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Sanitary Regulation of Pharmaceutical Products in Mexico (Sanitary Registration-Board Arrangement-Patent)—Monoclonal Antibody Case Study

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Abstract: The Federal Commission for Protection against Health Risks in Mexico (COFEPRIS) is responsible for the regulation and health promotion of the production, commercialization, import, export, publicity or involuntary exposure of medicines and technologies for health. For its part, the Mexican Institute of Industrial Property (IMPI) is a decentralized public body with legal personality, own property and legal authority to administer the industrial property system in our country. In the year 2000, on September 19, the official journal published the linking of patents related to allopathic medicines and the sanitary registry. Objectives: To publicize the process of linking the Sanitary-Patent Registry as a case study to delimit the scope of the new pharmaceutical products. Methodology: Request the information to COFEPRIS for the registration of a new pharmaceutical product; Establish flow diagrams for the registration of: innovative products, generic products, biotech products and bio similar products; Integrate the documents in the dossier of the pharmaceutical product for sanitary registration; Elaborate sworn letter of non-invasion of patents and study of patents; Submit the Health Registry; Intergovernmental consultation. Sanitary Registry Results: Search of patents in databases to elaborate state of the art, to write letter under protest to say truth that is not invading any patent, when developing a composition of cetuximab, as generic product since the patent molecule expired in 2016 and 11 patents related to compositions, preparations and finished product preparation processes. Conclusions: COFEPRIS will determine through intergovernmental consultation with the IMPI whether or not a patent is invaded, according to the case it will grant the registration or send the corresponding prevention for cetuximab, in case that invading can also be a refusal of grant.

Key words: Sanitary registration, patents, patent-health registration link, cetuximab.

1. Introduction

In Mexico, health regulation aims to avoid risks or health damages of the population in general, as well as encourage practices that have a positive impact on the individual and collective health. The Ministry of Health through the Federal Commission for Protection against Sanitary Risks (COFEPRIS) is responsible for the regulation and health promotion of production, merchandising, importing, exporting, advertising and technologies for health, dangerous and toxic substances, products and services, health at work, basic sanitation, and risks due to environmental factors that threaten Mexicans' health.

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In September 2013, the health regulation modified some of its articles in order to establish the link between the health records granted by this authority to pharmaceutical products and patents given by the Mexican Institute of Industrial Property (IMPI), this action is also known as linkage [1].

The patent is an exclusive right granted to a natural person who makes an invention, utility model or industrial design, and will have the exclusive right of exploitation for their benefit, by themselves or by others with their consent.

This linking system for patents related to allopathic medicines, was established through the amendments in the Regulation of Inputs for Health (RIS) and the Regulations of the Industrial Property Law (RLPI), specifically, through the inclusion of articles167 bis of

the RIS and 47 bis of the RLPI [1].

The link between patents and drugs is an obligation for the health authority COFEPRIS, for protecting the property rights and exclusivity of patents for allopathic drugs, in order to reject the granting of sanitary registrations that violate the protected rights by current patents, linking the granting of authorizations of drugs to the status held by patents given by the industrial property authority. This linkage integrates the (l) Gazette of Current Patents of Drugs Art. 47 bis of the RLPI, in order to make known the validity of the patents of allopathic drugs that should be subject to industrial protection, according to the substance or active ingredient that composes it and (2) intergovernmental format that consists of a technical cooperation between authorities such like COFEPRIS and the IMPI in order to give a conclusion if valid patent rights for exclusive use are invaded [2, 3].

In order to give an overview of this case study, it is important to mention that one of the diseases with the highest incidence in the world is cancer. This condition occurs as a result of the uncontrolled growth of cells when mechanisms of division and cell death are altered, this generates the development of tumors or abnormal masses, and can occur anywhere in the body, resulting in more than 100 types of cancer that are named according to the area of development, for example: breast cancer, colon cancer, brain tumor, etc. [4].

Cancer is a group of oncological diseases that can affect any part of the body, characterized by an overgrowth of malignant cells (known as cancerous) and a spread to nearby parts, which can lead to invasion of the surrounding tissue and sometimes in metastasis, causing death. These alterations are the result between genetic factors and external agents (physical, chemical, and biological carcinogens).

There are more than 100 types of cancer, named because of the affected organs or tissues or according to the type of cell in which they are formed. Oncological drugs are used in the treatment of oncological diseases at different stages and/or levels (Fig. 1).

