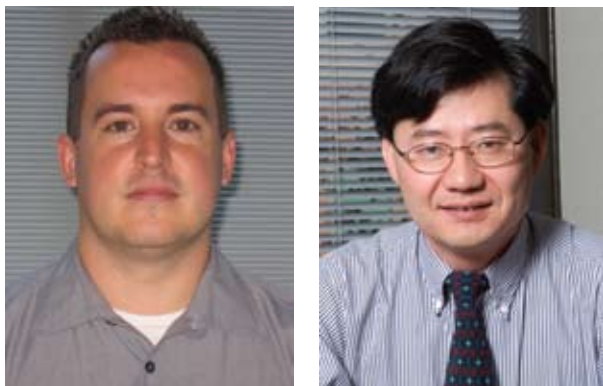


Current Considerations for Biosimilar Therapeutics

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Abstract

Biopharmaceuticals are typically large (protein-based), structurally complex, heterogeneous drugs produced by living organisms including bacteria, yeast, and mammalian cell lines. As patents for many of the currently marketed biopharmaceuticals will or already have expired, great interest and debate in the development and regulation of generic biopharmaceuticals has been evolving. Due to their complexity and heterogeneity, 'generic' is not an accurate term to describe follow-on versions of biopharmaceutical drugs. To better reflect the difficulties in their characterization as compared to conventional small molecule-based generic drugs, the terms biosimilar or follow-on protein products have been widely used. Worldwide regulatory authorities have realized that a pathway for development and marketing approval of biosimilars will require a different structure and guidelines as compared to conventional generics to ensure the quality, safety, and efficacy of the therapeutics. Systems of guidelines and regulations have already been put in place by many regulatory authorities (e.g. European Medicines Agency) and biosimilar products approved, while others (e.g. United States FDA) continue to debate the possibilities. This review will broadly cover the regulatory and development considerations for biosimilar products. Examples of currently marketed biosimilar products are also presented.

1. Introduction

Biopharmaceuticals include a broad range of therapeutic products produced by complex biosynthetic manufacturing processes that utilize living organisms for production. The diversity in biopharmaceuticals include differences in their sizes and structure, glycosylation patterns, manufacturing platforms, and uses. Some common uses of biopharmaceuticals include supplementation or replacement of factors that

are deficient due to a disease or treatment of disease, neutralization or stimulation of disease-related or -inducing molecules, and attack of cancerous cells or pathogenic organisms. This range of uses is reflected in the wide array of types of biopharmaceuticals including monoclonal antibodies, interferons, anti-hemophilic factors, hormones, vaccine products and others. As a result of their diversity and utility, the biopharmaceutical market is large and growing at twice the rate of conventional drugs. In 2007 the market was estimated to be \$79 billion and growing at a rate of approximately 15% per year^[1]. Patents on many of these biopharmaceuticals will be or already have expired creating an opportunity for generic biopharmaceutical development.

The term generic, as applied to conventional non-protein small molecule drugs, is not used to describe biosimilar versions of biopharmaceuticals due to their complexity and current limitations in their characterization. Conventional generic drugs are defined by the U.S. Food and Drug Administration (FDA) as “identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use”^[2]. Conventional small molecule-based generic drugs can be scientifically characterized and accurately described as being pure, homogenous, and containing the same active ingredient as the innovator drug. Biopharmaceuticals are large (thousands to several hundred thousand daltons), structurally complex, heterogeneous drugs produced by living organisms. As a result biopharmaceuticals can not currently be characterized to the same degree using state-of-the-art analytical methods. Instead one must rely on *in vitro* and *in vivo* comparative experiments and clinical trials to thoroughly characterize and compare the safety and efficacy of biopharmaceuticals. Due to these fundamental differences, the term “generic biopharmaceuticals” has not been used by the scientific community or the regulatory agencies worldwide to describe these therapeutics. To better reflect the difficulties in their characterization, more descriptive terms have been adopted, including “follow-on protein products” and “follow-on biologics” by the U.S. FDA and “biosimilars” by the European Medicines Agency (EMA). However, even when these terms are applied, much debate still exists around what defines a protein therapeutic as biosimilar.

Strong ethical and financial justification has driven the interest and debate in the development of biosimilar drugs. There is a great need for cheaper alternatives to branded biopharmaceuticals by the sick people who can be helped by them and the public and private insurances

that pay for them. Treatment with modern biopharmaceuticals can cost from tens of thousands to hundreds of thousands of U.S. dollars per year per patient. The U.S. Congressional Budget office has estimated that creating a pathway for approval and marketing of biosimilars could cut spending on prescription drugs in the U.S. by \$25 billion between 2009 and 2018^[3]. The definitions, development pathways, and regulations will continue to be debated, developed, and refined in the near future as further experience is gained in the development and use of biosimilars worldwide.

