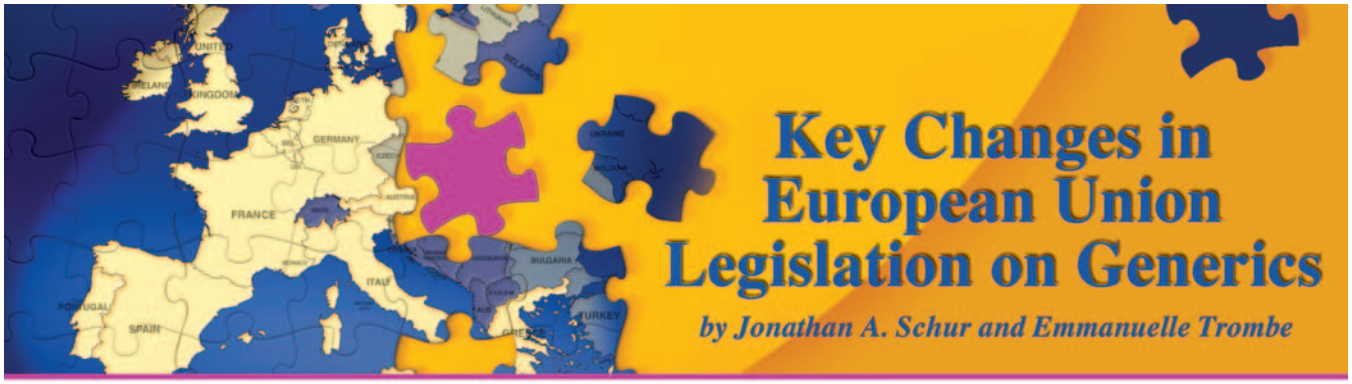

Key Changes in European Union Legislation on Generics

by Jonathan A. Schur and Emmanuelle Trombe

Major changes in European rules governing marketing authorizations for generic pharmaceutical products were adopted in 2004. At a time when research-based pharmaceutical and biotechnology companies are struggling to find innovative products and bring them to market, the new European rules threaten the ability of those companies to maintain current product revenue streams.

The changes come from two important pieces of European Union (EU) legislation[1] that will enter into force progressively, starting in 2005, in the 25 Member States of the EU. The new legislation:

- harmonizes the data exclusivity period for pharmaceutical products;[2]
- facilitates marketing authorizations for generic products (although the treatment of "biogenerics" remains open); and
- confirms and extends a number of previous decisions by the European Court of Justice (ECJ) regarding the impact of product extensions and new indications in generic product applications.

The new rules will push research-based pharmaceutical and biotechnology companies to reconsider research and development (R&D) efforts targeting improved versions of their existing products, and to redeploy their efforts toward new chemical entities and, to a lesser extent, new indications.

This article summarizes the changes made by the new EU legislation and the remaining areas of uncertainty. It also highlights key issues for pharmaceutical and biotechnology companies to consider with respect to their product strategies for Europe.

Definition of Generics

For the first time, the new EU legislation defines a generic medicinal product.[3] The definition replaces the prior concept of "essential similarity," which was developed through case law.[4] It is quite broad and covers all products with:

(1) *the same qualitative and quantitative composition in active substances*. The new legislation provides expressly that different salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives are considered to be the same active substances, provided that they do not differ significantly with respect to safety and/or efficacy. The new rule further specifies that the burden of proving that such products do not differ significantly with respect to safety and/or efficacy is on the generic applicant.[5]

(2) *the same pharmaceutical form*. The ECJ has held that, in evaluating the pharmaceutical form, the forms of presentation and administration must be taken into account.[6] The new EU legislation specifies that various immediate-release oral pharmaceutical forms are regarded as the same form.[7] The ECJ also has held, that, when a product is administered as a drinkable solution—whether it forms after dilution a macroemulsion, microemulsion, or nanodispersion—it does not change the "pharmaceutical form" of such product, as long as the differences in the form of administration are not significant "in scientific terms" (a concept not further defined by the ECJ).[8]

(3) *bioequivalence*, which has to be demonstrated by appropriate studies.[9] The new legislation provides that bioequivalence studies may not be required if the generic

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product meets certain criteria that will be defined in guidelines yet to be adopted.

