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Patents, trade and medicines: past, present and future

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ABSTRACT

This article analyzes the spread of intellectual property in trade agreements. We explain how the integration of intellectual property with international trade rules led to the globalization of pharmaceutical patenting, and then how additional provisions related to pharmaceutical products have been introduced by regional and bilateral trade agreements. We describe the additional 'TRIPS-Plus' rules contained in recent trade agreements, which go beyond the requirements of the World Trade Organization's TRIPS Agreement, and explain the potential challenges that they may create for developing countries. We draw attention to the conceptual and methodological challenges of assessing the effects of patent provisions in trade agreements on prices and access to drugs, with particular emphasis on the importance of timing. Depending on when countries began allowing drugs to be patented, TRIPS-Plus provisions have different effects; and when pharmaceutical patenting has been in place for more countries for more time, the effects of TRIPS-Plus provisions will change again.

KEYWORDS
TRIPS; TRIPS-Plus; pharmaceuticals; drugs; patents; prices

Historically most developing countries did not allow patents on pharmaceutical products. Patent offices existed, and patents were available for machinery and electronics and many other areas, but not drugs. This prohibition reflected a calculation that the costs of having private rights of exclusion over these sorts of inventions would outweigh the benefits. In the closing decades of the 20th century, however, the global politics of intellectual property (IP) underwent a fundamental shift: the World Trade Organization's (WTO) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) made pharmaceutical patent protection obligatory for all WTO members (Braithwaite & Drahos, 2000; Deere, 2008; Drahos, 1995; Dutfield, 2003; Maskus, 2014). By 2005 pharmaceutical patents were universally available, in all but the poorest countries.

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Since patents reduce competition, TRIPS generated fears that drug prices in developing countries would increase, public health budgets would come under strain, and patients would be left without access to essential medicines. These concerns intensified in the late 1990s and early 2000s, as the HIV/AIDS pandemic reached crisis proportions around the world. In some of the hardest-hit countries, such as South Africa, where one in five adults was HIV-positive, the medicines needed to treat HIV were patented and priced out of reach, and developed countries and companies argued that attempts to bring prices down would violate TRIPS (Treatment Action Campaign, 2003; Fisher & Rigamonti, 2005; Mbali, 2013). At roughly the same time, a flurry of regional and bilateral trade agreements was negotiated between developing countries in Asia, Africa, and Latin America and the USA (and also European Union). These newer agreements, with still more restrictive patent requirements that increase the level of protection beyond what is required by TRIPS, further intensified fears about the impact of trade agreements on drug prices and health.[1]

This article analyzes the spread of these 'TRIPS-Plus' rules in bilateral trade agreements, describes the patent provisions they include, and explains the challenges that they may create for developing countries.[2] We emphasize the conceptual and methodological challenges of assessing the effects of patent provisions in trade agreements on drug prices, including the choice of variables to focus on, how to operationalize these variables, and the importance of timing in analyzing the effects of TRIPS-Plus provisions. Because pharmaceutical patenting is new in many countries, and because of the lag time between when patents are applied for and when drugs are launched, the full effects of TRIPS and TRIP-Plus provisions are not yet felt — and some of ways that these provisions are being felt, are particular to this long period of gestation. Understanding the transitional elements of the spread of pharmaceutical patenting is essential for thinking about the effects of TRIPS-Plus provisions in trade agreements. Depending on when countries began allowing drugs to be patented, TRIPS-Plus provisions will have different effects. Once pharmaceutical patent regimes in more countries take full effect, the transitional elements of TRIPS will fade in importance, and as that happens, the effects of TRIPS-Plus provisions will likely change again.

The article has four sections. The first discusses sources of conflicts over patents on pharmaceutical products, and describes the process by which pharmaceutical patent protection has become globalized since the 1970s. The second examines the key TRIPS-Plus provisions related to pharmaceuticals that are present in the trade agreements that nineteen countries have signed with the US. We consider how each provision might affect competition and drug prices theoretically, and also describe variation in how such provisions are presented in different agreements. The third section argues that the effects of TRIPS-Plus provisions in any given country depends on when the country introduced drug patents, as well as details of how the provisions are implemented locally. We also explain that the types of effects these provisions are likely to have, on the existence patent protection or the duration of patent protection, differ according to how long countries have allowed drug patents, and thus are likely to change going forward. The fourth section summarizes the key arguments, underscoring the importance of focusing on the right sets of drugs in the right countries at the right times when assessing the impact of TRIPS-Plus provisions in trade agreements.

Pharmaceutical patents and developing countries: key issues and context

To understand the concerns that TRIPS and the TRIPS-Plus provisions have generated, a brief review of the basic law and economics of patents is useful. Patents grant exclusive rights over inventions for limited periods in the territories where they are granted. Applicants must convince examiners that they have created something novel, inventive (also referred to as 'non-obvious' in the US), and useful, and then, once granted, the patent will last for twenty years from the date of application. For as long as a patent in a given country is in effect, the rights to produce and sell goods in that country that include the protected knowledge lie solely with the owner of the patent.

By providing firms with means to appropriate the benefits of their investments in research and development, patents can create incentives for invention and innovation. Yet because patents convert knowledge, something that is non-rivalrous (everyone can use unlimited amounts of it without reducing anyone else's ability to use it) into private property controlled by a single owner, the same instrument that incentivizes new inventions also restricts their diffusion and use. After all, the idea behind the patent system is that the prospect of supra-competitive pricing during the period of protection is necessary for creating R&D investment incentives. The tradeoff between dynamic benefits (incentives for innovation) and static costs (higher prices, reduced access) is inherent to the patent system.

Historically, the relative weight that countries place on the dynamic benefits versus the static costs of patents influenced whether they favored more or less protection.[3] Countries with few innovative firms or small markets typically viewed the benefits of patents as limited, since small markets can do little to drive global R&D priorities, and local patents may do more to hurt the development of industry than stimulate invention in the absence of an industrial sector with inventive and innovative capabilities. Countries with such stronger industrial sectors, in contrast, perceived greater benefits in patents. The international politics of patents have reflected these different perspectives: developing countries have typically sought international rules that allow countries to restrict what sort of knowledge is eligible for patents and reduce patent-holders' rights of exclusion, and developed countries have sought rules that would make it easier for innovators to obtain and defend patents across the globe (Drahos, 1997; Maskus, 2014).

