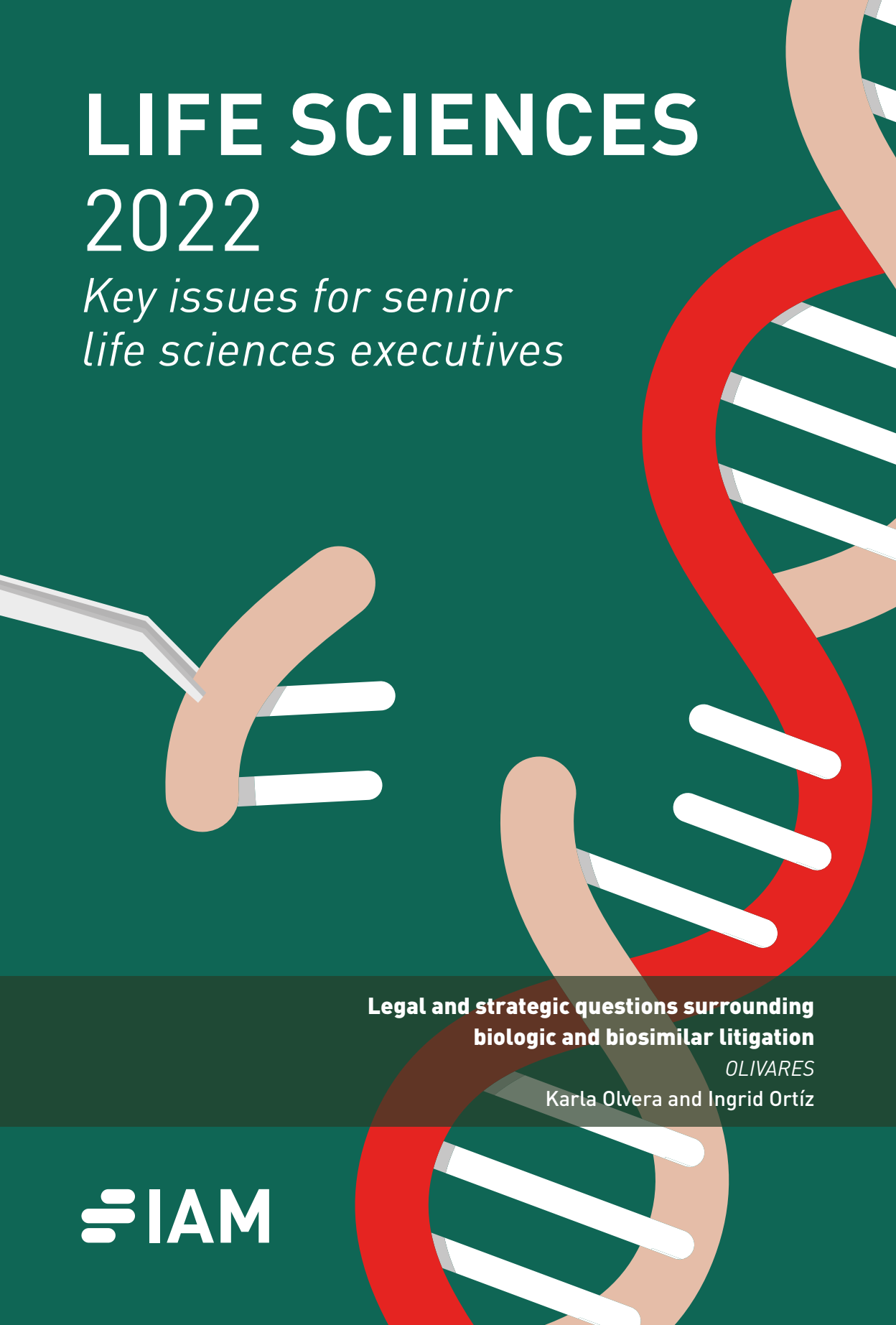
LIFE SCIENCES 2022

Key issues for senior life sciences executives



Legal and strategic questions surrounding biologic and biosimilar litigation

OLIVARES

Karla Olvera and Ingrid Ortíz

IAM

OUR LAWYERS KNOW **THE SCIENCE** OUR SCIENTISTS KNOW **THE LAW**

OLIVARES®
we know
MÉXICO

PATENTS
TRADEMARKS
COPYRIGHTS
LITIGATION
- IP LITIGATION
- ANTI-PIRACY | ANTI-COUNTERFEITING
- CIVIL LITIGATION | COMMERCIAL LITIGATION
- CONSTITUTIONAL & ADMINISTRATIVE LITIGATION
- ALTERNATIVE DISPUTE RESOLUTION (ADR) MEDIATION & ARBITRATION

LICENSING, TECH TRANSFER & FRANCHISING
CORPORATE AND COMMERCIAL LAW
REGULATORY LAW

+52 55 5322 3000
olivlaw@olivares.mx | www.olivares.mx

Legal and strategic questions surrounding biologic and biosimilar litigation

OLIVARES

Authors
Karla Olvera and **Ingrid Ortíz**

Regulatory background in Mexico

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 requirements 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, currently, the main legislation for this type of product, besides the General Health Law and its regulations, is 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 and/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:

- 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.
- 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.

These amendments to the Health Law Regulation, in general, 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 not different 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 the additional requirements to prove safety, efficacy and quality comparable to the reference biologic 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 is based on a case-by-case regulatory scheme of criteria, tests and requirements applicable to a given biosimilar product, which are determined based on the specific molecule with respect to which its comparability is intended; therefore, there is no standard process for all biosimilars.

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 be considered in light 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*

Karla Olvera
Attorney
karla.olvera@olivares.mx

Karla Olvera is an associate attorney in the litigation department of OLIVARES and is a member of the life sciences group. She holds a law degree from the Ibero-American University and an LLM in international and European intellectual property law from Trinity College Dublin, Ireland. Her professional practice focuses on litigation related to patents, trademarks, unfair competition, and regulatory and administrative matters.

Ingrid Ortíz
Attorney
ingrid.munoz@olivares.mx