In a significant change, the new EU legislation further provides that new strengths, pharmaceutical forms, routes of administration, and presentations, as well as any extensions or variations, are to be considered as "belonging to the same global authorization" for purposes of the abridged application rules.[10] This new provision is in line with a number of recent decisions by the ECJ, which held that, in certain circumstances, a generic application could rely on data relating to a reference product even though the generic product was not essentially similar to the reference product (due, e.g., to a difference in their pharmaceutical forms). The question referred to the ECJ was whether, when the protection period has elapsed for product A (e.g., a capsule form product), but not for product B (e.g., the liquid form of product A, authorized through an abridged procedure by referral to data related to product A), an application for product C (e.g., a generic of product B) could refer to the data submitted in product B's application proving that product B was similar to product A. The ECJ said yes.[11]

The new EU legislation also clarifies a portion of the ECJ's *Generics* decision, which held that a generic of a reference product whose data exclusivity period has elapsed is authorized for all therapeutic indications and all dosage forms, doses, and dosage schedules previously authorized for that reference product.[12] Certain local courts, such as the *Conseil d'Etat* (France's supreme administrative court), had found that the wording of the *Generics* case was ambiguous as to whether or not a generic application could obtain an authorization for dosages authorized for less than the data exclusivity period, and had granted additional protection to new dosages.[13] The new legislation makes it clear that new dosages and similar line extensions are not subject to an additional period of protection. On the other hand, the new law improves the protection of new indications.

New Indications

Under the *Generics* decision, it was thought that new indications would be given no additional protection,[14] but the new EU legislation provides that the addition of one or more new therapeutic indications may trigger an extension to the data exclusivity period.

Under the new legislation, if one or more new indications are authorized during the first eight years of the marketing authorization and such indication(s) are thought to bring a "significant clinical benefit" in comparison with existing therapies, the data exclusivity period for the product is extended by one year. This additional data exclusivity period may be granted only once, bringing the market exclusivity period to a maximum of 11 years.[15]

Similarly, a new indication for a "well established product" triggers an additional exclusivity data period of one year, provided that significant preclinical and clinical trials were carried out in relation to the new indication. This data protection period covers only the new indication[16]—a restriction that likely will reduce practical interest in attaining that protection; generic products of a reference product with a protected new indication likely would be prescribed off-label for the new indication.

"Biogenerics" or "Biosimilar" Products

Although it is frequently used, the term "biogenerics" is misleading because the definition of generics does not usually apply to biological products, particularly because of the differences in raw materials or manufacturing processes with the reference products. Therefore, the new EU legislation retained the terms "biosimilar" products;[17] the U.S. Food and Drug Administration (FDA) usually refers to "follow-on" biological products.

The new EU legislation contains specific provisions with respect to "biosimilar" products. The rule provides that "appropriate" preclinical and clinical tests must be conducted to establish biosimilarity and, therefore, entitlement to abridged marketing authorization.[18] The extent of such tests is set forth in Annex I to Directive 2001/83 and related detailed guidelines to be adopted.[19]

The biosimilarity test remains difficult to pass. Even generics of comparatively simple molecules (e.g., the human growth hormone (hGH)) have yet to be approved. For example, European authorities have taken a relatively cautious approach to Omnitrop® (Sandoz's (Novartis') hGH). Omnitrop® had received a positive opinion from the EMEA's Committee for Proprietary Medicinal Products in June 2003, but was then rejected by the European Commission—unusually—on the basis of filing irregularities. Sandoz has challenged the European Commission's decision before the European Court of First Instance.[20] Likewise, the application for Omnitrop® is reported to have been rejected by FDA. There seems to be, within European institutions—as within FDA—some internal divergence with respect to the appropriate regulatory pathway of biogenerics.

Data Exclusivity Periods: 8 + 2 +1

The new EU law provides for two types of protection periods: a data exclusivity period of eight years (starting on the date of first authorization of the product in the EU[21]) and a market exclusivity period of 10 years (starting on the same authorization date).[22] The market exclusivity period includes the eight-year data exclusivity period.

The result of these provisions is that an application for a generic product can be made, without submission of preclinical and clinical trial data, eight years after the issuance of the reference product's first marketing authorization in the EU, but that the generic product—even if authorized—may not be launched in the EU until 10 years after the issuance of the reference product's first marketing authorization in the EU. These rules allow the generic manufacturer to secure a marketing authorization and be in the starting blocks when the market exclusivity period expires.

