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REVIEW ARTICLE

Biosimilar insulins: a European perspective

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Biosimilar insulins are likely to enter clinical practice in Europe in the near future. It is important that clinicians are familiar with and understand the concept of biosimilarity and how a biosimilar drug may differ from its reference product. The present article provides an overview of biosimilars, the European regulatory requirements for biosimilars and safety issues. It also summarizes the current biosimilars approved in Europe and the key clinical issues associated with the use of biosimilar insulins.
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Introduction

Many first-generation biopharmaceuticals are facing patent expiry over the coming years, opening up the global biological products market to subsequent or follow-on products that might be called 'biosimilars'. In the insulin market, patent protections for a number of insulin preparations (human insulins or insulin analogues) have or will expire in the near future, including rapid-acting and long-acting insulin analogues such as insulin aspart, insulin lispro and insulin glargine [1]. The global insulin market is growing and is expected to reach in excess of $32 bn by 2018 [2], up from >$20 bn in 2012 [3]. Annual sales of insulin glargine alone (Lantus®; Sanofi-Aventis, Paris, France) in 2013 were worth ~$7.5 bn [4]. In view of this large and expanding market, it is clear that many companies will explore opportunities to introduce biosimilar insulins to the market. It is estimated that ~40 insulins are under development as biosimilar insulins [5]; however, before such insulins are approved as biosimilars, they will have to fulfill the regulatory requirements discussed below. In view of the potential availability of approved biosimilar insulin products, the clinicians treating people with diabetes may want to familiarize themselves with the following:

- the concept of biosimilars and how they differ from reference products (the originator insulins);
- the European regulatory requirements for biosimilars;
- the clinical considerations to be taken into account when using biosimilars;
- and the biosimilars that are already approved.

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The objective of the present article was to provide a brief overview of these topics from a European clinical and regulatory perspective.

Generic Versus Biosimilar Drugs

Simple chemical drugs (also called 'new chemical entities' or 'new molecular entities') are small molecules, produced synthetically. When the patents for a simple chemical drug expire, copies of the off-patent drug, known as generics, can be manufactured and marketed after regulatory approval. Generics are identical to the original drug in active pharmaceutical ingredient, dose, strength, route of administration and intended use. The generic manufacturer must show that the generic drug is bioequivalent to the reference drug, meaning they contain the same active moiety and that their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits [6]. Toxicology and clinical efficacy studies are not required. The European Medicines Agency (EMA) in the European Union (EU) and the Food and Drug Administration (FDA) in the USA have similar rules for the approval of generic drugs [7,8].

Biological drugs, often referred to as biologicals, biopharmaceuticals or therapeutic biologicals, are produced by living entities, such as organisms, cells or tissues. The first biopharmaceutical introduced into routine clinical use was recombinant human insulin (Humulin®, Eli Lilly and Company, Indianapolis, IN, USA) in 1982 [9]. Today, hundreds of biopharmaceuticals, including peptide hormones, growth factors, interferons, interleukins and monoclonal antibodies, have received regulatory approval around the world [10]. When the patents for such a biological drug expire, the process for approving another version of that biological as a biosimilar drug is much more complex than that for a generic drug.

Biopharmaceuticals are large recombinant proteins, e.g. human insulin (~5.8 kDa), filgrastim (18.8 kDa) and rituximab

(~145 kDa), in comparison with most generic drugs, which are generally much smaller, e.g. aspirin (180 Da) and omeprazole (345 Da). The complexity of a biological drug is determined by both the nature of the drug molecule itself and by the production process. Biopharmaceuticals can include complex proteins with unique tertiary and quaternary structures. The manufacturing protocols are the proprietary information of the originator pharmaceutical company, therefore, biosimilar manufacturers may not duplicate the production process of the reference product. Minor changes in the manufacturing processes may alter the biological function of the product, including immunogenicity, potentially affecting the safety and efficacy profile of the biosimilar drug [11] (see below).

Because of the complexity of these products and their manufacturing processes, biopharmaceuticals are expensive to develop and to manufacture compared with generic drugs, but progress made in recent decades in biopharmaceutical production techniques has also enabled many more companies to produce such substances at reduced costs. Biosimilars have the potential to reduce treatment costs, expand market competition and increase patient accessibility when they become available at lower costs; however, the cost savings of developing biosimilars compared with their originator products are not expected to be as large as those that are achieved with generics compared with their originator products [12]. Nevertheless, because of the chronic usage of biopharmaceuticals by many people, the absolute cost savings could be significant. Cost savings will, of course, be contingent upon the extent of adoption of biosimilars in the marketplace.