Ingrid Ortíz is member of the life sciences group at OLIVARES, focusing her practice on intellectual property, regulatory and administrative litigation, and regulatory and compliance advisory. She studied law at Tecnológico de Monterrey, and she holds an LLM in intellectual property from Bournemouth University, United Kingdom.

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.

Biologic and biosimilar litigation hurdles in Mexico

In the field of biological medicines, the characteristics of the product in question are determined by the process used in the manufacture of the respective biopharmaceutical. Any variation in the manufacturing process produces results in a different product that can have different effects on the organism that could even be fatal; hence, the manufacturing process of a biological medicine and, consequently, the process patents related to this medicine, are of special relevance.

The Industrial Property Law sanctions as an administrative infringement the use of patented processes without the consent of the patent holder or the respective licence and the offering for sale or the putting into circulation of products that are the result of the use of patented processes, knowing that they were used without the consent of the patent owner.

However, in practice, the enforcement of process patents related to biologics faces several challenges.

The Agreement on Aspects of Intellectual Property Rights Related to Trade (TRIPS) establishes in Article 34 that in proceedings regarding the infringement of the rights of the owner of a process patent when obtaining a product, the authorities will be empowered to order the defendant to prove that the procedure to obtain its product is different from the patented procedure. The authorities will establish that, unless proven otherwise, any identical product produced by any party without the consent of the patent owner has been obtained through the patented procedure.

> *Information submitted by the alleged infringer in a contentious procedure can be classified as an industrial secret and/or confidential and reserved information at the express request of the defendant*

As provided by TRIPS, Article 192*bis*1 of the Industrial Property Law establishes that in infringement actions related to process patents, the alleged infringer must prove that its product was manufactured under a process other than the patented one:

- if the product obtained by the patented process is new; or
- if there is a substantial probability that the identical product was manufactured by the process, and the patent holder cannot establish through reasonable effort which process was actually used.

