11. CHALLENGES AND OPPORTUNITIES FOR THE GENERIC PHARMACEUTICAL INDUSTRY IN THE USMCA

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ABSTRACT

Recently (August 27, 2018), Mexico renewed the North American Free Trade Agreement, now renamed the United States, Mexico and Canada Agreement (USMCA), with the final text approved by the Senate on 19 June 2019. In it, commitments were made to adapt legislation on intellectual property that will have a great impact on trade among the three countries. One of the industries being impacted the most is the pharmaceutical industry. Some of the most important commitments agreed upon that will have an influence on this industry, are the following: patentability, patent term extension, protection of clinical data, and linkage. The purpose of this article is to analyze these commitments and the way in which they will have a predictable significance in the Mexican pharmaceutical industry, wherein the majority of the business involves generic (or patent-free) medicines.

***Keywords**: USMCA, intellectual property, patents, Mexican pharmaceutical industry, generics.*

1. INTRODUCTION

Prior to the adoption of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), Mexico had a very lax industrial property system, e.g. the duration of a patent was 10 years from the presentation of the application.[1] In addition, patents related to therapeutic drugs were not allowed, among others.[2] This law did not allow the granting of patents on chemical and pharmaceutical products, therapeutic drugs and their processes. Instead, the law allowed for the granting of a certificate of invention with the right to charge royalties for their use.

Subsequently, the intellectual property system was reformed into a strong system that would give protection with international standards by adopting the specification of the Paris Convention for the Protection of Industrial Property,[3] TRIPS Agreement, and the commitments agreed upon in the North America Free Trade Agreement (NAFTA), that entered into force in 1994. NAFTA's purpose was to reduce trading costs, increase business investment, and help North America be more competitive in the global marketplace, seeking to encourage innovation and consequently, economic growth and the welfare of the population. [4]

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[1] Agreement on Trade-Related Aspects of Intellectual Property Rights [1994] 33 ILM 1197 [hereinafter TRIPS Agreement], is an international legal agreement between all the member nations of the World Trade Organization (WTO). It sets down minimum standards for the regulation by national governments of many forms of intellectual property (IP) as applied to nationals of other WTO member nations. <https://www.wto.org/english/docs_e/legal_e/27-trips_01_e.htm> accessed 27 May 2019.

[2] Law of Invention and Trademarks, 1976 (México).

[3] The Paris Convention for the Protection of Industrial Property, adopted in 1883, applies to industrial property in the widest sense, including patents, trademarks, industrial designs, utility models, service marks, trade names, geographical indications and the repression of unfair competition. <http://www.wipo.int/treaties/en/text.jsp?file_id=288514> accessed on 5 May 2018.

[4] The North American Free Trade Agreement (NAFTA) is a comprehensive trade agreement that sets the rules of trade and investment between Canada, the United States, and Mexico <https://www.nafta-sec-alena.org/Home/Texts-of-the-Agreement/North-American-Free-Trade-Agreement> accessed 23 May 2019.

However, by an initiative of the United States Government, it was necessary to renegotiate the terms of the NAFTA, resulting in the renamed United States, Mexico and Canada Agreement (USMCA) in which commitments were signed in the area of intellectual property, which, among others, have the objective of encouraging innovation, the transfer and dissemination of technology.[5] This was established in the chapter on intellectual property rights

> Article 20.A.2 Objectives
>
> The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and the transfer and diffusion of technology, for the reciprocal benefit of producers and users of technological knowledge and in a way that favors social and economic well-being, and the balance of rights and obligations.

This article will focus on the commitments made in the USMCA in relation to intellectual property, specifically in relation to chemical and pharmaceutical products, in an attempt to predict the impact that these changes will bring to the Mexican pharmaceutical domestic industry, mostly composed of laboratories manufacturing generic products.[6]

Proposals are also presented that could balance this impact between the protection and incentive of innovation and access to low-cost medicines, such as generics.

2. USMCA COMMITMENTS - PATENTABLE MATTER

A. INVENTIVE STEP

The USMCA establishes the principle of non-discrimination, that is, the possibility of granting patents in all fields of technology, as long as the invention is new, involves an inventive activity and is susceptible of industrial application. It also confirms that patents will be available for inventions derived from natural plants

In the final text of the treaty regarding inventive step, or non-obviousness, each country shall consider whether the claimed invention would have been obvious to a person skilled in the art, or having ordinary skill in the art, having knowledge of the prior art.[7] This could be interpreted as a reduction of level of requirement of inventive step in order to grant a patent. It will be very important how this commitment is going to be implemented in the domestic legislation.

B. CURRENT SITUATION

Currently, Mexican law establishes as an inventive step the creative process whose results are not obvious from the state of the art for a technician knowledgeable in the subject matter. It does not make a difference if said technician is an expert or has ordinary skills in the art. However, a trend has been observed towards the registration of a greater number of 'secondary patents.' These are variants of the protected subject matter in the original patents, such as different forms of already patented active ingredients (salts, esters, ethers, polymorphs, metabolites, isomers, etc.), new release forms of active compounds (immediate, prolonged, controlled, etc.); and changes in manufacturing, synthesis or purification processes, among other things.[8]

[5] United States of America, Mexico and Canada Agreement [hereinafter USMCA] <https://ustr.gov/trade-agreements/free-trade-agreements/united-states-mexico-canada-agreement/agreement-between> accessed 2 June 2019.

