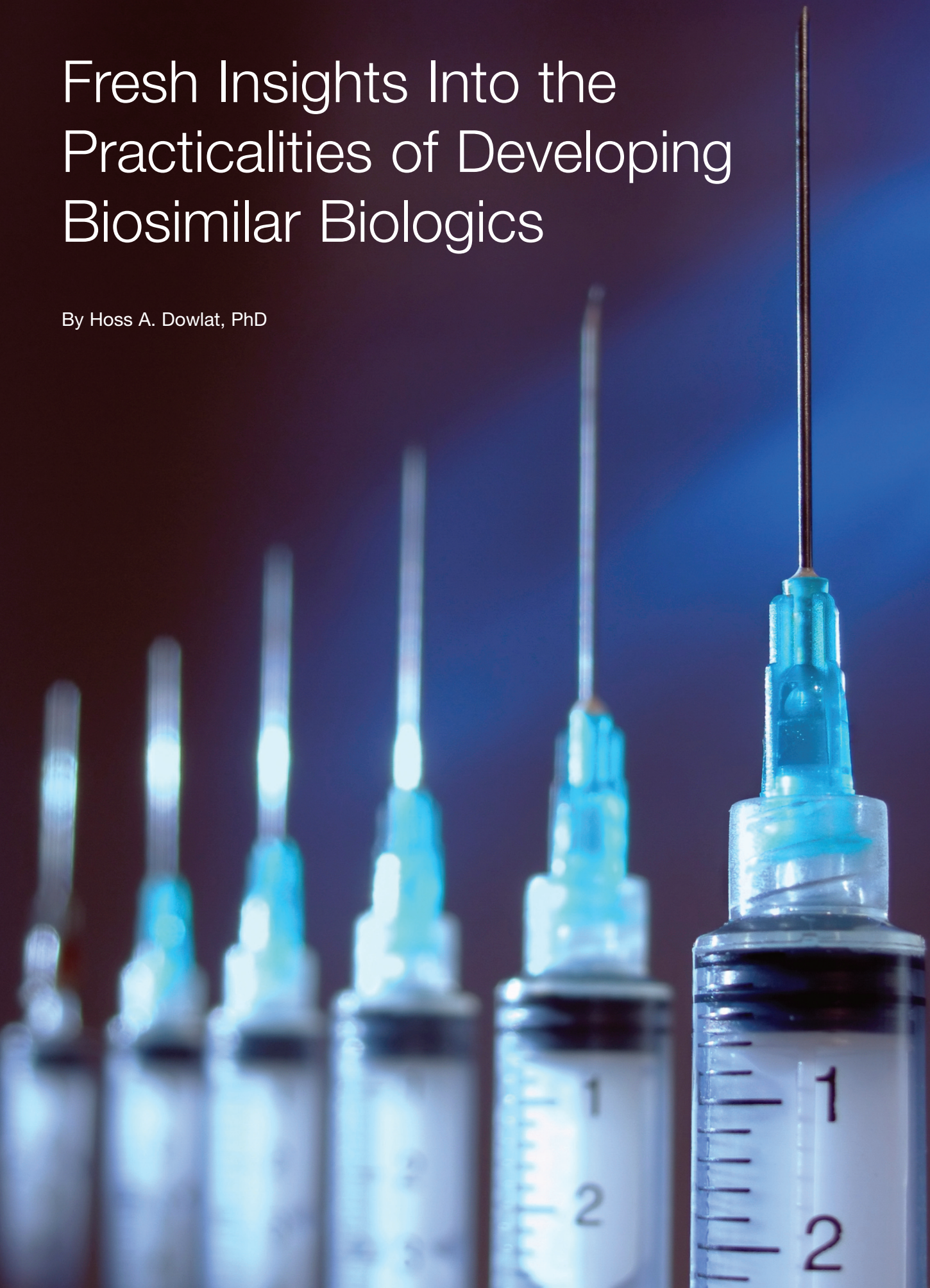


Fresh Insights Into the Practicalities of Developing Biosimilar Biologics

By Hoss A. Dowlat, PhD



Biotech products coming off patent afford a window of opportunity to obtain a marketing approval for a “follow-on biologic” by a new product developer. If the supporting data are sufficient to authorize interchangeability and substitution, the new product is defined as a similar biologic or “biosimilar.” Europe is leading the way in defining the regulatory pathway for biosimilars. This article shares lessons learned that can provide strategic insights to guide biosimilar development plans.