Regulatory Requirements and Legislation for Biosimilars

The regulatory requirements for the approval of a biosimilar are considerably greater than those for a generic drug. As discussed earlier, for a generic drug, it is usually sufficient to demonstrate pharmaceutical equivalence (identical amounts of same active ingredient in the same dosage form) and bioequivalence to the reference drug to obtain regulatory approval. In contrast, for a biosimilar drug, the EMA requires a comprehensive analysis [13–15], that includes an extensive head-to-head comparison of the new product's characteristics (physicochemical and biological activity), pharmacology and clinical safety and possibly efficacy outcomes, with those of the reference biological product. Guidelines on biosimilars were first introduced by the EMA in 2005 [13]. A number of biosimilar drugs were subsequently approved in the EU (see below); however, only one biosimilar insulin, an insulin glargine product jointly developed by Eli Lilly and Boehringer Ingelheim, has been approved (in September 2014) [16].

In Europe a biosimilar product is reviewed after a similar biological application as per Article 10(4) of directive 2001/83/EC [17]. This procedure allows cross reference to a product already authorized in the EU after the expiry of the data protection period afforded to the reference product. The EMA has produced overarching guidelines on biosimilars [13] in addition to guidelines on quality issues [15], non-clinical and clinical issues [14], and class-specific guidelines, including guidelines for soluble recombinant human insulin [18]. In December 2012, the EMA updated their guidelines on the non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues [19], and in April 2014, released for further consultation draft revisions to these guidelines [20]. This guideline, once finalized, will replace the EMA's February 2006 guideline on biosimilar human insulin [18]. The non-clinical section addresses the pharmacotoxicological studies and the clinical section addresses the requirements for pharmacokinetic, pharmacodynamic and safety studies, as well as the pharmacovigilance plan [19]. The EMA considers the 'demonstration of similar pharmacokinetic and pharmacodynamic profiles' as 'the mainstay of proof of similar efficacy of the biosimilar and the reference insulin' [19]. Cross-over, preferably double-blind, glucose clamp studies using single subcutaneous doses of the test and reference agents are considered most suitable for this purpose [19]. For the primary endpoints in the pharmacokinetic studies (i.e. the area under the curve and the maximum concentration), the goal is to show that the 90% confidence interval of the ratio test/reference is within the range 80–125%, the conventional acceptance range for bioequivalence, unless otherwise justified [19]. The primary endpoint for pharmacodynamic studies is based on the area under the curve of the glucose-infusion rate (GIR) over time and the maximum GIR. Secondary pharmacodynamic endpoints are the time to reach maximum GIR and the time to reach half-maximum GIR [19]. The EMA requires that clinical trials of at least 12 months' duration are conducted to collect safety and immunogenicity data, with a comparative phase of at least 6 months' duration to be completed before approval [19]. The primary outcome measure for immunogenicity is the incidence and titres of antibodies to the biosimilar and the reference insulin. Importantly, if this comparability exercise shows that the biosimilar can be shown to be highly similar for both pharmacokinetic and pharmacodynamic data, without raising any additional safety or efficacy questions that require clinical testing, the EMA does not require clinical efficacy studies [19].

In the USA, after the enactment of a specific approval pathway for biosimilars (as part of the Patient Protection and Affordable Care Act), the FDA in 2012 issued three draft guidance documents listing the requirements for the registration of a biosimilar [21–23]. No biosimilars have yet been approved in the USA, and products considered biosimilars in other regulated markets, such as the somatropin Omnitrope® (Sandoz GmbH, Kundi, Austria), gained US approval through a different regulatory pathway before the biosimilar law was enacted [24]. The FDA intends to use a 'risk-based, totality-of-the-evidence' approach for biosimilar application reviews and recommends use of a stepwise approach to demonstrate biosimilarity [21]. Once the analytical and preclinical studies have provided the totality of evidence data showing that the biological medicine and the FDA-licensed reference biological product are highly similar, an abbreviated clinical development programme and submission process for the biosimilar drug can be used [21]. While there may be differences between the EU and the USA in how biosimilars and similar biologicals are approved,

the scientific principles for demonstrating similarity are comparable.

In August 2014, the FDA granted tentative approval for an insulin glargine product developed by Lilly and Boehringer-Ingelheim [25]. With a tentative approval, the FDA has determined that the new insulin glargine product meets all of the regulatory requirements for approval; however, final approval cannot be provided by the FDA until ongoing patent litigation filed by Sanofi is resolved [25]. As the biosimilar regulatory pathway was not available for this product, it is not considered a 'biosimilar' in the USA; however, its approval was sought through the separate regulatory pathway 505(b)(2) that uses scientific and regulatory principles consistent with the biosimilar pathway [25].