2. Regulatory Considerations

An applicant attempting to gain approval for a conventional generic drug generally has decreased data requirements when they have shown the generic copy is identical to the innovator reference drug in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use. However, the requirements for approval of biosimilar products are greater and more complex when compared to a conventional generic. The requirements are usually decided on a case-by-case basis, based on the complexity of the therapeutic. Due to these complexities, regulatory authorities worldwide have realized that a pathway for marketing approval of biosimilars will require a different structure and guidelines as compared to conventional generics to ensure the quality, safety, and efficacy of the therapeutics. The European Union has led the world in creating such a pathway, putting in place a system of guidelines and regulations. Many other countries have also followed suit, including India, South Korea, and Japan^[4]. The US regulatory agency and legislature have not yet issued guidelines or decided on an approval route, but several Bills laying out such a pathway are currently under debate^[5-7]. The current and developing regulations and guidelines in Europe and the United States are discussed below.

2.1 Europe

Current European Union (EU) regulations define and handle biosimilar therapeutics differently and separately from conventional generic drugs. Under the EU system, marketing authorization for medicinal products can occur through two different routes, the centralized procedure and the mutual recognition procedure^[8,9]. All products derived from biotechnology are required to use the centralized procedure. A series of EU Directives^[10-12] created a general abbreviated approval pathway for biosimilars. Biosimilar therapeutics, according to Directive 2004/27/EC, “similar to a reference medicinal prod-

uct do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecule characteristics and therapeutic modes of action. When a biological medicinal product does not meet all the conditions to be considered a generic medicinal product, the results of appropriate tests should be provided in order to fulfill the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both". These Directives require comparability studies to establish the similarity between the biosimilar and a reference protein therapeutic. The reference protein therapeutic must already be authorized and marketed in the EU, and thus clinical data and experience will be available. If comparability, in terms of quality, efficacy, and safety, is established, the biosimilar can rely on some of the reference product data thus decreasing the nonclinical and clinical studies required for approval.

As part of creating a rational and efficient approval process for biosimilars, the European Medicines Agency (EMA) has developed a series of guidance documents providing an applicant with advice on both the general process for approval and product-specific recommendations for establishing similarity (Table 1). One of the earlier general guidance documents, entitled "Guideline on Similar Biological Medicinal Products", broadly defines the requirements for biosimilar candidates based on their complexity. In general, as the complexity (structure, glycosylation, etc.) of the therapeutic increases or there is minimal understanding of the mechanism of action or clinical experience, the amount of studies required for establishing similarity increases. For some biosimilar candidates that can not be characterized to a satisfactory degree due to their complexity or lack of analytical procedures or clinical and regulatory experience, approval using the "similar biological medicinal product" approach might not be possible. The EMA issues product-specific guidelines on a continuous basis and has already issued specific guidelines for recombinant erythropoietins^[13], granulocyte-colony stimulating factor^[14], somatropin^[15], insulin^[16], interferon alpha^[17], and low molecular weight heparins^[18]. In general, each of the product-specific guidelines broadly outlines the requirements for establishing similarity in a step-wise fashion, from non-clinical studies to clinical studies to post-marketing pharmacovigilance. As a detailed analysis of these guidelines is beyond the scope of this review, the reader is referred to the EMA website for full access to the bisimilar guidance documents (<http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>).

2.2 United States

In the United States (U.S.), amendment of the Food, Drug, and Cosmetic Act (FDC Act) through enactment of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) in 1984 created an abbreviated approval pathway for generic small molecule drugs. However, biopharmaceuticals are regulated under the Public Health Service Act (PHS Act) and must apply for market entry through a Biologics License Application (BLA) under that act. As a result, an abbreviated approval pathway for BLA-approved products does not yet exist. It should be noted that some simple biopharmaceuticals were approved under the FDC Act for historical reasons and thus it may be possible to get biosimilar versions of them approved through the abbreviated process. In fact, several biosimilars (more or less) have been approved in the United States using this process, including Hylenex (hyaluronidase), Hydase (hyaluronidase), Amphadase (hyaluronidase), Fortical (calcitonin), Glucogen (glucagon), and Omnitrope (somatropin)^[19]. For the majority of biopharmaceuticals, approved using a BLA, an abbreviated process for biosimilar development is not applicable and a barrier to market entry currently exists.

