Commentary

Biosimilars: Impact of Biologic Product Life Cycle and European Experience on the Regulatory Trajectory in the United States

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ABSTRACT

Background: *Biosimilars* are defined as biologic products that are highly similar to reference products, notwithstanding minor differences in clinically inactive components, with no clinically meaningful differences between the biologic product and the reference product in terms of safety profile, purity, and potency. Due to the high cost of innovator biologics, as well as an increase in the number of these products reaching patent expiry, the development of a process for approving biosimilar products has become a crucial regulatory issue in the United States.

Objective: This commentary explores the relationship between structural/biophysical variation and the risk/benefit profile of biosimilars and reference biologics that have undergone process changes in the context of the most recent biophysical, nonclinical, and clinical data available.

Methods: The search strategy used PubMed, EMBASE, and MEDLINE for the retrieval of documents pertaining to biologic manufacturing, comparative analysis of biosimilars and originator biologics, and relevant review articles on biosimilars. For regulatory documents pertaining to the processes of the approval of biosimilars, biologics, and generics, a search for legislative decisions, briefing summaries, concept papers, guidance, and evaluations of approved and rejected applications for biosimilars published by the World Health Organization, US Food and Drug Administration, European Medicines Agency (EMA), and other national regulatory authorities was conducted. Selected articles from key opinion leaders and manufacturers were also reviewed. These searches were conducted to provide a review of historical and contemporary issues in the consideration of the current status of worldwide biosimilar use and regulation.

Results: A total of 18 marketing applications covering 9 development programs were surveyed. Of these, 14 applications were approved and 4 were rejected by the EMA. None of the biosimilars were reported to have evidence of significant clinical variation relative to reference compounds in the absence of corresponding differences in biophysical properties. A single biosimilar (Omnitrope® [somatropin]) was reported to have evidence of significant variation in both biophysical and clinical parameters in premarketing studies. Biophysical variation in the absence of relevant differences in the efficacy and safety profiles compared with the reference brands was noted for 2 biosimilar epoetin products.

Conclusions: This commentary provides evidence that current EU guidelines have resulted in the approval of biosimilar therapeutics with comparable efficacy and safety profiles for the recommended indications of their respective reference originator biologics. It is anticipated that these precedents will serve as a starting point in the development of a process for approving biosimilars in the United States and worldwide to provide efficacious and tolerable biotherapeutics with a significant cost advantage for national health care programs and consumers. (*Clin Ther*. 2012;34: 400–419)

Key words: biologics manufacturing, biosimilar regulations, biosimilars.

INTRODUCTION

A new pathway for drug development emerged with the advent of recombinant DNA (rDNA) technology in the 1970s and 1980s. This technology enabled scien-

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tists to manipulate genes and cells to produce structurally complex drugs that would have been impossible to manufacture through chemical synthesis or to purify from natural sources.[1] The ability to produce, purify, and characterize complex molecules has correlated with gains in the understanding of disease mechanisms and has resulted in a variety of innovative drugs that have improved outcomes in areas of unmet medical needs, including cancers, rheumatoid arthritis, multiple sclerosis, and Gaucher disease.[1–3] The drugs produced through these new controlled manufacturing processes have been categorized as *biological products,* or *biologics*.[2] Biologics are derived from living organisms and may consist of proteins and/or sugars singularly or in combinations of varying complexity. This category includes monoclonal antibodies (MAbs), therapeutic proteins, immunomodulators, and growth factors. The sale of biologics garnered ~$93 billion across the global market in 2009.[4] The class of anticancer biologics alone produced revenue of $6.8 billion in 2006 and demonstrated a growth rate nearly 4-fold the overall pharmaceutical market in the United States.[5] Currently, many biologics, including Humira®,[a] Avastin®,[b] Rituxan®,[c] Herceptin®,[d] Remicade®,[e] Prolia®,[f] Lucentis®,[g] and Enbrel®,[h] are among the best-selling pharmaceuticals worldwide.[4] Despite the positive sales figures and cost coverage by health insurance providers, biologic therapies continue to be a less accessible and more expensive treatment alternative for patients with debilitating and life-threatening diseases.[3,5]

The Biologics Price Competition and Innovation Act of 2009 was a statutory provision in the Affordable Health Care Act of 2010 that provided the rationale for the establishment of an abbreviated regulatory procedure in the United States for licensing biosimilars as a means of providing lower-priced versions of biologics and promoting innovation.[6] The Act defines *biosimilar products* as biologics that have the same mechanism of action, route of administration, dosage formulation, and strength of active ingredient as the reference product and that are highly similar to the reference product. In the context of the Act, *highly similar* is defined as "no clinically meaningful differences between the biological products and the reference product in terms of tolerability, purity, and potency."[7]

In 2008, the Congressional Budget Office estimated that the enactment of the Biologics Price Competition and Innovation Act would reduce total expenditures on biologics in the United States by $25 billion through 2018, reduce budget deficits by $6.6 billion by 2018, and decrease Medicaid spending by $4 million by 2013.[8] In the United States, with the patents of many biologics approaching expiration or having reached expiration, biosimilar drugs are projected to bring about a cost savings of 20% to 40% once regulatory guidelines are determined.[2,5,8]

Despite the passage of this Act, the FDA is currently in possession of a backlog of applications from sponsors seeking the approval of biosimilars. At the time of this commentary, the FDA was evaluating 8 investigational or preinvestigational New Drug Applications for biosimilar products. This long queue for approval is largely the result of a lag in the development of a biosimilar approval process in the United States in comparison to the European Medicines Agency (EMA) and other regulatory bodies.[9] The delay has given sponsors of biosimilars time to accrue supportive data within the context of the pioneering regulatory agencies, but little direction as to the applicability of these data in the still-evolving FDA approval process.

The establishment of regulatory processes for structurally complex drugs such as biosimilars is a longstanding challenge that has become increasingly urgent due to rapid technological advances and the expiration of innovator patents in this class. As discussed by Dudzinski and Kesselheim,[2] the relative inability to compare the quality and purity of biologics in a manner similar to low-molecular-weight (LMW) drugs has resulted in longstanding regulatory divisions in the United States.[10] For LMW drugs, the establishment of legal requirements for quality and purity through the Pure Food and Drug Act of 1906 provided the foundation on which guidelines for the evaluation of efficacy, tolerability, and bioequivalence were subsequently created through the Federal Food Drug and Cosmetic Act (FDCA) of 1938, the Kafauver-

[a]Adalimumab (Abbott Laboratories Inc., Abbott Park, Illinois).
[b]Bevacizumab (Genentech USA, Inc., South San Francisco, California).
[c]Rituximab (Genentech).
[d]Trastuzumab (Genentech).
[e]Infliximab (Janssen Biotech, Inc., Horsham, Pennsylvania).
[f]Denosumab (Amgen Inc., Thousand Oaks, California).
[g]Ranibizumab (Genentech).
[h]Etanercept (Immunex Corporation, Thousand Oaks, California).

