Study on free market and competition in the expired-patent drug markets in Mexico

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ACKNOWLEDGMENTS

The Federal Economic Competition Commission (Cofece) appreciates all contributions received from the Federal Commission for Protection against Sanitary Risks (Cofepris), the Mexican Industrial Property Institute (IMPI), the Mexican Social Security Institute (IMSS) and the Ministry of Health; the Mexican Association of Interchangeable Generics Manufacturers (Amegi), the Mexican Association of the Pharmaceutical Research Industry (AMIIF), the National Medications Manufacturers Association (Anafam), The National Pharmaceutical Industry Chamber (Canifarma), the Ethics and Transparency in the Pharmaceutical Industry Board (Cetifarma). It also thanks consultant Eduardo González Pier and his team: Mariana Barraza Lloréns and Héctor Peña Baca, for their support in the preparation of the document.

Special thanks to the contribution by Nielsen Mexico & Nielsen Ibope Mexico, and its CEO, Armando Uriegas, for their help in preparing a questionnaire whose main purpose was to gauge the degree of trust that Mexicans have in generic drugs. 6,260-household were selected to participate in this study.

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EXECUTIVE SUMMARY

I. Background

The Plenary Session of the Federal Commission of Economic Competition (Cofece) ordered this study[1] considering the relevance of the market for drugs for the population´s well-being, the national economy[2] and the expenditure by the households.[3] The objective is to answer whether the market for drugs is working properly, efficiently and whether it fosters economic competition, once patents expire.

Patents are important because they stimulate the introduction of better drugs into the market. When granting the right to innovative laboratories to exclude others from the exploitation of the patented invention,[4] for a non-extendable period of 20 years, they incentivize the development of better products. But once the patent expires,[5] other laboratories may produce and trade generic versions, which, theoretically, may discipline the market and make drugs available to a larger public, at a lower price.

Generic drug products may be divided into branded generic drugs, (i.e., those identified by their commercial or distinctive name), and unbranded generic drugs (which are commercialized under the generic name that indicates the active substance[6] contained in the product). Additionally, drugs may be classified by the number of suppliers: those having a single supplier are called single-source, and those having more than one supplier in the market are called multiple-source. Those of single source may be

1 At the session of July 7, 2016 and based on article 12, fraction XXIII, of the Federal Act on Economic Competition (LFCE) and article 5, fraction XVIII, of the Organic By-Laws of the Federal Commission of Economic Competition.

2 In 2015, for example, the pharmaceutical industry accounted for 0.5% of the Gross Domestic Product (PIB) national wide and 2.7% of the manufacturing GDP, according to calculations from the information of the Bank of Economic Information of the National Institute of Geography and Statistics (INEGI). Available in: http://www.inegi.org.mx/sistemas/bie/.

3 According to the National Survey of Income and Expenditure of Homes 2014 released by INEGI, the share of expenditure onn drugs (prescribed, without prescription and healing material) accounts for 29% of the expense on health care.

4 The one known as innovative drug product is the original or first version of a pharmaceutical product or drug product. Usually developed and patented by the manufacturer that created it and that, then, holds exclusive rights produce it and trade it for a certain time period.

5 The same drug may have more than one patent related to it.

6 Substance contained in a drug and which is recognized as the one giving it its therapeutic effect.

protected by a patent or they may have expired patents and, still, be produced by a single supplier.[7] On the other hand, generic drugs, along with the innovative drug with expired patent, comprise the multiple-source drugs group.

To get sanitary authorization, and be able to commercialize the drugs, the generic versions should contain the same active substance and pharmaceutical form, with the same concentration, in addition to using the same route of administration as the original reference drug product; and it must be verified by means of regulatory tests required by the Federal Commission for Protection against Sanitary Risks (Cofepris).[8]

II. Contents

The present study analyzes the degree of competition in the private drug markets once the patent of the original drug expires. Different competition level measures were examined, such as the degree of competition and the speed of entry into the market of generic drugs, as well as their capacity to reduce prices.

At the same time, regulatory factors that may hinder the entry of generics, as well as those related to the incentives of the agents to abuse the legal system in order to extend their *de facto* exclusiveness in the market were also analyzed. The former includes: those linked to sanitary authorization, as well as those from the industrial property system itself and the prevailing law on prescription of drugs. And, the latter, strategies that may be used by laboratories, and which show some potential to deter the entry of competitors. Consideration was given to the possibility of low sensitivity of the demand to price reductions.

The study also includes aspects related to the consolidated purchase of drugs. In this regard, possible risks to economic competition were also identified using the empirical evidence collected; based on the analysis, several measures to mitigate them were proposed.

III. Main conclusions and recommendations

The study found competition problems in the markets for drugs with expired patents, identifying failures, both from the government and from the market itself, which prevent their complete efficient functioning. Among them, the ones that stand out are:

7 They include the orphan drugs, aimed at the prevention, diagnosis and treatment of "rare diseases" (also known as Little common, minority or Little frequent diseases), which are present in no more than five people for every 10 thousand inhabitants, because, due to their low production scale, it is not profitable to have the presence of more than one company in the market.

8 Art. 2, fraction XIV Bis of RIS states that the reference drug product is the one indicated by the Ministry of Health as such, which has the registration by said agency, which is commercially available and it is selected according to the criteria established in the Mexican Official Standards. The bioequivalence studies are the main tool considered to demonstrate, in short, that a generic drug product complies with the same characteristics of quality, security and efficacy as the reference drug product.

There are drugs with expired patents that face no competition, even when there are economic agents who got sanitary authorizations.[9]

- For four out of ten drugs analyzed, there are no versions in the market, although the patent is already of public domain, remaining single-source.

The entry of generic drugs into the market is late and slow:

- In Mexico, it takes, on average, more than two years between the expiration of a patent and the launch into the market of the first generic product; while in the United States, the generic product is introduced almost immediately, for the most widely sold drug products, and seven months in the European Union.

- Delays in the entry into the market show that the Bolar clause is not being fully used. This clause allows a manufacturer of generic drugs to request and start the paperwork to acquire a sanitary registration (including the necessary submission of bioequivalence tests), up to three years before the innovative drug's patent expires.

Generic drugs do not pose enough competitive pressure:

- In Mexico, after one year of the patent expiration, the average number of competing generic versions is 2.8 per original drug; while in the US this number is , for the most widely sold drugs.

- In Mexico, two years after the entry of the first generic , the penetration of generic drugs reaches 21.4% of the market, while in countries such as the United States, it reaches 89%, in Canada 74% and in the Netherlands 62.1% in the same period.

- Six months after the entry of the first generic product, the average price of generic drugs is 20% lower than the original drug, and 28.6% 24 months later. This difference, however, is less than what is observed in other countries; for example, in the European Union, the price reduction is of 40% at the 24 months mark.

Benefits for the consumer from better market performance:

- Should there be competition conditions like those existing in other nations, Mexican families may save around 2,552 million pesos per year on drugs thanks to a higher penetration of generics. This would happen, for example, if at the 24 months of the introduction of the first generic drug, the degree of penetration of generic versions in Mexico were twice as much as the one that is currently observed.

9 The sanitary registration is a necessary condition —but not sufficient—, for a drug product to be traded in the market, and that it is available for the consumer.

Strategies that laboratories use as an obstacle to the entry of generic drug products:

- Investigations regarding competition, which have been carried out in other countries, show that some laboratories adopt several strategies to delay or stop the entry of generic drug products. For example, several patents are granted for the same active substance, which increases the costs to third parties to enter the market. There may also be abuse of judiciary actions to deter potential competitors; among other activities.

- In Mexico, at least 22 drug products with several competition problems were identified; the main problems include: the absence of generic versions and the existence of disputes due to patent infractions.Annual sales for these drugs are estimated at around 6,285 million pesos.

Obstacles to competition conditions related to the industry regulations:

- The current health legislation restricts the possibility of substituting branded drugs for generics when the physician does not write down the generic name in the prescription.

- There is a lack of transparency in the linkage between the patent system and the procedures for sanitary registration of generic versions. This is because, unlike the systems in the United States and Canada, in Mexico there is no instrument that directly relates the reference drug products, by distinctive name and presentation, with the patents.

- There is a lack of public, updated, and complete information on the approved sanitary registrations, as well as information allowing to measure the deadlines to reach a resolution on sanitary registration applications and the extensions to health registration.

In order to strengthen the competition conditions in the market for drug products with expired patents and attain the full benefits of competition provided by generic drugs, COFECE recommends modifying the regulatory framework, as well as to encourage public policies in the following ways:

1. **Make the linkage system more transparent and reduce disputes whose aim is to delay the entry of generic drugs.** Innovative laboratories may extend the market exclusivity for their products by abusing judiciary procedures, and so, hinder the entry of generic drugs into the market. Therefore, it is important to establish clearer rules for the linkage system, thus limiting the roomfor discretional decisions and closing windows for disputes that are just aimed at stopping the entry of competitors. Moreover, assessments must be conducted on the convenience of including in the Regulation of the Act of Industrial Property, restrictions on granting some types of patents which are bound to be used in an abusive way by its holders, blocking the entry of competitors. All of this should be done following best international practices.

2. **Improve quality of information and promote the immediate entry of generic drug products.** The lack of certain specific information generates search costs and creates conflictive situations between innovative laboratories and laboratories of generics, resulting in lawsuits, delaying the entry of generics. This is why, it is recommended to implement actions that increase public access

to the following relevant information: specific duration of the process, complete and updated information that allows to identify the universe of drugs with valid health registrations and their main characteristics, as well as information on patents that protect the approved reference drugs. Furthermore, in order to incentivize the expedite entry into the market of generics, it is fundamental to promote the use of the "Bolar" clause and periodically publish the list of innovative drugs whose patent shall expire in the three following years.

3. **Eliminate obstacles to the entry of generics caused by regulations.** Reform the Regulation of Health Supplies (RIS) so that: i) the physician has the obligation of writing the generic name of the drug in the prescription; ii) the pharmacist may disclose to those interested, the generic drug products which are available; and iii) allow, in case of drugs of chemical synthesis,[10] the use of generic drugs (brand and non-brand), as long as they contain the same active substance, concentration and route of administration, and the physician does not prohibit it, expressly, in the prescription and that it is performed by a certified pharmacist.

4. **Promote the demand for generic drug products.** From a survey administered to 6,260 Mexican families, it was found that, even if most surveyed people are aware of the existence of the generic drugs, 53.9 % considers that their quality is regular and 14.5% have little trust in their consumption. In order to increase trust in generic drugs, the Ministry of Health may develop communication strategies aimed at physicians and families to increase trust on the quality of generic drugs.

5. **Remove obstacles related to the public purchase of drugs.** It is important to improve the purchase and payment times of drug products by the public sector, since it promotes the entry of small and medium-size laboratories that sell generic drugs to the health sector; this would, in turn, encourage increased production levels with the necessary scale for a larger entry and competition of generic drugs in the private market.

IV. Final remarks

This study may be taken as a first approximation by Cofece, to evaluate the functioning —from the competition point of view— of markets for drugs with expired patents in Mexico. In this study, evidence and punctual recommendations, aimed at public authorities to encourage actions that promote competition in the markets, were presented.

Worldwide, the pharmaceutical industry is one of the most regulated by the governments, due to the need to guarantee the safety, efficacy and access to drugs by the population. The analysis presented here, found different ways in which competition can be improved in this sector. Furthermore, it was found that if the level of competition were similar to that of other countries, consumers would save 2,552 million pesos per year on average. Better conditions of competition would provide the population with more options, with products of better quality and at better prices, for the benefit of all.

10 Chemically synthesized drugs are characterized by being small, fixed-structure molecules.

LEGISLATED MANDATE

The Federal Economic Competition Act (LFCE), Article 12, Section XXIII, empowers the Federal Economic Competition Commission (Cofece or Commission) to conduct studies, research works and general reports regarding the free market and economic competition. Based on Article 5, Section XVIII, of the Organic Statute of the Federal Economic Competition Commission, the Plenary of the Commission ordered a study on free market and economic competition in the expired-patent drug markets, per agreement CFCE-181-2016 adopted at a July 7 2016 meeting.

This study falls in the scope of the Cofece's 2014-2017 Strategic Plan, that establishes that studies are one of the main tools for encouraging competition and whose main purpose is:

i. To recognize priority sectors/subsectors, those with the greatest influence in economic growth, generalized consumables, the disbursement by low-income population, those with broad impact on other sectors and those with restrictive interventions or regulations, so Cofece can put all its effort into them.;
ii. To identify competition problems and the most efficient course of action to solve/mitigate them;
iii. To strengthen and broaden the proactive efforts by the Commission in identifying and attending competition problems in prioritized sectors.

The Commission, in said Plan, has also established six criteria to define those sectors/subsectors which should be a priority in each period. Based on these, the Plenary of the Cofece has ordered this study, without this implying neglecting competition problems in other sectors. Pursuit and publication of this study does not presuppose any potential violations to the LFCE.

1. INTRODUCTION

The drug market[11] is relevant due to its effects on life expectancy and the welfare, along with its importance in the domestic economy[12] and household expenses.[13]

In order to ensure the safety, efficacy and access to medications, the pharmaceutical industry is one of the most regulated worldwide.

One way to categorize medications is by the number of suppliers —those with a single supplier are known as "single source" and those with more than one supplier are known as "multiple source". Single-source may be protected by a patent (innovative medications[14]) or have expired patents, but are still being produced by a single supplier.[15]

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11 The General Health Act (Article 221, Section I) defines medication as *"A substance or mixture of substances of natural or synthetic origin with therapeutic effects (preventive or rehabilitating) in pharmaceutical form and which is identified as such in view of its pharmacological activity, physical, chemical and biological characteristics. Where a product contains nutrients, it will be considered a drug, provided it is a preparation individually or jointly containing: vitamins, minerals, electrolytes, aminoacids or fatty acids, in concentrations greater than those in natural foodstuffs and is presented in any pharmaceutical form as defined and the instructions of use anticipates therapeutic, preventive, or rehabilitating effects."*. New Act published in the Official Gazette of the Federation (OGF) on February 7 1984. Latest amendment published in the Official Gazette on January 27 2017.

12 In 2015, for instance, the pharmaceutical industry accounted for 0.5% of the Gross Domestic Product (GDP) and 2.7% of the manufacture GDP according to calculations performed as of the information of the Bank of Economic Information of the National Geography and Statics Institute (INEGI). Available at: http://www.inegi.org.mx/sistemas/bie/. Also, by 2016, the value in the drug market in México was estimated in about 200 billion pesos. http://www.inegi.org.mx/sistemas/bie/.

13 According to the 2014 National Survey on Income and Expenses published by INEGI, the share of the disbursement for medications (prescription medications, OTC, and healing material) accounts for 29% of the disbursement in healthcare.

14 An innovative drug is the original version or most primary version of a pharmaceutical product or drug. Usually developed and patented by the manufacturer that created it and who, thereby, holds exclusive rights to produce and market it during a certain period of time.

15 Among these are orphan medications, aimed to prevention, diagnosis, and treatment of "strange diseases" (also known as rare, minority, or infrequent diseases), present in no more than five people per 10 thousand inhabitants, since due to their low production scale, the presence of more than one company in the market is not profitable.

Most of the volume (98.5%) and value (84.8%) of drug sales in the Mexican market have no patent, including original products —innovators—,[16] that once enjoyed that protection.[17] In other words, innovative medications with a current patent[18] represent only 1.5% of the market volume, although, in value terms these are equal to 15.2% of the total.[19]

Patents allow the innovative laboratory to sell new medications, exclusively, for a non-extendable 20-year period. Patents allow innovative laboratories to recover their R&D expenses, as well as obtaining additional return on their investment. Therefore, these are a useful tool to encourage innovation.[20] The result promotes dynamic efficiency, generating new and better products down the road, for the granting of the patent entails the requirement of disclosure of information. This favors diffusion of knowledge once the patent has expired.[21]

Nevertheless, the patent system may produce distortions in the short term. These are a consequence of the loss of efficiency produced by monopoly prices. Patents, thus, imply an exchange between static inefficiency of the monopoly and dynamic efficiency produced by the innovation of products.[22]

Upon expiration of a patent for an innovative drug[23], other laboratories may produce and market that drug which until then was protected. These new medications are the generic version of the original and have the same therapeutic effect. In order to obtain the health registration to market, generics they must comply with all interchangeability tests[24] required by the Federal Commission for Protection against Sanitary Risks (Cofepris); that is, they shall have proven that their dissolution profile or their bioavailability[25], as the case may be, are equivalent to those of the innovative drug or product of reference.

It would be expected that, upon expiration of the patents and with the entry of generics, the drug market would go from a monopoly-like structure to one with a high degree of competition. In this sense, there is an intertemporal exchange between the regulation of the rights to industrial property (which encourages innovation) and competition and static efficiency (which equals a price at marginal cost

16 Section 2.2 discusses the topic of absence of competition among generics for those medications with no patent. In the same, it is shown that there is a significant percentage of medications with an expired patent for which no generics are available.

17 Barraza Lloréns M. and Guajardo Barrón V. (2013).

18 Those whose active ingredient (new molecule), formulation, or condition of use has a patent for its development (usually worldwide).

19 Barraza Lloréns M. and Guajardo Barrón V. (2013).

20 Encaoua et al. (2012)

21 World Intellectual Property Organization (2016).

22 Maybe another adverse effect would be that derived from patent races. These may create certain duplication of resources aimed to investment in R&D.

23 Section 3.1 explains that the same drug may have more than one patent associated with it.

24 Article 72 of the Rules of Health Suppliers (RHS). Published in the Official Gazette on February 4 of 1998. Latest amendment published in the Official Gazette on March 14 2014

25 Bioavailability is the degree to and the speed at which an active form (the drug or one of its metabolites) gains access to the circulation and thus reaches its place of action.

upon the patent expiration). In the aggregate, the entry of generics in the market brings static efficiency back to them - once innovations have been made and financially exploited. There lies the importance that generic drugs enter the market without unnecessary or unjustified delays.

Generics - along with the innovative drug with an expired patent - form the group of multiple source medications. Generics are categorized by their trademark name under branded generics (under a distinguishing designation) and brandless (under the name of the active substance[26]).
The prices of innovators and branded generics are, on average, seven times higher than the brandless ones - the cheapest drug option in the market.[27] Thus, the array of options and prices available for patients is widened as generics gain access - faster and in higher volume - to the market. This increases the chances for healthcare, in turn, reducing disbursement by the families. Entry is also fundamental to contain public disbursement on medications.

Over the last few years, the penetration level of generics has increased:[28] As a proportion of sales volume,[29] its share went from 84% in 2011 to 88% in 2015.[30] In terms of sales value, the share went from 44% to 49% over the same period.[31] When considering only the private market[32], its share in terms of sales volume increased from 62% in 2011 to 71% in 2015 and, as to sales value, it increased from 38% to 43% over the same period.[33]

For illustrative purposes: A study by the Organization for Economic Cooperation and Development (OECD), with data from 2013, shows that in countries with the highest consumption of generic drugs, the United States of America (US), the UK, Chile, and Germany, the share for this type of medications in its pharmaceutical market, was at least 80% greater than the 71% in Mexico (by volume).[34]

The main question addressed in this study is whether the drug market is working properly, in terms of efficiency and economic competition, once their corresponding patents have expired. With regards to this, potential risks on free participation and economic competition, based on the empirical evidence collected are identified and potential mitigation actions are proposed.

Among the potential cases to be examined are those derived from the very structure of the markets; any restrictions to entry or expansion of generic drugs; any circumstances that might give rise to conducts aiming at extending the protection period for patents, and the poor response from consumers in the face of changes in supply of medications, among others.

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26 Substance included in a drug and which is recognized as the one that generates its therapeutic effect (See Glossary)

27 Barraza Lloréns and Guajardo Barrón (2013).

28 This can be explained, at least partly, through the reduced price of generics with respect to the original.

29 It considers both the public market (purchases by the public sector) and the private market (sales through drugstores and private hospitals).

30 AMIIF (2016).

31 This increase is the result both of higher penetration of generics existing in the market and of the entry of new generics for expired-patent medications.

32 In this study, "private market" is understood as the sales of medications performed at drugstores and private hospitals; (i.e., are not considered purchases by the public sector).

33 AMIIF (2016).

34 Cofece with data from OECD (2015 B).

In order to comply with its purposes, the study is organized in the following manner: Section two shows an analysis on the degree of competition in the pharmaceutical industry - mainly in private drug markets[35], and a number of results on the degree of competition and the speed of entry to the market of generic drugs are established, as well as on their ability to discipline the market and cut prices down.

Sections three, four, and five study any factors that might be obstacles to entry. Section three analyses the regulation on medications, both on the health side and on the industrial property side, and explores a series of strategies with potential to be employed to stop competitors entering the market. Section four continues with the study of obstacles, discussing a low sensitivity of demand on medications on the face of price reductions. Finally, Section five discusses aspects regarding the intervention of health institutions in public markets.

35 Also, one chapter discusses purchases by the public sector.

2. COMPETITION IN THE MARKET

The purpose of this section is to determine if the entry of generics is expeditious and imposes competitive pressure on the markets. For this, the results on the competition of generic drugs upon patent expiration are shown.

First, it describes the composition of the universe of molecules that may be analyzed (also known as drugs, substances, principles, or active ingredients), beginning with identification of any molecules for which the patent expired over the 2003-2015 period. Then, the results of five indicators measuring competition among generics in the market are shown. An estimation of the approximate calculation of benefits for the consumer from better performance in the expired-patent drug markets is also shown. Additionally, the results of the price and sales analysis conducted for a subset of 35 molecules, using a database with information on prices and sales for the 2009-2016 period are also reported. Finally, an econometric model is estimated to explain the effect of the entry of generics on prices - both for the original drug and for the generics. This, with the purpose of reviewing any evidence on the potential existence of price discrimination between captive/non-captive consumers; (i.e., the strategy implemented by some laboratories to continue selling the innovative drug at the same price, in spite of expiration of the patent, while generics are sold at a lower price. That is, each version of the drug is focused on attending the demand from various groups of consumers.)[36]

2.1 Universe of analysis

The source of information used in this study comes from the listings of patents that are published in the Industrial Property Gazette – Current Drug Patents Art. 47 bis of the IPAR" (Medications Gazette or Gazette) of the Mexican Industrial Property Institute (IMPI), published in the 2003-2015 period.

The Medications Gazette is a tool that is part of the linkage system between the authority granting patents (IMPI) and the one issuing health registrations (Cofepris).[37] This system forces Cofepris to not

36 In general terms, this may be conceived as price discrimination of the third degree. It occurs when discriminator maximizes profits through collection of a high price to the consumer. Price elasticity of demand is low (a variation in the amount demanded for goods where price varies), and high-elasticity low price to the consumer. Source: Chapter 3, pp. 137-141 of Tirole (1994).

37 Cofepris, organized through a decree by the Federal Executive Power in July 2001, is the institution that issues health registrations - indispensable for medications to be marketed.

issue health registrations for medications which are protected by a current patent granted by IMPI.[38] The Gazette is published as of 2003 and is derived from an amendment to the Rules of the Industrial Property Act (IPAR)[39] and to the Rules of Health Suppliers (RHS). [40]

In this study, molecule-patent is defined as the combination of the ingredient, principle, or active substance along with the corresponding patent number. An active substance may have more than one patent. In such case, each molecule-patent pair is quantified separately. Because of this, there are more molecules-patents than molecules (or active substances).

On average, during the term of the study, 1.2 patents per molecule were observed - increasing to 1.8 for those of which the patent is still valid.[41] This indicates that more patents are registered on the same active substance over time. This strategy from innovative laboratories - widely documented in the literature - is usually used to extend, in practice, the exclusivity period for the active substance. Section 3.1 elaborates on this topic.

Several health registrations may be granted for the same molecule - at least one per drug in the market. The database used in this study also includes information on the market. This allowed to analyze the behavior of prices upon patent expiration. These data on prices and sales was requested from a number of economic agents. This information was available at their own sources for the period between January 2009 and August 2016.

Application of a number of filters - detailed in Annex 1 of this study - has allowed to analyze a total of 35 molecules with information on value and sales volume in the private market - both for the original drug and its generics during the period of analysis. This in order to observe what happens to the prices of the innovator and of generics upon patent expiration. Diagram 1 explains the universe of analysis and subsets - depending on the nature of the indicators calculated - used in the universe of the total analysis or any of its subsets.

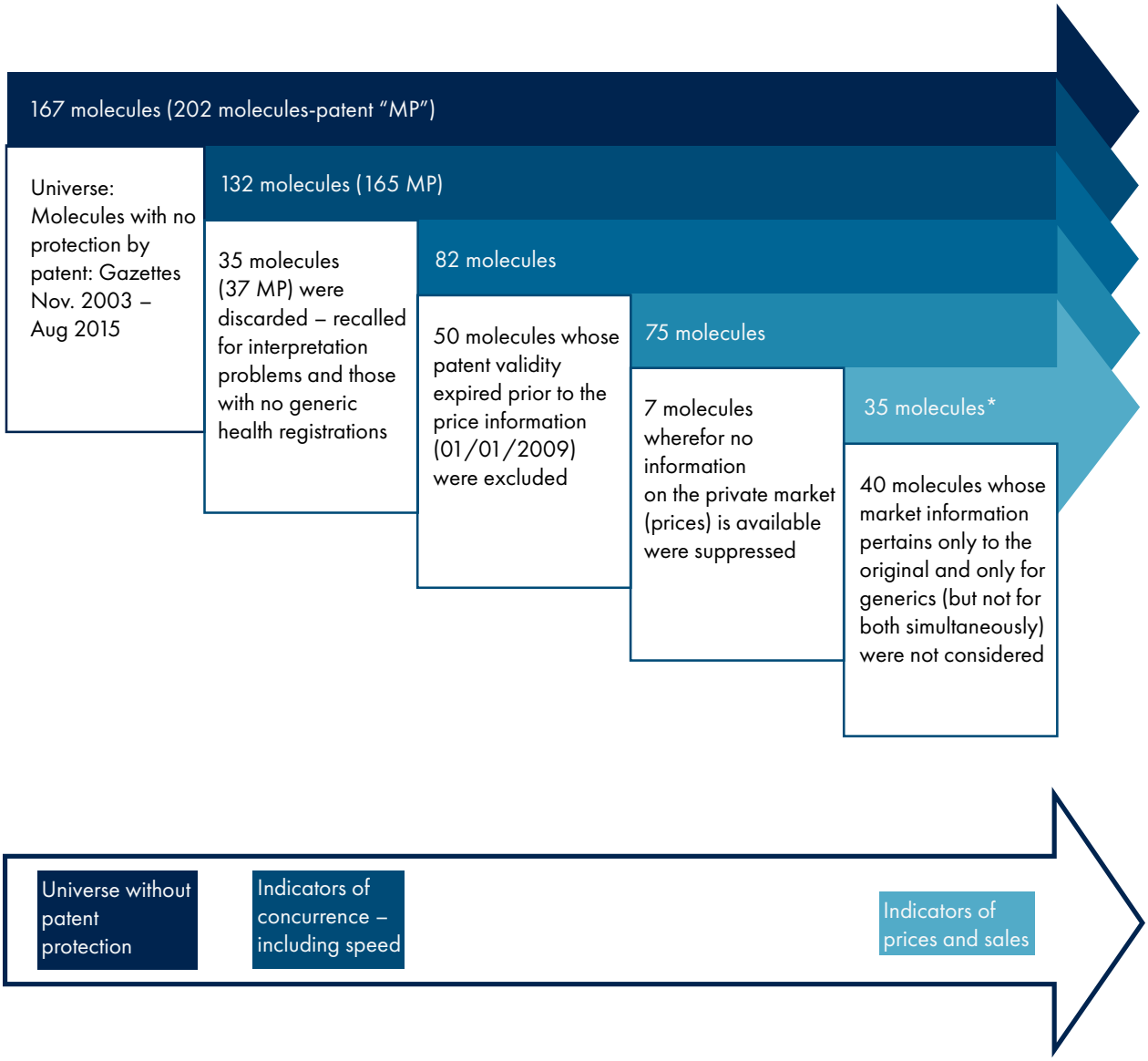
38 A health registration is an authorization issued by the health authority. This entails a procedure whereby medications are submitted to tests proving their safety, efficacy, and quality.

39 Published in the Official Gazette on November 23 1994. Latest amendment published in the Official Gazette on December 16, 2016.

40 Published in the Official Gazette on February 4 of 1998. Latest amendment published in the Official Gazette on March 14, 2014.

41 These figures are obtained by dividing 202 molecules-patent among 167 molecules, for molecules with an expired patent; and 802 among 441 for the molecules which have, at least, one current patent. This calculation may be underestimated for the Medications Gazette fails to report every patents protecting an active ingredient. As of the first publication of the Gazette and until pronouncement of the Supreme Court of Justice (SCJN) in 2010, mainly patents protecting an active ingredient - except for those inclusions derived from a decision or court order - were included. For a detailed explanation on this item, see section 3.1 hereof.

Diagram 1
Universe of Analysis and Subsets



Source: Cofece with data by González Pier et al. (2017).
* These molecules do not include orphan drugs.

2.2 Competition indicators

For the purposes of this study, the degree of competition refers to the intensity of competition faced by the innovative drug producer, derived from generic drugs.

The findings are that entry of generics in the Mexican market is usually not fast enough, nor does it have the scope required to discipline the market. This was observed in terms of penetration, number of competitors, and price behavior.

With respect to penetration, in Mexico an average of more than two years elapses between the expiration of a patent and the release of the first generic. In the United States, this happens immediately for the ones with the highest sales and in the European Union, within seven-months.[42] Also, after patents have been expired for one year, only four out of every ten medications have at least one health registration obtained by a competitor for selling in the private pharmaceutical market.

As for the number of competitors in the country, two years after the entry of the first generic, its penetration barely reaches 21.4% in the market, whereas in countries like the United States it reaches 89%, in Canada, 74% and in Holland, 62.1%.[43] Also, while in Mexico, the average of competitor generics is 2.8, after one year after patent maturity, in the United States this number is 10.1 for medications with the highest sales.[44]

In this study five competition indicators were calculated. This sheds light on the following dimensions:

i. Hypothetical Competition
ii. Observed Competition
iii. Intensity of Competition
iv. Speed of Competition
v. Delay of Competition

As for the first indicator, hypothetical competition measures competition faced by the innovative drug with an expired patent through the number of health registrations issued by Cofepris for generic drugs. It is considered hypothetical because the existence of a health registration is a pre-condition - but not a sufficient one - for competition to exist in the market. A laboratory may obtain a health registration and, for different reasons, fail to commercialize its generic product in the private market. It is calculated as the percentage resulting from dividing the number of health registrations for original medications with an expired patent where for at least one health registration of a generic version was identified, by the number of health registrations of original medications with an expired patent.

In terms of hypothetical competition, only 79% of the analyzed medications have health registrations of generic versions.

Also, we consider "observed competition" (second indicator) to be the percentage resulting from dividing the number of health registrations of original medications for which, at least one generic version with sales in the private pharmaceutical market was identified, by the number of health registrations of original medications with an expired patent.[45]

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42 European Commission (2009).

43 See Kanavos (2014) and Danzon and Furukawa (2011).

44 Grabowski, Kyle, Mortimer, Long and Kirson (2011).

45 All competition indicators (hypothetical and observed) were calculated using the universe of 132 molecules. For estimation thereof, using information on market prices was not required. In view that the same molecule may have more than one health registration, quantify the degree of competition based on health registrations of original medications associated with unprotected molecules seems more relevant. Thus, for all 132 molecules, 1,514 sanitary registrations were identified. Of these, 198 (13.1%) correspond to original medications and 1,316 (86.9%) to generic versions. Of the 198 registrations of associated original medications, 17% (34 registrations) shows at least one generic version linked to the laboratory manufacturing the original drug (i.e., the laboratory manufacturing the patented drug), upon expiration, keeps manufacturing that original version

Here, only in 63% of the cases analyzed there was at least one generic found in the private market - not manufactured by the laboratory losing the patent.[46] This indicator also suggests that a significant percentage of medications with an expired patent are still single-source (around 37%); (i.e., although the patent is already in the public domain), four out of every ten medications have no generics in the market. These results, however, should be taken with caution, since the case may arise where generic drugs are marketed only in the public sector and, therefore, were not captured in the information for the private market.

