of Sub-Saharan Africa, poor infrastructure, high debt burden, the absence of trained personnel and a "brain drain" effect and the remote nature of medical facilities. In contrast, patent factors are found to have a certain degree of impact – particularly in South Africa where patenting is high. In particular by limiting

generic imports from other producer countries that are now required to respect patent protections and that fear of reprisals if they supply medicines for export using the Doha procedure. Problematically, Sub-Saharan Africa does not have the technological capacity nor the financial resources that are necessary to set-up their own manufacturing facilities in order to supply such medicine. The findings thus show that both patent and non-patent factors contribute to the access problem. It is recommended that Sub-Saharan Africa review tariff and taxation policies, improve infrastructure and strengthen their health systems. Increased international financing, private-public collaboration and benefit sharing is also encouraged.

#### Technology transfer of the medical products and health technologies

97. Abbott's study (2011) compares the measures taken by Brazil, Singapore and Mexico, to promote transfer of technology and competitiveness in the pharmaceutical sector with Colombia. The object of the study is to propose alternative approaches that improve technological capacity and the international competitiveness of Colombia's domestic pharmaceutical industry. The study was conducted by engaging in information gathering and assessment visits to Brazil, analyzing written materials from Singapore and conducting interviews with Mexican industry representatives. Comparison is also made to the global pharmaceutical industry to establish Colombia's place within that structure. The findings reveal three important characteristics when making a comparison with the global pharmaceutical industry. Firstly, that there is a distinct difference between the technology transfer behaviors of originator and generic manufacturers, as most originator companies do not ordinarily provide technology transfer on high-margin/ high-profit patent-protected products. For Colombia, and most developing countries, this has limited local industry to the production of off-patent products. The second characteristic is the distinction between manufacturers of active product ingredients (APIs) and manufacturers of finished pharmaceutical products. For Colombia, who imports all APIs, this limits trade in the pharmaceutical sector. In Brazil, since the introduction of patent protection, the local API industry has decreased from 55 percent to less than five percent supply of the country's domestic requirements as API producers are not licensing their technologies. Thirdly, quality control standards of the OECD countries limit the ability of developing countries to export their pharmaceutical products and increase their market. After assessing the policy options of countries in the study, some recommendations are made, which include: upgrading of manufacturing facilities to meet US and EU standards; investing in the production of APIs through joint ventures with foreign enterprises to permit technology transfer; looking at new funding options; and initiating a government program to identify industrially useful patent information that may be employed without infringing patents.

98. The paper by Horner (2014) examines the impact of patents on the processes of innovation, technology transfer and health by conducting a comparative pre- and post-TRIPS analysis of India's pharmaceutical industry. Using a geography studies approach, the paper draws on a variety of secondary sources, as well as field research in India involving more than 85 interviews with various stakeholder in the pharmaceutical industry (firms, industry association groups, policy-makers and civil society groups) to make a firm-based assessment. The purpose is to address the contrasting arguments and the uncertainty surrounding the precise impact of patents on development in India. The findings on the pre- and post-TRIPS impact of patent protections on technology transfer reveal that pre-TRIPS Indian technology transfer was facilitated in the absence of product patents. Knowledge was transferred through reverse-engineering, journals and product manuals, contracts abroad and even friendship. The absence of patents gave India the absorptive capacity to develop pharmaceutical technologies and become the "pharmacy of the developing world". The findings also show that since 2005, when India reintroduced process patents, most firms remained unaffected by the change in patent law; unlike that which was predicted. Rather, larger Indian firms are increasingly found to be conducting their own R&D. In addition, the interviewees reported an increase in formal technology transfer, particularly through licensing, post-TRIPS. Yet despite the growth of formal

technology transfer through collaboration, Indian firms have not necessarily benefitted any more than they were previously able to benefit when using reverse-engineering. The results also show an increase in FDI in the Indian pharmaceutical sector post-TRIPS. Thus, the analysis concludes that both proponents and detractors of TRIPS have overestimated the significance of patents in influencing innovation, technology transfer and, indirectly, public health.

