Biosimilars: what differences between the EU and the US?

Generic versions of off-patent biological products are set to become more prominent fixtures of the pharmaceutical landscape. Robert F Church, Michael N Druckman and Elisabethann Wright provide contrasting perspectives on the regulatory systems governing biosimilar products in two of the world's major pharmaceutical markets

The distinction between generic medicinal products and "similar biological medicinal products", commonly referred to in the EU as "biosimilars", was directly acknowledged in EU legislation by the 2004 modification of the Community Code on Medicinal Products.

In the US, while there is existing legislation governing the approval of generic drugs in place, this does not currently extend to biosimilars. In this market, these products are often called "follow-on biologics". US law differs from the EU regulatory system in that it does not provide an abbreviated approval pathway for biosimilars. However, in the US, the issue of biosimilars is both a matter of some debate and the subject of a number of proposals for legislation.

Below we examine aspects of the current EU biologics market following the introduction of EU legislation governing the authorisation of biosimilars. We also consider aspects of the proposed US legislation on biosimilars.

EU aspects of biosimilars

The concept of biosimilars was not part of the original Community Code on Medicinal Products adopted in 2001. It was introduced in its initial form by the European Commission's 2003 revision to the Community Code. A subsequent revision of the Community Code in 2004 introduced a specific reference to similar biological medicinal products, distinguishing these from generic products and providing framework guidance on the process for their marketing authorisation in the EU.

Basic assumptions

The rules applying to biosimilar products in the EU are based on a number of overarching principles and assumptions. The first is that biologics are not chemical products. Biological molecules produced in living organisms are more complex than chemical products and are highly influenced by changes in their manufacturing process. Consequently, it is virtually impossible to produce an identical copy of a biologic product. Unlike chemical products it is not, therefore, possible to create a generic form of a biologic product.

It is important to underline, as the Community Code itself acknowledges, that biosimilars are not "biogenerics". They are similar to, but not identical to, the reference product on which their manufacturers seek to rely for their marketing authorisation in the EU. As a result, there are concerns that differences between the biosimilar and its reference product may impact the safety and efficacy of the biosimilar. It has been concluded that these issues should be addressed case by case and based on specific scientific guidelines that are developed in reflection of the nature of the biosimilar product.

Legal framework

A biological medicinal product can be authorised as a biosimilar in accordance with the provisions of the Community Code if it meets the requirements set down in the Community Code and the guidelines that have been prepared by the EMEA. These are essentially that:

- the reference product on which the authorisation of the biosimilar relies must have been authorised within the EU (although there is no requirement that the reference product must continue to be authorised when a request for biosimilar approval is submitted);
- the eight-year data exclusivity period to which the reference product is entitled under the provisions of the Community Code must have expired; and
- the similarity between the safety and efficacy profiles of the biosimilar and the reference product must have been demonstrated.

It is this last requirement that essentially establishes the difference between an application for a marketing authorisation of a "generic" medicinal product and that for a biosimilar product. According to the Community Code, biosimilars fail to meet the criteria for "generics" due to differences relating to raw materials or differences in the manufacturing process. As a consequence, the results of appropriate preclinical and clinical trials relating to those conditions must be provided.

EU practice and experience

Biosimilars are authorised exclusively by the European Commission and in accordance with the centralised authorisation procedure. The Commission makes its decision on an authorisation application after receiving a scientific opinion from the CHMP, the EMEA's expert scientific committee. This opinion is not binding on the Commission. However, should the Commission choose not to follow it, a justification must be provided for this decision.

As a general rule, claims that a medicinal product is biosimilar to a reference product must be substantiated by a direct and extensive comparability exercise between the two products. The same reference product must be used for all parts of the biosimilar dossier (quality, safety and efficacy). Moreover, if the reference product has more than one indication, the efficacy and safety of the biosimilar must be justified or, if necessary, demonstrated for each of the claimed indications. In some cases the "therapeutic similarity" shown for one indication may be extrapolated to other indications. However, there is no general rule and the approval of the extrapolation is product-specific and based on available scientific and clinical experience.

The type and amount of preclinical and clinical data required to support authorisation of a biosimilar is not defined in the Community Code. The assessment of an application for authorisation is made on a case-by-case basis and includes determination of precisely the type and amount of data required to support such an application. The conditions and requirements are communicated through specific EMEA guidelines. Examples of the Guideline published by the EMEA include the guidance on Similar Biological Medicinal Products, Recombinant Human Erythropoietin, and Recombinant Human Growth Hormone.