The intensity of competition (third indicator) quantifies the number of competitors present in the market per unit of time, after patent expiration. Intensity is measured as the average number of competitor generics per drug-presentation at 12 and 24 months after patent expiration.

This indicator shows the average number of competitor generics is 2.8 at 12 months and 3.3 at 24 months. Considering the full period (after 24 months) yields 5.2 competitors on average.

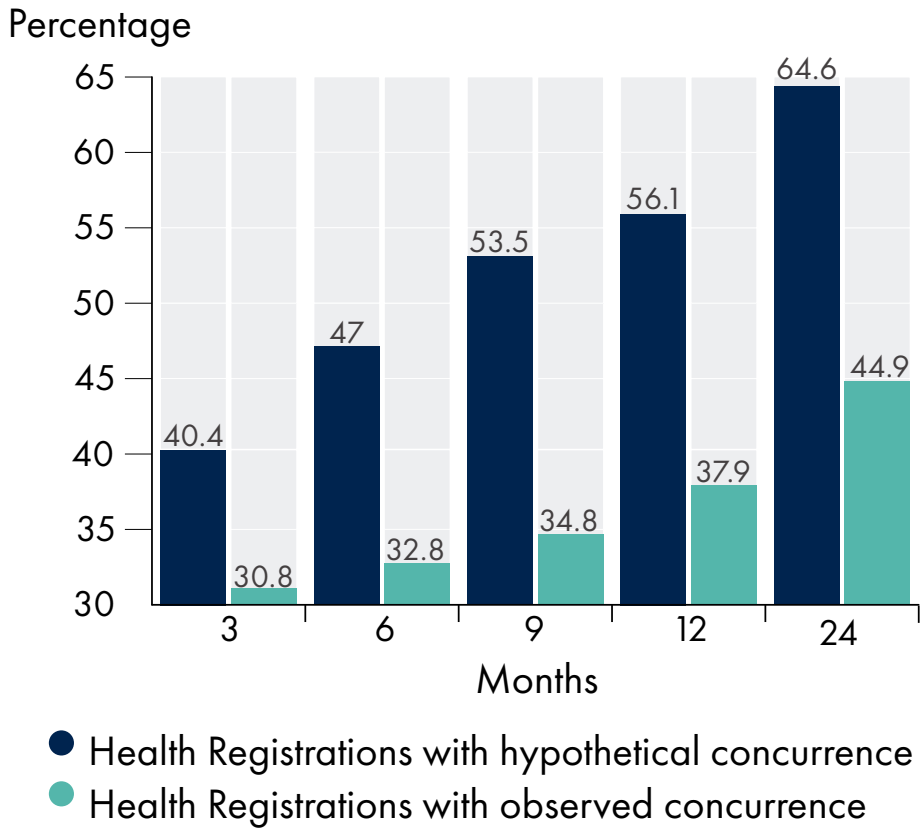
Speed of competition (fourth indicator), refers to the velocity with which generic drugs enter the market; and is obtained using the percentage of health registrations with hypothetical/observed competition at 3, 6, 9, 12, and 24 months after patent expiration.

The results indicate that, a year after expiration of the patent, a little more than half (56.1%) of all health registrations of the original medications face hypothetical competition of generics (Graph 1) (i.e., twelve months after patent expiration) only in six out of every ten original medications with an expired patent, one health registration of a generic version - which is not necessarily marketed - was identified. Considering the observed competition, this percentage is 37.9%; (i.e., at twelve months after patent expiration) for only four out of every ten original medications with an expired patent health registration of one generic version, with sales in the private pharmaceutical market. Results do not significantly change between the first and second years after patent expiration.

plus one or more generic versions of the same active substance. These versions were excluded from the calculation of the first and second competition indicators - these are not considered real competition. For subsequent indicators - where market information is used - the number of molecules analyzed decreases.

46 For purposes of these indicators, only the sources of market information on the private sector are considered. All information available on the public sector, which is considered purchases, for instance, by the Mexican Social Security Institute (IMSS), does not allow identifying whether the purchased drug is generic or innovator.

Graph 1
Speed of competition for entry of generics, 2009 -2015



Source: González Pier et al. (2017).

The average of competitors is relatively low with respect to other countries. For instance, the average competitors in twelve European countries is also 5.2, - but at 24 months after patent expiration;[47] while in the US, the average number is 10.1 for best-selling generics after twelve months.[48] In the aggregate, in Mexico, innovative medications face less competitive generics at two years after patent expiration.

Finally, the delay of competition (fifth indicator), measures the average time (in months) elapsed between the loss of the patent and the granting of the health registration for the first generic, as well as the time between the loss of the patent until the launch date of the first generic in the private market.

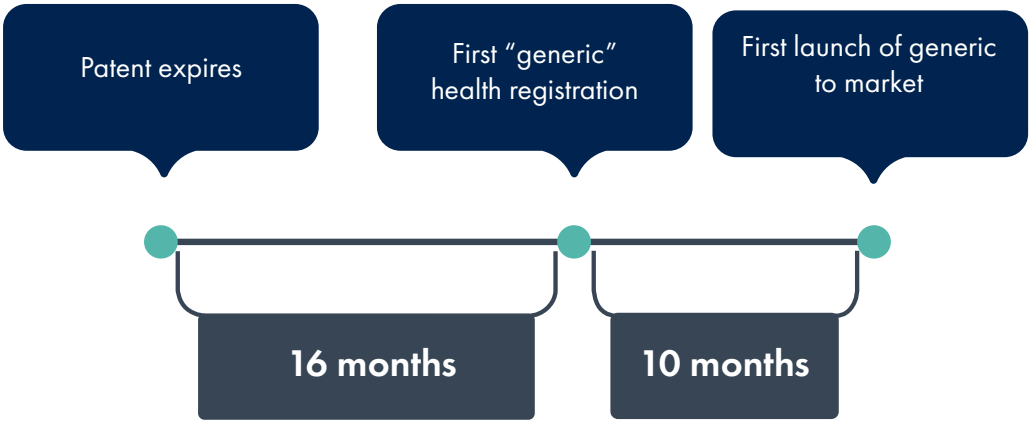
On average, 16 months elapse between the loss of the patent and the issuance of the first health registration for a generic. This time increases to 26 months when considering the time elapsed between the loss of the patent and the launch of the first generic (Diagram 2).[49]

47 Kanavos (2014).

48 Grabowski, Kyle, Mortimer, Long and Kirson (2011).

49 González Pier et al. (2017).

Diagram 2
Average time for actual entry of generics, 2009-2015



Source: Cofece with data by González Pier et al. (2017).

Delay in entry to market shows that the Bolar clause is not being fully utilized.[50] This clause allows a manufacturer of a generic version to apply for an authorization or health registration - including submission of bioequivalence tests,[51] up to three years prior to expiration of the patent of the innovative drug.

The legal term for Cofepris to resolve on an application for a health registration is 180 calendar days, for medications including active ingredients and with therapeutic indications already registered in Mexico.[52] This time is reduced in half if the application is filed along with a favorable technical report issued by a Third Party authorized by the Ministry of Health. Nonetheless, even when considering that the processing of the applications for health registration is frequently delayed —because these are filed incomplete or do not fully comply with all requirements in the law, being subject to prevention by Cofepris— the time gets delayed (Section 3.2 further discusses this topic).[53]

Furthermore, the time it takes for a product to get significant market share in the market - once having obtained the health registration - is also long (10 months).

50 In this study, it was not possible to estimate the degree of utilization of the clause, since the date of entry of the application for the health registration from all the generics laboratories was not available.

51 According to Cofepris, bioequivalence is the study of comparative bioavailability assessing the absorption efficiency of equivalent pharmaceutical products - same dose, same pharmaceutical form, and same salt.

52 Article 166 bis of the RHS.

53 Per the Federal Administrative Procedure Act (Article 17-A), *"where the writing submitted by the interested parties fails to contain data or fails to comply with all requirements as applicable, the appropriate decentralized agency or body shall notify any interested parties, in writing and on a single occasion, so that these will cure the omission within the term established by such decentralized agency or body"*. Also, in terms of the provisions in Article 17-B of the act above, *"the term for the appropriate body to resolve on the dealings will be suspended and resumed as of the working day immediately following that on which the interested party responds"*. Published in the Official Gazette on August 4 1994. Latest amendment published in the Official Gazette on April 9 2012.

Finally, upon observing the tendencies of different variables for each molecule within the universe of the analysis,[54] 22 out of 127 medications (17%) were identified. Their yearly sales are estimated in the aggregate to be 6,285 million pesos, belonging to any of the following four categories and that might warrant further research in the future:

i. Medications without hypothetical competition, (i.e., even if their patents have expired) there is still no generics health registration at the time of writing this report (Chart 1);
ii. Medications without observed competition, (i.e., on expired patents and generics health registration), but without sales having been identified in the private market (Chart 2);
iii. Medications protected by secondary patents[55] or on trial; (i.e., medications with generics health registrations) without presence in the private market due to a trial preventing its commercialization (Chart 3); and
iv. Medications where the entry of generics to market has not been translated into significant price reductions and/or high share in the generics market (Chart 4).

Chart 1
With expired patents and without health registration as generics

Generic Name	Innovator Laboratory[1]	Health registrations as originals	Valor de mercado (millones de pesos)
Abiraterone	Janssen - Cilag, S.A. de C.V.	1	73.0
Aprepitant	Merck Sharp & Dome de México, S.A de C.V.	1	83.2
Dutasteride	GlaxoSmithKline México, S. A. de C. V.	1	58.8
Eletriptan	Pfizer, S. A. de C. V.	1	56.5
Insulin Lispro	Eli Lilly y Compañía de México, S. A. de C. V.	2	616.7
Nadoparin Calcium	Sanofi-Aventis de México, S. A. de C. V.	1	115.1
Rosiglitazone	GlaxoSmithKline México, S. A. de C. V.	1	60.7
Trandolapril	Abbott Laboratories de México, S. A. de C. V.	2	59.5

[1] Refers to the holder of the registration of the drug of reference.
[2] Includes private sales and public disbursement by IMSS in 2015.
Source: González Pier et al. (2017).

Chart 2
With expired patents and health registration as generics, but without the presence of generics in the private market

Generic Name	Innovator Laboratory[1]	Health registrations		Market Value (million pesos)[2]
		Originals	Generics	
Efavirenz	Merck Sharp & Dome de México, S.A de C.V.	1	2	272.2
Linezolid	Pfizer, S. A. de C. V.	3	8	186.1
Valganciclovir	Productos Roche, S.A. de C.V.	1	5	193.9

[1] Refers to the holder of the registration of the drug of reference.
[2] Includes private sales and public disbursement by IMSS in 2015.
Source: González Pier et al. (2017).

54 These variables are: Price in the private sector of the original drug, prices and share of generics market in the public/private sectors, and number of effective competitive generics in the private market in each period.

55 The term "secondary patent" is explained in Section 3.1 hereof.

Chart 3
With health registrations as generics without presence in the private market, but under the protection of follow-on patents

Generic Name	Innovator Laboratory[1]	Health registrations		Market Value (million pesos)[2]
		Originals	Generics	
Celecoxib	Pfizer, S. A. de C. V.	1	6	1,058.9
Imatinib	Novartis Farmacéutica, S.A. de C.V.	2	5	191.
Tadalafil	Eli Lilly y Compañía de México, S. A. de C. V.	1	1	1,065.4
Voriconazole	Pfizer, S. A. de C. V.	2	4	111.5
Zolimtriptan	Astrazeneca, S. A. de C. V.	2	2	89.0

[1] Refers to the holder of the registration of the drug of reference.
[2] Includes private sales and public disbursement by IMSS in 2015.
Source: González Pier et al. (2017).

Chart 4
Any medications where the entry of generics has not been translated into significant price reductions and/or high share in the generics market.

Generic Name	Innovator Laboratory[1]	Health registrations		Generics with presence in the market	Market Value (million pesos)[2]
		Originals	Generics		
Capecitabine	Productos Roche, S.A. de C.V.	1	4	1	140.2
Problem: Patent expired since 2008 and only two competitors. The private market accounts for 45% and the public, for 55%.					
Enoxaparin	Sanofi-Aventis de México, S. A. de C.V.	1	1	1	609.0
Problem: Patent expired since 2011. The value in the private market accounts for 50%, same as the public market and only one generic in the market.					
Etanercept	Pfizer, S. A. de C. V.	1	2	1	803.6
Problem: Patent expired since 2009 and only two competitors in the market. Other current patents were identified in the Gazette. The prices in the public market and in the private market are similar.					
Exemestane	Pfizer, S. A. de C. V.	1	6	3	221.6
Problem: Patent expired since 2006. Only three competitors. The prices in the public market and in the private market are similar.					
Midazolam	Productos Roche, S.A. de C.V.	2	14	5	138.8
Problem: Patent expired since 2005. The prices in the public market and the private market are similar, same with market shares in the public (41%) and private (59%) markets.					
Valaciclovir	GlaxoSmithKline México, S. A. de C.V.	1	4	2	80.1
Problem: Patent expired since 2008 and only three competitors in the market.					

[1] Refers to the holder of the registration of the drug of reference.
[2] Includes private sales and public disbursement by IMSS in 2015.
Source: González Pier et al. (2017).

In addition, there are 22 drug codes that the Mexican public sector bought as a single-source in 2016, for which it was found that generic versions exist in other countries, as Canada, the United States and the European Union. Six of the drugs identified in Charts 1 to 3 are also in the list. (See Annex 5).

2.3 Potential benefits of higher competition for the consumer

In the sections above, the following was shown: i) some expired-patent drugs fail to face competition; ii) there are cases where the entry of generics in the market occurs at a lower-than-expected speed, and iii) there are situations where expiration of the patent causes a relatively low reduction in the price of the medications, as well as a slow penetration in the market share (volume).

In this section, the benefit that would ensue for consumers if penetration of generics increases from 21.4% to twice as much (i.e., to 42.8%), two years after the patent entered the public domain, is estimated. This share is conservative and feasible, when compared against that reported by other countries that are characterized by high competition among generics, such as Holland (62.1%), Denmark (55.7%), Germany (54.9%) and the UK (46.5%).[56]

In that regard, it was found that consumers would spend 2,552 million pesos less in medications a year, if penetration of generics were twice as much as that observed two years after patent expiration.[57] This estimation is conservative. Due to a lack of information, this calculation fails to include a number of medications.[58] It also fails to consider the benefit of greater usage of medications - caused by the lower price of generics.

2.4 Evolution of prices and sales

In the prices and sales analysis, it was found that, six months after entry of the first generic, the average price of generics is 20% lower than the price of the original and, for subsequent months, the price on generics continues to go down (Chart 5).[59] This is consistent with evidence from other countries, where the prices on generics with respect to the original show a decreasing tendency over time. However, the

56 See Kanavos (2014) and Danzon and Furukawa (2011).

57 For calculation, those medications with competition of at least one competitive generic - applying the following steps - were considered: i) The sales value of the original drug was calculated at the date of entry of the first competitive generic at the price of the original. ii) Subsequently, the sales value of the drug was calculated 24 months after entry of the first generic at a weighted average price conformed by the price of the original drug and the average price of generics available at that time. At calculating the observed savings, sales at 24 months of entry of the first generic were used; thus, in case that the demanded amounts will be increased over the analyzed period, observed savings may be overestimated. As a weighting factor of the average price of generics the average share observed for the competitive generics at 24 months after entry of the first generic in the private market (21.4%) was used. The weighting factor for the price of the original drug at 24 months after entry of the first generic was obtained as the difference between the unit and the weighting factor for the average price of generics. iii) the benefit observed for each drug resulted from the difference between steps i) and ii). iv) In order to calculate the potential transfer, the above exercise was repeated, modifying all weighting factors used. For this exercise a target share equivalent to the double as observed (42.8%), considering all international standards. v) The potential benefit for the consumer is the difference between steps (iii) and (iv).

58 For instance, those medications in the universe where for there was no market information were not used in the estimation

59 When including market information, our sample decreased - leaving only a set of 35 molecules.
The prices and sales analysis was conducted for the subset of 35 molecules. These meet the following conditions: i) their patent validity (first sales of generics) later than January 1 2009; ii) at least one health registration for generic was identified; and iii), there are data on prices and sales volume in the sources of information of the private sector, simultaneously for the original drug and for generics.
This exercise excludes generics produced by the same laboratory as the original.
All details of this selection are documented in Annex 1.

reduction observed in Mexico is less pronounced (28.6% at 24 months).[60] For instance, in the European Union, the reduction of prices is 40% at 24 months.[61]

On the other hand, the prices of the original medications slightly increase after entry of the first generic and, on average, after 24 months, move closer to the price they had upon entry of the first generic. This may be explained, among other things, by the existence of brand loyalty and the fact that laboratories utilize that situation to price discriminate between various groups of consumers, according to their preferences and payment capacity (third degree price discrimination).[62] This result is also observed in other countries - including a number of studies, the prices of the original medications increase more than the what was found in this study.[63] For instance, in the US, for 34 medications undergoing generics competition for the first time after 1991, the average price increase, between 1991 and 1994, was 22%.[64]

Chart 5
Evolution of the relative average price of generic and original drugs at 6, 12, and 24 months after entry of the first generic*, 2009-2015

Average relative price for medications:	Months after entry of the first generic		
	6	12	24
Generics (different to the generic of the original)	-20.6%	-23.2%	-28.6%
Originals (on expired patent)	2.5%	1.3%	0.4%

*Both for generic drugs and original drugs, prices relative with respect to the price of the original upon entry of the first generic (in real terms). All estimations consider a total of 35 molecules.
Source: González Pier et al. (2017).

Penetration of generics —measured as the market share in terms of sales volume— is another indicator of the degree of competition. This study found that the generics market share grows, but at a lower degree than in other countries. At six months after the entry of the first generic, these have an average share in the private market of 8%; 13% after one year, and 21.4% after two years (Chart 6).[65] Other countries show greater percentages of market share and faster penetration. For instance, two years

60 Aitken, Berndt, Bosworth, et al (2013); Danzón y Furukawa (2011); Kanavos (2014).

61 Comisión Europea (2009).

62 González Pier et al. (2017).

63 European Commission (2009).

64 Congressional Budget Office (1998).

65 González Pier et al. (2017).

later, in the US the share of generics in the market is 89% and in Canada, 74%.[66] In a number of countries, while having a lower percentage, it is greater than 50%, such as in Holland (61.2%), Denmark (55.7%) or Germany (54.9%).[67]

Chart 6
Average generics market share at 6, 12, and 24 months after entry of the first generic, 2009-2015

	Months after entry of the first generic		
	6	12	24
Average market share in terms of volume, of generics (different than the original) with respect to the total in the private market*	8.3%	12.7%	21.4%

* The volume of the generic versions manufactured by the same laboratory (or by a laboratory belonging to the same corporate group) manufacturing the original drug is excluded in the numerator. The denominator (total volume in the market) is included.
The indicator for the 24-month term may be underestimated. All data used for estimation consider molecules that lost a patent in 2015. These are not fully observed at 24 months after patent expiration.
Source: González Pier et al. 2017.

This result (along with the fact that the price of the original does not vary a lot after the entry of generics) indicates that there is demand for the original medication.[68] This, among other factors, may be the result of a combination of causes, such as brand loyalty (both by the medics and the patients), a lack of enforceability of using the generic name on the prescription and, as seen below (Section 4.1), the likely lack of trust in generics by consumers.

2.5 Third-degree price discrimination

The results in the last section show that the entry of generics fails to fully discipline the private drug market, but the laboratories producing the original medications keep prices high in spite of the entry of generics. This section analyses the possibility that the original laboratories carry out price discrimination between captive and non-captive consumers (i.e., in the face of the entry of generics, the innovator laboratory segments brand-loyal consumers and charge them a higher price than the brand-for-generic consumers). This behavior has been detected in the past in other parts of the world and is known as the generic competition paradox.[69]

66 Congressional Budget Office (1998).

67 Kanavos (2014).

68 Danzon and Furukawa (2011).

69 Explanation of this widely-accepted paradox considers that the same occurs in markets where it is feasible to separate the various types of consumers. Thus, the laboratories manufacturing the innovative drug, generally give up the part of the market

The analysis shown in this section uses information only from the private pharmaceutical sector. Prices are consumer prices. Considering that vendors and drugstores regularly fix a constant margin on the price at which they purchase from the laboratory or vendor, then the prices reflect differences in laboratory prices. Also, data does not necessarily reflect the conditions in the public market (purchases of medications in the public sector).[70]

In order to identify whether the generic competition paradox is also present in the Mexican market, an econometric model was estimated based on Regan (2008).[71] The methodology consists of estimating two independent equations to study the effect on prices - both on the original drug and generics - after the loss of patent. Reduced equations are as follows:

$$\ln(p_{it}^{p}) = \delta_0 + \delta_1 G_{it} + \delta_2 PM_{it}^{p} + \delta_3 Tiem_{it} + \delta_4 NP_{it} + \delta_x x + \varepsilon_{it} \quad (1)$$

$$\ln(p_{it}^{g}) = \theta_0 + \theta_1 G_{it} + \theta_2 PM_{it}^{g} + \theta_3 Tiem_{it} + \theta_4 NP_{it} + \theta_x x + u_{it} \quad (2)$$

Where p_{it}^{p} and p_{it}^{g} are the average price, per unit of measure, of the patent/generics drugs, respectively;[72] G_{it} the number of generics of the drug i in time t t; PM_{it}^{p} and PM_{it}^{g} are the market shares measured in marketed units of the drug with an expired patent and generics, respectively, where $PM_{it}^{p} + PM_{it}^{g} = 1$; $Tiem_{it}$ is the time in months elapsed as of entry of the first generic; NP_{it} is the number of presentations of the drug in the time t;[73] x is a set of binary variables connected with the characteristics of the market;[74] and finally, ε_{it} and u_{it} represent error terms.

It would be expected that, where third-degree price discrimination exists upon patent expiration, the price of the original drug would show an upward tendency over time (δ_3 positive), while the price of generics would show a decreasing tendency (θ_3 negative).[75] Should this result be ratified, existence of third-degree price discrimination in Mexico would be supported.

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that is the most sensitive to prices and focuses on the brand-loyal part (Frank and Salkever, 1992).

70 All market information was obtained through an information request (File REC-001-2016, folios 000093-000098 and 000178-000199).

71 The author considers two independent models. In the first one she explains the effect on the patent drug price using different explicative variables - among these, the number of competitors and the time elapsed after entry of the first generic. The second model explains the price of generics, using the same explicative variables as the first model. Its estimations consider several assumptions: First, Regan adjusted all regressions under the assumption that any errors in neither models are correlated. Also, the entry of generics is exogenous to the price. Also, it used a contrast of fixed and/or random effects. The second adjustment, relaxed the assumption of exogeneity for the entry of generics. In that case, it adjusted a two-stage model, controlling the entry of generics for the period granted by the Hatch-Waxman Act in the US.

72 A unit of measure refers to a "unit of presentation" of the drug: tablets, pills, capsules, vials, etc. Obtained through the quotient of the average trade price of the drug between the number of units of that presentation (price of the box divided into the number of pills, for instance). Also, this was broken down by dosage; (i.e., therapeutically, two medications manufactured based on the same molecule - but with different dosage - are considered different medications).

73 Refers to the number of marketed combinations of the active substance, prior to effective entry of generics, considering the presentation (pills, vials, etc.), and the dosage of the active substance (for instance, 100 mg, 200mg, or 500mg).

74 Information was included pointing out whether in the market generic drugs and branded generics simultaneously coexist, and if the laboratory and owner of the patent, also has its generic version.

75 As seen in section 2.3, the price of a number of medications with an expired patent may be increased over the period after entry of the first generic, though, with the passing of time, the same may decrease; (i.e., the effect price increase is possibly not permanent).

All medications used were taken from the universe of medications under analysis, already referred to in the sections above; (i.e., of the 35 molecules whose market information was available).[76] The sample, thus, consists of an unbalanced panel comprised of 21 medications with monthly observations over the period comprised by May 2009 and August 2016. A case-by-case analysis was performed. The fact that the price of the original drug is not reduced in the presence of generics was identified. This also applies to those medications wherefore there is a generic version produced by the innovator laboratory.[77]

All estimations suggest that the markets allow the laboratories to price discriminate.[78] The trend estimated for the original medications entails an increase of up to 0.2% in prices, over the period after entry of the first generic.[79] At the same time, the trend for the price of generics is reduced to a 1.5% rate. The latter, because lower introductory price with respect to the price of the original medications.[80] Relaxing the assumption of endogeneity, the estimations show that the effects do not change significantly. In this case, any evidence suggests that the price of branded drugs increases 0.4%, while that of generics decreases by 1% (the full results are shown in Annex 2).[81]

Results also indicate that in the markets where there are both branded and unbranded generics, the increase in price of the original may be up to 46% lower – with respect to the case where there are only unbranded generics. This means that branded generics compete more directly against the innovator than against unbranded generics.

Similarly, where the laboratory of the expired patent also has its own generic version, the increase in price of the original drug may be up to 58% lower, with respect to the cases where these laboratories do not produce generic versions; (i.e., where an innovator laboratory - apart from producing the patented drug - produces a generic version), the increase in price of the patented drug is lower.

Finally, the number or variety of presentations of the original drug, in the market prior to the entry of generics, also has some impact on prices. A greater number of presentations increases the price of the original up to 7.6%. This impact has been documented in studies for other countries. This result is usually

76 File REC-001-2016, folios 000093-000098 and 000178-000199.

77 All estimations were controlled upon inclusion of binary variables where, in the market, generic drugs and branded generics simultaneously coexist; as well as where the laboratory (patentee) also has its generic version.

78 Estimations by Cofece with data in the file REC-001-2016, folios:000093-000098 and 000178-000199 The method of estimation assumes that the equations of the model are independent, and initially assumed that there is no endogeneity for the number of generic drugs. Nonetheless, the assumption somewhat relaxed. The number of medications, using as a tool the volume of private market, 24 months prior to the entry of each generic version.

79 The number of periods (months) after entry of the first generic may vary for each drug. This is due to the fact that, for those medications that have lost their patent during the first years of the analyzed period, with respect to those that expired over the last year, has a large collection of observations. This fact may explain the scarce increase of original prices reflected by the model.

80 Following Regan (2008), any evidence that the price of the expired patent is increased, at the same time that the price of generics is reduced, suggests that the prices of the patent fails to react in the face of the entry of generics, and, thus, that the laboratory of the expired patent segments prices.

81 All estimators are statistically significant at yhe5%.

interpreted in the literature in the following manner: A greater number of presentations, prior to the entry of generics, may help the original laboratory to better position in the market - thereby restricting competition and entry of generics.[82]

Below, in the following sections, an analysis on the potential reasons for the lack of competition (regulatory obstacles and characteristics of demand) will be performed. The analysis does not presuppose any potential anticompetitive behavior that might exist in the pharmaceutical sector.

82 Regan (2008).

3. IDENTIFICATION OF REGULATORY OBSTACLES

According to the regulation, a generic drug needs to meet two legal conditions to enter the market:[83] i) does not infringe patent rights and ii) have a health authorization.[84] In order to ensure fulfillment of both conditions, the legal framework sets forth a linkage system consisting of subjecting the concession of a health registration to verification of the status of validity of patents granted by the authority as to industrial property.[85]

This section analyses the regulation on industrial property and the health registration with the purpose of identifying those provisions that might delay or hinder entry to the generic drug market. Also, with the purpose of contrasting the Mexican regulation against international best practices, an international benchmark of the procedures for attainment of health authorization in a number of countries which are major producers of generics is shown.[86]

3.1 Patent system

Patents are essential for the development of new medications. These grant the exclusive right to exploit an invention and, thus, have impact on the competition process in the sector.

Although during the time when the patent is active there is no competition among generics, in a number of cases, innovative medications face competition from other medications, their therapeutic equivalents.[87] However, this last type of competitive pressure is not discussed in this analysis.

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83 Article 167 and 167 bis of the RHS.

84 For this, the drug should contain the same drug or active substance and pharmaceutical form, in equal concentration or potency, which uses the same administration route and should verify, through all regulatory tests as required in the sense that their pharmacopeic specifications, dissolution profiles, or bioavailability, or other parameters, as the case may be, are equivalent to those of the drug of reference.

85 In other countries, the linkage system is known as *linkage*.

86 This benchmark included the US, the European Union and Brazil. In 2013, generics accounted for more than three fourths of the volume of pharmaceutical products sold in the US, the UK, Chile, Germany and New Zealand. The very former is the country with greater penetration of generics in the market with respect to volume. On its part, Brazil is the largest the pharmaceutical market in Latin America and the top ten in the world, according to OECD (2015 B) and Deloitte (2016).

87 González Pier and Barraza Lloréns (2011). Therapeutic equivalents have different chemical structures with respect to the original drug. Yet, they produce a therapeutic effect and a profile of similar adverse effects where administered to a patient at equivalent dosages. In view that therapeutic substitution is defined by health professionals (medic/pharmacist), the analysis of this type of medications was not considered for this study.

In Mexico - as in other countries - the criteria to grant a patent requires that a product or manufacture procedure fulfills all conditions of novelty, inventive step, and industrial application.[88] Application for a patent is based on a standard list of requirements.[89] Of these, both the detailed description[90] of the invention and any claims,[91] are the most important. The former describes how to perform and use the invention, while the claims determine the scope of legal protection to the invention.

During the first stages of the development of a new drug,[92] laboratories generally patent many molecules, formulations, and compositions with potential to be developed into new active ingredients and, eventually, into medications. Also, it might be the case that through further research new production methods or a second therapeutic use are found for a drug. These may also be patented.[93] Therefore, there are different types of patents according to the claimed matter. In general, these may be:[94] i) by product - protecting the active ingredient or initial chemical compound, as well as variants of a known active ingredient [95] ii) by formulation or pharmaceutical composition[96], iii) by use[97] or iv) by procedure.[98]

For the purposes of this study, the first patent of an active ingredient that is granted is known as primary or basic patent, and the rest are known as secondary patents or follow-on patents. It is important to note that these terms are not included in the patent legislation. The term "secondary patent" comes from the fact that it follows the primary patent in a timeline (i.e., the first active ingredient patent as granted), but does not entail a judgment on its importance. Secondary patents cover a variety of chemical agents, alternative forms of existing molecules, dosing, processes or uses regarding an active ingredient.

In most countries (including Mexico), patents for pharmaceutical products have a 20-year effective term that is not extendable as of the date of the application.[99]

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88 For further explanation, see the definition of patent in the glossary.

89 IMPI (2016).

90 IMPI (2016). The most important role of the description consists of disclosure of the invention. The description is comprised by - technical field, antecedents (state of the art), description of the invention, description of figures and best method known to make the invention.

91 A claim is *"the essential characteristic of a product or process whose protection is precisely and specifically claimed in the application for patent or registration. It is granted, as the case may be, in the corresponding the title".* Art. 12, Section V of the IPA.

92 Article 221, Section II of the GHA defines drug as *"Any natural, synthetic, or biotechnological substance with pharmacological activity and which is identified by its physical/chemical properties or biological actions - which is not presented in pharmaceutical form and meeting all conditions to be employed as drug or an ingredient of a drug; (…)".*

93 Abud, M. J., et al. (2015).

94 Cofece with information from IMPI (2016b) and Serra, J. C. (2010).

95 Laboratories tend to register subsequent patents as: analogs, polymorphs, metabolites, intermediates, specific salts, or crystalline forms for a known active ingredient.

96 Combination of adjuvant vehicles or excipients (inactive substance) and active ingredients. Include a combination of two or more active ingredients. It may also be about release systems, particle sizes of the active ingredient, etc.

97 Includes the first therapeutic indication of a product or a second use different to that originally patented.

98 Protect processes and procedures for attainment of the active ingredient.

99 This due to the fact that the Agreement on Aspects regarding the Rights to Intellectual Property regarding Commerce (Agreement on the ADPIC) of the World Trade Organization (WTO), established standards and basic principles on copyright in the multilateral trade system. The Agreement on the ADPIC points out that the patents may be obtained for all inventions - either products or procedures - in all fields of technology, though, grants countries freedom of action to exclude the patentability of certain inventions. Thus, the legal framework in the matter and the types of pharmaceutical patents granted by the authorities may vary between countries. OMPI (2015).

