IP in the Life Sciences Industries 2014

Key issues for senior life sciences executives

Mexico

Contributing firm - OLIVARES

The IP Media Group

iam

A supplement to *Intellectual Asset Management* magazine

www.iam-magazine.com

APIs, imports and the Bolar exemption: concerns and practical measures

The Mexican legal framework requires some improvements to grant legal certainty to both innovators and applicants for generic and biologic follow-ons

By **Erwin Cruz**, OLIVARES

No medicinal product for human use can be placed on the market in Mexico unless it has been approved by the regulatory agency, the *Comisión Federal para la Protección contra Riesgos Sanitarios* (COFEPRIS). Linkage regulations both prevent medicinal products from being approved in violation of patent rights and establish a type of Bolar exemption for generic and biologic follow-ons. Accordingly, under certain conditions, the exemption allows pilot production and tests to be performed in relation to such products. However, recent imports of considerable amounts of active pharmaceutical ingredients (APIs) covered by patent rights for the purposes of conducting trial activities have put both the rules and the involved agencies to the test.

This article analyses these concerns by summarising the legal framework for exclusivity rights and the Bolar exemption for the import of APIs into the European Union (and the United Kingdom in particular), and then by looking at these topics in the context of the Mexican legal framework. Finally, the article suggests measures that can be taken by stakeholders to prevent exclusivity rights violations.

Exclusivity rights and Bolar exemption in the European Union

Before considering the framework applicable in Mexico, it is important to examine the process for obtaining marketing authorisation, the exclusivity rights available for innovators and the Bolar exemption regarding applications for marketing authorisation for follow-ons according to EU law, as well as implementation of the Bolar exemption into the UK legal framework.

EU law

Applicants must prove the safety, efficacy and quality of their medicinal products through standard clinical trials. Depending on the API, an application can be submitted for evaluation under:

- a centralised procedure before the European Medicines Agency (EMA);
- a decentralised procedure in a number of EU member states at once;
- a mutual recognition procedure, when marketing authorisation has already been granted by another member state; or
- a national procedure.

The centralised procedure is compulsory for biotechnology products. These procedures are set forth in Title III of the EU Code for Human Medicines Directive (2001/83/EC, as amended) and Title II of the EMA Regulation (726/2004). In the United Kingdom, applications for marketing authorisation can be submitted before the Medicines and Healthcare Products Regulatory Agency (MHRA), and are primarily regulated by the Human Medicines Regulations 2012. The import of an API for investigational medicinal products is also subject to approval by the MHRA.

The EU Code for Human Medicines Directive (as amended by Directive 2004/27/EC) sets forth both the regulatory data exclusivity protections for medicinal products, in order to encourage R&D, and the abridged and hybrid-abridged procedures for follow-on products through

Erwin Cruz
Associate
OLIVARES
Mexico
Tel: +52 55 5322 3000
Fax: +52 55 5322 3001
ecs@olivares.com.mx

Erwin Cruz is an associate at OLIVARES, where he specialises in pharmaceutical law, IP litigation and enforcement.

Mr Cruz graduated with a bachelor's degree from the National Autonomous University of Mexico (UNAM) in 2006. Since then he has qualified from UNAM's IP specialisation programme (2009) and the litigation specialisation programme at the Federal Court for Tax and Administrative Affairs (2012). Mr Cruz is studying for an LLM in biotechnology, law and ethics at the University of Sheffield, United Kingdom. He is also a member of the Mexican Association for IP Protection. He speaks English and Spanish.

Mr Cruz is the author of several articles on intellectual property, which have been published both in Mexico and abroad. His recent relevant cases include the award of damages and lost profits in a case involving a patented blockbuster drug and the invalidation of a third-party marketing authorisation related to another patented blockbuster drug.

a type of Bolar exemption.

Under the provisions on regulatory data exclusivity, the originator company's pre-clinical and clinical data cannot be referenced in a marketing authorisation application for the same medicinal product for the first eight years after marketing authorisation has been granted for the originator's product. Subsequently, marketing authorisation applications for follow-ons may progress, but cannot be authorised until 10 years after such originator's approval (Article 10(1)). This period may be extended for up to one additional year if one or more new indications for the originator's product are registered, bringing a significant benefit in comparison with existing therapies. Additionally, one year of exclusivity can be obtained in view of a medicine classification change (Article 74a).

Generics qualify for an abridged procedure, relying on data for reference products without consent (Article 10(1) and (2)). Follow-ons that do not meet the generic definition (Article 10(2)(b)) and biosimilars qualify for a hybrid-abridged procedure, and appropriate data, pre-clinical testing or clinical trials should be provided (Articles 10(3) and (4)). The consequential practical requirements that apply under these procedures "shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products" (Article 10(6)).