Background

The legal framework for biosimilars in Europe was laid down by Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use and Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, opening the way for implementation by the European Commission and the European Medicines Agency (EMA). EMA defines a “biosimilar product” as “similar to a biological medicine that has already been authorised (the ‘biological reference medicine’). A biosimilar medicine contains the same active substance as the biological reference medicine. Biosimilar and biological reference medicines are used to treat the same disease at the same dose. There are no significant differences between the biosimilar and biological reference medicines in terms of safety or efficacy.”¹ Upon marketing authorization by the European Commission, therefore, the recommendation is that the current marketed product can be substituted by the biosimilar.

Many of the recombinant technology-derived biological products coming off patent in recent years were developed originally as orphan drugs in the US during the 1980s, after the US *Orphan Drug Act* of 1983 granted these products seven years of exclusivity and other benefits. For instance, Epoetin (epoetin alpha) received a US orphan drug designation in 1986 and was approved in 1989 for anemia in end-stage renal disease, or filgrastim (granulocyte stimulating factor, G-CSF) obtained the designation in 1990, with BLA approval of neutropenia in oncology patients and use in bone marrow stem cell healthy volunteers (for transplantation) in 1994. These first biotech products were introduced in Europe—mostly through National or Deconcentration or Mutual Recognition approval procedures—prior to the 1995 establishment of the European Medicines Agency (EMA), and before the subsequent compulsory requirement of the Centralized Procedure for these biotech products. Since that time, these products have benefited from an expanding market for non-orphan indications, achieving individual product sales in the billion-dollar range.

First Two Biosimilar Approvals

The first biosimilar products approved in Europe and the rest of the Western world were somatotropin (human growth hormone) products: Omnitrope, whose Market Authorization Holder (MAH) is Sandoz, Austria; and Valtropin, whose MAH is BioPartners, Germany (with Swiss headquarters). Both were authorized in the EU by the European Commission in April 2006.^{2,3} The pioneering development work was performed by these two Swiss companies—the former a multinational and the other a small, virtual pharmaceutical company spun off from E. Merck AG. The approvals were based on comprehensive pharmaceutical comparisons against two different Reference Medicinal Products: Genotropin for Omnitrope, and Humatrope for Valtropin. As a result, the two approved biosimilar products had different label claims for specific indications and pharmaceutical characteristics derived from their respective Reference Medicinal Products.

The Marketing Authorization Application (MAA) package for these products included comparative nonclinical and comprehensive comparative pharmaceutical studies. In addition, comparative clinical efficacy, bioavailability and safety data in children, based upon long-term, multicenter studies, were provided. For Valtropin, the pivotal study was a noninferiority,⁴ randomized, 12-month double-blinded phase, followed by a 12-month unblinded (open) extension phase of 149 prepubertal children 6-10 years old, in which the children were either switched from Humatrope to Valtropin or continued on Valtropin. The study also demonstrated equivalence⁵ of the adjusted mean ratio of the primary height velocity with a 95% confidence interval. For Omnitrope, the key study was a nine-month, open label, parallel design study in 89 prepubertal children 5-13 years old, followed by an extension phase with a switch from comparator to Omnitrope. Product accountability was required to ensure that compliance matched the protocol and the case report forms. These data demonstrated equivalence and provided the bridge to allow products to carry all of the label claims of the marketed products, including use in adults, based upon the studies of the most sensitive patient population—children.⁶

Omnitrope’s somatotropin drug substance was produced in an *E. coli* (bacterial) host. Valtropin, on the other hand, was produced in *Saccharomyces cerevisiae* (yeast) cells⁷ using recombinant DNA technology developed by LG Life Sciences, a Korean company. The previously marketed somatotropins are expressed in either *E. coli* (e.g., Humatrope, Genotropin, Nutropin) or in mammalian cells (Saizen), making the Valtropin yeast-cell process unique among growth hormones.

Legal concerns resulted in lengthy MAA submission validation times for the first biosimilars. Among the issues was the release to the rapporteur/co-rapporteur of regulatory

information on the reference product held at a national level. For example, Humatrope was approved by the old Concertation Procedure nearly two decades ago with the Netherlands as the Reference Member State. Therefore, with the submission of Valtropin, the original MAA data on Humatrope had to be released to EMEA. As a result of the pioneering nature of these submissions and the unprecedented regulatory and legal issues, Valtropin's validation took about three months instead of the standard 10 days.



