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STUDY ON PHARMACEUTICAL PATENTS IN CHILE

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1. The Annex to this document contains a Study on Pharmaceutical Patents in Chile prepared under the Project on Intellectual Property and Socio-Economic Development (CDIP/5/7 Rev.) approved by the Committee on Development and Intellectual Property (CDIP) in its fifth session, held in April 2010.

2. *The CDIP is invited to take note of the information contained in the Annex to this document.*

[Annex follows]

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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 members of the WTO to grant patents with a statutory lifetime of 20-years from the patent application also to pharmaceutical compounds.² Almost two decades after TRIPS, the empirical evidence on its effect on developing countries is at best mixed (see Section 2 below).

Despite the strengthening of IP protection brought about by TRIPS, many 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.³ Some developing countries, most prominently India, have used this freedom to restrict the granting of so-called secondary pharmaceutical patents.⁴ As opposed to primary patents which protect directly an active ingredient, 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.).⁵ Other developing countries, such as Brazil and South Africa, are currently debating new legislation that would emulate India’s approach to restricting the patentability of secondary patents.⁶

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 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 in Chile. This may have created strong incentives for originator companies to rely on new secondary patents instead.

² Still, a number of provisions that allow signatories to put restrictions on the granting and use of patents on pharmaceuticals such as price controls and compulsory licensing are included in the TRIPS Agreement.

³ TRIPS Article 27.3(a) allows countries to exclude therapeutic and diagnostic methods from patentability, which offers another legal justification for excluding new uses of existing drugs from patentability.

⁴ Section 3(d) of India’s Amended Patents Act of 2005 excludes from patentability the “mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.”

⁵ Note that there is no primary/secondary patent distinction in patent law. However, this distinction is commonly used to distinguish between different claim types in pharmaceuticals. For example, see Kapczynski, Park, and Sampat (2012). 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.

⁶ In Brazil, Article 3 of Bill No. H.R. 5402/2013 proposes to explicitly exclude new uses and new forms of existing medicines (including salts, esters, ethers, polymorphs, metabolites, isomers etc.) from what is considered an invention. South Africa’s Draft National Policy on Intellectual Property released in 2013 proposes similar provisions.

The sparse, available evidence on secondary patents, which focuses on the U.S. and the European Union (EU) (see Section 3 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.

Despite the widespread use of secondary patents and the current contentious policy debate, there is little evidence on their effect in developing countries. We document the use of primary and secondary patent by multinational originator companies in Chile.

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 mentioning in the patent claims of the active ingredient contained by a drug.⁷ We address 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 (regardless of whether the Chilean patent has been granted).⁸ Similarly, we undertake the same exercise using the Merck Index, which provides information on patents worldwide. Second, we use a dataset compiled by INAPI that contains the compound-patent mapping for all new compounds registered in Chile between 2005 and 2010. 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 matched all granted Chilean patents to drugs, either directly or through any of the other approaches. In contrast, applications that have *not* been granted (regardless of the reason) were only matched if they contained new compounds registered with the ISP between 2005 and 2010 or they matched via the Orange Book or Merck Index.

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 trademark database contains trademarks classified by field of use such as pharmaceuticals, health, etc. The pharmaceutical product data provides the names under which drugs are marketed, which 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 Registrar between 1991 and 2008 and with its successor, the Chilean patent office (INAPI) in 2009 and 2010. It includes all patent applications and trademark applications by domestic as well as foreign entities (see Abud et al., 2013). The pharmaceutical product data comes from the National Public Health institute (ISP). The institute maintains a database that links all registered drugs in Chile to the pharmaceutical compounds that they contain.⁹ The database also contains additional information on the drug (e.g. when it was registered), the owner of the drug, whether the drug is

⁷ Drugs are products that are marketed. Different products may contain the same active ingredient and a given product may contain multiple active ingredients.

⁸ We use the combination of priorities and inventors to identify equivalents. Our set of equivalents was verified by INAPI's patent examiners.

⁹ In Chile, all pharmaceutical products that are to be sold on the domestic market have to be registered with the ISP.

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 drugs.

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 Chile.

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

II. LITERATURE REVIEW

The economic evidence on the impact of TRIPS and more generally the patentability of pharmaceutical products is at best mixed. This is probably best illustrated by the example of India. The India Patents Act of 1970 denied patentability to pharmaceutical products.¹⁰ Chaudhuri et al. (2006) suggest that the absence of pharmaceutical product patents had indeed a strong effect on maintaining low drug prices in India. However, when India entered the WTO in January 1995, it also adopted the TRIPS agreement which forced India to recognize the patentability of pharmaceutical product patents, although India was allowed –as were all other developing country members- to postpone their introduction until January 2005.¹¹ In 2002 India brought its legal system further in line with TRIPS requirements by among other things introducing a 20-year patent validity term counting from the patent application date. Arora et al. (2009; 2011) analyze the response by Indian pharmaceutical companies to this regime change. Their findings indicate a strong increase in R&D intensity among domestic pharmaceutical companies following the introduction of pharmaceutical product patents. However, this increase is explained not as much by Indian companies beginning to invent their own new drugs, but instead is the result of investment in process innovations and improvements on existing drugs. These improvements enabled Indian producers to successfully compete in the world-wide generics and bulk drugs market. Arora et al. (2009) argue that this development can only be in part attributed to the strengthening of patents in pharmaceuticals in India. Kyle and McGahan (2012) also arrive at a negative assessment of the TRIPS effect on developing countries. While they confirm a positive association between patent protection and R&D investment in developed economies, they do not find any evidence that R&D spending on diseases that are disproportionately more prevalent in developing countries is driven by the implementation of TRIPS in lower income economies.

Based on the evidence for India in Chaudhuri et al. (2006), Goldberg (2010) argues that the most important concern with regard to pharmaceutical patents and TRIPS is access to patented drugs in developing countries. She argues that multinationals have incentives to delay or forego entry in developing countries because of “cross-country reference pricing.” That is, to avoid regulators using lower prices for drugs marketed in a developing country to set prices in

¹⁰ Pharmaceutical process inventions remained patentable, although their patent life was restricted to 7 years counting from filing date whereas the life of any other patent was 14 years. The 1970 Patent Act also enacted provisions that allowed compulsory licensing of pharmaceutical drug related process patents.

¹¹ However, according to TRIPS regulations, patentees were allowed to file pharmaceutical product patent applications already during this 10-year transition period through a so-called “pipeline” system (the mailbox system), adopted during the Uruguay round of negotiations.

developed countries, multinationals wait until prices are set in the lucrative developed economies before they consider entry in developing countries. Pharmaceutical patents assume a critical role if foreign originator companies use the patent system to strategically delay their entry in a developing country while keeping any potential generic competition at bay.

Kyle and Qian (2013) look at the decision by foreign originator companies to introduce a drug in a developing country and the quantity of drugs sold depending on whether the originator has obtained patent protection. Their results contradict Goldberg's (2010) concerns; using drug-level data from IMS Health for 1990-2011, they find that products are launched faster in markets that allow for pharmaceutical product patents. In fact, they find higher sales for patented drugs, and a lower price premium of patented drugs post-TRIPS in lower- and middle-income economies. That said, their analysis cannot rule out alternative influences, such as price controls, the threat of compulsory licensing etc. Cockburn et al. (2014) address some of these concerns by including broad measures of the regulatory environment (including price controls) in the countries included in their sample. Their findings still suggest that companies are significantly more likely to launch a new drug in a country that has strong patent protection.

