AN EMPIRICAL ANALYSIS OF PRIMARY AND SECONDARY PHARMACEUTICAL PATENTS IN CHILE[1]

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February 2014

Abstract:

We analyze the patent filing strategies of foreign pharmaceutical companies in Chile distinguishing between "primary" (active ingredient) and "secondary" patents (patents on modified compounds, formulations, dosages, particular medical uses etc.). There is prior evidence that secondary patents are used by pharmaceutical originator companies in the U.S. and Europe to extend patent protection on drugs in length and breadth. Using a novel dataset that comprises all drugs registered in Chile between 1991 and 2010 as well as the corresponding patents and trademarks, we find evidence that foreign originator companies pursue similar strategies in Chile. We find a primary to secondary patents ratio of 1:4 at the drug-level which is comparable to the available evidence for Europe; most secondary patents are filed over several years following the original primary patent and after the protected active ingredient has obtained market approval in Chile. This points toward effective patent term extensions through secondary patents. Secondary patents dominate "older" therapeutic classes like anti-ulcer and anti-depressants. In contrast, newer areas like anti-virals and anti-neoplastics (anti-cancer) have a much larger share of primary patents.

[1] The authors acknowledge financial support from WIPO and thank INAPI (in particular the pharmaceutical patents team), as well as Aisen Etcheverry, Catalina Olivos Besserer, Maria Lorena Chacon, and Alhena Fuentes for their generous support in constructing the data. We also thank representatives of ASILFA and Camara de la Innovacion Farmaceutica for insightful discussions. We also benefitted from the comments of two anonymous referees, Carsten Fink, Catalina Martinez, Keith Maskus, and participants of the 2014 Meide conference in Santiago and seminars at INAPI, UC Berkeley, and UC Davis.

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I. Introduction

Historically, pharmaceutical patents are among the most controversially debated issues with regard to intellectual property (IP) protection, especially in developing countries. During the negotiations of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, pharmaceutical product patents represented one of the most divisive issues, being opposed by developing countries because of concerns that stronger patent protection would hinder access to drugs and prevent the development of a domestic pharmaceutical industry. The TRIPS agreement forced developing country members of the WTO to grant patents with a statutory lifetime of 20-years from the patent application also to pharmaceutical compounds. Almost two decades after TRIPS, the empirical evidence on its effect on developing countries is at best mixed (Arora et al., 2009, 2011; Chaudhuri et al., 2006; Goldberg, 2010).

Despite the strengthening of IP protection brought about by TRIPS, some developing countries continue to apply a more restrictive approach than developed countries to the granting of pharmaceutical patents. While TRIPS requires the availability of patent protection for processes as well as products in "all fields of technology" (TRIPS Article 27.1), the agreement provides countries with substantial freedom to define the standards of patentability. Some developing countries, most prominently India (Section 3(d) of India's Amended Patents Act of 2005), have used this freedom to restrict the granting of so-called secondary pharmaceutical patents. As opposed to primary patents which protect an active ingredient directly, secondary patents protect a range of chemicals related to an active ingredient (such as crystalline forms of the original compound), methods of use, formulations, dosages, etc. Other developing countries, such as Brazil, Argentina and South Africa, are currently debating new legislation that would emulate India's approach to restricting the patentability of secondary patents.

In developing countries, secondary patents may have played particularly important a role for multinational originator companies during the years following the introduction of pharmaceutical patents. When developing countries began to allow the granting of pharmaceutical product patents, in many instances originator companies were unable to obtain patent protection for drugs that had already been patented abroad. In Chile, for example, pharmaceutical patents were introduced in 1991, but pharmaceutical drugs that had been patented abroad before the 1991 law came into effect were expressly not patentable. This may have created strong incentives for originator companies to rely on new secondary patents instead.

The sparse, available evidence on secondary patents, which focuses on the U.S. and the European Union (EU) (see Section II below), offers some evidence on the use of secondary patents by originator companies. Empirical and anecdotal evidence suggests that pharmaceutical originator companies use secondary patents extensively in those markets. There is also some evidence that secondary patents can be used to extend patent protection on a given drug in length and breadth and it may create legal uncertainty over the scope of patent protection of a drug. That said, secondary patents can be used to protect genuine follow-on innovation, although distinguishing strategic use of secondary patents from their use to protect follow-on innovation is very difficult and may not even be feasible when such patents serve both purposes.

Despite the widespread use of secondary patents and the contentious policy debate, there is little evidence on the use of primary and secondary patents in developing countries. Our objective in this paper is to shed light on the use of primary and secondary patents by multinational originator companies in Chile and to gauge their effect on creating and maintaining exclusivity.

From a data point of view, studying this question is challenging because it requires not only a distinction between primary and secondary patents, but also a mapping of patents to active ingredients and the corresponding pharmaceutical products. Linking patents to active ingredients is an enormous challenge because there is usually no explicit mention in the patent claims of the active ingredient contained by a drug (where drugs can contain multiple active ingredients). We create a new dataset that addresses this problem in three ways. First, we rely on the Orange Book of the U.S. Food and Drug Administration (USFDA) to identify U.S. patents on the compounds registered in Chile. We then construct patent families for these U.S. patents and verify whether there are any Chilean equivalents. Similarly, we undertake the same exercise using the Merck Index, which provides information on patents worldwide. Second, we use a dataset created by the Chilean patent office (INAPI) that contains the compound-patent mapping for all new compounds registered in Chile between 2005 and 2010. All of these matches are based on patent applications, whether granted or not. Third, we asked experts in pharmaceutical patents in Chile to match directly the remaining set of all *granted* Chilean patents to the complete list of drugs registered with the Chilean health authorities. This means that we attempted to match all granted Chilean patents to drugs, either directly or through any of the other approaches, although most of the patents do not match, as we show below. Unfortunately, for cost reasons, we were unable to search the remaining patent applications for matches to registered drugs, but based on our earlier match rates, we expect there to be very few of these.

Because companies can obtain competitive advantage also through brand recognition, we also match the pharmaceutical product-level data with trademark data. The mapping of drugs and trademarks is more straightforward than that of drugs and patents. The pharmaceutical product data provides the names under which drugs are marketed, which we search for in the relevant classes in our trademark database.

For the matching of patents and trademarks, we rely on a dataset that contains the universe of patent and trademark applications filed with the Chilean patent office (INAPI) between 1991 and 2010 (see Abud et al., 2013). The pharmaceutical product data comes from the National Public Health institute (ISP). In Chile, all pharmaceutical products that are to be sold on the domestic market have to be registered with the institute. It maintains a database that links all registered drugs in Chile to the pharmaceutical compounds that they contain.

Our study contributes to the sparse empirical literature on the use of secondary patents, in particular by foreign multinationals. It offers in particular for the first time empirical evidence on the use of secondary patents in a developing country.

The remainder of the paper is organized as follows. Section II discusses the distinction between primary and secondary patents and briefly reviews the corresponding existing empirical evidence. Section III provides background information on the relevant regulatory framework in Chile. Section IV describes the data and Section V our main results. Section VI offers a few concluding observations.

II. Primary and secondary patents

In the pharmaceutical industry, patents are usually filed already during the research phase in the development of a new drug. These early patents are filed to protect potential active ingredients that form the basis of the new drug. Since the early stages of drug development are characterized by an enormous amount of uncertainty (the European Commission (2009) suggests that 1 in 5,000-10,000 test active ingredients results in a successful drug), early patent filings reflect this, in that many of these filings will either not be pursued, or if granted, will never be related to a marketed drug. Patents on active ingredients are referred to as primary patents. In later phases of the drug development, patents are filed on other aspects of active ingredients such as different dosage forms, formulations, production methods etc. These patents are referred to as secondary patents. Secondary patents also emerge from changes to formulations and dosages or applications in new

therapeutic classes, discovered during clinical trials. Hutchins (2003b) reports that the usual filing strategy is to file many and broad primary patent applications and then to surround them with secondary patent applications.

A critical issue regarding secondary patents is whether they protect genuine follow-on innovation or whether they represent primarily a form of strategic patenting (although these two may not necessarily be mutually exclusive). There is little controversy about the innovation associated with new active ingredients. However, new uses of existing active ingredients in new therapeutic areas, new formulations, new modes of delivery, new combinations of known active ingredients etc. are sometimes regarded as incremental innovation. In this case, secondary patents represent a way of incentivizing and protecting potentially valuable follow-on innovation. This may be particularly valuable for generics producers that want to develop proprietary drugs by modifying existing active ingredients as a lower risk strategy. For example, consider a new formulation that allows administering an active ingredient in form of a temperature-stable pill instead of a temperature-sensitive soft-gel version (Amin and Kesselheim, 2012). It is clear that the pill has no added therapeutic benefit over the soft-gel version; at the same time the pill represents an improvement over the soft-gel in terms of ease of drug storage and administration. On the other hand, secondary patents may also be used to extend the time of market exclusivity and to maintain or even expand the market that the product covers during market exclusivity. These objectives can be supported by specific patenting strategies, in particular the creation of patent fences and clusters. According to Burdon and Sloper (2003), "a key element of any life cycle management strategy is to extend patent protection beyond the basic patent term for as long as possible by filing secondary patents which are effective to keep generics off the market."

The scarce available evidence on secondary patents suggests that secondary patents are pervasive and that they seem to be used overwhelmingly as a strategic tool. For example, the European Commission found in its 2009 pharmaceutical sector inquiry a primary to secondary patent ratio of 1:7 (EU Commission, 2009: 164). This ratio is higher for pending than granted patents (1:13 vs. 1:5), which suggests that a large number of secondary patent filings are not granted, presumably because they do not meet the statutory patentability requirements or because they are not pursued by the applicant, having served their purpose of increasing uncertainty. The inquiry shows that 57% of secondary patent filings protect formulations, 7% devices, 7% combinations of known active ingredients, 5% polymorphic forms, 4% salts, and the remaining 20% are accounted by a range of claims, such as hydrates or solvates (EU Commission, 2009: Table 20). The study also reveals that if the validity of an originator's patent is challenged either through post-grant opposition or an

invalidation action in court, the majority of secondary patents is invalidated as a result (or their claims restricted) (EU Commission, 2009: 191). Kapczynski et al. (2012) conduct a similar study for the U.S. They look specifically at patenting associated with 342 new active ingredients approved by the U.S. FDA between 1991 and 2005. They find that around 50% of drugs are protected by secondary patents. There is an increase in the share of drugs with secondary patents over time whereas the share of drugs protected by primary patents remains constant. This filing pattern was also found by Sternitzke (2013) who studies the patenting behavior of companies that market Phosphodiesterase Type 5 inhibitors (for the treatment of erectile dysfunction). He also finds that the originator companies included in his study, Pfizer, Bayer and Ely Lilly, file a large amount of secondary patents during later stages of the life-cycle of a drug. This is suggestive of the fact that secondary patents are filed later in the life cycle of a drug to extend the patent life. In fact, the data for the U.S. by Kapczynski et al. (2012) reveals that compound patents are filed before FDA approval whereas secondary patents are filed mostly after approval. The authors estimate that secondary patents generate between 4-5 years of additional patent life on top of compound patents associated with a drug. The mean masks considerable variation. For example, Amin and Kesselheim (2012) found for their case study of two HIV drugs that secondary patents extend patent protection up to 12 years beyond the lifetime of the original primary patents. Although this number might overstate the effective extension of a drug's patent protection because Amin and Kesselheim include patent applications (as opposed to grants) as well as granted patents not listed in the Orange Book (which may be a lot less effective in preventing generic entry). Another example is Sanofi Aventis's ARAVA arthritis drug in Australia. Sanofi Aventis effectively extended exclusivity by 10 years through secondary patents (Sanofi-Aventis Australia Pty Ltd v Apotex Pty Ltd (No.3) [2011] FCA 346). Other examples of blockbuster drugs are GlaxoSmithKline's antidepressant Paxil or Pfizer's cholesterol-lowering Lipitor. In both cases, secondary patents extend patent protection by several years relative to the original compound patents (Hutchins, 2003a, 2003b). It is, therefore, not surprising that the available evidence indicates a positive correlation between the number of secondary patents for a given drug and higher sales.