As the requirements and process for approval of biosimilar therapeutics is still being debated in the U.S., to better understand the potential requirements one can examine the several biosimilars approved under Section 505(b)(2) of the FDC Act and the several bills introduced in the U.S. Congress to create such a pathway^[5-7, 19]. The data included for FDA approval of the several eligible biosimilar protein products (glucagon, salmon calcitonin nasal spray, somatropin, erythropoietin- α , and interferon- β 1a), showed, in comparison to a reference product, high structural similarity, highly similar pharmacokinetics and pharmacodynamics, and comparable (or improved) immunogenicity and safety data. It should be noted that despite approval, these products have not been declared as directly substitutable for the reference products. The three most recent bills introduced in 2009 to the 111th U.S. Congress would amend the PHS Act to allow licensure of a biosimilar product if that product is proven to be highly similar to a reference product. One of these bills requires approval if the biological product is shown to be biosimilar to a reference product for each condition of use for which the reference product is approved and satisfactory inspection of the manufacturing facility occurs^[6]. This same bill prohibits evaluation against more than one reference product and does not allow approval until 12 years after the date on which the reference product was first licensed. The other two bills allow approval if a high degree of simi-

Table 1. *European Medicines Agency - Scientific Guidelines for Biosimilars*

Guideline Type	Reference Number: Title	Effective Date
General	CPMP/ICH/5721/03: Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substance – Quality Issues	Dec 2003
General	CHMP/437/04: Similar Biological Medicinal Product	Oct 2005
General	CHMP/42832/05: Similar Biological Medicinal Products containing Biotechnology –Derived Proteins as Active Substance – Non-clinical and Clinical Issues	Jun 2006
General	CHMP/49348/05: Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues	Jun 2006
General	CHMP/BMWP/101695/06: Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process – Non-clinical and Clinical Issues	Nov 2007
Immunogenicity	CHMP/BMWP/14327/06: Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins	Apr 2008
Immunogenicity	EMA/CHMP/114720/2009: Immunogenicity Assessment of Monoclonal Antibodies Intended for in vivo Clinical Use	Mar 2009 ¹
Specific - Insulin	CHMP/32775/05: Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Recombinant Human Insulin	Jun 2006
Specific - Somatropin	CHMP/94528/05: Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Somatropin	Jun 2006
Specific – G-CSF	CHMP/31329/05: Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Recombinant G-CSF	Jun 2006
Specific - EPO	CHMP/94526/05: Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Recombinant Erythropoietins	Jun 2006
Specific – interferon alpha	CHMP/BMWP/102046/06: Non-Clinical and Clinical Development of Similar Medicinal Products Containing Recombinant Interferon Alpha	Apr 2009
Specific – low molecular weight heparins	CHMP/BMWP/118264/07: Similar Biological Medicinal Products Containing low-molecular-weight-heparins	Oct 2009

¹Released for consultation

larity or interchangeability is shown compared to the licensed biological product (reference product) and the biosimilar product is safe, pure and potent [5,7]. These bills allow for a determination of interchangeability and grant market exclusivity to any biological product that is determined to be interchangeable. The debate on these bills is on-going and the date for passage of such legislation creating a regulatory pathway is uncertain.

3. Biosimilar Development Considerations

Development of a biosimilar molecule is essentially a comparability exercise, comparing the properties of biosimilar candidate molecules with those of a reference product. The goal of development is to match, as closely as possible, all of the known characteristics of the reference product. A company is starting with a known marketed, innovator molecule with established quality, preclinical, and clinical characteristics. As a result, the point at which a company begins work on a biosimilar therapeutic in the drug development process is typically much more advanced than when developing a novel biopharmaceutical. One must start with obtaining all the information possible about the reference product to allow proper design, manufacture, and comparability of the biosimilar product. Significant aspects of critical information for development may be unavailable or kept as trade secret, such as information related to manufacturing process, and will need to be developed.

3.1 Manufacturing

One of the earliest considerations is how the biosimilar therapeutic will be produced. A manufacturing platform/process that yields a biosimilar therapeutic that closely matches the innovator reference product is a critical challenge.

Biopharmaceuticals are produced using complex biosynthetic manufacturing processes that use living organisms, including mammalian cell lines, bacteria, or yeast, as producers. Even when the exact same cell type as the reference product is chosen for the biosimilar product, the resulting product may still differ in key biological properties including glycosylation, microheterogeneity, and immunogenicity. These living organisms have an inherent variability and one must ensure that their production process and resulting product are well defined and highly consistent. In comparison, most small molecule drugs are manufactured utilizing a series of chemical syntheses and purifications. Due to these production differences, the product of the chemical synthesis will be pure and homogenous while the biopharmaceuti-

cal product will be well defined yet heterogeneous. As a result, one can accurately characterize a generic small molecule drug as being pure, homogeneous, and containing the same active ingredient as the innovator drug while protein therapeutics can not currently be characterized to the same degree using state of the art science and analytical technology. For biopharmaceuticals, a classic term to describe these manufacturing challenges is 'process equals product'. Even minor variations in the manufacturing conditions of a biopharmaceutical can lead to large effects on the quality, safety, and efficacy of the final product. For biopharmaceuticals, most regulatory authorities require that not only the product meet defined criteria, is reviewed and approved, but also the manufacturing process and facilities meet requirements for consistent production. Thus, biosimilar product manufacturers must ensure their manufacturing process is consistently producing a biosimilar candidate that is comparable to the reference product.

