

# Biosimilar insulins: current and future perspectives



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Biological products, also known as biologics, may be defined as biopharmaceutical products derived from living entities, that is, human, animal or micro-organism sources [1]. Recombinant protein drugs produced by cell culture fermentation technology have become a cornerstone of medical and especially endocrine practice over the last 25 years [2]. Within this biopharmaceutical landscape, biosimilar medical products – also known as follow-on biologics – are intended to be clinically equivalent to an existing licensed biologic product [3].

When a licensed product reaches patent expiry other manufacturers have the option of producing biosimilar versions of the original. Following the introduction of the first examples in 2006 a range of biosimilar products belonging to several therapeutic classes is now available in Europe. Included among endocrine biosimilar products are growth hormone, [4] erythropoietin, [5] and follicle-stimulating hormone [6]. The first biosimilar insulin approval was granted by the EMA for Eli Lilly and Boehringer Ingelheim's insulin glargine (tradename *Abasagla*, previously *Abasria*, in the EU) in September 2014 [7].

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In the USA, the US FDA granted tentative approval for the product (with the provisional trade name *Basaglar*) in the same year. However, the approval became subject to an automatic ‘stay’ of up to 30 months as a result of litigation filed by Sanofi claiming patent infringement. Sanofi's blockbuster product - *Lantus* – leads the insulin market [8] with annual sales in excess of \$7.5 billion [7]. The companies entered a settlement agreement in September 2015 (see below) ahead of the expiry of Sanofi's patent.

## Recombinant human insulin & insulin analog manufacturing processes: implications for the development of biosimilar insulins

The development of a biosimilar insulin presents numerous challenges:

- Insulin has a large and complex molecular structures (primary, secondary, tertiary, quaternary);
- Complex manufacturing using biological systems with inherent variability are required;
- Potential for differences compared with the reference medicinal product that



## KEYWORDS

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may lead to altered pharmacokinetic and pharmacodynamic properties that affect the benefit-to-risk equation;

- Immunogenic potential;
- Delivery device related issues.

When a small-molecule patent protection expires the manufacturer of a generic product has only to demonstrate that the generic is the same chemical properties as the original and that pharmacokinetic studies support bioequivalence. In contrast, biologic products such as insulin are large complex proteins with primary (amino acid sequence), secondary (folding), tertiary (higher levels of folding) and quaternary (hexamer formation with zinc ions) characteristics [9]. Accordingly, the manufacture of biosimilars is far more complex compared with conventional generic drugs. Differences in the manufacturing process can lead to insulins that to some extent may differ from the originator insulin [3]. Thus, biosimilar insulins and insulin analogs can never be assumed to be identical copies of the innovator products [10].

Since biosimilar insulins are produced using specific proprietary manufacturing processes this raises potential concerns with respect to clinical efficacy and safety [11]. Differences at any stage of manufacture may ultimately influence the activity of the molecule. Moreover, the reliance on living organisms introduces inherent variability into the manufacturing process of biosimilars [12]. The process of insulin manufacture already differs between companies. For example, a different yeast as the primary fermentation organism by Novo Nordisk and Biocon, with Sanofi and Eli Lilly using *Escherichia coli* based systems [12]. Quality control with consistency of the manufacturing process is essential to ensure the quality of each production batch of insulin [11]. Data on the quality and consistency of the manufacturing processes are not in the public domain [13]. It seems possible that this consideration may prompt prescribers to place their trust in biosimilar insulin products from the well-established manufacturers.

• **Potential for immunogenicity**

Since biopharmaceuticals are produced in living systems they have the potential to induce inappropriate immune responses [11]. The risk of altered immune responses with biosimilar products is illustrated in the catastrophic pure red

cell aplasia (which resulted in deaths) that was attributed to the immune reaction induced by a biosimilar erythropoietin used to treat the anemia associated with renal failure [14]. Antibody-mediated neutralization of endogenous erythropoietin caused erythrocyte differentiation to be blocked. In the case of biosimilar insulins neutralizing antibodies are a particular concern [15]. A risk-management program is therefore required. However, since clinically important immunogenicity in patients treated with insulin is rare large observational studies over an extended time periods would be necessary to identify such a signal.

• **Pharmacokinetics & pharmacodynamics**

Insulin has a narrow therapeutic window and even small alterations in pharmacodynamics or pharmacokinetics may have an effect on glycemic status. A relevant case study is provided by the failed application by Marvel to the EMA for marketing authorization for recombinant human insulin in three different formulations: a soluble rapid-acting insulin, a long-acting isophane insulin product and a 30:70 mixture [10]. In brief, the EMAs Committee for Medicinal Products for Human Use (CHMP) was of the opinion that the Marvel biosimilars and the reference human insulins were not comparable in terms of pharmacokinetic and pharmacodynamic properties. The CHMP also noted that the dose-delivery properties of different presentations, that is, vials and cartridges, had not been adequately tested and validated (see below).

• **Insulin delivery devices**

A final consideration when considering biosimilarity of insulins is the device used for subcutaneous administration. Devices differ from company to company adding the possibility of disparities in dosing between delivery systems and other considerations that may be relevant to patients and healthcare professionals, for example, cartridge compatibility, when substituting a biosimilar insulin for a reference product. The EMA requires that device compatibility is demonstrated [12].