Supplementary protection certificates (SPCs) offer protection for the innovator's product after expiry of the patent, conferring the same rights, limitations and obligations as those conferred by the basic patent (EU Regulation 469/2009). In general terms, an SPC will expire five years after expiry of the patent. This protection may be extended for six months in case of new paediatric use.

UK law

The above exclusivity rights and the exemption are available in the United Kingdom as an EU member state. Furthermore, the United Kingdom implemented the EU Bolar exemption into statutory law in 2005 by inserting Section 60(5)(i) into the Patent Law 1977. This section excludes patent infringement for "an act done in conducting a study, test or trial which is necessary for and is conducted with a view to the application of... paragraphs 1 to 4 of article 10 of Directive 2001/83/EC [abridged or hybrid-abridged procedures]".

While there is no apparent case law regarding this section, the UK Intellectual Property Office (UKIPO) and the MHRA have published their views regarding the exemption and the import of APIs. The UKIPO's view is that the exemption covers the manufacture or import of batches of APIs "in quantities sufficient to provide material for preparing investigative batches of the medicinal product and to validate the processes to the satisfaction of the competent authorities" ("The Bolar Exemption, Activities covered by the exemption", www.ipo.gov.uk). The MHRA's view is that the exemption does not include APIs or finished products that are "not required for conducting the tests and trials necessary for gaining authorization or for providing small quantities as samples" (Annex A: Review of the EU Medicines legislation, proposal of implementation, page 15).

Recent cases in other EU member states

In 2011 the Spanish Supreme Court upheld its previous determination that the Bolar exemption as implemented in Spain from the EU Code for Human Medicines Directive differs from the purely scientific experimental exemption. The Bolar exemption covers use of an API only to conduct tests for obtaining a generic marketing authorisation (*Tribunal Superior, Sala de lo Civil*, Decision 766/2011, November 11 2011, page 19).

In 2012 both the Dusseldorf District Court in Germany and the Gdansk Appeal Court in Poland ruled that the Bolar exemption as implemented in each jurisdiction applies to the applicant for marketing authorisation of a follow-on product. However, it does not cover third parties manufacturing and selling the patented substance to such applicant (M Kolasa, "Germany: Directive 2001/83- 'Bolar Exemption (Solifenacin) — Germany' Case Comment" (2013) 44 (3) IIC, 361-362).

Exclusivity rights and Bolar exemption in Mexico

In Mexico, the exclusivity rights available for encouraging R&D and the Bolar exemption regarding the import of APIs into the legal framework are essentially as follows.

The Health Law and its regulations set forth an abridged procedure for generics. A hybrid procedure for biologic follow-ons (biocomparables) was also added recently. These regulations establish a type of Bolar exemption for these products. Applications can be submitted before the expiry of innovator patent rights, up to three years in advance for generics and eight years in advance for biologic follow-ons. Under certain conditions, the exemption allows

pilot production and tests to be performed.

Nevertheless, in contrast to EU law, Mexican law is silent with regard to regulatory data exclusivity. Additionally, in certain cases COFEPRIS has observed formulation patents while granting marketing authorisation, and recently approved non-authorised parties to import patented APIs in quantities far from those fairly required for pilot production and tests.

Regulatory data exclusivity

In view of the lack of domestic law, a legal strategy has been devised to obtain recognition for regulatory data exclusivity for originators' products, based on the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) and the North American Free Trade Agreement (NAFTA). Court precedents have been obtained, recognising regulatory data exclusivity and ordering COFEPRIS to observe these exclusivity rights.

In 2012 COFEPRIS published an internal memorandum on its website, providing guidelines for observing regulatory data exclusivity. According to these guidelines (and in line with the minimum term set by NAFTA), a marketing authorisation holder will have a five-year exclusive right, provided that its information cannot benefit or be used to support a third-party application for registration of a generic drug. This does not preclude generics from providing their own standard clinical trials to obtain marketing authorisation.

Although these guidelines show that COFEPRIS is willing to protect regulatory data exclusivity under both NAFTA and TRIPs, several concerns remain — for example, the legal status of an internal memorandum published on a website rather than in the *Official Gazette* is uncertain and the wording of the guidelines does not clearly address either the regulatory data exclusivity for biological products, the registration of new formulations and indications, or the proceedings and measures to enforce and observe such regulatory data exclusivity.

Linkage system

A linkage system is in place between COFEPRIS and the Mexican Institute of Industrial Property (IMPI), the authority in charge of granting patents. The system aims to prevent marketing authorisation being granted to non-authorised third parties for products that would fall within the scope of patents listed in the *Linkage Gazette* (a gazette periodically published by IMPI that 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, IMPI not only removed the need for patent rights holders to expend money and time on legal actions in order to have such patents included in the gazette, but also improved the application of the linkage system towards preventing violations of exclusivity rights.