An important element in the filing strategy of secondary patents is the creation of legal uncertainty. For example, in their study of HIV drugs Amin and Kesselheim (2012) found overlapping patent claims for a number of formulation patents. They also show that some of the formulation patents protect variations of known excipients (for example on new flavors such as peppermint or vanilla), or combinations of known excipients. According to their assessment, these patents are likely invalid. Burdon and Sloper (2003) report the case of AstraZeneca's Prilosec. While courts in the U.S. upheld secondary patents that AstraZeneca had filed to extend the time of patent protection on Prilosec,

the Patents Court in the U.K. invalidated the same formulation patents. This case illustrates that the question of validity of granted secondary patents is particularly unclear. Hemphill and Sampat (2012) even conclude from their analysis of patent challenges by generics companies in the U.S. that challenges target secondary patents and are thus mostly used to restrain attempts by originator companies to extend patent terms beyond the original active ingredient patents through secondary patents.

III. Regulatory framework

Registration of pharmaceutical products

Any drug marketed in Chile has to be registered with the Public Health Institute (ISP) – a government agency (Decree of the Health Ministry No. 1876 from 1995). The same rules apply regardless of whether the drug is imported or locally produced. Registration of new drugs with the ISP takes on average between 6 and 18 months. Registration fees are moderate (around US$2,300) and registrations have to be renewed after five years.

If a drug has already been registered on the ISP register, a company that wants to register a generic version can rely on the studies submitted for the first registration as proof of safety and efficacy provided the period of data exclusivity has expired. Also, since July 2008 (Resolution No. 3225/08), the ISP started requiring proof of bioequivalence for products that contain certain active ingredients. The number of affected active ingredients remained small during the period that we study (up to 2010), but has increased substantially since 2011 (see http://www.ispch.cl/medicamentos-bioequivalentes). For these products, the second party to register a drug has to submit studies of bioequivalence. However, because most drugs are still exempt from proving bioequivalence, most generics do not necessarily satisfy bioequivalence despite being pharmaceutically equivalent.

Patent protection is irrelevant for registration at the ISP. In contrast to the U.S. FDA for example, in Chile patent information concerning a new drug is neither requested nor verified when marketing approval is granted.

Apart from patent protection, the regulatory system in Chile also offers additional means for achieving exclusivity for new drugs. Data related to the safety and efficacy of new chemical entities provided for approval of new chemical entities is granted five-year exclusivity since 2005 (see also below), in cases where protection is requested by the applicant and granted by the ISP. This means that generics companies cannot refer to the data when applying for approval of a drug.

Patents

Pharmaceutical drugs became patentable in Chile in 1991 through Law 19.039. The law offers patent protection for both products and processes and initially provided a statutory patent life of 15 years from the date the patent was granted, regardless of subject matter. The law excluded, however, all patents that had been applied for anywhere else in the world before the law came into force. Although the law still offered a way to obtain patent protection in Chile even if a patent had been granted in another jurisdiction before Law 19.039 entered into force (Law 19.039, Article 39), pharmaceutical patents were specifically exempted from this provision (Law 19.039 Transitional Provisions, Article 1).

Law 19.039 was amended several times during the period that we study (up to 2010): in 2005 by Law 19.996 and in 2007 by Law 20.160 (Law 17.336 in 2010 did not affect the patents contained in our sample.). The amendments brought Chile's IP legal framework inline with TRIPS (taking advantage of the 10-year transition period for developing countries under TRIPS) and Chile's obligations under FTAs with the U.S. and the European Free Trade Association (EFTA). Apart from a general extension of the patent term from 15 years from the date the patent was granted to 20 years from the application date, the most relevant changes affecting specifically pharmaceutical patents are the introduction of supplementary patent protection due to delays in the granting of a patent or the sanitary registration (Law 20.160, Article 53), the 5-year data exclusivity for new active ingredients mentioned above (Law 19.996, Article 89), a Bolar exemption (Law 20.160, Article 49), a softening of restrictions on second use patents (Law 19.996, Article 37e), and international exhaustion of patent rights (Law 19.996, Article 49) which effectively legalized parallel imports as long as the products were marketed abroad by the patent holder (or with the patent holder's consent).

Finally, Chile joined the PCT system in 2009, which facilitates the international filing of patents. Although Chile's accession to the PCT is likely to have had some effect on patent filings by foreign pharmaceutical companies in Chile, the change occurred in June 2009, which means it does not affect patent filings observed in our dataset.

IV. Data description

To construct a dataset that combines patents and trademarks at the product level, we rely on a dataset that contains the universe of patents and trademarks filed with the Chilean patent office

since 1991. This includes all patent and trademark applications by domestic as well as foreign entities, regardless of whether or not they have been granted.

To map patents to pharmaceutical products, we use the pharmaceutical registration data available at the ISP. The institute maintains a database that links all registered drugs in Chile to the pharmaceutical compounds that they contain. The database also contains additional information on the drug (e.g. when it was registered), the owner of the drug, whether the drug is produced domestically or abroad. We use the bridge between compounds and drugs contained in ISP's database to link patents and trademarks at the product-level. Patents are linked to active ingredients whereas trademarks are linked to drug names. The link between patents and drugs represents a challenge as there is usually no explicit mention of the specific compounds in patent claims. Patents use the IUPAC (International Union of Pure and Applied Chemistry) classification to identify compounds whereas drugs rely on WHO's INN (International Nonproprietary Name). Although compounds are usually described by a Markush structure in the patent, the same structure comprises often many functionally equivalent active ingredients; only the combination of specific examples provided in the patent and the Markush structure reveals the specific active ingredient protected by the patent (see the *Online Data Appendix* for details).

We address this problem in three ways. First, we use a dataset compiled by INAPI that contains the compound-patent mapping for all new compounds registered with the ISP between 2005 and 2010. The mapping was undertaken by patent examiners specialized in pharmaceutical patents. Second, for all other compounds, we rely on the Orange Book of the U.S. FDA to identify U.S. patents on the compounds registered in Chile. We then construct patent families for these U.S. patents and verify whether there are any Chilean equivalents. Similarly, we undertake the same exercise using the Merck Index, which provides information on patents worldwide. Third, we asked specialists in pharmaceutical patents in Chile to match the remaining set of granted Chilean patents (nearly 3,000 patents) to our list of ISP products directly. As noted earlier, this leaves a large number of Chilean patent applications that neither matched to the Orange Book or Merck Index nor were granted that we were unable to search, but we expect that the matches to drugs in this set of patents will be very small in number.

The mapping between drugs and trademarks is more straightforward as the ISP database provides the names under which drugs are marketed, which we use to search for these drug names in our trademark database. In addition to matching drug names, we also match the names of all companies in the ISP database with the trademark register. Especially in the case of generics companies,

individual drugs may not be trademarked, but the name of the company – which presumably appears on the packaging – will be.

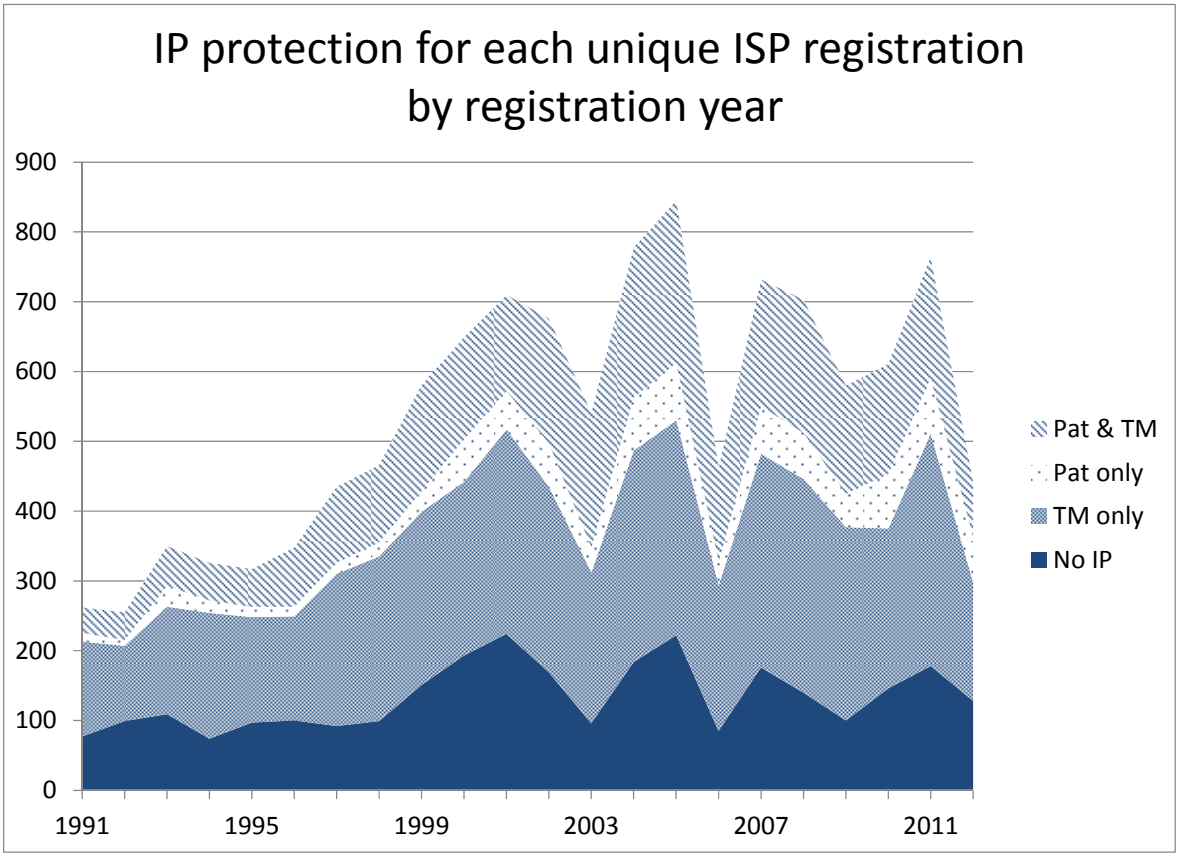
The Online Data Appendix describes the data construction in more detail and Table 1 gives a summary of our patent-trademark match to the ISP register. Of 12,116 unique products registered at the ISP, 3,709 match to at least one Chilean patent, whereas 9,273 match to at least one Chilean trademark. After cleaning and translation of the active ingredients (including some standardization of names), there are far fewer active ingredients than products, as one might have expected. Of the 2,630 distinct active ingredients (many of which are common chemical compounds, that is, generics – for example vitamins), 322 match to at least one Chilean patent (504 distinct patents) and 2,332 match at to at least one Chilean trademark (10,461 distinct trademarks). Overall 82 per cent of the products and 91 per cent of the active ingredients are associated with some form of IP protection, more often trademark than patent.

