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Current and Future Perspectives on the Development of Biosimilar Insulins for Diabetes Management

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Key Focus Points

- Biosimilar insulins are novel biologic products that are copies of an original insulin that are intended to be clinically equivalent to the licensed reference product.
- There are numerous technical challenges to developing a biosimilar insulin notably the fact that biosimilar products cannot be manufactured to be identical copies of the originator product, and the need to establish equivalence between the novel insulin and the marketed comparator product.
- While various methods are available for assessing the clinical equivalence of a biosimilar product to a licensed reference insulin the euglycemic clamp procedure is recognized as the method of choice.
- The European Medical Agency (EMA) has issued regulatory guidelines for the development of biosimilar insulins that emphasize clinical pharmacology studies and specific pharmacokinetic/ pharmacodynamic endpoints rather than efficacy evaluations. In the United States, biosimilar insulins are currently covered by the Food and Drug Administration's (FDA) 505(b)(2) pathway permitting evaluation of the reference product.

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Introduction

Insulin is a biologic product used in the treatment of all patients with type 1 diabetes and in a substantial proportion of patients with type 2 diabetes. Optimal insulin replacement that mimics normal physiology is a therapeutic challenge that has been attained at best partially. Recombinant insulin analogs with improved pharmacokinetics relative to human sequence insulin have become the mainstay of insulin therapy.

When a licensed insulin product reaches the end of its patent life the market opens for biosimilar products - also known as follow-on biologics. These are copies of the originator insulin intended to be clinically equivalent to the licensed product. Numerous technical challenges are encountered in producing and manufacturing a biosimilar insulin, one of which is that by nature of the manufacturing process of a biological product it cannot be an identical copy of the original. Given the time and expense that is required to develop a biosimilar insulin it is imperative that the clinical development programs for these compounds are carefully managed at all stages.

Biosimilar insulins have been approved by the European Medicines Agency (EMA). The first – LY2963016 insulin glargine (LY IGlar, Abasaglar®) in 2014 (the original European Union (EU) trade name of Abasaglar was Abasria). Using the name Basaglar, the product was approved in the U.S. under the 505(b)(2) pathway and launched in the US in December 2016. Of note, Basaglar was approved in the U.S. not as a biosimilar product but rather as a 'follow-on' insulin. In 2016 insulin glargine biosimilar, MK-1293 (MK Iglar, Lusduna®), was approved by the EMA. More recently, the EMA's Committee for Medicinal Products for Human Use (CHMP issued a positive opinion for insulin lispro 100 Units/mL (insulin lispro Sanofi); the FDA gave tentative approval for the product, named Admelog®, in September 2017.

Challenges in Developing Insulin Biosimilars

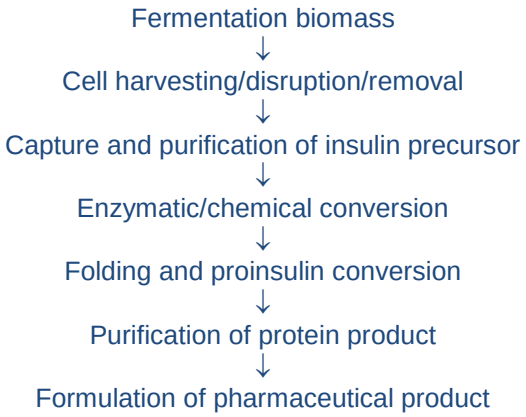
For a generic version of a small chemical molecule used in diabetes therapy, e.g. metformin, all that is required is demonstration that the molecular structure is identical to the original, purity of the product and evidence it can be manufactured consistently, and that it is absorbed reliably from the intestinal tract. In contrast, the development of a biosimilar insulin presents numerous additional challenges.

1. Insulin is a protein with a large and complex molecular structure (primary, secondary, tertiary, quaternary). Even minor alterations in any of these properties may affect function. The manufacturing process of biosimilar insulins, which are not identical to those used for the reference product, can lead to products with different characteristics to the originator insulin (Figure 1). Thus, biosimilar human insulin and insulin analogs can cannot be assumed to be identical copies of the marketed reference products.
2. Manufacturing of biosimilar insulins is highly complicated and uses biological systems with inherent variability; this complexity is challenging to regulate and poses potential concerns with regard to quality assurance and batch consistency.
3. Accordingly, there is potential for biosimilar insulins to differ from reference medicinal products. Even minor changes to the protein can impact the pharmacokinetic and pharmacodynamic properties of the biosimilar insulin compared to the reference licensed insulin. The therapeutic index for insulin in clinical practice is narrow and even minor alterations in the pharmacokinetic and pharmacodynamic properties of a biosimilar insulin could affect the cost- benefit equation.

