Bhaven N. Sampat and Kenneth C. Shadlen

TRIPS implementation and secondary pharmaceutical patenting in Brazil and India

Article (Accepted version) (Refereed)

TRIPS Implementation and Secondary Pharmaceutical Patenting in Brazil and India[1]

Bhaven N. Sampat
Columbia University (New York, USA) and NBER

Kenneth C. Shadlen
London School of Economics (London, UK)*

February 2015

For special issue of *Studies in Comparative International Development* ("Intellectual Property, Access to Medicines, and Health")

*Corresponding author: Department of International Development, London School of Economics and Political Science (LSE), Houghton Street, London WC2A 2AE, United Kingdom
Email: k.shadlen@lse.ac.uk
Phone: +44-20-7852 3681

[1]We are grateful to the Economic and Social Research Council (ES/K010999/1) and the joint LSE-Columbia University Research Committee for funding, and to Meriem Bekka, Kim Grauer, and Jennifer Reid for research assistance. The paper benefited from discussion at the authors' workshop organized by the Watson Institute (Brown University) in January 2014, and we thank the participants at the workshop, along with the journal's reviewers, for their helpful feedback. We are also received helpful feedback from participants at LSE's Comparative Politics/Comparative Political Economy workshop and from Shamnad Basheer. We thank Tahir Amin for his assistance in coding the applications and his suggestions on previous drafts.

Abstract

This article compares national approaches toward secondary pharmaceutical patents. Because secondary patents can extend periods of exclusivity and delay generic competition, they can raise prices and reduce access to medicines. Little is known about what measures countries have enacted policies to address applications for secondary pharmaceutical patents, how they function, and whether, in practice, these measures limit secondary patents. We analyze the cases of India and Brazil. We assemble data on pharmaceutical patent applications filed in the two countries, code each application to identify which constitute secondary applications, and examine outcomes for each application in both countries. The data indicate that Brazil is less likely to grant applications than India, but in both countries the measures designed to limit secondary patents are having little direct effect. This suggests, on the one hand, that critics of these policies, such as the transnational pharmaceutical sector and foreign governments, may be more worried than they should be. On the other hand, champions of the policies, such as NGOs and international organizations, may have cause for concern that laws on the books are not having the expected impact on patent outcomes in practice. Our findings also suggest that, at the drug level, the effects of countries' approaches toward secondary patents need to be understood in the context of their broader approaches toward TRIPS implementation, including when and how they introduced pharmaceutical patents in the 1990s and 2000s.

Keywords: Pharmaceuticals, Secondary patents, Section 3d, Prior Consent, TRIPS

Introduction

Prior to the 1990s many developing countries did not allow pharmaceutical products to be patented. The World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) changed this scenario. TRIPS requires all countries that are members of the international trade body to grant pharmaceutical patents. Patents provide rights of exclusion, and patented drugs are typically more expensive than drugs with "generic" competition from multiple suppliers. Accordingly, many observers fear that TRIPS will restrict access to medicines.

How TRIPS affects access to medicines will depend, in part, on how countries address "secondary" patents. Secondary pharmaceutical patents refer to new patents on existing drugs. Examples include alternative structural forms of known molecules, revised formulations and compositions, or new medical uses. Any given medication is likely to be the subject of multiple patents: a "primary" patent covering the base compound, and numerous secondary patents. Because secondary patents are filed later than primary patents, the grant of these patents can extend periods of exclusivity, increase drug costs, and restrict access to medicines.

The challenges presented by secondary patents are not unique to developing countries. In the US, for example, secondary pharmaceutical patents are often overturned during litigation after patent issuance (Hemphill and Sampat 2012). In contrast to the *ex post* approach of clearing secondary patents toward the end of their terms, developing countries are widely advised to adopt "pre-emptive" approaches, to use flexibilities in the TRIPS agreement to minimize the granting of such patents in the first place (Commission on Intellectual Property Rights 2002; Correa 2007; UNAIDS 2011; Matthews and Correa 2011; South Centre 2011).

Little is known about what sorts of steps countries have taken to address secondary patents, or the effects of such steps. We examine the cases of India and Brazil. In the 1980s and early 1990s these two countries were among the most active opponents to the TRIPS agreement and the requirement to make pharmaceuticals patentable. In terms of their initial compliance with this obligation, India's approach was to delay as long as possible while Brazil introduced pharmaceutical patents earlier. Though the two countries initially reacted differently to TRIPS, in the 2000s both countries introduced pre-emptive mechanisms to limit secondary pharmaceutical patents.

The Indian and Brazilian approaches toward secondary patents have generated significant attention from both detractors and supporters. On the one hand, representatives of the transnational pharmaceutical sector regularly assail both countries for failing to deliver sufficient levels of pharmaceutical patent protection, and the USTR typically repeats these complaints in the annual Special 301 reports on national IP practices.[2] On the other hand, NGOs and international organizations regularly cite these two countries as models for adopting "pro-health" flexibilities in TRIPS. This is particularly true of India: when NGOs and international organizations encourage developing countries to adopt measures to minimize the granting of secondary pharmaceutical patents, they nearly always recommend that countries emulate India's approach (South Centre 2011; UNAIDS 2011). Despite the attention that these two countries' pre-emptive mechanisms have generated, however, little is known about their effects.

To analyse how these measures function, we assembled novel data on pharmaceutical patent applications and outcomes. We distinguish between primary and secondary patent

[2] This page includes links to the Special 301 Reports and PhRMA's submissions. http://www.keionline.org/ustr/special301

applications, and we analyze the examination outcomes and prosecution histories of each application in the two countries. Specifically, we ask how grant rates differ across countries, and how commonly the countries' specific measures to address secondary patents are involved in these outcomes. In most of our analyses a patent application is the unit of analysis. We also present results on what the countries' approaches to pharmaceutical patents mean for one proxy for access to medicines: whether a drug is free from patent protection in a country, and thus open for generic competition.

We find that Brazil has a lower grant rate than India. However, in both countries the measures put in place to address secondary patents appear to have only limited direct roles. This is surprising, in light of the attention that these measures have received, from both critics and supporters, and points to gaps between laws on the books and laws in practice. Among the drugs in our dataset, we also find that India, despite a higher grant rate, still has fewer drugs covered by patents than Brazil. This finding, which reflects earlier policy choices regarding the introduction of pharmaceutical patents in the 1990s, highlights that different aspect of TRIPS implementation interact in shaping drug-level outcomes.

In addition to examining how these pre-emptive mechanisms function, and thus how patent laws on the books relate to patent prosecution in practice, our paper also provides a detailed look at the nuances of TRIPS implementation. This has been neglected in most previous work on intellectual property and development, which tend to treat TRIPS as having uniform implications for developing countries, and ignore details of TRIPS implementation (Ivus 2010; Falvey, Foster, and Greenaway 2006; Falvey, Foster, and Greenaway 2009; Qian 2007). The effects of TRIPS on outcomes of interest (e.g. innovation, access to medicines) will be affected by how countries create and implement new, TRIPS-compliant patent systems, including policies

on secondary patents. Though it is beyond the scope of our paper to make specific predictions on the effects of these policies on innovation and access, we show that TRIPS implementation is significantly different across the two countries, in ways that are likely to matter for the existence and duration of pharmaceutical patent protection.

In section two we examine the significance of incremental innovations to the pharmaceutical industry, the challenges created by secondary patents, and the policy responses available to governments. In section three we provide overviews of the new pharmaceutical patent regimes in Brazil and India, with a special focus on these countries' pre-emptive mechanisms to limit the grant of secondary patents and thus prevent the extension of patent terms. We then turn to the empirical analyses. In section four we describe the data and data collection strategy necessary to address our research question, in section five we present results, and in section six we discuss findings and conclude. Our primary objectives and contributions in this paper are descriptive: we illustrate how these two countries' prominent approaches to secondary pharmaceutical patents function, in practice, by examining patent prosecution outcomes. In the conclusion we also offer some tentative explanations for the outcomes we observe.

Secondary Patenting and Developing Countries

Patents are national, so the same applications are examined in every country where applicants file. Historically, many developing (and developed) countries did not grant patents on pharmaceuticals products (La Croix and Liu 2009). Since the introduction of TRIPS, all WTO members are required to make patents available for pharmaceutical products. Following these changes in national patent laws to comply with TRIPS, developing countries' patent offices have

received large quantities of patent applications. Most of these applications are from multinational firms based in developed countries.[3]

Many pharmaceutical patent applications are for secondary patents: applications covering alternative forms of existing molecules, new formulations, dosing regimens, and new uses of known molecules.[4] Secondary patents have become increasingly important to the pharmaceutical industry. WIPO data reveal an increase in secondary patenting worldwide over the 1996-2006 period (Shadlen 2011, 148–149). In the US, the share of drugs approved by the FDA that include secondary patents has increased sharply since the 1980s (Kapczynski, Park, and Sampat 2012; Hemphill and Sampat 2011; Hunt 2002).

Taking out multiple patents on different aspects of a drug in order to cordon off competitors is standard practice in the pharmaceutical industry. After all, secondary patents can protect market shares by extending periods of exclusivity beyond the dates in which patent protection would otherwise lapse. Devising patenting strategies to extend periods of protection is

[3] Six countries (the United States, Japan, Germany, France, United Kingdom, and Switzerland) account for 77 percent of pharmaceutical patent applications filed worldwide during the 1995-2006 period (WIPO 2011).

[4] Alternative forms of the same molecules may perform differently in the human body. In addition, once stable and effective molecular forms are found, pharmaceutical innovation also consists of establishing ways to deliver them. Consider that medications are typically consumed in tiny dosages, sometimes as little as five or ten milligrams of the active pharmaceutical ingredient (API). Delivering such miniscule amounts would be exceedingly difficult, if not impossible, were they not combined with a range of additional inert ingredients (excipients). Yet while excipients' role may ultimately be simply to consume space and to facilitate handling, they must be selected and included in the manufacturing process in such a way as to make for a deliverable and consumable medication that retains the desired biological effects of the API. And separate formulations must be undertaken for each dosage and different systems of delivery (e.g. capsules, pills, ointments, syrups, and so on). Finally, often the same molecules affect multiple parts of the body differently; when molecules intended for one therapeutic use turn out to be effective in ways other than intended, additional work is entailed to develop the drug for the "new uses." Each of these steps can generate additional patent applications. As a result, for any given medication it is common to see tens of patents covering the base compound as well as diverse molecular forms, formulations, and uses (Howard 2007; Amin and Kesselheim 2012).

widely acknowledged to be an important part of product "life cycle management."[5] Figure 1 presents a hypothetical example.

Because secondary patents can postpone the entry of low cost- generic competitors and the subsequent reduction in prices, and thus potentially reduce access to medicines, governments have implemented policies to address them (Scherer 2000; Vernaz et al. 2013). In the US, for example, evaluation (or, more precisely, re-evaluation) of secondary pharmaceutical patents tends to occur by courts after patents are granted, when questionable patents are litigated. Validity is essentially determined *ex post* in the course of litigation rather than *ex ante* in the course of examination.

