POR ALEJANDRO LUNA Y

JUAN LUIS SERRANO

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MEXICO'S DRUG REGULATORS ARE PREPARING TO ISSUE NEW RULES ON BIOCOMPARABLE DRUGS.

Mexico's General Health Law was reformed on June 11 2009 in ways that will have an important impact on patent owners within the pharmaceutical and life sciences industries. The law was amended to include an article 222 *bis*, which defined biotechnological drugs, and allows for the approval of so-called biocomparables. The decree came into force on September 8, 2009, and the Ministry of Health had a 180-day period to issue all the specific regulations pertaining to the approval of these biocomparables.

Even though the 180-day period expired on March 8 2010, the regulations were still being reviewed, with input provided by both the Mexican Association of Pharmaceutical Research (AMIIF) and the National Association of Drug Manufacturers (ANAFAM).

COFEPRIS (the Mexican drugs regulatory authority) recently made the project of regulations available to the public, through the official website of the Federal Commission for Regulatory Improvement (COFEMER).

At this point, a 30-working day period is running for any interested party to provide comments to the project through COFEMER's website, after which the project can be either published, or subjected to further analysis.

THE SCOPE OF THE REGULATIONS

The main items in this project are:

- A definition of comparability tests between an innovator and a biocomparable drug;

- An indication that biocomparable drugs will use the same name for the active ingredient as the innovator;

- The General Health Law regulations at present contain a three-year period that provide a *Roche-Bolar*-like research exemption (related to the possibility to submit an application for marketing authorization before the patent expires, with an intent to launch after the date of expiry). This three-year period is eliminated, and a submission can now be made at any time. The modification in the corresponding article will also be applicable to chemical drugs;

- A provision indicating that when an innovator or reference drug is manufactured in Mexico, the preclinical and clinical trials must be conducted locally; and

- The timelines that COFEPRIS will have for approving both innovator and biocomparable drugs.

Documents with comments have already been uploaded onto COFEMER's official website.

These documents include an official communication from COFEMER to COFEPRIS (the authority which oversees approvals) referring to the regulatory impact that the provisions will have, which was made public on August 9 2010. COFEMER is requesting, among other things, the following:

- A justification on the elimination of the three-year period in the *Roche Bolar*-like research exemption to verify compliance of provisions in the Industrial Property Law;

- Justification on each requirement to approve biocomparable drugs;

- Additional information on the cost implications that the new regulations will have for industry participants; and

- Additional information on the likely reductions in public health expenditures derived from the regulations.

This communication has been delivered by COFEPRIS which will have to make necessary justifications and adjustments to its proposal, before submitting it again to COFEMER. There is no specific deadline contemplated for this purpose. If modifications are made after the project is revised, a new 30-day period will be granted to the general public to provide comments.

The industry response

A second document contains a review carried out by the Mexican Association of Pharmaceutical Laboratories (AMELAF), with proposals for modifications to the project of regulations. Its proposals include the following:

- Concerning the *Roche-Bolar*-like exemption, AMELAF wants to change the wording in order for linkage review by COFEPRIS to be made only in regards to the first molecule (active ingredient) patent, which would be applicable both to biotech and chemical drugs. This goes directly against a decision by the Mexican Supreme Court, which interpreted linkage regulations to include patents covering pharmaceutical formulations as well. This specific proposal is very likely to be contended by AMIIF, and/or individual patent holders.

- AMELAF is also proposing to make most regulatory requirement for the approval of a biocomparable drug subject to the discretion of the Ministry of Health on a case-by-case basis. The present project contains mandatory pre-clinical and clinical trials, pharmacodinamics studies, immunity response studies in animals and *in vivo* studies. The proposal by AMELAF is to make all of these requirements applicable "if necessary".

- Additionally AMELAF is proposing that the term for COFEPRIS to approve a biotech drug be reduced from 235 to 180 working days, and that, if that term expires without a response, then the application is deemed to be granted. This last item is not likely to be approved, as it could lead to the authorization of drugs without full review of the applications by the corresponding authority, which might generate sanitary risks.

Comments were also provided by the National Association of Drug Manufacturers (ANAFAM) and are also available to the public, with the following relevant items:

- A note stressing that tests for follow-on drugs must be limited only to those strictly necessary to prove comparability in safety, quality and efficacy, to avoid high development costs.

- ANAFAM also provides arguments in favour of the removal of the time limit in the research exemption, citing as examples similar provisions in the US and Switzerland. They also recommend that the provision should be interpreted in the sense that a marketing authorization for either a generic chemical or a follow-on biologic drug should be granted immediately after the first active ingredient patent expires, regardless of further patents for polymorphs, formulations or uses.

- ANAFAM is requesting a removal of the obligation to hold pre-clinical and clinical trials locally when a drug will be manufactured in Mexico, on the grounds that this would inhibit business development.

Another submission from an R&D based company highlights some issues that need to be corrected from a regulatory standpoint to adapt the document to the World Health Organization's guidelines on evaluating similar biotherapeutic products.
In addition, AMIIF has filed a letter with COFEMER indicating that it is analyzing the project and will provide comments on the project in the coming weeks. These comments will most likely address both the technical and legal aspects of the issue, requesting that linkage, research exemptions and regulatory exclusivity are considered separately. AMIIF is expected to support the requirement to conduct pre-clinical and clinical trials locally when a drug will be manufactured in Mexico, without exception.

THE PRESENT SYSTEM

Until now, applications for both innovator and biocomparable drugs have been analysed and approved on a case-by-case basis, without a specific regulatory framework. This situation will continue until the regulations are finally passed. From a legal standpoint, the main issue is that the project lacks a provision contemplating a regulatory exclusivity period, as compensation for the expenses

incurred in pre-clinical trials, which will be mandatory to obtain an authorization for an innovator or reference biotechnologic drug.

The North America Free Trade Agreement (NAFTA), to which Mexico is a signatory, contains provisions contemplating a five-year minimum period after a drug containing a new chemical entity has been approved in which no other drug can be approved relying on the information contained in the innovator's dossier.

Although the Treaty, which came into force in 1994, does not specifically mention biotechnology, the same rationale should apply when analyzing the regulatory framework that is now being established, in which an innovator will necessarily have to incur a great deal of expense to prove a drug's safety and efficacy before COFEPRIS, regardless of whether or not a patent for the corresponding drug exists.

THE NEED FOR INCENTIVES

On the other hand, it is less expensive to prove the comparability of a follow-on biologic drug. This lack of balance when it comes to market entry can reduce incentives to innovate and bring new drugs and therapies to patients, unless an additional incentive is provided to the innovator.

Therefore, we consider that careful analysis of this issue should be made by Mexico's authorities, so as to determine a proper time period for regulatory exclusivity after a reference or innovator drug has been approved, before a follow-on drug based on comparability tests is allowed.