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**Regulatory pathways for biosimilar products**

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### • European Union

Within the EU, the EMA regulations pertaining to approval of biosimilar medicinal products have been in place since 2005 [16]. The EMA was the first regulatory body to issue guidelines of the development of biosimilars [7]. In 2014 the EMA issued additional guidance in draft form on the nonclinical and clinical requirements for biosimilar recombinant insulin-containing products [17]. The EMA requires extensive head-to-head comparison of the new biological product with the reference medicinal product. Key aspects of the guidance, which was updated in 2015 [18], include physicochemical properties, functional characterization and biological activity (including comparative binding and on-off kinetics at the human insulin receptor and insulin-like growth factor-1 receptor, receptor autophosphorylation, metabolic activity and mitogenic activity), pharmacology and clinical safety. The latter requires a specific focus on immunogenicity and the guidance indicates that a reasonable number of patients with Type 1 diabetes should be included. [17] The EMA guidance provides extensive information on practical considerations for comparative glucose clamp studies, including the selection of subjects and pharmacokinetic/pharmacodynamic assessments. While the EMA has provided leadership in establishing the regulatory requirements for biosimilar insulins the wide confidence interval (-20 to +25%) for certain pharmacokinetic parameters raises questions about whether clinical biosimilarity can be assured [13]. With the emphasis on glucose clamp data there is no anticipated need for specific efficacy studies since the EMA considers that the endpoints used in such studies, usually hemoglobin A<sub>1c</sub>, are not sensitive enough for the purpose of showing biosimilarity of two insulins. Applicants are required to present a risk management plan in accordance with current EU legislation and pharmacovigilance guidelines detailing how safety concerns, including those pertaining to the reference product, will be addressed post-marketing.

### • USA

The FDA developed an overall framework for biosimilars between 2009 and 2012. In June 2015, the FDA released its finalized guidance documents for industry on the development of biosimilars [19]. This announcement follows the approval in March 2014 of the first biosimilar by the FDA [20]. The updated guidelines

provide specific recommendations for companies developing products under the 351(k) biosimilar pathway that was created as part of the Affordable Care Act. The final guidance outlines a stepwise approach with emphasis on the desirability of frequent consultations with the FDA, and extensive pharmacokinetic/pharmacodynamic studies. The key steps, which may take place in parallel, include: structural and functional characterization of the proposed biosimilar product compared with the reference product; toxicity studies in animal studies; clinical studies of pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity. While applicable only to the 351(k) biosimilar pathway, and not the 505(b)(2) pathway that is relevant to biosimilar insulins, the document states that the guidance 'may be informative' for the 505(b)(2) pathway. The FDA used the latter pathway to review the aforementioned biosimilar insulin (*Basaglar*). The pathways will be consolidated in 2020 with products approved under 505(b)(2) being considered approved biosimilars at that point. As in the case of the EMA, the FDA guidance considers pharmacokinetic/pharmacodynamic assessments to be more important than clinical efficacy when assessing similarity to a reference product; accordingly, comparative efficacy studies may not be necessary.

### • Other markets

The WHO and countries including Canada, South Africa and Australia have developed similar regulatory approaches for biosimilar products based on the EMA model. In other parts of the world rather less rigorous requirements are in place. This has led to the approval of biosimilar insulins in countries including India, China and Mexico [13]. The situation in these countries contrasts with the stringent scrutiny of applications for biosimilar insulins in highly regulated markets such as Europe [21].

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### Current & future status of biosimilar insulins

The current focus of activity is on the development of biosimilar versions of basal insulin – specifically insulin glargine – rather than rapid-acting insulins. In Europe, Abasaglar is expected to be launched late summer 2015. This will provide the first case study in how biosimilar insulins will be perceived in the EU. In the USA, the patent litigation initiated by Sanofi that triggered a stay on full approval of Basaglar has now

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been resolved clearing the way for a launch in 3Q16 [7].

It seems reasonable to assume that several additional biosimilar insulins will come to market over the next few years. Merck (MK-1293 insulin glargine formulation in Phase III of development) [7], Biocon (Mylan) (insulin glargine biosimilar in Phase III trials) [13] and Sanofi (Insulin lispro formulation SAR342434 in Phase 3 trials) [7] are developing biosimilar insulins for highly regulated markets.

• **Pricing considerations**

The cost of insulin has been rising in recent years with insulin analogs driving the increases. While biosimilars in other areas of medicine are usually offered for a lower price than the originator molecules the impact on price of biosimilar insulins remains difficult to predict. For biosimilar insulins, many observers expect that biosimilars will be cheaper than their branded reference products. However, the discounts may not be as marked as those for small molecule generics due to the high development and manufacturing costs of biosimilars. Negotiations with government agencies and other stakeholders will be instrumental in determining the pricing of biosimilar insulins.

• **Positioning of biosimilar insulins in clinical practice**

Whether biosimilar insulins will contribute to better patient care remains to be determined. National charities that represent the interests

of patients with diabetes, for example, Diabetes UK, have adopted a cautious approach to the imminent arrival of biosimilar insulins emphasizing that any changes to therapy should be based on a joint decision between the person with diabetes and their healthcare professional [22]. Because biosimilars and their reference molecules are not identical changing a reference medicine for a biosimilar medicine needs to be based on informed opinion; careful transition that includes encouragement and support to self-monitor blood glucose is recommended [22]. Confirmation of biosimilarity does not necessarily imply interchangeability [13]. Whether the current regulatory requirements will provide sufficient confidence among physicians and their patients to permit such judgments is perhaps open to question given the expected paucity of clinically relevant data concerning comparability of glucose control and rates of nocturnal hypoglycemia [13].

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