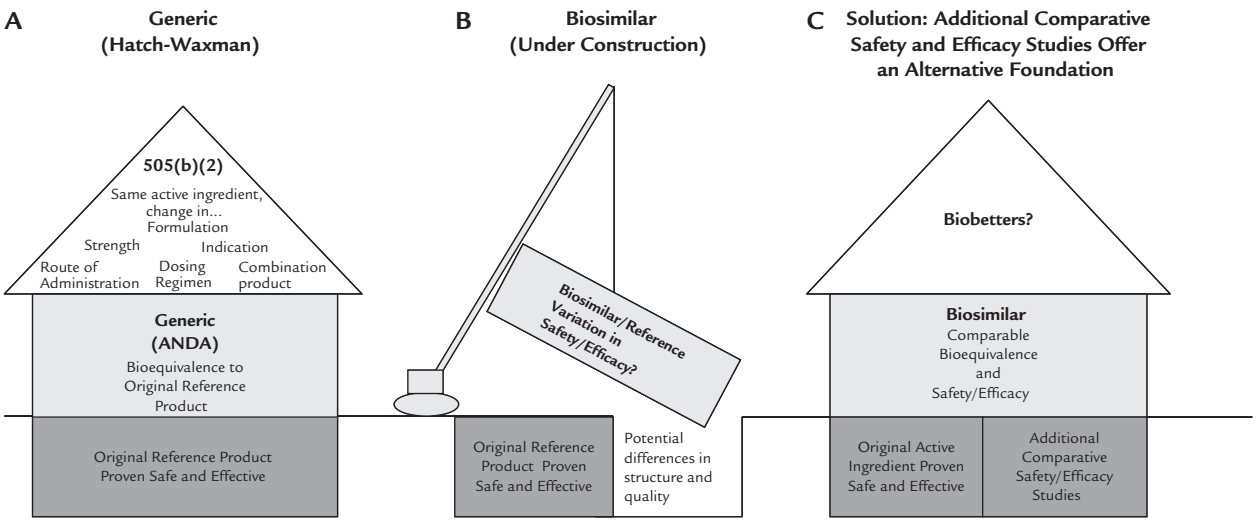

Figure 1. Comparison of Hatch-Waxman and biosimilar regulatory structures. (A) Illustration of the Hatch-Waxman regulatory structure for approval of generics (walls) and new drugs (roof) through reference to previously approved active molecules (foundation). (B) Depiction of fundamental difference in the foundational evidence supporting biosimilars in comparison to small molecule generics. The potential for differences in quality and structure between originator compounds and biosimilars creates a perceived gap in the foundation of comparability to the reference product. (C) The perceived gap can be filled through additional comparative efficacy and tolerability studies, creating a viable foundation for the approval of biosimilars.

Harris Act of 1962, and the Hatch-Waxman Act of 1984, respectively.[2] In contrast, biologics have been recognized in the United States as distinct from LMW drugs since the passage of the Biologics Control Act of 1902, which established regulations for the "viruses, therapeutic serums, toxins, antitoxins and analogous products" intended for the prevention and treatment of diseases.[11] Owing to the structural complexity of biologic products and the historical limitations in the ability to characterize their quality, this Act emphasized the oversight of manufacturing processes rather than the analysis of the purity of the end product.[2] Additional licensing requirements for biologics were mandated under the Public Health Services Act of 1944 and, in 1999, the biologics license application was created to combine the requirements for manufacturing and end-products into a single, harmonized application.[12] Although the guidelines for the efficacy and tolerability of LMW drugs established through the FDCA and the Kafauver-Harris Act also apply to biologics, the regulations for bioequivalence delineated by Hatch-Waxman do not. As a result, a steady stream of innovator biologics have been approved in the United States with little threat of future competition from biosimilars.

A combination of historical and scientific challenges prohibits the use of the expedited regulatory approval established by Hatch-Waxman. As illustrated in **Figure 1**, Hatch-Waxman established 2 new types of drug applications for FDCA products: the Abbreviated New Drug Application (ANDA) and the 505(b)(2). The ANDA covers generics, whereas the 505(b)(2) typically applies to drugs that contain an already approved active ingredient but that vary from the reference drug in terms of the dosage, route of administration, or indication. The foundation of both application types is the identical structural character of the active ingredient(s) in the reference product and the innovator product. Resting on this assumption of identical active ingredients is the concept of approvability through bioequivalence. The minimal studies required for the approval of generics typically compare their concentration and distribution in the body with those of LMW innovators, but they assume that the active molecule itself is identical based on chemistry manufacturing and controls (CMC) data.

Figure 1 illustrates one of the major challenges in the construction of an analogous regulatory schema for biosimilars. For many of these structurally complex drugs, the current technology is insufficient for establishing the identical nature of the active molecule in comparison to the approved reference. This issue is compounded by intellectual property laws that largely prevent manufacturers of biosimilars from using the production processes of innovators. Instead, the manufacturers of biosimilars must create an identical end-product despite differing source materials and a manufacturing process that may be technically dissimilar but analogous to the reference drug in complexity.[13] Hence, despite the establishment of a foundation of an acceptable efficacy and safety profile through the biologics license-application process, the original approval of the reference molecule may be inadequate to support the efficacy and tolerability of the biosimilar through CMC-based bioequivalence alone. The potential for undetectable differences between the biosimilar and the reference product creates a gap in this foundation that consequently prevents biosimilars from being accurately characterized as generics.

The primary risk of potential differences between reference products and biosimilars is that the treatments will have differing efficacy and tolerability profiles. This risk is amplified by the increased immunogenic potential of biologics relative to LMW drugs. The immunogenicity of biologics and biosimilars is generally understood to be a function of their complexity in terms of both production and final structure.[14] However, when immunogenic reactions do occur after exposure to a biologic, it can be difficult to determine their root cause. This difficulty is illustrated by the case of the antianemic drug Eprex®[i] (Epogen®[j]/Procrit®[j]/Erypo®[k]), in which increased immunogenic responses and elevated rates of pure red cell aplasia were observed following a process change in which human serum albumin was replaced with polysorbate 80 as an excipient.[15–18] Despite the established association between the manufacturing change and an increased risk for immunogenic events, the origin of these adverse events remains somewhat controversial. Scientifically supported arguments for both polysorbate 80–induced increases in immunogenic micelle content and elevated organic compounds leached from rubber stoppers have been presented, illustrating the difficulty in characterizing causal factors for immunogenicity at the structural level.[15–18] For this reason, issues of immunogenicity are a major concern when one considers the evidence gap introduced by potential undetectable differences between reference drugs and biosimilars.

For all biosimilar products, there is debate over the size of this gap and how it can best be filled. One solution would be the development of technology that is sensitive enough to establish clinically relevant thresholds of heterogeneity such that a Hatch-Waxman–style regulatory structure can be applied. Although simple in principle, the science involved is extremely challenging because it is difficult to establish a correlation between biophysical differences and clinical effects, and any established correlations would likely be specific to each reference/biosimilar pair. Another approach is to extend the evaluation of comparability to cover efficacy, tolerability, and bioequivalence. In this way, reliance on biophysical comparability is reduced through the conduct of clinical bioequivalence studies that evaluate the efficacy and tolerability of the biosimilar in direct comparison with the reference compound. This approach introduces the debate over the relative contribution of costly Phase III studies in establishing comparable efficacy and tolerability.[19,20]

Both approaches just described rely on the predictive value of biophysical evidence. To illustrate this, 4 possible associations between biophysical and clinical data are shown in Figure 2. These associations are roughly organized in terms of the regulatory direction they are likely to require, with one extreme end of the spectrum represented by duplication of the innovator application and the other by employment of a Hatch-Waxman–type architecture. Among these possible outcomes, the most damaging from the perspective of an abbreviated process development would be applications demonstrating statistically significant differences in clinical efficacy and tolerability between the reference and biosimilar compounds in the absence of detectable differences in quality and structure. Such results suggest a strong need for additional efficacy and tolerability data due to a lack of predictive biophysical data. In contrast, detectable biophysical differences can provide predictive value, both when correlated with clinical effects and when an absence of effects on

[i]Trademark of Janssen-Ortho, Inc., Toronto, Ontario, Canada.
[j]Trademark of Amgen.
[k]Trademark of Janssen-Cilag SA de CV, Mexico City, Mexico.