3.2 Comparability exercises

Due to this variability in the manufacturing process, drug complexity, and the inability to completely characterize the resulting biosimilar product to the same degree as done for conventional generic drugs, one must rely on comparability exercises at all steps in the biosimilar development process. Each of the regulatory authorities has developed or is developing their own set of guidelines/regulations laying out the general requirements for the types of comparability data that should be generated. One can examine the various guidelines that are available to get an idea of the common, general comparability exercises that should be conducted. These comparability exercises must occur at all levels of development, including comparisons of quality, pre-clinical efficacy and safety, and clinical studies (including immunogenicity). The goal of all of the studies should be the generation of the right kind and amount of data to detect differences and establish a high degree of similarity between the biosimilar and reference product allowing for regulatory approval and safe, efficacious clinical use.

During the initial development of the biosimilar product, a comparison of the quality of the biosimilar versus the reference product must be made. These quality comparisons typically include sequence, structural, and physico-chemical data. Differences or concerns in the quality of the biosimilar product will affect the type and amount of comparative nonclinical and clinical studies that will be required in further steps. Preclinical studies need to be performed to detect differences in the pharmacotoxicological response between the biosimilar and reference

products. These studies generally include *in vitro* studies (e.g. comparative bioassays), *in vivo* studies (e.g. pharmacokinetic (PK), pharmacodynamic (PD)), and toxicological studies (e.g. repeat dose toxicity). Clinical studies, including PK, PD, and efficacy studies, are a critical development component. In the EU, the EMEA guidelines typically recommend PK / PD studies in healthy volunteers, if appropriate. The EMEA also typically recommends a target study patient population, based on the product type, for demonstration of similar clinical efficacy. Required safety data can generally be generated from the efficacy trials. Most development plans stress the importance of comparative immunogenicity data. Finally, a pharmacovigilance plan where an applicant has developed a risk management plan taking into account identified and potential risks, immunogenicity, and rare/delayed serious adverse events is typically required.

3.3 Development of biosimilar monoclonal antibodies^s

The guidance for development and the approval pathway for larger, complex biopharmaceuticals, such as monoclonal antibodies, continues to be debated despite the approval of several more simple biosimilar products worldwide. Antibodies are large glycoprotein molecules, composed of four polypeptide chains (heavy and light chains) with an approximate molecular weight of 150 kDa (IgG). Due to this complexity compared to the currently approved more simple biosimilar products such as Omnitrope® or Biograstim®, the exercises to establish similarity between antibodies at both the preclinical and clinical levels will likely be a challenge. Designs for the production platform and processes for biosimilar antibodies must be carefully considered for their ability to produce a highly consistent, comparable product. Adding to this challenge, the production methods, characterization, and formulation are often kept as trade secrets or are protected by a complex myriad of patents. The methods for the initial comparability exercises at the preclinical quality level, including structural and physicochemical studies, are becoming more sophisticated with advances in the technology and are likely to detect differences. However, establishment of similarity at the quality level can still be debated. The increased complexity and less understood mechanisms of action of most therapeutic antibodies are also likely to lead to greater requirements for clinical studies^[19]. The EMEA has issued a draft document discussing the immunogenicity assessment of monoclonal antibodies, highlighting the critical value of the immunogenicity data generated from the studies^[20]. The continuing debate, lack of experience, and developing guidance and regulatory

documents make the challenges and risk for the current development of biosimilar antibodies higher than for other more simple biopharmaceuticals.

There have recently been two biosimilar monoclonal antibodies that have received marketing approval. The first biosimilar monoclonal antibody, called Reditux®, is a biosimilar version of the monoclonal antibody Rituxan® (rituximab; Genentech, Inc. and Biogen Idec, Inc.). This antibody was developed by Dr. Reddy's Laboratories and received approval in India in 2007 for the treatment of non-Hodgkin lymphoma^[21]. No information is currently available to study the exercises used to determine the similarity, safety, and efficacy of Reditux® compared to Rituxan®. A spokesperson for Dr. Reddy's claims the drug would act the same way and had the same properties as Rituxan®^[22]. The second biosimilar monoclonal antibody, called Clotinab®, is actually only the Fab fragment of an antibody. It was developed by a South Korean firm, Isu Abxis Co., as a biosimilar version of Reopro® (abciximab; Centocor and Eli Lilly and Co.)^[23, 24]. No further information is currently available to study the comparability exercises or the similarity, safety, and efficacy of Clotinab® compared to Reopro®.