Asssessment of the Safety of Biosimilars

It is not expected that the reference drug and the biosimilar drug will be identical. The aim of the Chemistry, Manufacturing and Controls comparability exercise is to show that the degree of variability between the reference drug and the biosimilar drug is not significant. Variability can be dependent upon many factors, including the cell culture process, stability, storage and transport conditions of the biological drug [26]. Manufacturers of biologicals must also ensure that the batch-to-batch variability associated with every biological drug meets the required quality standards.

Immunogenicity is always a major concern for protein drugs, irrespective of whether they are an originator drug or a biosimilar. Small changes in manufacturing processes, storage conditions, etc. can alter the immunogenicity of protein drugs, which may itself change over time. Such changes might introduce, for example, differences in the glycosylation pattern of the molecule [11]. The presence of impurities that are different or at different levels from those in the reference product can also provoke undesirable immune responses, which may alter the efficacy and safety profile of the biological drug [11]. The most sophisticated analytical methods, comparability testing and preclinical studies, cannot fully predict the efficacy and safety of a biological drug; thus, the best way to assess the biological effects of a biosimilar drug is via randomized clinical trials in people with the target disease. It will be reassuring if clinical trials of sufficient size and length are performed to fully assess the safety profile of the given biosimilar. In addition, immunogenicity issues may only emerge after long-term exposure to the product and only in certain people. For all of these reasons, an appropriate post-authorization pharmacovigilance plan has to be implemented.

According to the EMA draft guidelines on the non-clinical and clinical development of biosimilar human insulin and insulin analogues, the biosimilar applicant must present a risk management plan and pharmacovigilance programme with its application [20]. The risk management plan should take into account identified and potential risks associated with the use of the reference product and, if applicable, safety in indications licensed for the reference product that are claimed based on extrapolation [20]. Regular assessment of all safety data as well as periodic safety update reports to regulatory authorities are required.

Biosimilars in Europe

In 2006, two biosimilar somatropins, Omnitrope® and Valtropin® (Bio Partners GmbH, Zug, Switzerland), were approved in the EU. Biosimilars for erythropoietins and granulocyte-colony stimulating factor soon followed. Currently, there are 18 market-authorized biosimilars in the EU (Table 1). More applications were submitted, but three applications (including an insulin application, which was submitted twice) were either withdrawn, or in the case of Alpheon (recombinant human interferon α-2a), refused (Table 1) [27]. The marketing authorization for Alpheon was refused because of several concerns, including comparability issues between Alpheon and its reference product, and insufficient data on the stability of the active substance [28].

In September 2013, the European Commission gave final marketing approval to Inflectra™ (Hospira UK Ltd, Leamington Spa, UK) [29] and Remsima™ (Celltrion Healthcare Hungary Kft, Budapest, Hungary) [30], the first biosimilar versions of the monoclonal antibody drug infliximab (Remicade®, Janssen Biotech, Inc., Malvern, PA, USA). These drugs are used to treat a variety of autoimmune diseases, including rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriatic arthritis and psoriasis [29,30]. The approval of these biosimilars is a significant step for the biopharmaceutical industry because these drugs are the most complex biosimilars to date to be approved in Europe, and the first biosimilar antibodies available in a highly regulated market. When measured by size, monoclonal antibodies are >5-fold larger than biological products such as erythropoietin and insulin [31]. Naturally, creating a highly similar version of a monoclonal antibody will be inherently more difficult and complicated. In the cases of Inflectra and Remsima, the phase I and III clinical trials showed that they had a highly similar profile to the originator product Remicade® in terms of both safety and efficacy.

As mentioned earlier, only one biosimilar insulin, an insulin glargine product jointly developed by Eli Lilly and Boehringer Ingelheim, has been approved in Europe [16]. This was not the first application for a biosimilar insulin in the EU. In March 2007, Marvel Life Sciences Private Ltd. (Mumbai, India) submitted applications, which were withdrawn later that same year, for three different insulin formulations: (i) a soluble human insulin (Marvel Rapid); (ii) an isophane human insulin (Marvel Long); and (iii) their 30:70 mixture (30% soluble human insulin and 70% isophane human insulin; Marvel Mix) [32–34]. The Committee for Medicinal Products for Human Use raised several concerns about the applications, including inadequate product submission and failure to adequately demonstrate biosimilarity to the innovator product [32–34]. In November 2012, Marvel Life Sciences withdrew additional applications, which had been submitted to the agency in December 2011, for marketing authorizations for the human insulin formulations Solumarv, Isomarv medium and Combimarv [35]. In their withdrawal letter they indicated 'a need for more time to repeat and submit bioequivalence (PK [pharmokinetic] and PD [pharmacodynamic]) data on each clamp study in order to comply with the planned new biosimilar insulin guideline' [35]. These examples illustrate not only the complexity and difficulties of developing a biosimilar

Table 1. Biosimilar drugs in Europe*.

