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Follow-On Biologics

EU TAKES LEAD IN APPROVAL STANDARDS

by Peter Bogaert

In early 2006, the European Commission granted the first approvals for follow-on biologics in the European Union (EU), after many years of regulatory and legal discussions on the proper procedure and standards. The approvals cover two somatropin products—Omnitrope, made by Sandoz, and Valtropin, made by BioPartners. A third product, Alpheon, an alfa-interferon product made by BioPartners, received a negative scientific opinion in June 2006.

This article provides a general overview of the legal and regulatory framework for approving follow-on biological medicines in the EU. It also briefly discusses the early experience with biotechnology protein products and how the framework will apply to other biologics.

The pharmaceutical industry is one of the first sectors for which the EU—then the EEC— adopted harmonizing legislation. In response to the thalidomide scandal, the EEC adopted Directive 65/65, which holds key principles governing premarket approval, and was later supplemented with various other directives. The system developed into a comprehensive regulatory system, and today almost all the important regulatory decisions are taken at the EU level. The main rules are consolidated in Directive 2001/83, which was further amended in 2003 and 2004. Both amendments contained important rules on follow-on biological products.

Special Status of Biologics

Already early on, the rules recognized the special nature of biologics. In 1991, the rules on the content of an application for premarket approval stressed the importance of the manufacturing process and the need for specific procedures to define the active substance.[1]

In 2003, the rules were revised again, to implement the Common Technical Document. The revision also included more detailed rules on biologics, defined as follows:

> *A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control.*[2]

The new text also clarified that an Active Substance Master File can only be used with a closed part for a well-defined active substance, because a company holding the premarket approval must assume full regulatory responsibility for the product. Consequently, an Active Substance Master File cannot be used for a biological medicine.[3]

Over the last seven years, a detailed regime for follow-on biologics was put

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in place. From a legal point of view, the rules were adopted in reverse order. First, basic regulatory principles were expressed in the Committee for Medical Products for Human Use (CHMP) guidelines. In 2003, the first legal provisions were inserted in Annex I to Directive 2001/83 (which has a lower legal status than the main body of the Directive). Finally, in 2004, a formal legal basis for approving "similar biologics" was included in the main text of the directive as part of the broad overhaul of the pharmaceutical legislation. These rules call for the submission of non-clinical and clinical data.

These basic provisions are further implemented in CHMP guidelines. An umbrella Guideline of October 2005 recalls that "[d]ue to the complexity of biological/biotechnology-derived products, the generic approach is scientifically not appropriate" and that "by definition, similar biological medicinal products are not generic medicinal products."

Two more recent guidelines cover quality issues and non-clinical and clinical issues relating to biotechnology-derived proteins. They state that comparative clinical trials are ordinarily required to demonstrate clinical comparability, but that in certain cases comparative pharmacokinetic/pharmacodynamic studies may suffice. In addition, pre-authorization studies will normally not allow identifying all potential differences between the reference product and the follow-on version and a reliable pharmacovigilance and risk management program will be needed. Specific guidance on immunogenicity aspects is in preparation.

Product class-specific guidance supplements the general guidelines. So far, specific guidance is available on recombinant erythropoietins, insulin, somatropin, and rG-CSF. A guideline on recombinant alfa-interferon is in preparation. The selection of the specific product classes reflects interest by potential applicants and the guidelines often also take into account experience gained by the EMEA in the context of the scientific advice procedure.[4]

Somatropin Biosimilars Approved

The European Commission granted two approvals in early 2006 for follow-on somatropin products. The Omnitrope approval, obtained by Sandoz, is based in part on Pfizer's Genotropin and the reference product for BioPartner's Valtropin is Lilly's Humatrope. Both biosimilars were approved under the centralized procedure, which is mandatory for all biotechnology products.

The European Public Assessment Report (EPAR) summarizes what data were supplied by the applicants. The Omnitrope EPAR shows that Sandoz conducted one pivotal efficacy study, consisting of three comparative sub-studies, and one pivotal safety study. The EPAR also contains a summary of the risk management plan, which addresses possible diabetogenicity, immunogenicity, malignancies and special concerns for PWS patients.

Similarly, the EPAR for Valtropin shows that BioPartners conducted two comparative studies, including a 12-month double blind two-arm parallel controlled Phase III study. The risk management plan is also summarized and covers possible diabetogenicity, immunogenicity and risk of hypothyroidism.

On June 28, 2006, on the other hand, the CHMP adopted a negative opinion on an application by BioPartners for Alpheon, a follow-on interferon alfa-2a product for the treatment of hepatitis C. The application was based in part on Roferon-A by Roche. The Q&A published by the EMEA states that there were major concerns regarding comparability, because of differences identified in the products, including impurities. In addition, more patients experienced a return of hepatitis after treatment with Alpheon than with Roferon-A. There were also stability and process validation concerns and the CHMP considered that the immunogenicity study was not adequately validated.