The National Institute of Cancerology carries out a Registry of Cancer Survivors; by June 2016 it had 2,500 people registered (voluntarily and regardless of the institution providing treatment for their disease). The aim is to identify the surviving patients in order to understand their physical, emotional and social needs after overcoming this disease (Coordinating Commission of National Institutes of Health and High Specialty Hospitals, 2016; Ministry of Health [SSA], 2016) [5].

Monoclonal antibodies are an essential tool to identification, diagnosis and treatment of infectious, immunological and neoplastic diseases. The development of monoclonal antibodies, pharmaceutical compositions, manufacturing processes and therapeutic uses have risen a large number of patents, allowing the

Major body areas affected by cancer		
Lungs and bronchi Colon and rectum Pancreas Hodgkin lymphoma Leukemia Liver Brain and nervous system Multiple myeloma		Thyroid Kidneys and urinary tract Skin melanoma Non-Hodgkin lymphoma Small intestine Oral cavity (pharynx and larynx) Esophagus and stomach
Testicles Prostate		Ovary Cervix uterine

Source: Own elaboration based on the information found.

Fig. 1 Main body affected by cancer.

The antibodies also called immunoglobulins (Ig) are specialized glycoproteins that are part of the immune system, produced by B cells and with the ability to recognize specific molecules (antigens).

Antibodies are proteins that surround a complex structure delineated by the union of four protein chains: two heavy and two light, linked by a disulfide bridge [6] (Fig. 2). The property of binding antibodies with high specificity and affinity to a target molecule allows their use as essential tools in biomedical and clinical research.

Fig. 2 Scheme of monoclonal antibodies.

owner the commercial exclusivity for a period of 20 years and in the improvement of technological applications to the solution of social problems, taking into account the importance of access to oncological drugs for patients that suffer any kind of cancer, a disease that has high incidence in Mexican population.

The cytotoxic agents of monoclonal antibodies as drugs have emerged as therapy for the treatment of cancer during the last years, describing a number of strategies for the development of new pharmaceutical products with the aim of achieving greater antitumor activity and lower toxicity [7].

This work presents the process of linking Health Registry-Patent as a case study to delimit the field of action of monoclonal antibodies supported in the study of pharmaceutical patents.

2. Materials and methods

The registration process begins with the application for sanitary registration of the interested party. Article 167-bis of the Regulation of Supplies for Health (RSH) establishes that the applicant for the registration of a drug must attach the documentation that proves that he is the holder of the patent of the substance or active ingredient or who has the corresponding license, both registered with the Mexican Institute of Industrial Property, to follow up the registration process for innovative, generic, biotechnological and bio similar products. All the documents must be integrated in the dossier of the pharmaceutical product that is to be registered. Subsequently, the documentation that proves that the applicant is the patent holder of the substance or active ingredient, or has the corresponding license for its commercialization, and must be attached to the application for sanitary registration.

State under oath that, according to the list of drugs in force under the protection of Industrial Property and referenced in Article 47 bis of the Industrial Property Law Regulation (IPLR), complies with the applicable provisions on patents (no infringement during validity) according to the substance or active ingredient for the application for sanitary registration, and elaborates the sworn letter of non-invasion of patents and patent studies.

The study of patents involves the selection of the molecule of interest for the search. In this document a number of biotechnological molecules were enlisted, all marketed. The information obtained is key to the beginning of the technological search, and is available in technical sheets or technical information on health records of the product, from which it is possible to extract characteristics such as chemical name and structure, composition, therapeutic indication, and others useful aspects for the search in patent databases.

The selection of technological search can vary according to the needs of the laboratory for the development and marketing of a generic drug. It can be highlighted the group of drugs of commercial interest, economic remuneration, market positioning, and others.

For the practical case some random projects were considered. It was decided to approach the topic of the molecule called cetuximab, every keyword referring to the active principle within the search fields was identified (title, description, claim), in order to use the search engine of the Patent Office.

The international search was conducted in the patent databases of the European Patent Offices and the World Intellectual Property Organization (EPO and PATENTSCOPE), which offers access to patent applications and patents from other countries, as well

as information on patent documents. The national search was conducted in the SIGA patent database of the Mexican Institute of Industrial Property (SIGA-IMPI).

After the search, a list of found patents were made, we proceeded to read carefully the scope of each one and based on what we wanted to register, we requested information from the applicant to conduct the analysis to discard or include those patents that may affect the registration.