Given the complexity of patent examination – and that most patents are associated with drug development efforts that fail – granting patents liberally and allowing interested parties to litigate after they learn which patents are important (e.g. after drug approval) could be a rational way for resource-constrained patent offices to allocate their efforts (Lemley 2001).[6] However, invalidating patents through litigation is expensive and risky. Litigation also has public good characteristics, in that a challenger solely bears the costs and risks, but if successful the benefits accrue to any generic firm. To address this problem and incentivize patent challenges, in the U.S., for example, the Hatch-Waxman Act of 1984 created a bounty, in the form of a temporary

[5] This process is widely referred to as "evergreening." Pharmaceutical industry representatives tend to object to the use of this term (GSK 2007; IFPMA 2013), but no one denies that obtaining secondary patents constitutes a component of "life cycle management." Of course, not all secondary patents have equal blocking effects. Analyzing the conditions under which secondary patents deter competition is beyond the scope of this paper. For present purposes, the simple point is that secondary patents are used as part of firms' strategies to extend periods of market exclusivity.

[6] By contrast, Farrell and Merges (2004) question the appropriateness of ex post re-evaluation via litigation.

period of shared exclusivity, to the first generic to successfully overturn patent through ex post litigation (Hemphill and Sampat 2011; Hemphill and Sampat 2012).[7]

Hemphill and Sampat (2012; 2013) suggest that ex post litigation may be an effective mechanism for preventing the extension of patent terms of drugs based on secondary patents in the U.S. It may be less likely to work in developing countries, however, for several reasons.[8] First, the smaller size of markets means the gains to successful litigation are smaller, thus reducing the incentive to litigate. Second, the greater resource asymmetries between owners and challenges means the likelihood of succeeding in litigation may be less. Third, in many developing countries the introduction of pharmaceutical patenting, and the ensuing flood of pharmaceutical patents, may simply overwhelm the capacities of local legal systems to properly handle litigation. A final issue is search costs: not knowing how many patents exist on a given drug creates uncertainty, and conducting searches on patent landscapes in developing countries is particularly difficult (Amin and Kesselheim 2012). For all of these reasons, once patents are granted they may be particularly difficult to overturn in developing countries. Thus, rather than relying on post-grant litigation to weed out low quality patents, countries can introduce "pre-emptive" mechanisms, at the point of examination, to minimize the grant of secondary patents in the first place.[9]

---

[7]Our objective here is not to survey the array of responses to the challenges of secondary patents, but rather to use the U.S. as an illustration of an ex post, litigation-based approach. Our sense is that the US system is unique in offering this bounty, though further research on the variety of ex post mechanisms would serve as a useful complement to our analysis.

[8] This would be true even if developing countries had bounties for ex post challenges, which (to our knowledge) none do.

[9] Drahos (2008) makes a similar point, distinguishing between prevention and cure. According to Drahos, once patents are issued they are hard to remove, even if dubious, so countries may have an interest in adopting more restrictive granting practices.

Under TRIPS, countries are permitted to introduce such pre-emptive mechanisms. The remainder of the paper examines the cases of India and Brazil. In the next section we discuss the different approaches India and Brazil took to implementing TRIPS, both regarding the timing of introducing drug patents and then, specifically, their approaches to restricting secondary patents. Then, we turn to empirical analysis of grant rates in each country, and the roles of these pre-emptive mechanisms.

Pharmaceutical Patents and Pre-Emptive Mechanisms in India and Brazil

TRIPS allowed developing countries until 2005 to begin granting pharmaceutical patents. India took full advantage of the available transition period, waiting until 2005 to make pharmaceutical products eligible for patents. Per WTO requirements, applications for pharmaceutical patents could be filed in India beginning in 1995, but these were held in a "mailbox" until 2005, at which point the mailbox was opened and the applications began to be examined by the Indian Patent Office (IPO). Because the country used the full transition period, the mailbox included ten years of patent applications, from January 1995 until the time when pharmaceutical became eligible for patents in 2005.[10] By contrast, Brazil used little of the available transition period and made pharmaceuticals patentable beginning in 1997. In addition to introducing pharmaceutical patents early, Brazil's new patent law included a provision for "pipeline" patents. Pipeline patents recognize, retroactively, patents that had already been granted in other countries.[11]

[10]The 2005 amendments to the patent act also included a provision that allows any firm that was producing a drug prior to 2005 to continue to do so, even if a patent is later granted, after 2005 when patent examination began. This provision, essentially an automatic compulsory license with a small royalty payment, assured that there would be no retroactivity India.

[11]Consider the case of a drug where the a patent is applied for in 1990. In 1990 the patent could not be obtained in Brazil because pharmaceuticals were ineligible, but by 1997, when

The two countries' distinct policy choices made in the 1990s regarding the introduction of pharmaceutical patents set them apart in a pair of important ways. The first regards applications with international priority dates prior to 1995.[12] These are ineligible for patent protection in India, but eligible in Brazil under the pipeline. The second difference regards post-1995 applications that still preceded the introduction of pharmaceutical patents. India accumulated ten years of applications in the mailbox. Brazil received such applications for less than three years: from January 1995 until May 1997, when pharmaceuticals became eligible for patents. After this time, they began to be examined along with all other applications filed during this period.

Both India and Brazil introduced pre-emptive mechanisms to restrict the grant of secondary patents. In India, while introducing the final amendments to the patent act that would allow for pharmaceutical patents, in 2005, the government included a provision, Section 3d, that creates a high barrier for secondary patents. Section 3d stipulates that many secondary patents are not considered as inventions, and thus not eligible for patents, unless the applicants demonstrate that these have greater efficacy:

> The following are not inventions within the meaning of this Act… The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a

---

pharmaceuticals became patentable in Brazil, no patent would be available because by then the invention was no longer new. If in 1997, however, this drug was not yet on the market, but rather was still in development and undergoing clinical trials, i.e. it was in the "pipeline," it could be patented in Brazil for the remainder of the period of the original patent.

[12]The international priority date refers to the date a patent application was first filed in any country. According to the Paris Convention, applicants have one year after an initial filing to make subsequent filings in other countries where protection is sought without losing "priority" (that is, inventions that become known over that year cannot be asserted as "prior art" to reject claims in the application).

> known substance or the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. For the purposes of this clause, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations, and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.[13]

Section 3d, which was explicitly designed as a response to concerns that secondary patents on existing substances would be used to extend market exclusivity and delay generic competition, has gained global attention since its introduction. Most notable was the long-standing conflict between the Indian government and the Swiss pharmaceutical firm Novartis. In 2006 the IPO cited 3d in rejecting an application by Novartis for a patent on an anti-leukemia drug (Glivec). Novartis, in turn, filed a lawsuit challenging the constitutionality of 3d, but the Madras High Court ruled that 3d was constitutional.[14] Novartis also appealed the IPO's decision on the patent itself, and in 2013 the Indian Supreme Court upheld the original rejection.[15]

India's new law also included an expansive system of pre-grant opposition that allows a wide array of actors to influence the course of patent prosecution. Civil society organizations and generic firms can submit documents explaining why a given application should not be granted,

---

[13]Applying Section 3d thus entails two steps. First, a decision has to be made as to whether the claimed invention is subject to this rule (i.e. if it is derived from a known substance), and, if so, a second decision has to be made as to the efficacy of the claimed invention relative to the known substance.

[14] Novartis also charged that Section 3d violated TRIPS, but the High Court ruled that it lacked the jurisdiction to make such a ruling. Novartis would have to get the Swiss government to pursue that claim in the WTO, something that has not happened

[15] http://www.nytimes.com/2013/04/02/business/global/top-court-in-india-rejects-novartis-drug-patent.html

and these submissions become part of the formal examination proceedings with examiners required to respond to the oppositions raised (Amin 2013; Basheer 2009).

Brazil's pre-emptive mechanism, called "Prior Consent," emerged following 2001, when the government reformed the new patent law to change the way that pharmaceutical patent applications were handled. In doing so the government created a shared examination system: pharmaceutical patent applications must be approved by both the National Institute for Industrial Property (INPI) and the Ministry of Health's health surveillance agency (ANVISA) before being granted.[16] In the first step of this system, INPI receives and examines a patent application. If INPI determines that the patent should not be granted, then it is rejected and the process ends. However, if INPI determines that the patent should be granted, the application is then passed to ANVISA. In such cases ANVISA examines the application and INPI's technical report, often requesting additional material from the patent office and the applicants. If ANVISA issues its consent INPI then grants the patent,[17] and if ANVISA decides that the patent should not be granted it notifies INPI (and the applicant) of this decision. Though ANVISA lacks the legal authority to reject patents, INPI can only grant patents where ANVISA has given its Prior Consent.[18]

Although these India's and Brazil's pre-emptive mechanisms are functionally similar, in that they aim to achieve similar objectives, they exhibit distinct institutional designs. We

[16] To be precise, this change was announced in 1999, as part of a provisional measure (presidential decree), but in reality the examination system did not change until 2001, after the patent law was reformed.

[17] Note that even when ANVISA consents it may do so only after narrowing some of the patent's claims.

[18] The Prior Consent regulations were revised in 2012, with a new workflow introduced in 2013, such that now ANVISA evaluates pharmaceutical patent applications first, prior to INPI.

categorize pre-emptive mechanisms according to a typology consisting of three dimensions: whether they include outright statutory exclusions of some types of secondary patents, whether they involve coordination between patent offices and other government agencies, and whether they include opposition provisions allowing third parties to challenge applications. Considering India and Brazil in terms of this typology illustrates key differences. India's system is based on the restriction of patentable subject matter, in that Section 3d of the Patent Law stipulates that some things do not count as inventions and thus are not eligible for patents unless they demonstrate increased efficacy. By contrast, Prior Consent in Brazil entails application of standard patentability criteria. In India the IPO retains sole responsibility for patent examination. In Brazil responsibility is shared between INPI and ANVISA. India has a system of pre-grant opposition that invites actors from civil society and industry to challenge patent applications that the IPO is examining and includes these oppositions in the formal patent prosecution process. Brazil has a pre-grant system but it is less extensive: only "interested" parties are allowed to submit material to the INPI and the patent office is not obligated to address or consider these submissions.

The pre-emptive mechanisms have different political origins too. India's policy was the product of considerable parliamentary deliberation and represents a compromise between actors who wanted a more permissive approach to pharmaceutical patents and actors (particularly the Indian left parties and NGOs) that sought to prohibit all secondary patents.[19] After 2005, 3d was the subject of an expert commission that the government established to review the country's

[19]The precise language is said to have originated with the local pharmaceutical sector: according to Sengupta (2013, 45), "the language for Section 3d was provided by the Indian Drug Manufacturers Association (IDMA)." Gopakumar (2013, 57, note 2) provides an alternative account of the origins of the language, from within the judiciary.

approach toward secondary patents (i.e. to determine whether the strategy adopted during the parliamentary sessions of 2005 was the best way forward) and this commission, in turn, confirmed the approach.[20] Section 3d thus can be said to reflect the prevailing constellations of interests at the time of its creation, and it is reflective of successive Indian governments' long-standing position toward pharmaceutical patents. [21] It was also put into place with a precise and universally recognized objective. Like it or dislike it, supporters and critics of 3d know why it is there: to minimize the grant of secondary pharmaceutical patents.