Table 1

		Matched to		*Shares matched*	
	Total	*patents*	*trademarks*	*patents*	*trademarks*
Unique ISP registrations	14,504	4,304	9,695	29.7%	66.8%
Unique product names	12,116	3,709	9,273	30.6%	76.5%
Unique active ingredients	2,630	322	2,332	12.2%	88.7%

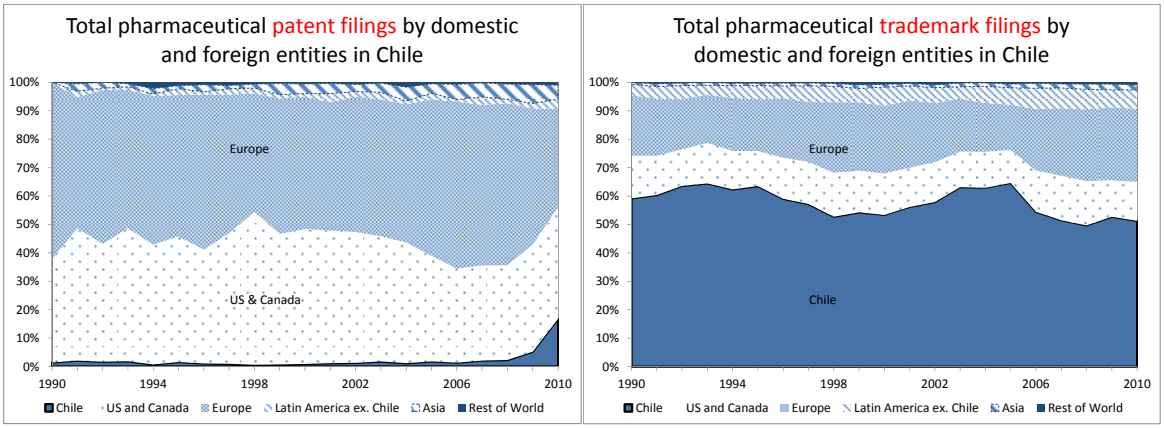
Figure 1 shows the time trends for the unique product-active ingredient combinations. There is a marked increase in the share using patents during the mid-1990s. Also the share relying only on trademarks increases substantially beginning the second half of the 1990s.

Figure 1: Time-trend patents and trademarks for unique product-active ingredient combination



When we examine the ownership of this IP, we see striking differences in the regional patterns. Figure 2 shows the share of trademark and patent filings coming from domestic and foreign entities in Chile, by date of the corresponding ISP registration. Almost all the patent filings are by entities based in Europe and the U.S., with the exception of a small increase in Chilean-origin filings during the most recent period. The total share of Chilean-origin filings is less than two per cent of total pharmaceutical patent filings, and none of these filings match to active ingredients in the ISP registration data. In contrast, over half the trademark filings are by Chilean entities, with the other half largely from Europe and the U.S. This pattern points to important differences in terms of the type of drugs marketed by domestic and foreign entities. Foreign originator companies rely on exclusivity through patent protection (in combination with trademark protection as shown in Table 3 below) whereas domestic companies compete (at least to some degree) through brand recognition in the generics market.

Figure 2: Time-trend patents and trademarks by foreign and domestic entities



VI. Results

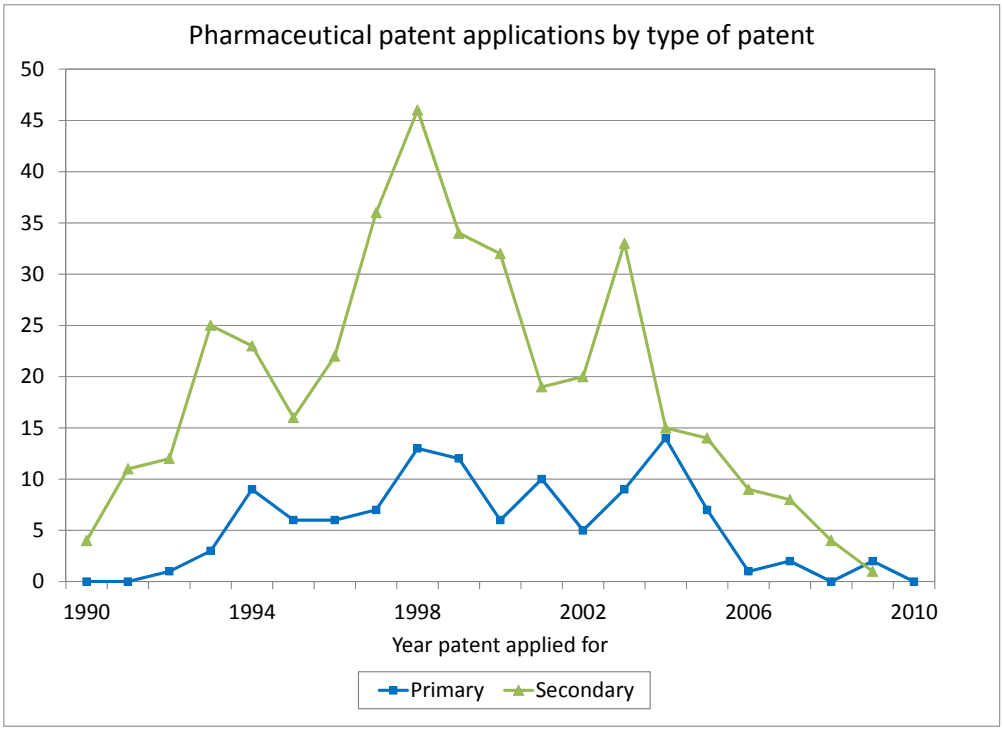
Our main interest is in the use of secondary patents by foreign originator companies in Chile. Collecting the relevant data for investigating this question is challenging. We rely on the identification of our patents as primary or secondary that was done by internal and external patent examiners at INAPI following the classification proposed by Kapczynski et al. (2012). Of the 504 Chilean pharmaceutical patents that match to our list of active ingredients, 113 (22%) were identified as primary patents, with the remaining 78% being secondary. This ratio of 1:4 is comparable to the ratio of 1:5 found for granted patents by the pharmaceutical sector inquiry of the European Commission. If we look at all granted patents regardless of whether they have matched to a product registered at the ISP, we find that there are more primary than secondary patents. This could simply be the result of secondary patents facing a higher likelihood of rejection by the Chilean patent office which would be consistent with the findings of the EU Commission discussed above. Hence this does not necessarily mean that the ratio of primary to secondary patents is the same for patent applications (pre-grant).

The 504 matched patents are associated with 322 of the 2,630 active ingredients. Of these active ingredients, less than one third (101) have at least one primary patent. In about 88% of the cases with a primary patent, a primary patent is the first patent on that ingredient; in the remaining cases, there is a secondary patent preceding the primary patent.

Figures 3, 4, and 5 examine the patent-active ingredient match more closely. Figure 3 shows the trends in ISP-matched pharmaceutical patent applications for the two types of patents separately for

the 1991-2010 period, by date of patent application. During the 1990s after the introduction of pharmaceutical product patents, both types of applications increase but after 2005 there is substantial decline, which may reflect the introduction of data protection (see Section III) and the worldwide slowdown in the introduction of new pharmaceuticals.

Figure 3: Pharmaceutical patent applications by type



Figures 4 and 5 focus only on the ISP registrations that contain a new active ingredient and use the date of the ISP registration rather than the date of the patent application. Figure 4 counts unique patent applications, showing the breakdown between primary and secondary patents by the date of the first ISP registration containing an active ingredient that has been associated with the patent. There are 316 such patents; the remaining patents are associated with later appearances of the same active ingredient, because they are on compounds rather than single chemicals. Clearly there are almost no primary patents associated with pre-1991 ISP registrations, as one would expect given the absence of pharmaceutical product patentability. There are a number of secondary patents, however, suggesting that new formulations or uses of older ISP-registered products were patented after 1991.

Figure 4: Pharmaceutical patent applications by year of first associated ISP registration

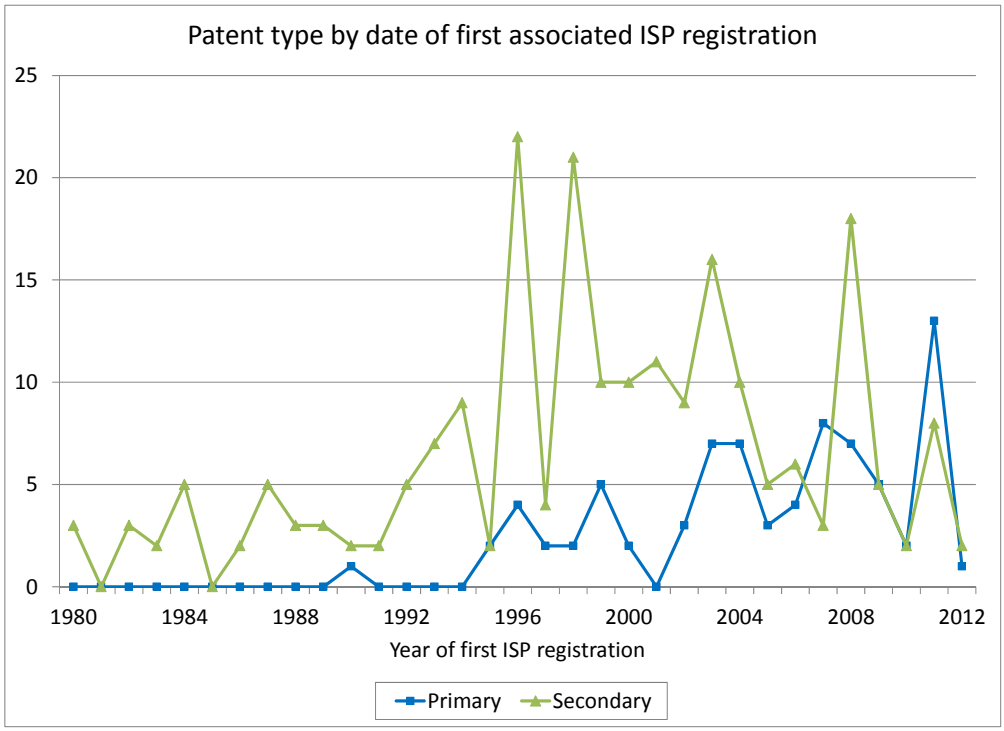
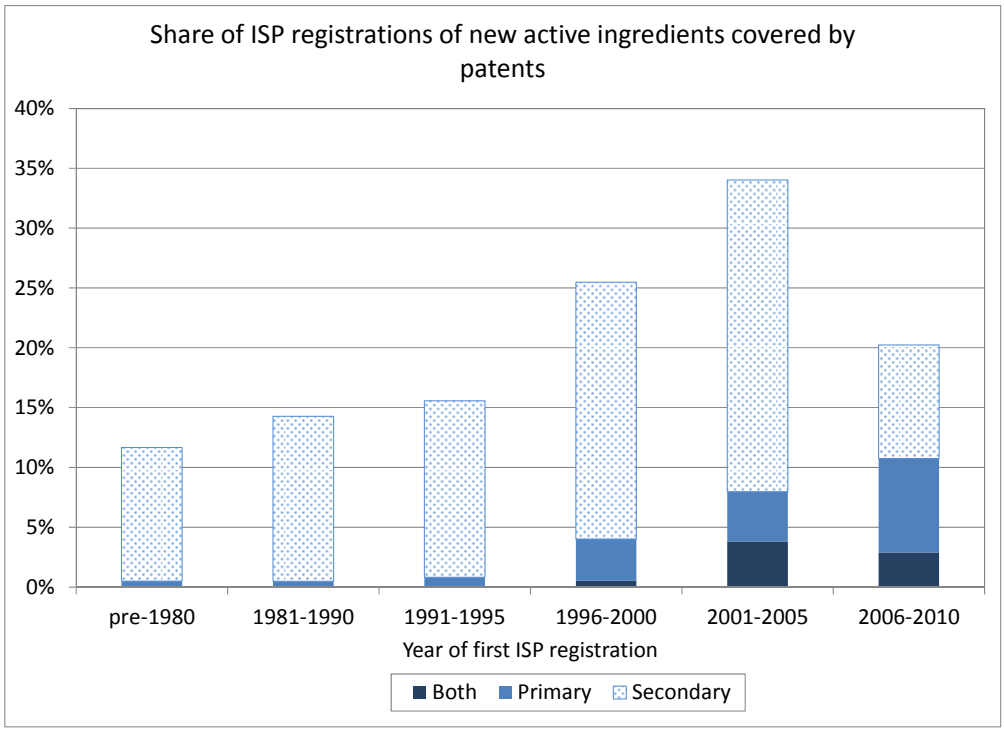