Conflicts over patents are particularly acute in the area of pharmaceuticals. Drug development is expensive (reported R&D/sales ratios are higher than in most other industries), both because of uncertainties in science (i.e. most research fails to yield marketable products) and the need to undertake clinical trials to receive regulatory approval for new products (Scherer, 2000). But once developed, drugs are easy to replicate: it is comparatively simple for one firm to produce an identical version of a drug developed by another firm.[4] The relative ease of replication means that patents are important for warding off competition and thus capturing the benefits of investments in technological innovation and product development.[5] Unlike other industries, where first-mover advantages, lead time, secrecy, and other factors are effective at helping firms appropriate returns from R&D, patents are rated as particularly important in the pharmaceutical industry.[6]

Another characteristic of the pharmaceutical sector that fuels originator firms' interests in obtaining and retaining patent protection are the considerable delays between invention and launch. Patent applications, to meet standards of novelty, need to be filed early, typically within one year of the invention being made, at a point when the associated drugs that the patent aims to protect ordinarily will still be in the product development stage. And the development stage in pharmaceuticals is long: the path from establishment of a new compound to having a useful product takes years, as do the clinical trials that are necessary to obtain regulatory approval. By the time a drug protected by a patent is placed on the market, a significant chunk of the 20-year patent term may have lapsed, and patent owners are fiercely concerned with their rights of exclusion in the remaining years. Originator firms typically do all they can to ward off competitors during the periods of protection promised by their patents and, if possible, to extend periods of protection.

The costs of providing single suppliers with exclusive rights to produce and sell drugs are well known. Many drugs have few functional substitutes. Patients with one condition (e.g. hypertension) cannot ordinarily be treated with medicines for other conditions (e.g., chronic pain); nor can pharmaceutical firms that produce hypertension drugs do so using molecules that reduce pain. Not only is the range of appropriate alternatives in each therapeutic class often limited, but even when alternatives exist, drugs that treat the same condition may have different side effects and be tolerated differently. Thus for many individuals there is in effect just one useful treatment.

Restricting access to new medicines lacking functional substitutes may thus have profound costs in terms of health and well-being. These costs are not always visible, as they are when patients unable to get essential medicines die. Instead, the costs may be incurred in terms of patients suffering on account of using older, inferior drugs (or none). There are also potential broader effects. When governments allocate the resources towards expensive patented medicines for one disease, less resources are available in healthcare budgets overall. To be sure, prices are not the only factor affecting access to medicines, but it is athreshold condition of access in many resource poor settings. Additional measures to prevent high prices, such as price controls, can ameliorate some of these harms if they are effectively deployed. But administering price control systems is challenging, because they are technically and administratively demanding. Where markets are small, companies may also respond to attempts to control prices by threatening to withdraw their products altogether, compounding the difficulty of effectively using these measures.[7]

Historically many countries have treated the costs of granting patents on drugs as exceeding the benefits.[8] Reluctance to grant pharmaceutical product patents reflects not only the costs discussed in the previous paragraphs, but also an expectation that any individual country's drug patent protection (except for very rich countries) has only limited impact on global R&D incentives.[9]

Until recently allowing pharmaceutical patents was the exception and not the rule around the world. While pharmaceutical patents have long been available in the USA, this was not the case in other wealthy countries. In Europe, for example, as of the early 1970s only Britain, France and West Germany allowed drugs to be patented. Japan did not begin granting pharmaceutical patents until 1976. Then, from the mid-1970s to the early 1990s, pharmaceutical patenting became the norm throughout the 'Global North': Belgium, the Netherlands, Italy, Sweden, and Switzerland in the late 1970s; Canada, Denmark, and Austria in the 1980s;

Australia, Greece, Ireland, New Zealand, Norway, Portugal, and Spain in the early 1990s.[10]

At the same time as pharmaceutical patenting was becoming normalized in the 'Global North', many countries in the 'Global South' resisted making patents available for pharmaceutical products.[11] Observers of IP often refer to a U-shaped relationship between national income levels and the extent of IP protection, with middle-income countries offering less protection than high-income and low-income countries (Chen & Puttitanun, 2005; Maskus, 2000). In the case of pharmaceuticals, this is not accurate over the course of history, as pharmaceutical patents were hardly available anywhere as of the mid-1970s, but accurately describes the situation as of the late 1980s and early 1990s, when negotiations over TRIPS were underway (La Croix & Liu, 2009).[12]

It was in this context, with pharmaceutical patents broadly available in wealthy countries but unavailable elsewhere, that the transnational pharmaceutical sector mobilized to universalize pharmaceutical patent protection. Drug companies and their representatives were among the leading advocates of TRIPS, and more generally, of the integration of IP into the trade regime (Drahos, 1995; Ryan, 1998; Matthews, 2002; Sell, 2003; Pugatch 2004). The pharmaceutical lobby's highest priority was to make sure that the protection available in developed countries was also available in developing countries. Through successful lobbying, the pharmaceutical industry made the goal of universalizing patent protection a priority of US and European governments, too. Increasingly IP became an important element of the US and European Community's foreign economic policies.

The TRIPS Agreement was the outcome of these efforts. Among other requirements, TRIPS mandates that all countries allow pharmaceutical product patents. Countries where this would be new, those that as of 1995 were not already granting pharmaceutical patents, had the option of waiting until 2005 to do so. Some did so earlier, in anticipation. By 2005 all but the world's poorest countries had begun to allow pharmaceutical product patents.[13]

Figure 1 illustrates the global expansion of pharmaceutical patenting from 1960 to 2005. The vertical axis shows the number of countries that allowed drug patent