[6] Pierre MoÔse and Elizabeth Docteur (2007) 'Pharmaceutical Pricing and Reimbursement Policies in Mexico' Organisation for Economic Co-operation and Development, Health Working Papers, DELSA/HEA/WD/HWP(2007)1 <https://www.oecd.org/mexico/38097348.pdf> accessed 5 May 2020.

[7] USMCA (n 5), art 20.36 footnote 29.

[8] Amy Kapczynski (2012) 'Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of «Secondary» Pharmaceutical Patents' PloS ONE, <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049470> accessed 23 May 2020.

C. EVERGREENING

There are countries where patents that do not offer significant advancement to the technique, or that are superficial (or sometimes sequential) modifications with the sole purpose of obtaining protection on the same product, are expressly prohibited.[9] It is true that on many occasions, pharmaceutical companies have opted to patent banal modifications on already patented subject matter, when what it is really sought is to extend the monopoly protection for the initial product. Critics have called this practice 'evergreening.'[10]

There has been a lot of discussion on the issue of allowing this kind of patents, especially second-use patents. There are countries that consider they are not patentable inventions, because they do not comply with the novelty requirements, since they fall within a known product, or else when a use has no industrial application.

In Mexico, although in the patent legislation, second uses are excluded from patentability, in practice it is a fact that patents of this nature are allowed.[11] The acceptance of these types of claims was adopted by the Mexican Institute of Industrial Property (IMPI)[12] under the scheme of the Swiss type claims (called 'Swiss Type' because Switzerland was the first country to allow this types of claim). Such claims are written in pharmaceutical and biotechnological patents as follows: 'use' of a composition 'X' for the manufacture of a medicament for the treatment of a therapeutic application 'Y'.[13] The acceptance of this type of claims in Mexico has no legal support; they are expressly prohibited by law but admitted in local practices leaving patent system users in a situation of uncertainty.

Secondary patents have an impact on the marketing of generics drugs, since they are linked to the same medicine, and each having different terminology. In practice, this implies the impossibility of marketing the generic product beyond the 20 years of the first patent. In addition, generic pharmaceutical companies are also facing litigations that patent holders implement as strategy to block the generic drugs entry into the market. From 2010 to 2015, IMPI reported that 74% of infringement litigations were related to secondary patents.[14] This discourages the generic drugs entry into the market since generic pharmaceutical companies can find themselves in long and expensive trials, with their investment stopped for a long period of time.

Those factors have caused very slow generics entry into the market. In Mexico the average number of generic competitors one year after the patent expires is only of 2.8, while in the United States it is 10.1. In addition, market penetration after two years of the first generic entry is 21.4%, while in United States and Canada it reaches 89% and 74%, respectively.[15]

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[9] Bhaven N. Sampat, Kenneth C. Shadlen, 'Indian pharmaceutical patent prosecution: The changing role of Section 3(d)´ (2018) Vol. 13, 4 e0194714 PLoS One <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5880378/> accessed 16 October 2019.

[10] John R. Thomas, 'Patent Evergreening: Issues in Innovation and Competition' (2009) Cong. Research Serv., 1 <ipmall.info/sites/default/files/hosted_resources/crs/R40917_091113.pdf> accessed 6 December 2019; Glyn Moody, 'OxyContin and the Art of Evergreening' (Techdirt, 2013). <https://www.techdirt.com/articles/20130423/11095922808/oxycontin-art-evergreening.shtml> accessed 20 May 2019.

[11] Industrial Property Law 1991(México), art 19 <http://www.diputados.gob.mx/LeyesBiblio/pdf/50_180518.pdf> accessed 20 May 2019.

[12] Industrial Property Law 1991 (Mexico), art 6. Mexican authority responsible for the application of industrial property legislation, as well as the granting of patents.

[13] *Patent Drafting Manual* (WIPO, 2007) <https://www.wipo.int/edocs/pubdocs/es/patents/867/wipo_pub_867.pdf> accessed 1 May 2020.

[14] 'IMPI en cifras' (IMPI 2016) <https://www.gob.mx/cms/uploads/attachment/file/60532/IMPI_en_CIFRAS_2015.pdf> accessed 4 May 2020.

[15] 'Estudio en materia de libre concurrencia y competencia sobre los mercados de medicamentos con patentes vencidas en México', (Comisión Federal de Competencia Economica, May 2017) <https://www.cofece.mx/wp-content/uploads/2017/11/estudio-de-medicamentos_vf-baja-1.pdf> accessed 22 May 2020.

Notwithstanding the foregoing, pharmaceutical companies maintain that any improvement in medicines implies costly investment in additional research and development efforts that deserve patent protection.[16] In fact, protecting innovation is the main objective of the patent system. It is important to understand that, although secondary patents are certainly related to issues such as health care and the blocking access to generic drugs in the market, they are not the only important factors. Matters of economic competition, regulatory linkage system or market itself need also be considered. A patent system must ensure the protection of innovation, every improvement is worth of protection, including inventions that solve the same problem but with alternative solutions as long as they meet patentability criteria, in order to avoid use the system as a tool to block or manipulate the market.