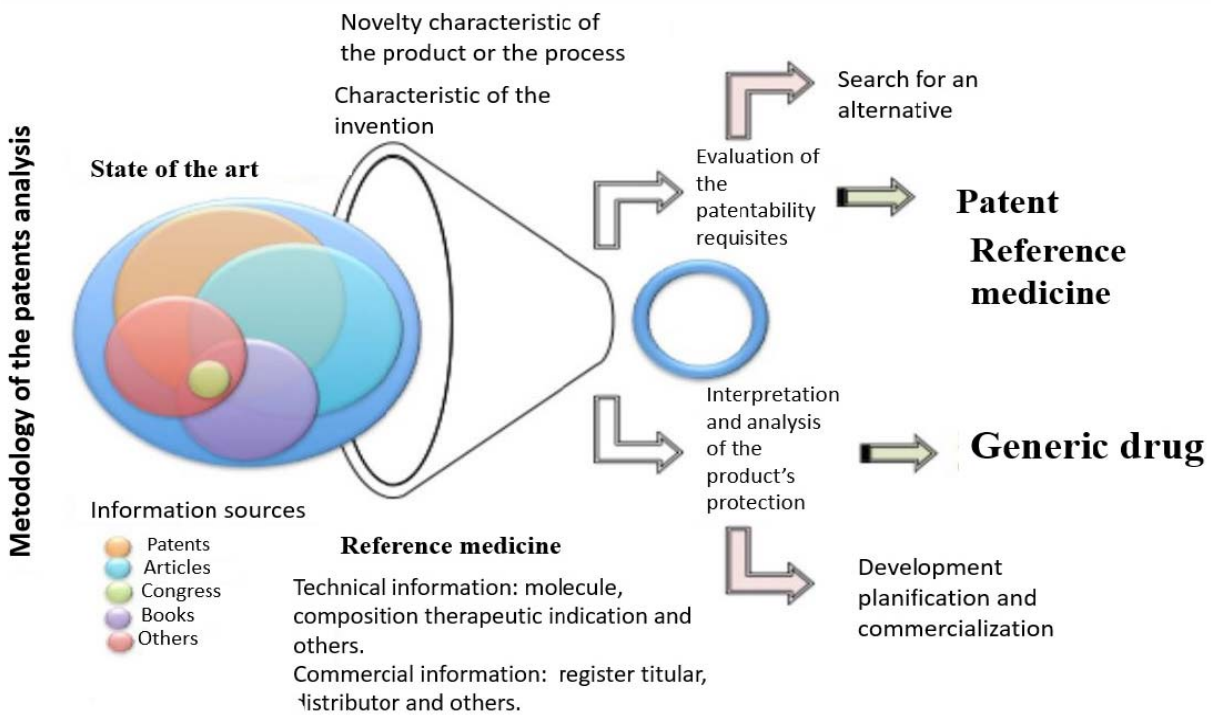
The analysis confidently allows us to submit the dossier. Once the application has been entered, COFEPRIS requests the IMPI, through an intergovernmental consultation, to verify that the sanitary registration requested does not invade in force patents.

3. Results

Before an investigation and a development, it is necessary to carry out a search about the state of the art in order to have an overview of the existing technologies of the owner and the legal status of their patents in Mexico for the decision-making, with respect to the product for marketing and positioning of the generic drug.

The process by which the search of the state of art is carried out is as follows. We had to look for all the information about cetuximab in several sources of information, subsequently compared with the characteristics of the invention, the ones of innovative drug or reference, the scope of each found patents and a discarding process is performed out to keep exclusively those that are closer to the product to register.

It is important to point out that before the search, the subject of study must be clearly defined, although during the development of the compositions, or even in the clinical studies, there may be aspects that could generate patentability criteria and the possibility of obtaining a patent. Even a composition for a generic drug with the use of an innovative additive that could give different and better characteristics to the formulation, can meet requirements of patentability or for development and marketing (Fig. 3).

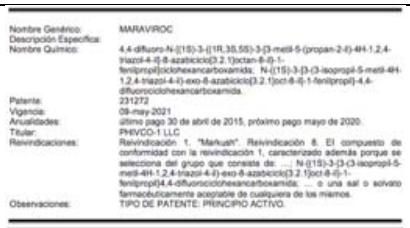
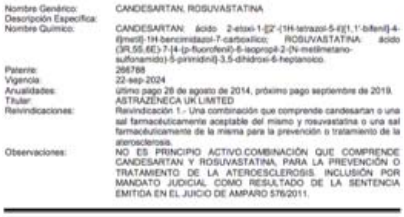


Source: Own elaboration based on accumulated knowledge and experience.

