The Guide to Life Sciences: Key issues for senior life sciences executives

2024

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The fourth edition of the Guide to Life Sciences delivers key analysis designed to help senior life sciences executives better understand the strategic and legal IP challenges that they face around the world. This specialist intelligence will help them to protect, enforce and monetise the IP rights that are so crucial to businesses in the space.

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Mexico: regulatory certainty for biosimilars on the horizon

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Summary

REGULATORY SCENARIO

The first time that biologics were officially recognised in the applicable legislation, the General Health Law, was in June 2009, with the inclusion of article 222-bis defining a 'biologic/biotechnological product' 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.

In October 2011, the Health Law Regulations were amended to establish the requirement to approve biologics and biocomparables (also known as biosimilars) – an area that was previously poorly regulated.

In 2012, a Mexican Official Standard Rule (NOM) was enacted to provide further clarity and certainty on the related regulatory process: Mexican Official Emergency Standard Rule NOM-EM-001-SSA1-2012.

After several amendments and other versions of the NOM, the main legislation for this type of product, besides the General Health Law and its regulations, is currently NOM-257-SSA1-2014 concerning biologics (NOM 257), which was published by the Federal Commission for Protection against Sanitary Risk (COFEPRIS) in the Official Gazette. NOM 257 essentially outlines key points to ensure that the safety, efficacy and quality of biologics are already regulated in other NOMs, such as those concerning clinical trials and pharmacovigilance.

Prior to the entry into force of the amendments to the General Health Law that gave recognition to biotechnological drugs, and during the subsequent period in which the legal framework was not yet defined or completed for the regulation of those medicines, COFEPRIS granted some marketing authorisations for non-innovative biotechnological medicines that were not properly classified as biosimilars according to the relevant criteria to guarantee their quality, safety and efficacy when compared to the reference medicine requirements and international health standards. Hence, non-innovative biotechnological drugs that were processed or granted prior to the formation of the corresponding legal framework and pending classification as biosimilars were known colloquially as biolimbos.

Owing to the above, one of the main objectives of NOM 257 was that all the non-innovative biotechnological drugs identified as biolimbos would be submitted to a new review process that would prove that those drugs have the required quality, safety and efficacy characteristics.

However, this regularisation procedure was not duly observed, so today there are some biocomparables that have never met the quality, safety and efficacy requirements established by current health legislation, in the terms indicated by NOM 257, and that consequently fail to comply with the new specifications for biocomparability studies and tests and the pharmacovigilance processes necessary to protect and guarantee the health of patients.

On 31 May 2021, the Ministry of Health issued a decree in the Official Gazette amending several articles of the Health Law Regulations. Among other things, the most relevant points of this decree for biologics were the following:

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regarding the approval of biocomparable medicines, the participation of the Subcommittee for the Evaluation of Biotechnological Products was eliminated and an opinion of the New Molecules Committee is now sufficient; and

- clinical studies in the country of origin of biocomparable medicines can be submitted as evidence for the marketing authorisation application. When applying for a renewal of the marketing authorisation, clinical studies in Mexico must be submitted.

In general, these amendments to the Health Law Regulation are focused on improving the analysis and resolution of various processes.

The Health Law Regulations define 'biocomparables' as products that must be comparable to reference products regarding safety, quality and efficacy. Innovative biological products are considered as the reference products for the approval of non-innovative products.

The Health Law Regulations and NOM 257 provide that an approved biocomparable may be a reference product for another follow-on if there is no longer an approved innovative product.

COFEPRIS divides marketing authorisation applications for biocomparables in accordance with the manufacturing of the product (national manufacturing or foreign manufacturing). Legally speaking, the review process and timeline for approval is the same for national manufacturing and foreign manufacturing.

COFEPRIS makes this classification to identify the requirements that applicants must meet. For example, for foreign manufacturing, applicants must submit official documents, such as good manufacturing practice certificates, which must be apostilled or legalised and translated into Spanish by an authorised translator.

In general terms, the standard dossier submission requirements for marketing authorisation applications for all medicines usually comprise: legal and administrative information; summaries; chemical, pharmaceutical and biological information; non-clinical reports; and trial reports.

