

## The Bolar provision: a safe harbour in Europe for biosimilars

**On April 19, 2006, the European Commission granted Sandoz, a division of the Novartis group, approval for the sale of Sandoz' recombinant human growth hormone Omnitrope.**

**This was the first European marketing authorisation for a so-called "biosimilar" product.**

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In order to obtain regulatory approval to sell a medicinal product, pharmaceutical companies must undertake an enormous exercise to prove that the product is effective and safe. Efficacy and safety are predominantly demonstrated by clinical trials. Manufacturers of generic versions of existing medicinal products can, however, refer to the original manufacturer's approval and clinical trials in order to avoid unnecessary – and even unethical – duplication of animal studies and human clinical trials. This requires the demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability products. Due to the complexity of biological products the generic approach is scientifically not appropriate for these products and a broader comparability exercise is required.

Obtaining a marketing authorisation for a generic product – and especially for a biosimilar – entails therefore studies and testing, and thus the use of a (biological) medicinal reference product for regulatory purposes. As it is common practice in the generic industry to enter the market immediately upon expiry of the patent of the reference product, this testing for regulatory purposes is done when the patent is still valid. One of the questions manufactures of generics/biosimilars are then faced with is the risk of patent infringement.

Until recently, pre-patent-expiry development and testing was not regulated at EU level. There was no specific regulation at hand for the use of a reference medicinal product for regulatory purposes, such as bioequivalence testing (for generics), providing bridging data (application of the "hybrid" procedure) or comparability studies (for biosimilars). The national courts in the different Member States all applied their own national rules to determine whether or not these types of studies and trials should be considered an infringement of the patent of the reference product.

It goes without saying that the unclear and inconsistent legal application of these so-called "research exemptions" or "experimental use exceptions" resulted in diverging and inconsistent judgments throughout the EU, hindering the functioning of the Internal Market. To avoid the risks of facing lengthy and costly patent lawsuits, generic manufacturers preferred to prepare their marketing authorisation ("MA") applications in Central and East European countries with generic-friendly legislation.

This situation was in contrast to other jurisdictions where there are specific statutory provisions allowing pre-patent-expiry testing. In the US, for example, the US Court of Appeals initially ruled in the case of *Roche v. Bolar* that the experimental use of a drug for the purposes of obtaining regulatory approval for a generic version of a patented pharmaceutical product constituted a patent infringement. Following this case, US patent law was amended to include an exemption to permit such activities. Hence, the name "Bolar" provision. It should be noted that the US Supreme court recently provided a broad interpretation of this provision in the case *Merck v. Integra Lifesciences* by including research activities to develop a new drug into the Bolar exemption.

This European uncertainty is however over now. Directive 2004/27/EC amending Directive 2001/83/EC on the EU code relating to medicinal products for human use contains the so-called "Bolar" provision, providing the manufactures of generics and biosimilars with an exemption for pre-marketing testing.

### . . . the Bolar provision in Europe

The experimental use exemption in Europe is governed by differing national patent laws, as interpreted by national courts. Especially with regard to clinical trials, the legal application of the "experimental use" provisions is unclear and inconsistent. Some countries, such as Germany, provide a broad exemption for clinical trials, while others, such as the UK and the Netherlands, have a much narrower exemption.

In order to harmonise the law in this area and to put the European pharmaceutical industry (and, in particular, the generics sector) on a more equal footing with the US, the EU introduced a new exemption in article 10(6) of Directive 2004/27/EC amending Directive 2001/83/EC: "*Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.*" It should be noted that this provision is not identical to the US exemption, and is therefore only a "Bolar-type" provision.

The general and ambiguous wording of this provision raises a number of interpretation issues. It is, for example, unclear which "trials and studies" are exempted. It was suggested at EU level to draw up a list of the types of studies and trials falling under the Bolar clause, but the idea was eventually abandoned. "Consequential practical requirement" is a particularly nebulous term and will inevitably lead to disputes. It is the accepted view that the purpose of Article 10(6) is to provide an exemption from patent infringement in respect of experiments and trials – both pre-clinical and clinical – conducted in pursuance of seeking regulatory approval for a generic or similar biological medicinal product. As part of this, it is a consequential and practical requirement that the active ingredient and batches must be manufactured/imported in order for such tests to be performed. Applying for a MA and providing samples to the regulatory authorities also amount to consequential practical requirements. The question whether stock-piling, pre-patent expiry marketing, taking pre-orders etc., fall within the scope of Article 10(6) remains undecided and will have to be assessed on a case-by-case basis by national courts.

Nor does Article 10(6) appear to provide an exemption for all activities. Only studies and trials in view of abridged applications (Articles 10(1) and 10(2)), hybrid applications (Article 10(3)) and biosimilar applications (Article 10(4)) are exempted from patent infringement. Bibliographical (Article 10a) and applications for new

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combinations of active substances (Article 10b) seem to be out of the scope of the exemption. It is also questionable whether an innovator company could carry out tests for the purposes of developing a new drug on the basis that the development data may ultimately be used for an application for a marketing authorisation for that new drug (*i.e.* the *Merck v. Integra Lifesciences* scenario). Furthermore, only studies and trials in view of filing applications for a marketing authorisation in the EU seem to fall within the scope of the provision. The use of trial information or production for applications outside of the EU, acts performed in view of exporting, etc. seem to be excluded. Such activities, however, will probably be exempted provided that they form part of an EU application for a marketing authorisation.