III. PRIMARY AND SECONDARY PATENTS

Patents play a crucial role 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 suggests that 1 in 5,000-10,000 test active ingredients results in a successful drug (EU Commission, 2009)), early patent filings reflect this. 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 the secondary patents is whether they protect genuine follow-on innovation or whether they represent primarily a form of strategic patenting. That said, strategic patenting and the use of patents to protect follow-on innovation are not necessarily mutually exclusive. There is little discussion about the innovation contained by new active ingredients, but for example the new uses of existing active ingredients in new therapeutic areas, new formulations, new modes of delivery, new combinations of known active ingredients etc. may be 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. Take for example 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.¹² These objectives can be supported by specific patenting strategies, in particular the creation of patent

¹² Despite the existence of secondary patents, there may be generic entry when the primary patent on an active ingredient expires. It is still true, however, that the existence of secondary patents may create uncertainty about potential patent infringement even when the patent on the active ingredient has expired (EU Commission, 2009).

fences and clusters. Burdon and Sloper (2003) put it bluntly “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 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. Another example is Sanofi Aventis's ARAVA arthritis drug in Australia. Sanofi Aventis effectively extended exclusivity by 10 years through secondary patents.¹³ 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 (Hutchins, 2003a, 2003b) relative to the original compound patents. 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 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

¹³ See Sanofi-Aventis Australia Pty Ltd v Apotex Pty Ltd (No.3) [2011] FCA 346.

and are thus mostly used to restrain attempts by originator companies to extend patent terms beyond the original active ingredient patents through secondary patents.¹⁴

While the literature reviewed tarnishes the use of secondary patents, recent research suggests that the larger the share of generic drug sales within a given therapeutic class, the lower the number of new compounds that enter pre-clinical and early-stage clinical trials (Branstetter et al., 2012). The evidence also suggests that the effect varies depending on “cross-molecular substitutability” within therapeutic classes. This would suggest that restricting secondary patenting might dampen investment in R&D on new compounds. That said, while such effects are conceivable in the world’s most important markets for pharmaceuticals, it is unlikely that generic entry in small emerging economies has any incentive effects on drug companies.

Although there is some recent evidence on secondary patenting by originator companies in Europe and the U.S., so far there is no empirical evidence on the effect of secondary patents on the behavior of generics producers and competition, neither in developed nor developing economies.

IV. 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.

For new drugs, the first step in the process is to request a new pharmaceutical product application (Solicitud para el Registro de un Producto Farmaceutico Nuevo). The ISP reviews the application on formal grounds. If the application complies with the ISP regulations, the applicant has to request an assessment of the drug at the pre-admittance unit of the national control department. For registration, product samples have to be provided, as well as detailed qualitative and quantitative formulae, all drug related studies, tests, and documentation on clinical trials.¹⁵ If approved, the applicant can request registration of the drug on the ISP register. Registration of new drugs 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 2011.¹⁶ For these products, the second party to register a drug has to submit studies of bioequivalence. However, because

¹⁴ This finding is reinforced by the fact that the EU Commission has found an increase in effective patent terms in Europe (EU Commission, 2009), which could be partly explained by weaker incentives for generic producers to challenge existing patents in Europe compared to the U.S.

¹⁵ Note that an existing FDA approval or the approval of any other foreign agency does not eliminate the ISP registration requirement.

¹⁶ For a complete list of active ingredients see <http://www.ispch.cl/medicamentos-bioequivalentes>.

most drugs are still exempt from proving bioequivalence, most generics do not necessarily satisfy bioequivalence despite being pharmaceutically equivalent.¹⁷

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.¹⁸

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 a five-year exclusivity period (see also below), in cases where protection is requested by the applicant and granted by the ISP. This means that after this term, generics companies can use the data that was previously submitted for the registration of the new drug, so they do not have to perform any clinical trials on their own. The 5-year limit on exclusivity thus helps avoiding inefficient duplication of expensive and time-consuming safety and efficacy tests.

PATENTS

Pharmaceutical drugs became patentable Chile in 1991 through Law 19.039.¹⁹ 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.²⁰ 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),²¹ pharmaceutical patents were specifically exempted from this provision.²² As we will show further below, this often explains why there is no primary patent but only secondary patents associated with a drug in Chile.

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 20.160.²³ 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

¹⁷ If a generic drug contains the same quantity of the same active ingredient as the originator drug, drugs are said to be pharmaceutically equivalent. However, to prove bioequivalence, additional conditions have to be met (quality, efficacy and safety). In the U.S. for example, generics have to prove bioequivalence to obtain market approval.

¹⁸ In the U.S., existing patents are taken into consideration in drug approval. Generics are not granted market approval if patents on the original drug are still in force, although the generics company may challenge the patent's validity or claim not to infringe the patent. In Chile, a proposal was submitted in 2012 for an amendment of Law 19.039 with the aim to create this type of patent linkage (Boletín N° 8183-03: Proyecto de Ley "Linkage").

¹⁹ Before 1991, Law DL 958 Article 5 established that all pharmaceutical drugs are excluded from patentable subject matter. Note that Chile also joined the Paris Convention in 1991.

²⁰ A specific feature of Law 19.039 is that patents cannot be invalidated after they have been in force for 5 (formerly 10) years (Article 50).

²¹ The provision limited the patent life in Chile for such patents to either the remaining lifetime abroad or 15 years, whichever is shorter.

²² Law 19.039 Transitional Provisions, Article 1.

²³ Law 17.336 in 2010 did not affect the patents contained in our sample.

registration (Law 20.160, Article 53),²⁴ the 5-year data exclusivity mentioned above (Law 19.996, Article 89),²⁵ a Bolar exemption (Law 20.160, Article 49), a softening of restrictions on second use patents (Law 19.996, Article 37e),²⁶ and international exhaustion of patent rights (Law 19.996, Article 49).²⁷

Finally, Chile joined the PCT system in 2009, which facilitates the international filing of patents.²⁸ 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.

V. 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 registrar (prior to 2009) and INAPI (after 2008). 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 rely on 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 mentioning 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).²⁹ Although compounds are usually described by a Markush structure in the patent,³⁰ 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 Appendix A for details).

²⁴ Supplementary patent protection is granted if the grant decision has taken more than five years counting from the application date of the patent or three years counting from the date when examination was requested. Supplementary patent protection is also granted if the sanitary registration takes more than a year.

²⁵ Data exclusivity is only available to new active ingredients. Article 90 of Law 19.039 defines how new active ingredients are distinguished from therapeutic uses, dosages, formulations, combinations, and polymorphs. Article 91 provides exceptions to this kind of protection. For example, when the holder of the information has engaged in conduct or practices declared anti-competitive; on justified grounds of public health, national security, non-commercial public use, national emergency or other extremely urgent circumstances declared so by the competent authority; or when a drug had already been registered abroad for at least 12 months.

²⁶ Prior to the 2005 amendment, new uses of known substances were patentable as long as they solved a technical problem (Law 19.039 Article 37 e) and improved the existing patented invention (Law 19.039 Article 40). Law 19.996 eliminated the improvement requirement (Article 40).

²⁷ Article 49 effectively legalized parallel imports as long as the products were marketed abroad by the patent holder (or with the patent holder's consent).

²⁸ Under the PCT system, applicants file a single application with the World Intellectual Property Organization (WIPO) that is, however, examined separately in each jurisdiction party to the PCT system in which patent protection is sought.

²⁹ The INN is the active ingredient's generic name that cannot be trademarked.

³⁰ A Markush structure describes sets of specific molecules with a common chemical structure.

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. Food and Drug Administration (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.

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 -- still is.

Appendix A 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 2,630 match 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.