Fig. 3 Scheme of the technological search process according to the molecule of pharmaceutical interest.

With the patents listed, we proceed to analyze each claim of the each patent we found, specifically the independent claims and according to their nature and description of the product or process, it is also complemented by the information contained in the gazette of patents in force of drugs in accordance with Art. 47 bis of the Regulation of the Industrial Property Law of the Mexican Institute of Industrial Property, and the information that complements Table 1 can be obtained. It is possible to observe that in the first column,

Table 1 Types of patents according to the Gazette of Current Drugs.

Type of claim	Type of patent	PVM Gazette Art. 47 bis of the RLPI. IMPI	Example GPI-PVM Art. 47 bis of the RLPI. IMPI
Product	Active principle Markush, Enantiomer, Salts, Polymorphic or crystalline forms	231272 269954 333916 235836	 Nombre Genérico: MARAVIROC Descripción Específica: Nombre Químico: 4,4-difluoro-N-[(1S)-3-[(1R,3S,5S)-3-[3-metil-5-(propan-2-il)-4H-1,2,4-triazol-4-il]-8-azabiciclo[3.2.1]octan-8-il]-1-fenilpropil]ciclohexancarboxamida; N-((1S)-3-[3-(3-isopropil-5-metil-4H-1,2,4-triazol-4-il)-exo-8-azabiciclo[3.2.1]oct-8-il]-1-fenilpropil)-4,4-difluorociclohexancarboxamida. Patente: 231272 Vigencia: 09-may-2021 Anualidades: último pago 30 de abril de 2015, próximo pago mayo de 2020. Titular: PHIVCO-1 LLC Reivindicaciones: Reivindicación 1. "Markush". Reivindicación 8. El compuesto de conformidad con la reivindicación 1, caracterizado además porque se selecciona del grupo que consiste de: ... N-[(1S)-3-[3-(3-isopropil-5-metil-4H-1,2,4-triazol-4-il)-exo-8-azabiciclo[3.2.1]oct-8-il]-1-fenilpropil]4,4-difluorociclohexancarboxamida; ... o una sal o solvato farmacéuticamente aceptable de cualquiera de los mismos. Observaciones: TIPO DE PATENTE: PRINCIPIO ACTIVO.
	Association of two or more active principles	266788	 Nombre Genérico: CANDESARTAN, ROSUVASTATINA Descripción Específica: Nombre Químico: CANDESARTAN: ácido 2-etoxi-1-[[2'-(1H-tetrazol-5-il)[1,1'-bifenil]-4-il]metil]-1H-bencimidazol-7-carboxílico; ROSUVASTATINA: ácido (3R,5S,6E)-7-[4-(p-fluorofenil)-6-isopropil-2-(N-metilmetano-sulfonamido)-5-pirimidinil]-3,5-dihidroxi-6-heptanoico. Patente: 266788 Vigencia: 22-sep-2024 Anualidades: último pago 28 de agosto de 2014, próximo pago septiembre de 2019. Titular: ASTRAZENECA UK LIMITED Reivindicaciones: Reivindicación 1.- Una combinación que comprende candesartan o una sal farmacéuticamente aceptable del mismo y rosuvastatina o una sal farmacéuticamente de la misma para la prevención o tratamiento de la aterosclerosis. Observaciones: NO ES PRINCIPIO ACTIVO.COMBINACIÓN QUE COMPRENDE CANDESARTAN Y ROSUVASTATINA, PARA LA PREVENCIÓN O TRATAMIENTO DE LA ATEROESCLEROSIS. INCLUSIÓN POR MANDATO JUDICIAL COMO RESULTADO DE LA SENTENCIA EMITIDA EN EL JUICIO DE AMPARO 576/2011.
	Pharmaceutical composition (formulations)	243363	 Nombre Genérico: DRONEDARONA Descripción Específica: Nombre Químico: N-(2-butil-3-[p-[3-dibutilamino)propoxi[benzoil]-5-benzofuranil]metanosulfonamida. Patente: 243363 Vigencia: 10-dic-2021 Anualidades: último pago 29 de noviembre de 2011, próximo pago diciembre de 2016. Titular: SANOFI-AVENTIS Reivindicaciones: Reivindicación 1. Composición farmacéutica para administración parenteral, caracterizada porque comprende: • La dronedarona o una de sus sales farmacéuticamente aceptables como principio activo. • Una solución de tampón fisiológicamente aceptable capaz de mantener el pH de la composición entre 3 y 5. Un derivado hidrosoluble de β-ciclodextrina fisiológicamente aceptable. Observaciones: TIPO DE PATENTE: COMPOSICIÓN FARMACÉUTICA.