Exclusions of secondary patents can be counterproductive discouraging improvements that today have resulted in valuable breakthroughs in treatments, formulas or even second uses.[17] For example during the current unprecedented health crisis caused by SARS-CoV-2, a global effort of historical proportions to find a therapeutic solution as soon as possible is based mainly on existing approved drugs for non-related indications.

However, to achieve balance in the patent system, there must be clear rules in criteria application of patentability requirements, especially the inventive step. Today, as mentioned, in Mexico the criteria to evaluate the inventive step are totally arbitrary and random, depending on every single examiner. There are not standardized guidelines, as there are in Europe, the United States or the Andean Community, for instance. Lack of guidelines for patent examination has been a recurring issue among users who demand a clear guide by which patent applications should be examined, thus providing certainty to this process. Such guidelines will grant essential legal certainty for all those directly or indirectly involved in the patent system and its scope, to those who are involved in the generation of innovation, in generic pharmaceutical companies, in the health system itself, as well as in the drug marketing approval system.

D. OBSTACLES AND OPPORTUNITIES

The signing of the USMCA consolidates the trend that Mexico has been aiming for, namely, to have an increasingly robust system in relation to the protection of inventions that are either transcendent technologically speaking or the protection of patents that may be of very questionable improvement in relation to the prior state of the art.

However, those changes in the Mexican legislation have not necessarily meant an advance in innovation or in the transmission of knowledge. Since the adoption of TRIPS Agreement and the signing of NAFTA, when the industrial property system in Mexico was modified (in 1991), standardizing it to international protection levels, Mexico has not grown in innovation.[18]

During the period after signing NAFTA, there have been several studies identifying low levels of innovation in Mexico showing little evidence that TRIPS Agreement had favourable effects to encourage it.[19] However, a study carried out for analyzing whether intellectual property rights reforms have stimulated innovation, concluded that Mexico is excessively dependent on its two NAFTA partners' technology. Likewise, those studies concluded that the major beneficiaries of intellectual property rights under TRIPS Agreement and NAFTA have been transnational corporations, especially

[16] Jaqueline Morovac, 'Investigation and Development of New Medication: From the Molecule to Drug' (2001) Revista medica de Chile, v.129 <http://dx.doi.org/10.4067/S0034-98872001000100015> accessed 2 May 2020.

[17] Christopher M. Holman, Timo Minssen, and Eric M. Solovy 'Patentability Standards for Follow-On Pharmaceutical Innovation' (2018) <https://doi.org/10.1089/blr.2018.29073.cmh> accessed 22 May 2020.

[18] 'IMPI en cifras' (IMPI, 2016) <https://www.gob.mx/cms/uploads/attachment/file/60532/IMPI_en_CIFRAS_2015.pdf> accessed 4 May 2020.

[19] Daniel Lederman; William F. Maloney, and Luis Servén, 'Lessons from NAFTA for Latin American and Caribbean (LAC) Countries: A Summary of Research Findings' (2003) Research Gate 1; Walter, G Park, 'Technology Trade and NAFTA' (2011) Economics Research vol. 25, 1.

those from the United States, with large royalties and payments.[20]

The difference between the number of patent applications by Mexican nationals and by non-Mexican nationals is quite significant, patent applications by non-Mexican nationals are significantly higher.[21] Evidently, the reform of industrial property legislation in Mexico has undoubtedly favoured transnational corporations. The predominance of non-Mexican national patents from the Mexican pharmaceutical industry shows that domestic inventive activity is minimal.

The foregoing reveals that since new technological knowledge (pharmaceutical products and processes) belongs to foreigners, the beneficiaries of patent monopoly exploitation are also foreign agents (transnational corporations, with some exceptions). [22]

Therefore, it is expected that the reforms in industrial property law under the commitment of the negotiated treaty, especially on patents, will not change the trend that has been occurring in the national generic industry. Thus, the new legislation will favour the presentation of more patents by non-residents, maintaining the huge technological dependence of Mexico.

While transnational companies have favourable expectations of commercialization, the generic pharmaceutical industry, whose growth is based on waiting for patents to expire, could see its possibilities for expansion become more and more limited. In addition, there is a technological trend towards the development of Biotechnological products. The majority of biopharmaceutical products are derived from biological processes including the extraction from living systems or the production by recombinant DNA technologies. Because of the size and complexity of bio drugs, chemical synthesis is currently not possible. For this reason, these bio drugs are difficult to copy.[23]

Nevertheless, it could be an important moment for the domestic generic pharmaceutical industry to be pushed towards investing in research and development to innovate, or else, it would result in having a much slower growth due to the protection conditions that have arisen under the new guidelines. A decision will have to be made for these companies: stop investing in imitating, and start investing in creating.