Figure 5 also counts only unique ISP registrations the first time an active ingredient appears. It shows the share of these registrations that are covered by primary, secondary, or both types of patents during six time periods. This figure also makes it clear that patent coverage of new drugs is increasing, and that an increasing number of these drugs are covered by primary patents. Note that there may be some truncation during the 2006-2010 period due to incomplete patent data (patent applications that follow the ISP registration in the later years will be missing, implying an undercount of secondary patents, in particular). In spite of the increase in patent coverage, it is still the case that several hundred active ingredients registered at the ISP for the first time after the year 2000 are not associated with any Chilean patent applications. Many but not all of these ingredients are new virus vaccines or new ingredients for over-the-counter preparations such as vitamin compounds, etc.

Figure 5: New ISP registrations and patenting



To investigate the timing between a Chilean patent application and the first associated ISP registration further, we computed the lag between the two and plotted the distributions for primary and secondary patents in Figure 6. This figure clearly shows that the great majority (86%) of the primary patents are applied for before the first time the associated ingredient is registered at the ISP. In contrast, only 56% of the secondary patents are applied for before the initial ISP registration. A nonparametric test of the difference between the two lag distributions yields a $\chi^2(1)$ of 37.5 and is highly significant. The median lag for primary patents is 6 years and for secondary patents it is 2 years. In a number of cases, the lags are over 5 years, which suggests delayed entry into the market.

Figure 6: Lag between patent application and product registration

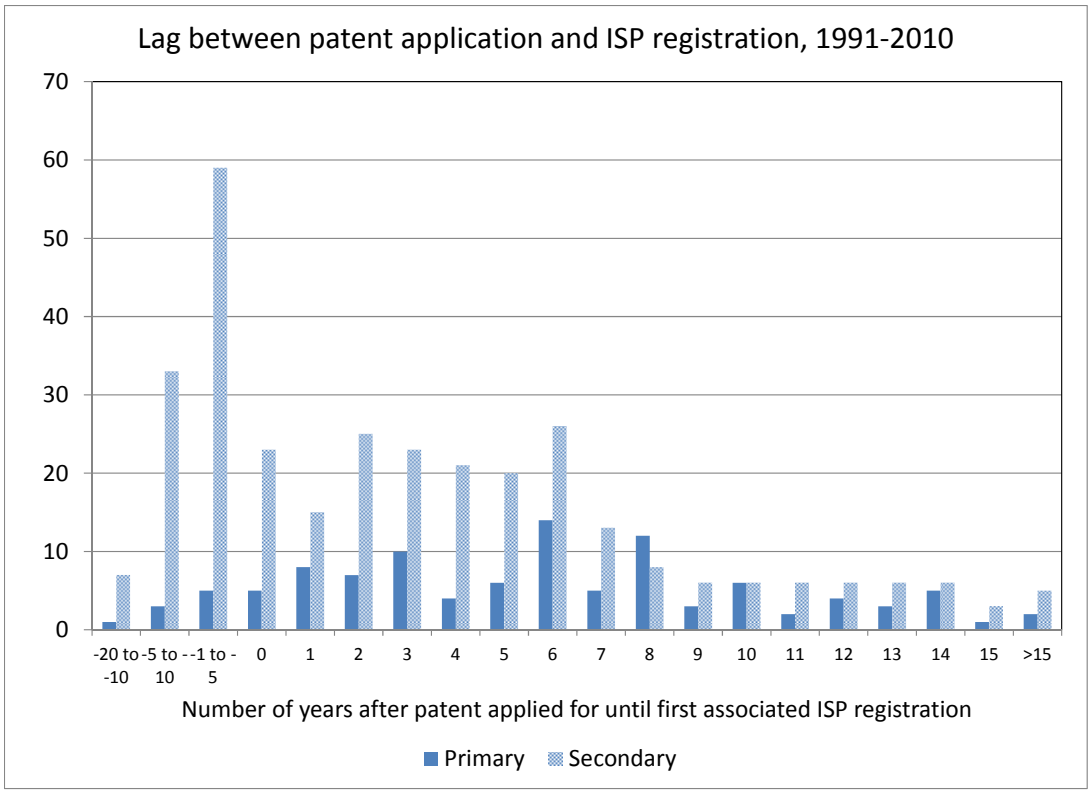


Figure 7 looks at the number of patents that protect a given active ingredient. About 55% of the active ingredients are protected by a single patent and 34% of active ingredients that are patent protected are protected by 2 or 3 patents. Very few active ingredients are associated with a larger number of patents. When we look at the breakdown into primary and secondary patents 72% of active ingredients that are protected by a single patent are in fact protected by a secondary patent. Among drugs that are protected by several patents, in most cases they are protected by only secondary patents or a combination of primary and secondary patents.

Figure 7

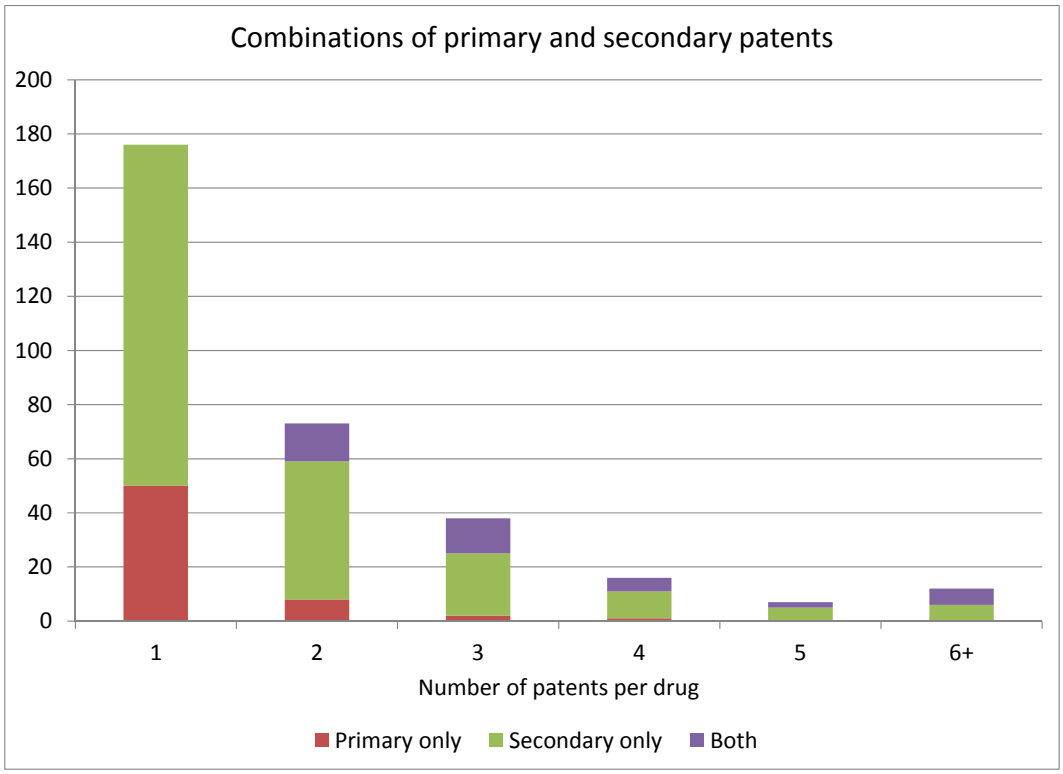


Table 2 combines the data on trademark protection with the information on primary/secondary patents. This provides additional insight into the IP strategies of foreign originator companies. The table shows that nearly all active ingredients that are protected by a patent are also protected by a trademark. This indicates that companies rely on a patent-trademark combination to achieve market exclusivity. Moreover, there are no significant differences between active ingredients that are protected by either primary or secondary patents. That said, it appears that active ingredients protected by a combination of primary and secondary patents are even more likely to rely on both trademark and patent protection.

Table 2

Type of IP protection and primary/secondary patents

IP type	*Active ingredient protected by primary*		*Active ingredient protected by secondary patent only*		*Active ingredient protected by primary and secondary*	
	#	*%*	*#*	*%*	*#*	*%*
Patent only	3	4.9%	11	5.0%	1	2.5%
Patent and trademark	58	95.1%	210	95.0%	39	97.5%
Total	61	100.0%	221	100.0%	40	100.0%

To gauge the effect of secondary patents on potential patent term extensions, Figure 8 looks at the lag between the application date of the first primary patent and that of the latest secondary patent by active ingredient. The figure shows that in most cases the lag is positive, meaning the application for secondary patent was filed after the primary patent, and in many cases this lag amounts to several years. If the secondary patent offered exclusivity to some degree, Figure 8 would suggest that in some cases, companies could gain a number of additional years of patent exclusivity through the filing of secondary patents. The median number of possible additional years is four, which is consistent with the numbers estimated by Kapczynski et al. (2012) for the United States. The active ingredient with the longest lag (15 years) is Posaconazole, an anti-fungal for which a crystalline form was patented in the United States 19 years after the original patent (see US patents 5278175 and 8435998).