Omnitrope was submitted twice before it achieved authorization by the Commission, even though the European Committee for Proprietary Medicinal Products (now the Committee for Human Medicinal Products, or CHMP) gave it a positive opinion following the first submission in 2004–05.⁸ The Commission would not agree to a bibliographic submission, which the applicant had advocated based upon the marketed product's well-established use. This legal basis was not accepted, and the applicant had to generate additional clinical data for a second application, including an open-label comparative study.

Subsequent Wave of Biosimilar Approvals

A number of additional biosimilar products have subsequently been submitted and approved in the EU. There were five approvals in 2007 for erythropoietin, developed by Sandoz and Stada, using Eprex/Erypo as the Reference Medicinal Product, with parallel MAAs (from Sandoz, Hexal and Medice; and Stada and Hospira) using the same erythropoietin product under different names.⁹ There were four approvals in 2008 for filgrastim granulocyte colony stimulating factor, developed by Ratiopharm and Teva, with Neupogen as the Reference Medicinal Product—again with parallel submissions using the same granulocyte colony stimulating factor product.¹⁰ There were two further filgrastim approvals in 2009 (Hexal and Sandoz).

Challenges in Biosimilars Development

The biosimilar approval experience in Europe demonstrates that the development and

submission of biosimilar products require a substantial and robust pharmaceutical development package of information, primarily due to the requirement for an extensive battery of biocompatibility tests. A clinical equivalence study is also required, except in certain cases where a clinically meaningful pharmacodynamic surrogate measure can be correlated with clinical effect; such cases are best justified through CHMP Scientific Advice. A precedent was set by Zarzio (filgrastim), which relied upon four comparative pharmacokinetic/pharmacodynamic (PK/PD) studies in 146 healthy volunteers as a basis of approval, but postapproval follow up commitments had to be made to conduct three phase IV clinical safety studies.¹¹

In spite of guidances for somatotropin, erythropoietin, granulocyte colony stimulating factor, interferon, insulin and other biosimilars, many applicants still seek official CHMP/EMEA Scientific Advice for their biosimilar products to ensure that they have properly interpreted the guidelines or, where they consider deviation from the guidelines, the deviation can be justified to allow an innovative or more-efficient program.

The first biosimilar consultations with CHMP/EMEA occurred in 2000, when very little was known about the data requirements for this new class of “generic” medicines and no regulations were in place. The first guidances were issued in 2004–05, arising out of Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use and Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (which provide the European legal framework). In 2006, those guidances¹² were expanded based upon the data and experience of the first somatotropin biosimilar approvals and Scientific Advice processes. The next biosimilars in the EU—erythropoietin and granulocyte colony stimulating factor—were approved in 2007–08 using both published guidances and Scientific Advice.

Apart from a large percentage of approvals upon submission to EMEA, there have also been nonapprovals. Alpheon (negative opinion interferon alpha) (2006), Bioferonex (interferon beta) (negative opinion 2009) and Marvel (insulin) (withdrawn MAA 2008) MAAs did not satisfy the requirements of the CHMP/EMEA as there were major objections to agreeing to a favorable risk/benefit ratio.

International Progress

The first international approvals for biosimilars occurred in 2006 and 2007, when G-CSF and monoclonal antibody mAb rituximab were approved in India based upon pharmaceutical,

nonclinical and pharmacokinetic/pharmacodynamic data. Biosimilars have also been approved elsewhere in recent years, including some South American countries and China. Canada, Australia and Malaysia have largely adopted the European guidelines. However, a regulatory framework has not yet been established in the US, Korea and many other countries.

In Japan, one epoetin biosimilar (EPO JR013) was submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) in 2008, by Japan Chemical Research and Kissei, using a virus-free, non-serum-based fermentation.¹³ Japan's Ministry of Health, Labour and Welfare (MHLW) published the draft *Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics* in September 2008 (step 1) and updated it on 4 March 2009 (step 2).¹⁴ There was also the first Japanese biosimilar approval made public in June 2009, that of somatropin (Sandoz); presumably its supporting dossier was submitted well before the current guideline.¹⁵ These developments appear to reflect the new openness of the Japanese MHLW/PMDA and acceptance of international data and innovation increasingly.