4. Immunogenicity is a concern in the manufacturing of biosimilar insulins, in part because of the reliance on living organisms during production. The presence of neutralizing antibodies that block the activity of the product should be carefully assessed and a risk management program for potentially autoimmune reactions is required. However, clinically important immunogenicity in patients treated with insulin is rare and so large and long-term observational studies are required to detect this safety signal; it is expected that biosimilar insulins will have similarly low immunogenicity, but this must be reliably confirmed for each biosimilar product.

5. Delivery device related issues also need to be considered. The design of the device used to administer a biosimilar insulin is critical. The delivery device can affect the accuracy of dosing. The European Medical Agency (EMA) requires that device compatibility be demonstrated.

Figure 1. Steps in insulin manufacture. Modified from Home, 2011.



Regulatory Pathways for Biosimilar Products

Once a biosimilar product has been developed it must go through a regulatory approval process. The manufacturing processes that may lead to slight variations between biosimilar insulins and reference insulin products are proprietary. In order to ensure clinical equivalence of a biosimilar with the reference product regulatory agencies have adopted the strategy of assessing the degree to which the action of the two products is similar.

To meet the stringent regulatory requirements in Europe and the U.S. manufacturers are required to undertake structured clinical development programs. Both Europe and the U.S. are highly regulated markets. The rigorous requirements of the U.S. and European regulatory authorities towards biosimilars reflect the complex nature of these biopharmaceutical products as well as proprietary manufacturing process. Details of the regulatory requirements for approval of biosimilar insulins differ in specifics between the EMA and the FDA, but both include evaluation of pharmacodynamic properties and immunogenicity.

European Medical Agency

Under EU requirements, biosimilar medicines must have comparable quality, safety and effectiveness to the reference product. The most recent EMA guidelines for biosimilar insulins were issued in 2014 in draft form and updated in 2015. The EMA guidance on recombinant human insulin and insulin analogs considers the design of

glucose clamp studies and approaches to pharmacokinetic/pharmacodynamic data analysis and interpretation as well as safety studies, the latter focusing on immunogenicity. The EMA also requires demonstration of delivery device compatibility.

Preclinical studies required by the EMA include *in-vitro* pharmacodynamic evaluation, in-vitro affinity bioassays, and assays for binding to insulin and insulin-like growth factor-1 receptors. For the clinical studies required by the EMA, the euglycemic glucose clamp plays a crucial role in the evaluation of the pharmacodynamics of a biosimilar insulin. The EMA's position is that the sensitivity to detect differences between insulin products is higher for euglycemic clamp pharmacodynamic studies than for clinical efficacy trials, data from which are considered to be supportive evidence. The EMA guidance provides extensive information on practical considerations for comparative glucose clamp studies, including the selection of subjects and pharmacokinetic/pharmacodynamic assessments. The guidance state that glucose clamp studies should include at least one single-dose crossover study design to be performed in patients with type 1 diabetes.

Manufacturers of biosimilar insulins are required to present a risk management plan in accordance with current EU legislation and pharmacovigilance guideline. This should detail how safety concerns, including those pertaining to the reference product, will be addressed post-marketing.

Food and Drug Administration

The FDA approval process for biosimilar products is covered under section 351(k) of the Public Health Service Act. The requirements are described in four draft documents issued between 2012 and 2014. However, biosimilar insulins are not regulated as biologics for historical reasons. Biosimilar insulins are instead regulated through the 505(b)(2) pathway. After April 2020, the status of insulin will be changed to that of a biosimilar, and the approval process will be the responsibility of the Center for Biologics Evaluation and Research.

The final guidance for developing biosimilars 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: 1) structural and functional characterization of the proposed biosimilar product compared to the reference product; 2) toxicity studies in animal studies; and 3) clinical studies of pharmacokinetics, pharmacodynamics, and immunogenicity.

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.

Pharmacokinetic and Pharmacodynamic Studies

Bringing a biosimilar insulin to market presents a higher hurdle than that required for a generic small molecular weight drug; having a well-designed clinical trial program helps to facilitate the process. Given the regulatory emphasis on pharmacokinetic and pharmacodynamic studies rather than clinical efficacy, it is critical that studies are technically sound and integrated within the overall clinical development program for the biosimilar product.

Partnering with experienced, rather focused specialty clinical research organizations can provide valuable support in terms of study design (including selection of subjects: Table 1); technical expertise, especially in euglycemic clamp studies (Table 2); and preparation of regulatory submissions. The EMA guidance may currently be used as a starting reference point for the design of clinical studies as it is both rigorous and has been widely applied.