The EMEA produces guidelines, both general and specific, on a variety of topics related to the authorisation of medicinal products in the EU. In general, these guidelines do not have legally binding effect on applicants for marketing authorisations. They are solely indicative and applicants can, if they feel it appropriate, depart from these on condition that appropriate justification is provided. However, in the case of biosimilars, compliance with the EMEA's guidelines is made compulsory by the provisions of Article 10 (4) and Annex I to the Community Code.

13 biosimilars, based on three active substances, have been approved since the governing provisions of the Community Code entered into force in October 2006. These include:

- the recombinant human growth hormones Omnitrope (somatropin) and Valtropin (somatropin);
- the erythropoietins Binocrit (epoetin alfa), Epoetin Alfa Hexal (epoetin alfa), Abseamed (epoetin alfa), Silapo (epoetin zeta) and Retacrit (epoetin zeta);
- the granulocyte-colony stimulating factors TevaGastrim (filgastrim), Ratiogastrim (filgastrim), Biograstim (filgastrim) and Filgastrim Hexal (filgastrim);
- Zarzio (filgrastim) and Filgastrim Hexal (filgrastim).

Two applications for marketing authorisation were rejected and three were withdrawn.

Outstanding issues

It can be argued that biosimilars have not had the impact on the EU market that biosimilar manufacturers had hoped and biologics manufacturers had feared. While the EU legal framework on biosimilars and its practical implementation appear to function efficiently and to deliver results, a number of outstanding challenges remain. Among these is the fact that economies of scale have not been as easily achieved as anticipated, as well as the continuing caution exhibited by physicians, particularly as regards the suitability of substituting a biosimilar for its reference product.

Two fundamental issues remain to be resolved: the questions of substitutability and of interchangeability, two terms which could be argued to represent the political and scientific sides of the same biological coin.

Determination as to the substitutability of a biosimilar for its reference biological medicinal product previously prescribed to a patient is, in the view of the national authorities, a financial question firmly within their prerogative.

However, the question as to whether two biologic products should share the same International Non-proprietary Name (INN), and can, thereby, be considered to be scientifically interchangeable is also a matter of debate. The INN identifies the compound within a family of compounds based on chemistry. It is used for prescribing, substitution of drugs, reporting of adverse effects, etc. Generics usually share the same INN as the reference product. Presently, biosimilars and the reference products also share the same INN.

Given that, as underlined above, biosimilars are not generics and have differences compared with the reference biological product, there is a continuing debate as to the suitability of their sharing an INN with their reference product and, thus, to be considered interchangeable with it.

Opinions are divided. The innovative industry advocates for a special INN system of nomenclature for biotechnology products reflecting the inherent differences between products. The biosimilars industry and the European Commission oppose the idea, while the World Health Organization (WHO) currently has no plans to address the matter.

The issues of substitutability and interchangability continue to overlap in the EU. On one hand, in some EU member states authorities consider determination of the suitability of substituting one biologic for another to be a matter of economics. Other EU member states acknowledge an absence of data concerning health risks that may be related to the substitution of biosimilars for their reference products. They have, consequently, adopted national legislation either excluding substitution of innovative biologics by biosimilars, as is the case in France and Italy, or placing restrictions on such substitution, as is the case in the UK.

The European Biopharmaceutical Enterprises (EBE) has requested that the European Commission and the EMEA issue guidance on the matter and clarify the concepts of "similarity", "interchangeability" and "substitution". The EBE considers this to be crucial for industry and the healthcare professionals. The Commission and the EMEA seem disinclined, however, to provide such guidance. They view the issue as beyond the scope of EU legislation, considering decisions concerning the question of the interchangeability of a biosimilar and its reference product to lie with a patient's treating physician.

Anticipated US biosimilar legislation

In order to fully understand the current debate over biosimilar legislation in the US, it is helpful to take a brief look back at the history of drug regulation in that market.

The Public Health Service Act

Biological products have been regulated in the US for more than 100 years. At the turn of the last century, after more than 20 children died in two separate incidents involving contaminated vaccines, the US Congress passed the Biologics Control Act of 1902. This was the first major pharmaceutical legislation in the US. This law was enacted to ensure the purity and safety of serums, vaccines and similar products. Under the Biologics Control Act, biologics approvals encompassed not only the product itself, but also the facility where the product was manufactured. This was in recognition of the particularly significant impact that the manufacturing process can have on biologics' safety, purity and potency. The Biologics Control Act was recodified in 1944 as section 351 of the Public Health Service Act (PHSA), which continues to govern biologics licensing to this day.