In Brazil, by contrast, Prior Consent was converted into law without parliamentary debate, and marked a rupture with previous policies. Just a few years prior to this, a five-year legislative debate on how Brazil should conform to TRIPS concluded with the introduction of the new patent law with the early and retroactive characteristics described above, hardly one that was oriented toward minimizing pharmaceutical patent rights.[22] Nor, in contrast to 3d, was Prior Consent created explicitly to address secondary patents. The 2001 reform, formalizing the 1999 decree, simply inserted a single clause into the patent law (Article 229-C), which states "The concession of patents for pharmaceutical products and processes depends on the prior consent of the National Agency for Sanitary Vigilance [ANVISA]." While it is clear that ANVISA's

[20] The Indian Supreme Court ruling in the recent Novartis case goes into detail on the legislative intent. Likewise, the Madras High Court, in its 2009 ruling that 3d was constitutional, also goes into the history and legislative intent.

[21]Stretching back to the 1980s, we can consider the Indian position toward pharmaceutical patents in three successive stages. Initially, in the TRIPS negotiations, India sought to prevent the inclusion of an obligation to grant pharmaceutical patents. Then, with TRIPS concluded and pharmaceutical patenting unavoidable, India used the full transition period available and did not allow retroactivity. Lastly, once the transition period expired and India was to begin granting pharmaceutical patents, the policy aims to minimize secondary patents.

[22] Prior Consent formed part of a larger set of initiatives by the then-Minister of Health to deal with the escalating price of drugs. ANVISA itself was created at the same time.

approval is required for pharmaceutical patents to be granted, the terms on which ANVISA is supposed to exercise its role and grant or deny its consent are left unstated. ANVISA converted Prior Consent, *de facto*, into a measure to curb secondary patents by subjecting applications to enhanced scrutiny. To do so, the health agency created its own IP division to undertake this new line of work, which in turn developed its own examination guidelines specifically for secondary patents.[23] Importantly, ANVISA's guidelines were designed to be more restrictive than INPI's (Shadlen 2012; Kunisawa 2009; Basso 2006).

As discussed, these countries' pre-emptive mechanisms have both gained significant international attention from both detractors and supporters. The transnational pharmaceutical sector complains about 3d (along with pre-grant opposition) and Prior Consent, and foreign governments regularly push for these measures to be removed. At the same time, the pre-emptive mechanisms receive abundant praise from NGOs and international organizations.[24]

Despite the attention that these mechanisms have received, positive and negative, there is limited data on how they actually function, and their effects on patent outcomes. The remainder of the paper aims to help to fill that void. Before turning to the empirical analyses, we emphasize that we are not taking a stand on whether these restrictions on secondary patents are desirable. Instead, we focus on the question of whether countries' policies on secondary patents are having

[23] ANVISA is based in the capital city of Brasilia, but its IP division is in Rio de Janeiro, which is where the INPI is located.

[24] It is notable that Brazil's pre-emptive mechanism has not received nearly as much attention from NGOs, health activists, and international organizations. Based on this, and the press they receive, Section 3d appears to be viewed as more a boon for those who seek to limit secondary patents than Prior Consent. The differences in attention could reflect many things—including that India is a large supplier of generic drugs for many developing countries, and that the Indian policy was the focus of a major Supreme Court decision in 2013 that captured international headlines. It may also reflect their different origins: that Prior Consent was not explicitly designed for secondary patents, and many observers are not aware of the fact that these two provisions are functionally similar.

the effects they intend: whether laws on the books map to outcomes in practice. The issue of whether these restrictions are good or bad from a welfare perspective (e.g. getting the balance between innovation and access "right") are difficult questions, as we will discuss more in the conclusion.

Data

We collected data on all non-injectable new chemical entities approved by the U.S. Food and Drug Administration (FDA) between 1996 and 2004 that have at least one U.S. patent listed on the FDA publication "Approved Drugs and Therapeutic Equivalents," commonly called the Orange Book. There are 159 unique drugs (active ingredients) in this dataset, and we identified all U.S. patents listed on the FDA's Orange book for each drug.[25]

We then sought to find each of these U.S. patents' corresponding patent applications in Brazil and India. As noted above, locating drug patent applications in developing countries is difficult. This creates challenges not only for potential generic entrants, but also for empirical analyses such as ours. Neither India nor Brazil provides official links between drugs and their patents similar to the U.S. Orange Book (nor do most countries, developing or developed). We thus had to construct patent "landscapes" for each drug. To do so, we relied on two commercial sources. First, we mapped each US patent to its "family" applications in other jurisdictions, based on data from the Derwent World Patent Index. Second, we collected information from IMS Patent Focus, which provides global patent data for "commercially important" pharmaceutical products (including all of the drugs in our sample). Using these sources, we

[25] See Hemphill and Sampat (2011) for a description of this data set. The Orange Book lists most (though not all) of the pertinent patents for drugs marketed in the U.S.

located a total of 373 Brazilian applications for the drugs in our sample, and 197 applications in India.

We then coded each application. Working with a pharmaceutical patent attorney, we read each patent application to classify it by type of claims: chemical compound, polymorph or other crystal form, enantiomer or other isomer, salt/metabolite/intermediate, formulation or composition, method of use, process, other.[26] For expositional clarity, for the analysis below we collapse the categories and focus on differences between "primary" patents (those with any chemical compound claims, what we earlier refer to as "base molecule") and "secondary" patents (all others).

Since our interest is in drug product patents, we dropped a small number of process patents from the dataset. And since pipeline patents are not subject to the same examination procedures, we drop them from the patent application level analysis as well.[27] This left a final sample of 167 patent applications in India (associated with 69 drugs) and 265 applications in Brazil (associated with 100 drugs). The smaller number of applications in India may reflect aspects of TRIPS implementation discussed above, that India introduced pharmaceutical patents much later than Brazil, that it did so without a pipeline, and the uncertainty in the late 1990s about the status of the mailbox in India. It is also possible that firms are more conservative in filing in India than Brazil, filing fewer applications for pharmaceutical patents, in general, or

[26] The coding scheme is adapted from Hemphill and Sampat (2011; 2012)

[27] Pipeline patents in Brazil were not examined, but rather "revalidated." If the patent was granted elsewhere, provided that no product was already being marketed, the patent was issued in Brazil too (with the same claims as granted abroad). Thus, to the extent that pipeline patents are assessed, they are not assessed with regard to novelty and inventiveness but simply to assure that (1) the patent had been issued abroad, and (2) the drug was not on the market (i.e. it was still "in the pipeline"). Of the Brazilian applications in our dataset, 94 (25%) of these are pipeline patents.

filing fewer applications for secondary pharmaceutical patents, more specifically. Since many of these applications were filed before it became clear that India would include Section 3d, we are sceptical of these scenarios, but in any event to guard against selection arising from firms' filing decisions we also analyze paired applications filed in both countries.

We collected information on the outcomes of the patent applications in each country, as of June 2013. For India, we searched the Indian Patent Office's "Application Status" database for each application's status, and aggregated to: granted (indicating the patent application was granted), pending (indicating the application is still being examined) and rejected/abandoned/withdrawn (indicating that application was rejected, abandoned by the applicant, or formally withdrawn).[28] We collapse the last three categories since withdrawals and abandonments themselves could be responses to examiners' requests for information that may suggest a likelihood of rejection (Lemley and Sampat 2008).[29]

In cases where applications are "rejected", we consulted patent prosecution documents (including Controller Decisions, Examination Reports, and Correspondence) on the IPO database to determine the reasons for rejections. We coded each application as to whether 3d was a reason for the rejection, and also whether it was the sole reason for rejection, i.e. whether or not other arguments (e.g. lack of novelty, inventive step) were cited as well. We refer to those with any 3d rejections as applications "Rejected 3d+" and those with pure 3d rejections as "Rejected 3d" below.

[28] Some of the patents coded as rejected are under appeal and may, ultimately, be granted, but the number of these is small.

[29] In ongoing work on set of applications for which more detailed data are available, we examine applications that are rejected on the merits separately from applications that are abandoned and withdrawn.

To analyse the other element of India's pre-emptive mechanism, we reviewed the prosecution documents to ascertain whether there was a pre-grant opposition. We supplemented these searches with information from "Controller's Decisions" at the Indian patent office (all oppositions generate a Controller Decision), and the MSF Patent Opposition Database (MSF n.d.). For the applications for which we identified oppositions, we read the text of the oppositions to determine the grounds on which oppositions were filed (3d or other grounds).

For Brazil, we searched the INPI database for each of the applications. The INPI website provides data on each transaction that occurs during the course of examination, which we used to determine whether applications were granted, pending, or rejected (including withdrawn and abandoned, for the same reasons noted above). We also consulted an ANVISA document that indicates the actions that the health agency has taken on each application it has received.[30] Using data from these two sources we determined whether Brazilian patent applications were granted, pending, or rejected, and ANVISA's role. For granted applications, we also obtained data from ANVISA on whether, during the course of review, the patent had specific claims narrowed or eliminated. For rejected applications, we determined whether the application was rejected by INPI alone, in which case it would not have been forwarded to ANVISA, or whether ANVISA was involved. We coded two types of ANVISA involvement associated with rejections: whether it did not consent to a grant and the INPI subsequently rejected the application, or whether ANVISA raised questions of INPI's initial evaluation that resulted in the patent office reversing its preliminary approval and rejecting the application. In both instances we code these as PC (Prior Consent) Reject. We also created a category "Frozen" for applications where ANVISA

[30] INPI usually (though not always) reports if an application has been sent to ANVISA, but even then it does not record data on what the health agency does with the application. Hence the need to consult both sources.

denied Prior Consent but were not acted upon by the patent office. INPI is prohibited from granting these patents, but has been reluctant to reject patents that it believes ought to be granted on the basis of the health agency's review.

We address three questions with these data. First, what has happened to applications for pharmaceutical patents filed post-TRIPS in India and Brazil? Second, and more specifically, what has happened to secondary patent applications? Third, what role have the pre-emptive mechanisms played?

Results

Figure 2 shows overall outcomes. In both countries there are many pending applications, likely reflecting the sheer resource constraints making it difficult to process applications quickly.[31] In the case of India, where 35 percent of all applications are pending, the fact that many applications were held in store in the mailbox until 2005 may also contribute to the application backlog. Removing the pending applications and focusing only on applications with final disposals (the bottom panel) indicates higher rejection rates and lower grant rates in Brazil than India: in Brazil 79 percent of the applications were rejected, while in India the rejection rate was 50 percent.[32]

The figures also illustrate the use of pre-emptive mechanisms. Again focusing on final disposals, in India while 17 percent of the applications were rejected on grounds including 3d, just 3 percent of the applications were rejected solely on 3d grounds. In Brazil, three quarters of

[31] Recall that the applications in our dataset constitute only a small portion of the total number of pharmaceutical applications received.

[32] To repeat, not all of these are formally rejected by the patent offices, as we count abandoned and withdrawn applications in the category of "reject."

applications were rejected by INPI alone, without being viewed by ANVISA, with only 4 percent rejected on account of Prior Consent.[33] Given our expansive characterization of this category – any application that ANVISA looked at that ended up rejected or that was abandoned or withdrawn by the applicant is coded as a prior consent rejection, regardless of whether ANVISA specifically recommended rejection or merely requested additional information – the minimal direct role that the pre-emptive mechanism appears to be playing in a country with a low grant rate is striking. The data suggest a limited role for the pre-emptive mechanisms: in both countries fewer than 5 percent of applications were rejected directly on account of the pre-emptive mechanism alone.[34] However, as we shall discuss below, the interpretation and significance of the low share is different for the two countries.

