Global regulators face up to "biosimilar" complexity

Despite some legislation on the books, there still are plenty of issues related to "biosimilars" or "follow-on biologics" in both the EU and US to be debated in a variety of fora in coming months and years. Linda Horton, Jaime Tomhave Gallimore and Jacqueline Mailly of law firm Hogan and Hartson set the scene.

In the EU, "biosimilars" are products that cannot meet the criteria for "generics" because they are large-molecule proteins and one cannot be sure that they are sufficiently close to the originator's product. The term "biogenerics" is also used, but that is a misnomer because the products are not identical.

The EU has had a regulatory pathway for biosimilars since the publication of a June 2003 Commission Directive (2003/63/EC) amending the Community code on medicinal products, establishing a new Annex on the required contents of an application for marketing authorisation.

Article 4 of the revised Annex I, Part II, sets forth the specific marketing authorisation dossier requirements for "similar biological medicinal products." The new 2004 medicines legislation, also amending the Community code (Directive 2004/27/EC), continues and codifies this prior law.

Article 10.4 of the directive states in its entirety that, "Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products... the results of appropriate preclinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided."

Many, many details remain to be worked out through a variety of possible means, including guidance documents and litigation.

...guidelines and concept papers

Late last year the EMEA published a guideline describing general principles for approving biosimilars. The guideline was accompanied by four "concept papers" outlining areas in which more targeted guidance would be forthcoming for classes of human recombinant products containing erythropoietin, human growth hormone, granulocyte-colony stimulating factor, or insulin. Interested parties had until the end of January to comment on the concept papers and have until February 28th to comment on the guideline itself.

"Follow-on biologics" is the preferred term for biosimilars in the US, where many of the same issues as those in the EU are being presented.

The FDA admits that it has no statutory framework for follow-on biologics for the vast majority of therapeutic proteins subject to biologic licensing under the Public Health Service Act.

The US agency asserts, however, that it can build a framework for a few large-molecule products (human growth hormones, insulin etc) that because of historical quirks have been regulated under the "New Drug" approval mechanism of its principal law, the Federal Food, Drug and Cosmetic Act. Innovative companies vigorously contested this view, however, and in September 2004 the FDA held public hearings on the subject but conceded that there were too many scientific, legal and policy issues to move forward on the issue.

In contrast to the murky US situation, the EU legislation provides a legal framework for biosimilars in which it is understood that such products will need less supporting data than had been required for the original reference product.

We would not call this a "clear legal framework", however. The issue will be how much data will be required for the follow-on applicants or, to put it another way, what data requirements might the biosimilar applicants be allowed to skip.

A partial answer was provided in Directive 2003/63/EC, which laid out the requirements for marketing authorisation applications and was followed by two guidance documents published in December 2003 by the key EMEA committee responsible for product assessments, now called the Committee on Human Medicinal Products. European regulators are very aware of the potential for immunogenicity and other safety problems with biologics, so immunology data are always to be required.

There has been enormous industry interest in seeing the European authorities issue additional guidance documents on biosimilars, such as product-class guidelines. However, what was published late last year did little to advance understanding.

In both the EU and the US, there is more transparency for stakeholders where a public process and guidance documents are used to announce what testing and data are required of applicants. In both jurisdictions, testing and data requirements are often worked out behind closed doors between an applicant and the reviewers, and the innovators whose data might be cited by biosimilar applicants are not in the room.

...innovators' data

One issue in the EU, as in the US, is the extent to which the regulators can rely on innovators' data in their agency files to cut data requirements for generics. For chemical drugs that can be copied exactly, the product is not so process-dependent, and copies can be produced through reverse engineering, good chemistry, tight specifications, and good manufacturing practices (GMP) for day-to-day consistency in actual production.

For biological drugs, there are always differences among different manufacturers' products, and "the process is the product, and the product is the process".

Consequently, the Biotechnology Industry Organisation (BIO), Genentech and Pfizer all submitted petitions to the FDA opposing the reduction of data requirements for follow-on competitors and claiming that, in addition to putting patients at risk, the FDA would inevitably have to rely on an innovator's trade-secret process information in approving a biosimilar competitor's product. This presents a US constitutional issue known as "taking" without due process or just compensation.

The petitioners also argue that the FDA does not have in its files all the information that one needs to produce a safe,

effective and high-quality biological medicine. Only the innovator really has mastery over this essential knowledge, and most of this information is trade secret and found only in the innovators' premises.

An interesting EU and US issue is the application for marketing authorisation of a biosimilar human growth hormone product, Omnitrop. Sandoz, the generics subsidiary of Novartis, is challenging in the European Court of First Instance the European Commission's refusal to publish the marketing authorisation of Omnitrop, a follow-on human growth hormone product. The Commission does not support the legal reasoning underlying the favorable opinion of the EMEA supporting Omnitrop's approval, under the 2001 Community code on medicinal products (rather than the new 2004 law).

In essence, the 2001 Community code did not provide a legal basis for the authorisation of a biosimilar based on less than a full complement of data. The recent legislation has cleared a regulatory path for biosimilars so that the Commission could not, post-October 30th, 2005 hold up a biosimilar approval due to lack of authority. Adding interest is the fact that Sandoz is simultaneously seeking the approval of both the European authorities and the FDA for what is apparently an abridged (abbreviated) application for approval of Omnitrop.

In the US, Sandoz has reportedly filed a "505(b)(2) application," similar to what is called a "hybrid abridged application" under EU law. Genentech and Pfizer both make human growth hormone products that were subjected to a full complement of regulatory requirements and have petitioned the FDA claiming that only a complete dossier will suffice for approval of a product of this type. The FDA was close to approving Omnitrop but, as described above, the agency decided it had to hold up its decision due to uncertainties about the legal and scientific issues at stake.

New UK category for generics

The UK Department of Health is finally bringing to an end the discussions surrounding the reimbursement of generic medicines, some six years after the generic crisis of 1999, which saw price hikes, shortages and a number of official investigations.

The Department is to introduce a new category in the drug tariff to cover a range of generic medicines, *Scrip* understands. The category will be called "M" because the Department will base reimbursement prices on information it collects from manufacturers. The new category will take effect from April 1st. The savings to be achieved through the new category will help fund the new pharmacy contract.

The move comes a month after the Department announced that "standard" branded generic medicines should be reimbursed in the same way as generic medicines. A "standard" branded generic medicine is an off-patent product to which the manufacturer, which is not the originator company, has applied a brand name.

The government hopes to save £10 million from taking 125 of these products out of the Pharmaceutical Price Regulation Scheme (PPRS), which controls the prices of branded medicines to the National Health Service. The consultation for this ends on April 15th.

The government has already made significant savings on the PPRS itself. Last year it brought in a 7% price reduction on all branded medicines, taking effect from January 1st. But some companies have gone further. Besides introducing a 7% across-the-board price cut this year, GlaxoSmithKline is understood to be planning a further price cut for 25 of its products. Some sources have put this at 12.5%.