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Key issues for senior life sciences executives

Key issues for biotech products in Mexico

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In January 2015 the Medicines Regulatory Agency (COFEPRIS) announced its approval of 26 innovative biotech products and two follow-on biotech products (biocomparables). In its annual report released at the beginning of the year – *COFEPRIS: Managing Public Health* – the agency pointed out that these products were approved under a fairly recent regulatory scheme. This has been developed over five years – from 2009, when the Health Law was amended to establish a basis for the regulation of such products, to December 2014, when a particular official norm for these products was issued (NOM-257-SSA1-2014).

The Mexican regulations for biotech products seem complete and in line with those of other jurisdictions. However, they do not yet properly address the significant concerns of several stakeholders. For example, there is uncertainty regarding data package exclusivity for biotech products. This article provides an overview of the regulatory pathway for the approval of biotech products, highlighting the advantages established for both innovative and follow-on products. It then briefly reviews key issues for those involved in this field, particularly with regard to automatic substitution, data package exclusivity, linkage regulations and the Bolar exemption.

Regulatory pathway for biotech products

Mexican law recognises that biotech products deserve special treatment as a result of their distinct characteristics, which include their complex structure, their size in comparison with chemically synthetised drugs and, in particular, their susceptibility to variation during the manufacturing process. The regulatory scheme distinguishes those products that have been manufactured by molecular biotechnology from other biologics and provides a robust regulatory process for their approval.

Article 222*bis* of the Health Law defines a 'biotech 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.

The Mexican Pharmacopeia recognises as biotech products those that have been manufactured by technologies such as rDNA technology, monoclonal antibody methods and controlled expression of gene coding for biologically active proteins in prokaryotes and eukaryotes.

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

In general terms, the standard dossier submission requirements for marketing authorisation applications for drugs

usually comprise legal and administrative information, summaries, chemical, pharmaceutical and biological information, non-clinical reports and clinical study reports.

The additional dossier requirements for biotech products include a description of the manufacturing process, information concerning the starting materials and biological origin materials, and a description of the manufacturing facilities and equipment.

Innovative biotech products may be used as reference products for the approval of non-innovative products. These products are called 'biocomparables' by the Health Law, since they must be comparable to reference products with regard to safety, quality and efficacy. The Health Law Regulations provide that one biocomparable may serve as a reference product for another biocomparable where the innovative product has not yet been approved in Mexico.

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

Innovative biotech products

The agency handles marketing authorisation applications (MAAs) for innovative biotech products that have already received approval in another jurisdiction.

Before submitting an MAA for an innovative biotech product, the results of clinical trials must be submitted to COFEPRIS's Committee on New Molecules. Based on the opinion of its Assessment Sub-committee on Biotech Products, this committee will assess whether these results are sufficient to show that the innovative product is safe, effective and of appropriate quality. The committee's favourable opinion must then be submitted along with the MAA.

Further to legal and administrative information, the essential dossier submission requirements for innovative products manufactured in Mexico are:

- pre-clinical and clinical trials;
- a certificate of good manufacturing practice for both the active pharmaceutical ingredients and the medicinal products;
- analytical methods and summaries;
- a manufacturing licence;
- prescription information;
- labels; and
- a pharmacovigilance programme.

For innovative products manufactured abroad, additional requirements apply - in particular, a certificate for export, a letter of representation with apostille and a legal representative with an address in Mexico. If the certificate of good manufacturing practice is not issued by an agency recognised by COFEPRIS (eg, the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA)), it will be necessary to carry out an inspection *in situ*.

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.

Under this special procedure, COFEPRIS relies on the dossiers submitted before these agencies in order to reduce the approval timeframe by up to 60 business days.

Non-innovative biotech products: biocomparables

COFEPRIS also divides MAAs for biocomparables between products manufactured in Mexico and products manufactured abroad. 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:

- *in vitro* studies/comparative non-clinical studies;
- a report of a comparative test of pharmacokinetics, if required by the Ministry of Health, to show pharmacokinetic comparability on key parameters between the follow-on and the product of reference;
- pharmacodynamics test reports; and

- comparative efficacy and safety clinical tests to show similarities between the follow-on and the product of reference.

Once approved, close pharmacovigilance should be followed.

COFEPRIS is currently working on guidelines to perform biocomparability studies. It has already issued guidelines for etanercept, filgrastim, infliximab, insulin and the analogous products of rituximab and somatropin.

Automatic substitution

The Health Law Regulations require that innovative biotech products be labelled with the acronym 'MB' and biocomparables with the acronym 'MBB'. Physicians must prescribe biotech products using their international non-proprietary name and may choose to indicate the preferred brand name.

At present, a proposal is pending to amend the Health Law in order to prevent automatic substitution/switching from innovative biotech products to biocomparables, and vice versa, as a result of potential health issues. This issue is not straightforward to handle within the Mexican legal framework, as a clear distinction between both types of product may cause them to have separate codes in the National Formulary, which in turn may result in unfair treatment when it comes to public acquisitions.

Data package exclusivity

The protection of data submitted to prove the safety and efficacy of a new product is known as 'data package exclusivity'. This exclusivity is designed to prevent the data from being relied upon to determine the safety and efficacy of any follow-on product.