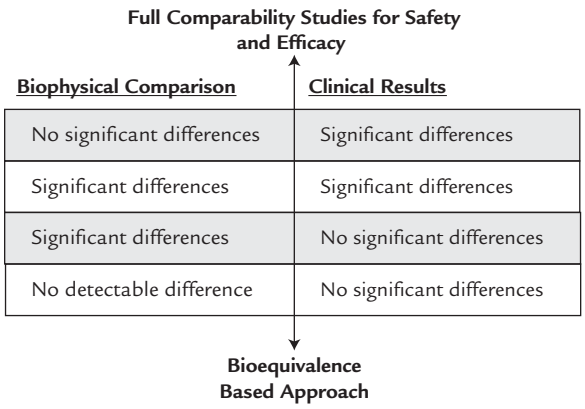

Figure 2. Possible biophysical and clinical outcomes for biosimilars possible biophysical and clinical outcomes for biosimilars. Illustration of the potential associations between biophysical and clinical data and the predicted effect of these associations on the development of regulatory processes of biosimilars. Increased predictability of the clinical effects resulting from quality/structural variation diminishes the need for full efficacy and tolerability studies.

clinical outcomes is reported. Monitoring of such differences reduces the need for clinical studies and facilitates the creation of drug-specific guidelines. The need for clinical trials may be further reduced when no detectable biophysical differences and no statistically significant clinical differences are reported for a biosimilar relative to the reference product.

When considering the potential effects of undetectable structural variation on the efficacy and tolerability profile of a biosimilar, the established risk/benefit profile of the innovator compound plays a crucial role. Specifically, when evidence suggests that a reference biologic has a consistent safety profile after manufacturing changes, it may signify a need for less stringent clinical data requirements to support subsequent biosimilar approval. Less stringent requirements can be justified largely because the manufacturing changes to the reference product may also introduce undetectable or minor structural variations, the effect of which can be monitored through nonclinical and clinical trials as well as subsequent tolerability reports. Thus, when no clinically significant differences are observed in such cases, the precedent could serve as a credible guidance to support reduced stringency of clinical study requirements for the approval of biosimilars.

This commentary explores the issues in the regulation of biosimilars by discussing the reasons for microheterogeneity in biologics as well as the ways in which heterogeneity has been evaluated and controlled by manufacturers of both reference and biosimilar products. That discussion is followed by a brief overview of the processes of the approval of biosimilars outside of the United States. In addition, the current literature comparing biosimilar and reference products is explored in the context of statistically significant changes in biophysical parameters, pharmacokinetics (PK), tolerability, and efficacy between biosimilar and reference products.

METHODS

To evaluate the process of developing biosimilars, the literature was investigated for comparative analyses of biosimilars and originator compounds with regard to quality, nonclinical, and clinical parameters. The search strategy used PubMed (mid-1960s–present), and EMBASE (1974–September 2011) for the retrieval of documents pertaining to biologic manufacturing, comparative analysis of biosimilars and originator biologics, and relevant review articles on biosimilars published before July 2011 without language restrictions. Key words used in the search process included the following: *biosimilar, follow-on biologic, biogeneric, second entry biological, unpatented biological,* and *multisource product*. In addition, all relevant drug-specific names for approved and rejected biosimilars were searched. Because the commentary was concerned with the entirety of the available data on biosimilars (including structural and nonclinical data), no randomized controlled trial filter was applied. A search of the Web sites of WHO, FDA, EMA, and global regulatory authorities was also conducted for legislative decisions, briefing summaries, concept papers, guidance, and evaluations of approved and rejected biosimilars. Whenever possible, data from the primary literature were reviewed. Where no data were available in the primary literature, regulatory publications (available in the public domain) were cited. Selected articles from key opinion leaders and manufacturers were also reviewed. These searches were conducted to provide a survey of historical and contemporary issues in consideration of the current status of worldwide biosimilar use and regulation.

Table I. Sources of variation in the production and manufacturing of biologics.

Process/Variable	Variation	Assay
Cloning[21–24]		
Coding gene	Mutation	DNA sequencing
Plasmid	Selection marker, epitope, promoter	Southern blot, northern blot, RT-PCR, SDS-PAGE
Transformation/transfection[25–31]		
Host cell	Species differences in protein expression, posttranslational modification	HPLC, SDS-PAGE, capillary electrophoresis
Method	Differences in protein expression based on the amount of coding DNA successfully introduced into the organism.	SDS-PAGE, Southern blot (to evaluate DNA levels)
Cell culture[10,30–33]		
Growth conditions (temperature, media, oscillation of cells)		
Purification[10,34]		
Method of purification	Amount of protein produced, presence of posttranslational modifications; presence of protein degradation products, aggregates and insoluble protein	HPLC, SDS-PAGE
Removal of epitopes	Presence of epitope in final formulation; additional damage to protein during removal	SDS-PAGE/western blot, capillary electrophoresis
Formulation and packaging[14,15]	Change in the level of aggregated protein.	HPLC-MS

HPLC = high-performance liquid chromatography; HPLC-MS = high-performance liquid chromatography–mass spectrometry; RT-PCR = reverse transcriptase–polymerase chain reaction; SDS-PAGE = sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

RESULTS

In total, our search revealed 22 original comparative analyses of biosimilars and originator biologics along with 24 reviews related to this topic. A total of 16 regulatory assessments of biosimilars were also reviewed along with a majority of the available regulatory guidance on the subject. In addition, 9 original research articles relating to process variation and its effects were reviewed.

Microheterogeneity of Biologics and Biosimilars

Biologic drugs are distinguished from LMW drugs by their microheterogeneity.[10] Their molecular complexity and sensitivity to environmental factors place constraints on the stepwise evaluation and control of production. Common sources of variation due to process are described subsequently and are summarized in Table I.[10,21–34]

Cell System

The first step in the manufacture of protein biologics is the development of genetically engineered cells by transfection of complementary DNA (coding sequence of a gene) expression vectors in specific cell systems to produce the protein (biologic) of interest.[21–24] The desired cell line is genetically engineered to contain selection markers that respond to an antibiotic or inducing

