Latest developments in biologic and biosimilar regulation

Mexico has over several years clarified the IP rules that apply to biotechnology products. But, as **Alejandro Luna**, **Agustin Azcatl** and **Ingrid Ortiz** of **Olivares** explain, there are still some areas that need to be addressed

In June 2009 biologics were included in the Mexican General Health Law (GHL) as: any substance that has been manufactured by molecular biotechnology; has therapeutic, preventive or rehabilitative effects; is provided in a dosage form; and is identified as such by its pharmacological activity and physical, chemical and biological properties. But at this time there was nothing else on biologics. Two years later, in October 2011, the Health Law Regulations were amended establishing some requirements to approve biologics and biosimilars (biocomparables); however this was still a very poorly regulated area.

Due to the lack of a specialised regulation on biologics jointly with the industry requirements, in 2012 the Federal Commission for Protection against Sanitary Risk (Comisión Federal para la Protección contra Riesgos Sanitarios) (COFEPRIS, the Mexican regulatory authority) issued a Mexican Official Standard Rule (NOM) of Emergency. This NOM mainly established some guidelines on good manufacturing practices, safety and efficacy requirements, applicable biocomparability tests and pharmacovigilance for biologics; however, the rush in issuing this NOM was evident since the requirements of the NOM did not show relevant differences to the regulations established for chemicals or small molecules.

COFEPRIS has kept working on a regulation for biologics, thus in September 2013 it issued a new NOM, this time mostly directed to biosimilars; it included the requirements for interchangeability and biocomparability tests.

Alejandro Luna

Alejandro Luna joined Olivares in 1996 and became a partner in 2005. He is instrumental in the IP litigation, regulatory and administrative litigation practices and co-chair of the life sciences and pharmaceutical law and industry group and he also coordinates the litigation department. Luna has been crucial to the heart of Mexico's IP legal system as one of the few true patent regulatory and administrative litigation experts in Mexico. He acts on behalf of his clients as an attorney and a lobbyist.

Luna has participated in questioning the constitutionality of certain provisions of the Industrial Property Law and the Federal Copyright Law. He is also the sponsor of an important proposal to modify the system of litigation and enforcement of IP rights in Mexico.

Luna has spearheaded a 10-year litigation strategy that has incorporated regulation changes and lobbying which has resulted in precedent for patent linkage regulations and life terms of pipeline patents in Mexico. This work has resulted in billions of dollars of protected revenues for the R&D pharmaceutical industry in Mexico. As a result of his involvement, he has been selected as the delegate to represent AMIIF, the industry association for R&D pharmaceutical companies who do business in Mexico, in the Trans-Pacific Partnership negotiations.

His practice is not solely devoted to life sciences; he represents clients across a myriad of industries. Luna has successfully litigated exclusivity for pharmaceutical patents and pioneered administrative court actions to seek recognition of DPE rights, which are not specifically contemplated by Mexican laws.

His commitment to just and fair law extends to his overall promise of client satisfaction; he lobbies to change the law to allow for proper patent protection and best serve his clients. Luna is also the author of several articles on patents, litigation and regulatory issues. He is a part-time professor at the Universidad Nacional Autonoma de México (UNAM).

Since biologics are products where technological advances are constant, the Mexican government is still seeking to establish a proper norm for these types of medicines.

Legal framework

Nowadays there is an accurate and specialized NOM for biologics, which entered into force in February this year, the Mexican Official Standard Rule NOM-257-SSA1-2014 "Regarding biologic medicines", that mainly established the guidelines for generating clinical protocols, quality management system, pharmacovigilance, biocomparability and establishing the reference products.

The standards to approve biotech products are essentially the same as for other drugs in Mexico: they must be safe and effective and have appropriate quality. The biotech products, however, must comply with a number of additional dossier requirements, in view of their distinct characteristics.

The additional dossier requirements for biotech products include, for example, describing the manufacturing process, providing information concerning the start date and biological origin materials, and describing the manufacturing facilities and equipment.

COFEPRIS divides marketing authorisation applications (MAA) for innovative biotech products into: (1) products manufactured in Mexico (2) products manufactured abroad, and (3) products already approved abroad.

Foreign companies can apply and hold marketing authorisations for biotech products as long as they have, among other requirements, a manufacturing licence issued by COFEPRIS or by an equivalent agency abroad, and an authorised warehouse and distributor located in Mexico.

Prior to submitting any innovative biotech product MAA, clinical trials must be submitted before the Committee on New Molecules of COFEPRIS (Comité de Moléculas Nuevas). This Committee, based on the opinion of its Assessment Subcommittee on Biotech Products (Subcomité de Evaluación de Productos Biotecnológicos), will assess whether these clinical trials are enough or are not enough to show the innovative product is safe, effective and has appropriate quality. The favourable opinion of this Committee has to be submitted along with the MAA.

Further to legal and administrative information, the essential dossier submission requirements for innovative products manufactured in Mexico are preclinical and clinical trials, certificates of good manufacturing practices (GMP) of the active pharmaceutical ingredient and the medicinal product, analytical methods, summaries, manufacturing licence, prescribing information, label and a pharmacovigilance programme.