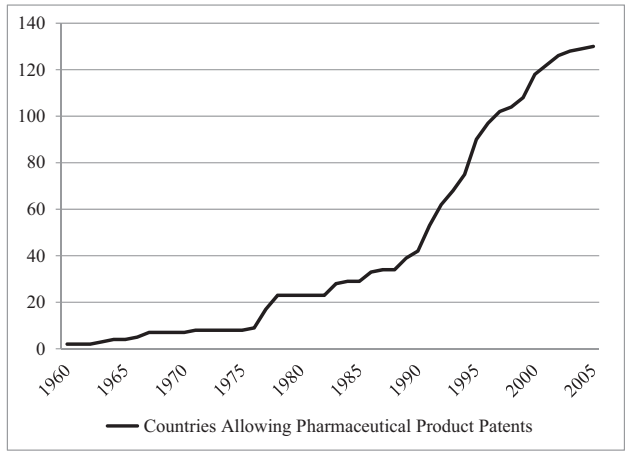

Figure 1. The globalization of pharmaceutical patenting.
Note: Authors' elaboration based on data in the supplemental appendices of Liu and La Croix (2015) and UNCTAD (1981).

protection. There are roughly three periods: (i) prior to the mid-1970s, pharmaceutical products were eligible for protection in only a few countries (e.g. in 1960 this was the case only in the UK and USA); (ii) from the mid-1970s to the early-1990s, pharmaceutical patenting became more widespread in the 'Global North'; (iii) from the mid-1990s onward it becomes nearly universal (in 130 countries).[16] With regard to the third period, much of the increase in the early 1990s was attributable to the adoption of pharmaceutical patents by post-Communist countries in East Europe and Central Asia (including new countries created by the breakup of the USSR and Yugoslavia), as well as countries introducing patent protection in anticipation of TRIPS; and then, the substantial increase after 1995 is a phenomenon of developing countries introducing pharmaceutical patent systems in compliance with TRIPS.

The transition period mentioned above is vitally important for understanding the impact of TRIPS and TRIPS-Plus elements of subsequent trade agreements. Although TRIPS entered into force in 1995, countries that were not already granting pharmaceutical patents were allowed up to ten years to begin doing so. However, regardless of how much of this transition period countries chose to utilize, whether they started allowing pharmaceutical patents in 1995, waited until 2005, or anytime in between, TRIPS also obligated countries to receive applications filed as of January 1995, when the Agreement formally entered into effect. These 'mailbox' applications would be examined once the country's transition period expired. For example, if in response to TRIPS a country changed its law to make pharmaceuticals patentable as of January 1, 2000, when this date came around the patent office would begin examining applications, not only from this date forward but those filed since 1995 and retained in the mailbox. But countries were not required to consider applications filed *prior* to 1995. For countries that did not previously allow pharmaceutical product patents, which was the case for most developing countries, it is if the world of drug patenting started in 1995.

The 1995 threshold means that the full effects of TRIPS on pharmaceutical markets would not be felt for a considerable period of time. The 'primary' patents on the compounds of most drugs put on the market in the late 1990s and early 2000s were first filed prior to 1995 (Sampat & Shadlen, 2015). For these drugs, in countries that adopted pharmaceutical patents after TRIPS but adhered to the 1995 cutoff date, patent protection could only be obtained, if at all, via weaker, 'secondary' patents on alternative forms, compositions, or uses of these molecules. But this is transitional: drugs based on post-1995 molecules are likely to be protected by primary patents in most countries. That is, going forward, we expect most new drugs to have at least one strong patent in all countries that are members of the WTO and party to TRIPS.[15] The 1995 cutoff date interacts with the specifics of a drug's patent landscape (i.e. which patents are applied for in which countries at which time) in influencing the likely impact of TRIPS-Plus provisions on generic competition and drug prices, as we discuss in more detail below.

TRIPS-Plus provisions in regional and bilateral trade agreements

As pharmaceutical patenting has become nearly universal, the relevant question is how countries' drug patent systems function. Even where countries grant patents, policymakers and regulators across the world can enact policies to try to mitigate the costs. For example, countries may try to ensure that once patents expire

competition can begin quickly, or that patent-holders' sole rights to sell their products do not lead to prohibitively high prices and impinge on access. Although TRIPS requires all countries to allow pharmaceutical patents, it leaves substantial leeway for countries to include provisions that may address these concerns (Commission on Intellectual Property Rights, 2002; Correa, 2000; Reichman, 1996, 2009b, 2009a; Shadlen, 2017; 't Hoen, Veraldi, Toebes, & Hogerzeil, 2018; UNCTAD-ICTSD, 2005). The effects of offering pharmaceutical patents thus depends in part on how actively countries take advantage of these TRIPS 'flexibilities'.

Regional and bilateral trade agreements also affect how pharmaceutical patent systems function but in the opposite direction. The United States, European Union and Japan have all negotiated a large number of trade agreements with developing countries, and these agreements typically include chapters on IP that place obligations on countries beyond what the WTO requires (see note 1). That is, regional and bilateral trade agreements remove many of the flexibilities available under TRIPS, subjecting signatory countries' patent systems to stricter provisions.

Not all 'TRIPS-Plus' provisions in trade agreements are relevant to pharmaceuticals or likely to affect drug prices, access to medicines and health. The most common – and controversial – provisions that may impede generic competition and raise the price of medicines are: (1) requirements that countries extend patent terms to compensate for regulatory delays (2) requirements to grant patents on new uses of existing medicines; (3) rules linking the activities of health regulators and patent offices around the launch of generic drugs; (4) requirements relating to exclusivity provided to test data and (5) restrictions on the use of compulsory licenses.

We describe these provisions below, and present data on which of the 13 US trade agreements (including 19 countries) include each. Our description of 'TRIPS-Plus' provisions is based on the final text of each trade agreement, available at the USTR's website (https://ustr.gov/trade-agreements/free-trade-agreements). For each agreement, we reviewed the chapters on intellectual property, and we also searched for additional provisions related to pharmaceuticals.

Patent term restoration

Obligations to extend the length of patent terms come from separate provisions in trade agreements, one on patent delays (relevant to all technological classes) and one on regulatory delays (specific to pharmaceuticals). Trade agreements with this first provision require countries to extend patent terms to compensate for 'unreasonable' delays in the course of patent office prosecution. While provisions of this sort appear in nearly all of the US agreements, there is some variation in how 'unreasonable' is defined and therefore when extensions become obligatory. Some agreements define 'unreasonable' as a delay of more than four years after the national filing date or two years after the applicant requested examination in the local patent office, while others define this as five years after the national filing date or three years after request for examination.[16]

Some trade agreements also include provisions that require countries to extend patent terms to compensate for 'unreasonable curtailment' of the patent term due to the time it takes for health regulators to authorize firms to commercialize their

drugs. (This idea is modeled on patent term restoration provisions in the US Hatch-Waxman Act of 1984.) Though language of this sort appears also in most agreements, most do not define what 'unreasonable' means. There is also variation here: some agreements present extension of the patent term as an obligation (i.e. countries 'shall' make it possible for the firm to obtain a request of the patent period), while other agreements stipulate that countries 'may' make extensions available.