The other aspect of India's pre-emptive mechanism we examine is pre-grant opposition. Roughly one-fifth of the Indian applications, 39 of the 167, had a pre-grant opposition.[35] Of these oppositions, the vast majority (30 of 39) included some 3d based argument. No oppositions cited 3d alone. We also found that applications with pre-grant oppositions are much less likely to be granted. The biggest source of this difference is that applications with pre-grant oppositions are much more likely to be rejected on "3d plus" grounds. These results point to the importance of pre-grant oppositions in enabling 3d. Of the eighteen rejections involving 3d, fifteen involved pre-grant oppositions.

[33] If we include the "frozen" applications, 6 percent of the applications were not granted on account of ANVISA's intervention.

[34] We address the question of indirect effects below.

[35] Two applications had post-grant oppositions, which we do not classify as "pre-emptive," and as a result we do not consider these two in the subsequent analyses.

We also distinguished by type of applications. Figure 3 shows outcomes by whether the patent application is a secondary application, which the pre-emptive mechanisms aim to restrict, or a primary application. All else being equal, we would expect secondary applications to be rejected more than primary applications. After all, even in the absence of special institutions to address particular types of applications, applications for chemical compounds are more likely to satisfy criteria of being novel and inventive. In India, the number of primary applications is small, and many of these are pending, leaving only nine with final disposals. Though the findings should be interpreted with caution given this small number, we note that, among applications with final disposals, secondary patents have a higher grant rate. This is surprising: if India's pre-emptive mechanisms were specifically targeting secondary applications, we would expect such applications to be more likely to be rejected. In Brazil the rejection rate for secondary applications is higher than primary applications, which is what we would expect. Yet, as we shall see, the sources of the rejections in Brazil suggest the story is more complex. These observations prompt us to look more carefully at how pre-emptive mechanisms are operating with regard to secondary applications.

The lower bars in Figure 3 show that in India, where secondary applications were rejected, the role of 3d was small. Focusing on the applications with final disposals, 35 percent of secondary applications were rejected by the IPO without involving 3d directly, 12 percent were rejected on grounds including 3d, but only 2 percent were rejected by 3d alone.

The data suggest that either alone or in combination with other grounds, 3(d) is involved in a minority of rejections. One caveat is that it is possible that 3d is having an indirect effect. Explicit prohibitions on some forms of secondary patents in Section 3d may deter some applications that would potentially be rejected on 3d grounds from being filed in the first place.

Also, more than half the of the secondary applications we count as "rejected" were withdrawn; it is possible that applications may be withdrawn because of 3d-inspired opposition, or threat of such opposition. Also, and perhaps most speculatively, the existence of 3d may alter the entire pharmaceutical patent examination process. After all, the same people – pharmaceutical patent examiners and patent office controllers – are responsible for applying different elements of the law and evaluating applications according to different criteria of patentability. The existence of 3d may make examiners more attuned to and sensitive of other aspects of patent law. For example, some of the non-3d grounds in that are cited in "3d-plus" rejections may not have been noticed or cited if not for 3d making the examination process more rigorous in the first place. But, the share of 3d-plus rejections is not that large either. In sum, these qualifications notwithstanding, the data suggest that 3d's effects on outcomes for secondary patents are not as strong as depicted by either its critics or supporters.

What about Brazil? Above we noted that secondary patent rejection rates were comparatively high in Brazil. However, Figure 3 shows that Prior Consent is not directly responsible for this outcome. Recall that ANVISA only received applications if INPI made a preliminary decision in favor of granting. What our data show is that INPI has been active in rejecting secondary patents by itself: 80 percent of secondary applications were rejected by INPI alone, without ANVISA's direct input. Here too it is possible that ANVISA has a more indirect effect, in that anticipation of ANVISA's review may shape INPI's behaviour, but all in all the role of Prior Consent in Brazil, as with 3d in India, is surprisingly small.

However, once ANVISA gets an application, it does shape outcomes on a significant share. Of the fifty applications that ANVISA reviewed, thirty-seven received ANVISA's consent and were granted, nine ended up rejected (either after being denied consent by ANVISA or after

being subjected to ANVISA's questions), and four were denied consent by ANVISA and subsequently frozen. Thus ANVISA directly affected outcomes on roughly a quarter of the applications it reviewed.[36]

The comparisons to here suggest that India is more liberal in granting secondary patents than Brazil. One problem with this reading is the possibility of selection: if secondary patents filed in India were disproportionately of higher quality than those in Brazil, we could see these differences even if India were no more lax (or even more stringent) than Brazil.

We address such concerns, and thus test the robustness of our findings, by comparing examination outcomes of paired applications. To do so we collected priority data for each application in our sample. The availability of priority data is a by-product of the 1883 Paris Convention (EPO 2014). As discussed above (see earlier footnote), inventors have twelve months from filing in one country to file in another, without losing "priority." To record this, patent applications list priority application numbers, i.e. the first application anywhere in the world by the same inventors that claimed the same material as a given national application. We can thus look at equivalent applications across the countries, those sharing exactly the same priority (EPO 2014). Examining outcomes for these twin applications allows us to control for unobserved heterogeneity in the applications examined in each country.

We collected priority information on Brazilian patents from the World Intellectual Property Organization (WIPO's) Patentscope database. It was more difficult to collect Indian priority data, since the Indian patent database reports priority information haphazardly, and

[36] Furthermore, even among those applications that received ANVISA's consent and were granted, in some cases ANVISA insisted on narrowing the claims.

international databases have less complete coverage of India and often reproduce mistakes from the Indian database.[37]

We focused on the subset of applications where both Indian and Brazilian information was available and we observed a clean one-to-one match between the two countries. We were able to locate 53 "twin" applications this way. We dropped three paired applications where our codings across the two cases did not match.[38] Since our objective here is to examine the robustness of the cross-country results on secondary patents, we also dropped three paired applications for primary patents. We thus limit these analyses to the 47 pairs of twin secondary applications with consistent coding across the two countries.

Figure 4 shows outcomes for the 47 twin secondary applications in Brazil and India. Here too, we see a much lower grant rate for secondary patents in Brazil than in India. Figure 5 illustrates the joint distribution of outcomes. In this heatmap, more intense shades of grey indicate more applications in a dyad. There are few 3d rejections and no prior consent rejections in this matched set, again providing evidence of the low incidence of these mechanisms overall. The modal outcome for this set of secondary patent applications is that Brazil rejected them (without ANVISA's direct involvement) and India granted them. Of applications rejected in Brazil, none of which involved ANVISA directly, forty percent (10/25) were granted in India. In contrast, of applications that we code as rejected in India (n=13), ten were rejected and one granted in Brazil (with two pending). In short, applications that are rejected in Brazil are

[37] An additional difficulty was presented by the quantity of "divisional" applications in India, where specific priority applications are broken into pieces yielding many Indian applications for a given Brazilian one.

[38] Our coding of whether primary or secondary matched in over 95 percent of the cases.

commonly granted in India, while applications that are not granted in India are ordinarily not granted in Brazil either.

The paired analyses, though based on a small subset of our data, are robust to the concerns about selection discussed above. Importantly, what we observe in the twin application is consistent with what we observe in the overall sample. The overwhelming impression from our data is that Brazil is more restrictive regarding the grant of secondary patents, and that in both countries the controversial pre-emptive mechanisms play less direct roles than expected.

Our focus to this point has been at the level of patents, as our overriding objective is to analyze the impact of the two countries' pre-emptive mechanisms on patent prosecution outcomes. We can also analyze the data at the level of drugs, examining how the pre-emptive mechanisms affected the existence and extent of patent protection on particular pharmaceutical products. To undertake these analyses we aggregated to the drug level, looking at all the applications for each drug in our sample. Table 1 shows the distribution of patents and outcomes for each drug, for both India and Brazil.

As we noted above, of the 159 drugs, 69 had one or more Indian patent applications. Of these, 40 had at least one granted patent. To assess the role that India's pre-emptive mechanism has at the drug level, we examined each of the 29 drugs without patents to determine the role of 3d in keeping them patent-free. Of these drugs, about one-third (11) had applications rejected at least partially on 3d grounds that, if granted, would still be in force as of 2013. For example, Novartis's Glivec is one of the drugs that is available as generic because of a rejection involving 3d. However, all of these rejections were based on 3d and other grounds; none were pure-3d rejections. Interestingly, each of the three drugs that had an application rejected on pure-3d grounds also had at least one other patent granted. Pure 3d rejections do not appear to have had a

role in whether drugs are currently under patent in India. But for these three drugs such rejections may influence the duration of exclusivity (i.e. the amount of time before all patents expire and generic competition is possible).

What about 3d in conjunction with pre-grant opposition? In the patent-level analyses we found that these two dimensions of India's pre-emptive system tend to be tightly coupled, in the sense that applications rejected on 3d grounds were nearly always opposed pre-grant (15 of 18). This interaction carries over to the drug-level analyses too. Of the eleven patent-free drugs with 3d rejections, in ten of these cases the rejected application was also the target of a pre-grant opposition.

For Brazil, we noted above that 100 of the drugs in our sample had at least one Brazilian application. This figure excluded pipeline patents, however, and to understand the effects of ANVISA on whether drugs have protection in Brazil we need to consider pipeline patents too. Altogether 125 drugs had either a pipeline patent or other patent application. Among these 125, twenty-nine drugs were free of patent protection (pipeline or non-pipeline). Of these twenty-nine, ANVISA denied consent for only three drugs.[39] Seven of the 96 drugs with at least one (pipeline or other) patent had another application rejected because of ANVISA denying prior consent.[40] In these cases ANVISA's interventions did not make the drugs patent-free, though they prevented additional, term-extending patents from being granted on these drugs. Like 3d, the Prior Consent mechanism appears to be more important for influencing the length of patent terms than whether or not drugs have patents.

---

[39] Another drug has no patents granted, but has an application that has been frozen following an ANVISA denial.

[40] ANVISA rejections are nearly twice as likely for drugs with pipeline patents, a point we return to in the Conclusion.

Discussion and conclusions

On the basis of our data, India's pre-emptive mechanism appears to be less important than one would expect. Secondary patent applications have a low rejection rate in India, and 3d rejections, especially pure 3d ones, are rare. We do see some evidence that pre-grant opposition helps enable 3d, but even with opposition, pure 3d rejections are rare. We have considered alternative interpretations of the data and alternative approaches to assessing the direct vs. indirect effects of 3d, but the takeaway from the analysis here is that we see a relatively small role for 3d for restricting secondary patents, despite all the attention it has generated.