Figure 8: Lag between earliest primary patent and latest secondary patent by active ingredient (active ingredients protected by both primary and secondary patents)

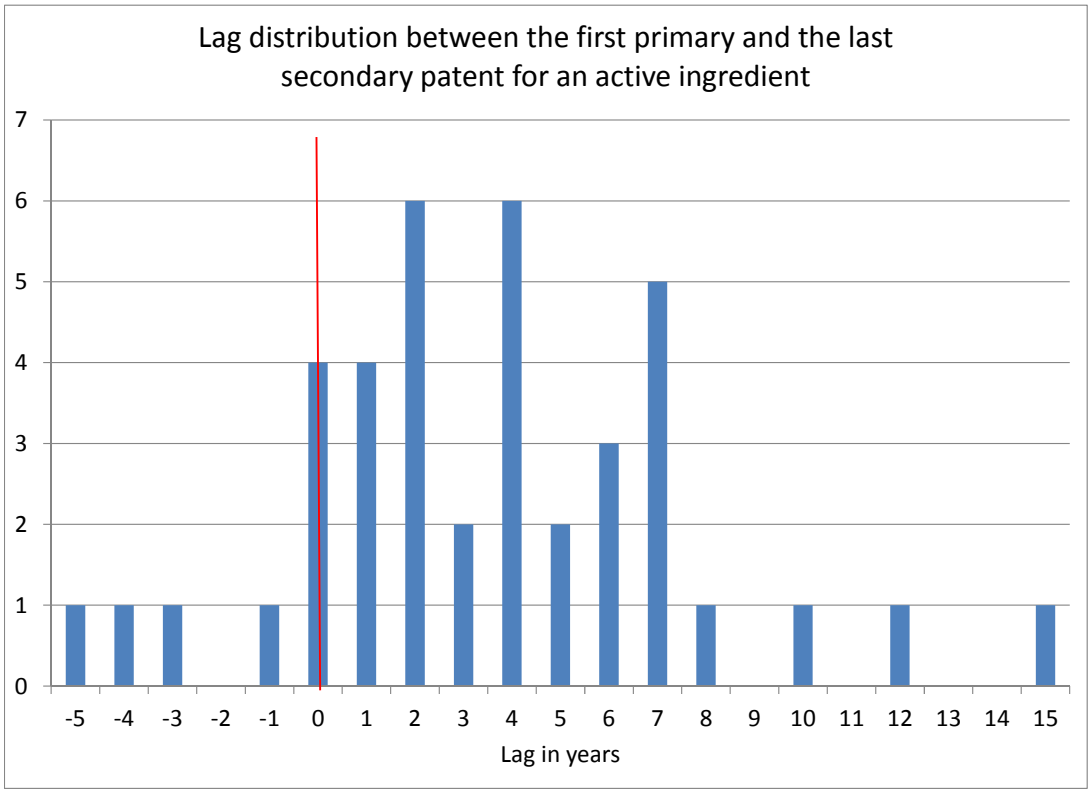


Table 3 shows the number of primary and secondary patents associated with each therapeutic class (the total number of entries in the table is 1,246 because there can be more than one class for a given patent - see also Tables A-7-A-9 in the online appendix). The shares of primary patents vary

considerably: recall that product patents were not available in Chile before 1991. This means that classes like anti-depressants and anti-ulcer (gastrointestinal agents) which had important patents prior to that date are covered largely by secondary patents. In contrast, newer areas like anti-virals and anti-neoplastics (anti-cancer) have a large share of primary patents.

Table 3

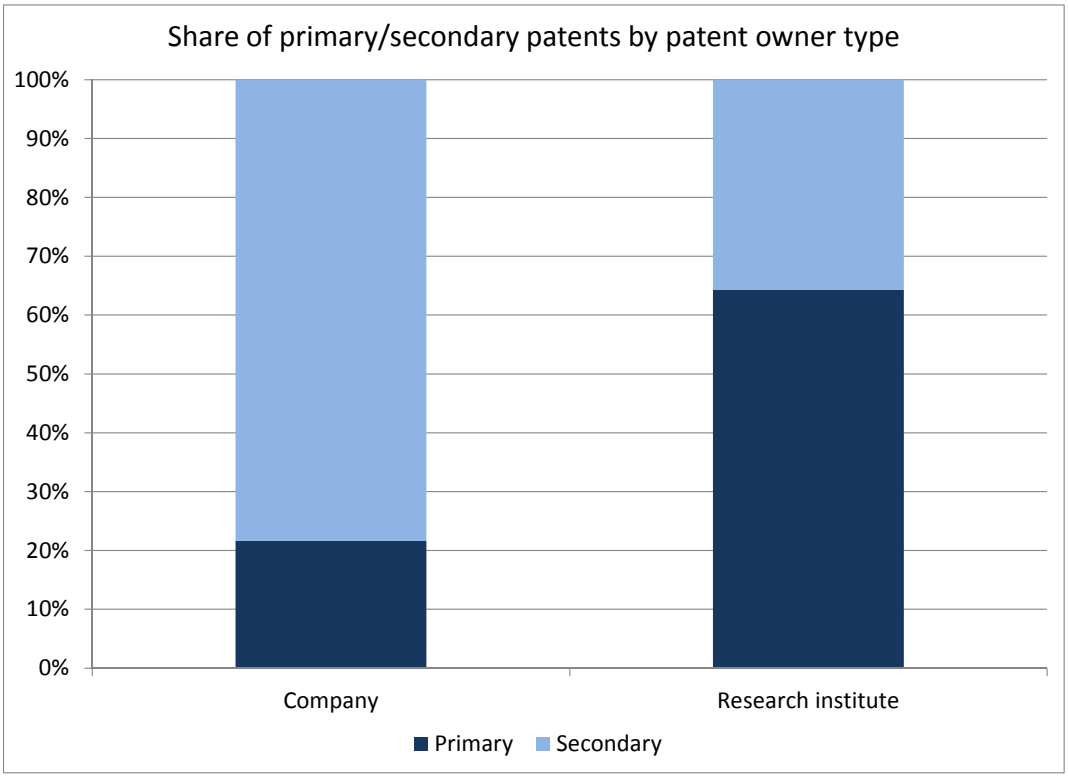
Number of patents per therapeutic class

	Number		*Share*
Therapeutic group	*Primary patents*	*Secondary patents*	*Primary patents*
anti-viral agents	20	41	32.8%
anti-neoplastics	14	23	37.8%
anti-depressants	2	33	5.7%
anti-psychotics	1	31	3.1%
anti-diabetic agents	8	24	25.0%
analgesics	8	23	25.8%
nonsteroidal anti-inflammatory agents	7	20	25.9%
immunologic agents	9	13	40.9%
antibiotics/anti-neoplastics	5	17	22.7%
gastrointestinal agents (anti-ulcer)	2	19	9.5%
anti-fungals	3	16	15.8%
broncho-dilators	1	18	5.3%
anti-asthmatic combinations	3	15	16.7%
anti-histamines	2	15	11.8%
agents for pulmonary hypertension	1	15	6.3%
bone resorption inhibitors	0	16	0.0%
quinolones	3	12	20.0%
cholesterol absorption inhibitors	3	11	21.4%
hormones	1	11	8.3%
narcotic analgesics	2	10	16.7%
anti-infectives	2	10	16.7%
remaining classes	63	421	13.0%
Total	**160**	**814**	

One of way of assessing the importance of secondary patents for extending market exclusivity is to analyze whether there are any differences in the use of secondary patents by type of patent owner – in particular distinguishing between for-profit companies and not-for-profit research institutes and universities. In Figure 9 we distinguish between these two types of assignees. The figure shows that the share of secondary patents among patent-protected active ingredients is significantly larger for

companies than for universities/not-for-profit research institutes. There are only 5 secondary patents that are assigned to universities and not-for-profit research institutes. However, with the exception of one secondary patent which is assigned to the Wellcome Foundation, all other secondary patents are co-assigned to universities/not-for-profit research institutes and private companies. This suggests that secondary patents are almost exclusively used by private companies as a tool to achieve exclusivity. That said, universities tend to focus on early stage research which is less likely to lead to the filing of secondary patents. Taking a closer look at patenting companies, we find that 76 out of 123 companies (62%) only file secondary patents whereas 25 companies (20%) only file primary patents (22 companies file both types of patents).

Figure 9: Share of primary/secondary patents by patent owner type



VII. Conclusion

Our objective was to take a first look at patenting of pharmaceuticals in Chile, with a particular focus on the distinction between primary and secondary patents. We provide a number of descriptive findings that show that pharmaceutical patents associated with drugs that have received market approval are almost exclusively the domain of foreign originator companies. Overall, we find

that only a subset of drugs with market approval is protected by patents, a much larger number of products are protected by trademarks. We also find that foreign originator companies rely on a patent-trademark combination whereas domestic companies rely only on trademarks. Nevertheless, we also find a substantial number of ISP registrations that are not protected either by a patent or a trademark. When we take a closer look at ISP registrations protected by patents, we find that the majority are protected only by secondary patents (few active ingredients are protected by more than 1-3 patents). This is especially true before the change to the patent law in 1991, although it takes a few years for number of primary patents to become significant. We also find that nearly all primary patents on active ingredients were filed before a drug containing the active ingredient was registered with the ISP. Secondary patents in contrast often follow with a lag of several years, that is, secondary patents are often filed after primary patents and after a drug has been registered at the ISP. The timing is also reflected in the fact that secondary patents dominate "older" therapeutic classes like anti-ulcer and anti-depressants. In contrast, newer areas like anti-virals and anti-neoplastics (anti-cancer) have a much larger share of primary patents. Our data also reveal that secondary patents are almost exclusively a tool used by private companies whereas universities and not-for-profit research institutes concentrate on primary patent protection.

This study is only a first step towards a better understanding of pharmaceutical patents in Chile. We have assembled a dataset that combines pharmaceutical products, active ingredients, patents, trademarks, and information on the corresponding companies. These data enable us to substantially deepen our understanding of the impact of patents on the pharmaceutical industry in Chile. Still, our approach and data have a number of obvious limitations. Perhaps most importantly, we only observe whether a drug has obtained market approval, but we have no information on actual demand or prices. This limits our ability to account for the importance of different drugs other than through their therapeutic classes.

We plan to extend this work to assess the impact that the combined use of primary and secondary patents has had on the ability of Chilean companies to compete in the generics industry. Such analysis could produce relevant insights for the current debate on secondary patents.

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Data Appendix:

Our analysis is based on a linked database constructed from three separate sources:

1. The list of pharmaceutical products registered at the Chilean National Public Health Institute (ISP).

2. A database of all patent applications filed with the Chilean Patent Office (INAPI) between 1991 and 2010.

3. A database of all trademark filings at INAPI between 1991 and 2010.

Constructing the linked database required matching the active ingredients in the pharmaceutical products with the associated patent application(s) and matching the product names with the associated trademark filing(s). In both cases there is no easy reliable way to do the matching and a large part of it was done manually. We describe the data sources and the matching effort in more detail in this appendix.

Description of the ISP database

Our data construction begins with a list of pharmaceutical products given to us by the National Public Health Institute (ISP). In Chile, all pharmaceutical products that are to be sold on the domestic market have to be registered with the ISP. The registration includes the name of the product, the form and size in which it comes, the principal active ingredient, and the specific active ingredient being registered. That is, a product may have one or more entries in the database depending on whether it comes in multiple forms, or has multiple active ingredients. Because many active ingredients are useful in several products, there are far fewer active ingredients listed than there are products or ISP registration entries. In addition, the names of the same active ingredient are sometimes given in differing ways, which required us to standardize the names by hand.[5] We obtained the ISP register in October 2012, which means it includes only products that have been registered up to five years earlier or that had been renewed.

Between 1934 and 2012, there were 14,504 ISP registrations for 12,116 pharmaceutical products.[6] Of these, 2,630 contained an active ingredient that had not yet appeared in an ISP registration.

[5] E.g., pentahydrate recorded as 5-hydrate on occasion. Calcium spelled out or recorded as the Chemical symbol Ca.

[6] 439 (3%) of the registrations were missing the ISP registration date and are not included in these figures.

Figure A1 shows three time series: all ISP registrations, those where the name of a drug appeared for the first time, and those where an active ingredient appeared for the first time. Until about 1975, each registration contained a new product and active ingredient; after this date the series begin to diverge and by the year 2000 the introduction of products with active ingredients that are new to the Chilean market begins to decline.

Figure A2 shows a distribution of the number of active ingredients per product. Almost 70 per cent of the products have only one active ingredient, and almost 90 per cent have 1 or 2. The products with more than 5 active ingredients tend to be things like multi-vitamins and minerals or alternative medicines. Figure A3 shows the distribution of the number of registrations associated with an active ingredient. About 37 per cent are registered only once, but 5 generics (ibuprofen, paracetamol, ascorbic acid, the antihistamine chlorphenamine maleate, and the decongestant pseudoephedrine) are registered more than 200 times.