Requirements to grant 'use' patents

Trade agreements may require countries to grant patents on new uses of existing drugs. Taking out multiple patents on different aspects of a drug in order to cordon off competitors is standard practice in pharmaceuticals. In addition to primary patents on compounds, firms commonly attempt to acquire secondary patents on alternative forms of molecules, different formulations, dosages, and compositions, and new uses of existing drugs (Howard, 2007; Kapczynski, Park, & Sampat, 2012). Because these additional patents are typically filed later and thus expire later, they can extend periods of exclusivity. Some countries have introduced measures to minimize the grant of secondary patents, including patents on new uses, on the grounds that they are less likely to satisfy traditional standards of novelty and inventive step (Correa, 2007; Sampat & Shadlen, 2017, 2018). While granting pharmaceutical patents is obligatory under TRIPS, restrictive measures toward some types of pharmaceutical patents, be they statutory or via patent office guidelines, are permissible. Provisions stipulating that countries must grant 'use' patents thus constitute another way that trade agreements may produce patent systems that go beyond what is required by TRIPS. This obligation is less common than term extensions, appearing in just five of the US agreements (Australia, Bahrain, Morocco, Oman, South Korea). There is variation in how this provision is phrased across agreements: some refer to new uses, others to new methods of use of known products, still others to new methods of treatment.[17]

Coordination between health and patent authorities ('linkage')

For a pharmaceutical firm to place a drug on the market, it needs regulatory approval. This is true for both originator drugs and follow-on 'generic' drugs. Ordinarily, regulatory approval is separate from patents, a different decision based on different criteria and made by different state actors. Some trade agreements, however, require that health and patent offices coordinate their actions, demanding health authorities to consider the patent status of a drug before granting marketing authorization. This form of coordination, joining the actions of two different state agencies, is often referred to as 'linkage'. Linkage can extend periods of exclusivity if marketing approval is denied on account of patents that, though granted, may be of questionable validity, or patents that, even if valid, are not being infringed by the proposed generic product. All of the US trade agreements negotiated in the 2000s include provisions of this sort, though again there is variation in what is required of partner countries. In some instances, the obligation is only to notify patent-holders of requests to obtain marketing approval made by third parties

while a drug is under patent, though more commonly the notification obligation is supplemented by a prohibition on the state granting marketing approval.[18]

Data exclusivity

How countries treat test data that firms provide health authorities can potentially affect generic competition, and thus prices. When an originator firm seeks to launch a drug in a country, the firm will submit clinical trial data to demonstrate the effectiveness of the product. If local health authorities use these same data to judge applications by manufacturers of generic medicines for regulatory approval of their follow-on drugs, then these products can be launched once the originator firm's patent protection ends. If not, however, firms either need to generate their own data, which is costly, or wait until the period of data protection ends, which would delay the onset of generic competition.[19] According to TRIPS, countries must protect test data against disclosure and 'unfair commercial use,' but without specifying what constitutes 'unfair commercial use.' As a result, TRIPS does not prohibit regulatory authorities from *relying* on, but not disclosing, the data submitted by originator firms for the sake of approving other firms' follow-on products.[20] Nor does TRIPS specify how long such protection should last.

US trade agreements exceed TRIPS on these dimensions, requiring that countries treat test data with exclusivity and specifying the periods of exclusivity. Here again there is substantial variation in what is required. Some agreements extend data exclusivity not just to new drugs but also to new uses or indications of existing drugs. Some prohibit countries from authorizing generic drugs on the basis of data provided to foreign regulators.[21] Others replace minimum periods of data exclusivity with minimum periods of market exclusivity. Some refer not just to chemical drugs but also biologic products (Shaikh, 2016; Gleeson et al., 2015). Data exclusivity provides originator drug companies with monopoly positions that are separate from the privileges provided by patents. Data exclusivity periods can run either shorter or longer than patent terms, depending on the length of exclusivity and expiration dates of relevant patents.

Compulsory licensing

Patent laws include exceptions to patent-holders' ability to exert control over the use of their intellectual property. Compulsory licensing is one important exception, where the government allows a private firm or government agency to produce or import and distribute a patented product without the patent owner's consent. Compulsory licenses can directly lead to lower prices by allowing generic competition. There is also a potential indirect effect: the ability to issue a compulsory license to a local or foreign supplier, including the ability to threaten to do so, can be a useful bargaining chip as countries seek to secure lower prices on patented drugs with single suppliers (Beall & Kuhn, 2012; Reichman 2009a; 't Hoen et al., 2018; Son & Lee, 2018). TRIPS leaves countries with discretion in establishing the grounds for making a patent subject to compulsory license and the procedures for taking such steps (discretion that was affirmed by the 2001 'Doha Declaration on the TRIPS Agreement and Public Health'), and most trade agreements are silent in

Table 1. US trade agreements and pharmaceutical patent provisions.

Partner country	Year*	Term restoration	Use patents	Linkage	Data exclusivity	Compulsory licensing
Australia	2005	√	√	√	√	√
Bahrain	2006	√	√	√	√	
Canada**	1994				√	
Chile	2004	√		√	√	
Colombia	2012			√	√	
Costa Rica***	2009	√		√	√	
Dom. Rep***	2007	√		√	√	
El Salvador***	2006	√		√	√	
Guatemala***	2006	√		√	√	
Honduras***	2006	√		√	√	
Jordan	2001	√		√	√	√
Mexico**	1994				√	
Morocco	2006	√	√	√	√	
Nicaragua***	2006	√		√	√	
Oman	2009	√	√	√	√	
Panama	2012			√	√	
Peru	2009			√	√	
Singapore	2004	√		√	√	√
South Korea	2012	√	√	√	√	

*Year of implementation, i.e. not year of signature but year into force.
**NAFTA.
***DR-CAFTA. Went into effect on different dates in 2006 El Salvador, Guatemala, Honduras, and Nicaragua, and then in following years in the Dominican Republic and Costa Rica.

this regard.[22] However, three agreements (Australia, Jordan, Singapore) stipulate more restrictive grounds and procedures that substantially circumscribe countries' ability to use this policy tool.