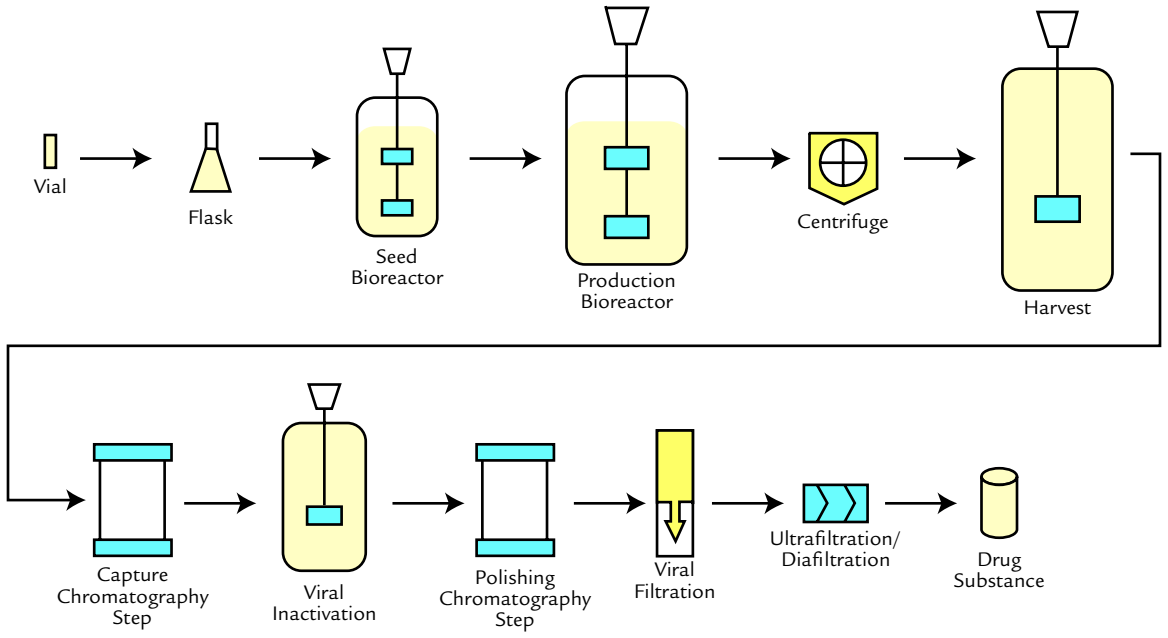

Figure 3. Overview of the manufacturing and production processes of a recombinant biologic in a mammalian cell system. The production process is initiated by the small-scale expansion of the master batch stock culture, which is checked for quality. The starter culture is expanded into a seed bioreactor for initial growth of the cells. In the production phase, seed cultures are transferred to the production bioreactor under conditions optimized for growth and recombinant protein production. The cultures are collected through an ultracentrifugation process. The cell- and debris-free supernatants are then harvested and purified. The recombinant protein is purified from the culture media by capture chromatography, and the eluted product is treated for viral inactivation and further processed by a specific polishing chromatography step and filtered to remove viral particles. Following a final ultrafiltration process, the recombinant protein (ie, the drug substance) is extensively characterized prior to formulation and packaging.

agent added to the bioreactor to facilitate large-scale production, secretion, or processing of the recombinant protein product.[35] Once a cellular population with optimum features has been identified, it is saved as a master cell bank for all future production use.

Commonly employed cell systems include yeast, baculovirus, *Escherichia coli,* and mammalian cells. The output of the desired protein is dependent on the choice of cell system; yeast and *E coli* are the organism(s) of choice for the production of nonglycosylated protein biologics (eg, insulin, growth hormone, calcitonin), and mammalian cell lines are preferred for the production of glycosylated proteins (eg, recombinant human [rHu] erythropoeitin [EPO], rHu granulocyte colony-stimulating factor [G-CSF], antibodies).[25–31,35] In mammalian cell systems, variability in the endogenous endoprotease activities and glycosylation patterns of proteins are species and tissue specific.[30] For example, rHu EPO produced in different cell lines (lymphoblastoid cells vs Chinese hamster ovary cells) has different patterns of glycosylation.[26] The incidence of *N*-glycan carbohydrate chains in rHu EPO products may also have an impact on the potential immunogenicity.[28,29] A brief overview of the typical manufacturing process for a protein biologic or biosimilar produced in a mammalian cell culture is provided in Figure 3.

Cell Culture Environment

The robustness and performance of a manufacturing system is measured by cell growth, productivity, and product quality.[32] Cell culture conditions used to propagate cells during the manufacture of biologics are crucial for optimizing yield, facilitating desirable post-translational modifications, reducing aggregation, preventing degradation, and minimizing

bath-to-batch variation.[32,33,36] Changes in fermentation media formulations may lead to heterogeneity in amino acid sequences, glycosylation patterns, and protein multimerzation.[10,34,37] Cell culture environments (temperature, pH, osmolarity, pCO_2), level of metabolites (glucose, glutamine, lactate, ammonia), and cell density must be carefully optimized to reduce cell stress during production. Cell stress can lead to aberrant glycosylation, protease activity, protein truncation, disulfide shuffling, and the release of undesirable byproducts and cellular wastes.[10]

Extraction, Purification, and Formulation of Proteins

Processes occurring during the extraction and purification of proteins, such as oxidation, reduction, deamination, and fragmentation, have the potential to cause damage to proteins through denaturation, conformational changes, and the formation of protein aggregates and process-related impurities.[10,20] Crucial considerations in purification include the choice of detergent or solvent for extraction, optimal filtration systems and column material, input protein concentration, pH, solvent system, and ionic strength and charge for the final purification steps.[10] Following purification, analytical techniques, such as peptide mapping, chromatography (eg, HPLC, MS, and nuclear magnetic resonance) must be used to verify integrity, purity, and homogeneity of the final product relative to a reference standard or innovator compound in the consideration of biosimilars.[10]

Regulatory Processes for Biosimilars

The EMA was the first regulatory body to establish a legal process and issue guidelines for the approval of biosimilars, in October 2005.[38] As of August 2011, 14 marketing authorizations were approved by the EMA (**Table II**).[39–63] The EMA guidelines for applying for the approval of biosimilars differ from the Hatch-Waxman–style ANDA in that the manufacturers of biosimilars must provide both comprehensive CMC data and data from preclinical and clinical comparisons of the proposed biosimilar and a reference originator product prior to market authorization (**Figure 1**). Manufacturers of biosimilars must also commit to levels of postapproval pharmacovigilance and risk management that are comparable to those of the reference product.[64] In addition to the EMA guidelines, WHO issued in 2009 general guidance on the development of biosimilars (aka similar biotherapeutic products) for its member countries.[65] Australia adopted the EMA guidelines, whereas Japan and Singapore issued guidelines in 2009, followed by Health Canada in 2010.[66–69]

The intent of these guidelines is to create a process for applicants seeking to demonstrate that a biosimilar product is similar to the reference product in terms of quality, efficacy, and safety profile. Major areas of emphasis include the use of a reference product as a comparator, a full quality dossier with reports of adequate comparability versus the reference product, and an abbreviated clinical data package.

Because biosimilar development is a stepwise process involving the initial demonstration of biosimilarity at the CMC and quality levels, followed by nonclinical studies and clinical trials, the EMA guideline specifies the use of the same comparator throughout development.[38] The active substance in the biosimilar must be highly similar to that of the reference product and should have been approved in, and procured from, the EU region. Additionally, the pharmaceutical formulation, strength, and route of administration should be the same as that of the reference medicinal product. Other international guidelines make similar recommendations, with varying degrees of flexibility in allowance for the use of reference drugs not marketed in the regulatory jurisdiction.[65–69]

Biosimilars must be fully characterized in their physicochemical and biophysical attributes, including amino acid sequence; secondary, and tertiary structure, impurity profile, excipients, and bioactivity.[70] The general EMA guideline for biosimilars suggests that current state-of-the-art tests be used to assess these quality characteristics, and that if multiple tests are available, orthogonal techniques be applied.[71] These tests are similar to those described in **Table I** and may include assays to evaluate structure at all levels, as well as size, charge, hydrophobicity, immunoreactivity, and glycosylation patterns. Following the demonstration of physicochemical comparability, studies in animals may be conducted to compare the in vivo bioactivity and tolerability of the biosimilar and the reference biologic. Quality assessments for biosimilars also include direct head-to-head comparisons to a reference biologic.[71] These comparability studies are similar to the traditional requirement of a full quality dossier for new biologic medications (which may include comparisons to the purified native compound) but represent an ad-

Table II. List of biophysical comparability findings and statistically significant differences in clinical efficacy and tolerability for EMA-approved applications of biosimilars.