In Mexico, the Industrial Property Act[100] (IPA) and its Rules[101] (IPAR) govern the industrial property system, while the Mexican Industrial Property Institute (IMPI)[102] administers it and is responsible for the registration of patents and brands.[103]

3.2 Health registration

A health registration is a certificate of safety, efficacy, and quality issued by the Ministry of Health through Cofepris - an indispensable requirement in order to market a drug. Unlike in the US and Europe,[104] in Mexico, a health registration should be extended every five years.[105]

The health registration for chemically-synthesized generic drugs[106] is granted if these contain the same amount of the active ingredient and pharmaceutical form than the drug of reference[107] (innovative drug), with equal concentration or potency to treat the same disease, use the same route of administration and should verify, through the bioequivalence studies,[108] that its pharmacopeic specifications, dissolution profiles or bioavailability or other parameters, as the case may be, are equivalent to those of the drug of reference.[109]

Nonetheless, the name of the drug, its appearance (color or shape), presentation, as well as any inactive components or excipients contained, may vary with respect to those of the drug of reference.[110]

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100 Published in the Official Gazette on June 27 1991. Latest amendment published in the Official Gazette on June 1 2016.

101 Published in the Official Gazette on November 23 1994. Latest amendment published in the Official Gazette on December 16 2016

102 IMPI´s Rules and its Organic Statute govern the performance of this authority.

103 A brand is any visible sign distinguishing products or services from others of the same species or class in the market.

104 In the European Union, health registrations after the first renewal have indefinite validity and only considers renewal every five years for those medications which due to exceptional circumstances, so require. In contrast, the US does not consider any type of renewal. (With information from Food and Drug Administration (FDA) and the European Drug Agency).

105 Article 376 of the General Health Act indicates that *"(…) The registration may only be granted by the Ministry of Health. It will have a 5-year validity, without prejudice of the provisions in Article 378 of this Act, such registration may be extended in equal terms, at the request of the interested party, in the terms established by the regulatory provisions. If the interested party fails to request for extension within the term established therefor or otherwise, will change or modify the product or manufacturer of raw materials, without prior authorization of the health authority. The authority will proceed to cancel or revoke the appropriate registration. (…)"*

106 Chemically-synthesized drugs are characterized by being small fixed-structure molecules. These are different from bio-technological medications. See the definition of innovator bio-technological drug and biocomparable drug in the glossary hereof.

107 Art 2, Section XIV Bis of the RHS points out that the drug of reference is that indicated by the Ministry of Health as such, which has the registration from such agency, which is commercially available and is selected according to the criteria set forth in the Mexican Official Standards in the matter.

108 Bioequivalence studies are the main tool considered to briefly prove that a generic drug meets the same characteristics of quality, safety, and efficacy that a drug of reference.

109 Art. 2, fracción XIV del RIS.

110 For new molecules, innovator and biocomparable biotechnological drugs - for attainment of the registration - these require the assessment and approval by the New Molecules Committee (NMC) (an agency for inquiry in support to analysis and assessment of information on safety, efficacy and quality for new health supplies or with new indications with purposes of registration or products that due to their characteristics require assessment by groups of specialists. For biocomparable bio-technological medications, the only way to demonstrate similarity between innovator and biosimilar drugs during development, is through clinical studies (e.g., pre-clinical comparative, clinical, and post-commercialization. Criteria to establish biocomparability for this type of medications is case-by-case. Biotechnological Medications Biocomparability Guides are issued

Bioequivalence studies may be performed by an authorized third party. These are people authorized by Cofepris to support the authority regarding health control and surveillance.[111]

From 2008 to date, Cofepris has adopted important measures to promote a more expeditious entry of generics. A highlight is the Strategy for Release of Generics for Savings to Mexican Families. This strategy consists of identifying medications with expired/soon-to-expire patents, as well as health registrations pending authorization, and to apply a number of priorization criteria to "release" (grant) the registrations, among them, that the substances where connected with the main causes of mortality in the Mexican population.[112] Health authorizations are disclosed in batches or "packages" of new health registrations as generics for various active substances. In accordance with Cofepris (2017), from October 2001 through April 2016, 486 new health authorizations for generic drugs have been released through fourteen packages, corresponding to 37 active substances.

This strategy is useful as a diffusion tool for disclosure to the public of new generics which are authorized and which are available in the market; however, this may give the wrong incentives to potential entrants. In a number of cases, issuance of health registrations by Cofepris have been collectively made, although applications for registration have been entered on different dates. Upon expiration of the patent protecting the innovative drug, the economic agents have incentives to expedite the process of health approval and be the first to market a generic version in order to gain market share. If the applications for the registration of a substance are simultaneously authorized (this entails that potential competitors may enter the market at the same time) fails to generate proper incentives for a manufacturer of generics to file its application early - for a collective approval it discourages the effort of the first applicant. In that regard, in Mexico, no incentives are granted to the first generics entrant as it happens in the US.[113]

Also, in 2010, Cofepris executed equivalence agreements with the health authority of the US (FDA) and in 2012 with the European Medicines Agency of the European Union, in order to accelerate the entry of generic versions of products commercialized by multinational companies.[114] Also, the removal of the plant requirement in 2008 was important to expedite import of generic drugs.[115]

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by NMC´s Bio-technological Products Assessment Subcommittee. Source: http://www.cofepris.gob.mx/AS/Documents/RegistroSanitarioMedicamentos/ESTRUCTURA%20DE%20EXPEDIENTES/17%20BIOTEC.pdf

111 There are three types of authorized third parties; currently 201 are in operation: 62 units of interchangeability and biocomparability, 119 testing laboratories and 20 verification units. (Listing of Authorized Third Parties. Electronic Inquiry at http://www.cofepris.gob.mx/TyS/Paginas/Terceros-Autorizados.aspx) (Inquired on March 30 2017).

112 Cofepris (2013).

113 A number of countries (e.g., the United States) have implemented incentives for entry of generics (e.g., the Hatch-Waxman Act of 1984, granting the first laboratory obtaining its registration for generics a 180-day period of exclusivity for commercialization. This mechanism has created incentives for competition among generics is increased in this country. While in the 1995-1998 period between two and six generics entered - depending on the size of the market, during the first year after entry of the first generic - in the 2009-2011 period, up to ten generics entered. (Grabowsky and Long, 2013)

114 Currently, Cofepris has agreements for acknowledgment of Good Manufacturing Practices Certificates (CBPF) (or its equivalents) in place with eight foreign health authorities. Source: http://www.cofepris.gob.mx/AS/Documents/RegistroSanitarioMedicamentos/Oficios%20CAS/Lineamientos%20Acreditaci%C3%B3n%20CBPF%20Oficio%20CAS-1-OR-20-2016.pdf

115 Prior to amendment to the RHS in 2008, Article 168 of the RHS established that an applicant for a health registration should prove possession of a laboratory or drug factory in the national territory. This amendment removed such requirement and added that "(..) for foreign manufacturers having a license, certificate, or document proving that the company has the permit to manufacture medications, issued by the appropriate authority in the country of origin is a requirement". Amendment to Article

In a sample of 381 health registrations issued by Cofepris between 2005 and 2016,[116] (corresponding to 102 active substances, of which, 88 underwent pre-assessment by authorized third parties) the findings were that in 44% of the cases, the registration was issued within the maximum term allowed: 180 days.[117] Therefore, in 56% of the cases, the health approval exceeded the term (Chart 7). Thus, the average time for issuance was 347 days. Graph 2 reports only the active substances where the issuance of health registrations of generic versions exceeded the maximum legal term as established.

Chart 7
Times for authorization of health registrations for generic drugs
(Includes registrations issued between 2005 and 2016)

Time of authorization	Number of registrations	Percentage
Up to 90 days	88	23
90 - 180 days	80	21
180 - 270 days	54	14
270 - 360 days	36	9
360 - 720 days	78	21
720 - 1080 days	22	6
+ 1080 days	23	6
Total	**381**	**100**

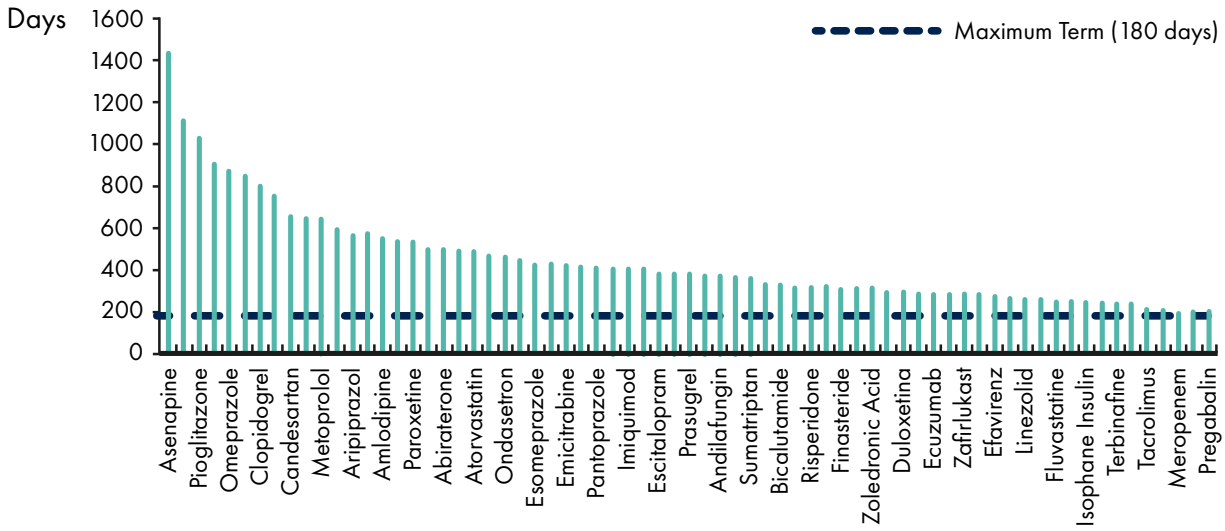
Correspond to 102 active substances.
Source: Cofece with information provided by Cofepris and a number of laboratories. File REC-001-2016. Folios: 000311 and 000312.

168 of the RHS published in the Official Gazette on August 05 2008.

116 To the date of this study, there is no public information allowing measuring health approval terms by Cofepris. Cofepris yearly publishes all listings with authorized health registrations, extension, and modifications, as well as allopathic drugs or reference. However, these do not include information on the date of filing of the application or the duration of the dealings (for greater detail on these listings, see section A.1.2 in Annex 1 hereof). Therefore, Cofepris was requested all information. This information was supplemented with various official notices for information to a number of laboratories. As of the sample collected, the number of days it took for each application for registration to resolve was calculated.

117 Over this period, Cofepris may request missing information from applicant for the registration through a notice of incompleteness - this delays the resolution period. The notice term is 1 - 60 calendar days. For resolutions of health registration for medications, these are resolved by denial by default.

Graph 2
Any medications whose average issuance time for a health registration exceeded 180 days



Source: Cofece with information provided by Cofepris and a number of laboratories. File REC-001-2016. Folios: 000311 and 000312

According to Cofepris, the use of an authorized third party reduces in half the time for processing an application. They perform a pre-opinion filed by the applicant of a new health registration, extension, or modification of an existing registration, with Cofepris.[118] Nonetheless, the average issuance time for a health registrations with pre-assessment by an authorized third party was 214 days - this term also exceeds 180 days (the maximum term as established).

Also, for a set of 55 applications for extensions, it was found that the average term for authorization was 397 days - where the maximum term for resolution is 150 calendar days (although according to the legal framework, in case the resolution is not issued within the time established, the "approved by default" application is understood as admissible.[119]

In the aggregate, these data and any evidence shown in the second section —late entry of generics to the market and the low number of competitors— suggests that there are areas of opportunity to facilitate the entry of generics to the market.

Firstly, in order to assess and follow up on the competition process in the markets, it is indispensable to have public information available allowing to measure the terms in which applications of health registrations and extensions to registrations for medications are resolved. This year, Cofepris created a

118 Electronic inquiry in: http://www.gob.mx/cofepris/acciones-y-programas/terceros-autorizados (Inquired on March 30 2017).

119 Article 190-bis 6 of the RHS points out that *"All applications for extension provided for in Articles 190 Bis 1, 190 Bis 2, 190 Bis 3 and 190 Bis 4 shall be submitted at the latest of one hundred and fifty calendar days prior to the date of expiration of the corresponding registration.*
The Ministry will resolve on any applications for extension of supplies in a maximum one hundred and fifty calendar-day term following submission of application. Where the last day of the term is a non-working day, it will be understood as extended up to the

website so that all applicants may inquiry about the status of their dealings; (i.e., if pending resolution or authorized);[120] however, access to information may only be gained through the number of application in the dealing.

Second, it would be beneficial for competition that Cofepris' online inquiry system will have full, standardized, updated information on health registrations as issued, available to the public in general and capable of identifying the universe of medications with a current health registration and its main characteristics. By April 19 2017, it was verified that the website "Inquiry on Health Registration"[121] at Cofepris does not have full information available. This makes it difficult to follow up on existing health registrations.

For instance, in an exercise prepared for all 486 generics authorized by Cofepris, within the Strategy for Release of Generics for Savings to Mexican Families, information on the registration was searched on Cofepris' website. Only about 10% has full information, while 60% came back blank for the inquiry.[122]

The absence of such information is reflected in the great number of requests for information regularly filed with Cofepris through the National Institute of Transparency, Access to Information, and Protection to Personal Data (INAI), with the purpose of obtaining information on existing health registrations. [123] The problem with full information is that it generates search costs and the potential to create conflicts between innovative laboratories and those who wish to introduce generics.

3.3 Linkage system

Like other countries,[124] Mexico adopted a system to link the patent system to all health authorizations for marketing generic versions, as a preventative mechanism to protect the rights to industrial property in

following working day. If the Ministry fails to issue the corresponding resolution in the terms set forth in this Article, application shall be understood as admissible.
For applications for extension, if applicant submits an opinion issued by an Third Party Authorized by the Ministry, the terms will be reduced in half."

120 Online: http://189.254.115.245/EstadoTramite/Default.aspx (Inquired on March 30 2017).

121 Online: http://189.254.115.245/BuscadorPublicoRegistrosSanitarios/BusquedaRegistroSanitario.aspx

122 For this exercise, information is deemed full if information on the following data is reported: Registration number, generic denomination, distinguishing designation, type of drug, therapeutic indication, active ingredient, holder of the registration, and manufacturer of the drug. (The latest inquiry was conducted on April 19 2017).

123 González Pier, et al (2017).

124 Patent linkage has been adopted in several countries. En 2011, 16 countries had this system in place: United States, Chile, Singapore, Jordan, Morocco, Oman, Bahrain, Colombia, Peru, El Salvador, Honduras, Guatemala, Nicaragua, Costa Rica, Dominican Republic, and South Korea. (Ravikant B. et al., 2013).

the pharmaceutical sector. In 2003, Article 167 bis of the RHS[125] and Article 47 bis of the IPAR[126] were added with the purpose of introducing such linkage.

This with the purpose of granting greater legal certainty to the concession of health registrations and ensure respect to the rights granted by a patent.[127] Based on that, the Medications Gazette regularly[128] publishes a list of current drug patents. This list contains all linkages between the generic denomination and pharmaceutical identity of the substance or active ingredient, the patent number, the nomenclature or form of identification on the patent, chemical name, patentee and other observations.[129]

As explained in section 3.1, in most cases, all medications have registered several patents; however, not all are published in the Gazette (as is the case with patents protecting production processes or formulation processes) and these might be identified through the "the Industrial Property Gazette Information System" (SIGA)[130] or through a direct inquiry to IMPI.[131]

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125 Article 167-bis of the RHS points out that *"Applicant for registration for an allopathic medication shall attach its application with all documentation showing it is the patentee of the substance or active ingredient or that it holds the corresponding license - both registered in the Mexican Industrial Property Institute.*
Alternatively - and according to the listing of products set forth in Article 47 bis of the Rules of the Industrial Property Act - it may state - under penalty of perjury - that it complies with all provisions as applicable regarding patents with respect to the substance or active ingredient subject matter of the application. In this assumption, the Ministry immediately will ask the technical cooperation of the Mexican Industrial Property Institute so that, within the scope of its competence, the latter determines at the latest of ten working days after receipt of the request, if current patent rights are breached. If the Mexican Industrial Property Institute concludes that there are current patents on the substance or active ingredient whereof applicant is not the holder or licensee, it will report so to the Ministry so that the Ministry will caution applicant with the purpose of it proving it is patentee or holds the corresponding license, within the term determined by the Ministry - which shall not be shorter than five working days as of notification has been effectively served. In the assumption that applicant fails to cure the omission, the Ministry will disregard the application and inform applicant the motives for this decision so that, as the case may be, it will settle the matter with the appropriate authority. Lack of response by the Mexican Industrial Property Institute within the appointed term shall be understood as favorable to applicant.
Without prejudice of the provisions in the two paragraphs above, registration for a generic with respect to a drug whose substance or active ingredient is protected under a patent may be applied for, in order to conduct all appropriate studies, tests, and experimental production, within the three prior years upon patent expiration. In this case, the health registration will be granted only upon patent expiration.
All information referred to in Articles 167 and 167 bis of these Rules with a confidential or proprietary nature under the provisions in the international treaties of which México is a party to and with all other legal provisions as applicable, will be protected against disclosure to other parties".

126 Article 47 Bis of the IPAR points out that *"When dealing with patents granted to allopathic medications, the Institute (IMPI) shall publish in the Gazette, and will make available to the public a listing of products which shall be subject matter of industrial protection according to the substance or active ingredient. It will specify the validity of the corresponding patent. This listing shall contain all correspondence between the generic denomination and the pharmaceutical identity of the substance or active ingredient and its nomenclature or form of identification in the patent. This shall be performed per the internationally-known name. The listing referred to in this Article shall not contain patents protecting production processes or drug formulation processes. If there exist a dispute with respect to the ownership of the patent of the substance or active ingredient, the interested parties may submit themselves- by mutual agreement - to arbitration, in the terms of the mercantile law".*

127 IMPI (2016).

128 The Medications Gazette may be inquired at:
http://siga.impi.gob.mx/content/common/descargaEjemplares.jsf

129 Para una lista exhaustiva de la información que contiene la Gaceta vea el Anexo 1 de este estudio.

130 SIGA is the Industrial Property Gazette´s Official Portal for diffusion, inquiry, and download of the Industrial Property Gazette in all its volumes, under Article 15. Section VII of IMPI´s Rules. Available at: http://siga.impi.gob.mx/content/common/principal.jsf

131 Por medio de servicios de información técnica que proporciona el IMPI. Para más información consulte: http://www.gob.mx/impi/acciones-y-programas/servicios-que-ofrece-el-impi-tarifas-tarifas-de-servicios-de-informacion-tecnica?state=published

At the start of the implementation of the linkage system, IMPI published only the patents for active ingredients in the Gazette. This caused uncertainty about which are the relevant patents that are considered for linkage. As of September 2012, by a court ruling, all patents for pharmaceutical compositions[132] are included in IMPI´s Gazette, while the patents of use are only included by court order. According to IMPI (2016b), the procedure for integration and updating of the Gazette may be at the request of The National Pharmaceutical Industry Chamber (Canifarma), at the request of a patentee, via an inquiry made by a public health institution or by court ruling - therefore, the list is not exhaustive.

According to Cofepris (2017), in order to issue a health registration, it must observe the validity of the active ingredient, formulation, and use patents, (i.e., if an active substance has registered patents of the three types, the manufacturers of generics shall wait for expiration of all of them to enter the market, as the case may be.[133] Therefore, for purposes of linkage, the patents list that are published in the Gazette is not exhaustive. Firstly, within the issuance process of a health registration for generics, Cofepris inquires in the Gazette and if sufficient information is found, it processes the application for registration and issues the resolution; otherwise, it inquires to IMPI through a intergovernmental inquiry form.[134] This form is for exclusive inter-institutional use.[135] The IMPI performs a case-by-case analysis. Therefore, the "linking" patent is determined in such analysis, without generalizing to avoid that any patent be a hindrance against the granting of a health registration.

Therefore, if the laboratories or the public in general wish to know all information included in the inquiry, these shall submit a request for information to Cofepris' Transparency Unit. This suggests the presence of an operational failure which, even with the publication of the Gazette, results in asymmetric information and uncertainty for economic agents, in terms of the application of the regulation. This results in greater search costs of information. Diagram 3 in Annex 4, lays out all information problems in the current linkage system, as well as simplification in the linkage system as will be proposed.

Additionally to Cofepris and laboratories, there are other governmental/non-governmental entities requiring information on the status on current patents. For instance, the Coordinator Commission for Negotiation of Drug Prices and other Health Supplies ("Coordinator Commission"),[136] needs information to determine the universe of medications subject to negotiation and under a current patent,[137] all research

132 On January 13 2010 Courtroom Two of the Supreme Court of Justice resolved on the conflicting lines of precedent 386/2009 and concluded that the patents referred to allopathic medications, that do not constitute production processes or drug formulation processes, and containing an ingredient, substance, or active ingredient in its composition or pharmaceutical formulation, under Article 47 bis of the IPAR, shall be subject matter of publication in the gazette of current drug patents. Review of the conflicting lines of precedent 386/2009 Courtroom Two of the Supreme Court of Justice. "Publication of allopathic medication patents or claims. Article 47 bis of the Rules of the Industrial Property Act".

133 Cofepris (2017).

134 Article 167 bis of the RHS.

135 Per the "Agreement whereby all provisions regarding integration, operation, and updating of the listing referred to in Article 47-bis of the Rules of the Industrial Property Act are disclosed, as well the inquiry form on allopathic medication patents. COFEPRIS-IMPI" published in the Official Gazette on February 4 2005 and modified on April 17 2013.

136 The purpose of the Coordinator Commission is to negotiate the price of medications and other health supplies included in the Basic Chart for the first tier of healthcare and in the Supplies Catalog for second/third-tier under a current patent or that are Single-source when contracting is scheduled and that are the subject matter of the procedure of direct award provided for in the Acquisitions, Leasings, and Services of the Public Sector Act (ALSPSA).

137 The Coordinator Commission is the only agency of the Federal Government that may yearly negotiate prices on medications

centers that wish to explore potential areas of innovation or the very generics industry. Therefore, it is desirable to have full, clear official information accessible to the different agencies. In this sense, the linkage system should be comprehensive.

In the US, all information on patents is submitted upon application for a health registration of innovative medications prior to a health approval by the Food and Drug Administration (FDA).[138] Afterwards, the holder of the registration has 30 days to send additional information on all relevant patents protecting the drug. After that term, more patents - which are no longer considered for linkage - may be submitted.[139] All eligible patents are published in the Orange Book, in the FDA's website - a listing that correlates the relevant patents with the innovative drug of reference for potential applications of generic versions.[140] These include those which: i) claim the active ingredient(s); ii) are pharmaceutical products including formulation/composition patents; iii) are use patents for a determined approved indication or method of use of the product; and iv) are certain types as detailed in FDA's 3542 Form. No process or manufacture patents are published.

In Canada, the department of the federal government– Health Canada– publishes and administers a list of patents associated with medications approved,[141] known as *Patent Register*.[142] This only lists those patents complying with all eligibility requirements set forth in the regulation.[143] The inquiry system allows to identify all medications by distinguishing name (brand), generic denomination, patent number or registration number of the drug.

Unlike the systems in the US and Canada, in Mexico there is no tool directly associating any medications of reference - by distinguishing name and presentation - with the patents. While the generic denomination reported in the Gazette allows the linkage of a patent with an active substance containing a drug (molecule-patent), associating any patents registered with other characteristics of the drug (e.g., pharmaceutical form, concentration, therapeutic indication, administration route, among others), proves uncertain. Ideally, the listing of medications of reference will contain information on all associated patents and their expiration date. This would reduce all search costs for all economic agents and provide greater transparency to the linkage system. The lack of transparency may give rise to trials surrounding patents. The latter is explained below.

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and other health supplies under a current patent or are Single-source. The universe of medications to be negotiated is determined in terms of the requirements of the public institutions of the National Health System based on the information granted by IMPI and Cofepris regarding validity of patents and sanitary registrations, respectively, for those medications and health supplies included in the Basic Chart and Supplies Catalog of the Health Sector.

138 All information on patents is sent to the FDA through an FDA 35425a form. Source: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf

139 Using the FDA 3542 Form. Inquired on: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM531595.pdf

140 Source: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf

141 This listing is additional to the Drug Product Database. Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

142 Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/patregbrev/index-eng.php

143 Patented Medicines (Notice of Compliance) Regulations. Inquire at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/patregbrev/ptnt-faq-mbreg-eng.php#a2

3.4 Strategic behavior

Research regarding competition conducted in other countries show that a number of laboratories adopt different strategies to delay or prevent the entry of generics. Those strategies include clustering of patents, diffusion of misleading information, replacement of product, and agreements between competitors.[144]

Evolution of the global pharmaceutical industry puts pressure on innovative companies because - on the one hand - many of them will face expiration of their patents (which in a number of cases represent up to 70% of their sales) and, on the other, generics companies in India, China, and Brazil are rapidly growing, creating strong competitive pressure worldwide.[145]

In a context of greater competition and where innovation is increasingly costlier, laboratories have incentives to try and extend the market exclusivity term granted by patents. Based on the stages in the process of development of a drug,[146] laboratories apply for successive patents for various inventions on the same active substance. These may be those connected with: i) second medical uses, and ii) incremental innovations.[147]

As for the first item, there is a global debate on their patentability. People who are in favor of this, argue that an additional medical use may be, per se, inventive and, in a number of cases, therapeutically more valuable than the first one. Opponents argue that such patents prevent the entry of generics to the market, reward non-inventive activities, and unnecessarily extend protection to an active substance.[148] As for the second item, incremental inventions refer to changes in formulation, dosage forms, or route of administration of a drug previously approved and which enhances the efficacy of the treatment.[149]

Sometimes, applications for patents on new uses or incremental innovations are strategies by innovative laboratories to block the entry of generics - especially where the assumed innovations have no additional therapeutic value or there is uncertainty on the validity of its inventive step. The literature identifies these strategies as evergreening of patents.[150]

The international literature suggests that innovative laboratories protect a molecule through a number of patents as a strategy to increase the costs for third parties to enter the market. This defensive strategy is known as patent clustering.[151] In order to prevent patent clustering, in other countries (e.g., Argentina, Israel, and India) restrictions on the granting of secondary patents have been imposed. In Argentina

144 OECD (2015).

145 UNCTAD (2015).

146 According to the FDA, the stages in the development of a drug are five: i) discovery and development, ii) preclinical research, iii) clinical research (four phases), iv) health approval and v) surveillance post-authorization. Source: https://www.fda.gov/forpatients/approvals/drugs/

147 WTO, WIPO y WHO, (2012).

148 Cf. OMPI, 2015.

149 As variants of an active ingredient, metabolites, intermediates, particle sizes of the active ingredient, dosages, release mechanisms, among others.

150 See OECD (2015).

151 See European Commission (2009), WTO, WIPO and WHO, (2012) and OECD (2015).

in 2003, it was declared that those inventions associated with second uses are not patentable. New guidelines were recently introduced for examination of patents in order to restrict secondary patents. In India, for instance, in early 2005 Section 3 (d) was added to the Patents Act. It was designed to minimize the concession of secondary patents, strictly as innovations of process; for metabolites of the medicinal ingredient; for an impurity present in the final pharmaceutical product; for a different chemical form of the medicinal ingredient or it uses, including salts, esters, polymorphic forms, and others derived from the medicinal ingredient. In May 2015, the Patents Office of Israel enacted directives to restrict certain secondary patents.[152] These countries have found it necessary to weigh between their domestic interest and the rights acquired through international obligations (e.g., free trade agreements and the Agreement on the ADPIC). This on occasions, have moved them away from a number of their trade partners.[153]

In Brazil, a different strategy was implemented - in 2001 the Patents Act was amended to establish that the concession of patents for pharmaceutical products and processes depends on approval both by the National Industrial Protection Institute and the National Sanitary Surveillance Agency.[154] Therefore, the health agency in that country has the authority to restrict the use of secondary patents through its own intellectual patents division. Like Brazil, in Egypt and Paraguay, the Ministries of Health intervene in the examination of applications for patents.[155] In that regard, the US regulation prevents patents granted after the innovative drug has obtained a health registration from being considered for linkage between any patents and a health approval. This restricts laboratories in the sense that any patent related to the drug has to be registered prior to obtaining the health registration.

Another strategy by the laboratories, that has been documented, is product switching. Product switching consists of addressing messages to medics and pharmacists in order to generate a change in the demand of the original drug to its new brand formulation, that is protected under a more recent patent.[156] In the US, product switching carried out in the following way has been documented: Prior to any application for generic drug being approved by the FDA, or slightly prior to expiration of the patent of the branded drug, the manufacturer of the branded drug files a new application for registration in order to modify the already-marketed drug. Modifications may consist of a new form (capsule, tablet, chewable, etc.), a new dosage or other marginal modification (e.g., prolonged release mechanisms of the drug). Upon the new application being approved, the manufacturer of the branded drug replaces commercialization of the prior version with the new one - in an attempt to switch the preferences in the market towards the new version.[157] In that case, the patentee switches products without a clear therapeutic benefit and only in order to delay competition. This allows drugstores to exchange the original drug with its generic equivalent, where doctors stop writing prescriptions for the older drug (original). The possibility

152 See Sampat and Shalden (2016).

153 Comments by IMPI to "(Extract as to patents) Study regarding free market and economic competition in the expired-patent drug markets". Submitted on April 06 2017.

154 Íbid.

155 Íbid.

156 See OECD (2015).

157 See Silber and Kuritz (2010).

of replacement of the original with the generic and, therefore, the possibility of competition among generics with respect to the first-generation drug is removed.[158]

In Mexico, product switching might be facilitated through modifications to the drug of reference.[159] In that regard, the National Medications Manufacturers Association (Anafam) pointed out that this practice exists because the same health registration may be modified to the conditions in terms of new patents.[160] Therefore, if the registration for a drug of reference is modified as an enhancement associated with a new current patent, this makes the entry of a generic impossible. In order to obtain the health registration, Cofepris should verify with the IMPI that no patents for the drug of reference are breached.[161] According to Anafam, a possible case is a drug containing the active substance clopidogrel. The active ingredient patent that protected this substance expired on February 17 2007.[162] However, the first generics entered the market in early 2012.

In all the pay for delay agreements documented in the US and the European Union, the laboratory manufacturing the innovative drug and the one intending to produce the generic, agree that the latter will be left out of the market during a given time, in exchange for some payment.[163] This practice negatively affects consumers. These will pay a higher price during the time entry of the generic drug to the market is delayed.[164] This type of agreements represents the most common cases of horizontal restriction that have been researched in such countries.

In the US, the health legal framework allows a manufacturer of generics to obtain approval by the FDA if the former shows that the relevant patent for the innovative drug is invalid (certification under Paragraph IV).[165] Under this condition, producers of generics have incentives to object to patents of the innovator laboratory - the first to file a full application obtains 180 days of exclusivity as the sole generic in the market. Nevertheless, filing an application under this certification is considered a breach of patent rights and, thus, may be objected to by the innovator laboratory in court. This causes a legal battle between the latter and the manufacturer of generics.

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158 Addy y Douglas (2014).

159 It is important to note that any modifications to the conditions of a drug health registration - either with or without changes in the manufacture process - should be authorized by Cofepris in accordance with Article 185 of the RHS.

160 These modifications may be of two types: i) without change in the manufacture process (for instance, change of additives or excipients, or changes of therapeutic indication, among others), and ii) with a change in the manufacture processes (for instance, changes in raw materials, processes, and finished products).

161 If the drug of reference is not available in the national territory (i.e., is not marketed or has been de-registered) a drug of international reference may be used. In accordance with the "Guidelines that shall be complied with by allopathic medications of reference and selection of a drug of international reference". Official circular No. CAS/01/OR/4/2016 of Cofepris. Available at: http://www.gob.mx/cms/uploads/attachment/file/163209/Lineamientos_para_medicamentos_de_Referencia_25-Ene-16.pdf (Inquired on 04-19-2017).

