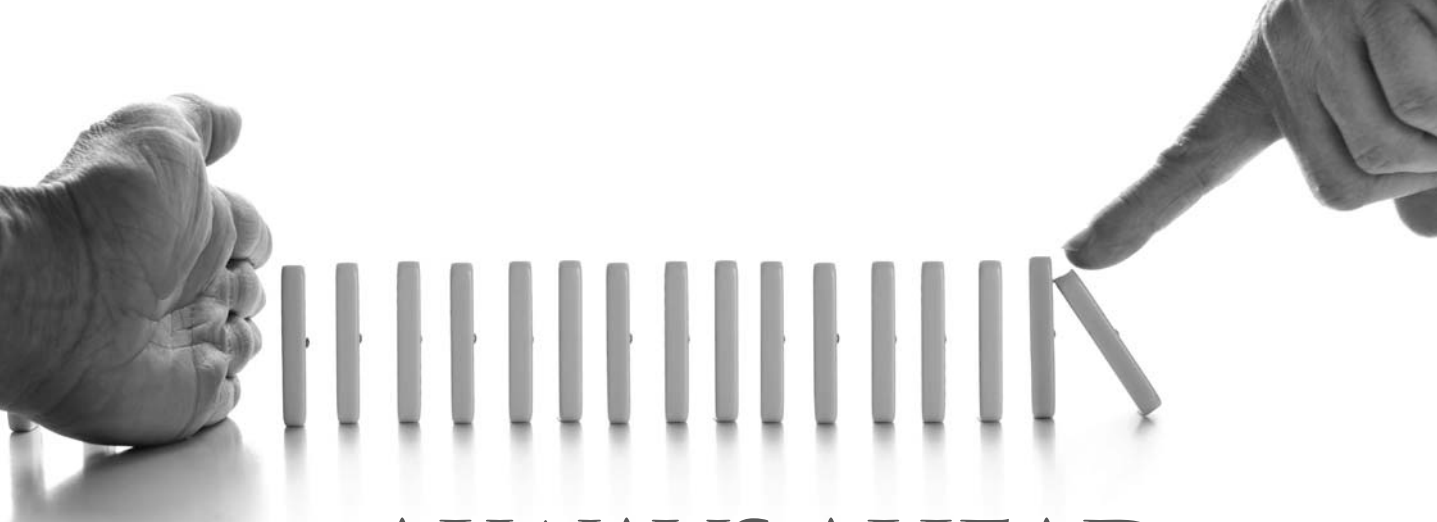

ALWAYS AHEAD
OF THE GAME

We're changing the way Life Science companies manage their legal risk in Mexico. Pharma, Biotech and Medical Devices companies now have the ability to manage all their legal needs under one roof.

IP is at the core of legal work for companies in the Life Science industries. Whether it's anti-trust in M&A and transactions, navigating the regulatory maze or drafting license agreements, you need corporate attorneys with an in-depth knowledge of IP.

With 40 years as a leading force in legal protection in Mexico, our all-encompassing Life Science Law Group has the experience to help you.

OLIVARES & CIA

Olivares & Cia. are proud to be the only firm in Mexico ranked in the "Tier 1/Band 1" in all IP related categories within both *Chambers Latin America* and *Managing Intellectual Property's* World IP Survey.

Pedro Luis Ogazón #17, Col. San Ángel , C.P. 01000, México D.F • T. 5322 3000
olivlaw@olivares.com.mx • www.olivares.com.mx

New regulations pending

Alejandro Luna and **Juan Luis Serrano Leets** of **Olivares & Compañía** looks at the main issues set forth by proposed regulations for the approval of biocomparable drugs

The Mexican General Health Law was amended on June 11 2009 to include an article 222 bis, which defined biotechnological drugs, and allowed for the approval of follow-ons, named "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 project of regulations was still being reviewed, with input provided by both the Mexican Association of Pharmaceutical Research (AMIIF) and the National Association of Drug Manufacturers (ANAFAM).

The final version of the regulations proposed by COFEPRIS (the Mexican regulatory authority) is still pending publication, but it was recently made available to the public through the official website of the Federal Commission for Regulatory Improvement (COFEMER).

For this version, several amicus briefs were considered, including the opinion of other government bodies, such as the Federal Antitrust Commission (COFECO), and publication without further modifications is expected in the short term.

Before we outline the issues addressed in the regulations, several important definitions are as follows:

- Biocomparable biotechnological drug - the biotechnological drug that shows comparability for safety, quality and efficacy with the reference biotechnological drug, through the tests established in the Law, regulations, and other provisions.
- Innovator biotechnological drug - the biotechnological drug thus defined by the Ministry of Health which was the first to obtain the corresponding marketing authorisation in Mexico.
- Reference biotechnological drug - the one determined by the Ministry of Health which is commercially available in Mexico and can serve as reference for the registration of biocomparables.