	Use (Swiss-type)	223993	 Nombre Genérico: PREGABALINA Descripción Específica: Nombre Químico: Ácido (S)-3-(aminometil)-5-metilhexanoico ó acido (S)-(+)-4-amino-3-(2-metilpropil)butanóico. Patente: 223993 Vigencia: 16-jul-2017 Anualidades: PAGO CUBIERTO HASTA EL FIN DE LA VIGENCIA. Titular: WARNER-LAMBERT COMPANY LLC Reivindicaciones: Reivindicación 1. El uso de un compuesto de la Fórmula I: H_2NCHCH_2COOH (R_1, R_2, R_3) o una sal, diastomero, o enántiomero del mismo, farmacéuticamente aceptable, en donde: R1 es un alquilo de cadena larga o ramificada de 1 a 6 átomos de carbono, fenilo, o cicloalquilo de 3 a 6 átomos de carbono, R2 es hidrógeno o metilo y R3 es hidrógeno, metilo, o carboxilo; para la preparación de una composición farmacéutica para el tratamiento del dolor. Reivindicación 3. El uso de conformidad con la reivindicación 1, en donde el compuesto es ácido (S)-3-(aminometil)-5-metilhexanoico y el ácido 3-aminometil-5-metil-hexanoico. Observaciones: TIPO DE PATENTE: USO. LA PATENTE NO AMPARA A LA SUSTANCIA O PRINCIPIO ACTIVO EN SÍ MISMO, SINO SÓLO EL USO DE DICHO PRINCIPIO ACTIVO EN LAS CONDICIONES PRECISADAS EN LAS REIVINDICACIONES. LICENCIA DE EXPLOTACIÓN A PFIZER, S.A. DE C.V. LICENCIA DE EXPLOTACIÓN A PHARMACIA & UPJOHN, S.A. DE C.V. INCLUSIÓN POR MANDATO JUDICIAL COMO RESULTADO DE LA SENTENCIA EMITIDA EN EL JUICIO DE AMPARO 371/2013.
	Biotechnology Microorganisms, Monoclonal antibodies, Nucleic acids, Sequences	290422 321431	 Nombre Genérico: SILTUXIMAB Descripción Específica: Nombre Químico: Inmunoglobulina G1-kappa, anti-(Homo sapiens interleukina 6 (IL6, IL-6)) cadena pesada gamma1 [1-449] [Mus musculus VH (IGHV5-9-4*01 -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -Homo sapiens IGHG1*01 (120-449)], (222-213')-disulfuro con la cadena ligera kappa (1'-213') [Mus musculus V-KAPPA (IGKV4-50*01 -IGKJ1*01) [5.3.9] (1'-106') -Homo sapiens IGKC*01 (107'-213')], dímero (226-226'':231-231'')-bisdisulfuro. Patente: 290422 Vigencia: 26-oct-2022 Anualidades: último pago 22 de septiembre de 2011, próximo pago octubre de 2016. Titular: JOHNSON & JOHNSON Reivindicaciones: Reivindicación 1. Un anticuerpo aislado o un fragmento de anticuerpo que se une a IL-6 humano, caracterizado porque comprende una región variable de cadena pesada que tiene la secuencia de aminoácidos de la SEQ ID NO: 7, una región variable de cadena ligera que tiene la secuencia de aminoácidos de la SEQ ID NO: 8 y una región constante derivada de uno más anticuerpos humanos. Reivindicación 2. Un anticuerpo aislado o un fragmento de anticuerpo que se une a IL-6 humano, caracterizado porque comprende las regiones de determinación de complementariedad (CDR) de cadena pesada y cadena ligera que tienen las secuencias de aminoácidos de las SEQ ID Nos: 1 a 6, y una región constante derivada de uno o más anticuerpos humanos. Observaciones: TIPO DE PATENTE: PRINCIPIO ACTIVO. LICENCIA DE EXPLOTACIÓN A JANSSEN-CILAG, S.A. DE C.V.
	Packaging or Primary packaging	-	-