162 In 2006, the holder requested from the IMPI that the validity of the patent was corrected so that the same would expire on June 19 2012. The IMPI denied extension of the requested validity, though, its resolution was objected to. Therefore, the patent remained valid—at least up to April 2008— due to the provisional suspension granted.

163 See Scott (2013).

164 The FTC (2010) estimates that pay for delay agreements cost US consumers 3.5 billion dollars a year.

165 The Federal Food, Drug, and Cosmetic Act. (FFDCA) requires that applicant of a registration for a generic selects in its application (ANDA) any of the following certifications per patent listed on the Orange Book of the innovative drug: i) that all information on the patent has not been submitted; ii) that the patent has expired; iii) that the patent will expire on a given date; or iv) that such patent is invalid or will not be breached by the drug which approval is requested.

In the US, the fact that payments for delay may arise as part of these trials has been documented.[166] Due to the costs and the uncertainty generated by a trial on patents, both the innovator laboratory and the manufacturer of generics have incentives to resolve it on their own account prior to the final decision by the court. This may result in an agreement including an economic compensation from the innovator to the manufacturer of generics upon the condition of delaying entry of the generic drug to the market.[167] This particular type of payment for delay is known as reverse payment patent settlement.[168] In the US, these agreements are considered anticompetitive if the payment exceeds the costs derived from the trial.[169]

In the aggregate, some of the patents may be used by laboratories to unnecessarily extend the right to exclusivity granted by a patent. Therefore, all figures in the patents shall be reviewed in order to restrict granting the patent to those more inclined to abuse it. How laboratories use different means to discourage entry of competitors to the market is detailed below.

3.5 Trials regarding patents and health registrations

When the linkage system started operating in Mexico, the IMPI published only the patents connected with the active ingredient.[170] Nonetheless, given that an active substance may have a number of patents associated with it, this gave rise to trials and uncertainty on the number and type of patents that were associated with a drug, along with the fact that the Gazette fails to explicitly indicate which medications such patents correspond to - unlike the Orange Book.

If in the Gazette only the active ingredient patents are published, then other current patents that may be infringed upon by the manufacturers of generics (e.g., composition/use) are omitted. All jurisdictional bodies have interpreted that, except for the patents of manufacture process or formulation process that area expressly forbidden, all other types of patents (i.e., active ingredient/ pharmaceutical composition/use) shall be included in the Gazette. On this topic, three associated events have marked its development.[171] First, in 2008 a Regional Room was created for Intellectual Property matters as part of the then Federal Fiscal and Administrative Justice Court (currently Federal Administrative Justice Court), which has competence to resolve on trials filed against final resolutions given based on all ordinances governing the matter in question.

Second, in 2010, the Supreme Court of Justice (SCJN) issued a criterion that forces publication in the Gazette of all allopathic medication patents or their claims that do not constitute a production processes or drug formulation process and whose pharmaceutical composition includes an ingredient,

166 FTC (2010).

167 The cases of payment for delay are numerous in the European Union where the patents system does not grant a reward of exclusivity to the first laboratory of generics successfully objecting to the patents. This suggests that there are other incentives propitiating this type of agreements -even without the exclusivity period of the "first-to-object" as applied in the US. (European Commission 2009).

168 See Meunier and Padilla (2015) and Edlin et al. (2013).

169 The FTC (2010) used a definition of "payment" that includes not only the direct monetary payment, but also other types of consideration involving the transfer of value from the original laboratory to the generics company.

170 According to the provisions in Articles 167 Bis of the RHS and 47 Bis of the IPAR.

171 González Pier and Barraza Lloréns (2011).

substance, or active ingredient.[172] By this court ruling, as of September 2012, the Gazette publishes all pharmaceutical composition patents.

Finally, in 2016, the Congress of the Union approved a bill or amendment to the IPA which forces publication in the Gazette of all resolutions issued in the administrative declaration procedures, as well as those presenting petitions with the purpose of modifying the conditions of patents or registrations.[173] Also, in 2010,[174] non-contentious opposition mechanism for patents that may help avoid evergreening.[175]

The linkage system is a preventative mechanism whose ultimate end is to avoid that the government grants health registrations breaching the rights of a current patent. However, its lack of transparency on the number and type of patents protecting a drug, has encouraged innovator laboratories using litigation to hinder the entry of generics into the market through different means as explained below.

In Mexico, innovative laboratories may block or delay the entry of generic drugs by two ways: i) a litigious activity associated to the patents system and ii) a litigious activity related with the issue of a health registration. In the latter, disputes may arise with respect to protection to patents, as well as to all information generated for the granting of the health registration (clinical data).

With respect to the patents system, the procedures involving disputes between manufacturers of innovative medications and of generics are mainly based on two legal actions:

i. Action due to breach. Patentee denounces a violation of its rights to exclusivity, with the purpose that a judicial body declares that the generic product is infringing upon the patent and orders prohibition to its production and commercialization up to its expiration.[176]
ii. Invalidity Action Manufacturers of generics may file an annulment action on the patent of the original manufacturer, with the purpose of the patent being declared invalid and, thus, they may enter the market, unless the drug is protected under other patents that have not been yet annulled.

In different countries, the fact that the trials mostly discuss secondary patents has been documented.[177]

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172 Review of the conflicting lines of precedent 386/2009 Courtroom Two of the Supreme Court of Justice. "Publication of allopathic medication patents or claims. Article 47 bis of the Rules of the Industrial Property Act". Available at: https://www.scjn.gob.mx/sites/default/files/resenias_argumentativas/documento/2016-11/res-SSAA-386-09_0.pdf (Inquired on 03-05-2017).

173 "Decree whereby different provisions of the Industrial Property Act are amended and added". Published in the Official Gazette on June 1 2016.

174 "Decree whereby different articles of the Industrial Property Act are amended and added". Published in the Official Gazette on June 18 2010.

175 This procedure allows any person to oppose granting of a patent from an application published in the Gazette, providing arguments or evidence on its inadmissibility due to failure to meet all requirements of novelty, inventive step, or industrial application, or if it falls in one of the assumptions of exception to granting of patents set forth in the law, or otherwise, if application contains claims intending to encompass rights additional to those linked to the description and the summary of the invention, or where such claims partially or totally include previously-patented inventions - even if dealing with patents of the same holder. All information as provided may be used for the baseline study, thus, opening the possibility of stating to the IMPI the existence of causes to file for an administrative declaration procedure ex officio.

176 In Europe, there exist an action of declaration of non-infringement as a counter-action by manufacturer of generics in order to obtain a declaration of the Court that its product does not infringe the patent of the original company. This action allows the generic product enter or remain in the market free of action on patents (European Commission, 2009).

177 For instance, in the US, the statistics on the validity of patents suggest that the likelihood of a patent being found valid in a litigious process, in average, is low. Out of the 15,000 patents issued by the US Patents and Trademarks Office (PTO) each month,

In Mexico, the legal framework on patents allows conducting the two litigious actions above.[178] The IMPI is empowered to file for - ex officio or upon request - the procedure of administrative declaration of invalidity, expiration, cancellation and administrative infringement set forth by the IPA,[179] as well to adopt any such interim measures as provided for in such ordinance.[180]

All trials associated with these legal actions are resolved in various instances and the time for resolution may be several years. This translates into costs for the parties involved. For instance, all final resolutions issued by the IMPI may be objected to through a contentious-administrative trial.[181] This is resolved with the Specialized Room as to Intellectual Property of the Federal Administrative Justice Court. Against the decision issued by the above Specialized Room (if contrary to the interest of the private party) the affected party may file a writ of direct relief.[182] This will be heard by the appropriate Administrative Chartered Courts of the First Judicial Circuit.

Objection to all acts of authority is a right enacted in the Constitution; though, the risk associated with the uncertainty of having to incur in lengthy onerous trials increases the costs of entering the production of generics.

According to information by the IMPI, between 2010 and 2015, 124 procedures of administrative declaration of infringement of patent rights were filed. 74% related with a secondary patent. To this date, only the administrative infringement in favor of patentee in 21 cases (17%) has been proven. These procedures lasted four years in average.

Also, over this period also 45 procedures of administrative declaration of invalidity of patents were reported. Of these, most (89%) are associated with a secondary patent. To this date invalidity of the patent has been declared in 5 cases (11%) - all of them secondary - and the average resolution term was 3.6 years. Chart 8 reports all procedures due to infringement and invalidity on active substance patents.

Additionally, to the litigious activity associated with a violation to the IPA, as part of the issue of a health registration by Cofepris, disputes may arise around the protection to the patents and the clinical data.[183] The legal means to formalize such disputes are administrative-contentious trials and writ of amparo

about 0.1% are the subject matter of trials and approximately half of these prove invalid.

178 Articles 187 - 202 of the IPA.

179 Art. 188 of the IPA.

180 Art. 199 BIS de la LPI.

181 According to Article 3, Section XII of the Organic Law of the Federal Administrative Justice Court. Published in the Official Gazette on July 18 2016.

182 In accordance with Article 170, Section I of the Writ of Amparo Act Governing Articles 103 and 107 of the Political Constitution of the United Mexican States. Published in the Official Gazette on April 2 2013. Latest amendment published in the Official Gazette on June 17 2012.

183 Protection to clinical data is a figure for protection to confidential/proprietary information related with the safety and efficacy of pharmaceutical products and which Cofepris receives through health registration application. Under the protection of the provisions in the North American Free Trade Agreement (NAFTA) and of the Agreement on Aspects of Property Rights regarding Commerce (ADPIC) of the World Trade Organization, this information is subject to protection against commercial/disloyal use and against disclosure by Cofepris. Official circular No. CAS/01/OR/896/2012 of Cofepris. Available at: http://www.cofepris.gob.mx/Documents/LoMasReciente/proteccion_info.pdf (Inquired on 03-05-2017).

trials where Cofepris is getting sued for:[184]

i. Granting (or imminent granting) of a health registration under the assumed invasion of patent rights by the holder.
ii. Protection to clinical data included in the dossier[185] attached by applicant of a health registration in the face of Cofepris, as well the use of such clinical data for issue of health registrations to third parties.

With respect to the former, this type of procedure is filed by the holder or licensee of a patent granted by the IMPI. In this procedure, they sue Cofepris for an assumed violation to exclusive rights protected under a patent, for granting or (imminent granting) of a health registration to a third party. According to Cofepris (2017), within this trial, plaintiff requests as injunctive relief the suspension of the effects of the issue of the registration or the procedure of application for registration. Therefore, should any of these measures be enforced, plaintiff enjoys exclusivity to market a product.[186]

Upon conclusion of the trial, if the appropriate judicial body proves that no invasion of patents existed by the granting of the health registration, or otherwise if Cofepris issues the registration, the injunctive relief as granted is removed and the health registration remains effective or, as the case may be, the health authority continues with the resolution of the applications for health registration. Average duration of these trials - once all recourses have been exhausted - is three years through resolution.[187]

As to the latter, this type of procedure is filed by the holder of a health registration wherein it requests from Cofepris the express acknowledgment of protection to clinical data.

In 2012, Cofepris issued the "Guidelines for protection to confidential information on medications containing pharma-chemicals as a new chemical entity"[188]. These guidelines set forth all requirements to demonstrate the protection. Nevertheless, item 5.5 of such guidelines is ambiguous. It points out as a requirement that attainment of the data should assume a "considerable effort" by applicant.

According to Cofepris (2017), in the trials regarding protection to clinical data, plaintiff requests as an injunctive relief that the authority does not allow that information submitted by the application for a health registration is used to support the health approval for any third parties. Upon conclusion of the trial, if the judicial body determines that all information submitted by plaintiff accounts for a "considerable effort" and warrants protection to data, then it orders Cofepris to issue the express acknowledgment of protection over a five-year period,[189] as of issue of or modification to a health registration.[190] To reduce

184 Cofepris (2017).

185 Refers to the file which comprises the application for a health registration with Cofepris.

186 Cofepris (2017).

187 Cofepris (2017).

188 Through official circular No. CAS/01/OR/896/2012. Available at: http://www.cofepris.gob.mx/Documents/LoMasReciente/proteccion_info.pdf (Inquired on 03-05-2017).

189 In a number of cases, laboratories have demanded protection to clinical data beyond the 5-year period set forth in the guidelines of Cofepris.

190 Cofepris (2017).

the number of trials around this topic, it is recommended that technical criteria be issued by Cofepris to conduct the declaratory judgment for protection to clinical data with respect to innovative medications.

At this date, fourteen trials associated with protection to clinical data and five cases have been recorded. Cofepris has granted protection to clinical data derived from the court decision. According to Cofepris, the average time for resolution of these trials - all recourses having exhausted - is one year and a half. Chart 9 summarizes all trials reported by Cofepris for active substances around invasion of patents and protection to clinical data.

In the aggregate, a litigious activity may negatively impact commercial decisions by a manufacturer of generics, before or after entering the market, for:

i. An original laboratory may persuade a manufacturer of generic drugs of launching its product into the market, by means of certainty that would generate long and costly jurisdictional procedures.[191]
ii. Disputes on a breach of patent rights may result in cautionary measures imposed by courts, which compel the companies of generic drugs to remove its products from the market, which would translate into losses (production without sales).[192]

While performing this Study, we were made aware that some publicly known active principle patent holders, have intended to cause confusion in the authorities on the acquisition of drug products for the public sector and the Courts, even trying to persuade its own competitors by warning them, informally, about the possible start of a breaching procedure in case of not refraining from the commercialization of any product related to the active principle.

As for disputes related to the granting of sanitary registrations and patents, when performing this study, it was known that these disputes have taken place mainly in recent years, because, partly, there is inconformity with the different interpretations and statements by Cofepris regarding the criteria in which said authority considers that there is applicability or not of the use of the linkage system or of its scope. Stemming from this, there is the importance of establishing more transparency and clearer rules in the linkage system, with rules that limit the spaces of discretion.

In Mexico, the evidence on dispute activity in the pharmaceutical sector shows that the disputes generally involve the drugs with the highest sales and whose active principle patents are expired, but have other patents registered. For example, there are cases like celecoxib and imatinib, where there is information on sanitary registrations of generic drugs, but there is no evidence of them being commercialized in the private market. In other cases, the demands due to breach which were started by innovative laboratories against generic producers have been dismissed because the patents in question have been nullified by IMPI because they lack industrial activity (such as levonorgestrel). In Annex 3, there is a summary of some of the most emblematic cases.

191 For example, in Europa, it is calculated that a dispute related to the contestation on the validity of a patent may last up to nine years, from the submission date until using the last instance (European Commission, 2009).

192 Magaña (2014).

In short, innovative laboratories may extend market exclusivity of its products by means of abuse of judiciary procedures, and so, hinder the entry of generic drugs into the market. That is the reason why the linkage system must be reviewed in order to have a transparent tool between sanitary authorizations and the protection to industrial property rights, and so, reduce the possible spaces for disputes whose aim is to delay the entry of generic drugs.

Table 8
Summary of procedures reported by IMPI (2010-2015)[1]

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Tadalafil	196955 223229 225078 231215	2015 2020 2020 2020	13	3	16	Eli Lilly y Compañía de México S.A. de C.V.	Sales y Materias Primas, S. de R.L. de C.V. Chemswiss México, S.A. de C.V. RETECMA, S.A. de C.V. MPI farmacéutica, S.A. de C.V. Laboratories Alpharma, S.A. de C.V. HELM de México, S.A. Laboratories Liomont, S.A. de C.V. Factores & Mercadeo, S.A. SICA, S.A. de C.V. QNOVA, S.A. Química y Farmacia, S.A. de C.V.	Sun Pharma de México, S. A. de C. V.	CIALIS	0	There is no generic product
Sildenafil	181244 195457 214691 214692	2011 2014 2017 2019	14	1	15	Pfizer, Inc. (patent 181244) Novartis AG. (patents 214691 y 214692)	Genoma Lab Internacional, S.A.B. de C.V. Compañía Internacional Médica, S.A. de C.V. Landsteiner Pharma, S.A. de C.V.	Protein, S.A. de C.V.	VIAGRA	18	01/09/2014
Ethynilestradiol, drospirenone	228386 314015	2020 2020	10	3	13	Bayer Pharma Aktiengesellschaft	Laboratories Liomont, S.A de C.V. Siegfried Rhein, S.A de C.V. Laboratories Elea México, S.A de C.V.	Sun Pharma de México, S.A de C.V. Siegfried Rhein, S.A de C.V. Laboratorios Liomont, S.A de C.V.	YASMIN	No data	No data

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Nitric oxide	206992	2013	12	1	13	The General Hospital Corporation	Praxair México, S. de R.L. de C.V. Instituto Nacional de Cardiología "Ignacio Chávez" Hospital Real San José, S.C. Fundacion Santos y de la Garza Evia, I.B.P. Christus Muguerza Sistemas Hospitalarios, S.A de C.V. Hospital y Clínica Oca, S.A de C.V. C. owner and/or holder	Praxair Mexico, S. de R.L. de C.V.	INOMAX (drug product) INOVENT (medical device)	No data	No data
Rituximab	239890 268683 266754 274364	2020 2024 2024 2020	12	-	12	Genentech, Inc. y Biogen Inc.	Probiomed, S.A de C.V. Proquigama, S.A de C.V. Silodisa Servicio Integral de Logística y Distribución, S.A.P.I. de C.V. Hospital Regional de Alta Especialidad del Bajío C. owner and/or lessor the real estate property located at boulevard Milenio no. 130, San Carlos la Roncha, C.P. 37660, León Guanajuato, México. Savi Distribuciones, S.A de C.V.	-	MABTHERA	No data	No data
Ketorolaco, tramadol	266401	2022	8	2	10	PPTM International, S.Á.R.L.	Mavi Farmacéutica, S.A de C.V. Comercializadora Farmacéutica de Chiapas, S.A.P.I. de C.V. Farmacias de Similares, S.A de C.V. SBL Pharmaceuticals S. de R.L. de C.V.	Farmacias de Similares S.A de C.V. SBL Pharmaceuticals S. de R.L. de C.V.	SINERGIX	No data	No data

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Sibutramin, metformin	262191	2029	8	2	10	International Pharma Labs S.A.R.L.	Laboratory Silanes, S.A de C.V. Investigacion Farmaceutica, S.A de C.V.	Farmacias de Similares S.A de C.V. SBL Pharmaceuticals S. de R.L. de C.V.	BADEFEM	No data	No data
Imatinib	190786 218673 244404 252475	2013 2018 2021 2023	7	2	9	Novartis AG	Sun Pharma de México, S. A. de C. V. Helm de México, S.A. Probiomed, S.A. de C.V. Farmabiot, S.A. de C.V. Laboratorios Pisa, S.A. de C.V. Sicor de México, S.A. de C.V. Distribuidora Internacional de Medicamentos y Equipo Médico, S.A. de C.V.	Probiomed, S. A. de C. V. Lemery, S. A. de C. V.	GLIVEC	0	There is no generic
Levonorgestrel	245428	2022	9	-	9	Richter Gedeon VegyészetI Gyár NyilvánoSAN Müködö RT	Ultra Laboratorios, S.A. de C.V. Farmacos Nacionales, S.A. de C.V. Farmacias ABC de México, S.A. de C.V. Grupo Casa Saba, S.A. de C.V. Nadro, S.A. de C.V. Casa Marzam, S.A. de C.V. Reder, S. de R.L. de C.V. Distribuidora Levic, S. de R.L. de C.V. Farmacéutica Delta, S.A. de C.V.	-	POSTINOR-2	11	01/03/2004

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Pregabalin	223993	2017	4	4	8	Warner-Lambert Company LLC	Sandoz, S.A. de C.V. Ultra Laboratories, S.A. de C.V. Lemery, S.A. de C.V. Laboratories Pisa, S.A. de C.V.	Asofarma de México, S. A. de C. V. Sandoz, S. A. de C. V. Ultra Laboratories, S. A. de C. V. Lemery, S. A. de C. V.	LYRICA	7	01/05/2016
Glatiramer	286217 316907	2025 2030	3	3	6	Teva Pharmaceuticals Industries, Ltd Yeda Research and Development Co., Ltd.	Nafar Laboratorios, S.A de C.V. Laboratories Pisa, S.A de C.V. Probiomed, S.A de C.V.	Probiomed, S.A de C.V. Laboratories Pisa, S.A de C.V.	COPAXONE	No data	No data
Calcium gluconolactate	213013	2022	5	1	6	Aristides Torres Velasco y Manuel Radames Torres Velasco	Laboratory Zerboni, S.A. Bioresearch de México, S.A. de C.V. Comercializadora Pharmaceutica Compharma, S.A. de C.V. Ragar, S.A. de C.V. Silodisa Servicio Integral de Logística y Distribución, S.A.P.I. de C.V.	Tecnofarma S.A de C.V.	VAN-CAL	No data	No data
Polivalent fabotherapic anti-scorpio or anti- spiders or anti-snakes	230257	2022	3	1	4	Instituto Bioclón, S. A. de C. V.	Veteria Labs, S.A de C.V. T.I. Health, S.A de C.V.	Veteria Labs, S.A de C.V.	Anti-venom Product	No data	No data

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Citicoli	219061	2024	2	-	2	Ferrer International S.A.	Serral, S.A de C.V.	-	SOMAZINA	No data	No data
Metformin hydrochlorate and glibenclamide	215895	2024	2	-	2	Abiogen Pharma S.P.A.	Laboratory Raam de Sahuayo, S.A. de C.V. Productos Farmacéuticos Collins, S.A. de C.V.	-	DIBENMIN	No data	No data
Formoterol, fluticasone propionate	227309	2020	-	2	2	Novartis AG	-	Glenmark Pharmaceuticals Limited	SERETIDE EVOHALER	No data	No data
Glimepiride and metformin	248617	2022	2	-	2	Laboratories Silanes, S.A. de C.V.	Laboratory Raam de Sahuayo, S.A. de C.V. Micrometrix, S.A. de C.V.	-	GLIMETAL LEX	0	There is no generic
Meloxicam, metocarbamol	249290	2021	1	1	2	World-Trade Import-Export, Wite, A.G.	Productos Maver, S.A de C.V.	Bionova Laboratories, S.A de C.V.	Procedure for preparing a pharmaceutical composition	0	There is no generic
Product (protein extract)	243816	2022	2	-	2	Edgar de Jesús Arroyo González	Nubio, S.A de C.V. Grupo Nutri Technologies, S.A de C.V.	-	GIALIVE	No data	No data
Fusion Protein (tnfr-ig)	268631	2024	2	-	2	Pfizer Ireland Pharmaceuticals y Pfizer, S. S. de C. V.	Probiomed, S.A. de C.V. Landsteiner Scientific, S.A. de C.V.	-	ENBREL	No data	No data
Rosuvastatine	227360	2020	1	1	2	Astrazeneca, AB.	-	Sandoz, S.A. de C.V.	CRESTOR	11	01/04/2015

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Trastuzumab (anti-erb2 antibody)	259512	2021	-	2	2	Takeda Pharmaceutical Company Limited	-	Celltrion, Inc	HERCEPTIN	0	There is no generic
Ibandronic acid	286782	2023	-	1	1	F. Hoffmann - La Roche AG.	-	Asofarma de México, S.A. de C.V.	BONVIVA	1	01/06/2014
Micophelonic acid (mofetil mico fenolate)	255667	2022	-	1	1	Novartis AG	-	Glenmark Pharmaceuticals México, S. A. de C. V.	CELLCEPT	5	01/07/2009
Adalimumab	272842	2023	-	1	1	Abbvie Biotechnology Ltd.	-	Probiomed, S. A. de C. V.	HUMIRA	No data	No data
Aminopiridine	293798	2025	-	1	1	Acorda Therapeutics, Inc.	-	Nafar Laboratories, S.A de C.V.	AMPYRA	No data	No data
Celecoxib	213466	2019	-	1	1	G.D. Searle LLC.	-	Hetlabs México, S. A. de C. V.	CELEBREX	1	01/12/2012
Dimethylfumarate	221370	2019	-	1	1	Biogen Idec International GMBH	-	Nafar Laboratories, S.A de C.V.	TECFIDERA	No data	No data
Docetaxel, trastuzumab	231665	2020	-	1	1	Aventis Pharma, S.A.	-	Celltrion, Inc.	TAXOTERE	5	01/05/2012
Glimepiride, pioglitazone	257152	2024	1	-	1	Nucitec, S.A. de C.V.	Representaciones e Investigaciones Médicas, S.A de C.V.	-	-	No data	No data
Disodium pemetrxed Heptahydrate (crystalline form)	227084	2021	-	1	1	Instituto Bioclón, S. A. de C. V.	-	Glenmark Pharmaceuticals Limited	ALIMTA	2	01/08/2014

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Inhibitor of carbonic anhydrase (dorzolamide) and of b-antagonist-adrenergic (timolol, betaxolol, carteolol, levobunolol, metipranolol)	182844	2022	-	1	1	Merck & Co. Inc	-	Precimex, S.A. de C.V.	TRUSOPT	3	01/09/2009
L- levalbuterol tartrate	258474	2023	-	1	1	Sunovion Pharmaceuticals Inc.	-	Glenmrk Pharmaceuticals Limited	XOPENEX	No data	No data
Method to produce tnfr-ig	268631	2026	-	1	1	Pfizer Ireland Pharmaceuticals	-	Probiomed, S.A de C.V.	ENBREL	No data	No data
Olmesartan; medoxomil	293583	2024	-	1	1	Daiichi Sankyo Company, Limited	-	Asofarma de México, S.A de C.V.	BENICAR	No data	No data
Raloxifen	212441	2017	1	-	1	International Pharma Labs S.A.R.L.	Lemery, S.A. de C.V.	-	EVISTA	0	There is no generic
Raloxifen, estrogen	254045	2028	1	-	1	Eli Lilly and Company	Farmacias de Similares, S.A de C.V.	-	EVISTA	0	There is no generic
Rifaximine	260156	2028	1	-	1	Alfa Wassermann S.P.A.	Interquim, S.A de C.V.	-	FLONORM	No data	No data
Travoprost	194308	2015	-	1	1	Alcon Laboratories Inc	-	Dankel Medical, S. A. P. I. de C. V.	TRAVATAN	0	01/12/2012

Generic name	Patents involved	Effective term of patent (year)	Procedures			Parties involved			Drug products		
			Breach	Nullity	Total	Patent Holder	Laboratories of generic drugs sued due to breach of rights	Laboratories that have started a lawsuit on the patent nullity	Associated Drug product or associated innovative product	Generic drugs with presence in the market[2]	Launch date of the first generic product
Several active principles (increaser of sensitivity to insulin and increaser of insulin secretion)	234559	2016	-	1	1	Takeda Pharmaceutical Company Limited	-	Representaciones e Investigaciones Médicas, S.A de C.V.	No data	No data	No data
Several active principles (a protein and a lipoprotector) trastuzumab, omalizumab	282656	2016	-	1	1	Genentech, Inc	-	Celltrion, Inc	No data	No data	No data
Several active principles, an antagonist of the angiotensin ii receptor (formula i compound) and one or more diuretics	236675	2022	-	1	1	Daiichi Sankyo Company, Limited	-	Asofarma de México, S.A de C.V.	No data	No data	No data
Total			124	45	169						

[1] It refers to administrative procedures started in the period from 2010 to 2015.
[2] With information from January 2009 to August 2015.
Source: Cofece with information from IMPI, Cofepris and information in Fiole REC-001-2016.
Folios: 000142- 000154.

Table 9
Trials due to patent breech and clinical data protection reported by Cofepris

Active substance	Trials due to patent breech		Trials due to clinical data protection
	Number of trials	Number of companies affected	
Abiraterone	-	-	Nullity: 1
Adalimumab[1]	-	-	Nullity: 1
Atomoxetine or tomoxetine	Nullity: 1	• 1 company affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Caspofungin	Nullity: 1	• 1 company affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Celecoxib	Amparo: 2 Nullity: 1	• 3 companies affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Eliglustat	-	-	Nullity: 1
Etanercept	Nullity: 2	• 2 companies affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Everolimus	-	-	Nullity: 1

Active substance	Trials due to patent breech		Trials due to clinical data protection
	Number of trials	Number of companies affected	
Mometasone furoate	Amparo: 1 Nullity: 1	• 2 companies affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Golimumab[1]	-	-	Nullity: 1
Infliximab[1]	-	-	Nullity: 2
Imatinib Mesilate	Amparo: 7 Nullity: 2	• 9 companies affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Sodium Mipomersen	-	-	Nullity: 1
Moxifloxacin	Nullity: 2	• 2 companies affected directly • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Palonosetron	Nullity: 2	• 2 companies affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-
Ranibizumab[1]	-	-	Nullity: 1
Rosuvastatin	-	-	Nullity: 1

Active substance	Trials due to patent breech		Trials due to clinical data protection
	Number of trials	Number of companies affected	
Sacubitryl /valsartan	-	-	Nullity: 1
Sevelamer	-	-	Nullity: 1
Tadalafil	Amparo: 4	• 4 companies affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	Nullity: 2
Trastuzumab	-	-	Nullity: 1
Trastuzumab emtansin	-	-	Nullity: 1
Travoprost	Amparo: 4	• 4 companies affected directly. • Indirectly: all applicants of sanitary registration of allopathic drug product which contains the active principle.	-

[1] Biotechnological.
Fuente: Cofece with information provided by Cofepris (2017).

3.6 Summary of Recommendations

Recommendation 1. That Cofepris, in the listing of approved reference medicines, explicitly specify the patents that protect the medicines and its expiration date, all of this in order to provide transparency to the linkage system and patent protection. Cofepris may integrate this listing with the information on patents provided by IMPI through the intra-governmental inquiry.

This recommendation requires establishing explicitly in the Regulation of Health Supplies, the obligation of Cofepris of releasing information on patents.

The objective of this measure is that participants in the pharmaceutical industry: public and academic institutions, Courts and the public, may know, the patents that protect inventions around a medicine. This would reduce the problem of incomplete and asymmetric information and, consequently, it would give more certainty to economic, administrative and legal agents, which would reduce the entry costs for new generic drugs.

Recommendation 2. Assess, along with IMPI and the Ministry of Health, the convenience of including in the Regulation of the Act on Industrial Property, restrictions on granting secondary patents, as it has been included in other countries.

This recommendation replaces the proposals aimed at making more transparent the linkage system, so, in case of improvements in that system, this one would become just reiterative.

Recommendation 3. Establish, explicitly, restrictions on the linkage system, so that the registered patents, after the sanitary registrations are granted, not be considered for linking the same reference drug.

This does not limit the laboratories to use their patents —granted after the sanitary registration is approved— for the development of second-generation medicaments or others.

Recommendation 4. That Cofepris grant a new health registration when a laboratory requests the modification of a registration of a reference drug from a marginal improvement, and which is associated to a new patent with validity after the registered patents when the registration was granted initially. This, instead of modifying a health registration of a reference drug. The registration of the original reference drug would remain valid after the expiration of its patents, so that the generic drugs may use it as reference.

The objective of this proposal is to prevent that marginal innovations on a reference drug whose patent is about to expire, hinder the entry of generic drugs regarding the original drug, because such innovations are usually associated with new patents.

Recommendation 5. That Cofepris promote the use of the Bolar clause by publishing the rules and criteria for applying to it, and periodically releasing, the listing of innovative drugs whose patent will expire in the following three years.

Recommendation 6. That Cofepris finish completing the online database of health registrations and available for the public, with information beyond five years, and keep it updated. The database should include public information on the inquiry request of Cofepris to the IMPI and the response times of Cofepris.

This information will be used to make transparent the process of entry into the market and with that, remove spaces of discretionality which may increase unnecessary obstacles to the entry.

Recommendation 7. That Cofepris guarantee and make it known that the process of health registration is carried out using first in, first out system, and not accumulate issuances of health registers in packages.

This mechanism aims at benefiting the laboratory that starts its paper work earlier, which provides an incentive to move ahead of all competitors and take advantage by positioning in the market. The strategy that currently operates such institution, consisting of announcing the release of registrations by "package", does not generate the proper incentives for the manufacturers of generic drugs to try to move ahead of the others in their registration request.