Generic/Reference Brand/Biosimilar Brand	Significant Biophysical Differences	Significant Clinical Variation		
		Clinical Pharmacology	Efficacy	Tolerability
Somatropin (rDNA origin) injection				
Genotropin®[a] (reference)				
Omnitrope®[b]	Yes[39]	Yes[40]	No[39,41–43]	Yes[39,41–43]
Humatrope®[c] (reference)				
Valtropin®[d]	No[44]	No[44]	No[45,46]	No[45,46]
Filgrastim				
Neupogen®[e] (reference)				
Nivestim™[f]	No[47]	No[48,49]	No[50]	No[50]
Zarzio®[b] and Filgrastim Hexal®[g]	No[51]	No[52]	No[52]	No[52]
XM02 (TevaGrastim®,[h] Biograstim®,[i] Filgrastim Ratiopharm®,[j] and Ratiograstim®[j])	No[53]	No[53–55]	No[56]	No[56]
Epoetin				
Epoetin alfa (Eprex®,[k] Epogel®,[e] Procrit®,[e] and Erypo®[l]) (reference)				
HX575 (Binocrit®,[b] Epoetin Alfa Hexal®,[g] Abseamed®[m])	Yes[57,58]	No[57,59]	No[57,60]	No[57,60]
Epoetin zeta (Retacrit®,[f] and Silapo®[n])	Yes[61]	No[61]	No[61–63]	No[61–63]

[a]Trademark of Pfizer Inc., New York, New York.
[b]Trademark of Sandoz, Holzkirchen, Germany; a Novartis company.
[c]Trademark of Eli Lilly and Co., Indianapolis, Indiana.
[d]Trademark of Biopartners GmbH, Baar, Switzerland, and LG Life Sciences Ltd., Seoul, Korea.
[e]Trademark of Amgen Inc., Thousand Oaks, California.
[f]Trademark of Hospira, Inc., Lake Forest, Illinois.
[g]Trademark of Sandoz, Kundl, Austria.
[h]Trademark of Teva, GmbH Radebeul, Germany.
[i]Trademark of CT Arzneimittel GmbH, Berlin, Germany.
[j]Trademark of ratiopharm, Ulm, Germany.
[k]Trademark of Janssen-Ortho, Inc., Toronto, Ontario, Canada.
[l]Trademark of Janssen-Cilag SA de CV, Mexico City, Mexico.
[m]Trademark of Medice Arzneimittel Pütter GmbH & Co. KG, Iserlohn, Germany.
[n]Trademark of Stada Arzneimittel, Bad Vilbel, Germany.

ditional requirement for demonstrating quality not routinely required for nonbiologic medications. WHO and some national guidance documents recommend approaches similar to those taken by the EMA, emphasizing the importance of comparative studies in ensuring that the quality of the biosimilar is comparable to that of the original formulation.[65–69]

Following the provision of reports of similarity in quality attributes and nonclinical assessments, it must be established that any detectable or undetectable structure/quality differences between biosimilars and reference products do not result in variation in PK properties, efficacy, or tolerability. The extent to which clinical studies are needed is defined on a case-by-case basis, depending on differences in quality and preclinical comparability, mechanism of action, target population, availability of direct or well-accepted surrogate end points in the target

indications, as well as the risk/benefit profile of the reference product.[39,44,53,57,61,72–80]

Clinical comparability exercises are conducted in a stepwise manner, beginning with PK and pharmacodynamic (PD) studies and followed by clinical efficacy and tolerability trials.[64] Whenever possible, these studies should take into account potential PD effects as well as any findings of toxicity from studies in animals. The comparability of PK characteristics, such as clearance and elimination half-life, following the administration of biosimilar or reference drugs should be explored together with absorption and bioavailability. In addition, the study design employed should be justified based on the known and expected PK profile of the product in its intended population. PK and PD studies should be conducted in populations that are expected to be most sensitive to any possible changes in PK and PD properties that may result from differences between the originator and biosimilar.

When clinical efficacy trials are required, the primary objective is usually to demonstrate that the efficacy and safety profiles of the biosimilar are comparable to those of the reference drug. As illustrated in **Figure 1**, efficacy and tolerability studies are typically conducted to establish a foundation for comparability in the absence of fully predictive biophysical data. Most comparative efficacy trials are bioequivalence trials with a prespecified and agreed-on margin for bioequivalence.[65] Bioequivalence studies bear similarity to noninferiority studies in that they rely on information from prior studies of reference compounds to establish an acceptable margin of effect preservation. However, bioequivalence studies are powered to demonstrate that a product is neither inferior nor superior to a reference product, whereas noninferiority studies are 1-sided and can demonstrate only that a biosimilar product is not less effective than a reference product.[81] This difference is crucial because the 2-sided approach (ie, powered to show that a drug is neither worse nor better) is arguably more consistent with the principles of Hatch-Waxman, which allow for the approval or generics under the assumption that they are identical to the reference product. Although there is no single definition of a bioequivalence margin for efficacy, the WHO guidance states that "the selected margin should represent the largest difference in efficacy that would not matter in clinical practice."[65] Because they are based on clinical judgment, equivalence margins for biosimilars are neither well established nor universally agreed on. Therefore, the choice of margin size must be well justified by the applicant prior to study initiation. Justification is generally based on a combination of expert opinion and published analyses.

The data collected from the Phase I PK/PD studies and Phase III efficacy and tolerability clinical trials may be sufficient to establish comparable tolerability. If tolerability varies by approved indication, then the safety profile of the biosimilar should be equivalent for indications mostly likely to show differences between the 2 products.

Immunogenicity is a safety risk of all protein drugs and, according to the EMA guidelines, must be investigated.[82] The approach to immunogenicity testing generally consists of antibody screening assays combined with an evaluation of long-term tolerability data. The evaluation of the immunogenicity of a biosimilar must be assessed in direct head-to-head comparative studies (which may initially include nonclinical testing). Once approved, biosimilars must be monitored on an ongoing basis through a postmarketing risk-management plan set in place prior to marketing.

Quality throughout the life cycles of most biologics is evaluated regularly for batch-to-batch variability. Quality may be compromised as a result of process drift or intrinsic variation in the manufacturing process. Such evaluations are typically limited to the biophysical characterization of the different batches (key parameters, with extrapolation of significance) and are regulated by the quality divisions of regulatory agencies.[10,83] For more extensive changes in manufacturing process or for process improvements, the FDA and EMA provide extensive guidelines for concluding bioequivalence under the same label between the pre- and postchange products.[70,71,84] These guidelines stress that changes should not be classified as major or minor because the extent of a change is not predictive of potential clinical consequences, and that comparability studies between the pre- and postchange products should take into account the complexity of molecular structure, types of changes that may have been introduced by the manufacturing process, and the impact of these changes on quality and tolerability.[71] Characterization of the pre- versus postchange products is usually limited to biophysical attributes but may also involve more extensive clinical comparisons of efficacy and tolerability.[71,84]

Comparative Data on Biosimilars

Information from 14 marketing authorizations covering 7 development programs and referencing 4 inno-

vator products are described subsequently and summarized in Table II. The goal of this section was to review data from reports of significant differences in the efficacy and safety profiles of biosimilar products versus reference products and to highlight any relationships between those differences and the biophysical characteristics of each drug. Whenever possible, comparisons between the results from biophysical and clinical assays are made. The amount of data provided by the developers of the biosimilars at their initial approval stage is highly variable from product to product because the extent of clinical data required for the development of biosimilars is assessed on a case-by-case basis, based on the findings from the CMC and preclinical comparability studies, the risk/benefit profile of the product class, and the development approach taken by the applicant.