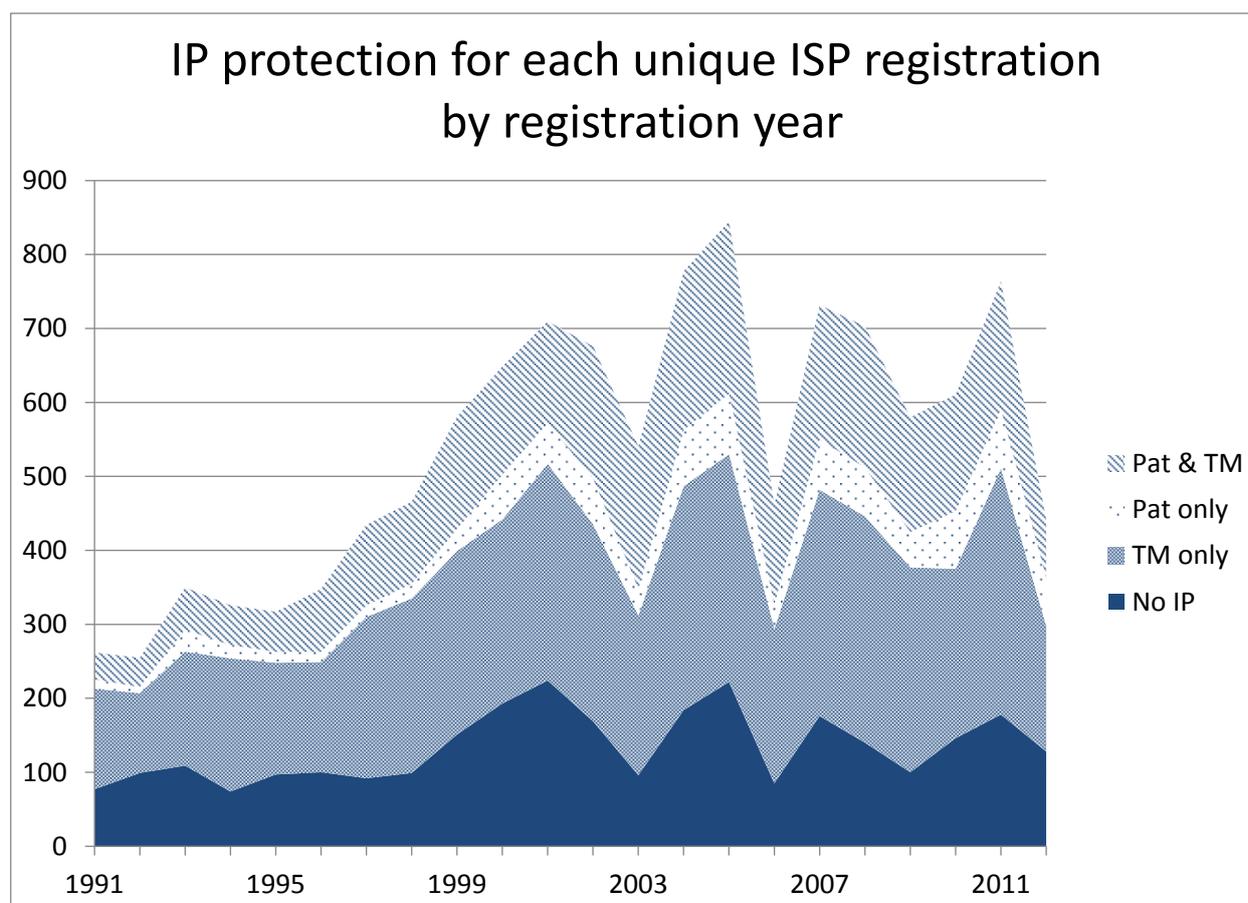
Table 1

	<i>Total</i>	<i>Matched to</i>		<i>Shares matched</i>	
		<i>patents</i>	<i>trademarks</i>	<i>patents</i>	<i>trademarks</i>
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%

VI. RESULTS

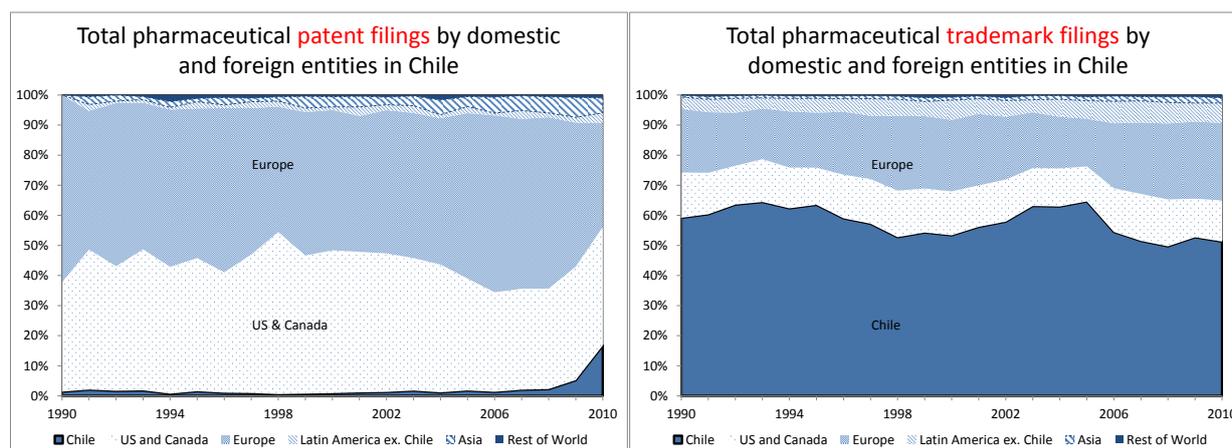
Figure 1 shows the time trends for the unique product-active ingredient combinations. There is a marked increase in the share using patents during the mid-1990s. Also the share relying only on trademarks increases substantially beginning the second half of the 1990s.

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.

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



An examination of the ISP registrants makes the reasons behind this phenomenon clear. Table 2 shows the number of ISP registrants from each region of the world that are listed as performing each type of function when they register at the ISP (a registrant may list several functions for each registration). Clearly Chilean firms do almost all of the importing, distributing, quality control, and local packaging of the drugs, whereas foreign firms are the source, licensor, or foreign packagers. Manufacturing can be done in either location. However, it is fairly clear that foreign firms are the source of originator drugs and therefore hold almost all of the patents, whereas marketing and distribution as well as the production of generics is the province of the Chilean registrants, who therefore hold a large number of Chilean trademarks.

Table 2: Functions performed by ISP registrants by country of origin

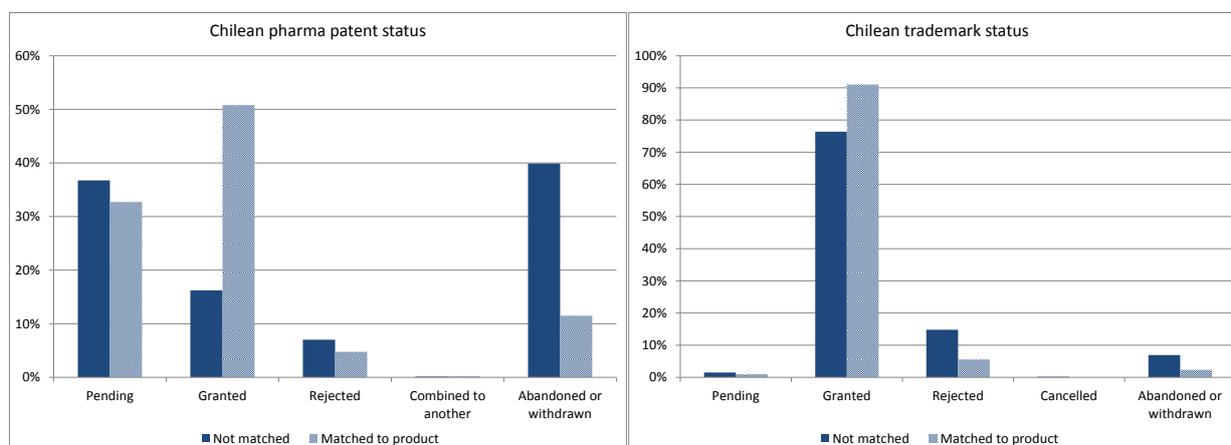
	<i>Chile</i>	<i>Europe</i>	<i>Latin America</i>	<i>US & Canada</i>	<i>Rest of world</i>	<i>Total</i>
Manufacturing	11,719	4,719	5,337	1,155	3,398	26,328
Source, licensor, foreign packager	37	8,731	7,652	2,907	3,971	23,298
Importer, distributor, quality control, domestic packager	37,760	170	158	23	4	38,115

However, note that Latin American countries other than Chile are frequently the source of the drugs (probably at the expense of U.S. firms, judging from the patenting numbers). It appears that some multinationals use one or two Latin American countries (usually Argentina, Uruguay, or Panama, sometimes Brazil or Mexico) as a base for production and distribution throughout Latin America.