(The last two definitions imply that the reference drug can be different from the innovator, which could lead to a scenario where a follow-on can serve as reference.)

- Biocomparability tests - the tests, trials and analysis which are indispensable to prove that a Biocomparable drug is comparable to the reference drug in terms of safety, efficacy and quality.

Main issues in the regulations

- Specific labelling requirements for biotechnological drugs, in addition to those requested for chemicals, to include the name and country of origin of the manufacturer, the place of packaging and, when applicable, the name of the importer.
- Concerning prescription requirements, the regulations indicate that prescriptions will contain the International Nonproprietary Name (INN). The inclusion of the trade mark or distinctive name is optional. The drafting of this provision will allow for substitution of the drug at the pharmacy.
- Separate definitions for biological active ingredient and biological drug. Biotechnological active ingredient is deemed any substance produced by molecular biotechnology, with pharmacological activity, identified by its physical chemical and biologic properties, and that can be used in a drug. Biotechnological drug is deemed any substance produced by molecular biotechnology, which is in pharmaceutical form and has a therapeutic, preventive or rehabilitative effect.
- Particularities of pharmacovigilance for biotechnological drugs are left for a future Official Norm. The regulations indicate that pharmacovigilance will take place throughout all stages of treatment.
- The process of approval of an innovator biotechnological drug will go through a specific Subcommittee of Evaluation, which reports to the New Molecules Committee.
- Pre-clinical and clinical studies will have to take place in Mexico in two cases: when the drug is manufactured in Mexico; and, for drugs manufactured

abroad, when it is thus decided by the Subcommittee of Evaluation on a discretionary basis.

- The regulations establish that applications for innovator drugs will be decided in a term of 235 working days, with a 120 day term to request additional information, and a 100 day term to respond. The corresponding provision also states that when the application is not decided in the established deadline, it will be understood as denied. The main problem with this provision is that it does not imply any real pressure on the authority to decide applications, since challenges against an implicit denial would most likely prove to be costly and time consuming.
- For the authorisation of biocomparables the regulations substitute the general need to provide pre-clinical and clinical trials (applicable to innovator drugs) with decisions on a case by case basis based on certain parameters (mentioned below). A provision is included making reference to the scope and amount of data that will be required to authorise biocomparables, stating that "the reach of the clinical biocomparability tests will be supported in the tests of characterization of the biotechnological active ingredient and drug. The more a drug is characterized and its physic-chemical comparability is proven, the less clinical evidence will be required".

The combination of these last two provisions leaves a wide margin for decision making by our Health Authority concerning criteria for comparability tests. The specific documentation required for biocomparables is:

- In vitro studies when necessary;
- Pre-clinical trials including a comparative report of pharmacodynamic effects and relevant activity for clinical application, a comparative toxicology report, and at least one repeat dose toxicity study (the reported duration of the trial must be technically justified to allow the detection of differences relevant towards toxicity and immune responses between the reference drug and the biocomparable). When these studies are not sufficient, relevant observations must be included in the repeat dose toxicity study, including local tolerability. Reports of other toxicology studies such as pharmacological safety, reproductive toxicology, mutagenesis and carcinogenesis will only be requested when derived from the repeat dose studies.
- A report, when applicable of comparative pharmacokinetics studies.
- Reports of Pharmacodynamics studies. Pharmacodynamics markers must be selected according to their relevance to prove therapeutic efficacy in the biocomparable. The pharmacodynamic effects of the biocomparable and the reference drug must be compared in a population allowing for observation of possible differences. The design and duration of the studies must be technically justified.
- Clinical trials of comparative safety and efficacy to prove clinical likeness between the biocomparable and reference drug, with the following characteristics: clinical biocomparability parameters and margins must be justified and specified before the trials are undertaken, and they must be clearly pointed out in the report submitted for evaluation; the Official Norms corresponding to good practices in clinical research, insuring scientific validity of the study must be followed; and, on drugs where the immune response can affect the endogenous protein or its biological functions, antibody tests as part of safety clinical studies.

This provision is subject to limitations when the characterisation of innovator drugs improves.

- When the Mexican Parmacopoeia is insufficient, usage of international guidelines is allowed.
- All preclinical and clinical trials for biocomparables must take place in Mexico
- The provisions also state that once biocomparability

Alejandro Luna

Alejandro Luna graduated from the Universidad Latinoamericana. He has obtained IP and litigation specialisation degrees from the Universidad Panamericana, and a Masters degree in intellectual property law at the Franklin Pierce Law Centre in Concorde, New Hampshire, US.