### ... national implementation of the Bolar provision

Although Directive 2004/27/EC, and consequently the Bolar provision, should have been implemented in national legislation on 30 October 2005 at the latest, most Member States have not fully completed the national implementation process. More importantly, however, there is disparity between EU Member States as regards the interpretation of the wording of the Bolar provision. For example, Germany and Italy have opted for a broader interpretation than the UK.

The UK enacted the Bolar clause by amending article 60(5) of the 1977 Patents Act. These amendments entered into force on 30 October 2005. The provision provides as follows: “An act which, apart from this subsection, would constitute an infringement of a patent for an invention shall not do so if (–) it consists of: (i) an act done in conducting a study, test or trial which is necessary for and conducted with a view to the application of paragraphs 1 to 5 of Article 13 of Directive 2001/82/EC or paragraphs 1 to 5 of Article 10 of Directive 2001/83/EC, or (ii) any other act which is required for the purpose of the application of those paragraphs”. The UK Medicines and Healthcare products Regulatory Authority (“MHRA”) has also set out its view on how the exemption should be construed by providing a broad list of exempted activities.

In Germany, the Bolar clause has been implemented and in force as from 6 September 2005. Article 3 of the German Medicines Act adds a new paragraph 2b to section 11 of the German Patent Act. The general exemption has been supplemented with the following provision: “The effect of a patent shall not extend to (–) 2. Acts done for experimental purposes relating to the subject matter of the patented invention (–) 2b. Studies and trials and the consequential practical requirements which are necessary to obtain an authorisation according to the Medicines Act for the marketing in the European Union or an authorisation according to the Medicines Act for the marketing in the Member States of the European Union or in third countries.” The German legislator has opted for the broadest possible implementation of the Bolar clause. Instead of implementing the exact wording and same ambiguities of Article 10(6), the German legislator added detail to determine the scope of the provision and to prevent future legal uncertainties. The German Medicines Act extends the Bolar exemption to trials and studies in view of applications outside the EU and the European Economic Area (EEA). The scope of the Bolar is not limited to merely generic, hybrid or biosimilar applications either, but can for instance also be invoked for studies and trials performed in search of new active substances.

Article 10(6) of Directive 2004/27/EC has not yet been implemented in France. Currently, a proposal is being discussed in Parliament to

amend article L.613.5 of the French Intellectual Property Code by introducing a new paragraph d): “The rights afforded by a patent shall not extend to: (–) (d) the studies and trials necessary in order to obtain a marketing authorisation for a medicinal product, as well as any acts necessary for their performance”. This constitutes a relatively broad implementation of the Bolar clause, since its scope is not limited to generic applications and, contrary to a prior proposal, applications filed in view of obtaining a marketing authorisation in the EU. Article 11 of the same proposal introduces an amendment of article L.5121 of the French Public Health Code, specifically with regard to biosimilars. It is explicitly stated that a marketing authorisation of a biosimilar can be obtained prior to patent expiry, but that the applicant for a biosimilar has to inform the patentee of the application at the time of filing.

In Italy, the Bolar provision had already been implemented into national law by amendment of article 68(1)a of the new Industrial Property Code, published on 4 March 2005: “Whatever the subject of the invention is, the exclusive right granted by the patent does not extend to: a) acts performed privately and for non-commercial purposes, or for experimental purposes even if aimed at obtaining, in any country, an authorisation to market a finished dosage form and at accomplishing the consequential practical requirements, including the preparation and the use of the active pharmaceutical ingredients which are strictly necessary.” As was the case in Germany, the Italian provision does not limit the effect of the Bolar only to those studies and trials required for a generic company pursuing an application for a marketing authorisation. The provision further includes all studies and trials necessary for the purpose of obtaining a marketing authorisation, inside or outside the EU.

In Belgium, the Bolar provision has been implemented by amending the Belgian Medicines Act (“BMA”) of 25 March 1964, rather than through an amendment of the Belgian Patent Act. Article 6bis, 1, of the BMA, which entered into force on May 26, 2006, reads as follows: “Conducting the necessary studies, tests and trials with a view to meeting the conditions and modalities referred to in the intends 1 to 7 of this paragraph and all the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates (–)”. Although this provision is a quasi literal copy of article 10(6), two subtle differences, or rather refinements, can be found in the text: the word “tests” has been inserted and it has been specified that “all” consequential practical requirements will not be considered a patent infringement.

### ... conclusion

The introduction of a Bolar type provision in the EU is undoubtedly a positive step. There is no discussion that the new exemption provides a safe harbour for conducting bioequivalence studies (generics) and comparability exercises (biosimilars). The scope of the exemption, however, remains unclear due to the use of ambiguous, vague and broad terminology. This is complicated by a diverging implementation in the various EU Member States.

It was also hoped that the Bolar provision would put the EU generics on a par with the US, but it seems that the broader exemption permitted by the US Supreme Court in *Merck v Integra* may not be permitted in various European countries. The scope of the Bolar will ultimately be determined by the European Court of Justice whenever a national court refers a question to it on the interpretation and/or national implementation of the exemption.