99. The article by Janodia et al. (2008) investigates the technology transfers that shape the pharmaceutical industry and its R&D activities, exploring both challenges and successes. Technology transfer is given a broad definition, being: the broad set of processes whereby a developer of a technology makes its technology and/or the know-how, experience and equipment available to a commercial partner to exploit, thereby extending the benefits for R&D to the society at large – especially in developing countries. Technology transfer is found to be heavily dependent on contracts for the sale of technology and on licensing agreements on the patent transfer. The article identifies five main facets of technology transfer: (1) Government labs to private sector firms; (2) Between private sector firms of the same country; (3) Between private sector firms of different countries; (4) From academia to private sector firms; and (5) Academia, government and industry collaborations, including public-private partnerships. One identified advantage of a technology transfer between a public and private sector, as well as between a small private firm and a big private firm, is the ability for the former to generate resources while the latter – industry – gains access to a technology that is protected under patents. In the case of India, the findings reveal an active pursuit of technology transfer. However, transfers of technology were lower when India had relative weak patent protections, i.e. pre-TRIPS, that only protected processes and not products. It is concluded that, in the pharmaceutical industry, technology transfers can create a win-win situation for industry and academia/ government, with the commercialization of new drug molecules.

100. The study by Padmanabhan et al. (2010) assesses the extent to which patents are a barrier to producing regionally manufactured, low-cost human papilloma virus (HPV) vaccines in India. To make this empirical assessment, the study examines the current HPV patent landscape, including relevant licensing agreements. Technology transfer of know-how is also considered as an additional, important element. The choice of India as the case study is based on the strong market incentives for India to engage in local manufacturing, as India accounts for 25 percent of the world's total disease burden of cervical cancer. The findings of the patent landscape reveal a complex patent landscape with over 81 US patents owned by 18 entities, 10 of which were not-for-profits (i.e. national health institutes, universities, etc.). A preliminary analysis is provided on each of the patent claims, based on the authors' understanding of the patented technologies and discussions with the researchers who developed them. The analysis reveals that, despite considerable patenting activity, manufacturing of first-generation L1-VLP-based HPV vaccines is not be precluded unless it is identical in formulation or strain coverage to the compositions claimed in granted Indian patents. It is admitted, however, that this analysis is limited by the lack of patent claim information publicly available in the Indian patent databases. The creation of resources to map and update the current patent landscape for novel HPV vaccines is thus recommended. In addition, universities are identified as having a primary role to play in the facilitation of regional manufacture and the Lausanne-Immunological partnership is an example of a successful relationship harnessing the capacity of a developing country vaccine manufacturer to commercialize a vaccine candidate despite being of little commercial interest for OECD countries. Technology transfer is also considered crucial for the accessibility of know-how. It is recommended that universities and other not-for-profits create collaborative technology transfer partnerships which could be modelled on the National Institute of Health (NIH) Rotavirus Technology Transfer program to expedite access.

Related literature: availability of essential or non-essential medicines

101. The study by Bazargani, Ewen et al. (2014) uses the WHO/Health Action International (HAI) methodology to determine whether essential medicines are more available than non-essential medicines as assessed in 23 low- and middle-income countries. All surveys on essential medicines included in the WHO/HAI database on 15 April 2012 were included in the study. A total of 28 surveys corresponding to 1130 medicines (886 essential medicines) and 2290 facilities were analyzed. The results show that the overall median availability of essential medicines for any product type was 61.5 percent while the availability of non-essential medicines was 27.3 percent. The difference in this availability was driven by generic medicines, with the median availability of generic essential medicines 3.3 percent versus 19.2 percent for non-essential generics. The median availability of both essential and non-essential medicines was greater in the private sector than in the public sector. The median availability of any product type of essential medicines in the public sector was 40 percent which is extremely suboptimal. However, the greater availability of essential than non-essential medicines in the public sector may indicate the preferential attention of governments towards essential medicine supply. The findings suggest that essential medicine policies may have been more successful in the public sectors of low- and lower-middle income countries than in upper-middle income countries. Additionally, the low availability of essential medicines, especially in the public sector, requires more attention from the local authorities. It is recommended that authorities use pooled procurement, more sustainable financing, better supply chain management and TRIPS flexibilities alongside enhanced local manufacturing to produce generic versions of essential medicines. The results conclude that while Essential Medicine Lists have influenced the provision of medicines and have resulted in the higher availability of essential medicines compared to non-essential medicines, the availability of essential medicines is still far from ideal, particularly in the public sector.