He has proactively participated in cases against the unconstitutionality and inefficiency of certain amendments to the Federal Law of Administrative Proceedings in Mexico, which have affected the venues to challenge the resolutions by the Mexican Institute of Industrial Property.

Luna is also the sponsor of a proposal to modify the litigation system of industrial property, limiting the Mexican Institute of Industrial Property to an exclusive registration authority, transferring the jurisdiction for litigation to civil courts in infringement cases, and to administrative courts in cases related to the annulment of trade mark registrations or patents.

Luna is the author of several articles on patents, litigation and regulatory issues that have been published both in Mexico and abroad. He is a distinguished member of several associations including the Mexican Association for the Protection of Industrial Property. He was named in the 2007 Guide to the World's Leading Patent Law Practitioners. Luna is partner in charge of the appeals department at Olivares & Compañía, and he is a part-time professor in the National University (UNAM).

has been proven, the same indications as the reference drug will be authorised, as long as the biocomoparable is in the same pharmaceutical form and dosage.
- A Roche-Bolar type research exception is established stating that applications can be filed eight years before patent expiration.
- The deadlines to decide applications for biocomparables are the same as those for innovator drugs.

The issue of the drafting of requirements for biocomparables was strongly contested by industry participants, with the final version reached as a middle ground solution by the regulatory authority.

From a legal standpoint, the main issue lacking within the project is a provision contemplating a regulatory exclusivity period, as compensation for the expenses incurred in the pre-clinical and clinical trials, which will be mandatory to obtain an authorisation for an innovator or reference biotechnologic drug.

The North America Free Trade Agreement (Nafta) of which Mexico is a part 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.

Whereas this treaty, which came into force in 1994, does not specifically mention biotechnology, the same rationale should apply when analysing the regulatory framework that is being set, in which an innovator will have to incur high costs in order to prove a drug's safety and efficacy before COFEPRIS, regardless of whether or not a patent on the corresponding drug is available.

On the other side, it is less expensive to prove comparability of a follow-on biologic drug. This unbalance in market entry can harm incentives to innovate and bring new drugs and therapies to patients, unless an incentive is provided to the innovator.

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

Several administrative actions, related to both small and large molecule drugs have been attempted to secure orders to the COFEPRIS to preserve regulatory exclusivity for specific drugs. Whereas these actions have not been decided, injunctions have been obtained in all the relevant cases.

Furthermore, an initiative to modify the General Health Law is under study before Congress, which would address the issue of implementing the corresponding Nafta provisions. This initiative contemplates a five year exclusivity period for small molecule drugs and a 12 year period for biotechnological drugs.

Another issue missing in this initiative is a cross reference to the linkage provisions, established in 2003 in the same Health Law Regulations.

These provisions have been the subject of several litigation proceedings, both challenging their constitutionality and seeking inclusion in the corresponding gazette of patents covering second uses or formulations. Even though the issue of linkage was reviewed by the Supreme Court with an order for our patent office (IMPI) to include formulation patents in the gazette, this order has not been followed without litigation on specific patents.

This lack of reference to linkage provisions can lead to confusion, and contradictory decisions concerning both the inclusion of patents referring to a biotechnological drug in the linkage gazette and the observance of these patents by COFEPRIS.

Even though several solutions to this issue have been proposed by IP specialists and the industry, there is no official proposal for a modification.

Juan Luis Serrano Leets

Juan Luis Serrano Leets graduated from the Universidad Panamericana with a degree in law, with a further specialisation in commercial law institutions. He also has a Masters degree in innovation law and policy from the University of Toronto.

Serrano joined Olivares & Compañía in 2003, and is now an associate attorney in charge of IP litigation, regulatory affairs, and administrative consulting and litigation. He specialises in pharmaceutical andbiotechnology cases including legal consulting on marketing authorisations, linkage regulations, patent term correction, and advertising authorisations. He also consults on public acquisition proceedings.

Serrano is a member of the Mexican Association for the Protection of Industrial Property, and has been an active member of the IP litigation commission of this association. He became a member of the Mexican Bar in 2007, and has since actively participated in the Administrative Law Commission of this Bar. He is a regular attendant at annual INTA meetings, and BIO industry conventions.

Serrano is also assistant professor on the graduate programme in the Universidad Nacional Autonoma de México (UNAM), and has previously been head professor on the intellectual property law module at the UNAM Faculty of Law. He has been invited as a visiting lecturer on various courses at the Universidad Panamericana, the Universidad Iberoamericana and the Escuela Superior de Administracion de Instituciones. He is the author of several articles on patents, litigation and regulatory issues.