Figure A1

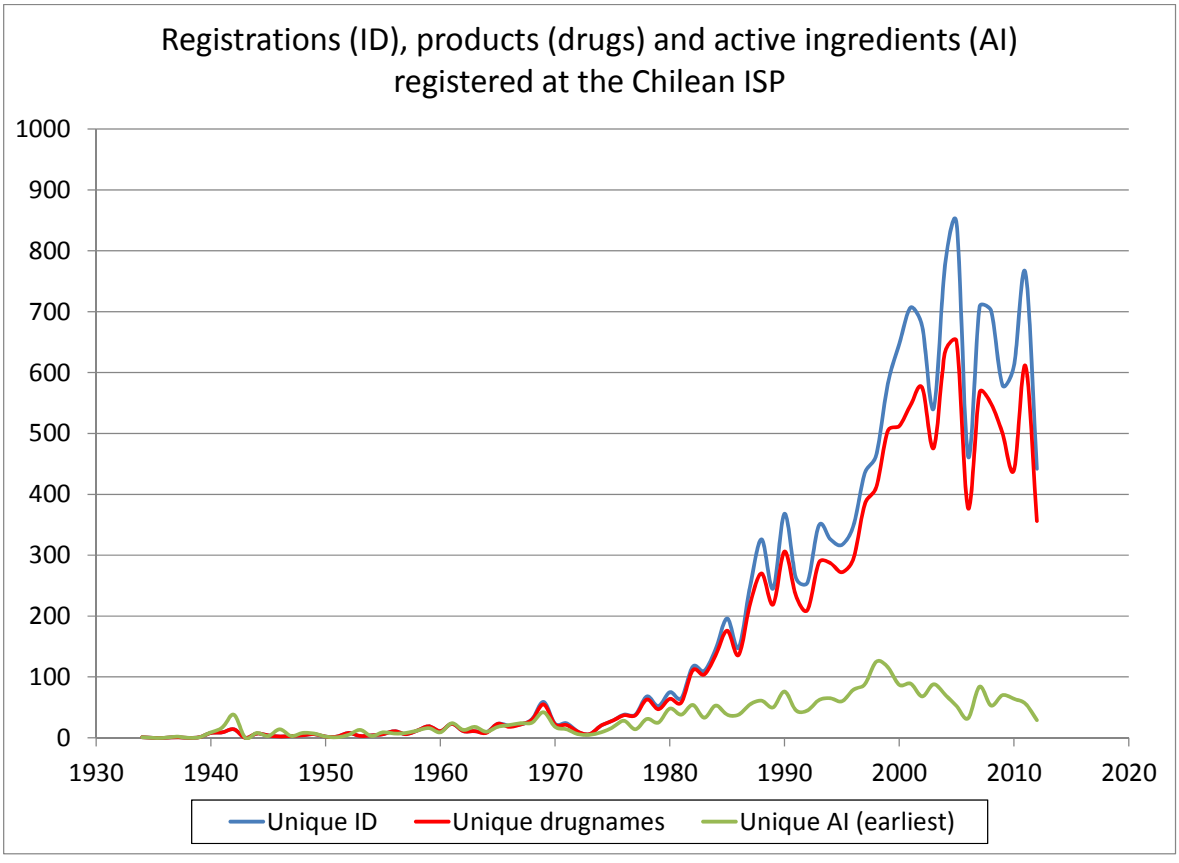


Figure A2

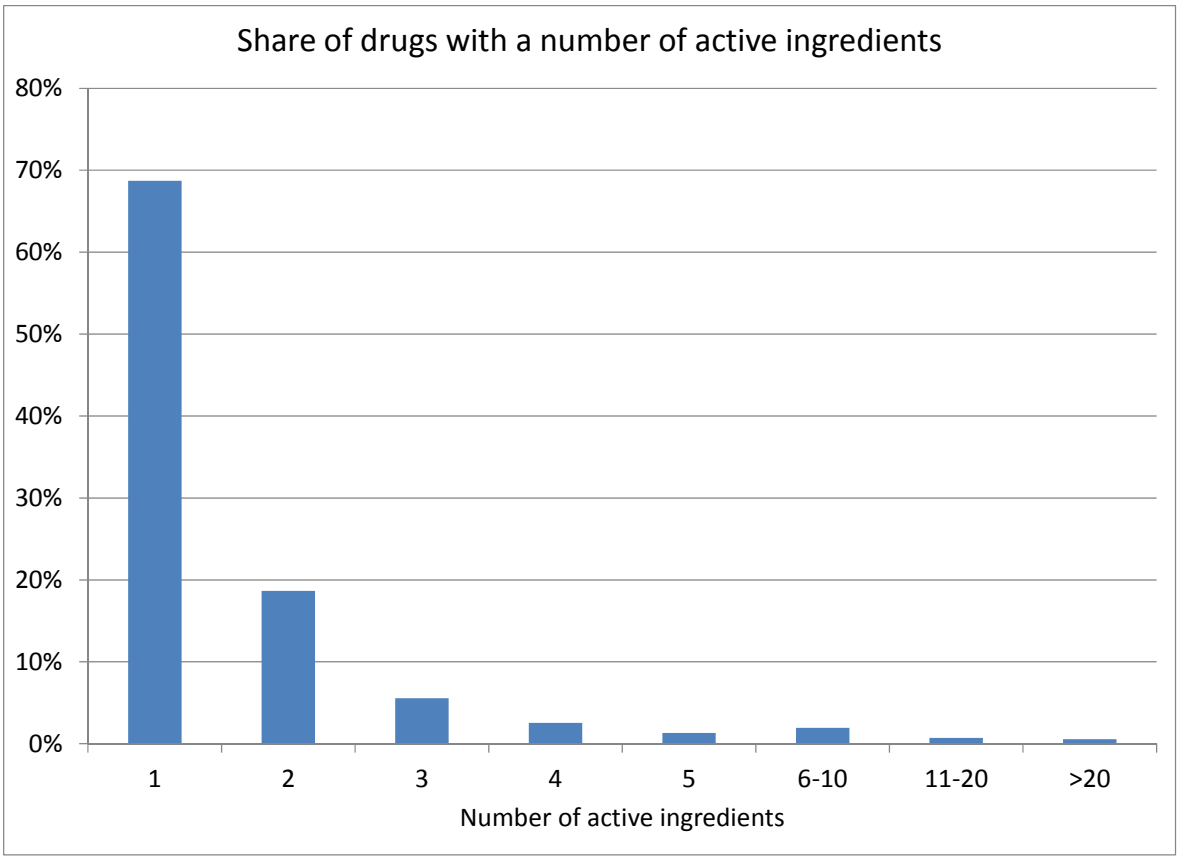
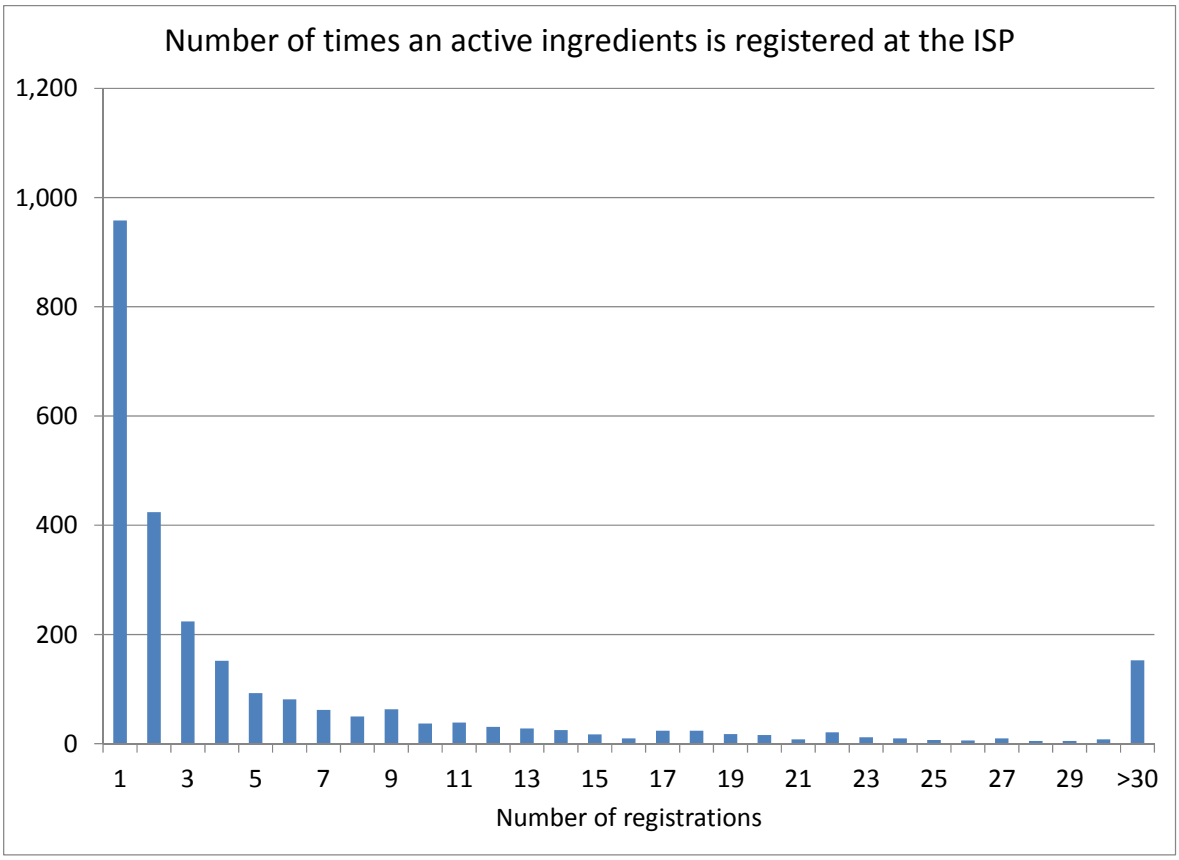

Share of drugs with a number of active ingredients
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
2
3
4
5
6-10
11-20
>20
Number of active ingredients

Figure A3



ISP registrants

The ISP database contains the names and addresses of organizations that are registering the product, but they are not standardized.[7] Our first step was to standardize the names by removing such things at "LTD" and "S A", but preserving the country associated with the name. This resulted in about 3,500 unique name-country combinations. These were examined by hand to correct misspellings and further standardize the names. The resulting list contained 2,322 unique name-country combinations. After cleaning, the largest number of companies associated with a single registration was 18 (for products Plavix and Adenosine, with much the same list of international firms plus the Chilean importers and quality control). The left hand panel of Table A1 gives the distribution of

[7] The raw file contains about 104,000 entries, with several for each ISP id, firms listed more than once for a single id if they performed multiple functions, and some duplication due to simple spelling errors.

these organizations across countries, and the right hand side gives the same thing weighted by the number of times the organization appears in the registry.

Only 15 per cent of the organizations have a Chilean address, but 68 per cent of the entries are for a Chilean organization. That is, the average number of ISP registrations for a Chilean firm is much higher than for firms from other countries.[8] Chile is followed in both lists by the U.S., Argentina, Germany, and India. The presence of India suggests the importance of the generics market in Chile.