Recommendation 8. That Cofepris issue the technical criteria under which it is considered that the collection of clinical data by the applicant represents a "considerable effort".

This measures aims at closing the door to disputes generated by alleged breaches to clinical data protection.

4. INSUFFICIENT DEMAND RESPONSE

One of the causes why the competitive behavior is poor in the private market of drug products with expired patents, is the insufficient demand response of the products that replace the original ones, with lower prices; that is, the weak response of demand to generic drug products.[193]

The problem originates from the asymmetry of information between patient and physician on which it is the best treatment. The physician does not have exactly the same incentives as the patient to prescribe the lower cost drug product. The issue is known in the economic literature as the agent-principal problem, in which the physician is the agent and the patient is the principal.

Furthermore, the literature has documented that the expenses in advertising and promotion may generate anti-competitive effects when they are focused on generating a certain positioning and brand loyalty, since it translates into an obstacle for a new competitor who may want to enter the market, laboratories of generic drugs must make strong investments in advertising to position its brand in relation to the quality reputation of the drug product of the innovative laboratory.[194] Brand loyalty may generate transfer costs that may stop consumers from changing from one brand to another, and so, they diminish the reaction capacity of current and/or potential competitors.[195]

The demand rigidity is also a consequence of the lack of general use of the generic name in the prescription, which limits the possibility of replacing brand drug products for generic drugs in

193 González Pier, et al. (2017).

194 With the same brand, the patient may perceive that quality is higher for a brandtrademark drug product either due to fixed supplies used or the care in the manufacturing of the drug product. If the patient is concerned about his/her health and it is adverse to risk, he/she may be willing to pay a higher Price for these perceived characteristics. A generic Company, on the other hand, competes on the basis of Price with other generic companies. (Feldman y Lobo, 2012).

195 For example, market research studies of certain drug product that is traded in Mexico, indicate that most consumers that go to a retail point-of-sale, have already planned the purchase of a specific brandtrademark, and in case that the brandtrademark that the consumer wishes to buy is not available, he/she prefers to go to another point-of-sale instead of buying a different Brand from the planned one. The results of this study show that consumers are loyal to the brand and few times, they decide to change from brand. (Public versión of Resolution CNT-045-2016, pp. 51).

dispensing,[196] along with the lack of awareness by patients of the bioequivalence[197] between patent and generic drug products.

This section goes deeper into the problem of the asymmetric information present in the market of drug products, as well as in the effects of promotion and advertising in the prescription of drugs, which limits and obstacles the competition of generic drugs.

4.1 Asymmetric information

There is asymmetric information when one of the parties has more information than the other one. In the relation between physician and patient, the former knows better than the patient the different alternatives (which may include treatments with innovative drug products or generic drugs), the reactions and contraindications of drug products and therefore, which is the best treatment to regain or improve the patient's health. In the agent-principal problem, the result obtained by the patient (principal) depends on the decisions made by the physician (agent).

In the economic literature, it has been documented that the main factors influencing the selection of alternatives taken by the physician between innovative and generic drugs are:

i. The physician does not have the same incentives as the patient to prescribe the lower price drug product.[198]
ii. According to studies performed in other countries, the sales force of the laboratories of brand drug products may influence physicians about the frequency of prescription of their own drug products, with preference over generic drug products.[199]
iii. Physicians and patients are prone to developing loyalty to brand drug products, maybe as a consequence of previous success experiences, when the drug product had the patent and there were no generic options.

Regarding the first item, the physician does not have incentives to prescribe the cheaper medicine, since he/she is less sensitive to price, because he/she does not make any reimbursement for the drug he prescribes and it may have the habit of prescribing drugs by brand name even when there are generic

196 It refers to the interpretation an assessment of a prescription, selection, manipulation or preparation of a drug product in a proper packaging according to the sanitary regulations, including that the pharmacist provides information and instructions to the patient to guarantee the safe and effective use of the drug product.

197 According to Cofepris, bioequivalence is the study of comparative bio-availability which assesses the efficiency of absorption of pharmaceutical equivalent products: same dose, same pharmaceutical form and same salt.

198 Iizuka, Toshiaki (2012) shows evidence that, in the Japanese case —where physicians who prescribe also dispense drug products—physicians do not internalize the costs of patients, which explains that the adoption of generic options is little frequent.

199 Venkataraman and Stremersch (2007) show evidence of the fact that marketing efforts directed to physicians —through informational visits and congresses— influence decision making of the physicians among the different brands. Of course, the decision to prescribe depends fundamentally on the characteristics of the drug product, of the effects of medicine, of its secondary reactions and of the patients' characteristics. Swanson et al. (1994) state that, in some surveys aimed for physicians in other countries, they recognize that the sales forces do influence the prescription behavior, although it is not the main factor in decision making. Bower and Burkett (1987) found that the families of physicians that depend less on the sales representatives tend to prescribe 33% more generic drug products. See also Vilar (2015).

replacements at a lower cost.[200] This is added to the fact that the physician may not have complete information about the existence of a lower-price replacement drug for the patient. First, the wide information and the high amount of new drug products in the market make it difficult for the physicians to get updates on all the therapeutic alternatives, in particular, the options available in generic drugs:[201] in México, for example, there are 5,928 drug products and every year, 270 are added, on average.[202] Second, according to a study from the Ministry of Health (2005),[203] although physicians get updated on the therapeutic alternatives, it is more difficult for them to know the different market prices and, finally, the incentives they have for paying the search costs of this information are low.

As for the second and third items, pharmaceutical laboratories are aware of the impact of their expenditures in promotion and advertising activities on the demand, since they are key for generating, from the perspective of physicians and/or consumers, a differentiation of its product regarding the rest of its competitors.[204] For example, in 2013, the ten main laboratories in the world spent, on average, 23% of their income in promotion and advertising, which accounted for seven percentage points more than in research and development.[205] For the expenditure in promotion and advertising, some studies find that that 68% is spent on direct promotion, through visits to physicians by some laboratory representative.[206]

If there is brand loyalty by patients or physicians, the negative effect on the competition is that a higher number of suppliers of generic drug products do not necessarily impact the price of innovative drug products or their market share, at least not significantly.[207] Competition in prices within a therapeutic class may be more intense if the demand is sensitive to price differentials between the kinds of drug products that it comprises . In the therapeutic classes with few rivals, competition does not necessarily focus on low prices, but on the expenses in advertising or in expenditure on research and development.[208]

Additionally, the patients' lack of information may encourage the use of branded drug products, because some of them consider them higher quality than generic drugs, and this prevents an effective competition in prices. Consequently, the competitive efforts of companies deviate to other variables different from price, such as medical promotion and the delivery of incentives to pharmacies, which does not translate necessarily into a higher benefit for patients.

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200 Scherer (1993).

201 Secretaria de Salud (Ministry of Health) (2005), p.140.

202 Calculations of Cofece with information from Cofepris in relation to drug products approved and extended in the period of 2011-2015. The calculation includes biological, herbal, innovative homeopathic, generic, biotechnological, vitamin products and vaccines.

203 Ministry of Health (2005), p.140.

204 Oberender (1992) stated that the brands influence the prescription habits of Young at Germany. Loyalty to the Brand created by the efficacy of the drug product is preserved and consolidated later, by means of visits of representatives of pharmaceutical companies. According to the author's trial, this gives the brandtrademark drug products de a competitive advantage over the possible alternatives, even when patents have expired.

205 Journalist note of BBC News (2014).

206 Pharma Marketing News (2014).

207 CFC-OCDE (2009).

208 Kyle (2007).

In January of 2017, Nielsen Company conducted a survey on the consumption of generic drug products in 6,260 homes in Mexico.[209] Results indicate that, even when most survey responders know about generic drug products (95.7%), there is still a segment of the population that trusts more in the branded drug products (38.3%).[210] Likewise, from the total amount of survey responders, 57.1% perceive generic drug products as equivalent to the branded ones, however, most of them consider that their quality is poor (53.9%) and some of them have little trust in the use of generic versions (14.5%). These results show that, in Mexico, there is certain resistance to generic consumption, and one of the reasons is uncertainty on their quality.

So, in order to encourage the penetration of generic drug products in the market, it is important to prevent patients and the medical community from rejecting them, for being considered, due to the lack of better information, as lower quality products.[211] Furthermore, the release of information about replaceability between drug products with expired patents and their generic versions would generate a wide benefit if prescription is oriented to lower price alternatives and with the same effect in the patient's health.

4.2 Participation of physicians in drug prescription

In prescribing drugs, there are many factors the physician must take into account, such as the variety and characteristics of the drug products, efficacy, risk, chemical properties, etc. Sometimes, the decision to prescribe generic or branded drug products is in function of the characteristics of the patient (the disease they had, the type of insurance, age, among others), mainly when there is no clear preference by the physicians for any of the two types of products.[212] However, habits may also play a part.[213]

In practice, the user, when requiring ambulatory health services,[214] receives a diagnosis and a prescription. According to the most recent data from the National Health and Nutrition Survey 2012 (Ensanut, 2012):

i. 61.2% of ambulatory services were provided by the public sector and 38.9% by the private sector.
ii. Considering only the ambulatory service provided by the private sector, independent doctor's

209 Nielsen (2017). The survey consisted of applying a questionnaire of 18 questions in six geographic areas of the Mexican territory. Representativity of the survey is of 62% of the population and 84% of consumption, nationalwide.

210 By social-economic level (SEL), the high SEL reported higher confidence in brand drug products (51.5%), compared to the medium SEL (38%) and the low SEL (31.5%).

211 Informing about bioequivalence to the public is a tool of public policy that would contribute to homogenize the perception about the quality of products and provide more information to patients, so allowing it to be led by the therapeutic efficacy of the product and not by other attributes related to the brand, so encouraging higher competition in prices.

212 Hellerstein (1998) tried to explain the agent-principal problem by performing an analysis on the state laws of the United States to detect some barrier or incentive for pharmacies to be able to provide different types of drug products due to the prescription made by the physician. The author, for quantitative analysis, prepared a model of fixed effects (panel) to explain the impact of the physician and other factors on the prescription of generic drugs. The dependent variable was divided into two groups, the physicians who prescribe generic drugs and those who do not. The rest of variables that was considered were related to the characteristics of drug products, of patients and of the health system. Data were obtained from a survey that was applied to physicians and patients. Among its findings, there are that the prescription of generic or brand drug products is in function of the patient's characteristics (such as the disease they had, the kind of insurance, age, among others) and that there is no clear preference of the physicians to any of the two types of drug products.

213 Caves et. al (1991), p.5.

214 It refers to medical services not requiring hospitalization.

offices are responsible for 58.5% of the appointments in that sector and the offices that depend on pharmacies, the remaining 41.5%.[215]

iii. Doctor's offices that depend on pharmacies serve 16.1% of the total ambulatory appointments.

iv. 63.9% of the prescriptions by the offices dependent on pharmacies included three or more drug products, so it is the ambulatory health service that prescribes the most drug products.

According to Pérez, R. et al. (2012), *"the high number of drug products prescribed indicates that the physicians who work at CMAFP [doctor's offices adjacent to private pharmacies] may have evil incentives for prescription..."*.[216] Furthermore, a trial conducted by Funhealth in 2014[217] identified some aspects that cause a higher influence of the pharmacy on the physician, e.g. kickbacks on drugs prescribed.[218]

In Mexico, the prescription of drug products is regulated in the RIS.[219] According to the regulation in place, when the physician only indicates in the prescription, the distinctive name (this is, the brand name) of the drug product, the pharmacy personnel may not replace the brand drug for a generic version.

This situation limits the possibilities to substitute between brand and generic drug products.[220] However, in the case of over the counter drugs,[221] the consumer is the one that makes the purchase decision, so he/she may choose among several drug products.[222]

In other countries, like the United Kingdom, the use of generic names is a general practice among physicians, accounting for 80% of prescriptions.[223] The replacement, as such, is not allowed expressly, but if the prescription is made under the generic name, the pharmacy employee may select the equivalent

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215 Doctor's offices that depend on pharmacies or doctor's offices adjacent to private pharmacies (CMAFP) came up from the regulation of sale of antibiotics with medical prescription, in 2010.

216 Pérez et al. (2012) p.4.

217 Barraza et al. (2014).

218 Barraza y Ramírez (2014) p. 71.

219 Article 31 of RIS states that "The issuer of the prescription shall prescribe the drug products according to the following:

I. When it comes to Generic Drug products, it would note down the Generic Name and if it wants, it may indicate the distinctive name of their preference;

I Bis. When it comes to biotechnological drug products, it should note down the Common International Name, and optionally, the distinctive name;

II. In the other cases, it may express the distinctive name or jointly the generic and distinctive names; When the prescription expresses the Distinctive name of the drug product, its sale or supply should be adjusted to this name and ***it may only be replaced when expressly authorized by whoever prescribes it.*** [Emphasis added]

The sale and supply of biotechnological drug products should get adjusted to the statement in the medical prescription".

In turn, article 32 indicates that *"Prescription at the public institutions shall be adjusted to whatever is indicated in them, having to use in every case, the generic names from the drug products included in the Basic Listing of Supplies for the first level or in the Catalog of Supplies for the second and third level. As an exception, and with the corresponding authorization, other drug products may be prescribed."*

220 They are the drug products that require a medical prescription for its sale and supply.

221 They are those whose sale, dispensing or supply do not require authorization or medical prescription and they may be acquired in pharmacies or other sites, such as self-service stores.

222 In Mexico, there are six classifications on how to sell or dispense a drug product. Article 226 of the LGS, indicates in fractions V and VI, the drug products that, for their sale and supply to the public, are of free Access. While fractions I to IV indicate that for some drug products, it is necessary to submit a medical prescription.

223 González-Pier and Barraza Lloréns (2011).

generic of a lower price. In France, pharmacy employees may replace products based on a list, unless the physician opposes to it (something that has happened less and less).[224]

In a comparative regulatory analysis between Latin American countries, regarding the powers of physicians in prescribing and of pharmacists in dispensing drug products, it was found that, in most of the countries studied, the physician is compelled to write down the common name of the drug product in the prescription. In Argentina, the regulation states that the physician must inform the patient about the medication options, write down in the prescription the common name and consider the patient's preferences at the moment of prescribing them.[225] Likewise, the pharmacist is allowed to orient the patient on the medication options and to provide a presentation different from the one prescribed by the physician, as long as it is the same formulation. In Brazil, the pharmacist is allowed to prescribe, because he has the professional knowledge to do it.[226] In all the South American countries in the sample, the pharmacist is required to have professional knowledge or training to conduct his/her activity.

In short, in comparison to other countries in Latin America, in Mexico, the physician is not compelled to write down the generic name when writing the prescription, or to replace the brand drug product for the generic one atthe moment of dispensing it, except when the physician expressly authorizes it. This prevents the demand of generic and brand drug products from being more sensitive to changes in prices, given that patients do not know the alternatives of equivalent drugs available, or that they may pay less for their medicines.

224 González-Pier and Barraza Lloréns (2011).

225 Decree N° 150/92, Law 25649/2002, Decree 987/2003 and Law 26.567.

226 Guide for prescription, dispensing and Commerce of Substances and drug products of special control, Practical Manual for drug products prescribed according to the Brazilian law, Resolution N ° 585 from August 29, 2013 regarding the regulation of the clinical attributions of the pharmacist and other measures.

4.3 Summary of recommendations

Recommendation 9. That the Ministry of Health develops a media campaign and instruments communication strategies directed to medical personnel, and to consumers in general, to increase trust in the quality of generic drugs.

This would contribute to make the demand for drugs more sensitive and to decrease the expenditure of those acquiring it. This may also be achieved by promoting under a focalized strategy to different population groups. Physicians, in both the public and the private sector, are the group of interests.

Recommendation 10. Amend the RIS so that: i) the physician is compelled to write the generic name of the medicine in the prescription, ii) the pharmacist may inform the interested parties about the generic drugs which are available; and iii) allow, in case of medicines of chemical synthesis, their replacement between generic drugs (with and without brand), as long as they contain the same active principle, concentration and way of administration, and the physician does not forbid it expressly in the prescription, and that it is made by a certified pharmacy employee.

As part of this proposal, it may be possible to incorporate, in the basic curriculum of the bachelor's degree in medicine[227] and other similar ones the promotion of prescriptions under the generic name.

227 Curriculum is a poly-semantic term used indistinctively to refer to academic curricula, programs and event to didactic implementation.

5. ENTRY OF GENERIC DRUGS INTO PUBLIC PROCUREMENT

The government purchases for drugs may influence the incentives faced by the laboratories to introduce generic drugs into the market.[228] This is because good functioning of the public market may give the manufacturers of generic drugs (new in the market), the scale needed to enter, successfully, into the private market. This, however, means that the characteristics of the execution of the consolidated purchases of medicines by public health institutions, must avoid creating barriers to entry.

In this section, regulations and procedures related to the public procurement of drugs are reviewed, and it assesses the implications they have on competition and on the entry of generic drugs into the market. It is stated that, although in recent years the consolidation process of public procurement has generated competitive pressures in the medicines market in the right direction, there are still aspects requiring an improvement in order to eliminate barriers to entry. First, the time between the bidding process and the start of delivery is short, thus affecting the number of bids; if that time were longer, that might encourage the entry of a higher number of bidders. Second, payment to suppliers may still be improved; since it its current state creates limits to the competitive process due to the reasons that will be explained in the corresponding section.

5.1 Short-term horizon

The public health institutions acquire a high volume of generic drugs through bidding processes.[229] Every institution, individually, may perform biddings; however, the Act on Acquisitions, Leasing and Services of Public Sector (LAASSP) allows them to perform the consolidation of acquisitions among several agencies and entities in order to get better quality, price and opportunity conditions.[230]

228 In 2015, the share of generic drugs in the public market, in terms of volume, was of 98.8%, however, in terms of value, it was of 65.1%. These calculations include generic drugs with and without brand. (AMIIF, 2016).

229 Just like any purchase of goods or services by the Federal government, the acquisition of drugs by the social security institutions is regulated by the LAASSP (Publicated in the DOF on January 4, 2000, last amendment publicated in the DOF on November, 10 2014) and its regulation: The Regulation of the Act on Acquisitions, Leasing and Public Sector Services (RLAASSP). The latter was publicated in the DOF on July 28, 2010.

230 Art. 17 of LAASSP.

The contracting process starts with the publication of the bidding project[231] and it concludes, officially, with the awarding and signing of the agreements. The publication of the bidding project is an important step, since it allows the manufacturers of drugs to know, anticipatedly, the volume that the public sector requires, technical information, as well as the timeline of activities.[232]

With respect to the duration of the bidding process, best international practices on supply management of drugs suggest that the time between the start of the bidding process and the contract officialization should be of at least five months.[233] According to Management Sciences for Health (2012), the period recommended to receive offers is between 15 and 20 days for domestic bids, between 45 and 60 days for international ones, while, once the contracts are awarded, the recommended time for the supplier to start delivering the drug and distribute it, is of six months. Likewise, for domestic bids, the time between the orders to the supplier and the initial deliveries should be of one month; however, for international suppliers, the delivery time must range between three months and one year.[234]

In Mexico, for a sample of 49 bids organized by the Instituto Mexicano del Seguro Social (Mexican Institute of Social Security, IMSS) between 2010 and 2016, regarding the consolidated purchase of drugs,[235] a calculation was made of the time between the publication of the bidding process and the preparation of the decision report, and the time between the award and the start of supply of the drugs. Results show that the average time for the procedure is of 44 natural days (Table 10), while the period that suppliers have for producing the drug, assuming that the production process starts from the time when a decision is made, is of 46 natural days on average.

231 Art. 26 of LAASSP.

232 In accordance with art. 29 of LAASSP, the tender states the bases to be used for developing the purchase procedure.

233 Management Sciences for Health (2012).

234 Ibid.

235 The base includes 19 domestic tenders, 25 international tenders under the coverage of Free-trade Agreements and 5 open international tenders. That database was built from the reports of social witnesses released in the Purchase Portal (Portal del Compras) of the IMSS. For tenders previous to2016 no information was found on the release dates of the tender projects. Therefore, the calculation is considered from the release date of the tender. Likewise, the tenders for healing material, laboratory or radiological material were discarded from the exercise.

Table 10
Duration of the auction process for the consolidated purchase of drugs, 2010-2016[1]

Nature of the auction	Number of auctions	Average number of bids	Average length of the process	Average days for production[2]	Recommended timeline for production
Open international	5	13	32	40	90 to 360 days
International by Treaties	25	41	57	37	90 to 360 days
Domestic	19	29	29	59	30 to 180 days
Total	**49**	**33**	**44**	**46**	

[1] Natural days.
[2] Time between the public tender process and the supply of drug products.
Source: Cofece with information for the Purchase Portal of IMSS.

Likewise, time varies according to the nature of the bidding process, because, for domestic ones, the period between the decision date and delivery is of 59 days on average, while, for international ones, under the coverage of Free-Trade Agreements, the average term is shorter, 37 days. When reporting participation in biddings, it was observed that there is a positive relation between the time that the process lasts and the number of bidders. Furthermore, the average number of bidders in international biddings under the Free-Trade Agreements is longer than in the domestic ones.

The fact that a molecule is acquired by public health institutions attracts competing generic drugs; however, the observed period that suppliers have for planning their production process is relatively short, which may discourage the entry of a higher number of participants in the bidding process.

5.2 Decentralized payment process

In consolidated purchases, the IMSS is the institution in charge of performing the consolidated procurement process;[236] however, each participant (entity or agency)[237] is responsible for officializing and managing the respective agreements, as well as for paying the suppliers.

From 2013 to 2016, the number of participating institutions in the consolidated purchases of drugs

236 Since 2009, IMSS has performed consolidated purchases, along with the Ministry of Defense.

237 For example, for the Consolidated Purchase in 2017, five agencies participated; IMSS, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (Institute of Security and Social Services of State Employees, ISSSTE), the Ministry of Defense (SEDENA), Petróleos Mexicanos (Pemex), the Ministry of the Navy, 18 states and 17 health institutes. For more details,

increased from 14 to 40, which implied a higher heterogeneity in payment processes, because every institution has different guidelines and specific payment systems for suppliers.

Therefore, even when the requirement and the purchase order of drugs are centralized, there might be delays in payment to suppliers. The LAASSP indicates that the payment to suppliers may not exceed 20 natural days starting from the delivery of the respective invoice.[238] However, evidence from the pharmaceutical industry shows considerable delays and unpaid invoices in the payments to suppliers at some institutions.[239]

One of the main causes for the delay in the payments is the inefficiency in the payment processes to suppliers and contract management by some participants in the consolidated purchase.[240] Furthermore, so far, there are no operation rules for this purchase scheme.

Delays in payments by the public sector may affect the survival of companies, because their liquidity may be affected, even forcing some of them to go out of the market.[241] Some effects of late payments are:

i. They affect negatively the cash flows of the company;
ii. They add financial and administrative costs; and
iii. Increase uncertainty for creditors.

In this sense, by affecting the cash flows, the companies may require external funding to manage the lack of liquidity, which increases administrative and financial costs. Therefore, late payments may give rise to insolvency and, ultimately, bankruptcy, and firms exiting the market.[242] The effect is higher for

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please refer to: http://www.imss.gob.mx/sites/all/statics/compraconsolidada/2016/participantes4.png

238 Art. 51 of the LAASSP.

239 Regarding this, the National Commission of the Pharmaceutical Industry (Cámara Nacional de la Industria Farmacéutica (Canifarma)), in its Yearly Report 2015, it indicates that, in a survey performed on its affiliates, 49% stated that some of the entities, agencies and organizations participating in the consolidated processes of purchase of drugs had not fully covered the amounts exerted during 2013 and 2014. (Searched on October 19, 2016 at: http://www.canifarma.org.mx/Documentos/1.pdf). Likewise, the National Association of Manufacturers of Drug Products (Asociación Nacional de Fabricantes de Medicamentos (Anafam)) indicated, in July 2016, that different health institutions are indebted to the pharmaceutical industry, for around 10 billion pesos since the consolidated purchase of drugs since 2015. Rodríguez A. (2016) "Institutos de salud, morosos: Anafam" at El Economista. July 20, 2016. (Searched on October 19, 2016 at: http://eleconomista.com.mx/industrias/2016/07/20/institutos-health-morosos-anafam).

240 For example, a recent study by the OECD (2013) indicates that from 2007 to 2010, almost 10% of the purchase processess atprocedures ISSSTE were subject to formal inconformities by suppliers. In the case of the IMSS, the inconformities accounted for 14.3% of the total of its purchase procedures. Likewise, the same press release indicates that the billing procedures and payment procedures are a common source of inefficiencies, both for ISSSTE and for its suppliers. On the other hand, a study by the Mexican Institute for Competitiveness (Instituto Mexicano para la Competitividad) (IMCO, 2011) found that the IMSS generally does not pay its suppliers on time, which brings about more defaults of the agreement. This is because when a supplier delivers the first replacement order and it has not received its payment on time, the incentive for the supplier to deliver the second order, diminishes. Along with this, if the IMSS has not paid yet, and the supplier defaults the second replacement order, the latter may be sanctioned and disabled according to the number of failures that it has.

241 A study by the European Commission estimated the effect of late payments by the government on the dropout rate of the companies for new sectors of the economy in 17 state members of the European Union, by using a panel of yearly data 2005-2010. The study found a negative and significantly statistical effect of late payments from the government on the drop-out rates of the companies: where a reduction of 1 point in the delay rate of payments translates into a decrease in drop-out rates of approximately 1.7 to 2 percent points. (Connel, 2014)

242 Connel (2014).

small- and medium-size companies, where access to credit is limited and costly, along with the fact that there are not always proper credit management systems to prevent or manage late payments.[243]

Ex ante, the expectation of being late in payments may affect competition in tenders and the offered prices. For this last point, the companies considering payment delays, may decide to participate in the tenders and submit proposals with high prices that allow to lessen the possible negative effects of lack of liquidity in the future. This situation would cause the public sector not to take full advantage of the benefits of consolidated purchases.

In short, the existence of delays in payments by some entities that participate in the consolidated purchase of medicines by the public sector, may be generating obstacles to entry into the market, particularly for small and medium-sized companies, due to the uncertainty of the supplier in view of the payment promise from the buyers. Therefore, in the medium and long term, only the companies with sufficient financial capacity would be under the conditions to bear the delays.

243 Ibid.

5.3 Summary of recommendations

Recommendation 11. The health institutions must instrument longer planning horizons in the procurement process, in order to grant a longer time between the result of the bidding process and the delivery of the medicines.

This requires that the planning of acquisitions by the health institutions must consider the time required for every step of the process,[244] in addition to considering adjustments to budgetary scheduling,[245] in order to speed up the contracting process, and grant suppliers a longer time to produce the drug.

There may even be an amendment to article 35 of the Federal Act on Budget and Financial Responsibility (Ley Federal de Presupuesto y Responsabilidad Hacendaria) so that agencies and entities that participate in the consolidated purchase do not have to request a "special authorization" to the Ministry of the Treasure to call upon, award, and, whenever needed, officialize the agreements, so they can start the process earlier .

Recommendation 12. The agencies and entities that participate in the consolidated purchase of drugs must establish the operation rules that include clauses to restrict the participation of institutions and/or entities that have debts in previous fiscal years, as well as make the payment procedures the same to all the suppliers among the different participants in the purchase. Providing more certainty to the suppliers, encourages the participation of more laboratories in the bidding processes.

244 This includes checking the times for different planning stages of the licitation, such as: the time required to gather all theacquisitionsrequire , because IMSS is the one in charge of consolidating the requirements (this is, the demand) of all the participants of the consolidated purchase.

245 Article 35 of the Federal Act on Budget and Financial Responsibility indicates that *"The agencies and entities may perform all the paperwork necessary to perform contracting of acquisitions, leasing, services and public Works, so that resources are exerted timely from the start of the corresponding fiscal year.*
The agencies and entities, under the terms of the Regulation, may request the Ministry to give a special authorization to call upon, award and, in its case, officialize such agreements, whose validity term starts in the fiscal year following the one in which it is requested, based on the budget draft projects. (...)"
A new Act released in the Official Gazette of the Federation on March 30, 2006. Last amendments to DOF on December 30, 2015.

6. CONCLUSIONS

The Plenary of Cofece ordered this study due to the importance of the pharmaceutical industry in the well-being and health of the Mexican population. Generic drugs would be expected to exert competitive pressure once the patent of original drugs expires, thus, allowing the population access to lower price drugs. In this study, the Mexican pharmaceutical market was analyzed, to evaluate the effects on prices, penetration level and the entry of generic drugs into the market when patents expire.

The study found competition problems in the markets for drug products with expired patents, market failures were identified, both from the government and from the market itself, which affect competition and generate a low impact of generic drugs on prices and market share.

It was found that, in many cases, generic drugs do not enter the market, even when they have gotten a sanitary registration. Other times, the entry of generic drugs is late and slow. And when they enter, it is usual that they do not exert enough competitive pressure in the market. Particularly, it is considered that the patent loss, more than generating a highly competitive structure, it might be used as a tool to price discriminate.

As an example of these findings, on average, more than one year elapses between the expiration of the patent and the issuance of the first sanitary registration, and more than two years between the expiration of the patent and the launch of the first generic product into the market. In the European Union, the entry into the market is seven months after the patent expiration and in the USA, the entry of the first generic product is immediately after the patent expiration of the most widely sold drug products.

Furthermore, the market share of generic drugs is lower than expected, and it grows slowly. For example, two years after the entry of the first generic product, the penetration of generic drugs reaches 21.4% of the market, when in countries like the USA it reaches 89% and in Canada, 74%. Furthermore, the number of competitors is lower than the one observed in other countries, and the speed of competition is relatively low. It must be mentioned that the observed trend is toward the registration of a higher number of secondary patents by originating drug product, pointing to the fact that the entry of new generic drugs may still be slower in the coming years.

In Mexico, the average number of producers of generic drugs is of 2.8 one year after the patent expired. And there is at least one generic product, not produced by the laboratory that loses the patent, in 63% of the cases studied. In the USA, the number is of 10.1 generic producers for the molecules with the highest sales.

On the one hand, prices of brand drug products increase by 2.1% within six months after the first generic product's entry,but it goes down to the original level after two years. This might be an indication of laboratories discriminating in prices, by taking advantage of factors such as brand loyalty.

Other important problems that affect the competition conditions in the market are those related to failures in regulation, mainly, in rights of industrial property, of sanitary authorization, and the link between those rights; and the market failures that increase the entry costs.

It must be highlighted that complexities in the linkage system and its lack of transparency, also related to the protection of more than one patent on the same drug product, favor that companies get involved in disputes whose effect is to, de facto, extend their market exclusivity.

Furthermore, on the issue of sanitary regulation, it was found that there was no updated and complete public information on the sanitary registrations making the mission of measuring the time it takes to authority (Cofepris) to grant the registrations a hard one.

As for the standard on matters of health, it currently restricts the possibility of replacing branded generic drugs when the physician does not write down the generic name.

Due to this, it was found that, in order to attain the full benefits of competition by generic drug products, it is necessary to modify the regulatory framework to eliminate the regulation obstacles that limit this competition, as well as to encourage public policies to promote and maintain the competition by generic drug products. The policy recommendations derived from this study were focused on solving the problems detected in three key phases of the introduction and consolidation of a generic drug product in the market.

First, in the patent protection phase, its granting and the corresponding publication of all patents in the Gazette, are a tool that would allow them to make the status of all patents known to the different economic agents. It must be recognized that the publication of the Gazette is one of the most important steps to providing certainty to the economic agents. However, more has to be done to provide the agents with more information, especifically, that the patent information be clearly related to every referenced drug , and that it is comprehensive.

Second, in the sanitary registration phase, that Cofepris is in charge of, three key moments are identified: one, the submission of the application of sanitary registration before the patent expiration (under the Bolar clause) and after the patent expiration, and the authorization of extensions to continue commercializing the medicine. According to the findings in this study, all these phases face challenges in operational and transparency terms, and once they are overcome, they may help to reduce delays in the entry of generics and to promote competition into the medicines market.

And third, once the products are available in the market, it is important to ensure that the physician and/or the patients, have the information to make a better choice in the market for generic drugs, thus improving the level of competition and reducing prices.