There is a great opportunity for further improving medicines. New formulas or combinations of drugs that improve adherence to treatment etc. This type of research involves lower costs, requires lesser time for research, and could be protected by a patent. In some cases, this kinds of patent can be the detonating point for national companies to become international. Even if the new patent is 'patent dependent,'[24] this can generate cross-licenses that imply a mutual benefit between the originating company and the developer of the new technology.

The pharmaceutical industry is a strategic sector in a country's economy due to its high social and economic impact. On the one hand, it is important to have an innovative industry that solves the most important health problems of the population, and on the other, it must have a system that allows access to low-cost medicines. To achieve this goal, there must be collaboration from the government and businesses, universities, institutes and in general, public and private

[20] Alenka Guzman, Hortencia Gómez and Francisco López, 'Patents and Economic Growth, the Case of Mexico during the NAFTA' (2018) Econ: teor. práct <http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S0188-33802018000300177&lng=en&nrm=iso> accessed 22 May 2019.

[21] ibid 19.

[22] Alenka Guzmán, and María Victoria Guzmán, '¿Poseen capacidades de innovación las empresas farmacéuticas de América Latina?: La evidencia de Argentina, Brasil, Cuba y México' (2009) Econ: teor. práct <http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S0188-33802009000300006&lng=es&nrm=iso> accessed 30 May 2019.

[23] Hussain Dahodwala and Susan T Sharfstein, 'Biosimilars: Imitation Games' (2017) ACS Medicinal Chemistry Letters Vol. 8, 7. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5512138/> accessed 20 May 2020.

[24] Defined as patent right subordinate of a previous patent, the owner of the second patent must have the consent of the first patent in order to use it.

institutions. It is also important that the legal framework regulating the sector maintain a balance between the parties involved.

3. USMCA COMMITMENTS - PATENT TERM EXTENSION

A. ADJUSTMENT OF THE DURATION OF THE PATENT BY UNREASONABLE DELAYS BY THE GRANTING AUTHORITY

In the current Mexican legislation, patents are granted for a non-extendable period of 20 years from the date of the application.[25] However, with the commitments under the new treaty USMCA, this will have to change. Patents may now enjoy an extraordinary period of term extension.

It has been established in the USMCA, if there are unreasonable delays in granting the patent, the patent holder can request compensation on the term of the patent to be adjusted for such delays. An unreasonable delay includes a delay in the granting of a patent for more than five years from the date of filing of the patent application or 3 years from the request for substantive examination, whichever occurs later.[26] Currently, under the Mexican national process it is not necessary to request the substantive examination, because the process consists of two examinations (form and patentability) without the patent applicant having to request any of them.[27]

B. ADJUSTMENT OF THE PERIOD OF THE PATENT FOR UNREASONABLE DELAYS BEFORE THE COMMERCIALIZATION AUTHORITY

The USMCA also provides for the possibility of compensating with an extension in patent term for unreasonable delays during the marketing approval process, in Mexico such authority is the Federal Commission for the Prevention of Health Risks (COFEPRIS)[28].

Both extensions, for delays by the marketing approval authority and delays by the granting authority, can be applied to the same product, because they are not mutually exclusive. Although currently, the period of granting a marketing approval is within reasonable parameters, it is possible to extend the term of a patent also based on a situation like the one described above.

C. ECONOMIC IMPACT

Each day that a pharmaceutical company maintains a monopoly on a specific drug, the associated costs are paid either by the public health service or by patients directly out of pocket.[29] It can be anticipated that the extensions or compensations on the term of a patent will bring very important economic impacts to the health sector, as well as to patients of the country. It will be of great importance that the processes of granting a patent as well as the marketing approval are as efficient as possible. This prevents situations where adjustment or compensation of the period of the patent could apply.

4. USMCA COMMITMENT - PROTECTION OF CLINICAL DATA

A. BACKGROUND

The protection of clinical data refers to the exclusivity granted by the marketing approval Authority (COFEPRIS) upon submitting data that proves safety and efficacy of an innovative new drug. Although the protection of clinical data has been mentioned as a 'novel' commitment with the review and signature of the USMCA, it is not. This commitment already existed in its predecessor, NAFTA[30], and in the TRIPS Agreement.[31] However, this commitment was never implemented in domestic Mexican legislation.

[25] Industrial Property Law 1991 (México), art 19.

[26] USMCA (n 5), art 20.44.

[27] Industrial Property Law 1991, (México), arts 50, 53.

[28] Regulations of the Federal Commission for the Protection against Sanitary Risks 2005 (México), art 30. fractions I and VI.I.

[29] Esteban Puentes-Rosas Sergio Sesma, Octavio Gómez-Dantés, 'Estimación de la población con seguro de salud en México mediante una encuesta nacional' (Salud Pública de México, February 2015) <http://saludpublica.mx/index.php/spm/article/view/4685/5157> accessed 14 October 2019.

[30] North American Free Trade Agreement (adopted on 17 December 1992, entered into force 1 January 1994) [1993] 32 ILM 289 [hereinafter NAFTA], arts 1711.5 and 1711.6.

[31] TRIPS Agreement (n 1), art 39.3.