(Table 1 continued)

Type of claim	Type of patent	PVM Gazette Art. 47 bis of the RLPI. IMPI	Example GPI-PVM Art. 47 bis of the RLPI. IMPI
	Active principle	-	-
	Intermediate products for active principle	-	-
	Intermediate product for pharmaceutical composition	-	-
Process	Finished product	264146	 Nombre Genérico: VALSARTAN Descripción Específica: Nombre Químico: N-(1-oxopentil)-N-[[2'-(1H-tetrazol-5-il)[1,1'-bifenil]-4-il]metil]-L-valina. Patente: 264146 Vigencia: 18-jun-2017 Anualidades: PAGO CUBIERTO HASTA EL FIN DE LA VIGENCIA. Titular: NOVARTIS AG Reivindicaciones: Reivindicación 1. Un proceso de manufactura de una forma sólida de dosificación oral que comprende: a) un agente activo que contiene una cantidad efectiva de valsartan, o una sal farmacéuticamente aceptable del mismo, y b) aditivos farmacéuticamente aceptables adecuados para la preparación de formas sólidas de dosificación oral mediante métodos de compresión, que comprende las etapas de i) moler el principio activo y los aditivos farmacéuticamente aceptables ii) someter una mezcla del agente activo y los aditivos molidos para compresión, para formar un comprimido, en donde la compresión para formar el comprimido requiere la compactación en seco, iii) convertir el comprimido para formar un granulado, y comprimir el granulado para formar la forma de dosificación oral. Reivindicación 8. Una forma sólida de dosificación oral producida de acuerdo a un método como es definido en cualquiera de las reivindicaciones 1 a 7. Observaciones: NO ES PRINCIPIO ACTIVO. PROCESO DE MANUFACTURA DE UNA FORMA SÓLIDA DE DOSIFICACIÓN ORAL QUE COMPRENDE VALSARTAN, Y ADITIVOS FARMACÉUTICAMENTE ACEPTABLES ADECUADOS PARA LA PREPARACIÓN DE FORMAS SÓLIDAS DE DOSIFICACIÓN ORAL MEDIANTE MÉTODOS DE COMPRESIÓN. INCLUSIÓN POR MANDATO JUDICIAL COMO RESULTADO DE LA SENTENCIA EMITIDA EN EL JUICIO DE AMPARO 1444/2010.

Source: Own elaboration based on the results of the search and patents analysis.

the type of claim appears, in the second one, the type of patent, if these appear in the Patents Gazette in force of drugs, it can be seen in column 3, and they have a patent number as well as the monographic data of the patent found.

Subsequently, the patents found according to the molecule or molecules of interest are listed, and the scope of their claims is analyzed, as well as the legal status and validity of each one.

The scope of the patents was developed according to the independent claims, specifically in the technical-scientific content of each, the content may be related to a molecule, a composition, a polymorph, a process, a physical or physical-chemical property, just to mention some topics. It can also be related to the wording, the semantics of a phrase, a conjunction or a disjunction between them, in such a way that we can find a conjunction like “and”, a disjunction like the letter “o”, a word like “besides”, “at least”, “comprehends”, “sufficient”, and so on... depending on the context and the wording, it established the form in which the invention is immersed.

From the above we can mention that the interpretation and scope of each patent must be done carefully since each case is different. After reading and analyzing the content of the claim, it is related to the subject of study, such as the molecule, composition, polymorph, additive, physical or physicochemical property, or some of the additives of the composition.

In the search for patents for cetuximab, the following information was produced (Table 2), it contains not only patents, but also patent applications and their monographic information, such as the applicant, technical content, patent number or application, as well as the current status and legal situation in Mexico, from the protection of the molecule.

4. Discussion

The pharmaceutical and biotechnological industry, based on research and innovation, has used the Industrial Property System as a strategy to guarantee the recovery of the investment made in research and development of new drugs.

Industrial property (IP) is understood in its broadest sense and applies not only to industry and trade proper, but also to the domain of the agricultural and extractive industries of all manufactured or natural products [8].

Table 2 Patents and patent applications related to cetuximab.