For innovative products manufactured abroad, additional requirements apply, which in particular are a certificate for export (certificado de libre venta), a letter of representation with apostille and legal representative with address in Mexico. If the GMP certificates are not issued by an agency recognised by COFEPRIS, such as the US Federal Drug Administration (FDA) or the European Medicines Agency (EMA), an inspection in situ will be required.

Agustin Azcatl

Agustin Azcatl joined Olivares in 2006. He is pharmaceutical biological chemist, with a degree from the National Autonomous University of Mexico (UNAM)) and has a master of business administration from La Salle University in Mexico City. He works in all areas of pharmaceuticals, biotechnology and life sciences.

Agustin has an expertise in the pharmaceutical business with a 23-year track record of activities in validation of pharmaceutical and biotechnological processes (sterile or non-sterile), calibration, quality assurance, quality control, audit quality, launching of new products and regulatory affairs. Over the last nine years, he has focused his practice on intellectual property, primarily in patent and design prosecution, consulting and patent infringement.

Agustin Azcatl is member of the life sciences and pharmaceutical law practice at Olivares. His practice is mainly focused on regulatory affairs. His main areas of practice allows him to interact with the Mexican sanitary agency, the Federal Commission for Protection against Sanitary Risks (COFEPRIS) and the Mexican Patent and Trademark Office (IMPI).

He is member of the Mexican Association for the Protection of Industrial Property (AMPPI), the College of Pharmaceutical Biological Chemists (CQFB) and the Mexican Association of Professionals in Health Regulation (AMEPRES).

Ingrid Ortiz

Ingrid Ortiz joined Olivares in 2011. She studied law at Monterrey Institute of Technology and Advanced Studies (ITESM Tecnológico de Monterrey) in Mexico City.

Ingrid is member of the life sciences and pharmaceutical law group at Olivares. Her practice is focused on intellectual property litigation, regulatory and administrative litigation, as well as regulatory and compliance advisory. Her main areas of practice allow her to interact with the Mexican sanitary agency, the Federal Commission for Protection against Sanitary Risks (COFEPRIS), the Mexican Patent and Trademark Office (IMPI), and the Courts of law, such as the Federal Court of Tax and Administrative Affairs, the Federal District Courts and the Federal Circuit Courts.

Ingrid has participated in cases wherein data protection exclusivity has been obtained for new chemical molecules, new indications, orphan drugs and biologics, despite the lack of a specific body of legislation in Mexico, and handled border measures against importation of medical patents.

She is member of the Mexican Association for the Protection of Industrial Property (AMPPI).

As an incentive for innovation, R&D companies can benefit from a special procedure for innovative biotech products that have been approved by the FDA, the EMA, Health Canada, the Swiss Agency for Therapeutic Products (Swissmedic), or the Australian Therapeutic Goods Administration (TGA).

This special procedure essentially implies that COFEPRIS relies on the dossier submitted before one of these agencies, in order to reduce approval timeframes by up to 60 business days.

Innovative biotech products may be used as the reference product for the approval of non-innovative products. These products are described by the Health Law as "biocomparables", since they must be comparable to reference products regarding safety, quality and efficacy. Interestingly, the Health Law Regulations provide that a biocomparable may be a reference product for another one if the innovative product has not been approved in Mexico yet.

COFEPRIS also divides MAA for biocomparables between: (1) national manufacturing and (2) foreign manufacturing. The essential dossier submission requirements for biocomparables are almost the same as those for innovative biotech products, except for the requirements to prove safety, efficacy and quality.

For this purpose, biocomparable applicants must submit essentially: (1) in vitro studies/comparative non-clinical studies, (2) a report of comparative test of pharmacokinetic, if determined by the Ministry of Health, to show pharmacokinetic comparability on key parameters between both the follow-on and the product of reference, (3) pharmacodynamics

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test reports, and (4) comparative efficacy and safety clinical test to show similarity between both the follow-on and the product of reference. Once approved, close pharmacovigilance should be followed.

At the moment, COFEPRIS is working on guidelines to perform biocomparability studies. It has issued guidelines for etanercept, filgrastim, infliximab, insulin and its analogues, rituximab and somatropin.

In addition to the implementation of the new regulation on this subject, there are other very important facts that certainly have had and may continue to have an impact on the legal framework of the pharmaceutical industry in Mexico: at the end of the 2013 a very relevant legal precedent was issued by the Mexican Supreme Court.

In this case, a pharmaceutical company developed an innovator biologic medicine. COFEPRIS granted the company an approval for the same product as a bioequivalent of the innovator biologic product. The innovator company filed a constitutional action contesting, inter alia, the following: (1) that COFEPRIS never called the innovator to the generic approval proceeding in violation of the civil right of due process of law; (2) that COFEPRIS never responded to certain legal and factual issues raised by the innovator during the generic approval proceeding; (3) that the generic approval was granted in violation of the Health Law and Regulations as the generic product never showed the required tests such as clinical trials and in-vitro studies.