At the international level, the World Health Organization began an initiative in 2008 to harmonize the definition of biosimilars and, in particular, the data requirements of the Reference Medicinal Product of biosimilars.¹⁶ This process is ongoing.

Reference Medicinal Product Comparator

One issue that significantly increases the time and cost of biosimilar development is the requirement to repeat studies against Reference Medicinal Product comparators that are sourced from different regions, even if the Reference Medicinal Product is manufactured by the same company using the same pharmaceutical form, strength and presentation. This requirement applies in Europe as of 2009—with no suggestion of change—as well as in Japan¹⁷ (where a Reference Medicinal Product is called a “precedent biotechnology drug”).

The biosimilar normally has the same pharmaceutical form, strength and route of administration as the comparator. In the EU, testing of the appropriate Reference Medicinal Product as comparator throughout the development program is critical. It must be authorized in the European Economic Community on the basis of a complete dossier (Article 8 of Directive 2001/83/EC, as amended). The data exclusivity period must have expired, and there should be no patent barriers. The market penetration and indications should be considered if there is more than one innovator biologic—which is often the case—depending upon the original Reference Member State approval.

Regional regulatory authorities continue to insist that the Reference Medicinal Product be

sourced within that region, e.g., an EU biosimilar filing must use a comparator manufactured in the EU or the European Economic Community (note that sourcing in Switzerland or Bosnia is not acceptable because they are not EU members). An agreement among regional authorities worldwide on a common Reference Medicinal Product, irrespective of where the biologic product is sourced, would save time, resources and expense, and allow biosimilar products to be approved more quickly, without duplication of effort and data.

The regulatory question is how to prove that one biologic is the same as another from region to region, even if the biosimilar is assumed to have identical pharmaceutical form, composition, manufacturing formulation and presentation, and even if the Reference Medicinal Product is manufactured by the same company. The expectation is that the Reference Medical Product's manufacturing process and production facility in different regions would have to be identical, and only the MAH holds that confidential information. There are also potential differences in impurities, potency, packaging and other factors that can affect safety and efficacy. At this point, the regulations require proof that the Reference Medicinal Product was purchased in a country that is under the jurisdiction of that regional authority—e.g., within the European Economic Community for a centralized submission to EMEA. The EU expansion, which brought 29 countries under EMEA's authority, has at least provided greater flexibility for this sourcing with the harmonization of regulations.

Where comparative data against a Reference Medicinal Product sourced from outside the region are generated, they can only be considered supportive, rather than pivotal in the EU. In one recent case, an applicant completed a two-year clinical study of its biosimilar product for the EU, during which time the specific pharmaceutical presentation of the Reference Medicinal Product used in the study was discontinued in the EU. The sponsor had to purchase the Reference Medicinal Product from the US to ensure the same packaging and maintain the study's blinding. Despite the fact that there was explicit FDA documentation proving that the US Reference Medicinal Product was identical to the EU Reference Medicinal Product previously used by the trial sponsor, the data for the US product were not considered pivotal by CHMP/EMEA¹⁸ and the clinical data had to be reanalyzed to exclude the results from the US-sourced Reference Medicinal Product. In view of the expense and shelf-life of biologics, stockpiling these products for a long study is not practical. This example demonstrates just one of the difficulties faced by biosimilar trial sponsors trying to meet the requirements of regional Reference Medicinal Product sourcing.

Changes Involving Manufacturing

It is critical to ensure that manufacturing changes to the product at the drug substance or drug product stage do not impact comparability with respect to potency, safety or efficacy by verifying these against the Reference Medicinal Product, which has a proven record of patient use.

The increased sophistication of state-of-the-art chemical and biological testing methodologies, combined with the power of spectroscopic techniques, has permitted an accurate assessment of comparability following manufacturing changes to the drug substance, such as the raw materials for fermentation, the master cell bank or the drug product. These advances have reduced the burden of additional testing, generally requiring limited or no clinical or nonclinical bridging studies upon making the change, for example. The knowledge gained by investigating changes in approved biologics' drug substance or drug product has formed the basis of the regulatory authorities' current guidance regarding biosimilar comparisons with Reference Medicinal Products. A thorough investigation of comparability continues to be an absolute requirement.