Figure 3 looks at the distribution of the status of the patent and trademark applications as a function of whether they have matched to our ISP product list. This figure also shows some interesting differences. Broadly speaking, trademark and patent applications associated with products and active ingredients that have been registered at the ISP are more likely to be either pending or granted, and much less likely to have been rejected, abandoned, or withdrawn. This is not unexpected, but it does suggest that these applications are of more economic relevance than the unmatched applications.³¹

³¹ In the case of patents, matching a larger share of granted patents to the ISP register is to be expected since we checked all granted patents whereas we matched patents that have not been granted only if (a) they protect a new
[Footnote continued on next page]

Figure 3: Legal status of patents and trademarks



Primary versus secondary patents

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. In this paper we rely on the identification of our patents as primary or secondary that was done by internal and external patent examiners at INAPI. 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 significantly lower than the ratio of 1:7 found 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. Of course, this may simply reflect the fact that secondary patents are more often rejected by the patent office precisely because they do not cover a new active ingredient.

The 504 matched patents are associated with 322 of the 2,630 active ingredients. Of these active ingredients, slightly more than one third (185) have at least one primary patent. In about half the cases (89 or 48%), the associated primary patent is the first patent on that ingredient, but in the remaining cases, there is a secondary patent preceding the primary patent. Figure 4 shows the trends in ISP-matched pharmaceutical patent applications for the two types of patents separately. During the 1990s after the introduction of pharmaceutical product patents, both types of applications increase but after 2005 there is substantial decline for reasons unknown to us, although this may reflect the worldwide slowdown in the introduction of new pharmaceuticals.

[Footnote continued from previous page]

active ingredient registered with the ISP for the first time between 2005-2010 or (b) if they match via the Orange Book or the Merck Index (see Section V).

Figure 4: Pharmaceutical patent applications by type

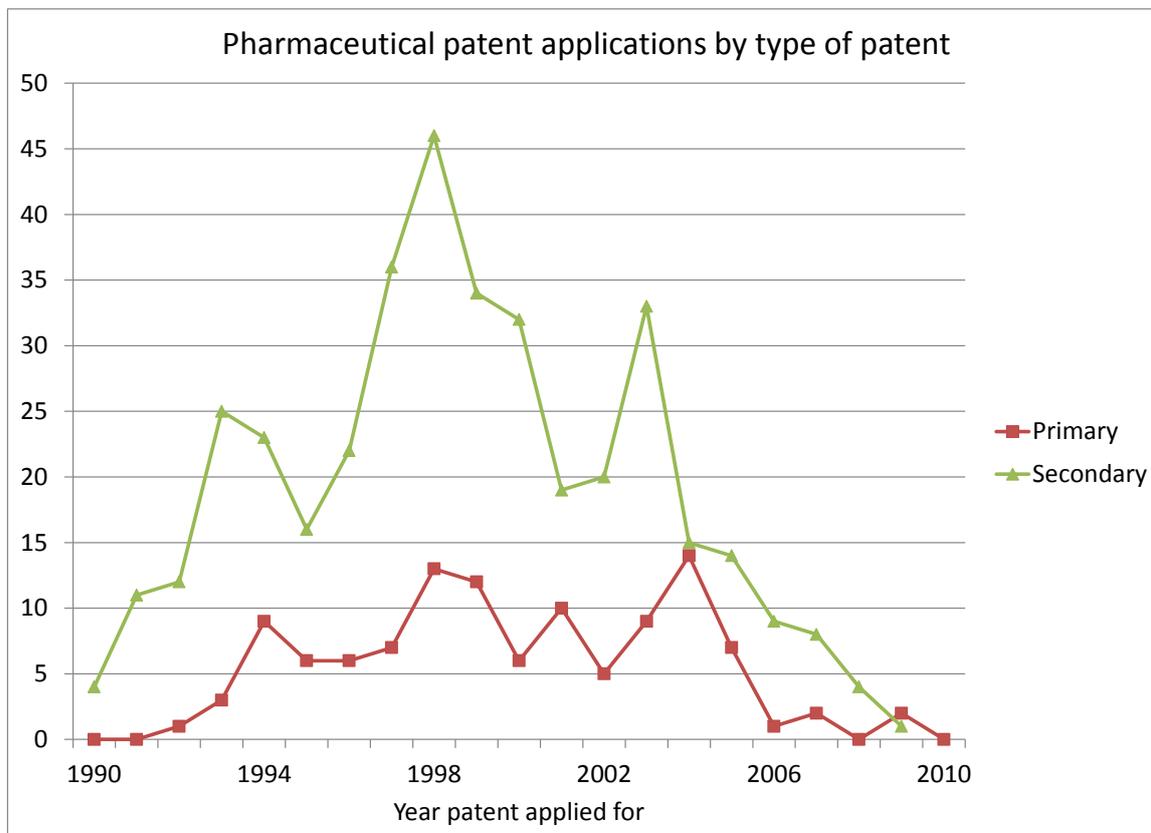
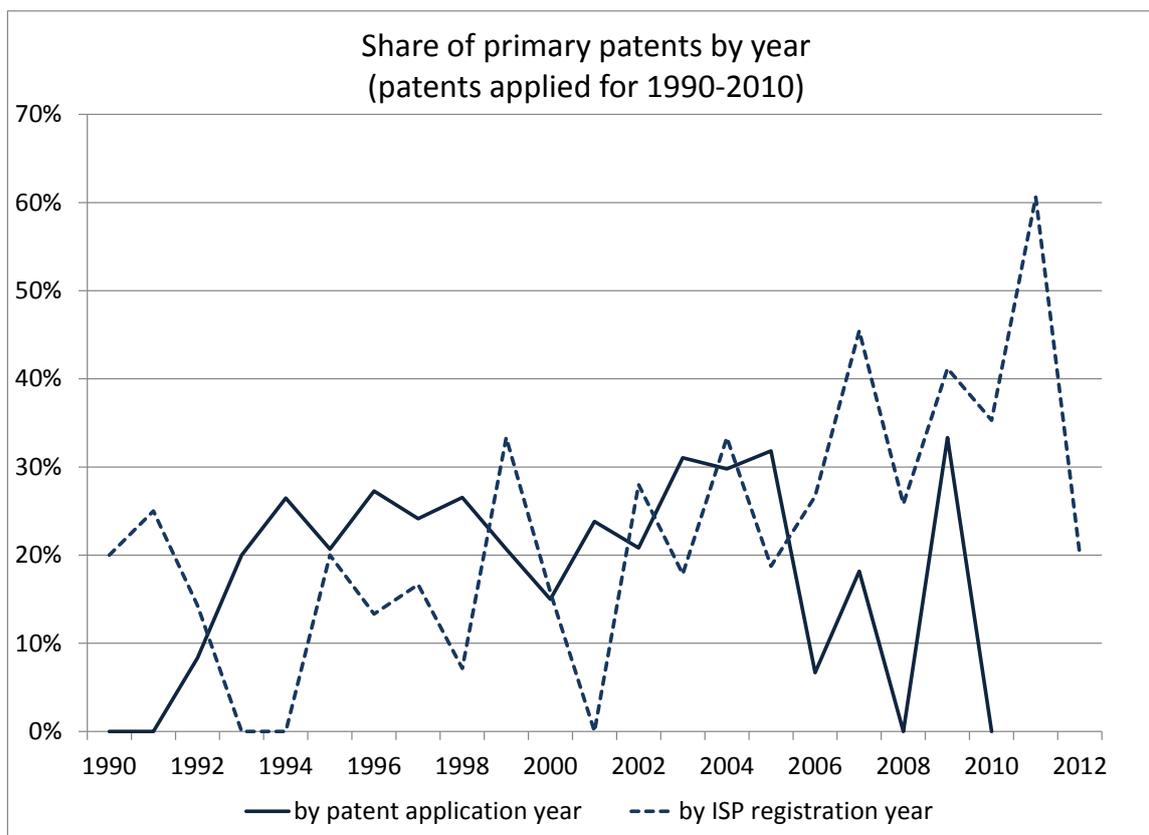


Figure 5 shows the trend in the share of matched patents that are identified as being primary patents in two ways: by the year of the patent application, and by the year of first ISP registration that includes the covered active ingredient. The trends show contrasting results suggesting highly variable lags between a patent application and the associated ISP registration. Although the share of patent applications that are primary declines very slowly over time, the share of patent-related new ISP registrations increases steadily over the period.

Figure 5: Primary patents by patent application year and product registration year



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 6.³² 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.