102. The study by Nguyen et al. (2009) conducts an empirical analysis of the availability and affordability of medicines in Vietnam. Using the WHO Health Action International methodology, the study collects and assesses the data of 42 medicines (of which 35 were essential medicines) in both the private and public sectors of five different regions within Vietnam. Affordability was measured based on the number of days' wages which were required for the lowest-paid unskilled government worker to purchase one course of therapy. The findings show that lowest-priced generics are more available than brand-name medicines in all sectors, with 34.8 percent availability in the public sector and 56 percent in the private sector, making Vietnam similar to the other low income countries in terms of the mean availability of generic medicines. However, public procurement prices were higher on both originator and generic products than that provided under the international reference price. When compared to other low income countries, which have an average procurement price of 17 percent higher than the international reference price, Vietnam's prices were 44-45 percent higher on average. The findings also reveal another trend that deviated from other low-income countries, as the price of medicines were higher in the public sector than the private sector for both originator and generic medicines in Vietnam. Finally, the surveyed medicines were found to be unaffordable to the large percentage of the population who earn the same as or less than the lowest paid unskilled government worker. It is, thus, recommended that Vietnam reduce prices through comparative pricing or through a reference pricing system. It is also recommended that Vietnam improve on procurement efficiency and regulate mark-ups to reduce prices in the public sector.

[Annex II, follows]

List of studies included in the review of existing research on patents and access to medical products and health technologies:

1. Abbas M. Z. and Riaz S. (2013), Flexibilities under TRIPS: Implementation Gaps between Theory and Practice, *Nordic Journal of Commercial Law*, No. 1, pp. 1-25.
2. Abbott F. M. (2011), Comparative Study of Selected Government Policies for Promoting Transfer of Technology and Competitiveness in the Colombian Pharmaceutical Sector. United States Agency for International Development – Programa MIDAS, 2007. Available at: [https://www.researchgate.net/publication/228247080\\_Comparative\\_Study\\_of\\_Selected\\_Government\\_Policies\\_for\\_Promoting\\_Transfer\\_of\\_Technology\\_and\\_Competitiveness\\_in\\_the\\_Colombian\\_Pharmaceutical\\_Sector](https://www.researchgate.net/publication/228247080_Comparative_Study_of_Selected_Government_Policies_for_Promoting_Transfer_of_Technology_and_Competitiveness_in_the_Colombian_Pharmaceutical_Sector).
3. Adusei P. (2011), Exploiting Patent Regulatory “Flexibilities” to Promote Access to Antiretroviral Medicines in Sub-Saharan Africa, *The Journal of World Intellectual Property*, Vol. 14, No. 1, pp. 1-20.
4. Amin Tahir and Aaron S. Kesselheim (2012), Secondary Patenting of Branded Pharmaceuticals: A Case Study of How Patents on Two HIV Drugs could Be Extended for Decades, *Health Affairs*, Vol. 31, No. 10, pp. 2286-2294.
5. Athreye Suma, Dinar Kale, Shyama V. Ramani (2009), Experimentation with Strategy and the Evolution of Dynamic Capability in the Indian Pharmaceutical Sector, *Industrial and Corporate Change*, Vol. 18, No. 4, pp. 729-759.
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