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A model approach

EU regulation on biosimilars may be a useful model for countries with no system in place, but the industry and other stakeholders are pushing for clarification on some matters

The distinction between generic medicinal products and 'similar biological medicinal products' – commonly referred to in the EU as biosimilars – was acknowledged in EU legislation by the 2004 modification of the Community Code on Medicinal (Directive 2001/83/EC). The European Commission (EC) seems to accept that the concept of the 'generic biologic' did not exist. It is possible to create a generic of a small molecule medicinal product but not possible, given the nature of biologic products, to create a generic of a biologic. A product that relies on the innovator of the biologic's data, although it may be similar to that product, will include basic differences.

DEFINING BIOSIMILARS

The concept of 'similar biological medicinal products' was not part of the original Community Code on Medicinal Products adopted in 2001. It was introduced in its initial form by the EC's 2003 revision to the Community Code Directive (2003/63/EC). A subsequent revision of the Community Code, in 2004, introduced a specific reference to "similar biological medicinal products" distinguishing them from generics. It also provided framework guidance on the process for their marketing authorisation in the EU (2004/27/EC). Although fewer biosimilars have been approved than were, perhaps initially anticipated, the system appears to function effectively. The European Medicines Agency (EMEA) has developed guidance documents for applicants and 13 authorisations of biosimilars have been granted. For countries that do not yet have a system to regulate biosimilars, the EU regulatory model may prove useful.

BASIC ASSUMPTIONS

The rules applying to biosimilar products in the EU are based on a number of overarching principles and assumptions. The first principle 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 the manufacturing process. Consequently, it is virtually impossible to produce an identical copy of a biologic product.

It is important to underline, as the Community Code itself acknowledges, that biosimilars are not 'biogenerics'. They are similar, but not identical, to the reference product on which their manufacturers seek to rely for their marketing authorisation in the EU. As Article 10(4) of the Code states:

"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, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided."

There is a concern that differences between the biosimilar and its reference product may impact on safety and efficacy. This should be addressed case by case, based on specific scientific guidelines developed in reflection of the nature of the product.

LEGAL FRAMEWORK

A biologic medicinal product can be authorised as a biosimilar if it meets the requirements set down in the Code and the EMEA guidelines – 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
- 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 marketing authorisation of a generic and a biosimilar. According to the Code, biosimilars fail to meet the criteria for generics because of differences relating to raw materials or differences in the manufacturing process. As a consequence, the results of appropriate pre-clinical and clinical trials relating to those conditions must be provided.

IN PRACTICE

Biosimilars are authorised exclusively by the EC and in accordance with the centralised authorisation procedure (Regulation EC 726/2004). The Commission makes its decision on an authorisation application after receiving a scientific opinion from the EMEA's Committee for Medicinal Products for Human Use (CHMP). This opinion is not binding but justification must be provided should the EC decide not to follow it.

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). If the reference product has more than one indication, the efficacy and the 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 pre-clinical 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 guidance on similar biological medicinal products, recombinant human erythropoietin, and recombinant human growth hormone.

As part of its role in the authorisation of medicinal products in the EU the EMEA produces guidelines, both general and specific, on a variety of topics related to the authorisation of medicinal products. In general, these guidelines are solely indicative and not legally binding on

applicants for marketing authorisation. If applicants decide to diverge from the guidelines it must be on the basis of appropriate justification.

In the case of biosimilars, however, compliance with the EMEA's guidelines is made compulsory by the provisions of Article 10 (4) and Annex I to the Community Code. As a result, applications for marketing authorisation of biosimilar products must demonstrate not only compliance with the provisions of the Code and provision of all data provided for in annex to the Code, but also respect for all requirements laid down in the EMEA guidelines relevant to particular biosimilars.

So far 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:

- recombinant human growth hormone – Omnitrope (Somatropin) and Valtropin (Somatropin)
- erythropoietin – Binocrit (epoetin alfa), Epoetin Alfa Hexal (epoetin alfa), Abseamed (epoetin alfa), Silapo (epoetin zeta) and Retacrit (epoetin zeta)
- granulocyte-colony stimulating factor – TevaGrastrim (filgrastim), Ratiograstim (filgrastim), Biograstim (filgrastim), Filgrastim Hexal (filgrastim); Zarzio (filgrastim) and Filgrastim Hexal (filgrastim).

Two marketing authorisation applications were rejected and three were withdrawn.

OUTSTANDING ISSUES

Biosimilars may not have had the impact on the EU market that manufacturers had hoped and biologics manufacturers had feared. The EU legal framework on biosimilars and its practical implementation appears to function efficiently and to deliver results. Among challenges that remain is the fact that economies of scale have not been easily achieved. In addition, there is continuing caution among doctors about the suitability of substituting a product with its biosimilar.

This caution reflects two fundamental issues yet to be resolved. These are the questions of substitutability and of interchangeability between biologics and related biosimilars; two terms which may represent the political and scientific sides of the same biological coin.

For the national authorities of EU member states determination as to whether a biosimilar may be substituted for its reference biologic medicinal product, which has been previously prescribed to a patient, is a financial question. In the absence of any legislative provisions at EU level, the individual prerogative of each of the 27 member states applies when considering the pricing and reimbursement of medicinal products and whether substitutability between products should be permitted or even actively encouraged.

Other 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 in the UK.

The present situation is unfortunate. There are some economic benefits to substituting a biosimilar for its reference biologic product. However, there is no EU process to determine the suitability and safety of such substitution.

Another issue is whether two biologic products should share the same international non-proprietary name (INN) and be considered to be scientifically interchangeable. The INN identifies the compound within a family of compounds based on chemistry and is used in prescribing or substituting drugs and in reporting of adverse effects. Generics usually share the same INN as the reference product. At present biosimilars and their reference biologic also share the same INN. Given that biosimilars are not generics and have differences compared to the reference biological product, there is a continuing debate as to whether the INN should be shared and considered interchangeable.

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 EC oppose the idea and the WHO, which is responsible for establishing INNs, has no plans to address the matter.

The European Biopharmaceutical Enterprises (EBE) has requested that the EC and the EMEA issue guidance and clarify the concepts of 'similarity, 'interchangeability' and 'substitution'. The EBE considers this to be crucial for industry and 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 governing their roles and consider that decisions concerning the question of the interchangeability of a biosimilar and its reference product should lie with the doctor.

The EU approach to biosimilars is a good model and pressure from stakeholders and the industry should lead to some clarifications of the regulations. In the US, the issue of biosimilars is already a matter of intense debates and subject to a number of proposals for legislation which have already demonstrated similarities with the EU approach.

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