Table A1

Geographic distribution of ISP registrants

By firm-country				*Weighted by the number of ISP regs per firm*			
Country	*Number*	*Share*	*Cum. Share*	*Country*	*Number*	*Share*	*Cum. Share*
CHILE	348	15.0%	15.0%	CHILE	46,281	68.4%	68.4%
USA	244	10.5%	25.5%	USA	2,487	3.7%	72.0%
ARGENTINA	154	6.6%	32.1%	ARGENTINA	2,436	3.6%	75.6%
GERMANY	151	6.5%	38.6%	INDIA	2,175	3.2%	78.9%
INDIA	130	5.6%	44.2%	GERMANY	1,659	2.5%	81.3%
FRANCE	115	4.9%	49.1%	CHINA	1,153	1.7%	83.0%
ITALY	113	4.9%	54.0%	SWITZERLAND	1,137	1.7%	84.7%
SPAIN	94	4.0%	58.0%	COLOMBIA	1,050	1.6%	86.2%
UK	93	4.0%	62.0%	BRASIL	1,007	1.5%	87.7%
CHINA	80	3.4%	65.5%	UK	919	1.4%	89.1%
BRASIL	78	3.4%	68.8%	MEXICO	906	1.3%	90.4%
MEXICO	72	3.1%	71.9%	FRANCE	895	1.3%	91.8%
SWITZERLAND	71	3.1%	75.0%	URUGUAY	794	1.2%	92.9%
COLOMBIA	62	2.7%	77.7%	SPAIN	641	0.9%	93.9%
CANADA	44	1.9%	79.6%	ITALY	608	0.9%	94.8%
PUERTO RICO	38	1.6%	81.2%	BELGIUM	458	0.7%	95.4%
IRELAND	36	1.5%	82.7%	NETHERLANDS	298	0.4%	95.9%
URUGUAY	36	1.5%	84.3%	PANAMA	271	0.4%	96.3%
Other countries	365	15.7%		Other countries	2,512	3.7%	
	2,324			**Total**	**67,687**		

The first panel counts each firm-country combination once.

The second panel counts every appearance of a firm-country combination in the ISP registry.

[8] Note that almost all of the organization names are in fact firm names, with a few individuals and universities in addition.

One advantage of the ISP database is that it contains information on the role that each registrant plays in the production and distribution of the drug being registered. In many cases a registrant will perform more than one function, sometimes as many as five (packager, importer, distributor, quality control, and manufacturer). This fact explains why there are 104,612 entries in the database but only 67,687 unique ISP id-firm-country combinations. Table A2 shows the distribution of the various functions performed by the registrants, by broad geographical region (Chile, the rest of Latin America, the U.S. and Canada, Europe, and the rest of the world). With a few minor exceptions, the distribution looks reasonable: Chilean firms specialize in finished manufacturing, packaging, importing, distributing, and quality control, whereas foreign firms manufacture, serve as the source or licensor of the product, and occasionally package, especially if they are European or Latin American firms.

Table A2

Functions performed by ISP registrants, by region

	Chile	*Europe*	*Latin America*	*US & Canada*	*Rest of world*	***Total***
Chilean mfg - finished	11,609	6	10	1	1	**11,627**
Chilean mfg - bulk	76	6	6	0	3	**91**
Foreign mfg - finished	25	3,483	4,008	879	2,839	**11,234**
Foreign mfg - bulk	9	1,006	1,313	269	503	**3,100**
Mfg of principal AI	0	218	0	6	52	**276**
Quality control	16,826	2	5	0	38	**16,871**
Source	9	4,577	6,513	1,028	3,421	**15,548**
Licensor	22	4,071	1,016	1,857	543	**7,509**
Foreign packager	6	83	123	22	7	**241**
Chilean packager	2,813	0	3	0	1	**2,817**
Packer	3,737	169	154	23	1	**4,084**
Importer	9,378	0	1	0	2	**9,381**
Distributor	21,832	1	0	0	0	**21,833**
Total	**66,342**	**13622**	**13152**	**4085**	**7,411**	**104,612**

As indicated in the introduction to this appendix, our main objectives in the data construction are twofold: 1) to link pharmaceutical products to the patents that protect the active pharmaceutical ingredients and processes embodied in the products; and 2) to link products to trademarks. The ISP provides us with data that contains information on products and active ingredients, that is, we have a database with all pharmaceutical products registered in Chile and the active ingredients that they contain. The challenge then consists in (a) finding all patents that protect the active ingredients

contained in the products and in (b) linking trademarks to products and companies. We divide our discussion below into these two challenges.

Finding and linking patents to active ingredients

We have data on all patent applications filed with the Chilean patent office (INAPI) between 1991 and 2010. This includes all patent filings by domestic as well as foreign entities. The objective is to identify those patents that protect the active ingredients listed in ISP's pharmaceutical product database. We also attempt to identify patents that protect the processes used in the production of the products, but this is more difficult because these cannot necessarily be identified directly from our data sources.

Linking patents to active ingredients is difficult for the following reasons:

1) Active ingredients are registered at the ISP using the International Nonproprietary (INN)[9] classification whereas patents rely on the International Union of Pure and Applied Chemistry (IUPAC)[10] classification. These classifications differ substantially. For example, the INN denomination for the active ingredient Imatinib is "imatinib mesilate" and its IUPAC is "4-[(4-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide."

2) While the ISP register lists the active ingredients that belong to a given pharmaceutical product, patents may protect a family of different pharmaceutical ingredients related to the active ingredient in question.[11] This means that a single patent may protect several different active ingredients. Specific ingredients covered by the patent can only be identified through the examples given in the patent application.

3) A product registered at ISP can be associated with a number of different patents. Only some of these patents protect the relevant active ingredient. This can occur for several

[9] The INN is the official nonproprietary or generic name given to a pharmaceutical substance designated by the World Health Organization (WHO).

[10] This organization names new compounds according to the rules of organic chemistry.

[11] This is due the "Markush" formula. This formula represents a group of compounds related with an active ingredient. These related compounds are usually modifications of the original active ingredient.

reasons. First, other patents protect different forms of the active ingredient, related ingredients, or for example the manufacturing process of the drug. Second, in the early stages of the development of a new drug, producers commonly patent a large number of molecules, formulations and compositions that have potential to be developed into new active ingredients. This means while there can be a large number of patents related to the eventually developed active ingredient, they need not all protect the ingredient. Third, it is possible to patent the "second use" of a drug.

Mindful of these challenges, we proceed as follows. As a starting point, we use data compiled by WIPO from information provided by INAPI that contain the active ingredient-patent mapping for all active ingredients contained in new pharmaceutical products registered with ISP between 2005 and 2010. The mapping was undertaken by patent examiners specialized in pharmaceutical patents.

For all remaining products registered with the ISP we proceed as follows:

1) The ISP products are grouped by active ingredients. For example, focusing on the active ingredients Imatinib and Drospirenone, we group thirteen ISP products under the active ingredient Imatinib and thirty-three products under the active ingredient Drospirenone. For the cases that a product has more than one active ingredient, we include the product in each group of its active ingredients. For example, the product "Femelle Fol Comprimidos Recubiertos" has three active ingredients: Drospirenone, Ethinyl Estradiol and Levomefolate. Therefore, the drug will be part of three different groups, one for each active ingredient.

2) Each active ingredient is translated from Spanish into English using online translators and our own expertise.

3) Each active ingredient is searched in the Merck Index (MI). The MI contains the first filings of patents on an active ingredient, which can be at any patent office around the world. This provides us with the direct association between active ingredient and corresponding patent(s). We search the priority dates, inventor names, title and abstract of the patent(s) listed in the MI. For example, Imatinib has two patents in the MI: EP564409 and US5521184 with priority date 03/04/1992. The inventor name for both patents is "Juerg Zimmerman."

4) The Orange Book (OB) of the U.S. Food and Drug Administration (USFDA) is used to identify U.S. patents on or related to the active ingredients of the products registered in Chile. The OB provides the patent-active ingredient mapping for all drugs registered with the USFDA, and patents filed with the USPTO. Patents may not only protect the active ingredient directly but also other features of a registered drug. We search for each active ingredient in the OB.[12] If an active ingredient is found in the OB, we extract the corresponding list of products that contain the active ingredient and the patents associated with these products.[13] We obtain priority dates, inventor names, title and abstract for the USPTO patents identified through the OB. The main challenge is to determine whether the patents found in this way protect the active ingredient or a related ingredient or process. For example, we found two registered products in the FDA that contain Imatinib: Gleevec 100mg and Gleevec 400mg. Each product has the same four USPTO patents. One of the four patents listed in the OB corresponds to the MI priority patent (US5521184), which means this is the one that protects the active ingredient Imatinib. If the product has only a single ingredient, it is likely that the other patents that do not protect the active ingredient directly, but a modification, a related process, manufacturing method, a second use, or treatment. If the product has several ingredients, the patents can also be associated with other ingredients. To determine this, each patent has to be assessed individually. We do not assess this directly, but rely on the assessment of the Chilean equivalent by patent examiners specialized in pharmaceutical patents. So for example, the three other U.S. patents found in the OB in the case of Imatinib (US6894051, US7544799 and US6958335) are indeed related to Imatinib. The first two patents are a crystal modification of the active ingredient and the third one is a treatment using Imatinib. This would only be relevant, however, if any of these patents had a Chilean equivalent.

5) The WIPO-INAPI database is searched for Chilean equivalents of the patents found in the MI and OB. We do this through inventor names, priority date, title and abstract of the patents found in the MI and OB. The Chilean patents found in this way, where we distinguish between the patents protecting directly the active ingredient and related patents,

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[12] The OB does not provide historical patent data, that is, if a patent expires or lapses at the USPTO, the patent is deleted from the register. Bhaven Sampat provided historical records that allow us to correct this problem.

[13] We could have also searched directly for the products contained in the ISP register, but going via active ingredients seems to be the 'cleaner' way of proceeding.

represent the patents that protect a given active ingredient and hence pharmaceutical product. For example, in the case of Imatinib we did not find a Chilean equivalent for US5521184 but we found an equivalent for US689405, a crystal modification of Imatinib (CL199801692). In this way we create patent families related to each active ingredient and pharmaceutical product.

In case we were unable to find an active ingredient in the MI or the OB, we link patents to ingredients directly. However, this is not straightforward as explained above and was therefore done by Chilean patent experts specialized in pharma patents. Due to the large number of pharmaceutical patents and the extremely labor-intensive process of matching patents and pharmaceutical products, we limited the direct match to the remaining set of unmatched granted pharmaceutical patents (approximately 3,000 patents).[14]

The ISP database contains additional information on pharmaceutical products such as the registration, expiration and renovation date, the owner of the drug, whether the drug is produced domestically or abroad, and drug packaging information. The information on the owner of the drug is especially useful for the patent-compound matching as it provides a possible cross-check with the assignee names of patents.

The match between drug names on the ISP and these various patent data bases yielded 602 unique Chilean patents: 463 from the Orange Book, 26 from the Merck Index, 44 from the WIPO-INAPI match for 2005-2010, and 69 from the search of remaining granted patents. After cross-checking of the matches by Chilean patent experts, this number was reduced to 504 unique Chilean patents matched to 322 unique active ingredients from 4,304 ISP registrations. There are 619 unique patent-active ingredient combinations. Table A3 below shows a count of the number of ISP registrations and the number of unique active ingredient names that are matched to no, one, two, etc. patents. The drug and active ingredient with the largest number of associated Chilean patents (9) is ciprofloxacin, an antibiotic. One third of the ISP registrations but only 12 per cent of the unique active ingredients match to at least one patent. Only 3 per cent of the patents in the organic fine chemistry, biotechnology, and pharmaceutical classes match to an active ingredient, but that is not

[14] The search for additional matches to the ISP ingredients in these 3,000 granted patents yielded 69 patents (2%). Therefore the remaining unsearched patent applications are unlikely to contain many additional matches, especially since they include a majority of rejected or abandoned filings.

too surprising, because many of the patents in these classes are associated with agriculture or aquaculture.