Table 1. Study design considerations in insulin time-action profile studies: selection of study population

Type 1 diabetes	Advantage of having no/negligible endogenous insulin secretion
Type 2 diabetes	Largest clinically relevant population. However, variable endogenous insulin secretion may confound results. However, well designed glucose clamp studies will allow the robust investigation of pharmacokinetic and pharmacodynamic characteristics of biosimilar insulins in this population.
Healthy volunteers	Endogenous insulin secretion should be suppressed by either (a) clamping at a target blood glucose concentration below fasting levels or (b) continuous intravenous administration of an appropriate dose of insulin

Pharmacokinetic Studies

The pharmacokinetics of a drug describes its concentration, along with those of its metabolites, in the body over time. In the case of insulin biosimilars, in order to meet regulatory requirements appropriate biosimilar-specific assays must be used to reliably measure the blood levels of the molecules in question.

Pharmacodynamic Studies

Of the available methods for quantifying insulin action the euglycemic glucose clamp technique is regarded as the reference method for the development of new diabetes drugs (Table 2).

Table 2. Assessing the pharmacodynamic properties of insulin biosimilars and reference insulins using the time-action profile glucose euglycemic clamp technique

Method	Measure	Advantages	Disadvantages	Value in Biosimilar Insulin Development
Euglycemic clamp: Insulin is administered by subcutaneous injection/inhalation, etc. Hypertonic glucose is infused intravenously at a variable rate to maintain plasma glucose at euglycemia	Maximal glucose infusion rate (GIR_{max}); time to GIR_{max} (t_{max}); area under the curve (AUC_{0-T})	Yields simultaneous detailed pharmacodynamic and pharmacokinetic data	Labor intensive; requires skilled technical staff; assessment of ultra-long acting insulins has limitations	Clamp-derived time-action profiles for insulin and biosimilar insulins are required by US and European regulators for market approval of new insulins

Adapted from: Krentz AJ, Heinemann L, Hompesch M. Methods for determining the time-action profile of insulin and other glucose-lowering drugs, In: Krentz AJ, Heinemann L, Hompesch M (Eds). *Translational Research Methods for Diabetes & Cardiometabolic Drug Development: Focus on Early Phase Clinical Studies.* Springer 2015.

Current and Future Status of Insulin Biosimilars

Because biosimilars and their reference molecules are not identical confirmation of biosimilarity does not necessarily imply interchangeability in clinical practice. The latter is subject to state and/or national regulations independent of the drug approval process. Whether current regulatory requirements will provide sufficient confidence among physicians and their patients to switch to biosimilar insulins is unclear given the paucity of clinically relevant data such as glucose control and nocturnal hypoglycemia. Delivery device compatibility is an additional consideration.

Conclusions

Many of the challenges in the development of biosimilar insulins are inherent to the product, and include the complexity of the insulin protein and the use of living organisms in the manufacturing process. The regulatory requirements for biosimilar insulins emphasize the use of pharmacokinetic and pharmacodynamic studies to establish clinical equivalence. While there are many methods of assessing pharmacodynamic equivalence, the euglycemic clamp procedure is the preferred method to investigate the PK and PD characteristics of biosimilar insulins because it is sensitive, robust, and reproducible.

Looking Ahead

The technical and regulatory challenges associated with developing a biosimilar insulin products mean that the barrier to market entry is higher than for generic small molecule drugs. As the global regulatory climate continues to evolve and become more harmonized staying current on the regulatory guidelines will be crucial to obtaining approval in multiple markets. A comprehensive clinical development program that incorporates the required pharmacokinetic/pharmacodynamic and safety studies is required. As more insulin biosimilars approach clinical trials, it will be necessary to ensure that the study populations, methods of assessing similarity, and safety assessments are comparable between studies. Working partnerships between biosimilar producers and experienced clinical study sites can provide valuable expertise to ensure a well-designed program and technically sound study data.

Further Reading

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As Senior Research Fellow at ProSciento, Prof. Krentz's research has involved investigator-initiated research in diabetes and cardiometabolic disorders. In addition to original articles, reviews and book chapters he has authored or edited a number of well-received textbooks on diabetes and cardiovascular disease including and *The Metabolic Syndrome and Cardiovascular Disease* (2007), *Drug Therapy for Type 2 Diabetes* (2013) and *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development* (2015). Previously, he was Professor of Endocrinology & Metabolism at the University of Buckingham, UK. Prof. Krentz serves on the editorial boards of a number of scientific journal. He is the founding Editor-in-Chief of *Cardiovascular Endocrinology*.

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