Table 1 lists each country that has a trade agreement with the US that include IP provisions, with the date the agreement went into effect. While the table indicates simply whether the agreement includes one of these 'TRIPS-Plus' provisions, as discussed in the text these should not be regarded as binary but rather continuous variables; countries that each have √ in the same column may have different obligations.[23] Most agreements include term restoration provisions, linkage, and data exclusivity rules. Restrictions on compulsory licensing, and language regarding use patents are less common. One agreement, between the US and Australia, included all of the provisions.[24]

Assessing the effects of TRIPS-Plus provisions and drug prices

The inclusion of these measures in bilateral trade agreements has led to concerns that they would have harmful effects on prices and access to medicines in partner countries. Most of the academic research on these issues involves hypothetical analyses of how different provisions might affect drug prices, with projections of what we should expect to happen as a result of the trade agreements. Some studies are mainly descriptive, reviewing what the provisions are in specific agreements and how they may affect the price of drugs (Abbott, 2011; Baker, 2008; Roffe & Spennemann, 2006). Others are in the style of 'impact assessments,' offering projections (typically quantitative) of the expected effects of agreements in specific countries based on estimations of demand for particular drugs. When Thailand was negotiating a trade agreement with the US, for example, Akaleephan et al.'s (2009)

forecast was based on a simulation of how data exclusivity, were it introduced, would increase the prices of patented and non-patented drugs in the Thai market.[25] More recently, in the context of the Trans-Pacific Partnership, a flurry of articles similarly warned about higher drug prices and diminished access to medicines on account of the projected effects of the various provisions in that agreement (Baker, 2016; Gleeson, Moir, & Lopert, 2015; Labonté, Schram, & Ruckert, 2016; Matthews, 2016; Moir, Tenni, Gleeson, & Lopert, 2018). Also of this type are the analyses, conducted in the context of negotiations for a trade agreement between the European Union and Mercosur, of the projected effects of term extensions and data exclusivity in Argentina (Bianco Docente & Bembi, 2017) and Brazil (Chaves, Gaspar, & Vieira, 2017). Both of these studies are based on Rovira et al.'s (2009) simulation model, which compares projected outcomes under existing rules in the absence of a trade agreement with projected outcomes under a range of scenarios.

In addition to these simulations, a handful of studies have attempted to directly assess the effects of the agreements after they were signed, using drug prices and related measures (e.g. drugs as share of health expenditures) as outcome variables. These analyses show mixed results. Malpani (2007) and Abbott et al. (2012) report higher prices in Jordan as a result of 'TRIPS-Plus' provisions in the trade agreement with the US. Shaffer and Brenner (2009) find similar results in Guatemala as a result of CAFTA. Bollyky (2016), by contrast, examines a larger set of countries that have had US agreements over a longer time period, and finds little impact on drug spending or prices.

It is not surprising that the results are noisy. Nor is it surprising that the main analysis finding no strong impact on aggregate measures so far (Bollyky, 2016) came to this conclusion. Assessing the impact on drug prices (or other outcomes) is extremely complicated, since the different provisions in these agreements will affect different drugs at different points in time, making identification of both the pre- and post-periods, as well as the treated and control sets of drugs, tricky. Readily available aggregate measures may not tell us much. And for some of the important provisions, it is just too soon to tell.

The 'priority year' after which drugs were patentable in a country is one crucial variable that will influence the impact of trade agreements. As Table 2 shows, most of the countries that have trade agreements with the US introduced product patent protection only after TRIPS. In these countries, only post-1995 patent applications were eligible. As discussed above, countries that introduced drug patents following

Table 2. Introduction of pharmaceutical patent protection in countries with US trade agreements.

Prior to TRIPS		Following TRIPS	
Australia	1990	Bahrain	2004
Canada	1983	Colombia	2000
Chile	1991	Costa Rica	2000
Mexico	1991	Dominican Republic	2000
Singapore	1994	El Salvador	2000
South Korea	1986	Guatemala	2000
		Honduras	2000
		Jordan	1999
		Morocco	2000
		Nicaragua	2000
		Oman	2000
		Panama	1996
		Peru	2000

TRIPS were required to receive applications from 1995 onwards, but had no obligation to consider applications with pre-1995 priority dates. Since patents expire 20 years from filing, the earliest these would expire is in 2015. By contrast, for countries in the left panel of Table 2, which introduced drug patenting earlier, patents would expire sooner as well.

Knowing countries' cutoff years for priority dates, and thus when patents will start to expire, is crucial, since several of the TRIPS-Plus provisions would plausibly affect competition and prices at (or near) the end of patent terms. The clearest case is patent term restoration to compensate for delays on the part of patent offices or health authorities. This provision is present in 9 of the US trade agreements (14 countries). By definition, term restoration affects generic competition and prices near the end of patent terms. For the 13 'later-patenting' countries, those listed in the right panel of Table 2, the soonest that provisions requiring term restoration could affect prices would be 2015. For the 6 'earlier-patenting' countries, the provisions could affect prices sooner, depending on the precise dates that patents became available and the precise cutoff priority years for specific drugs. Even here, for earlier-patenting countries that have term restoration requirements in their trade agreements (which not all do, as seen in Table 1) for these provisions to affect prices, they would need to apply retroactively to delays that occurred before the agreement came into force.

The role of timing on the potential effects of new use provisions and linkage is more complex, requiring consideration of both 'primary' and 'secondary' patents. In the later-patenting countries, for drugs whose main patents (the stronger primary patents discussed above) have priority years after 1995, new use provisions will be redundant to the primary patents until 2015, at least, and would have limited effect on prices prior to the expiration of the primary patents. However, for pre-1995 molecules – those whose main patents have priority dates before 1995 – use and other secondary patents are the only type available, and new use provisions may matter more.[26]

The existence of secondary patents on older molecules (drugs whose main patents have pre-1995 priority dates) also may make linkage provisions important for generic competition and prices, since health authorities may deny marketing approval to generic drugs on the basis of secondary patents that may not otherwise prevent generic launch. The likelihood of this depends on exactly how the linkage system functions, and which patents are included. If health authorities were not expected to consider some types of secondary patents, such as use patents (see the discussion of Mexico below), then the system's effects would be limited.