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

The essential dossier submission requirements for biocomparables are almost the same as those for innovative biological products, except for additional requirements to prove safety, efficacy and quality comparable to the reference biological product.

To prove safety, efficacy and quality, biocomparable applicants must submit:

- in vitro studies or comparative non-clinical studies;
- comparative pharmacokinetic test reports, if requested by the Ministry of Health, to show pharmacokinetic comparability on key parameters between both the biocomparable and the reference biological product;
- pharmacodynamics test reports; and
- comparative efficacy and safety clinical tests to show comparability between both the biocomparable and the reference biological product.

Once approved, close pharmacovigilance should be followed.

The average time to obtain approval is one to three years; however, this depends on each case.

In this context, the legal framework applicable in Mexico for biological medicines provides the basic requirements and allows certain directionality to the sanitary authority to act based on a case-by-case regulatory scheme of criteria, tests and requirements applicable to a given biosimilar product, which are determined by the specific molecule with which comparability is intended.

In addition to the above, the case-by-case scheme indicates that once a biosimilar has demonstrated its biosimilarity, the indications that the reference biological medicine has approved will be authorised as long as the biosimilar medicine is presented in the same pharmaceutical form and dose as the reference biologic and these indications share the same mechanism of action or the biosimilar drug has the same pharmacodynamic effect. In other words, extrapolation of clinical data to other indications of the reference product could be acceptable but must be scientifically justified.

If it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication or whether additional data will be required. Extrapolation should involve inclusion of the totality of the data (ie, the quality of non-clinical and clinical data). It is expected that safety and efficacy can be extrapolated when biocomparable biotechnological product comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data in one therapeutic indication.

This procedure is carried out between the applicant and the health authority so that the owner of the innovative drug does not have the recognised right or legal standing to assert before the authority technical and scientific elements of safety and efficacy related to the biologic medicine.

The lack of transparency in the process of evaluation and the granting of marketing authorisations for biosimilars by the health authorities means that it is unclear whether the authorities are observing the correct fulfilment of the applicable regulatory requirements and mechanisms and, consequently, whether they are observing the industrial property rights related to those products.

REGULATORY CERTAINTY FOR BIOSIMILARS IN MEXICO

This year, the Ministry of Health issued a document that proposes a 'Regulatory Certainty Strategy for the Pharmaceutical Sector: Biosimilars'.

This Strategy is mainly intended to promote the development of biocomparable biotechnological medicines, establishing an institutional and regulatory framework that is aligned with international standards, with the aim of promoting the industry's capacity in all phases of research and production of these products, in Mexico.

The installation of a Biocidal Products Regulation Committee is proposed – its main tasks would include developing recommendations for regulatory adjustments, and changing management activities and support and evaluation mechanisms to ensure the integration of biosimilar biotechnological medicines in the system.

COFEPRIS will establish the Specialized Unit in Biosimilars (UEBio), which will focus on eliminating the current fragmentation of processes and will promote an enriching interaction between specialists in the field and manufacturers in Mexico.

Also, a collegiate body of experts will be established, which will give recommendations that consider aspects of product development. This committee will evaluate all the evidence presented by a biosimilar to determine if it is comparable to the corresponding reference medicine. The opinion of CODEBio will be considered when obtaining health registration of a biosimilar.

The agenda of regulatory harmonisation and certification of national capacities raised in the Regulatory Certainty Strategy for the Pharmaceutical Sector 2023–2030 has been resumed, to raise national regulation to the standards of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), as well as the adoption of WHO guidelines, among other memberships in the field.

Following up on the adoption of the ICH standards, COFEPRIS plans to adopt safety practices through the issuance of Mexican standards, replacing the issuance of Mexican standards after the publication of the Quality Infrastructure Law. This was implemented in the first quarter of 2024 by the Standards Subcommittee, which will create the National Advisory Committee for Standardization of Health Regulation and Promotion.

One of the main commitments of the Strategy emphasises the comprehensive updating of the regulatory framework for the conduct and recognition of bioequivalence and biocomparability studies, focusing on:

- adoption of WHO guidelines on the matter;
- clarification of criteria in biocomparability tests, with clinical, non-clinical and quality aspects;
- allowing biosimilar medicines to be compared with biotechnological medicines that come from abroad;
- eliminating the mandatory requirement to conduct studies in the Mexican population and adopting the development of robust risk management plans; and
- improving the recognition mechanisms of biocomparability studies carried out in countries with health authorities recognised by the WHO as a regional reference, with standards similar or superior to those in Mexico, seeking harmonisation, homologation and mutual recognition.