³² We focus on the 1991-2010 period because pharmaceutical patents were introduced in Chile in 1991 (see Section IV). Note that there are truncation issues at both ends of the distribution. We recomputed the chi-squared for observations with lags between -10 and 10 and obtained a value of

Figure 6: Lag between patent application and product registration

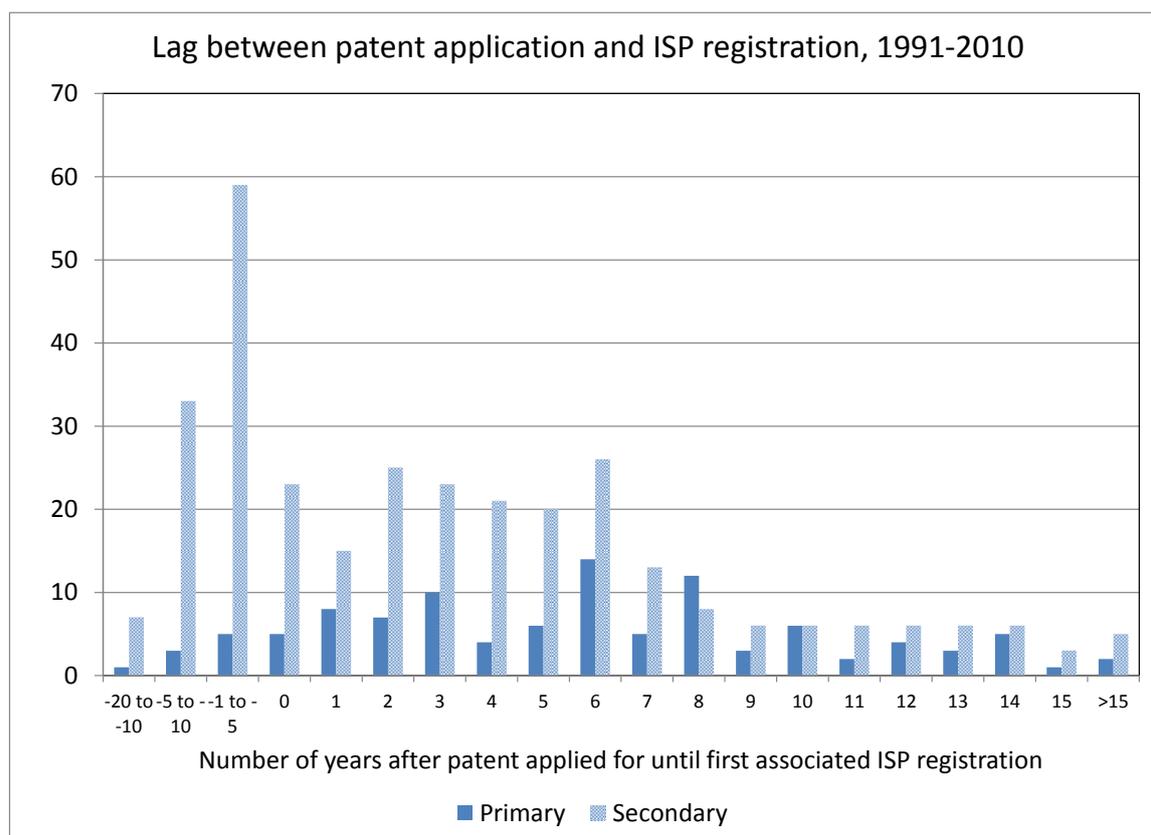


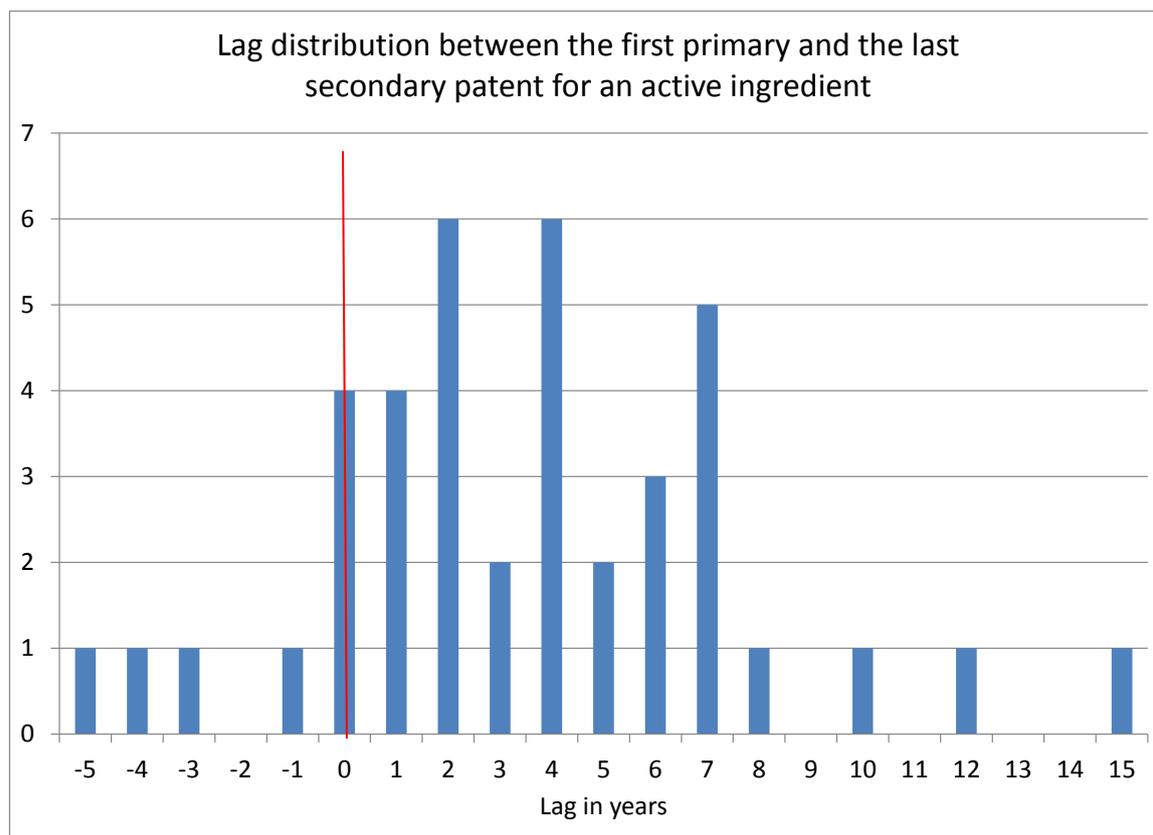
Table 3 looks at the number of patents that protect a given active ingredient. About 55 per cent of the active ingredients are protected by a single patent and 34 per cent of active ingredients that are patent protected are protected by 2 or 3 patents. Very few active ingredients are associated with 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.

Table 3

Combinations of primary and secondary patents				
Number of patents	Number of active ingredients	Shares		
		Primary only	Secondary only	Both
1	176	28.4%	71.6%	0.0%
2	73	11.0%	69.9%	19.2%
3	38	5.3%	60.5%	34.2%
4	16	6.3%	62.5%	31.3%
5	7	0.0%	71.4%	28.6%
6+	12	0.0%	50.0%	50.0%
Total	322	18.9%	68.6%	12.4%

To gauge the effect of secondary patents on potential patent terms extensions, Figure 7 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 7 would suggest that in some cases, companies could gain a number of additional years of patent exclusivity through the filing of secondary patents.

Figure 7: Lag between earliest primary patent and latest secondary patent by active ingredient (active ingredients protected by both primary and secondary patents)



THERAPEUTIC CLASSES

Nearly all ISP registrations include an indicator of the therapeutic class for which the drug is intended. After cleaning and standardizing their names as described in Appendix A, there are 183 distinct classes in 19 broad therapeutic groups. There may be up to 6 of these classes per product, although the majority (two-thirds) of the drugs indicate only a single class. Columns 1 and 3 of Table 4 below 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 4 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 4

Products or active ingredients per therapeutic class				
<i>Class</i>	<i>Number</i>		<i>Share</i>	
	<i>Products</i>	<i>Active</i>	<i>Products</i>	<i>Active</i>
		<i>ingredient</i>		<i>ingredient</i>
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		

Table 5 shows the number of primary and secondary patents associated with each therapeutic class.³³ The shares of primary patents vary considerably: recall that product patents were not available in Chile before October 1991. This means that classes like anti-ulcer which had important patents prior to that date are covered only by secondary patents. In contrast, newer areas like anti-virals and anti-neoplastics (anti-cancer) have a large share of primary patents.