This optimism has turned to scepticism, however, as COFEPRIS has only loosely observed formulation patents listed in the *Linkage Gazette* process of approvals for follow-ons (currently, COFEPRIS observes only compound patents). To a certain degree this undermines the preventative aim of the system — an issue that patent rights holders should bear in mind when monitoring potential infringement activities and enforcing their rights.

Imports

An approval by COFEPRIS for imports of APIs is a mandatory requirement before Customs in Mexico. However, neither the wording of the Bolar exemption nor the rules on importing APIs clearly address the amount of APIs that can be imported by applicants of follow-on products for the corresponding tests to be adequately met. In contrast to the MHRA's view in regard to the Bolar exemption, IMPI and COFEPRIS have not published their views on whether this exemption allows the import only of small quantities of APIs for conducting the tests and trials necessary for gaining marketing authorisation. This has led to scenarios where non-authorised parties are being practically allowed by COFEPRIS to import huge amounts of APIs covered by patent rights that are far greater than the small quantity needed to conduct pilot production and testing.

Approvals for considerable amounts of patented compounds, in most cases, take place when the relevant patent rights are close to expiry. This trend has increased during the past four years, following the removal of the requirement to have a facility located in Mexico approved to manufacture medicinal products. The pharmaceutical business in Mexico has changed substantially in view of the removal of this requirement, as many small and medium-sized foreign companies have started businesses in Mexico, not only by partnering with pharmaceutical companies already established in the country, but

also by introducing their products through brokers and distributors. This trend seems to be positive for ensuring a competitive market, but the phenomenon cannot be an excuse for violating exclusivity rights.

In certain cases, the substantial amount of imported material (eg, 4 kilograms of an API) would represent considerable sales of medicinal products, which is far from the small quantity needed for tests to obtain marketing authorisation for a follow-on product. As a consequence, patent rights holders have been forced to take several different paths when tackling violations of their exclusive rights, including patent infringement actions — where coordination between the patent and customs offices can be far from ideal — and legal actions against import permits issued by COFEPRIS.

On July 1 2013 COFEPRIS published in the *Official Gazette* an amendment to its guidelines for importing APIs stating, among other things, that with regard to the import of tadalafil, sildenafil, raloxifene and clembuterol substances, applicants must provide details of the substances' clients and justify the total amount to be imported according to the number of clients. Apparently, COFEPRIS has started to prevent violations of certain patented APIs (including three formerly published in the *Linkage Gazette*). This action, however, is focused on particular cases and clear rules applicable to any API covered by patent rights are still pending.

Patent enforcement

Among other things, the Intellectual Property Law grants a patentee the right to impede the import and manufacture of its patented subject matter by non-authorised parties. Although the law establishes an experimental exemption, the wording addresses scientific research with no commercial purpose, which might not be the case for marketing authorisation applications for generics.

The law also sets forth interim injunctions regarding alleged patent infringement. Recent efforts at the border have culminated in the creation of a database managed by Customs in coordination with IMPI, which contains the registered trademarks of owners interested in the surveillance of their rights along the 49 customs checkpoints situated at the country's borders, ports, bus and train stations and airports.

With regard to medicines, pharmaceutical substances, chemicals and APIs, the activities and efforts of Customs are focused and limited to detecting prohibited drugs and narcotics; the next step is to strengthen IP protection for patents within Mexico's borders, especially for those that protect pharmaceutical products.

Since June 2012 Customs has collaborated in the detection and seizure of APIs grounded in border measures granted by IMPI to IP rights holders. As a result of cooperation between the Customs Office and IMPI, the first seizure has taken place of an import of a patented API in bulk at the border, before its entry into Mexico.

Conclusions and recommendations

Several areas for improvement remain in the Mexican legal framework in order to grant legal certainty to both innovators and applicants for follow-ons. In the short term, immediate practical measures by the authorities to prevent the import of infringing APIs would be welcomed. For example:

- COFEPRIS should use and observe the *Linkage Gazette* when approving the import of APIs;
- COFEPRIS should establish standards for limiting the quantity of APIs adequate for compliance with regulatory tests for marketing authorisation for follow-on products and deny imports of amounts greater than these levels;
- COFEPRIS should require importers to declare the destination of the eventual imported products;
- IMPI should clearly establish, as appropriate, the differences between sole experimental use and the Bolar exemption;
- IMPI should, on a case-by-case basis, carefully review what is considered an adequate amount to be imported for tests regarding a generic application for marketing authorisation. In certain cases, a small amount of an API can facilitate the manufacture of thousands of infringing products, which may then end up on the grey or black market; and
- Customs should take advantage of the information contained in the *Linkage Gazette* to detect and stop substances that could enter the country in violation of exclusivity rights. ■

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