Table A3

	Number of patents associated with			*Number of trademarks associated with*			*Number of ISP reg. associated with*	
	ISP registration	*Product name*	*active ingredient*	*ISP registration*	*Product name*	*active ingredient*	*patent**	*trademark***
Total	14,504	12,116	2,630	14,504	12,116	2,630	17,956	148,696
0	10,200	8,407	2,308	4,809	2,843	298	17,452	138,235
1	3,845	3,250	176	2,440	2,264	261	217	2,845
2	400	392	73	4,812	4,629	675	67	2,861
3	35	42	38	993	974	252	40	1,117
4	10	11	16	629	600	186	31	1024
5	5	5	7	193	189	109	12	564
6-10	9	9	11	403	396	354	43	1234
>10	0	0	1	225	221	495	94	816
Nonzero total	4,304	3,709	322	9,695	9,273	2,332	504	10,461
Nonzero share	30%	31%	12%	67%	77%	89%	3%	7%

* Total of all patents in pharma classes, broadly defined.

**Total of all trademarks in pharma classes, broadly defined.

In Table A4 we look at the patent-active ingredient match by the grant status of the patents. We again restrict the Chilean patent database to those patents classified in ISIO 14 (organic fine chemistry), 15 (biotechnology), and 16 (pharmaceutical). Only 6 of our matched patents lie outside these classes and we have added these manually to the sample. In this table we show the match by the patent status. Clearly granted patents are more likely to be matched (at 8%) and abandoned/withdrawn patents are the least likely to be matched (<2%). However the overall match rate is fairly low (3%).

Table A4

Match of Chilean pharmaceutical patents to AIs

	Number		*Share*		
Patent status	*Not matched*	*Matched to AI*	*Not matched*	*Matched to AI*	*Share matched*
Pending	6,414	165	36.8%	32.7%	2.5%
Granted	2,830	256	16.2%	50.8%	8.3%
Rejected	1224	24	7.0%	4.8%	1.9%
Combined to another	23	1	0.1%	0.2%	4.2%
Abandoned or withdrawn	6,961	58	39.9%	11.5%	0.8%
Total	**17,452**	**504**			**2.8%**

Pharmaceutical patents are all patents in ISIO 14, 15, 16.

Linking products to trademarks

The ISP database provides the names under which drugs are marketed as well as their owners and potential licensees that might market products under their own name. We have all trademark filings with INAPI for the period 1991-2010, which contains filings by both residents and non-residents. To associate registered trademarks to pharmaceutical products, we search for product trademarks associated with the drugs' names as well as the owners as reported by ISP in INAPI´s trademark database. Needless to say, this is a very complex process and the current data file by no means exhausts the trademarks that might be associated with our products.

To give an idea of the difficulty, recall that there are about 12,000 pharmaceutical products in the ISP database. The trademark database has about 780,000 registrations (averaging 2 registrations per each distinct trademark), of which there are about 150,000 registrations in the NICE classes 3 (soaps and cosmetics), 5 (pharmaceuticals, dietary, medical supplies), 10 (medical and surgical instruments), and 44 (medical services & beauty care). About 50,000 of these registrations are renewals, leaving 100,00 unique trademarks. Matching even 12,000 names with 100,000 names requires an automated approach. Our initial algorithm cleaned each name (product and trademark) for special characters and did some standardization by removing frequently repeated words from the product name (e.g. "acido" or "compuesto"). We then matched on the first word in each name. The result of this match was examined for obvious errors, and those were removed. A manual search of the trademark database using the remaining unmatched drug names was then performed, which added a few more matches.

The resulting match contains 10,461 unique trademark registration numbers for 4,255 unique trademarks. 9,273 of the 12,116 product names (76%) have been matched to at least one trademark.[15] There are 1,323 unique names of trademark owners. About half of the registrations are renewals and the vast majority of the trademark names are from Nice class 5 (pharmaceuticals), as shown in Table A5 below.

Table A5

Number of trademarks matched, by Nice class

		Number		*Shares*	
NICE class		*All*	*Without renewals*	*Number*	*Without renewals*
3	Soap & cosmetics	775	521	7.4%	10.3%
5	Pharmaceuticals, dietary & medical supplies	9,448	4,385	90.3%	86.3%
10	Medical & surgical instruments	189	129	1.8%	2.5%
44	Medical & beauty services	49	44	0.5%	0.9%
	Total	**10,461**	**5,079**		

Only one NICE class per trademark chosen in order of importance: 5, 10, 3, 44

Table A6 shows the trademark status of the matched and unmatched patents. The majority (77%) of trademark applications are granted and about 21% are rejected or abandoned. As in the case of patents, pending and granted trademarks are much more likely to have been matched to a product in our ISP dataset, although the share that matched is still rather low.

[15] Multiple registrations correspond to the same trademark text: there are many renewals, and text that is the same even if the owner and true trademark are different. So the statistics here may require more work.

Table A6

Chilean pharma trademark status

	Not matched	*Matched to product*	*Not matched*	*Matched to product*	*Share matched*
Pending	2,067	102	1.5%	1.0%	4.7%
Granted	105,560	9,525	76.4%	91.1%	8.3%
Rejected	20,443	582	14.8%	5.6%	2.8%
Cancelled	241	7	0.2%	0.1%	2.8%
Abandoned or withdrawn	9,588	245	6.9%	2.3%	2.5%
Not known	336	0	0.2%	0.0%	0.0%
Total	**138,235**	**10,461**			

Pharma NICE classes are 3,5,10, and 44.

Therapeutic classes

The final step in our data construction was to standardize the therapeutic classes attached to each ISP registration. The raw data in the ISP register contained a total of 1,542 distinct therapeutic classes. 248 (1.7 per cent) of the ISP registrations were missing the therapeutic class and we filled in the missing information. The classes in the raw data do not follow a common structure and the same classes may be labelled in different ways. In addition, each entry potentially contains multiple therapeutic classes. We translated these classes and standardized them which included spelling corrections, name harmonizations, and the grouping of related classes (for example we group "antidepressant selective inhibitor of serotonin reuptake" and "antidepressant"), yielding 594 standardized therapeutic classes. In a final step we match the cleaned and standardized therapeutic classes to a hierarchical classification system maintained by www.drugs.com. This allows us to group therapeutic classes under broad headers and to collapse our data into 19 broad therapeutic groups consisting of 183 classes; we use these classifications for the analysis.

Table A7 shows the number of ISP registrations by broad therapeutic group and Table A8 shows the number of registrations for the more detailed classes that have 100+ associated registrations. In both cases, the numbers are weighted by the inverse of the number of classes attached to that registration.[16] Table A8 shows that many of the most common registrations are for products that are "off-patent", such as NSAIDs, vitamins, analgesics, penicillin, etc., as we expect. Finally Table A9 shows the distribution of products and active ingredients across therapeutic classes. Columns 1 and

[16] There may be as many as 4 classes per registration, although most have only one or two.

3 of Table A9 show that 19 therapeutic classes account for over half the products between them, with the remainder accounted for by the other 164 classes. The remaining columns (2 and 4) of Table A9 show the number of active ingredients associated with each therapeutic class. The class with the largest number of active ingredients is vitamins, which includes various homeopathic remedies that tend to be mixtures containing a number of ingredients.

Table A7

ISP registrations by therapeutic group

Broad therapeutic group	*Number*
allergenics	7
alternative medicines	4
anti-infectives	1936
anti-neoplastics	1055
biologicals	3
cardiovascular agents	1165
central nervous system agents	2856
coagulation modifiers	242
gastro-intestinal agents	878
genito-urinary tract agents	99
hormones	771
immunologic agents	315
metabolic agents	743
miscellaneous agents	256
nutritional products	711
plasma expanders	224
psychotherapeutic agents	880
radiologic agents	48
respiratory agents	1064
topical agents	1197
unknown	489
Weighted total	**14,943**

Table A8

ISP registrations by therapeutic class

Standardized therapeutic class	*Number*
analgesics	720
nonsteroidal anti-inflammatory agents	712
anti-neoplastics	586
agents for pulmonary hypertension	571
anti-viral agents	443
anti-depressants	397
vitamins	396
antibiotics/anti-neoplastics	377
anti-convulsants	364
anti-fungals	363
anti-histamines	361
anti-psychotics	330
gastrointestinal agents	304
anti-diabetic agents	288
anxiolytics,sedatives,and hypnotics	251
penicillins	249
topical steroids	244
anti-septic and germicides	242
plasma expanders	225
anti-asthmatic combinations	206
contraceptives	172
cephalosporins	165
immunologic agents	164
antacids	154
anti-cholinergics/anti-spasmodics	141
broncho-dilators	140
vasodilators	137
estrogens	136
anti-coagulants	136
macrolide derivatives	135
bone resorption inhibitors	132
anti-emetic/anti-vertigo agents	128
cholesterol absorption inhibitors	123
minerals and electrolytes	120
immuno-stimulants	119
quinolones	119
benzodiazepines	118
anti-tussives	117
topical acne agents	114
hormones	112
Remainder	4,746
Weighted total	**14,943**

Table A9

Products or active ingredients per therapeutic class

	Number		*Share*	
Class	*Products*	*Active ingredient*	*Products*	*Active ingredient*
analgesics	581	57	4.8%	2.2%
nonsteroidal anti-inflammatory agents	564	41	4.7%	1.6%
anti-neoplastics	464	93	3.8%	3.6%
agents for pulmonary hypertension	435	41	3.6%	1.6%
anti-viral agents	373	89	3.1%	3.4%
vitamins	366	249	3.0%	9.5%
anti-depressants	324	28	2.7%	1.1%
anti-convulsants	323	24	2.7%	0.9%
anti-histamines	303	39	2.5%	1.5%
anti-fungals	292	30	2.4%	1.1%
anti-psychotics	285	31	2.4%	1.2%
anti-diabetic agents	248	33	2.0%	1.2%
antibiotics/anti-neoplastics	247	55	2.0%	2.1%
antiseptic and germicides	223	59	1.8%	2.2%
topical steroids	215	34	1.8%	1.3%
plasma expanders	211	44	1.7%	1.7%
gastrointestinal agents	208	44	1.7%	1.7%
anxiolytics,sedatives,and hypnotics	191	31	1.6%	1.2%
anti-asthmatic combinations	178	16	1.5%	0.6%
penicillins	168	20	1.4%	0.8%
contraceptives	161	17	1.3%	0.6%
immunologic agents	155	41	1.3%	1.6%
antacids	136	25	1.1%	1.0%
anti-cholinergics/anti-spasmodics	132	24	1.1%	0.9%
anti-coagulants	127	37	1.0%	1.4%
estrogens	124	20	1.0%	0.8%
bone resorption inhibitors	121	24	1.0%	0.9%
immuno-stimulants	119	137	1.0%	5.2%
cephalosporins	118	21	1.0%	0.8%
topical acne agents	114	22	0.9%	0.8%
Remainder	4601	1200	38.0%	45.7%
Total	**12104**	**2626**		