Numerous biochemical, biophysical and immunochemical tests are required to ensure the identical primary structure and to compare the secondary and tertiary structure/conformation of the biosimilar against the Reference Medicinal Product. Relevant tests must be repeated if any changes are implemented. Every study should be performed with comparisons to internal and international (e.g., National Institute for Biological Standards and Control, European Pharmacopoeia or United States Pharmacopoeia) reference standards, if available, and the Reference Medicinal Product.

If the molecule can be compared using stress conditions—such as temperature, oxido-reductive, osmotic and pH stresses—using current sophisticated analytical methodologies, the resulting data can be very useful because they represent excursions from normal storage conditions. At minimum, however, fresh and aged batches of drug product should be compared. Changes in manufacturing processes, such as those shown in **Table 1**, would trigger the need for such comparability studies.

Clinical Safety Considerations

Biosimilar approvals also require an adequate safety database, which can vary widely depending upon the biologic's indication and nature. The available population for the safety data that form the basis of approval is usually limited, so the database must be supplemented by postmarketing data. Establishing therapeutic equivalence through bioavailability and clinical criteria alone is not adequate to ascertain safety. A clinical therapeutic setting, which allows more extensive exposure, is necessary to capture potential safety

signals such as those associated with immunogenicity issues.

Only through a Risk Management Plan (section 1.8.2 of the EU Common Technical Document) involving pharmacovigilance measures—often utilizing a registry—can there be adequate control of unexpected outcomes. The Risk Management Plan must be designed carefully and presented to the CHMP for its acceptance to properly mitigate risk. Scientific Advice can also be sought for the plan.

In Europe, some biologics coming off patent were previously approved by National or Deconcentration or Mutual Recognition Procedures, rather than the Centralized Procedure. As a result, EU regulatory expertise on biological products, such as experience with pharmacovigilance, is spread across assessors of multiple authorities. In the US, many approved protein products such as therapeutic proteins and monoclonal antibodies have been reviewed and approved by FDA's Center for Biologics Evaluation and Research (CBER), under the *Public Health Service Act*, giving this center a significant depth of knowledge about biologics safety. Whereas, interestingly, hormones and peptides were approved under the *Food, Drug, and Cosmetic Act* (as for small molecules) by FDA's Center for Drug Evaluation and Research (CDER). Furthermore, since 2004, responsibility of the review and approval of therapeutic proteins and antibodies has been transferred to CDER. While sponsors can benefit from CDER's and CBER's exceptional insights into biologic therapies, this expertise has not yet been leveraged by FDA to approve biosimilars.

It remains to be seen whether future biosimilars approved in the US would be eligible for an "AB" rating in the *Orange Book*, the US drug registry, or an equivalent procedure and process, which would allow the biosimilar to be "substitutable/interchangeable" for the innovator biologic. This is not yet the case in the US, even though several biologics, including recombinant and natural hyaluronidases, recombinant salmon calcitonin, glucagon and somatropin (Omnitrope), have been approved under an abbreviated NDA 505(b)(2) pathway since 2006, but are not therapeutic equivalents.

Immunogenicity as Part of Clinical Safety

If a biosimilar product is approved for a therapy that is already in use, it is clearly desirable that the biosimilar's efficacy and safety be equivalent to that of the innovator product. Under current regulations in Europe, the decision to allow the substitution of an EU authorized biosimilar for an existing biologic is left to individual Member States. Interchangeability or substitution is not regulated by EMEA after a successful Centralized Procedure in the EU, but the ultimate decision

Table 1. Typical Process Changes Impacting Drug Comparability

Change Being Effected	Impact on Product Assessed by Comparability Exercise*
2003 Original process DS and DP	DS 1, DP 1
2004 Changed DS WCB	DS 2, DP 2 DS 1 vs. DS 2, DP 1 vs. DP 2
2005 Changed DS raw materials & purification step	DS 3, DP 3 DS 1 vs. DS 2 vs. DS 3
2006 Changed DP lyophilization	DS 3, DP 4 DP 1, DP 2, DP 3 vs. DP 4
2007 Addition of device	DS 3, DP 5 DP 4 vs. DP 5 vs. DS

DS = drug substance; DP = drug product.