4. Summary of Currently Marketed Biosimilars

Over the past 3 to 4 years, a variety of biosimilar products have gained approval and are currently marketed, including biosimilar erythropoietin (EPO) in the EU^[25-29], human growth hormone (HGH) in the U.S. and EU^[30-32], filgrastim in the EU and India^[33-39], and interferon in Argentina^[40]. Interestingly, a biosimilar version of the monoclonal antibody Rituxan® (Genentech, Inc. and Biogen Idec, Inc.), called Reditux™ was approved in India^[21]. Additionally, a biosimilar version of the antibody Fab fragment Reopro® (Centocor and Eli Lilly and Co.), called Clotinab®, was approved in South Korea^[41]. Finally, a biosimilar version of etanercept was approved in China^[42]. Numerous biosimilar products have been approved in the EU under their organized biosimilar regulations and guidelines. In the US, several biosimilar versions of protein therapeutics originally approved under the FDC Act have gained approval. The approvals in the US are limited to those products approved under the FDC Act. A detailed analysis of all of the currently marketed biosimilar products worldwide is beyond the scope of this review. To gain a good understanding of the products currently being developed, several types of biosimilar products recently approved and marketed in the EU are briefly introduced below, including EPO, HGH, and filgrastim. A brief summary of biosimilar products that failed to gain approval in the EU is also presented.

4.1 Erythropoietin

Erythropoietin (EPO) is a 165 amino acid glycoprotein with a molecular weight of 30 kDa of which 40 percent in carbohydrate^[43]. It is produced mainly in the kidney in humans and is used clinically to treat anemia in chronic renal failure and cancer patients and to reduce the need for blood transfusion in adults with mild anemia or expected complications before major surgery. EPO is the leading class of biopharmaceuticals in terms of sales and is available from a number of manufacturers including Amgen and Johnson & Johnson^[44]. EPO has been and will continue to be one of the biopharmaceuticals most immediately affected by biosimilar products due to the large market and patent expirations worldwide.

There are five marketed biosimilar EPO products currently available in the EU: Binocrit® (Sandoz GmbH), Epoetin alfa Hexal® (Hexal Biotech Forschungs GmbH), Abseamed® (Medice Arzneimittel Putter GmbH & Co.), Silapo™ (Stada Arzneimittel AG), and Retacrit™ (Hospira Enterprises B.V.)^[25-29]. These were all approved in 2007 using an abbreviated application process under Article 10(4) of Directive 2001/83/EC (amended by Directive 2004/27/EC). The first three, Binocrit®, Epoetin alfa Hexal®, and Abseamed®, are the same recombinant epoetin alfa product produced by the same manufacturer, Rentschler Biotechnologie GmbH. Three separate yet identical applications for marketing authorization were submitted to the EMEA by each of the Companies. All used Eprex/Erypro® (epoetin alfa, Janssen-Cilag GmbH) as the reference product for development and comparability exercises. The final two EPO products, Silapo™ and Retacrit™, are the same recombinant epoetin zeta product produced by the same manufacturer, Norbitec GmbH. The Companies developing these biosimilar products also used Eprex / Erypro® as the reference product and submitted separate yet identical applications for marketing authorization to the EMEA. All five products were determined to have comparable quality, safety, and efficacy profiles to Eprex / Erypro® and marketing authorization recommended by the EMEA. The European Commission (EC) granted Binocrit®, Epoetin alfa Hexal®, and Abseamed® marketing authorization in the EU on August 28, 2007 and Silapo™ and Retacrit™ on December 18, 2007.

4.2 Human Growth Hormone

Human growth hormone (HGH) is a pituitary-derived hormone used clinically as a replacement therapy in pediatric patients who have growth failure due to inadequate

secretion of normal endogenous HGH. It is one of the less complex biopharmaceuticals, as it is a single chain nonglycosylated polypeptide hormone consisting of 191 amino acids with a molecular weight of 22 kDa. Earlier marketed versions of HGH were obtained from the pituitary gland of human cadavers. For obvious reasons, more recent recombinant versions, also known as somatropin, were approved in both the EU and U.S. where they are available from a number of different manufacturers including Pfizer, Eli Lilly, Novo Nordisk, Genentech, and Serono. There is wide interest in developing biosimilar HGH due to its limited complexity, high global sales (\$2.5 billion in 2006), and patent expirations^[44].