The interpretation of this provision of the NAFTA was subject to much controversy. On one hand, innovative pharmaceutical companies did not have (and do not have to date) a clear and direct legal precept in national legislation to protect the use of clinical data by a third party to obtain the marketing authorization by COFEPRIS, and on the other hand, generic pharmaceutical companies interpreted it as an patent term extension.

In addition, there was much discussion that the protection only obliged COFEPRIS to keep information submitted for marketing approval process, confidential. Therefore, the protection of clinical data of innovative pharmaceutical products was established through litigation and judicial criteria based on the interpretation of the aforementioned commercial treaties.[32]

This happened because, in practice, sanitary regulation allows (until the domestic legislation is adapted to the new treaty) the marketing approval of generic products without the requirement of present clinical data of efficacy and safety, only of interchangeability. Therefore, clinical data of the innovator is used indirectly, as scientific support for the efficacy and safety of generic drugs.

B. LONGER PROTECTION

In the renegotiated treaty, the protection of clinical data for a new pharmaceutical product has been maintained, but with some variations.[33] It includes the provision that COFEPRIS cannot give an authorization to a third party based on clinical data of the innovator product or based on prior marketing approval with clinical data generated in another country. The protection is the same as in the NAFTA, 5 years from the date of marketing approval of said pharmaceutical product.

The use of clinical data is also protected for 5 years from the marketing approval of new pharmaceutical products that contain a chemical entity that has not been previously authorized in that country. In other words, it refers to combinations of molecules, where one of them is a chemical entity not previously authorized for commercialization in the country.

C. BIOLOGICAL PRODUCTS

A biological pharmaceutical product is one produced using biotechnology processes and that is, or contains, a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative allergenic product, protein or analogous product. In the first signed text of the USMCA it was established that clinical or other undisclosed data on pharmaceutical products that are or contain a biological product, would be protected for 10 years, from the date of first marketing approval of that product. This provision was very controversial, because the implementation could block, with no justification, the entry of a generic version, for more time than an approved pharmaceutical drug. Nevertheless, in the final text, this provision was eliminated. As a result, a biological pharmaceutical product is now considered as a common pharmaceutical. This consideration gives it, five years of protection from the first marketing approval.

D. NO ALTERATION OF THE PROTECTION PERIOD

It is further clarified in the USMCA that, if a product is protected by a patent, and the term of this ends before the protection granted to clinical data, this protection will not be altered, therefore, clinical data protection may be longer than patent protection, because such protection starts from the date of marketing approval. This is establishing as follows:

> Article 20.51: Alteration of Period of Protection
>
> Subject to Article 20.48.3 (Protection of Undisclosed Test or Other Data), if a product is subject to a system of marketing approval in the territory of a Party pursuant to Article 20.45 (Protection of Undisclosed Test or Other Data for Agricultural Chemical Products) or Article 20.48 and is also covered by a patent in the territory of that Party, that Party shall not alter the period of protection that it provides pursuant to Article 20.45 or Article 20.48 in the event that the patent protection terminates on a date

[32] Alejandro Luna, 'Patentes de Invencion. Patentes farmacéuticas, protección de datos clínicos y otros temas de interés para la industria farmacéutica en Mexico' (2012) Instituto de Investigaciones Jurídicas de la UNAM and Comisión Federal para la Protección contra Riesgos Sanitarios, 413.

[33] USMCA (n 5), art 20.48.

> earlier than the end of the period of protection specified in Article 20.45 or Article 20.48. *(Emphasis added)*

Therefore, if the innovator does not market the product, a generic company cannot release it into the market, until the period of protection of clinical data expires, regardless of having or not patent protection.

Consequently, there could be a case where an invention that does not meet the requirements of patentability, could have registration exclusivity for the period indicated above: 5 years for new pharmaceutical products, and 5 years for combinations of drugs that contain a chemical entity that has not been previously granted marketing approval in the country. An exception may be maintained for the purposes of the regulatory examination, that is, prior to the expiration of the term of the protection of clinical data, a third party may request marketing approval supported by such clinical data, in order to market the product immediately after the expiration of said period of protection.

E. IMPLEMENTATION AND CONSEQUENCES

The way by which these commitments are adapted in domestic legislation will be of great importance. The argument for the protection of clinical data is justified by the substantial investment involved in its development. However, this is the same argument for the protection of a patent, therefore, there are two different, but cumulative types of protection based on the same justification.

The implementation of these new provisions will have a negative impact on the marketing of generic medicines. In some cases, the protection will apply to medicines that do not have a patent, or have a patent that has lost its term. As a result, the protection of clinical data can block the entrance of a generic medicine into the market, unless the applicant presented their own clinical data.

Likewise, in the case of medicines that are protected by a patent, the protection of clinical data could mean an extension on the monopoly of exploitation of the pharmaceutical product. As a result, the entry of generics into the market could be affected if there are no limits as to when a product can be marketed once the patent has been granted.

F. THE CASE OF TURKEY

Turkey is a country considered to have very strict industrial property legislation. Among its most significant provisions is the obligation of a patent holder to use effectively their right. The patent holder must market their patented product, if this cannot be demonstrated in the period of time established for that, it could become the subject of a compulsory license.