The EU has established a clear pathway for approving follow-on biologics, applying the critical assessment that is needed to safeguard patient safety. The process also shows the value of pooling available expertise in the EU to ensure a high quality review and regulatory consistency.

Before Omnitrope was authorized under the new Article 10.4, Sandoz had applied for a marketing authorization under pre-existing procedures and received a favorable scientific opinion from the CHMP in 2003. The opinion was based on scientific literature on existing somatropin medicines and extra clinical data. This "mixed bibliographical application" was filed before new Article 10.4 was enacted and was chosen because the CHMP had made it clear that the standard generic rules could not be followed.

The Commission, however, refused to grant the authorization because the revised Annex to Directive 2001/83 was just adopted. It held that a follow-on biological could only be approved through that route. Sandoz sought annulment of the refusal and the case is

still pending before the European Court of First Instance, but it is doubtful that the ultimate ruling will have practical impact as Article 10.4 now takes precedence as *lex specialis.*

Broad Concept of Biologics

The similar biologics rules do not only apply to biotechnology products. The concept of biological products is, as mentioned, much broader. For certain classes, the similar biological route seems to be excluded or only possible in rare cases. The umbrella CHMP Guideline of October 2005 holds that "currently, it seems unlikely that [vaccines] may be thoroughly characterised at a molecular level" and the same applies to allergens. The same guideline provides that in view of the complex and variable physico-chemical, biological and functional characteristics of immunoglobulins, plasma-derived antithrombin products, and Factor VIII and IX products, a full application dossier will be needed.

The Biological Working Party of the CHMP also confirmed that low molecular weight heparins and pancreatins are biological products and that follow-on versions cannot be approved as generic products but must follow the biosimilar route. This was confirmed by the Coordination Group (CMDh), which groups national agencies in the EU:

> The CMD(h) has agreed the view of the BWP that low molecular mass heparins and pancreatins should be considered biological medicinal products. Therefore, applications for marketing authorisation as generic medicinal products will not be accepted and should be submitted in accordance with Article 10 (4) of Directive 2001/83/EC, as amended —'Similar biological application', with additional physico-chemical characterisation and clinical data.[5]

Low molecular weight heparins are much less characterized than unfractionated heparins because they are derived from the latter by fractionation or depolymerization via various methods resulting in products that are dissimilar in physical, chemical and biological properties. Even if similar depolymerization processes are used, the properties of heparins vary as, for example, the end sites of the polysaccharide chain can be differently charged or have different oxidized forms, and the composition of the molecular weight of the products can vary. This significantly increases the complexity of the products and the way in which the manufacturing method defines the substance. That follow-on versions cannot be approved as generics is illustrated by the fact that various applications for enoxaparin products that were filed in 2004 and 2005 in Finland were subsequently withdrawn, most likely following queries on the regulatory basis for the filings. A concept paper on biosimilars containing low molecular weight heparins is now being released for public consultation.

Conclusion

The EU has taken the lead in establishing a detailed and well-structured basis for approving follow-on biological medicine. The rules aim at avoiding unnecessary testing and making follow-on products available, while maintaining a high level of patient safety. Their success will depend on a strict and consistent application of the underlying principles, taking each time the specific characteristics of the product class and the individual products in mind. The EMEA and the CHMP are well positioned under the centralized procedure to perform that role, but the same approach will have to be adopted by national agencies—where relevant in the context of decentralized or mutual recognition procedures—for products that are not necessarily subject to the centralized procedure, such as low molecular weight heparins and pancreatins. If need be, dossiers that raise concern could be referred to the CHMP for a European Commission determination.

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1 Similarly, the guidelines on Good Manufacturing Practices (GMP) have for many years included specific principles for biologicals. The 1992 version of the guide on GMP for Biological Medicinal Products for Human Use states: "The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture." The guide applies amongst others to "vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA)."

2 Revised Annex I to Directive 2001/83, also containing basic rules on applications for follow-on biological products (see next section).

3 This was explicitly confirmed by the CHMP, the scientific and regulatory advice unit within the EMEA, responsible for human medicines: "Marketing Authorisation Holders (MAHs) and applicants are advised that the concept of Active Substance Master files, as laid down in Directive 2001/83/EC, as amended, cannot be applied in the context of biological medicinal products. The characterisation and determination of biological active substances' quality requires not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control." (Monthly Report of the Oct. 2004 CHMP Meeting). The same report confirms that master files for vaccines and plasma products cannot have closed parts.

4 The guidelines and concept papers are available on the EMEA website (www.emea.eu.int).

5 Statement contained in the CHMP and CMDh reports of their June 2006 meetings.

6 CHMP/BMWP/496286/2006.