Moreover, it is important to move forward the date of the purchases and the payment by the public sector. That could facilitate the entry of small and medium-size laboratories selling generic drugs to the health sector, and in that way, generate the scale needed for a higher entry and competition of generic drugs in the private market.

GLOSSARY[246]

Active substance / active principle or ingredient/ molecule / drug substance. A substance contained in a drug and which is recognized as the one giving rise to its therapeutic effect. LGS (article 221, fraction II) defines drug substance as: "Every natural, synthetic or biotechnological substance that has some pharmacological activity and which is identified by its physical, chemical properties or biological actions, which is not present in pharmaceutical form and which meets the conditions to be used as drug or ingredient of a drug product; (...)".

Authorized third party. They are people authorized by Cofepris to support the authority on the control and sanitary surveillance by performing several analytical tests, verification tests or to perform bioequivalence and/or biocompatibility studies.

Bioavailability. It is the degree and speed with which an active form (the drug substance or one of its metabolites) accesses the bloodstream, and so, it reaches its target. Bioavailability of a drug substance depends, up to a certain degree, on the properties of the pharmaceutical form, that, in turn, depend on their design and manufacturing.

Biocomparable drug. Biotechnological non-innovative drug in accordance with article 222 of the LGS.

Biological drug. Those based on active principles of biological origin (human or animal tissues or of microbiological origin) obtained from living organisms or those prepared through molecular biology processes.

Biotechnological drug product or biodrug substance. Every substance that has been produced by molecular biotechnology, which has a therapeutic, preventive or rehabilitation effect, that is present in pharmaceutical form, which is identified as such by its pharmacological activity and physical, chemical and biological properties.

246 Several of the definitions contained in this glossary were taken from the Mexican legal framework, as well as of literature and, particularly, of González Pier and Barraza Lloréns (2011).

Bolar Clause. It is a legal standard that allows researchers to start the processes of experimentation and obtention of governmental authorizations necessary to commercialize a product (normally a drug product, but it may be any other that requires a governmental approval before commercialization) before a patent has expired. The Bolar clause does not enable the researchers to commercialize the product but only to experiment,conduct studies and start the governmental paperwork. Such clause originates in a Sentence provided by the Appeals Court of the Federal Circuit of the USA in 1984 in the issue of Roche Products Inc. Vs Bolar Pharmaceutical Co. Inc., where the Court came to the conclusion that the preparation phase of the authorization and trading of the product did not breach the patent. In the Mexican legal framework, the equivalent provision is in article 167 bis of the Regulation of Supplies for Health, which states that "(...), it may be requested to have registration of a generic product regarding a drug whose substance or active ingredient is protected by a patent, in order to perform the corresponding studies, trials and experimental production, within three years previous to the patent expiration. In this case, the sanitary registration will be granted only when the patent´s valid term concludes". Likewise, article 22, fraction I of the Act on Industrial Property indicates that: "The right conferred by a patent shall not produce any effect against: I.- A third party that, in the private or academic field, and with non-commercial aims, performs purely experimental scientific or technological research activities, or teaching, and for that purpose, they manufacture or use a product equal to the one patented; (...)".

Combined product or drug. Drug that contains more than one active ingredient.

Competition. It refers to the entry into the market of products corresponding to generic versions of the drug whose patent has expired.

Concentration. Quantity of the active substance contained in a drug according to its pharmaceutical form.

DCI or INN by International Non-proprietary Name. Designation adopted by the World Health Organization used to identify, in a generic form, the pharmaceutical substances or active pharmaceutical ingredients used in drugs. Every international common name is unique, worldwide recognized and considered as public domain.

Dispensing. It refers to the interpretation and assessment of a prescription, selection, manipulation or preparation of a drug in the proper packaging, according to the sanitary regulations, including the fact that the pharmacist provides information and instructions to the patient to guarantee the safe and effective use of the drug.

Distinctive name. It is the commercial or brand name of the drug. In Mexico, in article 2, fraction IV of RIS, it is defined as the name that, as a commercial brand, the laboratory or manufacturer assigns to its products in order to distinguish it from other similar ones, with previous approval by the sanitary authority and registration before the competent authorities.

Drug. According to the article 221 of the LGS, it is "Every substance or mix of substances of natural or synthetic origin that has therapeutic, preventive or rehabilitating effect, which is present in pharmaceutical form and that is identified as such for its pharmacological activity, physical, chemical and biological

characteristics." Furthermore, "When a product contains nutrients, it shall be considered as a drug, as long as it is a preparation that contains, individually or jointly: vitamins, minerals, electrolytes, aminoacids or fatty acids, at concentrations higher than those of natural foods, and that is presented in some defined pharmaceutical form and the instructions consider therapeutic, preventive and rehabilitating effects". Article 224 of the same Law classifies drugs according to its preparation form (magistral, officinal and pharmaceutical specialties) and their nature (allopathic, homeopathic and herbal). The same drug may be commercialized under different presentations.

Drug product of chemical synthesis. Drug product whose active principle corresponds to chemical substances generated by means of extraction or chemical synthesis in which there is no intervention of elements of biological origin, but only chemical components.

Evergreening. Concept used in the literature to refer to the strategy used by the pharmaceutical companies that produce original drug products to extend the duration of the market exclusiveness derived from the patent protection by requesting successive patents for different attributes of the product, instead of requesting all of them at once. Usually, such patents protect attributes that represent marginal innovations.

Follow-on patent (Secondary patent). The term follow-on (or secondary) patent derives from the fact that it follows the primary one, and it is not related to its quality.

Generic drug / generic version. Bioequivalent, and therefore, exchangeable versions of a product or original drug product whose patent has expired, and which contain the same quantity of the active ingredient(s). There are brand generic drug products which are traded with a registered commercial name (distinctive name), and unbranded drug products, which are used under the generic name indicated in the name of the active substance(s) contained in it.

Generic name. Name given to the drug which corresponds to the active substance that it comprises. Usually, the international common name (DCI) although, in some cases, they also use the names defined in the Pharmacopeia of the United Mexican States. In Mexico, in article 2, fraction V of RIS it is defined as: The name of the drug, determined through a preset method, which identifies the drug substance or active substance, internationally recognized and accepted by the sanitary authority.

Hypothetic competition. Percentage of drugs without patent protection for which there is at least one sanitary registration of a generic version (not produced by the original laboratory), after the patent expiration.

Observed competition. Percentage of drugs with no patent protection for which at least one generic version (not produced by the original laboratory) is commercialized, after the patent expiration.

Orphan drug. They are aimed at preventing, diagnosing and treating strange diseases, which are the ones present in not more than five out of every 10 thousand inhabitants. They are characterized by be offered by a single supplier, although they have no current patent.

Original or innovative drug. Original version or first version of a pharmaceutical product or drug. Usually developed and patented by the manufacturer who created it and that, therefore, holds exclusive rights to produce it and commercialize it for a given period. An original product may have one or more trademarks used for its commercialization. In case of biotechnological drugs, it is possible that the product may be original, but it does not have patent protection.

Over the counter drug. Those whose sale, dispensing or supply, do not require authorization or medical prescription and which may be acquired in pharmacies or other sites, such as self-service stores.

Patent. The right to exclude others from the exploitation of the patented invention, this is, a right to prevent unauthorized third parties from manufacturing, using, selling, offering in sale, and importing the invention.

Patent clustering. It is done through multiple applications for patents in new formulations, processes, indications and pharmaceutical forms on the same active substance. In other countries, this strategy includes the "divisional" applications , which happens when the applicant divides a patent into one or more with a more limited or restricted scope.

Patented drug. Drug that is protected with a patent and grants an exclusivity period for the manufacturing and trading to those holding it or whoever has acquired a license from the patent holder.

Pay for delay agreements. They are agreements of payment between innovative and competitor generic producers and they involve alleged payments made by the original laboratory with a patented drug product to one or more laboratories of generic drugs to delay their entry into the market. Within that kind of agreements, there are the *reverse payment patent settlement* which derive from disputes on a patent of an innovative laboratory and the generic drugs one.

Pharmaceutical form. It is the individual provision to which a drug (active principles) and excipients (pharmacologically inactive matter) adapt to constitute a drug. They may be in solid form (tablets, powder or capsules); semi-solid form (ointments and creams); liquid form (drops, injectables, syrups); or gaseous form (inhalers). It is the mixture of one or more drug substances with or without additives to allow their proper dosing, preservation and administration.

Prescription drug. Those that, for sale and supply to the public, require a medical prescription.

Presentation. Characteristic of a drug that is given by its pharmaceutical form, way of administration, concentration and the quantity of units contained in the package.

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ANNEX 1. METHODOLOGY

This annex was put together using the methodology devised by the consultants for the collection and analysis of the sales and prices database of several medications during the 2009-2015 period.

A.1.1 Identification of the molecules universe (active substances) which have lost their patent

As the starting point of the study, the universe of active molecules or ingredients that have lost their patent was identified. The database used is the Industrial Property Gazette – Medications patents in force, Article 41 BIS of the Regulations of the Industrial Property Act, published by the IMPI (hereinafter referred to as the IMPI's Medications Gazette or the Gazette).

The IMPI's Medications Gazette is a publication available on the IMPI's webpage. There are 85 issues to date.The publications may be of two types: periodical sections which include the universe of active substances with patent in force in the period corresponding to the publication or addenda in which new active substances with patent in force are added or corrections to the content of prior publications are indicated. In the first years of publication, they were published once or twice a year, while in recent years, it is common to have multiple issues and addenda.

To identify the universe of molecules or active substances that have lost their patent in accordance with that published in the Gazette, the information of 80 issues were considered, from November 2003 (publication of the first IMPI's Gazette in compliance with the amendments of the Industrial Property Act and the Regulations of Health Supplies of September of the same year, that establish the linkage of IMPI/COFEPRIS) to August 2015.[247] The reason is that, independently of the concurrency analysis of the generic competitors and the price evolution, with this information it is feasible to analyze the evolution of the medication patent protection.

A database was prepared as follows:

247 The last Gazette published in 2015 corresponded to August of that year. However, between September 4, 2015 and February 18, 2016, one erratum and eight addenda were published that must be considered as part of the full copy of August 2015. For this reason, henceforth, when the text refers to the August 2015 Gazette, this shall be understood that this includes the aforementioned erratum and addenda.

i. Since the contents of the Gazette are not available in database format, the information was extracted from the medications available in the Portable Medication Format (PDF) or in image format.
ii. Given that the medications listed in the Gazette correspond to active substances and their respective patents, the term medication and molecule or active substance were taken as synonyms.
iii. The copies were processed to create a database on which every registrationregistration corresponds to each one of the enlisted molecules or active substances, and the patent which protects or had protected it. Each registrationregistration was prepared with each one of the attributes published for each medication in the Gazette. There are cases in which for the same active substance there is more than one patent enlisted in the Gazette identified, therefore, in these cases, the database has more than one registration associated to the same active substance.

The information that invariably appears for each medication listed in the Gazette and which is included in the database is as follows:

i. Generic Name: Active substance or generic denomination of the medication.
ii. Specific Description: Generic denomination that includes the chemical formulation of the active substance with greater detail.
iii. Chemical Name: Nomenclature or chemical formula.
iv. Patent: patent number.
v. Validity: Expiration date of the patent.
vi. Annual payments: Indicates the last payment due for the patent.
vii. Holder: Individual or company holding the patent.
viii. Claims: List of the characteristics or specific aspects that are the subject matter of the paten protection
ix. Remarks: Additional information about the patent type in question (active principle or other type of patent); if the patent has been granted under license to another company; if the patent has been included in the Gazette as the result of any judicial ruling, etc.

However, in some cases, the Gazette includes additional attributes for certain medications. For this reason and only for certain molecules, the following attributes were also extracted:

i. Legal Situation: a note that describes a its legal situation.
ii. Initial Term: original expiryation date of the patent.
iii. Modified Term: modified expiry date in which the patent will expire, usually as the result of a certain judicial ruling.

The set of medications extracted from each one of the gazettes published between November 2003 and August 2015 provided as a result the universe of 962 molecule-patents (combination of the molecule or active ingredient and the patent that covers it). From thIS universe, the medications were separated between those that still have a valid patent from those whose patent is no longer valid.

A medication was listed as having lost its patent when:

i. The medication appears in the gazettes prior to the August 2015 Gazette, but does not appears as valid in the August 2015 Gazette, and
ii. ts patent indicates a validity prior to August 21, 2015.

The requirement to comply with both conditions was established because there is a group of medications that appear in the gazettes prior to August 2015 and that do not appear as valid in the August 2015 Gazette, but whose patent exhibits a termination date after August 21, 2015 (publication date of the referred gazette).[248]

Defining "molecule-patent" as the combination of the active ingredient and the patent number that covers it, and considering the previous criteria to identify those cases covered by the patent whose patent protection has expired, 202 molecules-patents were identified (corresponding to 167 molecules or active substances) that lost the protection of the patent in the period covered by the Gazettes from November 2003 to August 2015.[249]

The Gazette is a valuable source of information, since it is a public-domain periodical publication, and, in general, the information is consistent over time. However, some limitations were identified:

i. Until May 2016, the Gazette was published in image or PDF format, without the option of obtaining the information in the database format. This hindered the continuous and systematic analysis of the medications' patents. From August 2016, the IMPI began to include with the Gazette a file in XML format, structured as a database.
ii. Some inconsistencies were identified, e.g., there are medications identified in issues prior to August 2015 whose patent expiration date is after that date; however, they do not appear in the August 2015 Gazette.
iii. Sometimes, repeated active ingredients are published because they are in English and Spanish or include some kind of typographic error. Sometimes active ingredients followed by some adjective also appear, and in others the adjective is before the active ingredient.
iv. It is possible that it is not an exhaustive list of all the patents that protect a given medication.

A.1.2 Identification of the generic medication that entered the market at the end of the patent protection

For the name of each one of the molecules without a patent identified in the previous section, an information search was performed in the sanitary records corresponding to the original medications and the respective generic version which obtained the sanitary registration during the 2003-2015 period.

The information source used is from Cofepris, since it is the institution responsible for granting the medications' sanitary registries in Mexico.

For this purpose, the medications were not only identified in terms of molecule or active substance, but also according to a series of characteristics that allow the identification of different products and presentations that have sanitary registration. These characteristics include the sanitary registration

248 The medications of this group are in the review process to identify the reasons why they do not appear in the Gazette anymore, notwithstanding that their patent seems to be kept as valid.

249 The last Gazette published in 2015 corresponded to August of that year. However, between September 4, 2015 and February 18, 2016, one erratum and eight addenda were published that must be considered as part of the full copy of August 2015. For this reason, henceforth, when the text refers to the August 2015 Gazette, this shall be understood that this includes the aforementioned erratum and addenda.

number (which includes the issue year of the registration), the name of the laboratory holder of the sanitary registration, the distinctive denomination or brand, the pharmaceutical form, the concentration, and the amount contained in the packing or container.

To do so, a cross search of the following sources of information of Cofepris was performed:

i. List of 37 medications, for which 486 generic versions have been approved, in the generic release strategy framework promoted by Cofepris since 2011. In addition to the generic name and distinctive denomination, patent number and innovative medication laboratory, the information obtained includes for the respective generic versions: brand, holder of the sanitary registration, validity date (in year format and in some cases, in a more precise date format). The generic versions´ presentations are not detailed.
ii. Annual list of the sanitary registries of the allopath medications authorized for the years 2003 to 2016. This information is useful to identify distinctive denominations or brands, as well as the laboratory that holds the registration and its pharmaceutical form, although it does not include enough information to identify all the presentations available for each medication.
iii. List of the reference medications until June 30, 2016. This list is an estimate of the molecules universe in which there is a potential entry of generic medications, since they are medications considered as reference for the bioavailability and bioequivalence tests necessary to obtain the sanitary registration of a generic medication. For each molecule, the list includes information about the sanitary registration number, generic and distinctive denomination, pharmaceutical form and concentration, and holder of the registration. This list was used to identify the original medications, since in most the cases the original medication is considered as the reference medication.[250] The limitation of the list is that it is dynamic and the date on which each medication was included, considered as reference medication, is unknown.[251] Although the most recent version of this list replaces the previous versions, those previous versions were consulted when there was not enough information about the original medication.

This information was complemented with the information officially provided by Cofepris about the sanitary registries of the medications that lost their patent in the analysis period and their generic versions. As from this information, it was possible to identify 390 products, defined as sanitary brand-registration combinations that must be incorporated to the generic versions with a sanitary registration.

The information about the sanitary registries of the original medications and their generic versions was incorporated to the database and was matched to the molecules-patent without patent protection universe of the previous section, in order to identify the number of medications that have competitors and the number and description of the generic versions recorded in Cofepris.

250 Sometimes, another medications or presentations may be considered as reference medications. E.g., when the original medication or some presentation is not available in the Mexican market, anther generic medication or another presentation may be considered as reference for bioequivalence and bioavailability verification purposes.

251 On January 25, 2016, Cofepris published new guidelines relative to the list of reference medications which established, with regard to the innovative medication or new molecule that has obtained the sanitary registration and at the request of the holder of the registration to be acknowledged as reference medication, that the medication shall be assigned to a list of innovative medications and three years after the expiry of the patent, it shall be integrated to the list of reference medications.

The matching only considered the medications that include, the name of the molecule whose patent has expired. Thus, the sanitary registries of medications with combined formulations which include the molecule with expired patent and some other medication are excluded. Only combined medications were included when the literal combination was subject of patent protection.

This first matching between the IMPI and Cofepris´ information allowed the classification of the medications whose patent expired in two groups: the medications that face generic competition and the medications that, although their patent expired, still have a single manufacturer. The existence of sanitary registries different from the original medication whose patent expired, is a first competition measure. For the purposes of this study, this is considered as *hypothetic competition*, since having a sanitary registration is a necessary condition – but not necessarily enough – for a medication to be commercialized in the market and be effectively available to the consumer.

The next step was to establish the time elapsed between the expiration of the patent and the granting of the sanitary registration. However, this was possible only in those cases in which we had the full date (dd/mm/yyyy) of the issuing of the sanitary registration. Not having the full date of the sanitary registration issuance is a limitation for the analysis about the time elapsed between the loss of patent and the entry of the generic versions. As an alternative, for the cases in which there is no exact registration issuance date, the estimated date of the registration issuance was calculated subtracting five year from the full validity date of registration, in the case of medications whose first registration was granted after January 24, 2010.[252] In the case of medications whose first registration was granted before this date, the issueance date was estimated considering the day and month included in the validity date, and the year as it is presented in the sanitary registration number.[253]

The period for the competition analysis was defined from the initial universe of 202 molecules-patent matched with the Cofepris information, and 37 molecules-patent not suitable for the analysis were excluded due to the following reasons:

i. They do not have a sanitary registration, i.e., they are not commercialized or had a registration at a certain time, but it was revoked or was not renewed. In the first case, it is about molecules whose development failed and they were not commercialized in any country or are molecules that were recently approved by the sanitary authority of the USA or of other country and they are beginning their commercialization; although, in the future, the sanitary registration may be requested in Mexico for these cases; at the moment, they do not constitute a market susceptible for analysis. The second case deals with molecules which, although they had a sanitary registration, they were withdrawn from the market due to safety reasons.
ii. Do not present competitiors (no sanitary registries were identified) but other valid patents were identified in the medications Gazette of the IMPI. These cases are excluded from the initial universe since they have some kind of protection, although in most cases the expired patent corresponds to

252 With the amendment of Article 376 of the 2005 General Health Act, a 5-year validity term was established for the sanitary registration with renewal possibility. The amendment came in force in 2005 with a transitory period that ended on February 24, 2010.

253 The sanitary registration number is comprised by a series of alphanumeric characters, which include the sanitary registration issue year.

the active substance.

iii. Two molecules-patent (two molecules) for which no market information was obtained because the molecule name listed in the Gazette generated ambiguity in requests for sanitary and market information, therefore, there is no available information necessary for the analysis.

Thus, from the initial universe of 202 molecules-patent (167 molecules), 37 molecules-patent (35 molecules) were excluded, therefore, the feasible analysis universe (analysis universe) is comprised of 165 molecules-patent corresponding to 132 molecules.

It is worth mentioning that several cases were identified in which the sanitary registration precedes the expiration date of the patent. This could be explained since they are sanitary registries granted during the transition phase of the Article 376 amendment or perhaps there is another previous patent that may be the effective patent for the authorizations of the generic versions. Due to the uncertainty of these cases, they were excluded from the analysis.

A.1.3 Construction of the price time series and sales volume for medications before and after the loss of the patent

Once the universe of medications with expired patent and their generic versions registered in Cofepris was integrated, the next step was to add the market information in order to prepare the price time and volume series for each one of these medications, before and after the loss of the patent.

The private sector sales information was used as the primary source of market information, since it is the most complete and disaggregated available information for this study.

The private sector represents 81.5% of the value and 59.9% of the sales volume of the total pharmaceutical market, which almost entirely composed of retail sales.[254]

Likewise, the private sector information provides more representative price information of the products' offer, since the variety of available presentations is usually greater than the available ones in the public sector.

The primary information for the private sector was obtained from several sources. The available information comprises sales data in the private sector for the period from January 2009 to August 2016. With this information, different presentations available in the private market were identified and were matched with the different brands and presentations with the information of sanitary registries and molecules-patent included in the database. From this, prices were calculated and sales volumes were obtained at the "medication-presentation" level. The prices correspond to prices listed at the distributor-drugstore and consumer price level.

These prices do not consider the effect of possible discounts or price variations from the retailer, depending on the type of retailer or the sales channel in question, or, discounts in the price finally

254 Barraza Lloréns and Guajardo Barrón (2013).

paid by the consumer. This could generate an overestimate of the prices to be analyzed. Likewise, this information not necessarily covers the entire market, since it does not cover 100% of the private sector sales, in particular, those sales performed on markets known as "not audited". However, these information sources are considered as robust enough to analyze trends and to achieve the study objectives. Likewise, it is the first time that a so detailed trend analysis market information database has been compiled.

Once the market information has been integrated to the database, the generic medications – for which a sanitary registration was identified and are effectively commercialized in the private Mexican market were identified. This is taken as a measure of observed competition, because it reflects whether the generic alternatives are a feasible alternative for buyers, individuals or public or private institutions. Likewise, average price time series and sales volumes were generated.

The IMSS information was used in a complementary manner, whose purchases represent around 50% of the medications purchased by the public sector. The information available for this study corresponds to the value and volume of those codes of the Basic Frame and Catalog of Supplies of the Health Sector (CBCI) acquired in the January 2005 to July 2016 period, which has some competition in the identified universe of molecules-patent without patent protection.

The available information for IMSS includes price and monthly consumption volume at the CBCI code level. However, it has two important limitations:

i. Before 2012, an identifier is not included that allows to distinguish the specific presentation acquired in the case of CBCI codes that include more than one presentation is not included. Therefore, it is not possible to calculate the price per extended unit before this date, since there is no certainty of the presentation that corresponds to the price and volume information. This identifier is only included from 2012.
ii. No supplier or sanitary registration of the product acquired is identified, therefore, it is not possible to know if the purchase corresponded to the original or to the generic medication and, if applicable, to which generic version.
iii. Due to these limitations, the IMSS information was considered to:
    a) Identify those molecules that participate in public purchasing, independently of which product is acquired (original or generic).
    b) Incorporate price time and volume series as from 2012 for the public sector, as part of the market evolution analysis and observe what happens in general with the price paid in the public sector according to the generic drugs entry.
iv. Although the price information of the IMSS was not included with the generic prices of the private sector, the purchase volume was added to the sales volume of the private sector to estimate the total size of the market for each molecule. This variable is relevant for the analysis of the determinants and to estimate the savings lost due to a possible lack of competition of generic drugs or due to possible delays in the generic drugs competition.

The universe of products is heterogeneous as per the administration means and pharmaceutical form. In order to compare and average the price information of the different presentations under which the medication is marketed, it is necessary to calculate a price per extended unit. The extended unit is determined by the size of the presentation, the route of administration and the pharmaceutical form.

In the case of oral and solid formulations, such as tablets, capsules and pills, the concentration of the active principle is usually measured in milligrams or micrograms, and the price calculation per extended unit is easier to do, being at the tablet or milligram level.

However, in the case of non-solid formulations, this calculation is not so direct, since the concentration is usually expressed as the amount of the active substance contained in a determined amount of the solution in the case of liquids (20 mg per each 100 ml), or as a concentration percentage in the case of ointments, to mention a few examples. And the active ingredient amount depends on the size of the presentation. In some cases, the concentration measure is expressed in International Units.

Thus, the non-solid formulation calculation is feasible, but requires a more detailed analysis of the different presentations for comparison. In particular, we must be even more careful when there are different pharmaceutical forms of the same molecule (e.g., pill and IV solution). Most of the literature identified as reference for this study presents price behavior data only in the solid oral formulations. In this study, all available formulations are included.

Additionally the price calculation per extended unit, the latter were deflated using the National Consumer Price Index (INPC) of the Statistics and Geography National Institute (INEGI) taking as the base period January 2009. Likewise, to calculateprice indicators, both the original price as well as the average price of the generic drugs are normalized, taking as a reference the first price of the original medication reported in the information sources of the private market.

For each presentation, corresponding to the same sanitary registration of a generic medication, identified in the information sources of the private sector market, the average price was calculated at the distributor level based on the observations of the different data sources. The average price of generic medications associated to a molecule results from calculating the average price of the different brands and presentations associated to the different sanitary registries of the generic medications. In the case of original medication, the price was also calculated as the average price per extended unit of the different presentations. When an original medication had more than one associated sanitary registration, the prices were also averaged. In these cases, the price per extended unit used to normalize is the average of the price per unit of the associated sanitary registries. To define the baseperiod, the period corresponding to the sanitary registration or the original medication with the oldest date was considered.

The time series were prepared at a medication-presentation level, as the main analysis unit. As secondary analysis unit, the average price at medication level was calculated (or molecule/active substance) using the weighted average of the different prices of the medication at the presentation level, in which the weighting factor is the relative volume of purchase or sale of each presentation. The price series were deflated using the INEGI's INPC, taking as base year January 2009.

It is worth mentioning that the price information is quite robust between the information sources used. However, in the case of the volume information it is not possible to identify in which cases the information sources are mutually exclusive or not; therefore, there is not enough information to decide in which cases the sources must be added instead of averaged. The option chosen was to average the volume information.

A.1.4. Analysis of price and sales behavior of the medications analyzed the sector environment

A.1.4.1 Analysis of price and sales behavior

Since the information about the price and sales volume is only available from January 2009, a subset of the molecules for the market evolution analysis that complies with the following criteria was defined: [255]

i. That all expired patents associated with a given molecule has an effective protection validity date after January 1, 2009. This is the date from which the market information exists, i.e., price and sales. This restriction is necessary because, when there is no information for the previous year, it is not possible to identify the market conditions of the original medication before the expiration of the protection and after it.
ii. They faced competition from at least one generic version (at least one generic sanitary registration was identified) and there is prices and sales volume data available in the information sources of the private sector, at least for the original medication. For the calculation of the price indicators and the market participation, information on the generic versions market was also required.

The purpose of this analysis is to see what happens with the medication price whose patent has expired (original medication) and see what happens with the price of each generic version, as the generic versions enter the market. It is also intended to analyze what happens with market participation, volume, of the original medication and of the generic medications and with the total sales of the medication (including original and generic medications). Likewise, as a reflection of this, it is intended to measure the effect of the average price of the generic medications and in the average price of the medication (considering both the original medication as well as the generic medications), as new generic versions come about.

A first analysis was made in a graphic manner for each molecule using the average price and the aggregated volume. To determine the average price and the market participation at the medication level, it is necessary to guarantee the data comparability between presentations. The price per extended unit volume was considered. In other words, calculate, e.g., the price per tablet, capsule, gram, milligram, etc.[256]

The objective is to detect if there is any erosion in the price of the original medication and of the different competitor generic medications. The difference between the price of the original medication and the price of the competitor generic medications was calculated at different times, depending on theentry of the competitor generic medicatione. The time between the moment of entry of the competitor generic medication and the moment of the price response by the original medication was identified. In the cases in which information on volume was available, the evolution of the market participation in terms of volume was also analyzed.

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255 In accordance with our sources, the prices and amounts reported, for some medications, are not available for the entire studio period, since, among other things: i) some medications were incorporated to their databases after the laboratories, drugstores, or distributors, as the case may be, sign a data supply agreement with the information suppliers, and ii) in certain periods, their suppliers do not report sales.

256 See the previous subsection and Frank and Salkever (1995).

To compare the prices over time, these were normalized by the price of the original medication-presentation at the moment prior to the entry to the market of the first generic version. The results are presented in an indexed manner.

The average price per medication is the weighted average per purchase or sales volume.

The possible determining factors of the prices and market participations were analyzed, trying to relate these changes with the number of incoming competitor generic medications, the period between the loss of the patent and the entry date of the generic medication, the type of generic medication (with brand, without brand, generic version of the laboratory that manufactures the original medication), the total sales as an estimate of the market size and other variables considered as possible behavior differentiators (e.g.: type of patent, coverage by the public sector, if the medication is include in the reference medications of Cofepris, route of administration, if it is of predominantly hospital use or outpatient use, etc.).

Medications with combined formulations were excluded from the analysis due to the associated complexity of constructing a price that may be comparable and that can be added to the price of simple formulations. The medications with combined formulations distort the assumption of direct competition at the active substance level and if the active substance with which it is combined also has some kind of patent protection, there could be implications in the terms of the date on which the medication effectively losses the patent.

A.1.4.2 Competition indicators

Based on the literature and in a complementary manner, the analysis described in the prior section, a series of indicators were defined which, in a synthetic and jointly manner, reflect the competetion or market performance of the medication that lost its patent.

These indicators are not exhaustive or replace those that could be developed in the future, based on more complete information. Neither replace the more detailed analysis that is included in this study.

The proposed indicators are grouped based on four dimensions that reflect the competition or performance level in this market:

i. Competition. It refers to the market entry of products corresponding to the generic versions of the medication whose patent has expired.
ii. Speed of competition. It refers to the time elapsed between the loss of the market exclusivity granted by a patent and entry to the market of the first generic version and of the subsequent generic versions.
iii. Effect in price. It is the change observed in prices, both the original medication whose patent has expired, as well as that of the generic versions.
iv. Level of penetration (market participation effect). How much and how fast the generic versions increase their market participation (in volume).

The indicators for each dimension are shown in the boxes below. Under each one of these boxes there is a list of variables/indicators obtained from the literature as a support for the proposal.

1. Competition indicators

1.1 Percentage of medications without patent protection for which there is at least a sanitary registration of a generic version (not produced by the original laboratory), after the expiration of the patent (hypothetic competition).
1.1 Percentage of medications without patent protection for which at least one generic version is commercialized in the market (not produced by the original laboratory) after the expiration of the patent (observed competition).
1.2 Average number of generic competitors per presentation, , at 12 and 24 months after the patent expiration.

Variables/indicators identified in the literature

1. Percentage of medications with expired patent that face competition at 12 and 24 months.[257]
2. Any entry and number of generic medications producers.[258]
3. Average number of generic medications producers per medication after 12 and 24 months (average and per medication)[259, 260]
4. Average number of generic medications per presentation.[261]
5. Average number of competitor generic medications per laboratory-molecule-formulation which experiment exclusivity loss.[262]

2. Speed of Competition

2.1 Percentage of original medications sanitary registries without patent protection for which there is at least one sanitary registration of a generic version (hypothetic competition) at 3, 6, 9, 12, and 24 months after the expiration of the patent.
2.2 Percentage of original medications sanitary registries without patent protection for which there is at least one combination of brand-presentation identified in the market information (observed competition) at 3, 6, 9, 12, and 24 months after the expiration of the patent.
2.3 Average time (months) elapsed between the loss of the patent (binding) of a medication and the granting of the first sanitary registration of a generic medication (that is not from the laboratory of the original medication)
2.4 Average time (months) elapsed between the granting of the sanitary registration of the first generic medication (that is not from the laboratory of the original medication) and the realisingof any generic medication in the private market.
2.5 Average time (months) elapsed between the loss of the patent (binding) of a medication and the realising of any generic medication in the private market.