Article 39(3) of the Agreement on Trade-Related Aspects of IP Rights (TRIPs) requires signatory countries to protect such data packages. Articles 1711(5) and (6) of the North American Free Trade Agreement (NAFTA) go even further and require that such data be protected for at least five years.

Canada and the United States provide longer protection periods of data package exclusivity for biotech products than the minimum period set out by NAFTA. Canadian law provides an eight-year term of data package exclusivity for either biologic or chemical innovative products (Food and Drug Regulations §C.08.004.1). In the United States, new drugs receive up to five years of data protection, while 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)).

However, unlike in the United States and Canada, Mexican law is silent with regard to data package exclusivity. COFEPRIS did issue guidelines in 2012 stating that data package exclusivity should be protected for five years. However, these guidelines were issued as an internal memorandum on COFEPRIS's website rather than in the *Official Gazette*. In addition, they do not provide protection regarding biotech products, new formulations and indications; nor do they set out specific proceedings and measures for observing and enforcing data package exclusivity.

In view of this lack of clear protection in Mexican law, legal strategies have been devised to obtain data package exclusivity of innovative products, including biotech products and orphan drugs, new formulations and indications. Through these strategies, based on TRIPs and NAFTA, the courts have ordered COFEPRIS to observe these exclusivity rights.

Linkage system

There is a linkage system in place between COFEPRIS and the Mexican Institute of Industrial Property (IMPI), the authority responsible for granting patents. The system aims to prevent marketing authorisations from being granted to non-authorised third parties for products that would fall within the scope of patents listed in the *Linkage Gazette*. This gazette is published periodically by IMPI and lists the patents that protect medicinal products.

In line with Supreme Court jurisprudence, and after eight years of publishing only compound patents, in 2012 IMPI listed pharmaceutical formulation patents in the *Linkage Gazette* for the first time. By doing so, it not only removed the need for rights holders to spend time and money on legal actions in order to have such patents included in the gazette, but also improved the linkage system's ability to prevent exclusivity rights from being violated.

The challenge now is for COFEPRIS to observe formulation patents relating to biotech products in the *Linkage Gazette* when assessing applications for follow-on products. Rights holders of biotech products should bear this issue in mind when monitoring potential infringement activities and enforcing their rights.

Bolar exemption

The Mexican regulatory scheme establishes a type of Bolar exemption for follow-ons. Applications can be submitted before the innovator patent rights expire, up to three years in advance for generics and eight years in advance for biocomparables. 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 amounts of APIs that are sufficient for such tests. Moreover, IMPI and COFEPRIS have not published their view of whether this exemption allows small quantities of APIs to

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Alejandro Luna joined Olivares in 1996, becoming a partner in 2005. He is instrumental in the IP litigation, regulatory and administrative litigation practices, co-chair of the life sciences industry group and also coordinates the litigation department. Mr Luna is a crucial part of Mexico's IP legal system as one of the few true patent regulatory and administrative litigation experts in the country. He is also the sponsor of an important proposal to modify the system of litigation and enforcement of IP rights in Mexico. Mr Luna has successfully litigated exclusivity for pharmaceutical patents and pioneered administrative court actions to seek the recognition of data package exclusivity rights, which are not specifically contemplated by Mexican law.

be imported for conducting the tests and trials necessary for applying for an MAA in advance.

This has led to situations in which non-authorised parties are being approved by COFEPRIS to use or import amounts of APIs that are covered by patent rights in quantities far greater than the small amounts needed to conduct pilot productions and tests.

Trans-Pacific Partnership

Mexico is currently taking part in negotiations on the Trans-Pacific Partnership (TPP). While these negotiations remain confidential, it has been made public that the main topics relating to intellectual property include effective customs measures and pharmaceutical and agrochemical patents.

In the case of pharmaceutical patents and regulations, the main proposal appears to be that all signatories to the partnership should commit to having additional mechanisms for IP protection, such as patent linkage, extensions or compensations for the term of patents where there are regulatory delays, and data package exclusivity for new compounds and formulations, as well as second uses.

These negotiations and Mexico's eventual integration into the TPP have created a new and valuable opportunity for the country to overhaul its IP regime and adopt higher, more efficient standards of IP protection.

Conclusion

In Mexico, a comprehensive regulatory process is already in place for the approval of both innovative biotech products and biocomparables.

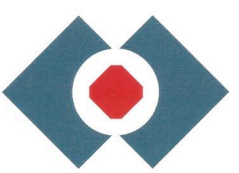
For innovative biotech products that have already been approved abroad, the major regulatory advantage is the special procedure established by COFEPRIS to reduce the timeframe for approval by up to 60 business days.

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

However, several areas remain in need of improvement in order to provide legal certainty to both innovators and followers. In particular, these include the need for:

- clear and enforceable rules for the protection of data package exclusivity for biotech products;
- COFEPRIS to observe formulation patents listed in the *Linkage Gazette* when assessing applications for follow-on products; and
- immediate practical measures to be introduced to prevent the import of infringing APIs.

There are hopes that Mexico will view its involvement in the TPP negotiations as an opportunity to introduce improvements in these areas and to establish more efficient standards of IP protection. *iam*



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