A product may obtain an extra data exclusivity period for new indications and for so-called switch data (i.e., "significant" preclinical and clinical trial data used to support a change in the product classification, generally a switch from prescription to over-the counter (OTC) status).[23] In such a case, no application for a generic OTC product may refer to the reference product's switch data for a year after the change in the classification of the reference product is authorized.

"Euro-Generics"

The new EU legislation allows for the approval of a generic product in a country where the reference product is not approved or has not been approved for eight years, by reference to the marketing authorization granted in another Member state or in the EU (through a centralized authorization) for more than eight years.[24] This provision contrasts with the rules previously in force, which prevented an abridged application for products that were not authorized in the Member State where the abridged application was filed.[25] This change means that pharmaceutical and biotechnology firms must now adopt a pan-European strategy for regulatory purposes.

The pan-European approach of the new legislation also is evident in its 10-year market exclusivity provisions: such period starts on the date of the first authorization of the reference product in *any* Member State. Therefore, a product that has been authorized for 10 years in a single Member State will now be subject to generic competition all over Europe.

To facilitate references to data of products authorized in other Member States, a process that has sometimes been complicated by local variations in Summary of Product Characteristics (SmPCs), the new legislation provides that SmPCs must be progressively harmonized throughout the EU.[26]

In addition, a generic application can make reference to a marketing authorization that has been withdrawn. This puts an end to a defense against generics consisting of withdrawing a potential reference product's marketing authorization before the expiration of the data exclusivity period.

Bolar Amendment

The so-called "*Bolar* amendment," by reference to the U.S. litigation on the matter, relates to the possibility of conducting tests to support a generic application (in particular, bioequivalence tests) during the patent protection period. Before the adoption of the new EU legislation, the law in Europe differed from one country to another, creating uncertainty and leading to calls for harmonization. The new legislation provides that tests "necessary" to support an abridged application and its "consequential practical requirements" (which should include, e.g., sample submissions) do not constitute a patent infringement.[27]

The new EU legislation does not address, however, the World Trade Organization (WTO) General Council's decision of August 30, 2003, (the Doha Agreement), pursuant to which the manufacturing of products for export to countries with insufficient manufacturing capacities, where the product has no patent protection or is subject to a compulsory license, would not constitute a patent infringement.

Timeframe for Implementation

Directive 2004/27/EC of March 31, 2004, is not directly enforceable, but has to be transposed in the law of the Member States no later than October 30, 2005. Some Member States (e.g., France) already have implemented portions of the new legislation.[28] Regulation (EC) 726/2004 of March 31, 2004, is directly applicable and is effective November 20, 2005.

The new legislation provides, however, that new periods of protection do not apply to reference products for which an authorization application has been submitted before a certain date.[29] Although the drafting of this provision is unclear, that date—in our view—is October 30, 2005, with respect to Directive 2004/27/EC, and November 20, 2005, with respect to Regulation (EC) 726/2004. The ambiguity in drafting does leave room for different interpretations.[30]

The scope of this exception also is unclear. Products for which marketing authorization applications have been

submitted by the above dates should be subject to the previous protection periods (i.e., from six to 10 years) in most of the European states, but less in some of the new countries that joined the EU on May 1, 2004.[31] What about the other provisions of the new legislation, concerning, for example, the status of line extensions and other modified products? The new legislation refers only to an extension of the "periods of protection," but it is not always possible to consider such periods of protection independently from other provisions. The law is silent on the question of whether such other new rules (e.g., the possibility for a generic application in a Member State referring to a reference product's authorization in another Member State) will be applied to grandfathered products. One can argue that the new "periods of protection" cannot be dissociated from their rules of application and that such other changes made by the new legislation should not apply.

Early Implementation by the ECJ

Although the deadline for transposing the new legislation is Fall 2005, and the effective date of certain provisions is further deferred, European courts already have begun to follow the new provisions. Advocate General Jacobs, using the test of "essential similarity" developed by the case law on the basis of the former legislation (Directive 65/65/EC), held that the application for a salt of an active substance could refer to the data of such active substance, provided that they were not significantly different in terms of safety and efficacy.[32] In doing so, Jacobs interpreted the former legislation in light of the new EU legislation and its definition of generics.