There are two marketed biosimilar HGH products currently available in the EU: Omnitrope® (Sandoz GmbH) and Valtropin® (BioPartners GmbH)^[30, 31]. They were both approved in 2006 using an abbreviated application process under Article 10(4) of Directive 2001/83/EC (amended by Directive 2004/27/EC). The products were developed and applications submitted before the EMEA adopted guidelines addressing the development of biosimilar HGH, which only came into effect in June 2006. The development program for Omnitrope® used Genotropin® (Pfizer; originally approved in the EU in 1988) as the reference product while Valtropin® used Humatrope® (Eli Lilly; originally approved in the EU in 1990). Of note, Valtropin® was produced in yeast whereas the reference product was produced in *E. coli*, exemplifying the possibility of using a different host cell for biosimilar development. An initial application for marketing approval of Omnitrope® was submitted in May 2001, received a positive review by the EMEA, but was denied approval by the EC as a legal basis for the approval did not yet exist. The EU eventually created the approval pathway. Sandoz resubmitted its application (with additional data), and was granted marketing authorization on April 12, 2006. Valtropin® was shown to have comparable quality, safety, and efficacy to Humatrope® and was granted marketing authorization on April 24, 2006. Finally, Omnitrope® was also approved in the U.S. in May 2006 using an abbreviated pathway under Section 505(b)(2) of the FDC Act. This was possible as the reference product, Genotropin®, was approved in 1985 under Section 505(b)(1) of the FDC Act.

4.3 Filgrastim

Filgrastim is a recombinant version of human granulocyte colony-stimulating factor (G-CSF) that is used clinically to treat patients with neutropenia due to chemotherapy, HIV, or a history of severe, repeated infections (see^[45] for a review). Its activity is the same as that of

endogenous human G-CSF, but filgrastim is produced in *E. coli* and thus is not glycosylated and has an added N-terminal methionine. Branded filgrastim and pegfilgrastim (filgrastim conjugated to PEG) are sold under the brand names Neupogen® and Neulasta® from Amgen. Filgrastim is an attractive biosimilar candidate due to its ease of manufacture (*E. coli*), large market size (\$5.6 billion in 2007), and patent expirations^[46].

There are currently six marketed biosimilar filgrastim products available in the EU: Biograstim® (CT Arzneimittel GmbH), Filgrastim ratiopharm® (Ratiopharm GmbH), Ratiograstim® (Ratiopharm GmbH), Tevagrastim® (Teva Generics GmbH), Filgrastim Hexal® (Hexal AG), and Zarzio® (Sandoz GmbH). The first four filgrastim products, Biograstim®, Filgrastim ratiopharm®, Ratiograstim®, and Tevagrastim® are the same filgrastim product (active substance referred to as XM02 in applications) produced by the same manufacturer, SICOR Biotech UAB. Four separate yet identical applications for marketing authorization were submitted to the EMEA by each of the Companies. All used Neupogen® (filgrastim, Amgen) as the reference product for development and comparability exercises. The final two filgrastim products, Filgrastim Hexal® and Zarzio®, are the same filgrastim product produced by the same manufacturer, Sandoz GmbH. The Companies developing these biosimilar products also used Neupogen® as the reference product and submitted separate yet identical applications for marketing authorization to the EMEA. All six products were determined to have comparable quality, safety, and efficacy profiles to Neupogen® and marketing authorization recommended by the EMEA. The European Commission (EC) granted Biograstim®, Filgrastim ratiopharm®, Ratiograstim®, and Tevagrastim® marketing authorization in the EU on September 15, 2008 and Filgrastim Hexal® and Zarzio® on February 6, 2009.

4.4 Several Biosimilar products fail to meet EU regulatory requirements

Examination of products that have failed to gain marketing approval is just as important as studying those products that have gained approval. In the EU, the EMEA has not recommended approval for all biosimilar applications that have been submitted. The EMEA has recommended refusal of marketing authorization for a biosimilar interferon called Alpheon®. Additionally, marketing applications were withdrawn for Marvel® Insulins, biosimilar insulins, after the EMEA issued a list of questions and concerns. A brief introduction and reasons for refusal or withdraw are presented for each below.

4.4.1 Alpheon®

Alpheon® was developed by BioPartners GmbH as a biosimilar version of Roferon-A®. These products contain the active substance interferon alfa-2a. The marketing application for Alpheon® requested approval for use to treat adult patients with chronic hepatitis C. Of note, the reference product Roferon-A® is produced in *E. coli* while Alpheon® is produced in *Saccharomyces cerevisiae*. BioPartners GmbH had submitted non-clinical quality (including structure of the active substance, composition, and purity) and clinical data to establish similarity to the reference product. The clinical data included a randomized clinical trial in 455 hepatitis C patients to establish comparable efficacy and safety.