* Investigation of change by an extensive battery of physiochemical, biologic, and chemical tests exploring primary, secondary, and tertiary structure; also conformation and solution dynamics, against the Reference Medicinal Product and one or more Reference Standards for biopotency and identity.

is still controlled by each country’s national healthcare system.¹⁹

One of the concerns about switching from an existing therapy to a biosimilar is the issue of immunogenicity, which, for some human versions of proteins such as epoetin, has been associated with inducing autoimmune neutralization of endogenous epoetin. Immunogenicity can be a critical consideration during a biosimilar’s approval process as part of the risk/benefit assessment. As previously noted, any change in a biologic product—whether an innovator product or a biosimilar—has the potential to impact immunogenicity, thus immunogenicity must be rigorously tested and constantly monitored.

The immunogenicity of biopharmaceuticals may have serious clinical consequences, such as:

- development of neutralizing antibodies against the product
- impact on pharmacokinetics, requiring dose adjustment to keep plasma levels stable
- reduced efficacy, weakening of the clinical effect or reduced duration of response despite protein load
- impact on safety signals, such as increased adverse drug reactions by infusion or subcutaneous administration, hyperimmune reactions or delayed hypersensitivity

The antibodies against the drug product can display different characteristics:

- binding—impacting bioavailability/plasma clearance
- neutralizing—binding to the active moiety and preventing it from further action
- precipitating—causing adverse events (mild injection site reactions, cutaneous reactions), systemic effects (arthralgia and fever) or anaphylactic-type reactions
- cross-reacting with natural proteins—inducing autoimmune disease

Immunogenicity-derived toxicity is route dependent, with the subcutaneous route being the most immunogenic. Hypersensitivity reactions are a particular risk for the subcutaneous route of administration. One example of this phenomenon is epoetin alfa, which was contraindicated from December 2002 to May 2006 for subcutaneous (but not intravenous) administration in the EU for patients with chronic renal failure due to the increased frequency of anti-erythropoietin, antibody-induced, pure red cell aplasia.²⁰

Methodologies and strategies for investigating immunogenicity must be well-validated and well-conceived to avoid critical regulatory deficiencies during dossier assessment. Also, competent interpretation and positioning of the results are important. In the development of the somatropin biosimilars, for example, an early Omnitrope formulation elicited a significant antibody response in patients to both somatropin and host cell proteins, until improved downstream manufacturing purification was carried out.²¹

Immunogenicity can only be investigated in a definitive way in man, not in animal studies. If the biologic molecule is endogenous in man and not the animal model, the antibody reaction could neutralize the protein, thus putting in question the relevance of that species. EMEA, CHMP and the Biosimilar Medicinal Products Working Party have produced two current guidance documents on immunogenicity: one on proteins and one monoclonal antibodies.²²

CDER reviewing divisions currently tend to raise the question of immunogenicity prior to an NDA submission and can involve CBER-trained reviewers, now within the Office of Biotechnology Products of CDER, with particular attention to determination of assay cut-off points and related assay method development.²³

The most significant challenge is to identify the potential safety signals arising from each biologic’s immunogenicity when subject to specific manufacturing, packaging and formulation variables. This can only be accomplished with

postapproval marketing pharmacovigilance experience in a wider population. Predicting immunogenicity effects using a database that is limited at the time of approval requires collective agency experience, as well as good scientific and empirical reasoning.



Conclusion

As with generic small molecules, there is the opportunity to have several MAHs for the same drug substance—each with a profitable market share—because of the strong contribution biologics make to human health. Such competition offers the possibility of greater affordability in a category of medicine that is presently very expensive. Biologics coming off patent in the near future include interferons, interleukins and monoclonal antibodies—each with its own unique challenges to developing new biosimilars.

However, any company venturing into this field must carefully plan its development strategy. Experience with the approval and medical use of biosimilars is limited worldwide, and there are inherently high regulatory and legal hurdles, and also barriers for gaining acceptance by healthcare professionals and patients. Europe has established precedents for biosimilar approvals, and has the widest experience. Other major ICH regions, such as the US, must make significant strides before their regulatory frameworks facilitate approval of improved biologics as true biosimilars, while Japan has made progress in 2009.

It is clear that biosimilars are an exciting new frontier in generic medicines. However, each biosimilar presents its own unique scientific and regulatory challenges that must be addressed and overcome if it is to fulfill its potential to increase the availability and reduce the cost of biological therapies for patients around the world.

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