Cetuximab					
Patent and published applications					
Application/ publication number	Applicant	Country of origin	Year	Technical content	Current status in Mexico
US 7060808 WO 9640210	Imclone Systems Incorporated	US	1996	Monoclonal antibody.	Public domain
MX 223492 WO 1998/022136	WO 1998/022136	EP	1997	A stable lyophilized pharmaceutical preparation of monoclonal or polyclonal antibodies, characterized in that it contains a sugar, or an amino sugar, an amino acid and a surfactant.	Public domain
MX 259392 WO 03053465	Merck Patent Gesellschaft Mit Beschrankter Haftung	DE	2002	Lyophilized pharmaceutical preparation of mono or polyclonal antibodies aimed against the EGF receptor (cetuximab), which have one sugar or one amino sugar, an amino acid and a surfactant.	In force
PA/a/2004/000340 WO 2003007988	Merck Patent Gesellschaft Mit Beschrankter Haftung	DE	2002	Liquid pharmaceutical formulation characterized by the inclusion of cetuximab, a phosphate damper with a pH between 6-8 and a fatty acid ester of polyoxyethylene sorbitan.	In force
MX 309721 WO 2005051355	Merck Patent Gesellschaft Mit Beschrankter Haftung	DE	2004	Preparation process of a crystal MabC225	In force
MX 278174 WO 2005058365	Merck Patent Gesellschaft Mit Beschrankter Haftung	DE	2004	Aqueous preparation characterized in that it comprises an anti-EGFR antibody, a buffer, an amino acid and a surfactant.	In force
MX 303983 WO 2005077414	Merck Patent Gesellschaft Mit Beschrankter Haftung	US	2005	Preparation process of a highly concentrated liquid formulation that includes a Mab C225 content of 50-180 mg/mL by ultrafiltration	In force
MX 292287 WO 2007121465	Wellstat Biologics Corporation	US	2007	Method for testing a protein (EGFr, ERCC1 RRM1, thymidylate synthetase or beta-tubulin) of cancer cells in a blood sample.	In force
MX 295330 WO 2008051363	Amgen Inc.	US	2007	A formulation characterized by including a damper which has a pH of 4.0 to 6.0, a divalent cation between 5-150 mM, an excipient which includes one sugar or polyol and an effective amount of a therapeutic antibody with a specific binding activity for EGFr, where the therapeutic antibody retains at least about 80% of stability for up to two months in solution.	In force
MX 295331 WO 2008045373	Amgen Inc.	US	2007	A formulation characterized by including a pH regulator of acetic acid, a pH regulator of glutamic acid or a pH regulator of succinic acid with a pH of about 4.5-7, at least one excipient that includes one sugar or a polyol and an effective amount of a therapeutic antibody with a specific binding activity to the human epidermal growth factor receptor (EGFR), which therapeutic antibody retains at least about 80% of stability for up to two months in solution.	In force
MX/a/2008/015852 WO 2007147001	Imclone LLC	US	2007	A lyophilized formulation that includes an EGFR-antibody, lacto bionic acid and a damper.	In force
MX/a/2010/005919 WO 2009073569	Abbott Laboratories	US	2008	An aqueous formulation that includes one protein and water, the formulation has a conductivity lower than 2.5 mS/cm, the concentration of the protein is at least about 20 mg/mL and the protein has a higher molecular weight (Mw) of 47 kDa.	In force

(table 2 continued)

Cetuximab					
Patent and published applications					
Application/ publication number	Applicant	Country of origin	Year	Technical content	Current status in Mexico
MX/a/2015/010429 WO 2014125382	Laboratoire Francais Du Fractionnement Et Des Biotechnologies	US	2014	A glycosylated antibody characterized by including (a) a heavy chain comprising SEQ ID No. 1; (b) a light chain that includes SEQ ID No. 2; the glycosylated antibody has fewer portions of galactose-β-1,3-galactose than the antibody produced in non-mammary cell culture.	In force
Trade mark					
Brand		ERBITUX			
Registration in Mexico		750147 972881			

Source: Own elaboration based on the state of the art for cetuximab.

In order to protect their inventions, pharmaceutical companies and/or Research and Development (R&D) departments have acquired the Search of Technological Information services as the state of the art relative to an active principle or pharmaceutical product, obtaining valuable, accurate and updated information through the documentary search carried on the internal and external database of Intellectual Property.

The state of the art calls, to the set of technical knowledge that has been made public through an oral or written description, by exploitation or by any other broadcast medium in the country or abroad [9-11].