The EMEA recommended refusal of marketing authorization on June 28th 2006, due to major concerns of the comparability at the non-clinical and clinical levels between the two products^[47, 48]. The non-clinical data failed to establish similarity to Roferon-A® due to the following deficiencies: Qualitative and quantitative differences existed in the impurity profile. There were insufficient stability data representative of the drug substance available and a shelf life could not be assigned. Finally, the manufacturing process was not adequately validated. The clinical data also failed to establish similarity to Roferon-A® due to the following deficiencies: There were clinically and statistically significant differences in virological relapse rates found between the end of therapy and the end of the observation period. The data was inconclusive in the response rate for the “difficult-to-treat” genotype 1 patients. Additionally, there were different rates of adverse and laboratory-related events judged as clinically relevant. Finally, there was incomplete validation of the immunogenicity assays and methods leading to inadequate documentation of immunogenicity.

4.4.2 Insulin Human Marvel®

Insulin Human Marvel® (three separate medicines - Insulin Human Rapid Marvel, Insulin Human Long Marvel, and Insulin Human 30/70 Mix Marvel) was developed by Marvel LifeSciences Ltd. as a biosimilar version of Humulin® (Eli Lilly & Co.). These products contain the active substance insulin human. The marketing applications for Insulin Human Marvel® requested approval for use to treat patients with insulin-dependent diabetes mellitus, for the initial control of diabetes mellitus, and diabetes mellitus in pregnancy. Marvel LifeSciences had submitted limited non-clinical quality and clinical data to establish similarity to the reference

product Humulin. The clinical data included studies in 24 healthy volunteers looking at the effect of Marvel insulins on blood sugar levels compared with the Humulin insulins and a study in 526 diabetes patients receiving either Marvel insulins or Humulin insulins for up to 12 months.

The marketing application was withdrawn by Marvel LifeSciences at day 120 in the EMEA process after the Company received a list of questions from the EMEA [49, 50]. These questions related to the concerns with the application and the provisional opinion that the Marvel insulins could not be recommended for approval. The main concerns with the application were that the comparability of the Marvel insulins and the Humulin insulins had not been shown. The EMEA believed that Company had not submitted enough information on how the active substance or the finished products were made. They also believed that the processes used to make the products had not been validated. Additionally, it was the opinion of the EMEA that the studies in healthy human volunteers did not show that the Marvel insulins had the same effect in lowering blood sugar levels as the Humulin insulins. Finally, the major study in diabetic patients showed a trend in favor of Humulin. The Company withdrew its applications, citing the reason as not being granted an extension to the timeframe given to them to respond to a list of questions (one three month extension was already granted by EMEA) [51].

5. Summary

As one surveys the developing and existing worldwide biosimilar guidelines and regulations, overall common themes become apparent. One of the loudest common themes is that the guidance and regulations for the development and approval of biosimilar products can not simply be constructed by mirroring that which has been put in place for conventional small molecule generic drugs. Even once an approval pathway is in place, the diversity of types of biopharmaceuticals requires a flexible system, with data requirements for proving comparability determined on a case-by-case basis. The challenges and requirements become larger as the complexity of the biopharmaceutical is increased (e.g. monoclonal antibodies). Finally, even once a system is in place and biosimilar products are approved, interchangeability with the reference product is not likely. Currently, as a result of evolving biosimilar debates, guidance, regulations, and experience there is much opportunity yet uncertainty and risk associated with the development of biosimilar products.

The complex nature of biopharmaceuticals has led to debate on the very definition of biosimilarity and the regulations required to ensure the marketing of safe and efficacious biosimilar products. The EU has taken the lead in creating a comprehensive system of development and other countries have followed suit including India, South Korea, and Japan. The U.S. legislature and regulatory agency are still debating an approval pathway. While regulations are being developed and refined worldwide, many biosimilar products have gained marketing approval, including thirteen biosimilar product approvals in the EU. In nearly all cases, comparability exercises were conducted to prove similar quality, safety, and efficacy profiles to a reference product. It is clear that any regulations that are enacted must carefully balance the ability to develop safe, efficacious, and competitive biosimilar products with the protections and incentives for continued innovation.

References

1. Evers, P.; Delivering New Biopharmaceutical Therapies: Challenges & Opportunities. 2009; <http://www.thepharmacy.com/shop/product.php?xProd=2360&xSec=90&jssCart=2cb691be4926f78bb8fc12cf6ac455b7> .
2. What are Generic Drugs; <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm144456.htm>.
3. Wadman, M. *Nature*, 2009, 458, 394-395.
4. Joung, J.; et al. *Biologicals*, 2008, 36, 269-276.
5. Promoting Innovation and Access to Life-Saving Medicine Act; <http://www.govtrack.us/congress/bill.xpd?bill=h111-1427> .
6. Pathway for Biosimilars Act; <http://www.govtrack.us/congress/bill.xpd?bill=h111-1548> .
7. Promoting Innovation and Access to Life-Saving Medicine Act; <http://www.govtrack.us/congress/bill.xpd?bill=s111-726> .
8. Permanand, G.; et al. *Clin Med*, 2006, 6, 87-90.
9. Pignatti, F.; et al. *J Ambul Care Manage*, 2004, 27, 89-97.
10. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use; <http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:EN:PDF> .
11. 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; <http://eur-lex>.

- europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:159:0046:0094:EN:PDF .
12. 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; <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF> .
 13. Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Erythropoietins; <http://www.emea.europa.eu/pdfs/human/biosimilar/9452605en.pdf> .
 14. Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Biosimilar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor; <http://www.emea.europa.eu/pdfs/human/biosimilar/3132905en.pdf> .
 15. Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Somatropin; <http://www.emea.europa.eu/pdfs/human/biosimilar/9452805en.pdf> .
 16. Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Human Insulin; <http://www.emea.europa.eu/pdfs/human/biosimilar/3277505en.pdf> .
 17. Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha; <http://www.emea.europa.eu/pdfs/human/biosimilar/10204606enfn.pdf> .
 18. Similar biological medicinal products containing low-molecular-weight-heparins; <http://www.emea.europa.eu/pdfs/human/biosimilar/11826407enfn.pdf> .
 19. Woodcock, J.; et al. *Nat Rev Drug Discov*, 2007, 6, 437-442.
 20. Concept paper on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use; <http://www.emea.europa.eu/pdfs/human/biosimilar/11472009en.pdf> .
 21. Dr. Reddy's Launches Reditux - Monoclonal Antibody Treatment for Non-Hodgkin's Lymphoma; http://www.drreddys.com/products/bio_mproducts.html# .
 22. Dr. Reddy's launches Rituxan biosimilar in India; <http://www.drugresearcher.com/news/ng.asp?n=76261-dr-reddy-s-roche-biosimilars-india> .
 23. Clotina; http://www.abxis.com/eng/products/products_Frm.asp?cmd=301 .
 24. Kudrin, A.; *J Clin Pharmacol*, 2009, 49, 268-280.
 25. Abseamed: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/abseamed/H-727-en1.pdf> .
 26. Binocrit: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/binocrit/H-725-en1.pdf> .
 27. Epoetin alfa HEXAL: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/epoetinalfahexal/H-726-en1.pdf> .
 28. Silapo: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/silapo/H-760-en1.pdf> .
 29. Retacrit: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/retacrit/H-872-en1.pdf> .
 30. Omnitrope: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en1.pdf> .
 31. Valtropin: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/valtropin/H-602-en1.pdf> .
 32. Omnitrope: Approval Letter; http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021426s000LTR.pdf .
 33. Biograstim: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/biograstim/H-826-en1.pdf> .
 34. Filgrastim ratiopharm: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/filgrastimratiopharm/H-824-en1.pdf> .
 35. Ratiograstim: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/ratiograstim/H-825-en1.pdf> .
 36. Tevagrastim: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/tevagrastim/H-827-en1.pdf> .
 37. Filgrastim Hexal: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/FilgrastimHexal/H-918-en1.pdf> .
 38. Zarzio: EPAR summary for the public; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Zarzio/H-917-en1.pdf> .
 39. Grafeel: Filgrastim Injection; <http://www.drreddys.com/products/pdf/grafeel.pdf> .
 40. Di Girolamo, G.; et al. *Arzneimittelforschung*, 2008, 58, 193-198.
 41. Crucell announces STAR technology research

- license with Korean-based Isu-Abxis; <http://www.reuters.com/article/pressRelease/idUS111764+14-Jan-2008+MW20080114> .
42. Two recombinant products attained production licenses; http://www.cpgj-pharm.com/en/news_view.asp?newsid=83 .
 43. Mocini, D.; et al. *Curr Med Chem*, 2007, 14, 2278-2287.
 44. Marchant, J.; *The Future of Biosimilars. Key opportunities and emerging therapies*; Business Insights Ltd, 2007.
 45. Frampton, J.E.; et al. *Drugs*, 1994, 48, 731-760.
 46. Datamonitor; *Biosimilars Series: Stakeholder Analysis; A panoramic view of the emerging biosimilars landscape*; Datamonitor, 2008.
 47. Questions and answers on recommendation for refusal of marketing application for Alpheon; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/alpheon/H-585-RQ&A-en.pdf> .
 48. Refusal assessment report for Alpheon; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/alpheon/H-585-RAR-en.pdf> .
 49. Marvel LifeSciences Ltd withdraws its marketing authorisation applications for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel; <http://www.emea.europa.eu/pdfs/general/direct/pr/243508en.pdf> .
 50. Questions and answers on the withdraw of the marketing authorisation application for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel; <http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/419308en.pdf> .
 51. Withdraw letter; http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/withdrawal_letter.pdf



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