The Federal Food, Drug, and Cosmetic Act

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (FDCA). Under this law, pharmaceutical companies had to prove that all new drugs were safe before marketing. The FDCA also required that companies submit NDAs for unapproved new drugs. Under the 1938 Act, no "new drug" could lawfully be introduced into interstate commerce unless, and until, an NDA for that product had been filed with the FDA and become effective. If the FDA did not refuse approval of the NDA within 60 days, it was automatically deemed effective. Importantly, the NDA provisions of the 1938 Act only applied to small-molecule drugs. Those approval provisions did not apply to vaccines and other biological products, which continued to be licensed under the Biologics Control Act.

The Drug Price Competition and Patent Term Restoration Act

In September 1984, the new drug provisions of the FDCA were amended by the Drug Price Competition and Patent Term Restoration Act of 1984, (the "Waxman-Hatch Amendments" or "Waxman-Hatch"). It is commonly recognised that Waxman-Hatch represented a compromise by which Congress sought to balance the consumers' need for lower priced drug products with the innovator industry's need to receive a sufficient return on its investment to develop new products and improve existing products.

Under Waxman-Hatch, the FDA is authorised to approve generic products, without requiring original safety and effectiveness data, if the generic is shown under an abbreviated new drug application (ANDA) to be "the same as" the pioneer. Generally, a proposed generic drug must be the same as the pioneer reference drug with respect to:

- active ingredient(s);
- dosage form;
- route of administration;
- strength;
- bioavailability (ie, it must be bioequivalent); and
- labelling.

Patent certifications Under Waxman-Hatch

In addition to showing "sameness," the sponsor of an ANDA must submit one of the following four certifications with regard to each patent listed in the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the "Orange Book") for the reference listed drug:

I. that no patents have been submitted;
II. that the patent has expired;
III. that the patent will expire on a specified date; or
IV. that the patent is invalid or will not be infringed by the manufacture, use or sale of the product for which the ANDA is submitted.

If a certification is made under paragraph I or II, the FDA is authorised to approve the ANDA application whenever all of the other requirements for approval have been met. If the sponsor makes a paragraph III certification, the FDA will make approval of the ANDA effective on the date the patent expires. Paragraph IV certifications, by contrast, trigger a number of additional statutory requirements that provide a framework for the resolution of any patent disputes between the innovator and the generic applicant.

Waxman-Hatch exclusivity

Waxman-Hatch also created several exclusivity periods for which innovative and generic drugs may be eligible. Market or data exclusivity is a statutory mechanism under the FDCA that delays the approval or bars the acceptance of certain types of applications for set periods of time.

Perhaps most significantly, after a product is approved under an NDA, it may be eligible for new chemical entity (NCE) exclusivity. Under the FDCA, a drug that has not been previously approved (including any ester or salt of the active ingredient) may receive five years of exclusivity. The effect of this exclusivity period is that no ANDA that contains the same active moiety as the approved drug and that includes a paragraph I, II or III certification may be submitted with FDA until the expiration of five years after the date that the innovator NDA was approved.

ANDAs that include a paragraph IV certification may be filed four years after the NDA approval. However, if the NDA sponsor initiates patent infringement litigation within 45 days of receiving notice of the paragraph IV certification from the generic company, the FDA may not approve the ANDA for 30 months from the notification date (a provision known as the "30-month stay").

However, if the innovator initiates infringement litigation before the end of its five-year exclusivity period, the FDA may not approve the ANDA sooner than seven and a half years from the date the NDA was approved (five years of NCE exclusivity plus the additional 30 months). The FDA may approve an ANDA application earlier, however, if before expiration of the 30-month stay, the

infringement litigation ends with a determination that the patent is invalid or not infringed.

In addition to five-year NCE exclusivity, Waxman-Hatch also created three-year new use exclusivity. Among other things, this provision of the FDCA comes into play when a sponsor submits a supplement to an approved NDA proposing a change in the conditions of use of an approved drug. In these cases, when certain statutory criteria are met, the product may receive three years of marketing exclusivity if the application contains data from one or more studies that the FDA considers essential to approval.