The aim is to define a regulatory framework for risk analysis applicable to biosimilar biotechnological medicines, through a guide that will be developed.

A regulatory update is sought for good manufacturing practices (GMP) and promotion of recognition of GMPs issued by Mexico through the establishment of GMPs for the manufacture of biopharmaceuticals. This entails a modification to NOM-059-SSA1-2015, including new criteria issued by PIC/S and ICH in terms of quality (first semester of 2026), with a reasonable time of entry into force to allow in-depth adaptability within the sector.

Regulatory support is also required, through technical sessions and goodwill verification visits at manufacturing sites for raw materials and finished products (first quarter of 2024).

The scope of this support will be implemented from the review of manufacturing site plans, prior to construction, through to on-site visits throughout construction and equipment.

The Strategy provides for comprehensive restructuring of the Committee on New Molecules, reactivation of the Subcommittee for the Evaluation of Biotechnological Products, homologating it with the operating criteria of CODEBio and establishing criteria that link technical opinions issued by the Subcommittee for making decisions in the product evaluation process. There is also a commitment to standardise criteria for the evaluation of finished products with a training plan aimed at the UEBio.

There is a plan to intensify pharmacovigilance work with general criteria and case-by-case evaluation methodologies, which includes regulatory support for the development and updating of risk management plans for biosimilars.

In addition, there is a proposal to implement a continuous training plan for distributors and points of sale in good storage and distribution practices, including the enactment of new criteria for dispensing medicines in hospitals and pharmacies.

Finally, the participation of the Ministry of Economy and the National Council of Humanities, Sciences and Technologies (Conahcyt) is proposed to create a Council for National Pharmaceutical Development that encourages investment in scientific projects and the inclusion of courses in universities or research institutes focused on the development of biotechnology for pharmaceutical purposes.

Concerning the IP field, among the proposals, the Strategy points out the need to clarify the scope of the 'Bolar Clause'. This patent exception allows unauthorised parties (ie, pharmaceutical companies) to use patented matter (ie, pilot production and tests to be performed) to eventually obtain a marketing approval for a specific (follow-on) health-related product. Currently, the Health Law Regulations provide that such use can be conducted only within eight years before the expiration date of the patent; the clarification proposed in the document is focused on eliminating this time frame and allowing the use of patented matter under such exception at any time during the lifetime of the patent. It is worth mentioning that any exception to the rule should have limits and it should be well established; therefore, if such time frame is eliminated and eventually the applicable provisions lack clarity, it may result in abusive practices.

The document that contains the strategy also mentions that the linkage system should be reviewed. Also, a legal framework for clinical data protection should be created. To achieve such objectives, COFEPRIS proposes to specify the limits and applicability of each legal instrument, implement more effective mechanisms to appeal and request clarification for the interested companies.

In this regard, it seems that the proposal is purposeful and is intended to consider the provisions and standards indicated by international treaties. In this sense, we must be attentive to the urgent need to promulgate a Regulation to the Federal Law on the Protection of Industrial Property, as well as the modification of health legislation.

The 'Regulatory Certainty Strategy for the Pharmaceutical Sector: Biosimilars', in fact, includes relevant topics related to industrial property rights and innovation that apparently aim to observe the international standards indicated in international treaties; however, it is necessary to consider that it has a diverse approach that is far from promoting and protecting innovation.

Nevertheless, Mexico is holding elections in 2024 and the strategy proposed by the current administration may be impacted by the plans of the new one. Thus, while this document provides an idea of what the trends are regarding the regulatory field for biologics and biosimilars in Mexico, so far it does not provide any certainty.

In brief, the hurdles in the Mexican system do not look so different from those faced in other jurisdictions; the challenges that are faced by innovators to enforce and defend their exclusive rights depend on the level of development of the regulatory framework in connection with the approval processes and policies by the authorities and the criteria by the courts and the administrative authorities in charge of analysing patent cases, as well challenges of uncertainty that are faced by the biosimilar industry.

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