Somatropin

Somatropin (injectable rHU growth hormone) is a nonglycosylated 22-kD polypeptide growth factor produced in *E coli*. Somatropin is indicated for the normalization of growth in pediatric patients with growth hormone deficiency, short stature associated with Turner syndrome, idiopathic short stature, short stature homeobox–containing gene deficiency, and growth failure in children born small for gestational age. The drug is also indicated for growth hormone deficiency in adults.

Somatropin was initially marketed in the US and Europe beginning in 1987 under the brand name Humatrope®.[l,85] Somatropin marketed under the trade name Genotropin®[m] was approved in Europe in 1987 and in the US in 1995.[86] A biosimilar version of Genotropin, marketed as Omnitrope®,[n] became the first biosimilar product approved in the European Union, in December 2006. Omnitrope was approved in the United States, although not as a biosimilar, in May 2006 under Section 505(b)(2).[41] EU approval of somatropin marketed as Valtropin®,[o] a biosimilar formulation of Humatrope, was granted by the EMA in April 2006.[45] Subsequently, Valtropin gained FDA approval in April 2007.[46]

A 9-month Phase III comparison of Omnitrope to Genotropin was conducted in 89 prepubescent children deficient in growth hormone. The primary end points were height, height standardized for age and sex (height SD score), and height velocity SD score (HVSDS). In this study, similar increases in height and height velocity were reported with Omnitrope and Genotropin, including a HVSDS equivalent to an increase of 10.7 cm/y with both drugs (CI for the estimate of the difference in height velocity, −1.35 and 0.92).[42]1 Over the period of 9 months, the height increases were 113.3 to 121.9 cm and 109.3 to 117.7 cm (CI for the estimate of the difference in height between treatment groups, −0.59 to 1.06) in the Omnitrope- and Genotropin-treated groups, respectively. In a 12-month, Phase III, noninferiority efficacy study (noninferiority margin for the primary end point of height velocity at 12 months, −2.0 cm/y) in prepubescent children diagnosed with growth hormone deficiency, mean (SD) increases in height and height velocity were not significantly different between the groups treated with Valtropin and Humatrope (11.3 [3.0] and 10.5 [2.8] cm/y, respectively).[44] The 95% CI for the adjusted mean difference in height velocity for Valtropin was −0.71 to 0.90 and thus Valtropin was considered noninferior to Humatrope. When both the upper and lower confidence limits were considered, the 2 drugs were assumed to be bioequivalent.[44]

Filgrastim

Filgrastim (injectable methionyl rHu G-CSF) was initially marketed as Neupogen®[p] in 1991 for the treatment of cancer therapy–induced neutropenia and associated infections.[87] Since its launch, the approved indications for Neupogen in the United States have broadened to include bone marrow transplantation procedures, severe congenital neutropenia, aplastic anemia, and myelodysplastic syndromes.

Three biosimilar nonglycosylated formulations of filgrastim were approved for use in the European Union in September 2008 (Table II). All 3 are 175–amino acid, nonglycosylated methionyl rHu G-CSFs expressed in *E coli*. One is marketed under the name Nivestim™.[q] One is marketed under 2 brand names: Zarzio®[r] and Filgrastim Hexal®.[r] The third, called

[l]Trademark of Eli Lilly and Co., Indianapolis, Indiana.
[m]Trademark of Pfizer Inc., New York, New York.
[n]Trademark of Sandoz, Holzkirchen, Germany.
[o]Trademark of Biopartners GmbH, Baar, Switzerland.
[p]Trademark of Amgen.
[q]Trademark of Hospira, Inc., Lake Forest, Illinois.
[r]Trademark of Sandoz, Kundl, Austria.

XM02, is marketed under 4 brand names: TevaGrastim®,[s] Biograstim®,[t] Filgrastim Ratiopharm®,[u] and Ratiograstim®.[u] Filgrastim Ratiopharm was approved but subsequently withdrawn following the purchase of ratiopharm by Teva.

In a Phase I comparison of Zarzio/Filgrastim Hexal and the reference molecule Neupogen in healthy volunteers, the area under the effect curve was increased with increasing doses, but the dose-response effects of both drugs were modest (increases of ~20%).[78] The areas under the effect curve for neutrophil counts with Zarzio/Filgrastim Hexal and Neupogen use were not significantly different (for doses of 2.5, 5, and 10 μg/kg, geometric mean ratios ranged from 99.37% to 102.16%, with a 95% lower confidence limit ranging from 96.30 to 99.49 and an upper limit ranging from 102.54 to 104.91) and within the predefined acceptability limits for bioequivalence (2.5 μg/kg/d, 87.25–114.61; 5 or 10 μg/kg/d, 86.50–115.61).[78] A Phase III efficacy study in patients with breast cancer compared the duration of severe neutropenia during cycle 1 (the primary efficacy end point in that study) between XM02 and Neupogen. There were no significant differences in the durations of severe neutropenia (mean difference, 0.028 days [95% CI, −0.261 to −0.316]).[56] Similarly, in a Phase III efficacy comparison of Nivestim and Neupogen in patients receiving a doxorubicin/docetaxel combination therapy for breast cancer (margin for bioequivalence, absolute neutrophil count $<0.5 \times 10^9$ g/L in cycle 1), that the durations of severe neutropenia were not significantly different between the 2 treatments (adjusted mean difference, 0.38 days [95% CI, 0.08 to 0.68]).[50]

Epoetin

EPO injection is an endogenous 30-kDa glycoprotein indicated for the treatment of anemia. It stimulates erythroid proliferation and differentiation by interacting with erythropoietin receptors on committed red cell progenitors, particularly at the level of the CFU-erythroid.[88]

Epoetin alfa, a recombinant formulation of EPO produced as Epogen in the United States, received approval from the FDA in 1989 and was subsequently also made available as Procrit on the US market and as Eprex/Erypo worldwide.[89] In contrast to Epogen/Procrit, which contains human serum albumin as a stabilizing and antiadsorbent excipient, Eprex contains polysorbate 80.[90]

rHU EPO is produced by transfection of a mammalian system with either the EPO gene or EPO complementary DNA linked to an expression vector.[23] HX575 was the first EPO-stimulating agent with European marketing authorization (approved in August 2007) as a biosimilar to epoetin alfa and is distributed as Binocrit®,[v] Epoetin Alfa Hexal®,[w] and Abseamed®.[x]

Epoetin zeta is another epoetin biosimilar marketed in Europe (approved in December 2007) and distributed as Retacrit®[y] and Silapo®.[z] Both HX575 and epoetin zeta have glycosylation patterns different from that of epoetin alfa; however, both are approved as biosimilar formulations of epoetin alfa (**Table II**).