This finding is puzzling given the political origins and trajectory of India's pre-emptive mechanisms. Why would a system that was created with a clear objective, and that has since been affirmed by a high-level government commission and defended by the Indian courts, tend to be under-utilized? While providing full explanations of institutional performance is beyond the scope of this paper, we suggest three possibilities. A first is that, for all of the clarity of the intent of 3d to minimize secondary patents, the terms of the law itself, and thus the guidance provided to examiners, were ambiguous. This is particularly so with regard to what is meant by "increased efficacy." Even where applications are deemed to be derivative of existing substances and thus fall within the remit of Section 3d, these are still patentable provided the applicants demonstrate increased efficacy. How the IPO is meant to make such judgments, against what benchmark examiners are to determine whether a claimed product satisfied this requirement, are complex and unresolved issues (Basheer and Reddy 2008).[41] A second relates to the heavy

[41] Although the Supreme Court's ruling of April 2013 (in the Novartis case) went some way toward clarifying this issue, determining that efficacy is to be judged strictly and narrowly in

reliance of 3d on pre-grant opposition. As noted above oppositions play an important contributory role in rejections (3d and otherwise) in India. But oppositions are public goods and subject to coordination problems among and between civil society groups and generic firms. A third possibility is that the results reflect insufficient resources to enforce Section 3d. The IPO operates under severe resource constraints. Over-stretched examiners facing pressures to clear applications (Kapczynski 2009) may result in the patent office not being able to examine patents – and subject them to 3d tests – with sufficient robustness to block patents that perhaps should not be granted. It is also possible that, in this context, IPO examiners have incentives to mimic decisions of the US and/or Europe, limiting the impact of 3d (Kapczynski 2009; Sampat and Amin 2013; Drahos 2010). A final scenario is that many secondary patents are in fact granted because they meet the efficacy standard. While we have not collected data on this, we believe that difficulties inherent to making efficacy assessments suggest this cannot be major part of the explanation, but this is something we are exploring in ongoing research.

Though Brazil appears to be more successful in terms of restricting secondary patents, ANVISA has a limited direct role. A striking feature of Brazilian prosecution is the high share of patents that are rejected (including abandoned and withdrawn) without ever leaving INPI and being passed to ANVISA. As indicated, this finding could reflect an indirect effect of the Prior Consent system: the anticipation of a second level of review provided by ANVISA may lead examiners to be more rigorous in their appraisal of applications, knowing that any grants of low quality patents could be overturned by ANVISA.

---

terms of therapeutic efficacy (in contrast to other, perhaps physical, properties of a drug), it is too early to see effects of this ruling on patent prosecution more generally.

Interestingly, the Prior Consent system has been the subject of extensive conflict in Brazil. Though controversy over Prior Consent is surprising if we compare ANVISA activity to outcomes overall, it is understandable if we focus on outcomes conditional on ANVISA review. As noted above, a quarter of the applications that INPI wanted to approve were held up by ANVISA. We have also seen that ANIVSA tends to be less likely to approve applications that correspond to drugs that also have pipeline patents. As such drugs are already on the market and providing revenue streams to the patent-holding firms, the material effects of ANVISA's actions here are likely to be felt more immediately than the case of denials of patents for products that are in earlier stages of development. ANVISA's involvement thus may have notable effects on – and elicit strong hostility from – patent-holding pharmaceutical firms.[42]

Our analysis has several limitations. One issue is timing. In India, all of our data focus on drugs before the courts clarified the meaning of 3d, and it is possible that this provision will have more of a role in the future. In Brazil, the patent office reportedly became more permissive after 2006, under the direction of a new INPI President, introducing new examination guidelines for second use applications and polymorphs that would make secondary patents easier to obtain (Shadlen 2011). Yet all of the post-2006 applications in our sample are pending.[43] Thus, it is possible that our analysis focuses on a particular period when the IPO was unable to apply 3d forcefully, and when INPI had more rigorous practices.

Another issue is comparability across the countries. We examined "twin" applications to ensure that our results did not reflect selection of applications filed in each country, and found

[42] Shadlen (2011) also discusses the ambivalent position of the domestic pharmaceutical sector in Brazil.

[43] Given that our database is based drugs authorized by the FDA prior to 2004, any application attached to one of these drugs filed in 2006 or beyond would by certainty be for a secondary application.

our results were robust to doing so. However, for the reasons we noted we were not able to reliably pair up all applications. Going forward, we are repeating the analyses by selecting on twin applications – international applications filed in many jurisdictions, including Brazil and India – and comparing outcomes. This will also allow us to see how other idiosyncratic features of the dataset used in this paper may affects results. The analyses in this paper are based on a dataset in which all of the applications were granted by the USPTO and all are attached to drugs that survived the full product development phase and were approved by the FDA. These characteristics have strengths, in that we are only looking at important applications that pharmaceutical firms will want to pursue. The dataset thus provides a window to examine how countries deal with important applications. But these characteristics of the dataset present weaknesses too, particularly that the applications we study here are not representative of the universe of applications India and Brazil have received. Also, because the applications in our dataset are older, and older applications tend to have less complete coverage in the proprietary databases that we use to find national application numbers, we run a higher risk of missing applications at the national level.

Although the limitations posed by the dataset in this paper caution against making broad assessments of the relative effectiveness of these two countries' approaches toward secondary applications, the results so far indicate that in both countries the controversial provisions on the books are having relatively small direct impacts in practice. This suggests that critics of these policies (such as the pharmaceutical sector and USTR) may be more worried about them than they should be. At the same time, champions of the policies may have cause for concern that laws on the books are not having a strong impact on patent outcomes in practice. While the sources of these gaps are the focus of ongoing research, their presence highlights the importance

of looking at actual patent prosecution outcomes in assessing the effects of TRIPS and policies to restrict secondary patens. Differences across the countries in grant rates of secondary patents, even if not direct results of 3d and Prior Consent, are large, with important implications for the extent of patent protection on drugs and when generic entry will be possible.

The results also suggest that other nuances of TRIPS implementation matter: the policy decisions made in the 1990s about transition periods and pipeline patents continue to have important effects on drug-level outcomes. We see this by blending the patent-level and drug-level analyses. At the patent level, we have seen that Brazil has a significantly lower grant rate than India, overall and specifically with regard to secondary patents. At the drug level, however, the overall extent of patent protection is considerably greater in Brazil on account of this country's provision of pipeline patents (of the 96 drugs in our dataset with patents in Brazil, more than half of these drugs are protected only by pipeline patents). One interpretation of these findings is that, in terms of the existence of patents on drugs, the effects of both countries' pre-emptive mechanisms may be outweighed by the lingering effects of the original TRIPS implementation decisions taken in the 1990s with regard to the introduction of pharmaceutical patents. India used the full transition period and thus has fewer of the drugs in our sample under patent, even if the pre-emptive mechanisms themselves seem to have had less incidence than expected. Brazil used little of the transition period and granted patents retroactively through the pipeline, and thus more of the drugs in our sample are under patent, even if the country appears to have more restrictive examination practices. That the countries are still feeling the impact of the policy choices made in the 1990s regarding transition periods and retroactivity is not surprising, as these were major decisions whose significance was understood at the time. Yet this also suggests that the importance of the pre-emptive mechanisms will *increase* in the future.

After all, as each year goes by the 2005 transition period in India recedes further into the past, and at some point (by 2017, roughly) all the pipeline patents in Brazil will have expired. As the direct effects of the policy choices made in the 1990s diminish, the countries' approaches toward pharmaceutical patent examination, including their pre-emptive mechanisms, will gain greater responsibility for the extent of pharmaceutical patents and the availability of generic drugs.

Finally, we have not taken a stand on whether secondary patents are good or bad from a social welfare perspective. The assessment of the effects of drug patents in developing countries on innovation incentives is difficult (Sweet and Eterovic Maggio 2015; Kyle and McGahan 2012; Qian 2007; Arora, Branstetter, and Chatterjee 2008) as is the assessment of the effects of secondary patents on the rate and direction of innovation (Hemphill and Sampat 2012). Even whether incremental innovations are valuable is the subject of much debate (Berndt, Cockburn, and Grépin 2006) debate. Similarly, assessing the effects of secondary patents on access is complicated. Secondary patents clearly can delay the timing of first possible generic entry, but the extent to which they actually affect access to medicines will interact with other practices (e.g. marketing, extent of price discrimination), policies (e.g. compulsory licensing, national health insurance) and other factors beyond patents (e.g. strength of health systems, national budgets). We cannot resolve these important issues here. Instead we have focused on how policies that aim to restrict secondary patenting function in practice.

Nonetheless, our analysis has broader implications. Though there are different perspectives on the direction and magnitude of their effects, there is widespread belief that patents in developing countries matter for innovation and/or access. If that is true, national differences about TRIPS implementation, including policies and practices regarding the granting of secondary patents, are relevant to future theorizing and empirical work on patents and

development. In particular, if there are gaps between patent laws on the books and how patent prosecution works in practice – as our sample appears to show for India and Brazil – the common approach of characterizing countries' patent systems based on statutory and treaty provisions could yield misleading impressions (Liu and La Croix 2015; Morin and Gold 2014; Park 2008). We hope that the approach introduced here, based on tracing of actual patent prosecution outcomes, can contribute to a more nuanced understanding of the effects of TRIPS among both scholars and practitioners.

References

Amin, Tahir. 2013. “Re-Visiting the Patents and Access to Medicines Dichotomy: An Evaluation of TRIPS Implementation and Public Health Safeguards in Developing Countries.” In *The Global Governance of HIV/AIDS*. Edward Elgar Publishing.

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 (Project Hope)* 31 (10): 2286–94.

Arora, Ashish, Lee Branstetter, and Chirantan Chatterjee. 2008. “Strong Medicine: Patent Reform and the Emergence of a Research-Driven Pharmaceutical Industry in India.” *NBER Conference on Location of Biopharmaceutical Activity*.

Basheer, Shamnad. 2009. “Patent Oppositions in India: The ‘Efficacy’ of Section 3(d).” *Spicy IP*. http://spicyipindia.blogspot.com/2009/09/patent-oppositions-in-india-efficacy-of.html.

Basheer, Shamnad, and Prashant Reddy. 2008. “The “Efficacy” of Indian Patent Law: Ironing out the Creases in Section 3(d).” SSRN Scholarly Paper ID 1086254. Rochester, NY: Social Science Research Network.

Basso, Maristela. 2006. “Intervention of Health Authorities in Patent Examination: The Brazilian Practice of the Prior Consent.” *International Journal of Intellectual Property Management* 1 (1/2): 54–74.

Berndt, Ernst R., Iain M. Cockburn, and Karen A. Grépin. 2006. “The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilisation in Original and Supplemental Indications.” *PharmacoEconomics* 24 Suppl 2 (December): 69–86.

Commission on Intellectual Property Rights. 2002. *Integrating Intellectual Property Rights and Development Policy*. Commission on Intellectual Property Rights.

Correa, Carlos María. 2007. *Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective*. ICTSD.

Drahos, Peter. 2008. “‘Trust Me’: Patent Offices in Developing Countries.” *American Journal of Law & Medicine* 34 (2/3): 151.

———. 2010. *The Global Governance of Knowledge: Patent Offices and Their Clients*. Cambridge University Press.

Falvey, Rod, Neil Foster, and David Greenaway. 2006. “Intellectual Property Rights and Economic Growth.” *Review of Development Economics* 10 (4): 700–719.

———. 2009. “Trade, Imitative Ability and Intellectual Property Rights.” *Review of World Economics* 145 (3): 373–404.

Farrell, Joseph, and Robert P. Merges. 2004. “Incentives to Challenge and Defend Patents: Why Litigation Won’t Reliably Fix Patent Office Errors and Why Administrative Patent Review Might Help.” *Berkeley Technology Law Journal* 19 (1): 943–70.