Once the patent is granted, the owner has 3 years from the publication of the granting or 4 years after the application is submitted (whichever expires later), to prove the uses of the patent. If the use of the patent has not been demonstrated in that period, any third person can request a compulsory license. The same applies to a cessation of uninterrupted use for 3 years without justified reason.[34]

The foregoing is justified in the fact that a patent is a legal monopoly, but it must not be an instrument to block the market or healthy competition with it. For this reason, and, based on the case of Turkey, the Mexican system could prevent the protection of clinical data from being used as a blockade on marketing of generic pharmaceutical products, if the requirement of verification of use is established by the patent holder.

The Turkish system could be implemented in Mexico based on the same provisions of the USMCA treaty; the lack of use of a patent could even mean grounds for its revocation.

The possibility of revoking a patent based on unfair conduct by the owner has been established in the USMCA under Chapter 20, Intellectual Property Rights, Section F: Patents and Undisclosed Test or Other Data, Article 20.F.3, as follows:

> Each Party shall provide that a patent may be cancelled, revoked, or nullified only on grounds that would have justified a refusal to grant the patent. A Party may also provide that fraud, misrepresentation, or inequitable conduct may be the basis for cancelling, revoking, or nullifying a patent or holding a patent unenforceable

[34] Industrial Property Code 2016 (Turkey), art 130.

It is a reality that obtaining a patent and not using it can be considered as inequitable conduct or unfair behaviour because it violates the very essence of industrial property law and economic competition law.

A limit, such as the one described above, would establish a balance between protection afforded to innovative companies through both patents and marketing approval, and avoid clinical data protection from becoming an instrument for blocking trade and the entry of generic pharmaceuticals products into the market.

5. USMCA COMMITMENT - LINKAGE

The linkage is the relationship between the marketing approval that an applicant is seeking to obtain on a medicine and the compliance of this pharmaceutical product with patent legislation. In Mexico, as previously mentioned, the administrative authority responsible for the authorization of pharmaceutical products is COFEPRIS.

The commitment acquired in the USMCA, in Chapter 20, Section F, Article 20.50, establishes that, the parties it shall provide:

(i) A system to provide notice to a patent holder to be notified prior to the marketing of such a pharmaceutical product, that another person is seeking to market that product during the term of an applicable patent, in order for the patent holder to have the opportunity to resort the available resources and prevent said commercialization.

(ii) Adequate time and sufficient opportunity for such a patent holder to seek, prior to the marketing of an allegedly infringing product, available remedies and

(iii) Procedures, such as judicial or administrative proceedings, and expeditious remedies, such as preliminary injunctions or equivalent effective provisional measures, for the timely resolution of disputes concerning the validity or infringement of an applicable patent claiming an approved pharmaceutical product.

Further, it may also provide:

(i) Effective rewards for a successful assertion of the invalidity or non-infringement of the applicable patent; and

(ii) Procedures, consistent with its obligations of the USMCA, to promote transparency by providing information regarding applicable patents and relevant periods of exclusivity for pharmaceutical products that have been approved in the country.

A. CURRENT SITUATION

Since 2003, COFEPRIS must demand (by presidential decree), as a requirement for marketing approval, proof that the applicant is the patent holder or a licensee. [35] In addition, COFEPRIS, in order to approve the marketing of a pharmaceutical product, reviews a list of pharmaceutical products with patent, which for this purpose is published by IMPI, called 'Medicines Patent Gazette' (hereinafter, gazette)[36].

Consequently, IMPI has the obligation to publish this gazette every six months with a list of products according to the protected substance or active ingredient linked to their corresponding patent(s). It is important to mention that the inclusion on the gazette was established only for active substances or active ingredient, that is, it does not cover patents that protect processes or drug formulation, pharmaceutical compositions, polymorphs, Markush type, doses, metabolites, etc.

Notwithstanding, the holders of this kind of patents, have obtained in tribunals, the right to include their patents in the gazette.

The inclusion of these patents has the effect of blocking the marketing of those patent-related products. The problem with this inclusion is that, in case of doubt about the interpretation of an application of marketing approval, COFEPRIS may consult IMPI, as a technical authority, and in this process between COFEPRIS and IMPI, neither the applicant nor the patent holder intervenes. Therefore, a marketing approval can be granted or denied without either

[35] Decree Amending the Regulation of Health Supplies and the Regulation of the Industrial Property Law 2003 (México).

[36] Reglamento de Insumos para la Salud (1998) México, art 167 bis.

authority having heard arguments from any party that could obviously benefit or be affected from that decision. As a consequence, an applicant cannot obtain the marketing approval, even if the product does not infringe the patent, specially a product related to processes or drug formulation, pharmaceutical compositions, polymorphs, Markush type, doses, metabolites, etc (mentioned before) whose infringement mainly is based on the interpretation of claims.

A process where concerned parties are not involved and where there is no legal certainty as to how the IMPI and COFEPRIS interpret whether an application infringes a patent or not, is considered very biased and without a balanced legal basis.