257 Kanavos (2014).
258 Danzon y Furukawa (2011).
259 Kanavos (2014).
260 Grabowsky, Kyle, *et al* (2011).
261 Danzon and Furukawa (2011).
262 Conti and Berndt (2014).

Variables/indicators identified in the literature

1. Average entry time of the first, second, and other generic competitor medications.[263]
2. Percentage of medications which have generic competition at 3, 6, 9, and 12 months after the loss of patent.[264, 265]
3. The delay of entry of a product is defined as the number of months between the release of the first original medication and the entry of the first generic medication, acknowledging that this delay may reflect legal barriers and economic factors.[266]
4. Average duration of market exclusivity (defined as the release date of the first generic medication minus the release date of the original medication).[267]
5. Effective market exclusivity (time between the approval of the sanitary registration of the original medication and the entry of the first generic medication). [268]
6. Since the litigations, the labelling regulations and the aspects related to the beginning of manufacture may *de facto delay* the entry beyond the approval date of the sanitary authorization, the first month that registers sales and positive sales volume is taken as the entry date of the generic medication.[269]

3. Indicators of the effect in prices

3.1 Evolution in the average relative price of the generic medications (different from the generic version of the original medication) at 6, 12 and 24 months after the entry of the first generic medication.*

3.2 Evolution in the average relative price of the original medication at 6, 12 and 24 months after the entry of the first generic medication.*

**The price is relative tothe price of the original medication at the moment of entry of the first generic medication. The generic medications of the original medication are excluded.*

Variables/indicators identified in the literature

1. Change in the relative price of the generic medications at different times (12, 24 months).[270]
2. Change in price of the original medication at different times (12, 24 months).[271]
3. Reduction after one month of the loss of exclusivity in the average price of the molecule per day of therapy observed at the moment of the loss of exclusivity.[272]
4. Average price per prescription of original and generic medications. The sales value in retail drugstores for a given type of medication is divided by the number of dispatched prescriptions. The medication types are: original from multiple sources and generic medications from a sole source.[273]
5. Percentage change in the prices of the original and generic medications. This is compared

263 Kanavos (2014).

264 Kanavos (2014).

265 Congressional Budget Office (1998).

266 Danzon and Furukawa (2011).

267 Grabowsky, Kyle, et al (2011).

268 Aitken, Berndt, Bosworth, et al (2013).

269 Conti and Berndt (2014).

270 Kanavos (2014).

271 Kanavos (2014).

272 Aitken, Berndt, Bosworth, et al (2013).

273 Congressional Budget Office (1998).

between those medications that face generic medications competition and those that do not face competition.[274]

6. Prices of generic medications relative to the base price of the original medications. These are normalized prices at the presentation level and are calculated as the average price of the generic medication, weighted by the volume of all the generic versions of such presentation and normalized (divided) by the corresponding presentation price of the original medication at the moment of entry of the generic medications. This normalization provides a measure of price free from the effect of the units and allows the comparison of trends in time and between molecules for products that may have very different absolute price levels. Another option is using price per dose 2 years after the entry of the first generic medication.[275]
7. Relative price of the original medications. It is calculated in a similar manner as the previous one where the price of the original medication is normalized with respect to the original price at the moment of entry of the generic medications.[276]
8. Monthly prices adjusted by inflation at the presentation level, before the loss of exclusivity and entry of generic medications, and after the loss of exclusivity and entry of generic medications, added at the original medication level and generic versions for each molecule-presentation. [277]
9. Average monthly prices (at constantprices) observed in the last 2007 quarter with respect to the total number of medications entering the market in all years after the loss of exclusivity (including the original medication).[278]
10. Average generic price (indexed to 100) after one year. [279]
11. Average daily cost of treatment before the entry of generic medications and 12 and 24 months after the entry of generic medications.[280]

4. Generic medications´ degree of penetration indicators

4.1 Average market participation (volume) of generic medications (different from the original medication) 6, 12 and 24 months after the entry of the first generic medication.

4.2 Percentage change in the average market participation (volume) of the original medication 12 months after the entry of the first generic medication.

4.3 Number of months thatit takes the generic medications to reach 50% market participation, on average .

Variables/indicators identified in the literature

1. Market participation (volume) of generic medications after 3, 12 and 24 months.[281]
2. Reduction in the market participation of original medications 12 months after the entry of the first generic medication, defined as the participation in units of the original medications divided by the

274 Íbid.

275 Danzon and Furukawa (2011).

276 Íbid.

277 Conti and Berndt (2014).

278 Íbid.

279 Berndt and Aitken (2010).

280 Íbid.

281 Kanavos (2014).

sum of the original medications´ volume and their generic versions.[282]

3. Average market participation of prescriptions for original and generic medications. The types of medications are of multiple source and original and generic sole source. The market participation is the percentage of the total of dispatched prescriptions for each kind of medication. It is measured one year after the entry of the generic medications.[283]
4. Market participation (volume) of generic medications.[284]
5. The market penetration of generic medications can be measured in different ways – participation of extended units of generic medications dispatched (tablets, capsules, vials, accountable units) – and as a percentage of generic medications prescriptions.[285]
6. Penetration rate of generic medications as proportion of all the prescriptions of a given molecule that are dispatched.[286]
7. How much time (months) it takes a molecule to reach the determined thresholds of generic medications´participation? The 60% and 90% thresholds, in terms of sales volume participation, have been considered.[287]

A1.5 Analysis of the sector's structure

The sector environment determines, not only the feasibility that there is effective competition after the expiration of the patent, but also the magnitude of the effect that this may have in prices. The analysis of the sector´s structure consisted in analyzing the presence of possible government or market failures. To do this, the tools for competition evaluation by the Organization for the Economic Cooperation and Development (OCDE) (OECD 2015c, 2015d y 2015e) were used as general reference.

Regarding government failures, it is important to consider two major areas in which regulation influences the introduction of a medication into the Mexican market. The first is the regulation in matters of industrial property that determines the market exclusivity by means of the patent protection, whose administration is the responsibility of the IMPI. The second one is the provision for the issuance of sanitary registrations by Cofepris.

In the event of market failures, thebarriers to entry and the cost increase for the competitor must be considered. In particular, in accordance with the results of section two, some business practices by the incumbent may, *de facto*, be extending the market exclusivitydiscouraging the entry of competitors or limiting the size of the decrease in the generic versions prices.

282 Grabowsky, Kyle, et al (2011).

283 Congressional Budget Office (1998).

284 Danzon and Furukawa (2011).

285 Berndt and Aitken (2010).

286 Aitken, Berndt, Bosworth, et al (2013).

287 Íbid.

A1.6. Calculation of the potential benefits for the consumer of greater competition

Based on the price analysis of medications and times of entry and volumes of competitor generic medications and the environment analysis, the presence or not of possible government or market failures was analyzed, and, if such failures were identified, an approximate calculation of the potential benefits for the consumers of medications in Mexico's public and private sector was prepared. The following steps were taken:

For those medications that haveat least one generic competitor:[288]

i. The value of the sales of the medication was calculated at the entry date of the first generic competitor.
ii. The value of the slaes of the medication was calculated 24 months after the entry of the first generic medication as a weighted average price comprised of the price of the original medication and the average price of the generic medications available at that moment. The average participation of thethe competitor generic medications after 24 months of entry of the first generic medication in the private market (21.4%) was used as a weighting factor of the average price of the available generic medications. The weighting factor for the price of the original medication 24 months after the entry of the first generic medication was obtained as the difference between the unit and weighting factor for the average price of the generic medications.
iii. The benefit observed for each medication is the difference between (i) and (ii).[289]
iv. To calculate the potential benefit, this last exercise was repeated modifying the weighting factors used for the original and generic medications 24 months after the entry of the first generic competitor. In this case, the weighting factor becomes a reference variable or an objective variable, instead of an observed variable. Considering that, in countries with relatively acceptable market competition, the participation of generic medications is located in the range between 40% and 90%, an objective participation equivalent to the double of the observed participation was used for this exercise; i.e., the weighting factor for the price of generic medications was fixed at 42.8% to calculate the potential savings. In consequence, the weighting factor for the price of the original medication was fixed at 57.2%
v. For the calculation, only the data on the medications sales in the private sector wasused, since the public sector information available is not strictly comparable with the one of the private market.
vi. The unrealised savings is the difference between (iii) and (iv).

The savings are calculated considering the generic medications market participation observed in the private market and the result is extrapolated to the whole sector.

288 Apart from facing at least one generic competitor, the included medications must also present complete data at the moment of entry of the first generic medication and 24 months after this occurs.

289 In calculating the savings observed in this manner, a dilemma is faced similar to the one faced when calculatingusually calculates price indexes and results in a different calculation depending on whether the prevailing basket of goods is taken before the price changes or the resulting basket once the prices are already changed. In the case of the calculation used in this study, the sales/purchase value after 24 months of entry of the first generic medication was used. Therefore, under the assumption that the demanded amounts have increased, the observed savings may be overrated.

A1.7 Initial universe and universe of analysis

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
1	ABACAVIR	183639		
2	ABIRATERONE	196492		
3	IBANDRONIC ACID	181402		
4	ZOLEDRONIC ACID	174759		
5	ALCAFTADINA	186030		
6	ALEFACEPT	208133	YES	Withdrawn from the market
7	ALISKIREN	209361		
8	ALMOTRIPTAN	206375		
9	ALOSETRON	175992	YES	Withdrawn from the market
10	AMIFOSTINE	200513		
11	AMLODIPINE	176958		
12	ANASTROZOL	182808		
13	ANIDULAFUNGIN	208319		
14	APREPITANT	197681		
15	ARIPIPRAZOL	186552		
16	ASENAPINE	197583		
17	ATROVASTIN	178535		
18	ATRASENTAN	210935	YES	No sanitary registration was granted
19	BICLUTAMIDE	178918		
20	BOSENTAN	178416		
21	CANDESARTAN	190105		
22	CANGRELOR	190978	YES	No sanitary registration was granted
23	CAPECITABINE	173347		
24	CAPECITABINE	185169		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
25	CASPOFUNGINA	186806		
26	CEFDINIR	184703		
27	CEFEPIMA	188780		
28	CEFEPIMA	188781		
29	CELECOXIB	200516		
30	CYCLOSPORINE	205645		
31	CILOMILAST	187418	YES	No sanitary registration was granted
32	CISATRACURIO BESILATO	184814		
33	CLEVIDIPINO	196540	YES	No sanitary registration was granted
34	CLEVIDIPINO	251685	YES	No sanitary registration was granted
35	CLOPIDOGREL	178820		
36	COLESEVELAM	205855		
37	ALPHA DARBEPOETIN	207794		
38	DARIFENACIN	178595	YES	Without competition but with other patents in force in the IMPI's medications Gazette
39	DELAVIRDINE	189647		
40	DELAVIRDINE	217492		
41	DOCETAXEL	181403		
42	DOCETAXEL	188291		
43	DOCETAXEL	189634		
44	DOCETAXEL	191820		
45	DOCETAXEL	206380		
46	DOFETILIDE	177265	YES	No sanitary registration was granted
47	DOLASETRON	182605		
48	DONEPEZILO	181349		
49	DORIPENEM	192701		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
50	DORZOLAMIDE	181723		
51	DRONEDARONA	185586	YES	*Without concurrence but with other patents in force in the IMPI's medications Gazette*
52	DULOXETINE	176549		
53	DULOXETINE	185030		
54	DUTASERIDE	200989		
55	ECULIZUMAB	238000		
56	EFAVIRENZ	192812		
57	ELETRIPTAN	183407		
58	ELETRIPTAN	213692		
59	EMTRICITABINE (ASYLUM ENANTIOMER)	252110		
60	EMTRICITABINE	221134		
61	ENOXAPARIN	178029		
62	EPROSARTAN	175849		
63	ERLOTINIB	231292	YES	Without competition but with other patents in force in the IMPI's medications Gazette
64	ERTAPENEM	188551	YES	Without competition but with other patents in force in the IMPI's medications Gazette
65	ESCITALOPRAM	182606		
66	ESOMEPRAZOLE	191066		
67	ESOMEPRAZOLE	192674		
68	ESOMEPRAZOLE	197310		
69	SPARFLOXACINO	176454	YES	Withdrawn from the market
70	ETANERCEPT	256282		
71	ETOPOSIDO	173843		
72	EXEMESTANE	181201		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
73	EZETIMIBA	196935		
74	FELODIPINE AND NIFEDIPINE	176260	YES	Without data for the interpretation of the molecule name in the patent
75	FILGRASTIM	181200		
76	FINASTERIDE	177770		
77	FLIBANSERIN	188611	YES	No sanitary registration was granted
78	FLUVASTINE	179953		
79	FLUVASTINE	186288		
80	FOLITROPINA ALPHA	178224		
81	GEFITINIB	185311	YES	Without competition but with other patents in force in the IMPI's medications Gazette
82	GEMCITABINE	183670		
83	HUMAN CHRONIC GONADOTROPIN	216352		
84	GRANISETRON	181348		
85	IMATINIB	190786		
86	IMIQUIMOD	177242		
87	INSULIN	261279		
88	INSULIN LISPRO	178720		
89	INSULIN LISPRO	191522		
90	IRBESARTAN	176397		
91	LAMIVUDINE	176805		
92	LAMIVUDINE	193791		
93	LAMIVUDINE	203587		
94	LANSOPRAZOLE	182131		
95	LASOFOXIFENE	205143	YES	No sanitary registration was granted
96	LETROZOLE	174756		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
97	LEVOFLOXACIN	183197		
98	LINEZOLID	197282		
99	LOSARTAN	178771		
100	MEROPENEM	173359		
101	MEROPENEM	182285		
102	METOPROLOL	173252		
103	MOLFETHYL MICOFENOLATE	177872		
104	MIDAZOLAM	179391		
105	MIZOLASTINE	175371	YES	Without competition but with other patents in force in the IMPI's medications Gazette
106	MOLGRAMOSTIM	190796		
107	MIZOLASTINE	177307		
108	MOMETASONE FUROATE	208950		
109	MONTELUKAST	179763		
110	MOROCTOCOG ALFA	190184		
111	MOXIFLOXACIN [ENANTIOMERIC (S,S)]	202941		
112	MOXIFLOXACIN	189629		
113	NANDROPARIM CALCIUM	186561		
114	NARATRIPTAN	177060		
115	NATALIZUMAB	198845	YES	Without competition but with other patents in force in the IMPI's medications Gazette
116	NELFINAVIR	191584	YES	Withdrawn from the market
117	NEVIRAPINE	176695	YES	Without competition but with other patents in force in the IMPI's medications Gazette
118	OLANZAPINE	173791		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
119	OMEPRAZOLE	179340		
120	OMEPRAZOLE	194930		
121	OMEPRAZOLE	197296		
122	ONDANSETRON	177059		
123	OPRELVEKINA	184567		
124	OXYCODONE	193465		
125	PALONOSETRON	176794		
126	DISODIUM PAMIDRONATE	185996		
127	PANTOPRAZOLE	177372		
128	PANTOPRAZOLE	181529		
129	PARICALCITOL	176824		
130	PAROXETINE	177132		
131	PEGFILGRASTIM	205205		
132	PEMETREXIDA	179345		
133	PIOGLITAZONE	181354		
134	POSACONAZOLE	196272	YES	Without competition but with other patents in force in the IMPI's medications Gazette
135	PRAMIPEXOLE	181303		
136	PRASUGREL	192564	YES	Without competition but with other patents in force in the IMPI's medications Gazette
137	PREGABALIN	215885		
138	PROPOFOL	209419		
139	PROPOFOL	255660		
140	QUETIAPINE	177810		
141	QUINUPRISTIN	181203	YES	No sanitary registration was granted
142	RABEPRAZOLE	179117		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
143	RALOXIFENE	195385		
144	RALOXIFENE, ESTROGEN	188784	YES	No sanitary registration was found
145	RALTITREXED	179683		
146	RASAGILINE	236132		
147	REMACEMIDE	183546	YES	No sanitary registration was granted
148	REMIFENTANIL	187818		
149	RIMONABANT	192617	YES	Withdrawn from the market
150	RISPERIDONE	176311		
151	RISPERIDONE	200991		
152	RITONAVIR	191767		
153	RITONAVIR	192638		
154	RIZATRIPTAN	189544		
155	ROBALZOTAN	189259	YES	No sanitary registration was granted
156	ROFECOXIB	194277	YES	Withdrawn from the market
157	ROPIVACAINE	178451		
158	ROSIGLITAZONE	194435		
159	RUPATADINE	183975		
160	SALMETEROL	182960		
161	SAQUINAVIR	173630		
162	SERTINDOLE	176214		
163	SEVELAMER	236045		
164	SEVELAMER	251295		
165	SIBUTRAMINE	177057		
166	SILDENAFIL	181244		
167	SILDENAFIL	195457		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
168	SUMATRIPTAN	179644		
169	SUMATRIPTAN, SULFATE	181644		
170	TACROLIMUS	185242		
171	TADALAFIL	196955	YES	Without competition but with other patents in force in the IMPI's medications Gazette
172	TEGASEROD	189745		
173	TELYTHROMYCIN	191778	YES	Without competition but with other patents in force in the IMPI's medications Gazette
174	TELMISARTAN	190103		
175	TEMSIROLIMUS	193369		
176	TERBINAFINE	182129		
177	TIBOLONE	182007		
178	TIGECYCLINE	186553		
179	TIOTROPIUM (BROMIDE)	185142	YES	Without competition but with other patents in force in the IMPI's medications Gazette
180	TIPRANAVIR	203768		
181	TIROFIBAN	188859		
182	TIZOXANIDA	201055	YES	No sanitary registration was granted
183	TOLCAPONE	183747	YES	Withdrawn from the market
184	TOPOTECAN	177962		
185	TRANDOLAPRIL	182069		
186	TRAVOPROST	203527		
187	VALACYCLOVIR	188922		
188	VALGANCICLOVIR	195601		
189	VALSARTAN	177165		
190	VENLAFAXINE	178370		
191	VENLAFAXINE	195968		

No.	Molecule (name as shown in the Gazette of the IMPI)	Patent Number	Excluded from the initial universe	Exclusion reason
192	VERAPAMIL AND TRANDOLAPRIL	180913	YES	Withouth interpretation data of molecule name in patent
193	VETREPORFINA	180362		
194	VETREPORFINA	192703		
195	VORICONAZOLE	178140		
196	ZAFIRLUKAST	184659		
197	ZANAMIVIR	183013		
198	ZANAMIVIR	190102		
199	ZANAMIVIR	204829		
200	ZIPRASIDONE	173362	YES	Without competition but with other patents in force in the IMPI's medications Gazette
201	ZIPRASIDONE	184189	YES	Without competition but with other patents in force in the IMPI's medications Gazette
202	ZOLIMTRIPTAN	185978		

Source: González Pier, E., et al. (2017), with information of the Medication's Gazette of the IMPI, information of Cofepris and Internet research.

ANNEX 2. ESTIMATION RESULTS

Price regressions

Estimated Strategy	Lineal				Instrumental Variables					
Dependent variable	ln(Pp)		ln(pg)		ln(Pp)		ln(pg)			
Effects	FE (1)	RE (2)	FE (3)	RE (4)	FE (5)	RE (6)	FE (7)	FE (8)	RE (9)	RE (10)
NP	0.0428**	0.0418**			0.0765***	0.0741***				
	(0.0190)	(0.0188)			(0.0172)	(0.0175)				
G	-0.0228**	-0.0228**	-0.0473***	-0.0474***	-0.0646***	-0.0641***	0.145**		0.166**	
	(0.00955)	(0.00956)	(0.0116)	(0.0116)	(0.0198)	(0.0203)	(0.0641)		(0.0722)	
PM (original)	0.0701	0.0699			-0.133	-0.131				
	(0.0701)	(0.0704)			(0.0991)	(0.101)				
PM (generic)			-0.0193	-0.0179			-1.046***	-0.271***	-1.147***	-0.270***
			(0.104)	(0.104)			(0.348)	(0.0400)	(0.389)	(0.0400)
Time	0.00193*	0.00193*	-0.00145	-0.00145	0.00399***	0.00397***	-0.0101***	-0.00358***	-0.0111***	-0.00358***
	(0.00099)	(0.00099)	(0.00214)	(0.00214)	(0.00102)	(0.00104)	(0.00298)	(0.000472)	(0.00336)	(0.000471)
d_gmyg		-0.693*		-0.710*		-0.619**			-0.926**	-0.758*
		(0.419)		(0.421)		(0.313)			(0.458)	(0.428)
g_2009		0.275		1.055***		0.0319			1.584	1.173
		(0.321)		(0.274)		(0.973)			(1.414)	(1.329)
gm_pantent		-0.859**		-0.793*		-0.882**			-1.039	-0.848
		(0.378)		(0.422)		(0.440)			(0.645)	(0.606)
segm		0.114		0.0470		0.128			0.0663	0.0513
		(0.385)		(0.395)		(0.288)			(0.419)	(0.396)
Constant	3.824***	4.552***	3.633***	4.321***	3.908***	4.599***	3.551***	3.613***	4.374***	4.333***
	(0.0990)	(0.295)	(0.0546)	(0.293)	(0.0532)	(0.248)	(0.0322)	(0.0106)	(0.357)	(0.337)
Remark	1,387	1,387	1,428	1,428	1,387	1,387	1,428	1,428	1,428	1,428
Square Root	0.146		0.299					0.220		
Molecule No.	21	21	21	21	21	21	21	21	21	21

The robust errors are shown between parenthesis; *, ** and *** represent significance level at 10, 5 and 1%. Where d_gmyg=1 if they exist in time "t", simultaneously, generic medications and generic medications with brand, and "0" on the contrary; g_2009=1 if a generic medication was identified before 2009, and "0" in another case; gm_pantent=1 if the laboratory of the original medication also manufactures a generic version and "0" in another case; segm=1 the trend of the patent medication price is positive, and "0" in another case.

ANNEX 3. MEDICATION CASES

CELECOXIB

Celecoxib is a drug substance used for the treatment of osteoarthritis and rheumatoid arthritis, originally developed and patented by G.D. Searle LLC.,[290] which granted an exploitation sub-license to Pfizer, S.A. de C.V. in 2005. Pfizer commercializes this substance under the brand Celebrex in 100 and 200 mg presentations. With data up to 2015, its market value in Mexico is estimated in around 1.059 billion pesos. The patent of the active principle expired on November 24, 2014 (No. 200516); however, Pfizer S.A. de C.V has an exploitation license of a second patent (No. 213466) of pharmaceutical composition that covers particle sizes from 25 to 200 µm., which expires on November 30, 2019.

Anticipating the expiration of the active principle patent, on January 2014, Pfizer, S.A. de C.V. began to distribute its own generic medication. In August 2016, six generic medications sanitary registries were identified in Cofepris, but there is no information that the generic medications are commercialized in the private market. To that respect, there are trials for patent invasion concerning celecoxib (see Box 9.). In accordance with Cofepris (2017), due to these litigations, three companies have been directly affected. Likewise, in accordance with the Generic Medications Mexican Association (AMEGI), the generic medications laboratories that tried to commercialize this substance could be practically unable, since the range of the particle size protected by the second patent hinders its production. This could represent a *patent clustering case*, since the secondary patent still in force, obstructs, albeit hinders, the entry to the market. In view of the absence of generic medications produced by competitor laboratories, the price of the original medication increased as from January 2014.

In 2015, Hetlabs México, S.A. de C.V. began a nullity procedure of the pharmaceutical compositions patent; however, at the moment of preparation of this report, it is still pending.

In the United States, Pfizer has been accused of creating "false litigations" to keep the generic versions of Celebrex out of the Market. Pfizer tried to extend the protection of tis medication by registering patent of use for the treatment of diverse illnesses, which term was extended 18 months after the expiration of the active principle and of the composition in May 2014.[291] However, this was declared invalid on March 2014 by a federal judge in Virginia under the judicial doctrine which prohibits the "double patent". [292]

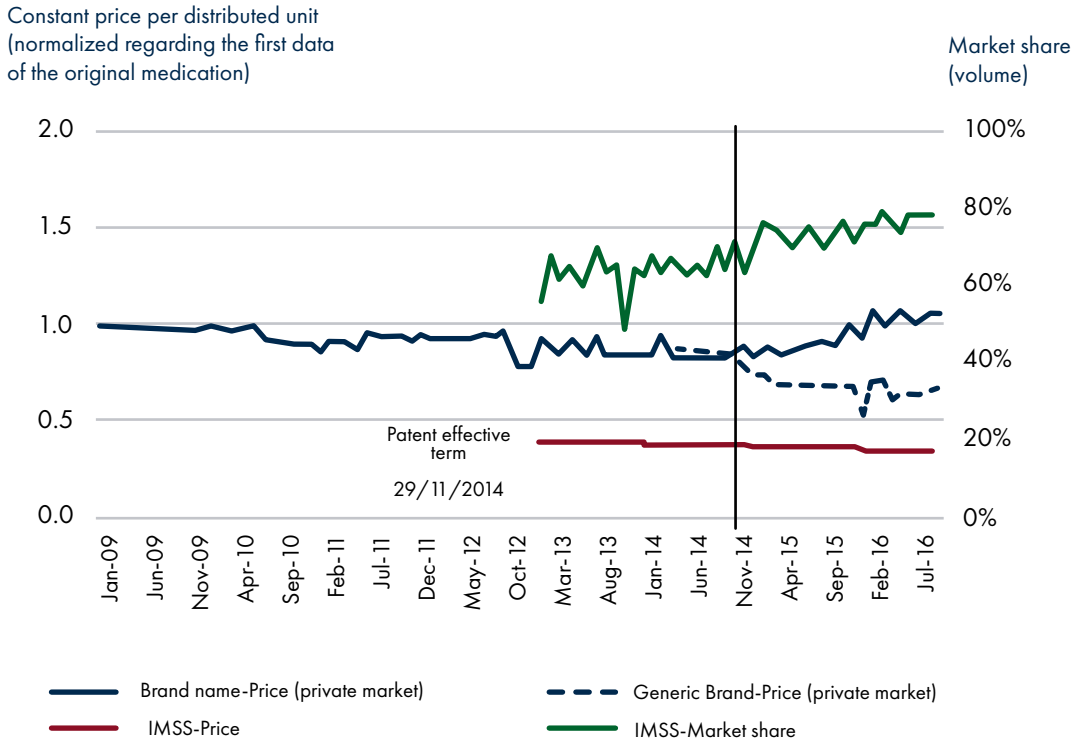
290 Today, G.D. Searle, LLC is a commercial brand fully owned by Pfizer Inc., which, in 2003, acquired Pharmacia Corporation. In April 2000, Pharmacia Corporation was created by the merger of Pharmacia & Upjohn with Monsanto and its Searle Unit. Source: http://www.pfizer.com/about/history/pfizer_pharmacia

291 Source: http://fortune.com/2014/03/13/judge-cuts-18-months-off-patent-life-of-pfizers-celebrex/ (Enquired on 10-03-2017).

292 Source: https://www.law360.com/articles/613816/pfizer-schemed-to-block-celebrex-generics-new-suit-says (Enquired on 10-03-2017).

Recently, in Chile, a federal prosecutor asked the competence court to impose a penalty of 15.5 million dollars to GD Searle LLC, and affiliate company of Pfizer Inc., for unduly obtaining a patent to extend the protection of celecoxib. Before the exclusivity period of Searle expired in 2014, the company requested and obtained the approval of a patent of celecoxib that extended its protection until 2029. However, the investigation found that the second patent did not represent any significant innovation in the existing medication.[293]

CELECOXIB



Source: González Pier et al. (2017).

293 Source: https://www.law360.com/subscribe/email_verification?article_id=805905&section=competition (Enquired on 10-03-2017).

IMATINIB

Imatinib is a drug substance used to treat myeloid leukemia and certain cancer types, developed by the Swiss pharmaceutical company Novartis under the brand Glivec. With the 2015 data, its market value un Mexico is estimated around 191.5 million pesos. Its active principle patent (No. 190786) expired on April 2, 2013, but has another three patents still in force: i) of active principle (No. 218673), ii) of second use (No. 244404) and iii) of pharmaceutical composition (No. 252475), which is possibly blocking the entry of generic medications into the market. Up to August 2016, five sanitary registries of Cofepris were identified, but no information about generic medications commercialized in the private market is available. To that respect, there are trials for patent invasion concerning imatinib mesilate (see Box 9). In accordance with Cofepris (2017), these litigations have affected nine companies in a direct manner.

Between 2012 and 2014, Novartis started proceedings for violation of patent rights against the following laboratories: Sun Pharma de México, S.A. de C.V., Helm de México, S.A. de C.V., Probiomed, S.A. de C. V., Farmabiot, S.A. de C.V., Laboratorios Pisa, S.A. de C.V., Sicor de México, S.A. de C.V., and Distribuidora Internacional de Medicamentos y Equipo Médico, S.A. de C.V. Likewise, in 2013, Probiomed, S. A. de C. V., requested the nullity of patent 218673 before IMPI. A year later, Lemery, S.A. de C.V, requested the nullity of the patent of second use. Up to this date, these proceedings are still pending, therefore, it is not possible to see the dossiers, since they are confidential.

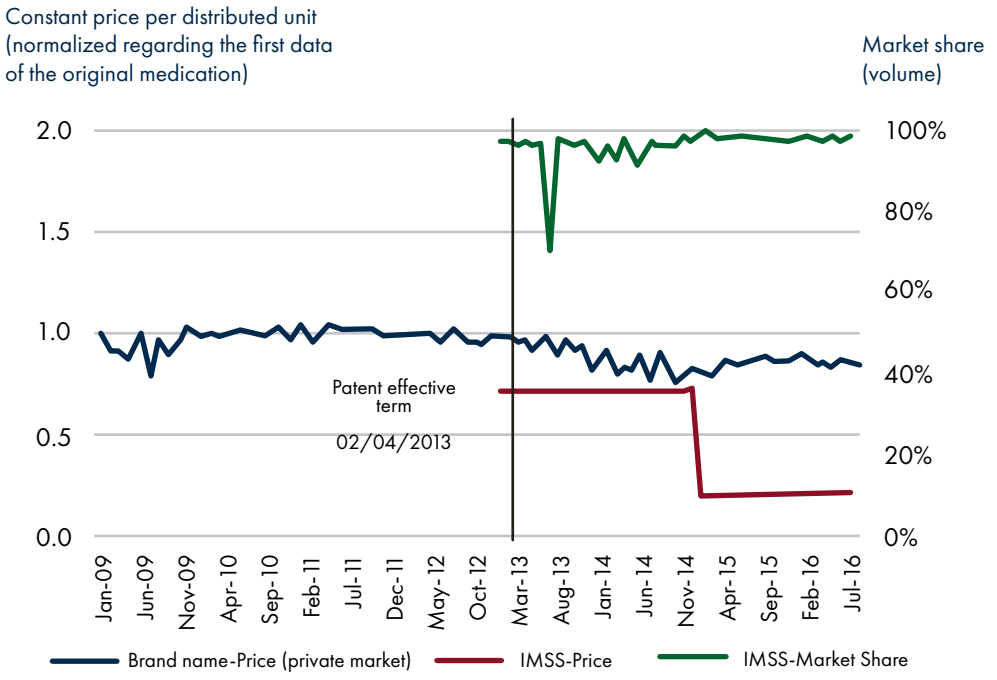
Novartis has faced problems to register secondary patents of imatinib in other countries. In India, on April 1, 2013, the Supreme Court rejected patent application of Novartis;[294] in 2015, the China's Patent Office invalidated the patent that protected Imatinib, due to lack of inventive step.[295] In Colombia, on June 14, 2016, the Ministry of Health and Social Protection declared the patent of imatinib of public interest, due to the high prices of the medication and as a measure to correct the abuses of patent rights and anti-competition practices, thus decreasing its price in 44%.[296]

294 Source: http://supremecourtofindia.nic.in/outtoday/patent.pdf (Enquired on 10-03-2017).

295 Source: http://www.twn.my/title2/intellectual_property/info.service/2016/ip160102.htm (Enquired on 10-03-2017).

296 Source: http://www.portafolio.co/negocios/empresas/colombia-baja-el-precio-de-el-glivec-medicamento-de-novartis-502414 (Enquired on 10-03-2017).