Thus for two of the common TRIPS-Plus provisions in trade agreements (term restoration and linkage) and one of the less common provisions (new use patent requirements), the effects vary based on when a country introduced drug patenting, the cut-off date for priority year, the patent landscape in the country (what types of applications are actually filed and granted there), and the specific language of the provisions. For each of these provisions the right 'treated' set of drugs is not all drugs, and the right 'pre' and 'post' periods are not based on the date of the trade agreement but instead the other institutional details discussed above.

Especially for the provisions that mainly affect generic competition near the end of patent terms, in the 'later-patenting' countries, the number of molecules affected by these provisions so far will be quite small, and the effects in terms of extending periods of protection will be seen only after the post-1995 filed patents expire. These provisions may, eventually, extend periods of protection, once the primary

patents on a larger number of post-1995 molecules expire. But as of now, it is, arguably, too early to see the effects, especially in broad analyses looking at aggregates like overall drug prices or pharmaceutical expenditures as a share of health budgets (e.g. Bollyky, 2016).

What about data exclusivity? For drugs that obtain primary patents, data exclusivity periods may be redundant: if there is a primary patent in force, the data exclusivity period will likely expire before the patent. But data exclusivity can also matter for older drugs whose primary patents pre-date a country's cutoff date, i.e. and thus there are no patents or only weaker secondary patents. In these situations, data exclusivity can support monopolies by single suppliers, even in the absence of patent protection. Indeed, that is very much the point of data exclusivity provisions.

Restrictions on countries' abilities to issue or threaten to issue compulsory licenses is the area where the issues of timing we have discussed are least relevant. Regardless of when a country introduced drug patents, the ability to issue a compulsory license could help governments secure lower prices, and conversely the inability to do so remove originator firms' incentive to lower prices. This is one area where we would expect to see effects (if any) for any patented drugs on the market after the trade agreement was implemented. However, as discussed above (and in Table 1), such provisions are rare: only three agreements address this, for the most part countries with trade agreements have the same rights regarding compulsory licensing as counties without such agreements.

In addition to timing, other details of these TRIPS-Plus provisions matter as well, including their relationship to national law and practices. Consider the case of patent linkage in Mexico, for example. Although not required to do so by its trade agreement with the US (NAFTA), Mexico introduced a linkage system in 2003. This required the patent office to publish a gazette of drug patents in force, and prohibited health authorities from granting market authorization to any drug with a patent listed in the gazette. When Mexico's linkage system was introduced, it was not expected that the patent office would include patents on medical uses in the gazette. But the transnational pharmaceutical sector, through litigation, secured a change to the patent office's practices such that such patents (indeed, all secondary patents) are included in the supplementary gazette, and thus have blocking power that allows them to extend periods of exclusivity (Cofece, 2017; Shadlen, 2017, pp. 180–183). This again illustrates the difficulties of evaluating the relationship between patent provisions in trade agreements and outcomes. None of these aspects would be captured by looking whether a trade agreement requires linkage, or even looking just at whether a country has linkage. If, for example, we were to compare prices in countries with trade agreements requiring linkage to those without such a requirement, we would place Mexico in the latter category, but doing so would be misleading. Or, if we were to compare prices in countries with linkage systems to those without, regardless of the trade agreement, the results would make little sense without taking into account the particular characteristics of Mexico's (and other countries') systems.

Or consider the effects of data exclusivity on prices. The analytic challenge is to see if market dynamics (e.g. number of competitors, prices) change on account of data exclusivity provisions. Bollyky (2016), for example, examines prices in two countries (Colombia and South Korea) before and after their trade agreements requiring

data exclusivity went into effect.[27] However, both of these countries began offering market exclusivity based on test data years before they had trade agreements with the US (Andia, 2011; Cortés et al., 2012; Son, 2016). For analyses of the effects of data exclusivity, one needs to look at the correct pre- and post-dates; if Colombia and Korea already had such provisions, the pre-vs-post analyses are flawed, and drawing conclusions of the effects of data exclusivity in before-and-after analyses based on the wrong dates is problematic (Kapczynski, Sampat, & Shadlen, 2017).

We have emphasized that, especially in 'later-patenting' countries, several of the provisions are only recently going to have an impact on drug prices, and that it may be premature to assess the impact of trade agreements. More generally, the details matter: in most cases it is not the date of the trade agreement per se, but rather other institutional details that matter for identifying drugs affected by the agreements.

Not only will different provisions affect competition and prices differently in different countries according to when countries introduced drug patents, the filing dates of drugs' primary patents, and the details we have discussed, but the *types* of effects that these provisions may have will change over time too. As discussed, in the 13 later-patenting countries in the right panel of Table 2, not enough time has passed for requirements to issue use patents and create linkage systems to extend periods of protection on many drugs, but it is possible that they have affected the existence of exclusivity for older drugs that lack primary patents on account of pre-1995 priority dates. But such effects are transitional, and misleading indicators of how these provisions are likely to matter going forward. As 2015 recedes further into the past, and more drugs have primary patents even in countries that did not allow pharmaceuticals to be patented until after 1995, the effects of these provisions will be on the duration – not the existence – of patent protection.