The new EU legislation on generic product applications will wreak havoc on certain product defense strategies of pharmaceutical and biotechnology companies. Strategies based on line extensions will no longer be effective, and R&D for all but major innovations is likely to suffer. Europe is moving to a single, 10-year period of marketing protection for products included within the scope of the newly-created "global authorization," thus reducing incentives for the development of products that cannot meet profitability standards during this period and forcing companies to obtain—by setting the highest possible prices—the greatest return while still possible. One can only expect that the impact on European R&D will be felt quickly as companies redeploy their resources.

[1] Directive 2004/27/EC (Mar. 31, 2004), amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use; Regulation (EC) 726/2004 (Mar. 31, 2004), Laying Down Community Procedures for Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency. A European Regulation is directly enforceable in EU Member States, while a European Directive provides for a mandatory framework for legislation in each EU Member State. Thus, Member States are obliged to adopt national legislation to implement Directives.

[2] The data exclusivity period is the period after which a marketing authorization for a generic pharmaceutical product can be made without filing data supporting the safety and efficacy of the product. Efforts required to obtain such data comprise a principal cost/risk area for manufacturers of the reference or princeps product; generic manufacturers' ability to file marketing applications without bearing such cost and risk drives their competitiveness with research-based companies.

[3] *See* Directive 2001/83/EC, art. 10.2(b), as amended.

[4] In particular, C-368/96, Generics (ECJ Dec. 3, 1998).

[5] *See* art. 10.2(b), *supra* note 3.

[6] C-106/01, Novartis Pharmaceuticals (ECJ Apr. 29, 2004).

[7] *See* art. 10.2(b), *supra* note 3.

[8] *Novartis*, *supra* note 6.

[9] *See* art. 10.2(b), *supra* note 3.

[10] *See* Directive 2001/83/EC, art. 6.1, as amended.

[11] *Novartis*, *supra* note 6; C-36/03, Eli & Lilly & Co. (ECJ Dec. 9, 2004).

[12] *Generics*, *supra* note 4.

[13] Conseil d'état (Negma Nov. 26, 2001).

[14] A medicinal product that is essentially similar to a product which has been authorized for not less than 6 or 10 years and is marketed in the Member State for which the application is made may be authorized, under the abridged procedure provided for in Article 4.8(a)(iii) of Directive 65/65, as amended, for all therapeutic indications already authorized for that product.

Generics, *supra* note 4 (emphasis added).

[15] *See* Directive 2001/83/EC, art. 10.1, last paragraph, as amended.

[16] *See* Directive 2001/83/EC, art. 10.5, as amended. The text of the new legislation is not specific on this point, providing that "where an application is made for a new indication for a well established substances, a non-cumulative period of one year of data exclusivity shall be granted … ." Applying the protection period to all indications would raise practical difficulties because generic applications relying on data for the former indications might have been filed before the new indication is approved. We interpret "non-cumulative" to mean that the period can be granted only once. "Well established" is likely to refer to a product authorized for more than eight years; before the end of an eight-year period, a new indication may trigger the above-described one-year extension of market exclusivity, which is more advantageous because it relates to the product as a whole.

[17] *See* Directive 2001/83/EC, art.10.4, as amended.

[18] *See id.*

[19] Prior to enactment of the new legislation, there already were several guidance documents (e.g., Directive 2001/83/EC, Annex 1, as amended; CHMP Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Aspects; and CHMP Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical and Clinical Issues).

[20] T 15/04 O.J. (C 71/35) (Mar. 20, 2004).

[21] *See* Directive 2001/83/EC, art. 10.1, as amended.

[22] *See* Directive 2001/83/EC, art. 10.1, second paragraph, as amended.

[23] *See* Directive 2001/83/EC, art. 74(a), as amended.

[24] *See* art. 10.1, *supra* note 21.

[25] *E.g.*, Directive 2001/83/EC, former art. 10.1(a)(i).

[26] *See* Directive 2001/83/EC, art. 30.2, as amended.

[27] *See* Directive 2001/83/EC, art.10.6, as amended.

[28] *E.g.*, French Public Health Code, L. 5121-1, as amended.

[29] *See* Directive 2004/27/EC, art. 3; Regulation 726/2004/EC, art. 90.

[30] The text of Directive 2004/27/EC refers to the "date of transposition" of the Directive (which may differ among Member States), instead of referring to the deadline for transposition of the directive (i.e., Oct. 30, 2005).

[31] Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia.

[32] Case C-74/03, SmithKline Beecham plc v. Laegeddelstyrelsen (Sept. 16, 2004).