Gopakumar, K. M. 2013. “The Need to Curb Patents on Known Substances.” *Economic and Political Weekly* 48 (32): 55–57.

GSK. 2007. *Evergreening*. GlaxoSmithKline Briefings. GlaxoSmithKline.

Hemphill, C. Scott, and Bhaven Sampat. 2013. “Drug Patents at the Supreme Court.” *Science* 339 (6126): 1386–87.

Hemphill, C. Scott, and Bhaven N. Sampat. 2011. “When Do Generics Challenge Drug Patents?” *Journal of Empirical Legal Studies* 8 (4): 613–49.

———. 2012. “Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals.” *Journal of Health Economics* 31 (2): 327–39.

Howard, Leighton. 2007. “Use of Patents in Drug Lifecycle Management.” *Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector* 4 (3): 230–36.

Hunt, Michele. 2002. *Changing Patterns of Pharmaceutical Innovation: A Research Report*. The National Institute for Health Care Management Foundation.

IFPMA. 2013. “Incremental Innovation: Adapting to Patient Needs.” International Federation of Pharmaceutical Manufacturers & Associations. http://www.ifpma.org/innovation/ip-rights/incremental-innovation.html.

Ivus, Olena. 2010. “Do Stronger Patent Rights Raise High-Tech Exports to the Developing World?” *Journal of International Economics* 81 (1): 38–47.

Kapczynski, Amy. 2009. “Harmonization and Its Discontents: A Case Study of TRIPS Implementation in India’s Pharmaceutical Sector.” *California Law Review* 97: 1571–1649.

Kapczynski, Amy, Chan Park, and Bhaven Sampat. 2012. “Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of ‘Secondary’ Pharmaceutical Patents.” *PLoS ONE* 7 (12): e49470.

Kunisawa, Viviane Yumy Mitsuuchi. 2009. “Patenting Pharmaceutical Inventions on Second Medical Uses in Brazil.” *The Journal of World Intellectual Property* 12 (4): 297–316.

Kyle, Margaret K., and Anita M. McGahan. 2012. “Investments in Pharmaceuticals Before and After TRIPS.” *The Review of Economics and Statistics* 94 (4): 1157–72.

La Croix, Sumner, and Ming Liu. 2009. “The Effect of GDP Growth on Pharmaceutical Patent Protection, 1945-2005.” *Brussels Economic Review* 52 (3/4): 355–75.

Lemley, Mark. 2001. *Rational Ignorance at the Patent Office*. SSRN Scholarly Paper ID 261400. Rochester, NY: Social Science Research Network. http://papers.ssrn.com/abstract=261400.

Lemley, Mark, and Bhaven N. Sampat. 2008. “Is the Patent Office a Rubber Stamp?” *Emory Law Journal* 58: 181 – .

Liu, Ming, and Sumner La Croix. 2015. “A Cross-Country Index of Intellectual Property Rights in Pharmaceutical Inventions.” *Research Policy* 44 (1): 206–16.

Matthews, Duncan, and Carlos Correa. 2011. “The Doha Declaration Ten Years on and Its Impact on Access to Medicines and the Right to Health.” United Nations Development Program.

Morin, Jean-Frédéric, and Edward Richard Gold. 2014. “An Integrated Model of Legal Transplantation: The Diffusion of Intellectual Property Law in Developing Countries.” *International Studies Quarterly* 58 (4): 781–92.

MSF. n.d. “Patent Opposition Database.” *Médecins Sans Frontières (MSF) International*. http://www.msf.org/article/patent-opposition-database.

Park, Walter G. 2008. “International Patent Protection: 1960–2005.” *Research Policy* 37 (4): 761–66.

Qian, Yi. 2007. “Do National Patent Laws Stimulate Domestic Innovation in a Global Patenting Environment? A Cross-Country Analysis of Pharmaceutical Patent Protection, 1978–2002.” *Review of Economics and Statistics* 89 (3): 436–53.

Sampat, Bhaven N., and Tahir Amin. 2013. “How Do Public Health Safeguards in Indian Patent Law Affect Pharmaceutical Patenting in Practice?” *Journal of Health Politics, Policy, and Law* 38 (4): 735–55.

Scherer, F.M. 2000. “The Pharmaceutical Industry.” In *Handbook of Health Economics*, Part B, 1:1297–1336.

Sengupta, Amit. 2013. “Two Decades of Struggle.” *Economic and Political Weekly* 48 (32): 43–45.

Shadlen, Kenneth C. 2011. “The Political Contradictions of Incremental Innovation: Lessons from Pharmaceutical Patent Examination in Brazil.” *Politics & Society* 39 (2): 143–74.

———. 2012. “The Rise and Fall of ‘Prior Consent’ in Brazil.” *WIPO Journal* 3 (1): 103–12.

South Centre. 2011. “The Doha Declaration on TRIPS and Public Health Ten Years Later: The State of ImplementationPolicy Brief 7, November 2011.” Policy Brief 7.

Sweet, Cassandra Mehlig, and Dalibor Sacha Eterovic Maggio. 2015. “Do Stronger Intellectual Property Rights Increase Innovation?” *World Development* 66 (February): 665–77.

UNAIDS. 2011. *Doha+10 TRIPS Flexibilities and Access to Antiretroviral Therapy: Lessons from the Past, Opportunities for the Future.* http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2260_DOHA+10TRIPS_en.pdf.

Vernaz, Nathalie, Guy Haller, François Girardin, Benedikt Huttner, Christophe Combescure, Pierre Dayer, Daniel Muscionico, Jean-Luc Salomon, and Pascal Bonnabry. 2013. “Patented Drug Extension Strategies on Healthcare Spending: A Cost-Evaluation Analysis.” *PLoS Med* 10 (6): e1001460.

WIPO. 2011. *World Intellectual Property Indicators: 2011 Edition*. World Intellectual Property Organization.

Table 1: Patent coverage by drug

This table shows the distribution of drug level outcomes for drugs in our sample that had a patent application in India and/or Brazil. The columns "Brazil" and "India" indicate outcomes for each patent application on a drug. In Brazil, "PIP" indicates a pipeline application, "GRA" a granted application, "INR" an application rejected by INPI, "PCR" an application rejected via Prior Consent, "FRO" a frozen application, and "PEN" a pending application. In India, "GRA" and "PEN" represent granted and pending applications, "REJ" those rejected without 3d, "R3D" pure 3d rejections, and "R3+" applications rejected on 3d and other grounds. The "Patented" columns indicate whether a drug has any patent protection (including pipeline patents for Brazil), and the "Preemptive" columns indicate whether a pre-emptive mechanism led to a rejection of one or more patents associated with a drug. In India, an "O" in the pre-emptive column indicates one or more applications on the drug drew pre-grant opposition.

[INSERT TABLE FROM EXCEL]

Figure 1: Why secondary patents matter

Consider a firm that applied for a patent on a new molecule XYZ for treating diabetes in 1994. Through subsequent research the firm discovered that an alternative form of the molecule, XYZ*, would work better and applied for a patent on XYZ* in 2000. In 2003, after completing clinical trials, the firm received authorization from health authorities to place a drug based on XYZ* on the market. The patent on the base molecule XYZ expires in 2014, while the patent for the alternative form XYZ*, if granted, would not expire until 2020. How countries treat these applications has important implications. Any country that grants the XYZ* application will be extending the drug's period of market exclusivity for six years beyond 2014. This could affect prices, the government health budgets, and access to medicines.