The effects of data exclusivity may also be different going forward. Again, data exclusivity can create monopolies where patents are absent, as is the case with many older drugs. Indeed, the three previous studies of the association between TRIPS-Plus provisions and higher drug prices in Jordan and Guatemala (Abbott et al., 2012; Malpani, 2007; Shaffer & Brenner, 2009) focused on data exclusivity, and noted that the reason why data exclusivity mattered for prices was the lack of patent protection for many drugs during the time periods studied. Where drugs have primary patents, however, these are likely to outlast (or at least substantially overlap with) the data exclusivity mandated in trade agreements. Thus, assuming we move to a world in which most drugs have primary patents, data exclusivity may become increasingly redundant, and its effects may diminish.[28]

The effects of compulsory licensing provisions may also be different going forward. These have been used (or threatened) by some developing countries since TRIPS, and this may have affected prices. But in many cases compulsory licensing was possible because drugs in demand lacked patent protection in India, which did not allow for drug patents with pre-1995 priority dates. Most compulsory licenses either authorize (or threaten to authorize) importation of drugs from India ('t Hoen et al., 2018; Waning, Diedrichsen, & Moon, 2010; Shadlen, 2007). If primary patents become more common in India, then, in the absence of local production capabilities in importing countries, compulsory licensing may become less effective.[29] Conversely, restrictions on compulsory licenses may matter mainly for secondary patents that are granted in some countries but not others.[30]

Conclusion

While TRIPS required countries to adopt pharmaceutical patents, which many did not do until that point, bilateral and regional trade agreements negotiated since then have tended to expand on the protections in TRIPS with additional provisions. This article placed the inclusion of 'TRIPS-Plus' provisions in trade agreements in the context of the broader spread of pharmaceutical patenting since the 1970s. We have examined the key provisions that are relevant for pharmaceuticals, considering how they appear in different agreements and the ways they may affect market dynamics and prices. We have also presented the principal challenges to observing the effects of these provisions, challenges related to timing and to the proper selection of drugs. The argument is not that trade agreements raise prices, or that they do not, but rather that it is for the most part too early to tell. Because of the timing of when countries began granting drug patents, the existence of drugs on the market without primary patents in many countries, and the nature of the TRIPS-Plus provisions we have discussed, analyses are bound to be inconclusive.

Moreover, to the extent that TRIPS-Plus provisions have had effects, the sorts of effects they will have are likely to change going forward. In later-patenting countries that did not start allowing pharmaceutical patents until TRIPS, provisions that have been affecting the existence of patent protection will come to mainly affect the duration of patent protection, under the assumption that most drugs will eventually have a primary patent in these countries. Indeed, as 1995 recedes further into the past, and if most drugs have primary patents in most countries, the importance of precisely when countries began allowing pharmaceutical patents will fade in significance.

How can the effects of these provisions on prices be evaluated until then? Looking at the right sets of drugs in the right countries at the right points in time is crucial. Several previous analyses of TRIPS-Plus provisions in trade agreements, and even TRIPS, have found limited effects of pharmaceutical patent provisions on drug prices, and concluded that concerns about patents and prices were 'overblown' (Bollyky, 2016), that developing countries may be circumventing their obligations in these agreements, that drug patent protection may work differently than we understand from the US experience, or that drug companies may be less aggressive in pricing in developing countries than in the past (Bollyky, 2016; Duggan, Garthwaite, & Goyal, 2016). These mechanisms are each theoretically plausible, but in our view should be tested directly rather than asserted.

More importantly, before falling back on these residual explanations it is essential to focus on the specific drugs affected by the trade agreements, with precise attention to the national-level institutional details of implementation. As we have emphasized throughout this article, for some provisions in trade agreements that influence competition near the end of patent terms, the number of affected drugs may still be small in many. More generally, we suggest that theoretical and empirical analyses of these agreements going forward (and the policy discussions of these agreements) should carefully distinguish between their transitional effects and the long-run steady state effects in developing countries.

One way of capturing the steady state effects on drug prices would be to focus attention on the earlier-patenting countries that were allowing pharmaceuticals to be patented prior to TRIPS and that have trade agreements with the US, i.e. those

on the left side of Table 2. In these countries, where most drugs (even pre-1995 molecules) are likely to have obtained primary patents and many of these primary patents have reached their expiration dates, the transitional dimensions of TRIPS that we have emphasized throughout this article are less relevant. As a result, we can observe how the TRIPS-Plus provisions in trade agreements function in contexts that are more akin to how the world will look going forward. Does patent term restoration extend periods of patent protection? Do use patents and linkage add additional years of exclusivity beyond the expiration of primary patents? Does data exclusivity matter for drugs that already enjoy patent protection? Does generic competition commence and do prices decrease after primary patents expire? Addressing these questions could provide a fruitful avenue for future research.

Notes

1. The immense literature on IP in bilateral trade agreements includes El Said (2007), Fink and Reichenmiller (2005), Krikorian and Szymkowiak, (2007), Kuanpoth (2008), Mercurio (2006), Morin (2006, 2009), Osgood and Feng, (2017), Roffe and Spennemann, (2006), Sell (2007, 2010b), Seuba (2013), Shadlen (2005, 2009), Son, Lopert, Gleeson, and Lee, (2018), Townsend, Gleeson, and Lopert, (2018), Braun (2012).
2. While this article focuses on the effects of particular provisions in bilateral and regional trade agreements, an extensive literature examines the spread of such agreements (Baccini, Dür, & Elsig, 2015; Baldwin & Jaimovich, 2012; Manger, 2012; Manger & Shadlen, 2014; Mansfield, Milner, & Rosendorff, 2002; Mansfield & Milner, 2012).
3. Chang (2002); Maskus (2014); May (2007); May and Sell, (2006); Wallerstein, Mogee, and Schoen, (1993).
4. Where replication is particularly easy is in the case of the chemical-based pharmaceutical products. Replication of protein-based biological drugs is more complex.
5. The investments made by pharmaceutical firms may be in-house investments, or they may entail licensing or purchasing patents from smaller firms or public sector researchers. Sampat and Lichtenberg (2011) and Cleary, Beierlein, Khanuja, McNamee, and Ledley (2018) discuss the relative roles of private and public actors in pharmaceutical research and development.
6. Dutfield (2003); Grabowski (2002); Levin et al. (1987); Mansfield (1986); Mansfield, Schwartz, and Wagner, (1981). In addition to patents, pharmaceutical firms also rely on trademarks to promote their brand names and preserve market shares in the absence of patents. The concern with trademarks is not restricted to originator firms, however, as producers of off-patent 'branded generics' use trademarks too.
7. The extent to which countries have price controls on patented drugs, and these are enforced, is not clear. One important study on the effects of pharmaceutical patent protection (Kyle & Qian, 2014), acknowledging the difficulty of observing price controls, uses fixed effects to capture the impact of all countervailing measures at the country level that might mitigate the effects of patents (including, potentially, price controls).
8. Chaudhuri (2005); Dutfield (2003); La Croix and Liu (2008, 2009); Mazzoleni and Nelson, (1998); Nogués (1990, 1993); Watal (2000); WHO (1997).
9. Some countries also expressed moral objections to patents on drugs (Ayyangar, 1959).
10. Finland, which allowed pharmaceutical patents in 1995, was the last West European country to do so. La Croix and Liu (2009), Liu and La Croix, (2015), and Qian (2007) provide cross-national data. See also discussions in Boldrin and Levine (2008), Cassier (2008), Dutfield (2003), Gaudillière (2008), UNCTAD (1981), WHO (1997).
11. Patents on pharmaceutical processes are easier to circumvent and constitute a weaker form of protection. In this article, 'pharmaceutical patents' is used to refer to patents on products, including active ingredients and different compositions and forms of drugs.
12. In fact, there was a moment, in the late 1960s and early 1970s, before many postcolonial countries that had inherited pharmaceutical patent regimes altered their