Table 5

<i>Therapeutic group</i>	<i>Number</i>		<i>Share</i>
	<i>Primary</i>	<i>Secondary</i>	<i>Primary</i>
	<i>patents</i>	<i>patents</i>	<i>patents</i>
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-inflammato	7	20	25.9%
immunologic agents	9	13	40.9%
antibiotics/anti-neoplastics	5	17	22.7%
gastrointestinal agents	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 hyperte	1	15	6.3%
bone resorption inhibitors	0	16	0.0%
quinolones	3	12	20.0%
cholesterol absorption inhibit	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	

ACTIVITIES OF CHILEAN FIRMS

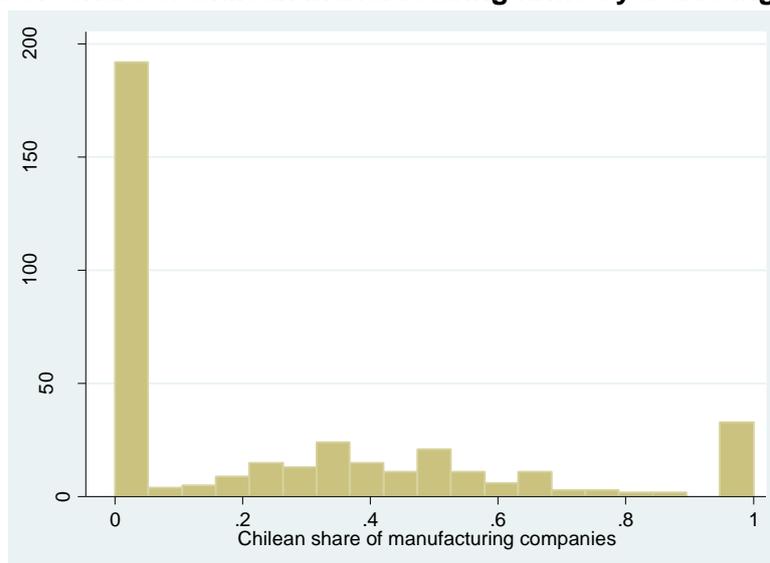
As we report in the appendix, ISP registrations include the function of the various firms attached to the production and distribution of the relevant product. Chilean firms are rarely the source or licensor for a product, which is consistent with their lack of patenting in pharmaceuticals. The only two drugs for which a Chilean firm is listed as the source are the antibiotic Meropenem

³³ There is usually more than one class for a given patent, so the total number of entries in the table is 1,246 rather than 569.

Trihydrate (M Moll Quality Control) and the anticoagulant Warfarin Sodium (Volta Lab), neither of which has associated patents. There are approximately 14 distinct drugs for which a Chilean firm is listed as a licensor: half of these belong to D&M Lab and the remainder to a range of firms including Pfizer Chile. They are largely not patented, as they are predominantly older antibiotics, analgesics, and vitamins.

About 100 Chilean firms are engaged in various kinds of pharmaceutical manufacturing and they are associated with 6,930 ISP registrations. 2,152 of these registrations (31 per cent) are associated with a Chilean patent application and 109 (1.6 per cent) with a primary Chilean patent application. Thus the Chilean firms do not seem to be manufacturing products that are covered by a primary patent, not surprisingly, although they do manufacture products covered only by secondary patents. As we describe in the data appendix, when drugs are registered at the ISP, a number of registrants are supplied, and their functions given. The first four of these functions are those associated with manufacturing of the drug, with 11,718 registrations that include Chilean manufacturing firms and 14,334 registrations that include foreign manufacturing firms. For each of the 381 patent-protected active ingredients, we constructed the share of associated manufacturing firms that were Chilean. This allows investigation of the extent to which Chilean firms are involved with manufacturing patent-protected drugs. Figure 8 shows the distribution of these shares: a large number of active ingredients have no associated Chilean manufacturing firms and a slightly smaller number have only Chilean firm.

Figure 8: Share of Chilean manufacturing firms by active ingredient



In order to investigate the role of Chilean manufacturing further, we regressed the share of Chilean companies on some characteristics of active ingredient patenting: a dummy for whether there was any associated primary patent, the log of the number of associated ISP registrations, and the log of the number of associated patents. The results are shown in Table 6; because of the large numbers of zeros and ones for the share, our preferred estimates are those using the two-limit Tobit model, shown in the second set of columns. They show that active ingredients covered by a primary patent are far less likely to be manufactured by a Chilean firm, which is consistent with the lack of patent ownership. In addition, those active ingredients with a large number of ISP registrations are more likely to be manufactured by Chilean firms, as one might have expected. These active ingredients tend to be generics that have some patent coverage via secondary patents on formulation, delivery type, etc., but the coverage is not really exclusive.

Table 6

Predicting the share of Chilean manufacturing companies for each active ingredient

<i>Method of estimation</i>	<i>OLS</i>			<i>Tobit</i>		
D (any primary patent)	-0.15	(0.04)	***	-0.42	(0.10)	***
Log (number of ISP regs)	0.05	(0.01)	***	0.17	(0.03)	***
Log (number of patents)	-0.01	(0.03)		-0.03	(0.06)	
Year dummies	insignificant			no		
Standard error	0.304			0.635		
R-squared	0.166			0.109		

381 observations

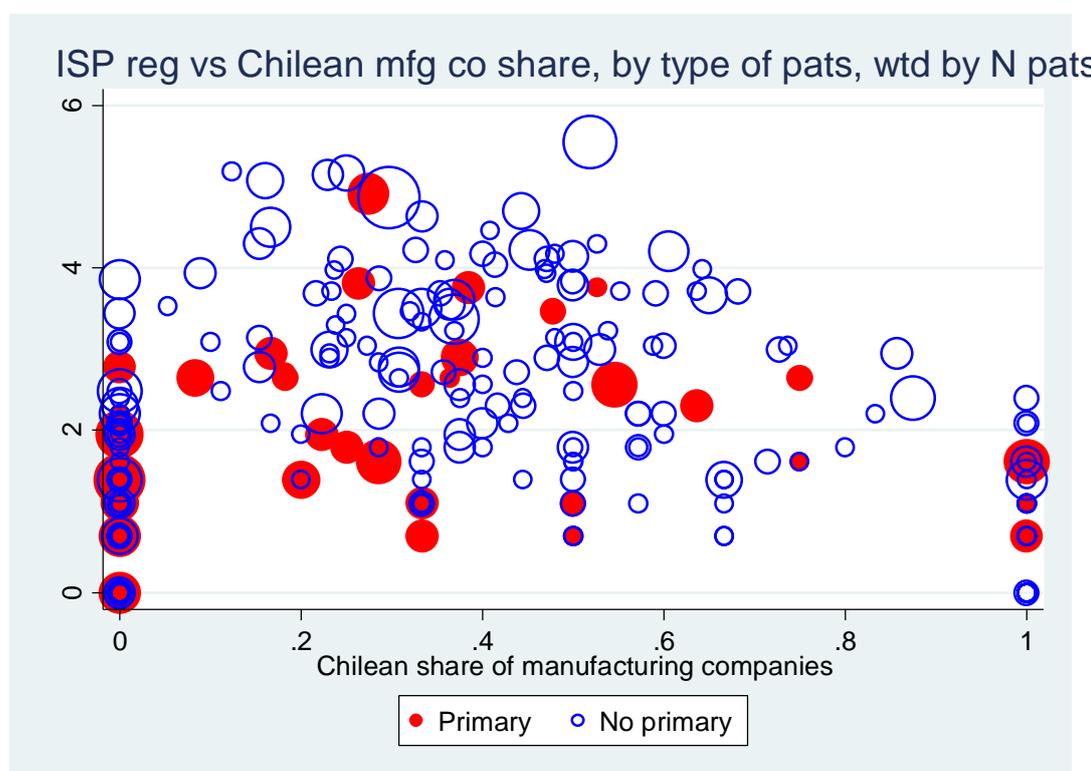
Coefficients and standard errors robust to heteroskedasticity are shown.