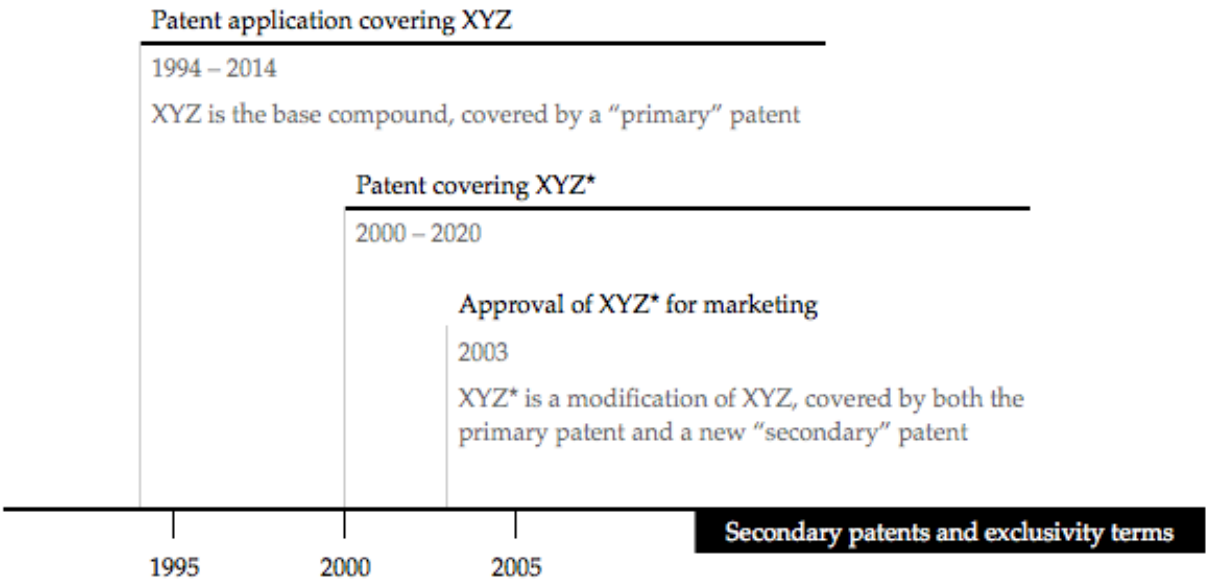

Figure 2: Outcomes for Patent Applications in India and Brazil

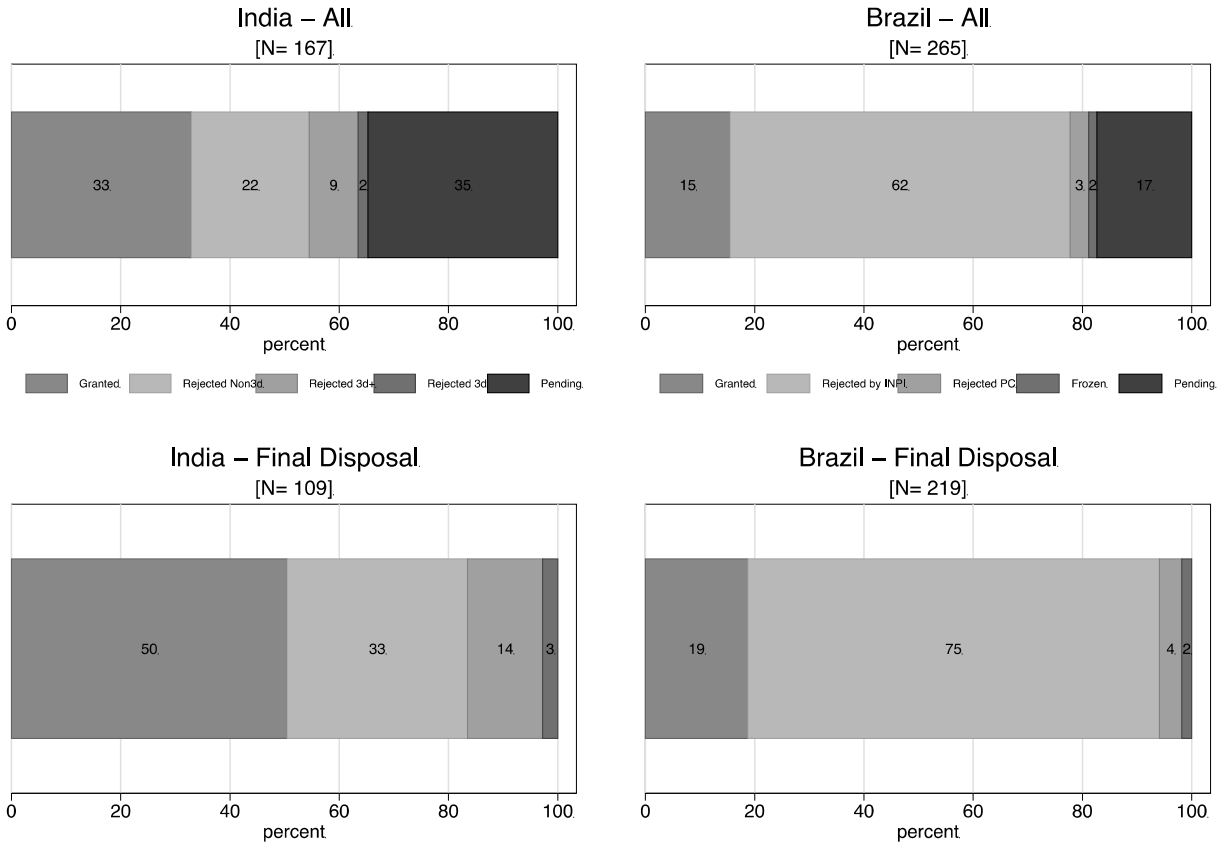

Figure 3: Outcomes for Patent Applications in India and Brazil, by Category

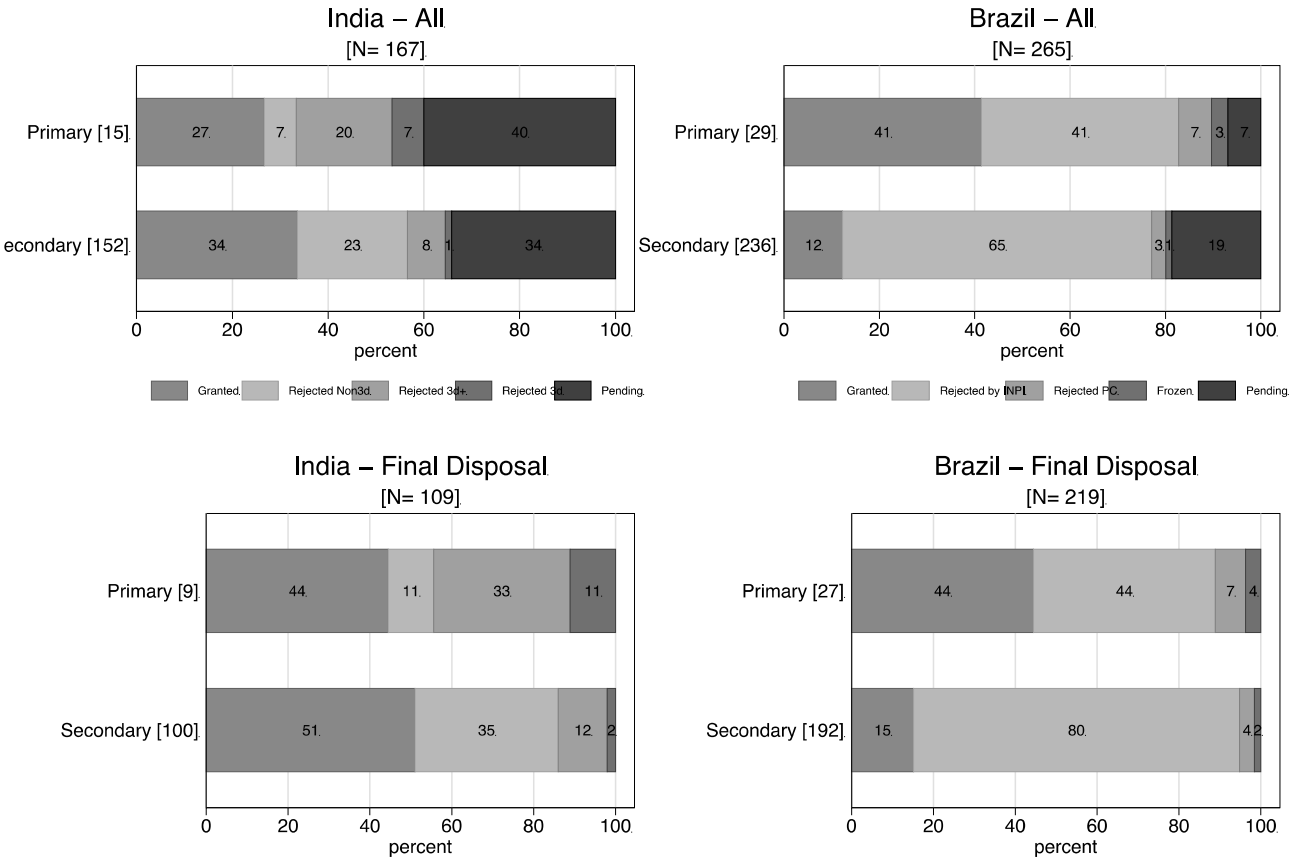

Figure 4: Outcomes for the 47 "Twin" Patent Applications Filed in Both India and Brazil, Secondary Applications Only

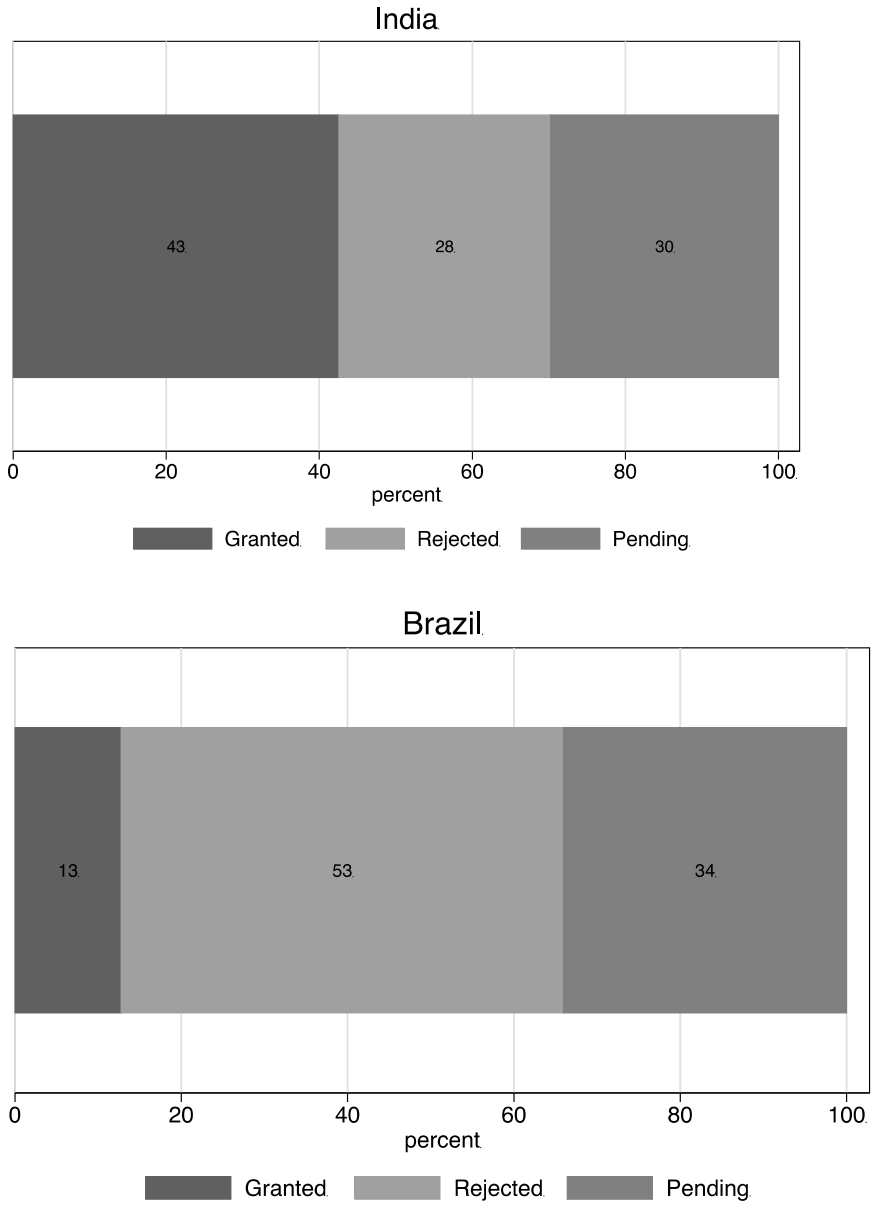

Figure 5: Joint distribution of outcomes for 47 Twin secondary applications filed both in India and Brazil

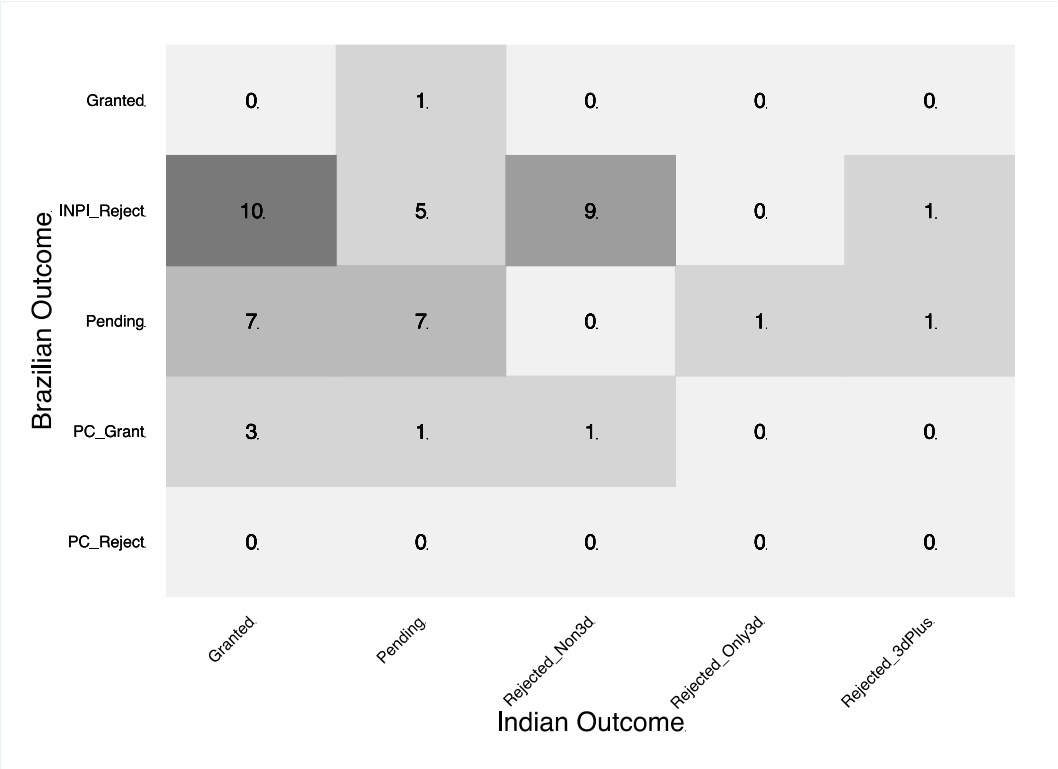

Table 1: This table shows the distribution of drug level outcomes for drugs in our sample that had a patent application in India and/or Brazil. The columns "Brazil" and "India" indicate outcomes for each patent application on a drug. In Brazil, "PIP" indicates a pipeline application, "GRA" a granted application, "INR" an application rejected by INPI, "PCR" an application rejected via Prior Consent, "FRO" a frozen application, and "PEN" a pending application. In India, "GRA" and "PEN" represent granted and pending applications, "REJ" those rejected without 3d, "R3D" pure 3d rejections, and "R3+" applications rejected on 3d and other grounds. The "Patented" columns indicate whether a drug has any patent protection (including pipeline patents for Brazil), and the "Preemptive" columns indcate whether a pre-emptive mechanism led to a rejection of one or more patents associated with a drug. In India, an "O" in the pre-emptive column indicates one or more applications on