rules and before many wealthier countries began to allow pharmaceutical patents, that more countries in the Global South formally allowed pharmaceutical patents than did countries in the Global North.

13. The transition period for Least Developed Countries was until 2016, subsequently extended to 2033 (https://www.wto.org/english/news_e/news15_e/trip_06nov15_e.htm). Yet even for LDCs this is a transition period and not an exemption. Eventually, all WTO members will be obligated to allow pharmaceutical patents.
14. Note that the figure may overstate the existence of pharmaceutical patenting in the pre-TRIPS era by counting only formal aspects of legislation, as many of the countries that introduced patents were newly independent states in West Africa that emulated the French or British patent systems but where de facto protection remained weak.
15. See Sampat and Shadlen, (2015) for an elaboration of this argument. As discussed there (see also Sampat & Shadlen, 2018) this assumption would be incorrect if countries implemented provisions that restricted grants of primary patents. As far as we know no countries have such provisions on the books, but it is possible that provisions to minimize secondary patents, such as Section 3(d) in India, could spill over to primary patents as well.
16. The trade agreement with South Korea is intermediate, defining an unreasonable delay as four years after filing and three years after the applicant has requested examination.
17. Use patents (including methods of use and treatment) are but one form of secondary patents. In the negotiations for the Trans-Pacific Partnership (TPP), there was at one point a proposed provision to prohibit clauses like India's Section 3(d), which aims to create a higher barrier for the grant of a wider array of secondary patents, but this broader language is not in US agreements (nor the final text of the TPP).
18. The most recent agreements (Colombia, Panama, Peru) include both notification and prohibition clauses and also encourage governments to create mechanisms that simplify the process by which firms seeking to commercialize their drugs can challenge the validity of existing patents or make the case that their product is non-infringing. This provision is closest to the way 'linkage' functions in the US. In fact, the relevant passages of these three agreements also call for rewards to be made available to incentivize generic firms to challenge the validity of existing patents, a hallmark of the US system (Hemphill & Sampat, 2012).
19. Protection of test data is also relevant for agricultural chemicals, though the discussion here is restricted to the case of pharmaceutical products.
20. According to many legal scholars, doing so does not amount to 'unfair commercial use' and is acceptable under TRIPS. The US disagrees and has tried to advance an alternative interpretation. The US filed a WTO dispute against Argentina, demanding data exclusivity, but Argentina refused to buckle and the US dropped the case.
21. Potentially, a country could get around the obligations imposed by strict data exclusivity by allowing generic competitors to enter the market if their products are approved by health regulators elsewhere. Some agreements close that loophole, meaning that, if a firm obtains marketing approval for a new drug in one country it may receive a period of exclusivity even if generic competitors have already been authorized in other countries. As discussed below, data exclusivity can create situations of single suppliers even in the absence of patents.
22. For countries lacking local pharmaceutical manufacturing capabilities, the purpose of a compulsory license would be to secure the drug from foreign suppliers. If the drug is patented in the country where that supplier is based, then two compulsory licenses would be needed. This process is complicated – though not prohibited – by TRIPS' more restrictive rules regarding compulsory licenses for export (Abbott & Reichman, 2007).
23. In no area is the point that some TRIPS-Plus provisions in trade agreements are not binary as important as in the case of data exclusivity. For example, one prominent index that is used to compares data exclusivity provisions in US and EU trade agreements is based on 25 different components (Shaikh, 2016). Similarly, in Osgood and Feng's (2017) coding of 23 different IP provisions in trade agreements (not just those related to pharmaceuticals), 9 provisions are treated as non-binary variables;

seven of these are scored on a 0–2 scale and data exclusivity (along with IP protection for animals and plants) ranges from 0 to 5.

24. The provisions in the table and discussed in the text are not the only ways that trade agreements may affect competition in pharmaceutical markets and prices. Restrictions on government procurement and the use of competition policy can undermine countries' efforts to control drug prices, for example, and pharmaceutical firms' rights to pursue arbitration against states via investor-state dispute settlement panels can impede governments' efforts to regulate drug markets.
25. Negotiations on the US-Thai agreement were launched in 2004 but suspended after the 2006 military coup.
26. Many drugs approved until relatively recently have pre-1995 priority dates for their primary patents (Sampat & Shadlen, 2015), reflecting long lags between initial patent filings and launch.
27. Two other countries are discussed, as well, though with sample sizes that the author acknowledges are too small to allow for conclusions.
28. It is possible that data exclusivity may matter more for large molecule, "biologic" drugs, where patent boundaries are less clearly defined, than for the small molecule, chemical drugs we have focused on throughout this paper. This is perhaps also why data exclusivity rules for biologics was a major point of debate in the TPP (and TPP-11, after the US's withdrawal) and the revised version of NAFTA ('USMCA') (Gleeson et al., 2015).
29. Note that this is an area where data exclusivity can matter. Even if alternative suppliers exist and a government issues a compulsory license, if the country offers data exclusivity, and this is still in effect, registration of the alternative product may be blocked.
30. To illustrate, imagine a drug for which the primary expires in 2030 in both India and in Country X that has a trade agreement with the US. If X – but not India – also granted a secondary patent that expires 2032, and X's trade agreement restricts compulsory licensing, then, in the period between 2030 and 2032 the restriction on compulsory licensing will prevent X from acquiring the drug from India.

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