In a bioequivalence study in patients with anemia as a complication of renal insufficiency and who were undergoing hemodialysis, the mean (SD) changes in hemoglobin were 0.147 (0.092) and 0.063 (0.117) g/dL in the HX575 (biosimilar) and Eprex/Erypo (reference) groups, respectively. The treatment difference was 0.084 g/dL (95% CI, −0.170 to 0.338; predefined bioequivalence margin, ±0.5).[59,60]

In a bioequivalence study in anemic patients with end-stage renal failure receiving epoetin and long-term hemodialysis, the mean weekly dosage of epoetin alpha or epoetin zeta per kilogram of body weight was calculated and mean hemoglobin levels were measured during the last 4 weeks of treatment with Retacrit/Silapo (biosimilar) and Eprex/Erypo (reference).[62] Hemoglobin levels were maintained at ~11.4 g/dL with both Retacrit/Silapo and Eprex/Erypo. In the last 4 weeks, the mean (SD) hemoglobin values were 11.61 (1.27) and 11.63 (1.37) g/dL in patients treated with Retacrit/Silapo and Eprex/Erypo, respectively.[62] The 95% CI of the mean difference was −0.245 to 0.201 (predefined margin for bioequivalence, ±1.0). The mean weekly epoetin dosages by weight were 182.20 (118.11) and 166.14 (109.85) IU/kg/wk in Retacrit/Silapo and Eprex/Erypo, respectively. The 95% CI of the mean difference was −3.21 to 35.34. During the

[s]Trademark of Teva GmbH, Radebeul, Germany.
[t]Trademark of CT Arzneimittel GmbH, Berlin, Germany.
[u]Trademark of ratiopharm, Ulm, Germany.
[v]Trademark of Sandoz.
[w]Trademark of Hexal Forschungs Biotech GmbH, Oberhaching, Germany.
[x]Trademark of Medice Arzneimittel Pütter GmbH & Co. KG, Iserlohn, Germany.
[y]Trademark of Hospira.
[z]Trademark of Stada Arzneimittel, Bad Vilbel, Germany.

maintenance phase of the study, the 95% CI of the intraindividual difference (test/reference) in mean hemoglobin levels was 0.09 to 0.28 and was within the margin for bioequivalence (±0.6). Additionally, the 95% CI of the intraindividual mean difference in weekly dosage by weight was −4.67 to 4.29 and was within the margin for bioequivalence.

Quality, Structural Data, and Clinical Outcomes of EMA-Approved Biosimilars

The quality and clinical data reported for these biosimilars can be organized roughly according to the schema illustrated in **Figure 2**. None of the biosimilar compounds have been reported to have evidence of significant clinical variations from the reference formulations in the absence of corresponding significant biophysical or quality differences (**Table II**). Biosimilars for which no significant biophysical, PK, or clinical differences were observed between the biosimilar and reference formulations throughout the EMA approval process included Valtropin,[44–46] Nivestim,[47–50] Sandoz Filgrastim,[51,52] and XM02.[53–56]

Only Omnitrope was reported to have evidence of significant variation in both biophysical and clinical parameters in premarketing studies.[39–41] increased anti–human growth hormone antibodies were reported in up to 60% of patients exposed to an early noncommercial preparation of Omnitrope lyophilisate.[39,40] This variation was attributed to increased levels of undesirable host cell proteins in early Omnitrope preparations from a single manufacturing site. The presence of these antibodies did not demonstrably alter the efficacy or safety profile of Omnitrope.[41] Study drug from that site was not commercialized, and changes were made to the purification process of subsequent formulations.

Applications for which biophysical variations between biosimilar and reference formulations were observed in the absence of statistically significant variations in clinical parameters included the biosimilar epoetin formulations HX575 (Binocrit, Epoetin Alfa Hexal, and Abseamed) and epoetin zeta (Retacrit and Silapo).[57,61,91]

Characterization of the protein structure of HX575 using peptide mapping with different proteases revealed an identical primary structure.[74] Investigations of the secondary and tertiary structures reported correct folding of the molecules and batch-to-batch consistency. On monosaccharide and site-specific glycan analysis of the active substance isolated using immunoaffinity chromatography, levels of phosphorylated mannose-6-phosphate (HM6P) structures were higher in HX575 than in Eprex/Erypo, located exclusively on glycosylation site Asn-24. These structures were considered to be common glycoforms of recombinant EPOs; similar structures have been described for other recombinant cytokines and a large variety of nonlysosomal proteins from human plasma.[59,91–93] In receptor binding studies, the HM6P-structures on EPO showed weak binding affinity to the M6P receptor in contrast to classic M6P-binding proteins such as lysosomal hydrolases and, therefore, were not expected to mediate internalization under physiologic conditions. The level of HM6P observed in HX575 did not affect the efficacy or safety profile of the drug product.

HX575 was reported to have lower values of *N*-glycolyl-neuraminic acid and diacetylated neuraminic acids compared with Eprex/Erypo. A comparison of the total molecules with respect to molecular size and aggregation state, binding affinity, and biological activity in vitro and in vivo did not report any remarkable differences. Peptide mapping comparability exercises between the drug products HX575 and Eprex/Erypo reported some differences in the region corresponding to fragments, including the *O*-linked glycan, due to a higher sialylation. For the 2000-IU/mL presentation, HX575 tended to have a lower content of the oxidized variant, significantly lower amounts of subvisible particles, and a lower content of silicone oil than Erypo/Eprex. Findings from comparisons performed at the drug-product level were generally considered to be within the variability of Eprex/Erypo.[59] Following the regulatory approval of Binocrit in Europe, evidence of additional differences in quality between Binocrit and Eprex was reported, including the presence of a unique isoform, and variation in isoform ratio relative to Eprex/Erypo.[91] Despite these variations, no increased immunogenicity was found with HX575 versus Eprex/Erypo. In 2 pivotal PK studies in healthy volunteers, after multiple-dose intravenous and subcutaneous administration, the 90% CIs of the treatment differences in AUC and C_{max} fell completely within the acceptance range of 80% to 125%.[59] The pivotal therapeutic equivalence study for the approval of Binocrit was a comparative study of intravenous Binocrit in patients with chronic renal failure on hemodialysis. In that study, the CI of the treatment difference in mean absolute change in hemoglobin was within the predefined range of ±0.5.[59]

Table III. Biophysical comparability findings and statistically significant differences in clinical efficacy/tolerability for EMA-rejected applications of biosimilars.

Generic/Reference Brand/Biosimilar Brand	Significant Biophysical Differences	Significant Clinical Variation		
		PK	Efficacy	Tolerability
Interferon alfa-2a				
Roferon-A* (reference)				
Alpheon†	Yes[94,95]	Yes[94,95]	Yes[94,95]	Yes[94,95]
Human insulin				
Humulin®‡ (reference)				
Insulin Human Rapid Marvel, Insulin Human 30/70 Mix Marvel, and Insulin Human Long Marvel§	Insufficient data[96]	No[96]	Yes[96]	No[96]

*Trademark of Hoffmann-La Roche Inc., Nutley, New Jersey.
†Trademark of Biopartners GmbH, Baar, Switzerland.
‡Trademark of Genentech USA, Inc., South San Francisco, California.
§Trademark of Marvel LifeScience Ltd., Middlesex, United Kingdom.