B. FINDING BALANCE

In the current system, the concerned parties in the marketing approval process are not heard by neither IMPI nor COFEPRIS. Therefore, the only existing beneficiary of the linkage system is the patent holder, because once his patent is entered in the gazette, no one can obtain a marketing approval for a pharmaceutical product related to that patent.

Moreover, until now, there is no opposition system in Mexico before the granting patent authority, whereby the patentability of an invention can be questioned. Hence, the applicant of a marketing approval for a generic medicine is heard neither at the marketing approval process, nor at the granting of a patent process. This tilts the balance only to the protection of patent owners, leaving the applicant for a generic medicine marketing approval defenceless.

There is the possibility of claiming the invalidity of a granted patent. However, this process involves long and expensive trials. A judicial resolution that invalidates a patent, will lead to market entry of a generic pharmaceutical product, and a benefit, not only to the plaintiff, who has invested in the legal process, but all generic pharmaceutical companies as well.

With this perspective, it is not economically viable to initiate a patent invalidity proceeding. Normally an invalidity patent trial lasts so long, that the patent in dispute usually expires before the legal process itself is over, and involve damages claims that are practically impossible to quantify.

It is a fact that existing patent invalidity trials come along mostly in response to patent infringement claims and are not initiated as only questioning the validity of a patent. It is unlikely that many would want to spend millions and sustain a long trial period at the end of which the concerned product is rendered generic, capable of being sold by the patent litigation initiator and by more than 770 other pharmaceutical companies in the country[37].

C. THE ORIGIN OF LINKAGE IN MEXICO

Under this scenario, it is important to keep in mind how the idea of the linkage arose. In Mexico, the linkage process was adopted in 2003. It was however, born in the United States in 1984 with the initiative of Senators Orrin Hatch, and Henry Waxman, known as the Hatch-Waxman Amendment[38].The objective of the implementation of this amendment in the United States was to encourage the entry of generic medicines into the market, without weakening the industry for patented medicine.

Under the Hatch-Waxman Amendment, applicants for new drugs provide information on the patents covered by the product of the drug to be marketed. If the drug is approved, the Federal Drug Administration (FDA)[39] publishes the patent information related to that specific product in a publication list titled 'Approved Medicinal Products with Approved Drugs

[37] Oscar García Correa, 'Industria Farmaceutica' (2015) Unidad de inteligencia de Negocios PROMEXICO <https://www.gob.mx/cms/uploads/attachment/file/76324/111115_DS_Farmaceutico.pdf> accessed 26 December 2019.

[38] The Drug Price Competition and Patent Term Restoration Act of 1984 (USA).

[39] FDA is an US agency within the Department of Health and Human Services responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

Products with Therapeutic Equivalent Evaluation', also known as the 'Orange Book.'[40]

However, the FDA, for the marketing approval of a drug, does not analyze whether the patent is valid or not, nor does it interpret claims or consult with the United States Patent and Trademarks Office (USPTO). It is constrained to be an administrative authority in the assessment of the safety and efficacy of medicines.

Unlike the current Mexican system, in the US, there is no interpretation by authorities without intervention from the parties, leaving it in the hands of patent holders to act or not on a potential patent infringement of their pharmaceutical product.

The Hatch-Waxman Amendment establishes four possibilities when requesting a marketing approval. One of them, known as ´certification under paragraph IV' or also as ANDA IV,[41] the applicant must notify the owner of the patent involved so that he can oppose the request for such marketing approval, and if after 45 days, a patent infringement trial has not been initiated, the marketing approval will be granted.

On the other hand, if there is opposition to the marketing approval, the potential granting of the generic authorization process will freeze for 30 months or the duration of the trial (whichever is shorter). With this system, a marketing approval can be requested at any time during the term of a patent, it is not limited to 3 years prior to patent expiration, as is the case in the Mexican system.

In addition, the Orange Book is limited to publish only patents on drug substance (active ingredient), drug product (formulation or composition), and/or method of using the approved drug product.[42] In the Mexican case, as already mentioned, the gazette lists patents for drug substance (active ingredient), but also those that are second generation on a first invention.

Finally, in the US marketing approval procedure, the possibility exists of obtaining a reward for a successful assertion of the invalidity or non-infringement of the applicable patent: the exclusivity of marketing for 180 days in favour of the first applicant who obtains said nullity. This form of reward was established in the USMCA, as was mentioned before.

As already described, a patent invalidity trial is not currently economically viable in Mexico. Further, without a system for opposition prior to granting of a patent, generic companies do not have many possibilities to demonstrate patent invalidity by not meeting the requirements of patentability.

The Hatch-Waxman Amendment succeeded in promoting the introduction of generics into the market. In 1983, before the implementation of that law, only 35% of the high-sale drugs with expired patents had generic competition and only 12% of the prescriptions were generic. By contrast, in 2012, 84% of prescriptions were for generic products.[43]

D. IMPLEMENTATION OF COMMITMENT

The current linkage system in Mexico can be improved. As it currently stands, only patent holders are protected, without counterbalance for generic pharmaceutical companies.