IMATINIB



Source: González Pier et al. (2017).

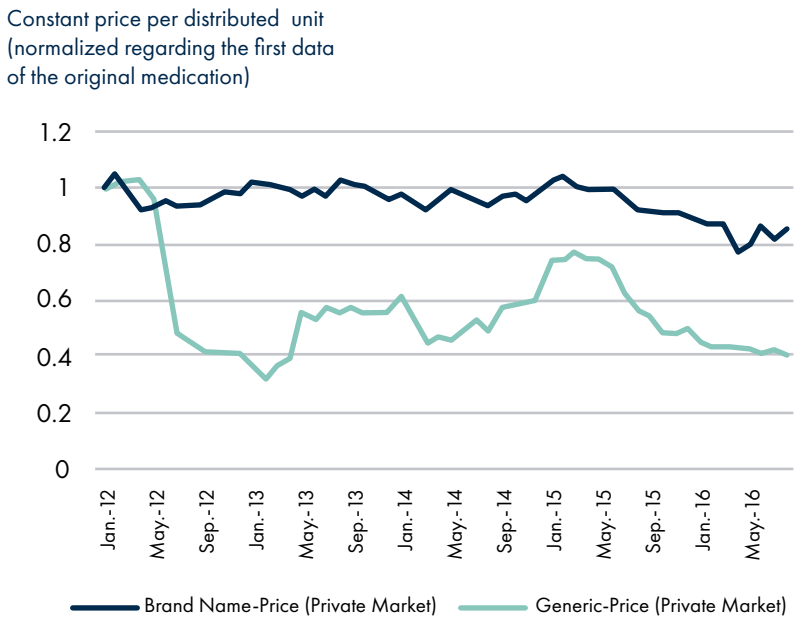
LEVONORGESTREL

Levonorgestrel is the active principle used in the emergency contraceptives. It was developed by the Richter Gedeon pharmaceutical company under the brand Postinor-2. This medication is commercialized in two presentations: The first one comprise two 0.75 mg tablets and the second one is a single 1.5 mg dose.

In Mexico, since 2006, there are generic medications in the single-dose presentation and as from 2004, in the version of two 0.75 mg tablets. In 2011, Richter Gedeon requested IMPI, nine times, to begin proceedings for violation of patent No. 245428 against the generic medications laboratories and distributors that commercialized levonorgestrel in a single dose, since such patent cover a pharmaceutical composition as a sole application dose and expires in November 26, 2022. However, in the same year, IMPI declared the nullity of the patent, at the request of Bayer de México, S.A. de C.V. Therefore, IMPI discarded all requests of violation administrative statement concerning this medication, thus, all generic medications are still commercialized in the market.

In Spain, on June 18, 2015, the Supreme Court revoked the patent of levonorgestrel, 1.5 mg sole dose due to lack of inventive step.[297]

LEVONORGESTREL
(1.5 mg presentation)



Source: González Pier et al. (2017).

297 Source: http://www.internationallawoffice.com/Newsletters/Intellectual-Property/Spain/Grau-Angulo/Supreme-Court-

PREGABALIN

Pregabalin is a substance for analgesic use, anticonvulsive, anxiolytic and is indicated for the treatment of fibromyalgia syndrome. In Mexico, it is commercialized since 2004 under the brand Lyrica, which belongs to Pfizer, S.A. de C.V, in doses of 25, 50, 75, 150 and 300 mg. This medication was protected until May 20, 2013 by the active principle patent (No. 215885), which holder is Northwestern University, that granted Pfizer the exploitation license. Lyrica was originally developed for epilepsy; however, additional research showed that it can also help patients with neuropathic pain and most of today's prescription are for the treatment of such pain.

The expiry of the basic patent allows the manufacturers of generic medications to release versions at a lower price, but limiting its use to epilepsy and general anxiety disorder. Four months after the expiry of the patent, the first generic version of the medication was commercialized and, with data up to August 2015, a record of 18 generic medications was observed with presence in the market. Pfizer keeps a secondary patent (No. 223993) in Mexico, which covers the use of pregabalin for neuropathic pain, valid until July 16, 2017. Initially, the holder of this patent was Warner-Lambert Company LLC; however, in 2000, Pfizer acquired Warner-Lambert.[298] As from December 13, 2013, Pfizer, S.A. de C.V. has the exploitation license and since January 15, 2016, Pharmacia & Upjohn, S.A. de C.V. is also licensee. It is worth mentioning that the patent does not cover the active substance or principle by itself, but only the use of such active principle in the conditions indicated in the claims. Its inclusion in the Medications Gazette of the IMPI was by judicial order as a result of the ruling issued in the amparo trial no. 371/2013.

In the United Kingdom, Pfizer tried to extend the market exclusivity of Lyrica with the use patent (valid until July 2017), because it submitted a lawsuit against the generic medications manufacturers for violation of rights, arguing that it was inevitable that the generic versions may be dispatched for pain. However, in 2015, the Supreme Court of London declared such patent as invalid.[299]

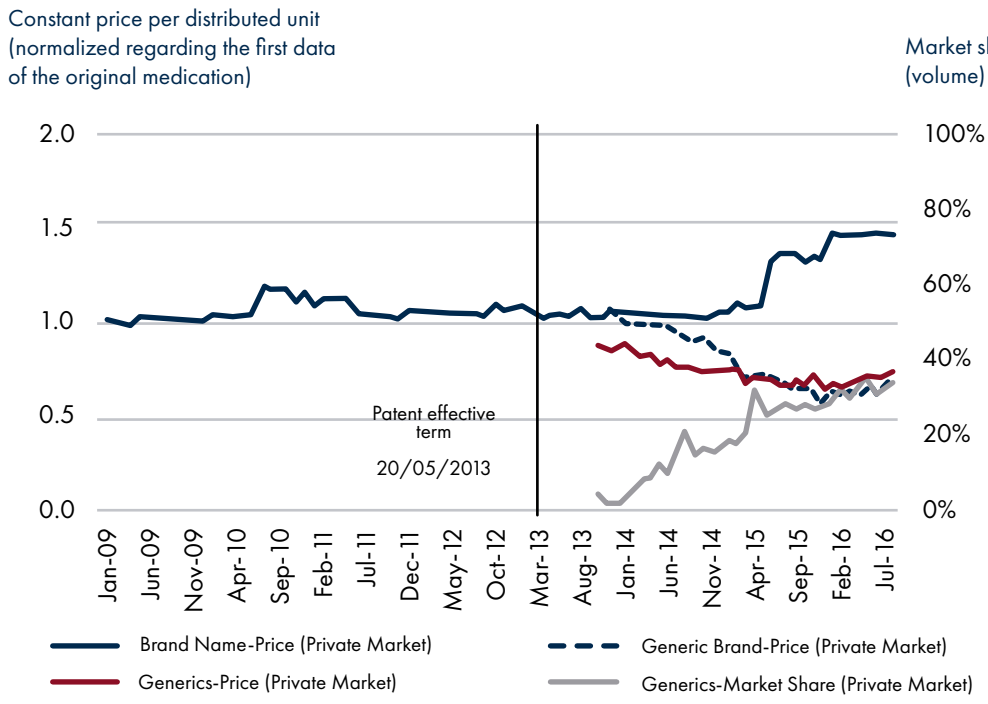
In Mexico, there are currently eight litigious pending proceedings concerning the second use patent of Pfizer. In 2014, the holder of the patent requested IMPI to begin proceedings for violation of rights against Sandoz, S.A. de C.V, Ultra Laboratorios, S.A. de C.V., Lemery, S.A. de C.V and Laboratorios PISA, S.A. de C.V. On its part, in 2013, Asofarma de México, S. A. de C. V., requested the nullity of patent no. 223993 before IMPI. A year later, Sandoz, S.A. de C.V, Ultra Laboratorios, S.A. de C.V., and Lemery, S.A. de C.V, also requested the nullity of the same. Until now, these proceedings are still pending, therefore, it is not possible to consult the dossiers, since they are confidential.

revokes-single-dose-levonorgestrel-patent-previously-upheld-on-appeal (Enquired on 13-03-2017).

298 Source: http://www.pfizer.com/about/history/pfizer_warner_lambert (Enquired on 09-03-2017).

299 Jeff Christensen (2015). "Pfizer loses UK patent case over use of Lyrica drug in pain". Health News. March 5, 2015, available at: http://www.reuters.com/article/uspfizerbritainlyricaidUSKCN0RA1G120150910 (Enquired on 09-03-2017).

PREGABALIN



Source: González Pier et al. (2017).

RITUXIMAB

Rituximab is a biotechnological medication used to treat certain autoimmune illnesses and certain kinds of cancer. Specifically, it used for the treatment of Hodgkin's lymphoma, chronic lymphocytic leukemia, arthritis rheumatoid, granulomatous with polyangiitis and microscopic polyangiitis. In Mexico, Productos Roche, S.A. de C.V. commercialized Rituximab under the brand Mabthera, which is the reference biotechnological medication.

In accordance with IMPI, the rituximab active principle is of public domain; however, Genentech, Inc. and Biogen Inc. are holders of the patent classified as active principle (No. 239890) with validity term up to May 4, 2020. As from 2011, F. Hoffmann-La Roche Ltd. laboratory, has the exploitation license and Productos Roche, S.A. de C.V. has the exploitation sublicense. Likewise, with the information provided by IMPI, it was identified that rituximab has three other registered patents: i) No. 274364 with validity up to September 09,2019, ii) No. 266754 with validity up to April 6, 2024, and iii) No. 330266 (of pharmaceutical composition) with validity up to September 10, 2030.

In 2010, Cofepris granted Probiomed the sanitary registrationregistration of the test medication "Kikuzumab", which contained rituximab. In accordance with Cofepris, on such year, Roche interposed an amparo trial against Probiomed, arguing that Kikuzumab tried to unduly replicate the innovative biotechnological medication (Mabthera), previously registered, and that did not fulfill the clinical, in-vitro studies, necessary to prove the safety, efficacy, and quality of the biotechnological medication. In accordance with Cofepris, the Kikuzumab did not had, in fact, the clinical studies, since the legislation in force at the moment of granting the sanitary registrationregistration did not establish such studies as a requisite. On March 2014, Cofepris revoked the sanitary registrationregistration number 123M2010 SSA of the medication Kikuzumab, in compliance to resolution of Amparo Trial 737/2012 issued by the Supreme Court of Justice of the Nation on October 23, 2013. This case is a significance antecedent to identify the faculties of Cofepris concerning patents and sanitary registries of medications.

Likewise, with the information provided by IMPI, it was identified that between 2010 and 2013, Genentech, Inc. and Biogen Inc. began violation rights procedures, for the four patents of rituximab, against: Probiomed, S.A. de C.V., Proquigama, S.A. de C.V., Silodisa Servicio Integral de Logística y Distribucion, S.A.P.I. de C.V., Hospital Regional de Alta Especialidad del Bajío, and Savi Distribuciones, S.A. de C.V. In four of these proceedings, IMPI declared the violation and on the others discarded or denied the action.

Finally, with the public information of Cofepris, the current development of biocomparable medications of rituximab were identified and up to November 2016, two biocomparable finished medications already exist in Mexico, although it is unknown if Cofepris already issued the sanitary registries of these medications (Box 11).

Box 11
Biocomparable Rituximab Medications in Mexico.

SEPB Meeting Date	Distinctive denomination	Corporate name of the applicant	Type of product	Therapeutic area
January 29, 2015	NA	Laboratorios Clínicos de Puebla de Bioequivalenca, S.A. de C.V.	Product in development	Oncology
February 12, 2015	NA	PPD México, S.A. de C.V.	Product in development	Oncology
June 18, 2015	NA	Laboratorios Pisa, S.A. de C.V.	Product in development	Oncology
July 9, 2015	NA	Hetlabs México, S.A. de C.V.	Product in development	Oncology
October 8, 2015	MABTAS	Accord Farma, S.A. de C.V.	Finished product	Oncology
November 26, 2015	NA	Probimed, S.A. de C.V.	Product in development	Oncology
July 28, 2016	NA	Probimed, S.A. de C.V.	Product in development	Rheumatology
November 10, 2016	TRUXIMA	Celltrion Heathcare México, S.A. de C.V.	Finished product	Oncology

Source: Meeting schedule atended by the Biotechnological Products Evaluation Subcommittee.
SEPB meets once a week on Thursdays, however, meetings ate not open to public.

SILDENAFIL

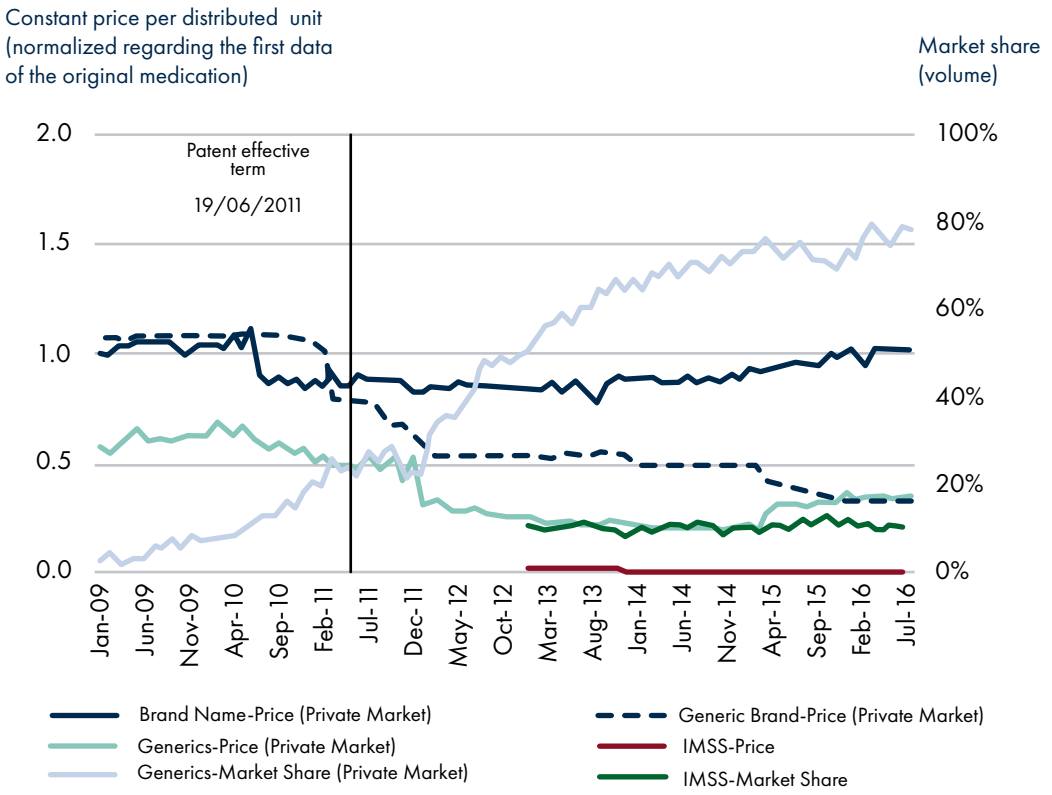
Sildenafil is a drug substance developed by Pfizer Inc., which is mainly used for the treatment of erectile dysfunction, although it is also prescribed for the treatment of pulmonary-origin arterial hypertension. In Mexico, Pfizer, S.A. de C.V. commercializes sildenafil with the name of Viagra for the first use and as Revatio for the second use.

In 1991, the pharmaceutical company requested before IMPI the registrationregistration of the first patent (No. 181244), for arterial hypertension, over the Viagra compounds – sildenafil citrate – which term was valid until June 19, 2011, while still performing research with the drug substance. When sildenafil showed its efficacy for erectile dysfunction and became number one on sales, Pfizer registered a new patent (No. 195457) to cover this indication, which term was extended up to March 22, 2014.

In 2010, anticipating the expiry of the first patent, several generic medications manufacturers began sanitary registrationregistration proceedings before Cofepris to begin the manufacturing of sildenafil generic medications. However, these were blocked, since Pfizer submitted lawsuits for patent rights violations. From 2005 to 2010, the pharmaceutical company requested IMPI to begin proceedings for violation of rights in 14 times. On October 2011, the judge of the fourteenth district court in administrative matters granted the pharmaceutical company a definitive suspension in order that the Ministry of Health and Cofepris refrain to grant permits to manufacture medications as from sildenafil. On its part, in 2011, Protein, S.A. de C.V. requested IMPI the nullity of the second use patent, but the latter rejected the request.

Finally, the generic medications of sildenafil have been entering the market, and with data up to August 2015, 18 generic medications with market presence are on record.

SILDENAFIL



Note: Before the expiration of the active principle patent, two generic medications were commercialized: Apodefil of Protein-Apotex and Maxifort-Zimax of Degort's Chemical, S.A. de C.V. Pfizer submitted lawsuits against these laboratories for patent violations. IMPI declared the administrative penalties in 2011.
Source: González Pier et al. (2017).

TADALAFIL

Tadalafil is a drug substance used for the treatment of erectile dysfunction developed by Icos Corporation and on January 19, 1995, they submitted the patent international application. In Mexico, tadalafil obtained patent No. 196995 with a validity term up to January 19, 2015. On June 14, 2000, Eli Lilly y Compañía de México, S. A. de C. V. obtained an exploitation sublicense of such patent. Tadalafil is commercialized in Mexico under the Brand Cialis. The annual market value of this medication is estimated in 1.065 billion pesos, with data up to 2015.

For this medication, we identified generic medications sanitary registries in Cofepris, but did not found evidence of the presence of generic medications in the private market. This is because there are patent invasion trials concerning tadalafil, as well as for the protection of clinical data (see Box 9). In accordance with Cofepris (2017), four companies have been directly affected due to these litigations. This could represent a case of *patent clustering*, since tadalafil is protected by nine patents, the last of which has its expiry on April 01, 2024.

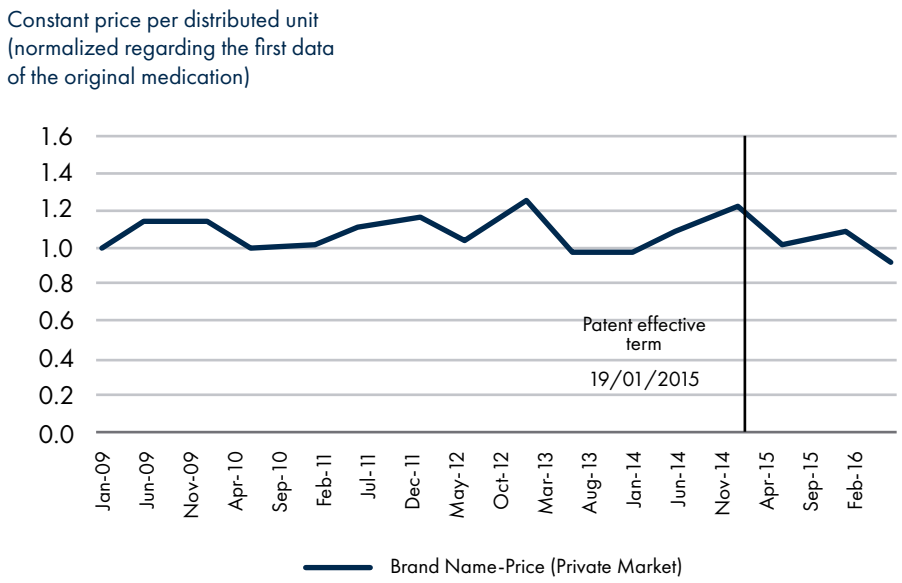
Between 2012 and 2014, three generic medications manufacturers (Laboratorios Alpharma, S.A. de C. V., Liomont, S. A. de C. V. and Química y Farmacia, S. A. de C. V.) obtained before Cofepris the Import Sanitary of tadalafil with research purposes and which objective was to benefit from the Bolar Clause, which allows begin the sanitary registrationregistration proceedings up to three years before the patent expiry of a reference medication, with the condition that the registrationregistration is issued at the expiry of the patent.

However, Eli Lilly y Compañía de México, S. A. de C. V. requested IMPI the enforcement of provisional measures consisting in the seizure of the imported raw material for considering that the exclusive exploitation rights of patent 196955 were violated. This precluded the generic medications manufacturers to benefit from the Bolar Clause and to continue with the development of the generic version of Cialis.

The pharmaceutical company holder of the patent began before IMPI the administrative proceedings for patent violation against those three laboratories. In the three cases, IMPI ruled that the technical examination did no applied since they performed the exception derived from Article 22, Subsection I of the Industrial Property Act, which allows a third party which, in the private or academic environment with no commercial purposes, carries out merely experimental scientific or technological research activities, assays, or teaching, and to do this, manufactures or uses a product or uses a process equal to the patented process.

Although the patent of tadalafil expired on January 19, 2015, at the moment of preparation of this report, there are still no sanitary registries of generic medications before Cofepris. This could be the case in which the litigations about the patent rights delay the generic versions entry into the market.

TADALAFIL



Source: González Pier et al. (2017).

TRASTUZUMAB

Trastuzumab is a biotechnological medication used for the treatment of breast cancer. It was originally developed and patented by Genentech Inc., that, in 2012, granted an exploitation sub-license to Productos Roche, S.A. de C.V., and in 2015 to Novartis Farmacéutica, S.A. de C.V. In Mexico, Productos Roche, S.A. de C.V. commercializes this substance under the brand Herceptin SC., which is a biotechnological reference medication that generated sales to Roche of US$ 6.700 billion in 2016, being one of the more successful antibodies in the world.[300]

Trastuzumab has several patents registered in Mexico. On July 23, 2016, the pharmaceutical composition patent expired (No. 282656); however, Genentech Inc. also has two pharmaceutical composition patents registered (No. 241308 and No. 279187) that expire on May 3, 2019 and for which Productos Roche, S.A. de C.V has an exploitation sub-license. On its part, F. Hoffmann-La Roche AG, is the holder of the pharmaceutical composition patent (No. 312767) with validity up to July 28, 2030. Productos Roche, S.A. de C.V has the exploitation license of this patent.

With the information provided by IMPI, it was identified that, in 2012, Celltrion Inc. requested the nullity of three patents related to trastuzumab: i) of the pharmaceutical composition in combination with the substance Docetaxel (No. 231665), which holder is Aventis Pharma, S.A., ii) of the pharmaceutical composition (No. 282656) which holder is Genentech, Inc., and iii) the second use patent (No. 259512) which holder is Genentech, Inc. In neither cases the nullity of patents was declared. Likewise, in 2014, IMPI began the nullity ex officio proceeding of the second use patent. Up to this date, this proceeding is still pending, therefore, it is not possible to consult the dossier since it is confidential.

Finally, with public information of Cofepris, biocomparable medications of trastuzumab that are currently developing in Mexico were identified (Box 12), and there is, at least one finished medication of the manufacturer Landsteiner Scientific, S.A. de C.V., although it is unknown if Cofepris has already issued its sanitary registrationregistration.

300 Source: http://clustersalud.americaeconomia.com/acuerdo-mylan-despeja-camino-la-copia-biosimilar-del-herceptin-roche/ (Enquired on 21-03-2017).

Box 12
Trastuzumab comparable medications in México.

SEPB Meeting Date	Distinctive denomination	Corporate name of the applicant	Type of product	Therapeutic area
January 22, 2015	NA	Quintiles México, S. de R.L. de C.V.	Product in development	Oncology
February 12, 2015	NA	PPD México, S.A. de C.V.	Product in development	Oncology
March 12, 2015	NA	Probiomeb, S.A. de C.V.	Product in development	Oncology
March 17, 2016	CANMAB	Landsteiner Scientific, S.A. de C.V.	Finished product	Oncology

Source: Meeting schedule atended by the Biotechnological Products Evaluation Subcommittee.
SEPB meets once a week on Thursdays, however, meetings are not open to public.

In India, on 2014, the Superior Court of Delhi issued a judicial order to block the generic medications pharmaceutical companies Biocon and Mylan to commercialize the comparable version of trastuzumab, after Roche alleged that the manufacturers did not performed the adequate clinical tests.[301]

Recently, on March 2017, the generic medications pharmaceutical company Mylan stated that an agreement was reached with Roche, derived from a patent dispute with the Swiss pharmaceutical company. In accordance with the Mylan communication,[302] the global license will provide a clear path so that Mylan can commercialize its biocomparable medication of trastuzumab in several markets worldwide, beginning in the validity dates of the license which are confidential. The licenses belong to all countries except Japan, Brazil, and Mexico. In addition to eliminate all legal uncertainties regarding the release of the Mylan's trastuzumab, the agreement eliminates the patent litigations expenses associated with Genentech and Roche. Likewise, as part of such agreement, Mylan accepted to withdraw the challenges against Genentech in the United States (6,407,213 and 6,331,415).

In this manner, Roche assures the global licenses of the generic pharmaceutic environment, over the biocomparable version of the Herceptin medication. It is worth mentioning the Mylan and its partner Biocon are already selling the biosimilar medication in 14 countries and the medication has been subject to approval in Europe and in the United States.[303]

301 Source: https://www.ft.com/content/f1d8b1ce-8fd6-11e3-aee9-00144feab7de (Enquired on 21-03-2017).

302 Source: http://newsroom.mylan.com/2017-03-13-Mylan-Announces-Global-Settlement-and-License-Agreements-with-Genentech-and-Roche-on-Herceptin-R (Enquired on 21-03-2017).

303 Source: http://clustersalud.americaeconomia.com/acuerdo-mylan-despeja-camino-la-copia-biosimilar-del-herceptin-roche/ (Enquired on 21-03-2017).

ANNEX 4. DIAGRAMS

Diagram 3
Information problems in the current linkage system

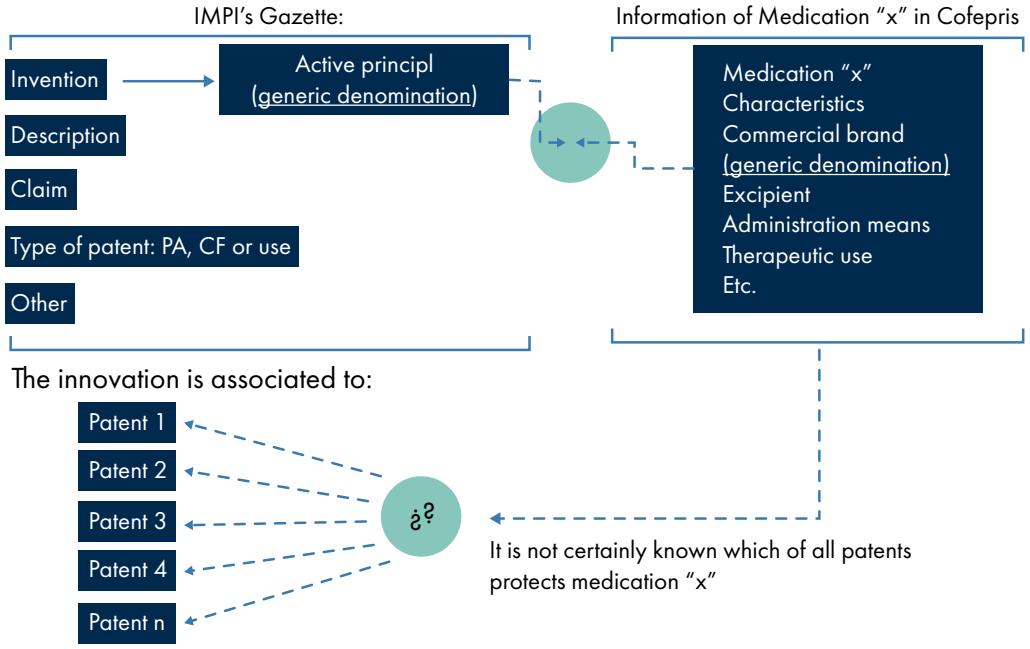
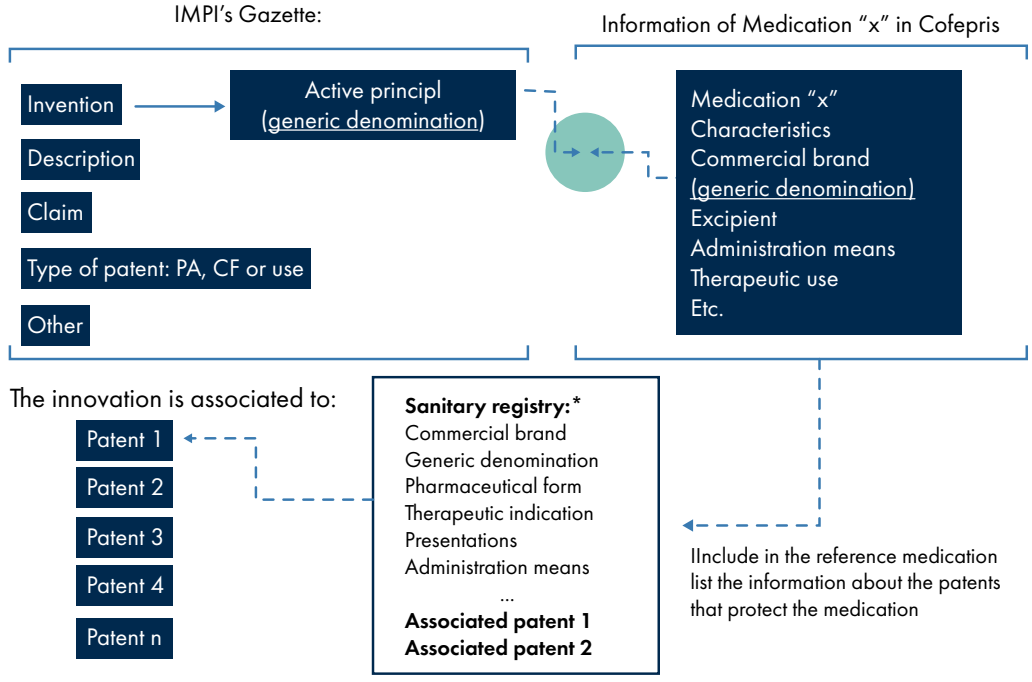


Diagram 4
Proposal to transparent the linkage system



* Non-exhaustive list
Source: Cofece.

ANEXO 5. SINGLE-SOURCE MEDICATIONS

Box 13
Codes of Single-Source Medications with generic versions in other countries

Code	Generic Denomination	Holder of the Registration[1]
010.000.5900.00	Almotriptan malate	Almirall de México, S. A. de C. V.
010.000.5439.00	Amifostine	Schering Plough, S.A de C.V.
010.000.4442.00	Aprepitant	Schering Plough, S.A de C.V.
010.000.5322.00	Didanosine	Bristol-Myers Squibb de México, S. de R. L. de C. V.
010.000.5323.00	Didanosine	Bristol-Myers Squibb de México, S. de R. L. de C. V.
010.000.5319.00	Dutasteride	GlaxoSmithKline México, S.A. de C.V.
010.000.4370.00	Efavirenz	Schering – Plough, S.A de C.V.
010.000.2417.00	Isioniazid and rifampicin	Sanofi-Aventis de México, S. A. de C. V.
010.000.4291.00	Linezolid	Pfizer, S. A. de C. V.
010.000.1761.01	Mercaptopurina	Wyeth, S. de R.L. de C.V.
010.000.5760.00	Moroctocog alfa	Pfizer, S. A. de C. V.
010.000.5761.00	Moroctocog alfa	Pfizer, S. A. de C. V.
010.000.5424.00	Nilutamide	Sanofi-Aventis de México, S. A. de C. V.
010.000.5171.01	Octreotide	Novartis Farmacéutica, S. A. de C. V.
010.000.4150.01	Rosiglitazone	Glaxosmithkline México, S.A. de C.V.
010.000.5087.00	Sirolimus	Pfizer, S. A. de C. V.
010.000.5753.00	Somatropin	Pfizer, S. A. de C. V.
010.000.5754.00	Somatropin	Pfizer, S. A. de C. V.
010.000.5174.00	Biosynthetic Somatropin	Pfizer, S. A. de C. V.
010.000.5315.00	Voriconazole	Pfizer, S. A. de C. V.
010.000.5317.00	Voriconazole	Pfizer, S. A. de C. V.
010.000.5318.00	Voriconazole	Pfizer, S. A. de C. V.

[1] Refers to the holder of the registration of the drug of reference listed at reference medications website of Cofepris.

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