Like other drug approval provisions in the FDCA, Waxman-Hatch is not applicable to the licensing process for biological products under the Public Health Service Act. Nevertheless, precedent and experience under Waxman-Hatch undoubtedly will inform the legislative debate over an abbreviated approval pathway for biologics, as well as the manner in which the FDA and the courts will interpret the language in any legislation that Congress enacts.

Recent efforts to create an abbreviated approval pathway for follow-on biologics

With its continued focus on the cost of healthcare, the US Congress has begun working to create an abbreviated approval pathway for follow-on biologics. As an example, in March 2009, Representative Henry Waxman (one of the authors of the Waxman-Hatch amendments to the FDCA) introduced a bill into Congress entitled the "Promoting Innovation and Access to Life-Saving Medicine Act". Mr Waxman's bill is not the only piece of draft legislation that merits attention, but given his keen interest in the subject and his position as chair of the Energy & Commerce Committee, it will be an important reference point for all future discussions on biosimilars.

Mr Waxman's bill is complex and a full assessment of it is beyond the scope of this article. However, the following discusses specific noteworthy aspects of the legislation.

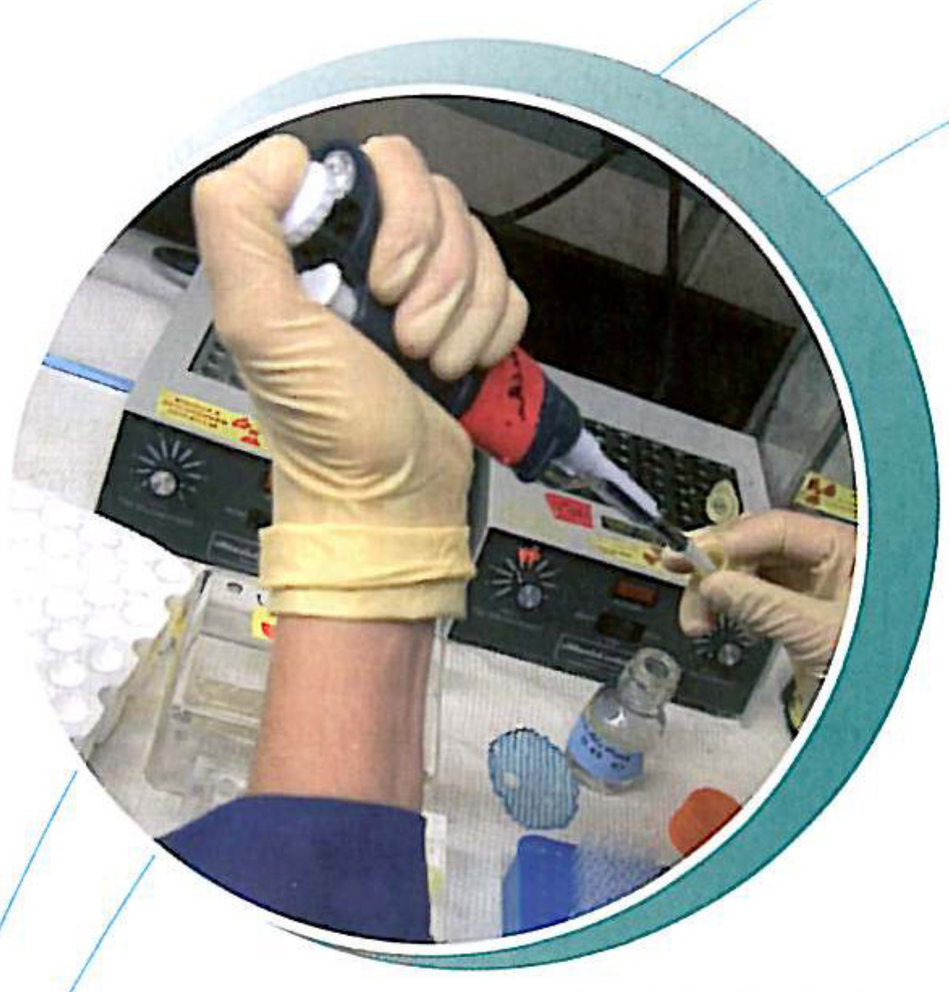
Approval of biosimilars

Biosimilarity or interchangeability would be demonstrated by (1) chemical, physical and biological assays and other non-clinical laboratory studies, and (2) "necessary" clinical studies sufficient to confirm safety, purity and potency. The FDA would determine what clinical studies, if any, are necessary, and the bill warns that any studies must be designed to avoid duplicative and unethical clinical testing. These provisions suggest that product- or process-specific assays may assume a greater role in an abbreviated approval pathway for biologics.