For epoetin zeta (Retacrit), biophysical characterization showed intact primary and secondary structures with correctly linked disulfide bonds, integrity of the *C*- and *N*- termini, minimal degradation caused by oxidation and deamidation, and alpha helix bundle topology conforming with that known for EPO. In comparability exercises, evidence of a similar profile with respect to antennarity and sialylation was provided, even on subfractionation of glycans of both products.[61] Based on high-performance size exclusion chromatography and ELISA data used for the assessment of monomer content, the mean (SD) ratios of the total AUC of the fluorescence detection and the AUC ultraviolet detection at 280 nm were comparable between Binocrit (6.62 [0.27]), Retacrit (6.74 [0.07]), and Eprex (reference; 6.57 [0.37]). Furthermore, Binocrit and Eprex were reported to have similar protein content, whereas Retacrit was reported to have a numerically but not significantly lower protein content than Eprex ($P = 0.06$).[91] Retacrit was also reported to have evidence of reduced monomer content and variation in isoform proportions relative to Eprex/Erypro.[91] The therapeutic equivalence of intravenously administered Retacrit and the reference product Erypo was evaluated in 2 Phase III clinical studies (correction and maintenance phases) in patients with anemia due to chronic renal failure undergoing hemodialysis.[59,63] In both the maintenance and correction phases, the 95% CIs of the intraindividual differences (test/reference) of the mean hemoglobin level and mean weekly dosage were within the predefined range for bioequivalence of ±0.5 to 0.6.[59,63]

Rejected and Withdrawn EMA Applications

Not all biosimilar applications to the EMA have met with favorable review, and the regulatory timeline from the initial solicitation of advice from the EMA's Committee for Medicinal Products for Human Use (CHMP) to final approval varies from case to case. In addition, as of July 2011, the EMA had rejected 1 biosimilar application, and 3 applications were withdrawn based on CHMP determinations (**Table III**).[13,94–96] In the case of Alpheon®,[aa] one of the major concerns raised by the CHMP regarded the comparability of Alpheon and Roferon®-A[bb] (reference), noting in particular differences identified between the 2 medicines (eg, impurities).[95] In addition, there was concern about insufficient data on the stability of the active substance and of the medicine to be marketed. The CHMP also stated that the process used for making the finished medicine had not been adequately validated. In terms of clinical comparability, Alpheon and

[aa]Trademark of BioPartners GmbH.
[bb]Trademark of Hoffmann-La Roche Inc., Nutley, New Jersey.

Roferon-A were similar in the treatment of hepatitis C; however, the rate of disease return and the prevalence of adverse events were greater in the Alpheon group, suggesting inferiority.[13] Finally, the tests used to monitor for immunologic responses were not sufficiently validated. Thus, it was the opinion of the CHMP that Alpheon could not be approved as a biosimilar formulation of Roferon-A.[95]

The requests to market 3 formulations of human insulin (Insulin Human Rapid Marvel, Insulin Human Long Marvel, and Insulin Human 30/70 Mix Marvel[cc]) as biosimilar formulations of Humulin(R)[dd] (Humulin S, Humulin I, and Humulin M3) were also withdrawn following determinations by the CHMP.[96] The main concern of the CHMP was a lack of evidence for the comparability of the Marvel insulins and the Humulin insulins. In fact, it was the opinion of the CHMP that the main study indicated a trend in favor of Humulin in lowering blood glucose levels in healthy volunteers compared with the Marvel insulins (suggesting their inferiority). The CHMP was also concerned that the company had not supplied enough information on the manufacturing processes of the active substance and the finished products, and that those processes had not been validated. It was the view of the CHMP that Insulin Human Rapid Marvel, Insulin Human Long Marvel, and Insulin Human 30/70 Mix Marvel could not be considered as biosimilar to the reference medicinal products Humulin S, Humulin I, and Humulin M3.[96]

DISCUSSION

Variation among and between originator biologics and their biosimilars is an attribute of their molecular complexity and the manufacturing processes that contribute to their heterogeneity. Regulatory processes seek to quantify and understand these effects. Currently, the question of how similar a biosimilar must be to a reference drug to gain approval cannot be answered by any single standard set of methodologies. Abbreviated approval processes for biologic products present challenges given the scientific and technical complexities associated with their larger and often more complex structures compared with LMW chemically synthesized products. In 2006, the EMA became the first regulatory body to establish a process and to provide guidance for the approval of biosimilars. Since that time, 7 biosimilars (with multiple marketing applications) have been approved under these guidelines. Data from comparability evaluations and clinical trials supporting these applications are reported widely in the literature, allowing for guarded assessment of this regulatory process. Such an assessment has important ramifications for the regulation of biosimilars in the United States, where the recently established approval pathway currently lacks the detailed product-specific guidance enacted by the EMA. Recently, EMA officials developed relationships with the US regulatory bodies to serve as consultants in the development of the US guidelines.[97]

The EMA guidelines emphasize comparable quality, tolerability, and efficacy, as well as the need for clinical trials and postmarketing risk management. Going forward, it will continue to be important to evaluate the predictive value of each of these exercises in terms of the subsequently available postmarketing efficacy and tolerability data; thus, the predictive value of detectable variations in quality is of key importance. Given the trend toward both the increased complexity of biosimilars and an increased ability to detect biophysical variation, comparative studies are likely to paint differences in quality with an ever-finer brush. Regulatory bodies have taken the position that for a treatment to be designated as biosimilar to the reference drug, evidence of molecular similarity to the reference drug must be provided at the maximum resolution achievable by current state-of-the-art technologies available for physicochemical characterization, in addition to functional assays and clinical trials. Failing to meet this standard, the compound can be approved only via the pathway for novel biologic agents. From the standpoint of public access to high-quality, affordable biologic medicines, an approval process that results in full applications for clinically equivalent biologics is highly undesirable because it may lead to a proliferation of essentially identical agents, each with minor changes in prescribing criteria. Such a system may generate confusion among health care providers in choosing appropriate treatments, and it may not result in any cost savings. This situation would be especially problematic in cases in which the compounds have no discernible clinically differentiated target populations.

Qualitative comparability requirements between an originator biologic and its biosimilars are similar in scope and technical rigor to the detailed comparability exercises that manufacturers of originator biologics

[cc]Marvel LifeScience Ltd., Middlesex, United Kingdom.
[dd]Trademark of Eli Lilly and Co.

are required to carry out for major in-house changes in manufacturing processes for the certification of new batches and process improvements. Batch consistency reflects the quality of the development process and production procedures. Although variations in the batch-to-batch consistency of biologics are quite common, these variations, if maintained within the acceptable range, are usually not clinically meaningful based on the available data on approved biosimilars (**Table II**) and originators that have undergone manufacturing changes.[83] Manufacturing-process changes undertaken with most biologics can be extensive over the course of the product life cycle but rarely require systematic clinical trial evaluation of comparability between the pre- and postchange products. Empirical evidence suggests that microheterogeneity in biophysical parameters among originators and biosimilars does not necessarily result in any significant differences at the clinical level. Biosimilars and originators that have undergone manufacturing changes have been approved in the European Union despite minor differences in comparability versus respective reference products, either in physicochemical or PK characteristics, and evidence of similarity in their clinical efficacy and safety profiles has also been reported.[58,59,74,83] For these reasons, the requirements for clinical trials should be evaluated case by case.

CONCLUSIONS

Observations from comparative studies of approved biosimilars offer an opportunity to frame the discussion beyond the microheterogeneic level and suggest that careful consideration is needed of the role of active-controlled clinical trials for the assessment of the efficacy and tolerability profiles of biosimilars. Experience from Europe and other regions support the concept that the quality and comparability standards applied for process changes for the originator biologic products may be applied for biosimilar-development programs when the risk/benefit profile of the originator is well characterized. The outcome of the ongoing discussion of these issues will affect the availability of affordable biosimilars for target populations in the near future.

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All authors contributed equally to the conduct of the study and creation of the manuscript.

CONFLICTS OF INTEREST

Dr. Ahmed is employed by Hospira, Inc. Dr. Sharma and Mr. Kaspar are employees of MMS Holdings Inc., a contract research organization that supports Hospira with various activities, including data programming and writing.

The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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