Medicine name	Active substance	Manufacturer	Status	Year of authorisation/ withdrawal/refusal
Omnitrope®	Somatropin	Sandoz GmbH	Authorized	2006
Valtropin®	Somatropin	BioPartners GmbH	Withdrawn	2006
Alpheon	Recombinant Human Interferon α-2a	BioPartners GmbH	Refused	2006
Abseamed®	Epoetin α	Medice Arzneimittel Pütter GmbH & Co. KG	Authorized	2007
Binocrit®	Epoetin α	Sandoz GmbH	Authorized	2007
Epoetin Alpha Hexal®	Epoetin α	Hexal AG	Authorized	2007
Retacrit™	Epoetin Zeta	Hospira UK Ltd	Authorized	2007
Silapo®	Epoetin Zeta	Stada Arzneimittel AG	Authorized	2007
Biograstim®	Filgrastim	AbZ-Pharma GmbH	Authorized	2008
Filgrastim ratiopharm®	Filgrastim	Ratiopharm GmbH	Withdrawn	2008
Ratiograstim®	Filgrastim	Ratiopharm GmbH	Authorized	2008
Tevagrastim®	Filgrastim	Teva GmbH	Authorized	2008
Filgrastim Hexal®	Filgrastim	Hexal AG	Authorized	2009
Zarzio®	Filgrastim	Sandoz GmbH	Authorized	2009
Nivestim™	Filgrastim	Hospira UK Ltd.	Authorized	2010
Grastofil	Filgrastim	Apotex Europe B.V.	Authorized	2013
Ovaleap®	Follitropin α	Teva Pharma B.V.	Authorized	2013
Inflectra™	Infliximab	Hospira UK Ltd	Authorized	2013
Remsima™	Infliximab	Celltrion Healthcare Hungary Kft.	Authorized	2013
Bemfola	Follitropin α	Finox Biotech AG	Authorized	2014
Abasria®	Insulin glargine	Eli Lilly and Company and Boehringer Ingelheim	Authorized	2014

*European Medicines Agency [27].

insulin but also the standards expected in the application process. Notably, there are several other biosimilar insulin candidates in the pipeline, both for rapid-acting and basal insulin reference products. These include an insulin glargine candidate from Merck (MK-1293) [36] and an insulin lispro candidate from Sanofi (SAR342434) [37].

Key Clinical Issues for the Use of Biosimilars

The upcoming introduction of biosimilar insulins poses a challenge for scientific societies and advocacy groups which will be expected to issue guidance for healthcare professionals. To date, the European Association for the Study of Diabetes and the American Diabetes Association have not released position statements. In anticipation of the arrival of biosimilar insulins to the UK market, Diabetes UK released a position statement in October 2013 [38]. In this statement, the authors emphasize that the decision about which insulin is most appropriate should always be made jointly between patients and their healthcare providers [38]. Patients who are already established on a given set of insulin products and who show good metabolic control should continue with that treatment, and not be made to change one or more of their insulin formulations to a biosimilar insulin.

Patient perspectives on biosimilar insulin will be an important determinant of the success or failure of biosimilar insulins. A recent survey carried out in people with type 1 and type 2 diabetes suggested that the majority are willing to consider biosimilar insulins [39]. Common areas of concern identified by this survey included effectiveness, side effect profiles and delivery device design [39]. Insulin pens are an additional consideration for the introduction of and approval of all insulins, particularly in the EU, where this form of insulin delivery is used by the majority of patients [40]. When compared with vials and syringes, insulin pens improve ease of use, patient's confidence, treatment satisfaction and quality of life; they may also increase adherence to the therapy [41, 42]. A wide variety of prefilled and reusable insulin delivery pens are currently available [42]. Many insulin pens have convenience features, such as a memory function or an audible click, which may influence user-friendliness and patient preference for a given type of a pen [43,44]. Optimally, biosimilar insulins should be available with compatible pens which have the features desired by patients.