It is proposed that, like the American system, imposing limits could be established in the introduction of patents to the gazette to only those patents that are of new drug substance and not the subsequent patents based on the same invention. This would prevent such inventions becoming barriers for generic versions of the drug substance, because the infringement of this inventions (pharmaceutical composition, formulation, second uses, doses, metabolites etc.), is subject

[40] The publication identifies medicines approved based on safety and effectiveness and related patent and exclusivity information.

[41] Abbreviated New Drug Application (ANDA) for marketing a generic drug based on an existing approved drug. The ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, which provides for the review and ultimate approval of a generic drug product.

[42] FDA Instruction for Filing Application Form 3542 <https://www.fda.gov/media/102047/download> accessed 5 May 2020.

[43] Garth Boehm, Lixin Yao, Liang Han, Qiang Zheng, 'Development of the Generic Drug Industry in the US after the Hatch-Waxman Act of 1984' (September 2013) 3(5)Acta Pharmaceutica Sinica B, 297

to interpretation, while the infringement of the patent on the drug substance is not.

Likewise, as the new treaty guidelines establish, in order to safeguard the exclusivity right of a patent, the holder of a pharmaceutical patent can be notified of a third party's intention to market the product protected by said patent. The authority should not however block the product from marketing since it is the exclusive right of the patent holder to enforce it. Therefore, it must only be the latter's decision to take action against said third party and the authority must only decide on the marketing approval. For this reason, to notify, and in case of litigation, suspending the marketing process, is considered a valid system, which safeguards the patent right, and on the other hand, it does not block the process of marketing of pharmaceutical products.

Moreover, an opposition process, whereby anyone can oppose the grant of a patent for not meeting the patentability requirements, should be considered. This will avoid subsequent litigation of invalidity and damages caused to generic companies, as well as to the health sector and to patients who finally end up paying the price of a patent exclusive medicine.

However, a 180- day reward implementation of exclusive commercialization for those who successfully invalidate a patent will generate the additional benefit of having only strong patents that achieved all patentability requirements. This could of course promote patent litigation by granting the winner an exclusive right over a product that does not deserve exclusivity. However, the compensation for the patent system merits it. Instead of having a pharmaceutical product exclusivity for 20 years, when the patent was not valid, it could be for a much shorter period of time, only 180 days after invalidity of such patent and allows in a secondary way to compensate the damages that are otherwise very difficult to quantify. This justifies the granting of such marketing exclusivity. The health system, patients and generic companies will benefit, as well as the litigator who invested to invalidate a patent that did not deserve exclusivity.

6. CONCLUSIONS

The Mexican pharmaceutical industry, similar to those of India, China, Argentina, Brazil and some others, has been classified as an industry with real imitation capabilities of novel pharmaceutical products, according to a United Nations study.[44]

Reforms brought to the system of industrial property in Mexico by adhering to the TRIPS Agreement, as well as the NAFTA in the 1990's, aimed to create a more rigorous system than the previous one. To the contrary, however, they have not resulted in a growth in innovation in Mexico and have in fact increased the number of requests from non-Mexican residents and, consequently, increased the technological dependence of the country on its commercial partners

The national pharmaceutical industry in Mexico has not had the initiative to be oriented towards innovation, but only to imitate development.

The signing of the renewed and renamed USMCA implies commitments that have strengthened the protection of industrial property, with special emphasis on the protection of patent holders, such as the possibility to compensate the term of a patent for delays in the granting or marketing approval process, clinical data protection and linkage. None of these commitments benefits the entry of generic medicines into the market in Mexico, despite the fact that the national pharmaceutical industry is composed mostly of pharmaceutical companies marketing generic medicines.

It is postulated that along with the implementation of these commitments, measures are also applied to counterbalance the generic drug industry and so that a balance is reached in the system in general, preventing the reforms from an unnecessary and unjustified delay of generic medicines entry into the market. Such implementations can be the following:

[44] 'Intellectual Property Rights and Foreign Direct Investment' (United Nation Transnational Corporations and Management Division and United Nation Department of Economic and Social Development, 1993) UN Doc ST/CTC/SER;A/24 UN Sales No E93 II.A.10 (1993) New York.

- Encourage research, either from the government, such as project financing or private initiative with the collaborative research model, in order to take advantage of patentability reforms in their favour, as part of a process to move from imitative model to the innovative model.
- Efficient processes both in the granting of patents and in the process of marketing approval to avoid the granting of compensation for the term extension of patents, whose economic consequence falls on the public health system, as well as on the patients themselves who ultimately absorb the monopoly market costs.
- Establish temporary limits for the beginning of the use of patents, with the consequence that, if a patent is not used, the privilege of the patent could be lost, in such a way that the exclusivity of clinical data does not become a tool for blocking of the commercialization of generic pharmaceutical products.
- Implement a system of opposition prior to the granting of a patent, in such a way that any person can question the patentability of an invention, thus preventing patents of doubtful patentability from being granted, as well as the damages and losses that this entails.
- Alternatively, the implementation of a marketing authorization exclusivity, for a short period of time, for those who promote and invalidate a patent. The health system, patients and generic companies will benefit, as well as the litigator who invested in the legal process to invalidate such patent that did not deserve exclusivity.

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