*** denotes significance at the 0.001 level.

The year dummies are for the year of the first associated patent application.

Figure 9 combines information on companies that are engaged in pharmaceutical manufacturing, their corresponding ISP registrations (products), and the patents that protect the active ingredients contained by these ISP registrations. The figure distinguishes between active ingredients with at least one primary patent and others. It shows that most active ingredients that are patent-protected are protected only by secondary patents. The figure also shows that Chilean manufacturers account for a substantial fraction of manufacturers of drugs associated with a given active ingredient protected only by secondary patents. This is less the case for products that contain active ingredients that are protected either only by primary patents or by a combination of primary and secondary patents. In both cases, most drugs that contain such active ingredients are exclusively manufactured abroad.

Figure 9: Primary vs secondary patents and products vs share of Chilean manufacturers



VII. CONCLUSION

The objective of our study is to take a first look at patenting of pharmaceuticals in Chile, with a particular focus on the distinction of 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. Chilean pharmaceutical companies have only recently begun to obtain market approval for a few patented drugs. Overall, we find that only a subset of drugs with market approval is protected by patents, a much larger number of products is protected by 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 is protected only by secondary patents. It would be interesting to explore to what extent this is due to the fact that the 1991 law did not allow companies to obtain patent protection in Chile for active ingredients that had been patented before abroad. This question is particularly interesting as we also provide some tentative evidence that among all patented active ingredients, Chilean pharmaceutical companies are more active in manufacturing of drugs that contain active ingredients that are associated only with secondary patents.

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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APPENDIX A: DATA CONSTRUCTION

This report 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; and
3. A database of all trademark filings at the 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.³⁴ 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.³⁵ Of these, 2,630 contained an active ingredient that had not yet appeared in an ISP registration. 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.

³⁴ E.g., pentahydrate recorded as 5-hydrate on occasion. Calcium spelled out or recorded as the Chemical symbol Ca.

³⁵ 439 (3%) of the registrations were missing the ISP registration date and are not included in these figures.