DRUG	BRAZIL	PATENTED	PREEMPTIVE	INDIA	PATENTED	PREEMPTIVE?
ABACAVIR SULFATE	PIP INR INR INR INR GRA GRA	X		GRA	X	
ADAPALENE	PEN PEN PEN PEN			GRA GRA	X	
ADEFOVIR DIPIVOXIL	PIP INR INR	X		PEN PEN REJ R3+		XO
ALFUZOSIN HYDROCHLORIDE	GRA	X		GRA GRA	X	
ALMOTRIPTAN MALATE	PIP	X				
ALOSETRON HYDROCHLORIDE	PIP INR	X				
AMPRENAVIR	PIP INR INR INR INR GRA GRA	X				
APREPITANT	INR INR			GRA	X	
ARIPIPRAZOLE	PIP INR INR PEN PEN	X		GRA PEN PEN	X	
ATAZANAVIR SULFATE	INR GRA	X		PEN PEN PEN		O
ATOMOXETINE HYDROCHLORIDE	INR					
ATORVASTATIN CALCIUM	PIP INR INR INR INR INR PEN GRA	X		PEN PEN R3+ REJ REJ		XO
BALSALAZIDE DISODIUM				PEN		
BEXAROTENE	PIP	X				
BIMATOPROST				PEN		
BOSENTAN	PIP INR	X				
BRIMONIDINE TARTRATE	INR INR INR PEN PEN PEN			PEN		
BRINZOLAMIDE	INR					
CANDESARTAN CILEXETIL	PIP	X				
CAPECITABINE	PIP	X				
CEFDITOREN PIVOXIL	GRA	X				
CELECOXIB	PIP INR INR	X		PEN		O
CERIVASTATIN SODIUM	PIP	X				
CINACALCET HYDROCHLORIDE	INR PEN					
CLOPIDOGREL BISULFATE	PIP INR GRA	X		GRA PEN	X	O
COLESEVELAM HYDROCHLORIDE	INR INR INR PEN					
DARIFENACIN HYDROBROMIDE	PIP FRO INR	X		GRA PEN REJ	X	O
DELAVIRDINE MESYLATE	INR			GRA PEN	X	
DESLORATADINE	INR INR INR INR INR			REJ		
DOFETILIDE	PIP INR	X				
DONEPEZIL HYDROCHLORIDE	PIP	X				
DOXERCALCIFEROL	INR INR PEN PEN			GRA	X	
DULOXETINE HYDROCHLORIDE	PIP INR GRA	X		REJ		
DUTASTERIDE	PIP	X				
EFAVIRENZ	PIP INR INR PEN	X		PEN R3+ REJ		XO
ELETRIPTAN HYDROBROMIDE	PIP FRO INR	X		GRA	X	
EMTRICITABINE	PIP INR INR PEN GRA	X		PEN R3+		XO
ENTACAPONE	PIP INR	X		GRA	X	
EPINASTINE HYDROCHLORIDE	INR			GRA	X	
EPLERENONE	INR INR INR PEN PEN			GRA	X	
EPROSARTAN MESYLATE	PIP INR GRA	X		GRA	X	
ERLOTINIB HYDROCHLORIDE	INR INR PEN GRA	X		GRA GRA PEN PEN R3+	X	XO
EXEMESTANE	PIP INR	X				
EZETIMIBE	PIP INR INR INR INR INR PEN PEN	X		GRA GRA REJ	X	
FEXOFENADINE HYDROCHLORIDE	PIP INR GRA	X				
FORMOTEROL FUMARATE	INR INR INR INR INR INR					
FROVATRIPTAN SUCCINATE	PIP	X				
GALANTAMINE HYDROBROMIDE	INR INR GRA	X				
GEFITINIB	PCR		X	R3+		XO
GEMIFLOXACIN MESYLATE	PIP INR	X				
GREPAFLOXACIN HYDROCHLORIDE	PIP	X				
HYDROCHLOROTHIAZIDE; IRBESARTA	PIP	X				
IBANDRONATE SODIUM	PIP INR INR INR	X		REJ REJ REJ		
IMATINIB MESYLATE	PIP INR INR INR PEN	X		PEN PEN R3+ R3+ REJ		XO
INDINAVIR SULFATE	PIP INR INR	X				
IRBESARTAN	PIP	X				
KETOTIFEN FUMARATE	INR					
LANTHANUM CARBONATE	PEN GRA	X		PEN		O
LATANOPROST	PIP	X				
LEFLUNOMIDE	PIP	X				
LETROZOLE	PIP INR INR INR INR INR	X		REJ REJ		
LEVETIRACETAM	PIP PEN	X		PEN		O
LINEZOLID	PIP INR INR INR INR	X		GRA GRA GRA R3D R3D REJ	X	X
LOTEPREDNOL ETABONATE	INR INR					
MEMANTINE HYDROCHLORIDE	PEN			GRA	X	
MIGLITOL	PIP	X				
MIGLUSTAT	INR					
MODAFINIL	PEN PEN GRA	X		GRA GRA	X	
MONTELUKAST SODIUM	PIP INR INR INR INR	X				
MOXIFLOXACIN HYDROCHLORIDE	INR PEN GRA GRA	X		GRA GRA GRA REJ REJ	X	O
NARATRIPTAN HYDROCHLORIDE	PIP	X				
NATEGLINIDE	PIP INR	X		GRA PEN PEN	X	
NELFINAVIR MESYLATE	PIP PEN PEN	X		GRA GRA	X	
NITAZOXANIDE	GRA GRA	X		GRA	X	
OLANZAPINE	PIP INR INR INR INR PEN GRA GRA PCR	X	X	GRA REJ	X	
OLMESARTAN MEDOXOMIL	PIP INR	X				
OLOPATADINE HYDROCHLORIDE	PIP PEN	X				
ORLISTAT	PIP	X		REJ REJ		O
OSELTAMIVIR PHOSPHATE	GRA	X		REJ R3+		XO
OXCARBAZEPINE	INR			PEN R3+		XO
PANTOPRAZOLE SODIUM	INR INR PEN PEN PCR		X	GRA PEN REJ	X	
PENCICLOVIR SODIUM	INR					
PIMECROLIMUS	PIP INR PCR	X	X	PEN R3+ REJ		XO
PIOGLITAZONE HYDROCHLORIDE	PIP INR INR	X				
PRAMIPEXOLE DIHYDROCHLORIDE	PIP PEN PEN	X		PEN PEN		
PREGABALIN	INR INR GRA GRA PCR	X	X			
QUETIAPINE FUMARATE	PIP PCR	X	X	PEN PEN		
RABEPRAZOLE SODIUM	INR PCR		X	R3+		XO
RALOXIFENE HYDROCHLORIDE	PIP INR INR INR GRA GRA GRA PCR	X	X	GRA GRA GRA REJ	X	
REPAGLINIDE				REJ		
RIFAXIMIN	INR INR PEN			GRA PEN PEN	X	
RISEDRONATE SODIUM	GRA INR INR INR INR INR PEN PEN	X		GRA PEN REJ REJ	X	
RITONAVIR	PIP INR INR GRA GRA PCR PCR	X	X	PEN PEN REJ REJ		O
RIVASTIGMINE TARTRATE	PIP INR INR	X				

RIZATRIPTAN BENZOATE	PIP	X				
ROFECOXIB	PIP INR INR INR INR	X				
ROPINIROLE HYDROCHLORIDE	PIP	X				
ROSIGLITAZONE MALEATE	PIP INR INR INR INR INR INR	X		GRA PEN PEN REJ	X	
ROSUVASTATIN CALCIUM	INR INR INR INR INR INR PEN GRA	X		GRA GRA PEN REJ REJ REJ	X	O
SEVELAMER HYDROCHLORIDE	PEN					
SIBUTRAMINE HYDROCHLORIDE	PIP	X				
SILDENAFIL CITRATE	PIP FRO INR GRA PCR	X	X			
SIROLIMUS	PIP INR INR GRA GRA	X		GRA PEN REJ	X	
SODIUM OXYBATE				GRA PEN	X	
TADALAFIL	INR INR INR INR INR INR PEN GRA	X		GRA GRA PEN R3D REJ	X	XO
TEGASEROD MALEATE	PIP	X				
TELITHROMYCIN	GRA	X				
TELMISARTAN	PIP INR INR	X		GRA GRA	X	
TEMOZOLOMIDE	PIP PEN	X		PEN PEN		
TENOFOVIR DISOPROXIL FUMARATE	INR PEN			GRA PEN PEN PEN PEN PEN R3+ R3+ R3+ R3+	X	XO
THALIDOMIDE	PIP PEN PEN	X				
TIAGABINE HYDROCHLORIDE	FRO INR			GRA	X	
TIOTROPIUM BROMIDE MONOHYDRAT	PIP INR INR PEN PEN PEN PEN	X		GRA GRA PEN PEN PEN PEN PEN R3D REJ RE	X	XO
TOLCAPONE	PIP	X				
TOLTERODINE TARTRATE	PIP INR INR	X		GRA PEN	X	
TOPIRAMATE	INR					
TRANDOLAPRIL	PIP	X				
TRAVOPROST	INR					
TROGLITAZONE	PIP INR	X				
TROVAFLOXACIN MESYLATE	PIP INR INR	X				
UNOPROSTONE ISOPROPYL	INR					
VALDECOXIB	INR GRA	X				
VALSARTAN	PIP INR INR INR INR PEN PEN	X		PEN PEN R3+ REJ		X
VARDENAFIL HYDROCHLORIDE	GRA GRA	X		GRA	X	
VORICONAZOLE	PIP GRA GRA	X		PEN		O
ZANAMIVIR	PIP	X				
ZILEUTON	PIP	X				
ZIPRASIDONE HYDROCHLORIDE	PIP INR INR INR INR GRA	X		GRA PEN	X	
ZOLMITRIPTAN	PIP GRA INR	X				