The possibility of switching between reference insulin products and biosimilars is an important consideration for healthcare professionals, payers and authorities. Widespread switching could happen if biosimilar insulins are considered interchangeable or substitutable. Substitution (sometimes referred to as automatic substitution) occurs at the point of dispensing and refers to the practice of a pharmacist dispensing a generic/biosimilar medication in place of the prescribed drug, without the prior consent of the healthcare provider. Interchangeability refers to a decision made by a national or regional

health authority that a biosimilar drug has met the data requirements needed for automatic substitution with the reference product. In the EU, the EMA has stated it does not intend to make decisions regarding interchangeability [45], and therefore will leave the matter to individual member states to determine their policy on pharmacy substitution of biosimilars. This is in contrast to the USA where legislation authorizes the FDA to designate a biosimilar as interchangeable with its reference product [46].

The interchangeability of biosimilar drugs and reference products remains a controversial issue, partly because of the lack of standardized terminology. The terms 'switching', 'substitutable' and 'interchangeable' are often used inconsistently. Although meeting the regulatory criteria to approve biosimilar medication for a given indication on the basis of comparative studies with the reference product may be sufficient to support switching, substitution of insulins at the pharmacy level will require more substantial clinical data. Repeated switching between the reference and biosimilar product may present postmarketing safety surveillance challenges to differentiate adverse events for each product; therefore, data should show that repeated switching from reference product to biosimilar (and vice versa) has no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity. This could be accomplished through crossover studies with multiple switches over a sufficient period of time conducted in an appropriate patient population [47]. It is possible that payers in certain markets may enforce substitution at a pharmacy level, as exemplified recently when the French parliament approved a measure allowing pharmacists to substitute a biosimilar for the prescribed biological when initiating a course of therapy [48]. This approach could create significant problems in the case of insulin, in which any change in therapy might require additional monitoring, a change in the delivery device, re-training etc. As stated in the summary of product characteristics of many insulin products, 'transferring a patient to another type or brand of insulin should be done under strict medical supervision' [49–51]. Moreover, pharmacy switching (i.e. switching not prescribed by a healthcare professional) from one type of biological to another will make evaluation of adverse events, in particular causality (e.g. hypersensitivity or other immune-mediated reactions), difficult. To prevent this situation, prescribers may have an opportunity to prohibit pharmacy switching, by indicating 'Dispense as Written' on prescriptions. It is important that clear criteria for interchangeability and substitution of insulin preparations are developed and adopted, and ideally they should be identical across Europe, particularly for safety reasons. These should preferably include data from clinical trials in which specific populations are switched between therapies, and postmarketing experience. Appropriate advice, information and education needs to be made available to all healthcare professionals involved in the prescribing and administration of biosimilars in this disease area.

Conclusions

In the coming years, clinicians and people with diabetes across Europe may see the availability of various new biosimilar insulins. A certain amount of confusion can be predicted to be accompanied by such a change in the marketplace. Both medical and practical differences, such as choice of delivery device and patient support programmes, may exist between biosimilar insulins and their originator products. The advantages of biosimilar insulins may relate to the increased range of treatment options, choice of delivery devices and support programmes available. Advantages may also include lower price (although the price drop will probably not be as large as that seen with many generics), increased patient access to treatment, and reduced costs for healthcare systems. The use of biosimilar insulins, however, also raises some concerns. It is important that manufacturers of biosimilar insulin can maintain the necessary long-term quality standards. Approvals should be supported by a sufficiently robust data package and implementation of proper postmarketing surveillance. As with all insulins, switching between an originator product and a biosimilar drug, if it happens, should be performed under medical supervision. Decisions on considering these drugs interchangeable should be based on robust data from clinical trials and postmarketing experience, which indicate that repeated switching between an originator product and a biosimilar is safe.

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Conflict of Interest

J. H. D.V. is an advisor on long-acting insulins for Novo Nordisk, an invited speaker for Eli Lilly and Company and Novo Nordisk, and has received research support from Sanofi for a meta-analysis on insulin glargine. S. C. L. G. is an advisor on insulins for Novo Nordisk, Eli Lilly and Company and Sanofi, and has received honoraria from Novo Nordisk, Eli Lilly and Company and Sanofi as an invited speaker. J. K. is a full-time employee and shareholder of Eli Lilly and Company. L. H. is a consultant for a number of companies developing new diagnostic and therapeutic options for diabetes treatment and is a member of a Sanofi advisory board for biosimilar insulins.

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