The FDA may give a biosimilar the same official or non-proprietary name as the reference product, even if the two products are not found to be interchangeable. This may raise substitution issues under state pharmacy laws, given how prescriptions are written.

Marketing exclusivities

A Biologics License Application (BLA) would be given five years of exclusivity if the product contains no "major substance" that has



been approved in any previous BLA or that is highly similar to a major substance approved in a previous BLA. The circumstances under which five-year exclusivity would be awarded are not clear, given that "major substance" is not defined in the Waxman bill. Also, because the exclusivity would bar approval of an Abbreviated Biologics License Application (ABLA), but not its submission or its review by the FDA, the benefit to the innovator would be less than what is available under the Waxman-Hatch NCE exclusivity.

Three-year exclusivity would be available for a biologic that contains a major substance that was in a biologic previously-approved via a BLA, if new clinical investigations are required. However, the exclusivity would be rewarded only if the product represents a "significant therapeutic advance," such as a "significant" new indication or subpopulation, other than a paediatric indication. An applicant could not receive three-year exclusivity for such innovations to its own product, unless they resulted in a product requiring submission of a new BLA (as opposed to a BLA supplement). Thus, the issue of whether a new BLA is required or permitted for a given change or improvement may take on even greater significance.

An applicant would be able to extend its three- or five-year exclusivity by six months by obtaining approval of a BLA supplement that requires new clinical investigations and that incorporates a significant therapeutic advance. Only one six-month extension would be allowed for any product, and the supplement would have to be approved before the final year of the exclusivity period. Additionally, if the product has annual US sales greater than w$1 billion, the extension would be reduced to three months. Taken together, these provisions indicate that it will be difficult for an applicant to obtain significant benefits from many product innovations.

Despite the fact that there appears to be general support in Congress for biosimilar legislation, there is still considerable uncertainty and disagreement regarding a number of key issues. Chief among these is the number of years of "new major substance" market exclusivity that would be available to innovative biologics. While the Waxman bill proposed five years of exclusivity, others in Congress have proposed that the exclusivity period should be as long as 12 years.

Another central issue in the debate is the extent to which exclusivity is necessary as an incentive for innovators to continue to improve their already-approved drugs, and how that exclusivity should be framed. The single six-month extension for improvements in the Waxman bill, as well as the requirement that a supplement containing the improvement be approved before the final year of exclusivity, appear to be designed to address claims that the current system encourages innovators to wait until the end of their exclusivity to seek approval for product improvements, and to employ product improvements in a manner that unfairly extends their market protection.

A third significant issue is whether Congress should impose minimum requirements or prescribe minimum standards for the amount of clinical data that a follow-on sponsor must submit to obtain approval.

Nevertheless, despite the significant issues that still remain unsettled, most FDA-watchers agree that Congress is likely to pass a follow-on biologics bill either this year or next.

Conclusion

Some aspects of the obligations to be fulfilled in an application for authorisation of a biosimilar in the EU are reflected in the proposed Waxman bill. Biosimilarity between the two products would be demonstrated in accordance with requirements similar to those laid down in EU law. Moreover, the biosimilar may, as in the EU, have the same INN as its reference biologic.

However, giving biosimilar applicants a regulatory pathway to demonstrate interchangability would reflect both a fundamental difference between EU and US laws concerning authorisation of biosimilars and a fundamental difference between the roles of the European Commission and the FDA in the authorisation of medicinal products.

The difference between the EU and US approaches to the issue of market exclusivity that is found in existing legislation governing the marketing of medicinal products (small-molecule drugs in the US) is also reflected in the proposed US legislation on biosimilars. Currently, while an innovative product placed on the market in the EU, whether it is a chemical product or a biologic, is entitled to market exclusivity of 10 years, the equivalent non-biologic drug product would be entitled to only five years' market exclusivity in the US (recognising that the US exclusivity period may be extended in the event that the innovator's patents are litigated). If the Waxman bill is adopted in its present form, it would adopt a similar five-year marketing exclusivity period for biosimilars.

At present, it seems likely that biosimilars will become the subject of specific legislation in the US. Whether this will lead to any type of a harmonisation of approach between the US and the EU will, however, remain to be seen.

The authors are partners at the law firm Hogan & Hartson. Robert F Church is based in Los Angeles, Michael N Druckman in Washington, DC, and Elisabethann Wright in Brussels.