Therefore, once the period of validity of a patent is over, anyone can freely exploit the patented technology and enter the market with a generic drug, as long as there are no other intellectual property rights associated to the technology that prevents the exploitation of the invention.

The analysis and scope of the patents is vitally important for the state of the art, as well as its objective, if we want to register an injectable product that contains cetuximab, it must enter, with the application, a letter made under oath that patents are not invaded, which is why it is necessary to carry out the state of the art study, in order to analyze the situation of the project.

As we can see, the molecule of cetuximab can be used since its legal and technical situation allows it, but in the case of the injectable, it is not possible to develop a lyophilisate, nor an injectable solution that contains some of the additives mentioned in German patents. If a lyophilisate is developed, it cannot use sugar or an amino sugar, an amino acid and a surfactant; the developer will have to consider an alternative to not invade the patent, nor use a monoclonal or polyclonal antibody for the composition, which limits the possibilities to work the lyophilized. It is necessary to review the dependent claims to consider if it is possible to use cetuximab.

It is not possible to develop a liquid composition with cetuximab, a phosphate damper with a pH between 6-8 and a polyoxyethylene sorbitan fatty acid ester. Also, the use of components of the formulation, as well as the pH maintained with that phosphate damper solution is not feasible. It must be taken into account that it is an injectable and the condition of its administration in the body for the systemic route so the development of the drug does not invade this or another patent nearby.

Another composition that can be developed for cetuximab should not use a damper of the pH between 4.0 and 6.0, nor use a divalent cation between 5-150 mM, an excipient which includes one sugar or polyol and an effective amount of a therapeutic antibody, which has specific binding activity for EGFr, and the

therapeutic antibody retains at least about 80% of stability for up to two months in solution. Stability is involved, and to use the composition, it must have a stability greater than two months, with additives that use a different damper than that to maintain pH 4.0 and 6.0.

The state of the art not only offers the panorama of the patents, but it is constituted as a source of important information. It gives ideas to have alternatives and make proposals to increase the distance to the existing patents.

For example, it is necessary to look for or use glycolized antibodies or different additives that have been used for different compositions and that could be compatible with this one or maintain a greater stability. There are no easy options, but patents as a source of information are an inexhaustible source of ideas that can provide alternatives to the researcher on a given subject. The Drug Master File contains the process to obtain the molecule and the formulation to register for a review not only of the molecule or the composition, but also of each component, as pH, preservation, packing material and so on.

After the study has been done and the dossier is delivered with the letter of non-invasion of patents to COFEPRIS, the intergovernmental consultation to the IMPI is made in order to review the case and send the confirmation. If there is any doubt, the IMPI sends a notification to COFEPRIS who question the applicant and have to answer and justify the non-invasion, show the license or present the owner proof.

If the interested party on the registry does not answer, the process is rejected and can be requested again with the necessary corrections. If the doubts are solved and delivered in time, the registration will be granted in the time that the process requires.

Finally, if the patent is invaded, the procedure is rejected, and if the applicant wants to modify the process, a different formulation has to be done. This requires a lot of time and money invested that is not worth losing.

5. Conclusions

Applicants for a pharmaceutical record must make the state of the art study before developing any product to avoid a waste of time, money and effort in developing a drug that may infringe a patent and not only do not grant a registration, in case of obtaining it, the patent owner’s lawsuit could be very expensive and exhausting.

The pharmaceutical companies that have their entrenchment in the generic market, should see the advantages of investing a little more in a study like this and be sure of the process, perhaps with additives that nowadays offer many advantages, giving the compositions not only therapeutic advantages, bioavailable and of better quality, efficacy and safety, but that may be susceptible to obtain a patent for a product with improvements in bioavailability, bioequivalence and release.

The study of the state of the art and the analysis of patents can not only avoid the infringement of the same, but can provide information and ideas important for the development of new molecules and pharmaceutical products, which favor the therapeutic scheme of diseases such as cancer and other conditions that now prevail in the country. In the case of biotechnology products do not forget the relationship of the process by products.

The monoclonal antibodies are the example that not only the molecule, its isomers, salts, and combinations with other drugs can be important alternatives when their patents expire so that they are commercialized in the generic market, which makes possible the access to them by part of the population.

In the same way, the analysis of patents allows establishing market strategies in different areas of opportunity when considering alternatives different from that of its competitors.

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