Figure A1

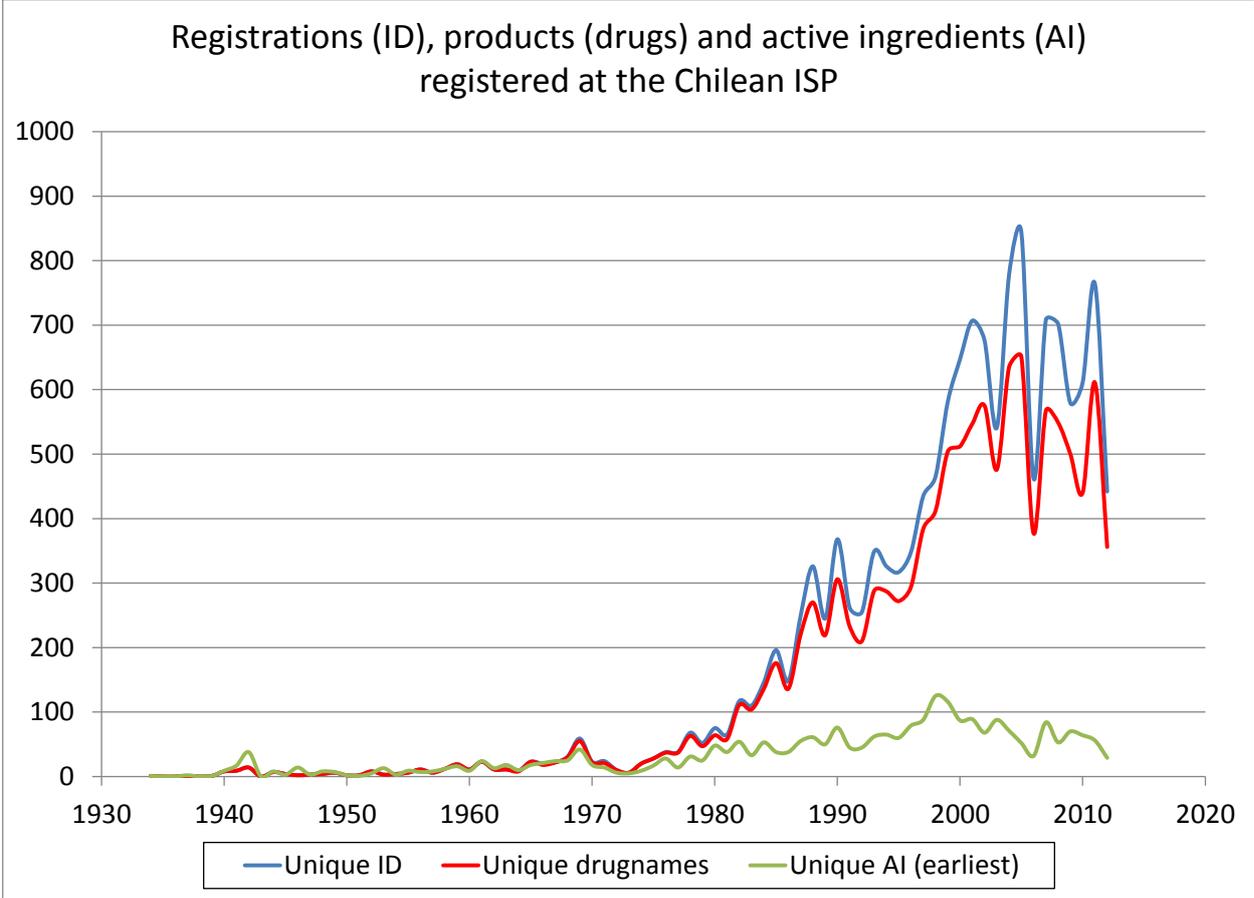


Figure A2

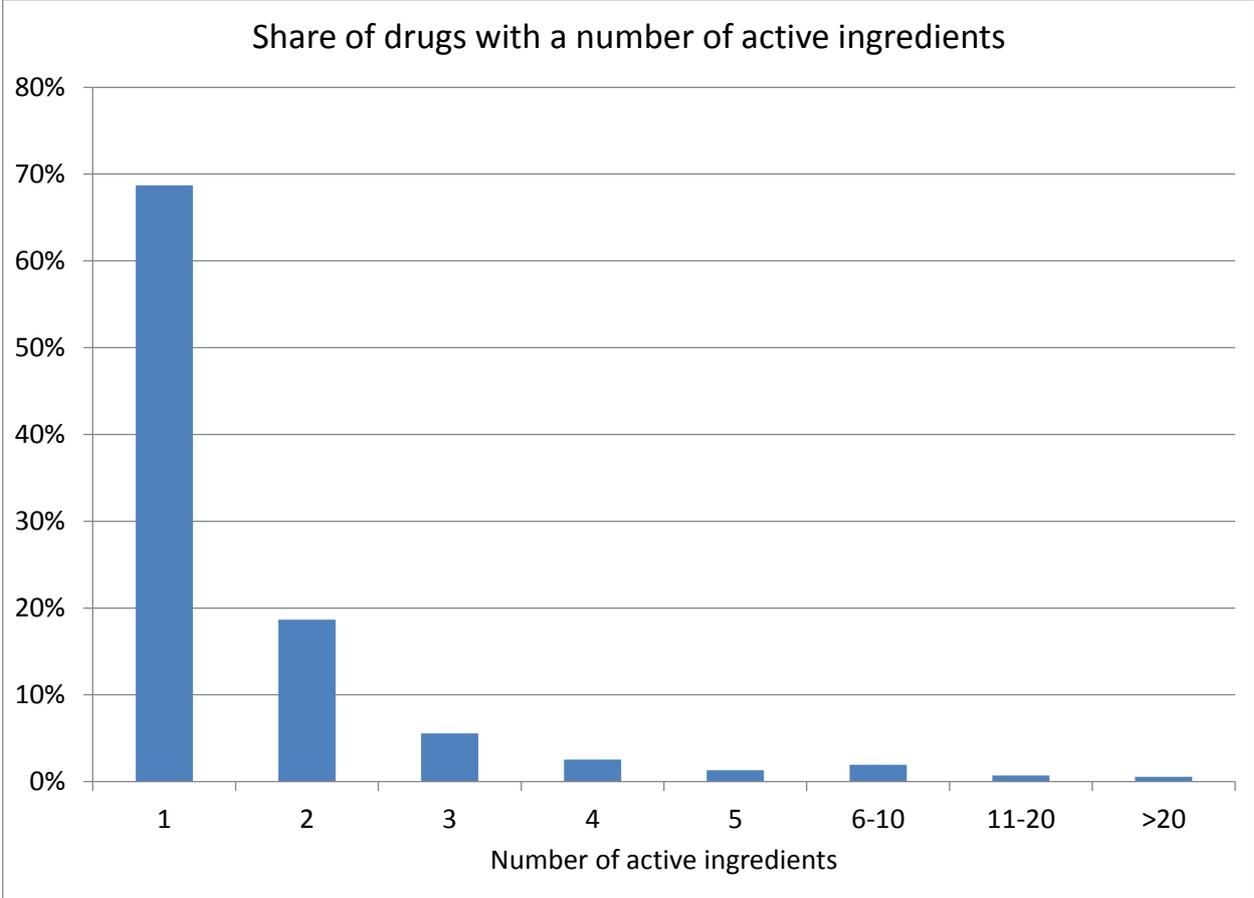
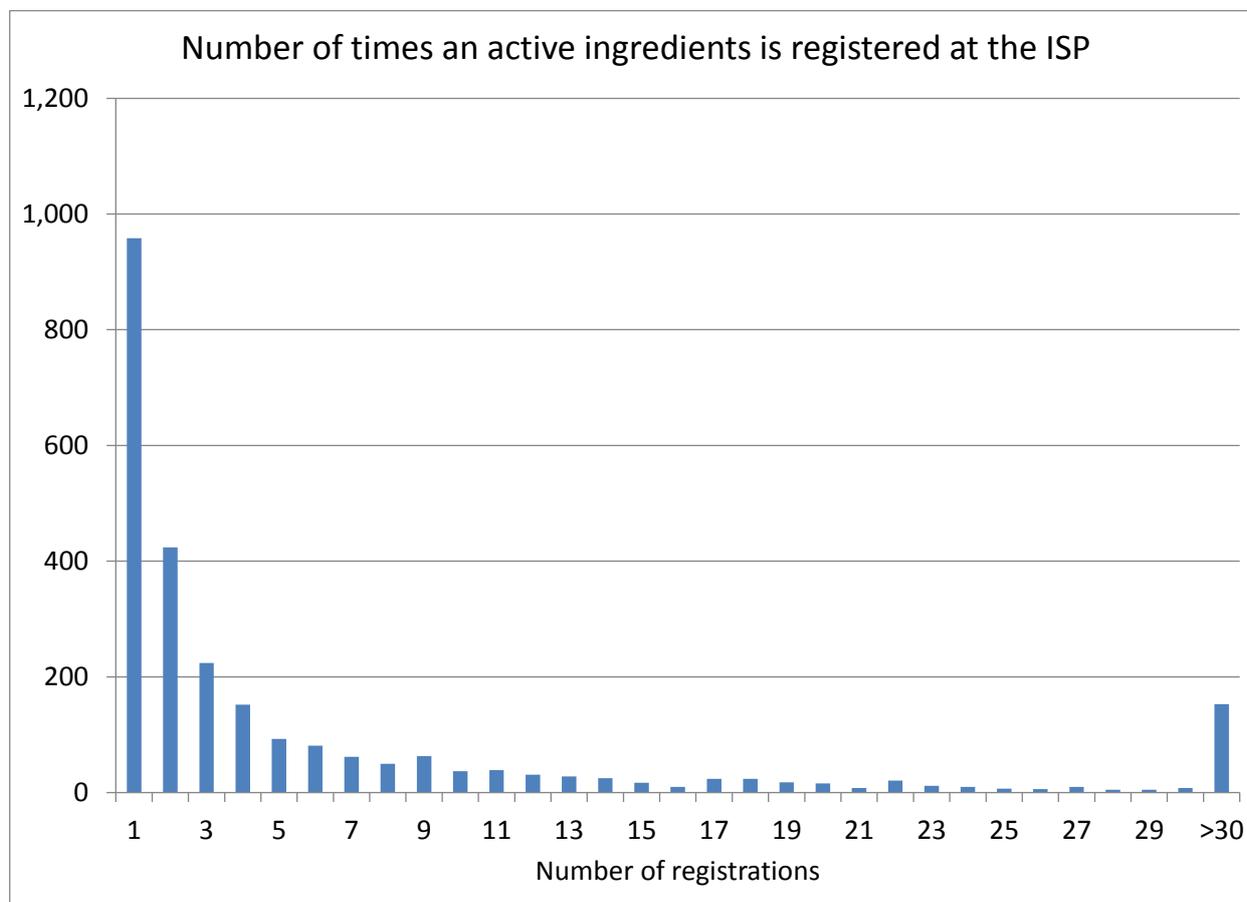


Figure A3



ISP registrants

The ISP database contains the names and addresses of organizations that are registering the product, but of course they are not standardized.³⁶ Our first step was to standardize the names by removing such things as “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 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.

³⁶ 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.

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.³⁷ 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

<i>By firm-country</i>				<i>Weighted by the number of ISP regs per firm</i>			
<i>Country</i>	<i>Number</i>	<i>Share</i>	<i>Cum. Share</i>	<i>Country</i>	<i>Number</i>	<i>Share</i>	<i>Cum. Share</i>
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.

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

³⁷ Note that almost all of the organization names are in fact firm names, with a few individuals and universities in addition.

(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

	<i>Chile</i>	<i>Europe</i>	<i>Latin America</i>	<i>US & Canada</i>	<i>Rest of world</i>	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)³⁸ classification whereas patents rely on the International Union of Pure and Applied Chemistry (IUPAC)³⁹ 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.⁴⁰ 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 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 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.”

³⁸ The INN is the official nonproprietary or generic name given to a pharmaceutical substance designated by the World Health Organization (WHO).

³⁹ This organization names new compounds according to the rules of organic chemistry.

⁴⁰ 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.

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.⁴¹ 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.⁴² 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, 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).⁴³

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.

⁴¹ 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.

⁴² 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.

⁴³ The search for additional matches to the ISP ingredients in these 3,000 granted patents yielded 70 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.

The match between drug names on the ISP and these various patent data bases yielded 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 too surprising, because many of the patents in these classes are associated with agriculture or aquaculture.

Table A3

	<i>Number of patents associated with</i>			<i>Number of trademarks associated with</i>			<i>Number of ISP reg. associated with</i>	
	<i>ISP registration</i>	<i>Product name</i>	<i>active ingredient</i>	<i>ISP registration</i>	<i>Product name</i>	<i>active ingredient</i>	<i>patent*</i>	<i>trademark**</i>
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**

<i>Patent status</i>	<i>Number</i>		<i>Share</i>		<i>Share matched</i>
	<i>Not matched</i>	<i>Matched to AI</i>	<i>Not matched</i>	<i>Matched to AI</i>	
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 drugnames 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.⁴⁴ 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.

⁴⁴ 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 A5

Number of trademarks matched, by Nice class

<i>NICE class</i>		<i>Number</i>		<i>Shares</i>	
		<i>All</i>	<i>Without renewals</i>	<i>Number</i>	<i>Without renewals</i>
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.

Table A6

Chilean pharma trademark status

	<i>Not matched</i>	<i>Matched to product</i>	<i>Not matched</i>	<i>Matched to product</i>	<i>Share matched</i>
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.⁴⁵ 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.

Table A7

<u>ISP registrations by therapeutic group</u>	
<i>Broad therapeutic group</i>	<i>Number</i>
allergens	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

⁴⁵ There may be as many as 4 classes per registration, although most have only one or two.

Table A8

ISP registrations by therapeutic class

<i>Standardized therapeutic class</i>	<i>Number</i>
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

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