

Biosimilars: A Portrait

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Known under various labels — *generic biologicals* or *follow-on biologicals*, for instance — biosimilars represent an extraordinary opportunity for generics companies. Roughly \$10 billion worth of brand-name biopharmaceuticals, many of which cost \$1000/month or more per patient, will lose their patent protection within the next three years. Because of the blockbuster earnings of many biopharmaceuticals during their patent lifetimes, generics companies will inevitably try to produce and market lower-priced biosimilar versions. But important differences between these and traditional chemical-based generics will complicate the entry of biosimilars to the market.

A heated debate is under way concerning the requirements for marketing authorization of biosimilars. It is not simply a case of proving chemical identity and bioequivalence to a reference drug, as with traditional generics. To prove similarity of biotech drugs, it is highly likely that some clinical data will have to be provided. How much data will depend on the individual products, but clinical testing could prove to be a costly proposition for companies hoping to offer cheaper alternatives to brand-name biopharmaceuticals.

THE MAJOR DIFFERENCES

Chemical entities have well-defined, easy-to-characterize molecular

structures with impurity profiles that depend on their synthesis methods. In vivo safety and efficacy are unrelated to product origin. Produced by living cells, biologics are 100- to 1000-fold larger than chemically synthesized products, with sophisticated three-dimensional structures, and can be mixtures of protein isoforms (rather than pure homogeneous entities) with limited stability. Even minor modifications of a biologics manufacturing process can cause variations in important properties of a product. And manufacturing a generic version implies a completely new process because the generics manufacturer has no insight into the originator process. This could be based on a different host/vector system with different process steps, facilities, and equipment. Changes in bioavailability, pharmacokinetics, bioactivity, and immunogenicity are the main risks associated with the manufacturing of biosimilars.

Because of inherent variability in biological processes, these products in many cases are not single, homogeneous molecular populations, but rather complex mixtures of various protein isoforms. Such mixtures may include molecular variants that do not have properties comparable to those of the desired product regarding activity, efficacy, and safety (product-related impurities, e.g., precursors and degradation products). Some



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molecular variants may be active, but have no deleterious effect on safety and efficacy. It is not always known precisely which component(s) constitutes the major active ingredient, and sometimes it may be the sum rather than one part that is effective.

QUALITY, SAFETY, AND EFFICACY

Clearly the quality of a protein therapeutic depends highly on its manufacturing process, formulation, and storage conditions. Validated in-process controls and analytical methods, well-established reference standards, definitive drug substance and product release specifications, and definitive stability specifications are important issues that define safety and efficacy. So just as for conventional chemical products, the prerequisites

for marketing authorization of a biosimilar are proof of quality, safety, and efficacy.

Sometimes analytical methods can elucidate differences between one biopharmaceutical molecule and a copy of it, but such tests cannot provide information about how it will affect patients. Some differences might be irrelevant and harmless; others could provoke an immune reaction. Quite often we do not know enough at the development stage to predict the behavior of a biopharmaceutical molecule. So manufacturers of biosimilars will have to perform tests to prove that their copies are just as safe and efficacious as the original products. That is the only way to maintain patient safety.

EUROPE'S REGULATORY FRAMEWORK

US Food and Drug Administration (FDA) policies on comparability of biologics apply only to situations in which a single manufacturer is implementing a change. The European Union has passed two Directives — 2004/27/EC (amending Directive 2001/83/EC) and 2003/63/EC — that provide a legal basis for approval of biosimilar medicinal products. The crucial question: When can it be assumed that a biosimilar and originator product are the same? That is important because once a generic manufacturer can demonstrate that its product is the same as the original biopharmaceutical, with the same characteristics (essentially similar), that manufacturer can refer to the originator's data on product efficacy and safety (as laid down in Directive 2001/83). And that could save time and money that otherwise would have been needed for development.

A product is considered essentially similar when it has the same qualitative and quantitative composition in terms of active substance, when it has the same pharmaceutical form, and when it is bioequivalent. That means it behaves the same way in a patient's body: with the same absorption rate,

distribution, metabolism, and excretion. Because available diagnostic methods cannot predict the behavior of a biopharmaceutical molecule in a patient's body, additional tests are necessary. Directive 2004/27/EC says that some preclinical and/or clinical data will have to be provided where there are differences between biosimilars and originators such as raw materials used, manufacturing process characteristics, molecular characteristics, and therapeutic modes of action. The extent of data needed to prove efficacy and safety may vary, and the data required will be determined case by case.

CASE BY CASE

Some biopharmaceutical molecules are relatively simple and easy to identify and isolate. An example is insulin, a peptide hormone with a relatively simple molecular structure that is comparatively straightforward to identify and copy. Molecules such as interferon and erythropoietin, which are glycosylated and/or contain different isoforms, are more complex and rather difficult to identify.

It is the process that makes the product. Changes in a manufacturing process may lead to structural variations and different pharmacodynamic and pharmacokinetic properties of a product, which can alter safety and efficacy. Because we are unable to predict the result with current technology, it is important for patient safety that appropriate product characterization is carried out case by case.

COMPARABILITY IS KEY

These issues are addressed when assessing comparability between a biosimilar and an originator product: evaluation of the significance of manufacturing deviations, and the limits of analytical characterization including potency determination by bioassays and immunogenicity.

Significance of Manufacturing

Deviations: Biologics manufacturing process differences may apply to the expression system, fermentation or

culture process, purification process, drug substance (e.g., batch definition, pooling strategy), formulation and filling, and general parameters affecting all manufacturing steps (e.g., water quality, temperature, personnel). All such manufacturing changes can affect process-related impurities, culture/fermentation-derived impurities, purification-derived impurities, and product-related impurities. Thus, any deviation from an originator's process may have a minor or major impact on product quality, safety, and/or efficacy.