The main points addressed by the Supreme Court were the following: (1) although it was not the main issue subject of analysis, the Supreme Court stated that a patent holder has a subjective right that is transformed in proper legal standing to questioning any proceeding that may violate its exclusive rights; and (2) in the absence of a subjective right such as a patent, based on the human right conferred in the Mexican Constitution to healthcare a pharmaceutical company having a valid marketing authorisation for an innovative medicine has the proper legal standing to question and request COFEPRIS to issue an approval for a bioequivalent product only if it fully complies with all the applicable law and regulations, otherwise the healthcare right provided in the Mexican Constitution would be jeopardised.

Although this Supreme Court precedent did not order COFEPRIS to cancel the biocomparable approval and emphasised that COFEPRIS was not bound to call the innovator to the biocomparable's approval proceeding, it is a valuable and positive case law confirming that based on the human right to health recognised in the Mexican Constitution, a pharmaceutical company as part of the health system, in order to prevent health risks, is entitled to question and request COFEPRIS to observe all the applicable regulation for the approval of a medicine.

Above all, several areas remain pending improvement, which is required to grant legal certainty to both innovators and followers.

Related issues

Although the sanitary authorities are working on the construction of a proper legal framework for biologics and biosimilars, there are still several issues that have not been addressed, and COFPERIS missed a good opportunity to do so; some of them are data protection exclusivity, the Roche/Bolar exception and extrapolation.

The protection of the data submitted to prove safety and efficacy of a new product is known as data package exclusivity. This exclusivity essentially means to protect this data from being relied upon for the determination of the safety and efficacy of any follow-on product.

The principal reason for this protection relies on the fact that undertaking clinical trials to prove safety and efficacy means major costs for obtaining the approval of a new product. These costs use to be importantly high for innovative biotech products as a result of their particular characteristics.

The Agreement on Trade-Related Aspects of IP Rights (TRIPs), Article 39(3), requires signatory countries to protect this data package, and the North America Free Trade Agreement (NAFTA), Articles 1711(5), 1711(6), going further, requires protecting this data for no less than five years.

Canada and the US provide longer protection periods of DPE for biotech products than the minimum period required by NAFTA. Canadian law provides an eight-year term of DPE for either biologic or chemical innovative products (Food and Drug Regulations § C.08.004.1). In the US, new drugs receive up to five years of data protection and new biological products receive 12 years of protection (Public Health Service Act § 351(k)(7), Federal Food, Drug, and Cosmetic Act §505(c)(3)(E), 505(j)(5)(F).

In contrast to the US and the Canadian laws, the Mexican Law is silent with regard to DPE. Certainly, in 2012 COFEPRIS issued guidelines to protect DPE for a five-year period. These guidelines show COFEPRIS's willingness to protect DPE. The guidelines, however, not only are questionable but also do not provide complete protection. On the one hand, they were issued as an internal memorandum on COFEPRIS's website rather than in the Official Gazette. On the other hand, they provide neither protection regarding biotech products, new formulations and indications, nor proceedings and measures to observe and enforce DPE.

In view of this lack of clear protection in the Mexican law, we

have devised legal strategies to obtain protection of DPE of innovative products, including biotech products, orphan drugs, new formulations and indications. Through these strategies based on TRIPs and NAFTA, courts have ordered COFEPRIS to observe these exclusivity rights.

Turning to a different subject, the Mexican regulatory scheme establishes a type of Bolar exemption for follow-ons. Applications can be submitted before the expiry of innovator patent rights, up to three years in advance for generics and eight years in advance for biosimilars. Under certain conditions, the exemption allows pilot production and tests to be performed.

Unfortunately, neither the wording of the Bolar exemption nor other regulations, such as the rules for imports of active pharmaceutical ingredients (APIs), clearly address the number of APIs that is adequate for the corresponding tests. Moreover, IMPI and COFEPRIS have not published their view of whether this exemption allows small quantities of APIs for conducting the tests and trials necessary for applying for a MA in advance.

This has led to scenarios where non-authorised parties are being approved by COFEPRIS to use/import amounts of APIs covered by patent rights far from the small quantity to conduct pilot production and test.

Passing to extrapolation, the Health Law Regulations establishes that when the biocomparability of a biosimilar has been "proved", it would be also authorised for all the therapeutic indications that were approved for the innovator; however, until proper guidelines are established, extrapolation may constitute a sanitary risk, so decisions on interchangeability should be based on appropriate scientific and clinical data.

Room for improvement

In Mexico, there is already a comprehensive regulatory process to approve both innovative biotech products and biocomparables.

For innovative biotech products already approved abroad, for example, the major regulatory advantage is the special procedure established by COFEPRIS to reduce approval timeframes up to 60 business days.

For biocomparables, COFEPRIS has been working on providing clear guidelines for biocomparability tests. It has already issued specific guidelines for six biotech APIs.

Several areas, however, remain pending improvement, which is required to grant legal certainty to both innovators and followers. These include clear and enforceable rules for protection of DPE for biotech products, and a proper system for extrapolation and the Roche/Bolar exception.