The reversal of the burden of proof derives precisely from the evidential difficulty inherent in the petitions for an administrative declaration of infringement related to process patents where, in most cases, the defendants will be the only ones who will be able to fully prove the process they used to manufacture the product of interest.

Therefore, in a request for an administrative declaration of infringement of a process patent in which the existence of a significant probability that the defendant's product is manufactured by the process claimed by a patent has been demonstrated, and the plaintiff has made considerable efforts to determine the procedure actually used, the burden of proof is reversed, and it is the alleged infringer that must demonstrate with suitable evidence that its product is manufactured under a process other than the one protected by the patent in question.

In practice, the information submitted by the alleged infringer in a contentious procedure can be classified as an industrial secret and/or confidential and reserved information at the express request of the defendant.

Under the argument of being information classified as an industrial secret and confidential and reserved information, the plaintiff is prevented from having full access to the documents, and what was supposedly proved by this evidence is not expressly analysed by the authorities in the corresponding resolutions. This means that, under this defence, there is no way for the plaintiff to thoroughly verify what is argued by the alleged infringer or the authorities, leaving them in a clear state of defencelessness regarding the claimed infringing conduct.

Losing sight of the fact that to be able to resolve a request for an administrative declaration of infringement of a process patent and to technically and scientifically verify the arguments of the defendant, regarding the alleged fact that the process used to manufacture its product is different, it is essential to show scientific evidence of the allegedly different process and the plaintiff must be allowed access to that information to be able to analyse it. This does not happen in many cases under the argument that the defendant requested such information to be classified as an industrial secret and reserved information.

In this regard, it is important to highlight that the industrial secret and/or the character of confidential information in the Mexican legal framework does not confer the right to the defendant to avoid demonstrating in a contentious administrative procedure what the production process of its product is, as these figures are intended to preserve the confidentiality of certain information against a competitor to ensure that it is not unduly disclosed. In no way can it serve as a defence in litigation, when the defendant has the burden of proof to show that its process is different.

In the Mexican legal system, an industrial secret entails a right and a duty. The defendant has a right to preserve its process's secrecy and to prevent its disclosure to third parties through the adoption of measures by the authorities. In addi-

tion, the defendant has a duty to demonstrate, in an administrative infringement procedure related to a process patent, that the process is different, as the issuance of a resolution that decides the controversy depends on this analysis.

The IP Law obliges the Mexican Institute of Industrial Property to adopt the necessary measures to prevent the disclosure of industrial secrets to third parties in any administrative procedure in which any of the interested parties is required to reveal an industrial secret. Therefore, the necessary measures must be adopted to prevent disclosure to third parties unrelated to the dispute so as not to leave the plaintiff defenceless.

In this context, it is essential that the alleged infringer reveals and demonstrates the production process to prove his or her defence. By hiding behind an industrial secret to prevent his or her evidence from being duly analysed in the administrative procedure by all the parties and the corresponding authorities, the infringer does not provide the appropriate technical and scientific evidence to demonstrate that it has not carried out the claimed infringements, as there is no verifiable technical or scientific information that establishes that its method is different from that claimed by the patent of interest.

In this regard, the courts have already ruled on an isolated criterion related to generic products that, in accordance with the fundamental right to information provided for in Article 6 of the Constitution, a generic drug, unlike a reference product, owing to its nature, does not possess confidential commercial information that grants a competitive advantage to a certain person, nor can it be considered a commercial secret, meaning that access to information on the generic drug held by the health authorities cannot be prohibited to individuals.

In brief, the hurdles faced 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, as well as the criteria by the courts and the administrative authorities in charge of analysing patent cases.

OLIVARES
Pedro Luis Ogazón 17
San Ángel
Mexico City 01000
Mexico
Tel: +52 55 5322 3000
Fax: +52 55 5322 3001
www.olivares.mx