Comparing results of in-process controls of intermediates can give a first hint of such product changes. However, such comparisons would be possible only for originators because follow-on manufacturers will not have access to the originator's process intermediates. Deviant conformations, altered posttranslational modifications, and different selections of subtype isoforms are potential consequences of process deviations that could result in altered microheterogeneity. The glycosylation pattern for the same protein may differ between tissues. Substitution of a single amino acid can alter biological activity. Patterns of absorption may be influenced by formulation. Finally, the batch-to-batch variability inevitable with biologic products contributes to comparability difficulties.

Limits of Analytical

Characterization: Biotechnological products often have an ambiguous structure–activity relationship. Available physicochemical methods may not fully characterize a product or discriminate all variants and impurities, and in vitro bioassays or in vivo potency assays in animals are sometimes too imprecise to ensure that a generic has a comparable activity level to the original. Additionally, assurance needs to be provided that assays themselves are comparable.

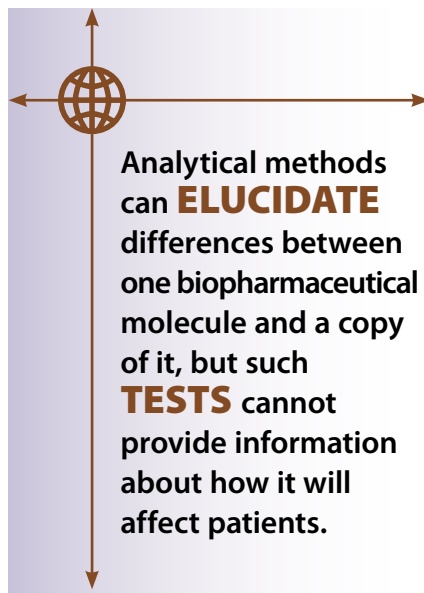
Complex products can have multiple activities (e.g., interferons), and not all activities may be

measurable in robust potency assays. Physicochemical and biological in vitro methods thus are mainly used to demonstrate that no evident difference is present, but they cannot exclude the impact of a manufacturing change on safety and efficacy because subtle modifications in molecular structure/function might go undetected. The utility of pharmacokinetic assays in animals is limited by species specificity (because of receptor mediated clearance) and immunogenicity — and it depends on the methodology used (immunoassay or bioassay).

Immunogenicity: Most therapeutic proteins are immunogenic despite the fact that their amino acid sequences are identical (or nearly identical) to endogenous proteins. Formation of antibodies often appears to have no clinical effect. In some cases, however, the clinical effects are significant and cause more severe disease. Immunogenicity may result in a loss of efficacy or enhanced function, altered biodistribution and pharmacokinetics, increased active dose and toxicity, and interference with other diagnostics and therapeutics. It may also cause hypersensitivity reactions or cross-neutralization of endogenous substances with immune reaction or changes in physiological function.

General factors that influence the occurrence of an immune response include specific properties of an immunogen, its molecular size and solubility, the route of administration, storage methods, dose levels, and length of treatment. Furthermore, immunogenicity depends on host factors such as genotype, age, concomitant diseases associated with immune dysregulation, or previous exposure to other therapeutic proteins that might cause cross-reactivity.

Most current physicochemical characterization assays are inadequate for predicting protein immunogenicity. The only satisfactory means so far of assessing relative immunogenicity of a biosimilar and its marketed counterpart is to compare and them in a trial using the same assay, then validate the results to show differences between products.



GUIDELINES FOR COMPARABILITY STUDIES

Comparability can generate evidence substantiating the similar nature of biosimilar and originator products — in terms of quality, safety and efficacy. The European CHMP (Committee for Medicinal Products for Human Use) issues specific guidelines addressing the planning and conduct of comparability studies to substantiate claims of similarity used as the basis for the marketing authorization for any biological medicinal product — e.g. products

containing biotechnology-derived proteins as their active substance (1).

Advances and limitations of analytical methods and techniques available today for the full characterization of biosimilars have prompted the CHMP to initiate a number of specific guidelines relevant to quality, non-clinical, and clinical issues. Product-class-specific guidelines on preclinical and clinical studies will be made available. (Annex Guidelines are already available for recombinant erythropoietins, recombinant granulocyte-colony stimulating factors, somatropins, and recombinant human insulins).


COMPARING APPROACHES

In principle, the concept of a “similar biological medicinal product” can apply to any biological medicinal product. However, the success of such development approaches will depend on the ability to characterize products and demonstrate their similar natures.

Biologics are usually more difficult to characterize than chemically derived medicinal products. Parameters such as three-dimensional structure, acido-basic variants, and posttranslational modifications can be significantly altered by changes initially considered to be minor in the manufacturing process. The standard “generic” approach — demonstration of bioequivalence with the originator product by appropriate bioavailability studies — normally applied to chemically derived medicinal products is scientifically inappropriate for these products. Therefore, the “biosimilar” approach, based on comparability studies, will have to be followed.

The data needed for a biosimilar product will probably be less than for an originator biotech product. However, because of necessary comparability studies, the investment for developing a follow-on biologic is still far beyond the investment needed for conventional chemical generics. By taking advantage of the fact that the similarity to an approved product facilitates development (e.g., preclinical testing or dose ranging). It may be quicker and easier to develop a biotechnological generic as a new entity rather than establishing a comparability exercise.

REFERENCES

- 1 European Medicines Agency. CHMP/437/04: Guideline on Similar Biological Medicinal Products. 30 October 2005. www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf. 

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