FOCUS PAPER

Clinical Research Considerations for Biosimilar Insulins

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. When a licensed insulin product reaches the end of its patent life, the market opens for biosimilar products. 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.

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 shows no significant difference in the rate and extent of absorption from the intestinal tract. In contrast, the development of a biosimilar insulin presents numerous additional challenges.

- 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. Thus, biosimilar human insulin and insulin analogs cannot be assumed to be identical copies of the marketed reference products.
- Manufacturing of biosimilar insulins is complex and changes to the process may result in undesired consequences, such as higher variability or impurities as compared to the reference insulin product. Accordingly, there is potential for biosimilar insulins to differ from reference medicinal products. Even minor changes to the protein can impact the pharmacokinetic, pharmacodynamic, or immunogenic 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 properties of a biosimilar insulin could impact safety and efficacy, which would affect the cost-benefit equation.
- 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.

Regulatory Pathways for Biosimilar Products

Once a biosimilar product is 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 the U.S. and Europe, manufacturers are required to undertake structured clinical development programs. Both the U.S. and Europe are highly regulated markets. The rigorous requirements of the FDA and EMA 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 FDA and EMA, but both include evaluation of pharmacodynamic properties.

Food and Drug Administration

Per FDA guidance, as of March 23, 2020, any approved drug application for a transition biological product is now “deemed” to have a biologics license (BLA) instead of a New Drug Application (NDA) approval and will be interchangeable with the reference product.

The FDA 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. The FDA guidance considers pharmacokinetic/pharmacodynamic assessments to be more important than clinical efficacy when assessing similarity to a reference product.

When the Biologics Price Competition and Innovation Act (BPCIA) was enacted on March 23, 2010, it required marketing applications for biological products (that previously could have been submitted under section 505 the FD&C Act) be submitted under section 351 of the PHS Act. However, the BPCIA also provided a ten-year transition period for certain biological products to allow time to prepare for the change in law. That transition period ended on March 23, 2020, and any approved drug application for a transition biological product is now “deemed” to have a biologics license (BLA) instead of a New Drug Application (NDA) approval. An insulin product currently approved as a “follow-on” will now be deemed a biosimilar and will be interchangeable with the branded products.

European Medical Agency

Under EU requirements, biosimilar medicines must have comparable quality, safety and effectiveness to the reference product. 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 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. 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 states 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 guidelines. This should detail how safety concerns, including those pertaining to the reference product, will be addressed post-marketing.

Clinical Study Design Considerations

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 efficac , it is critical that studies are technically sound and integrated within the overall clinical development program for the biosimilar product.

Partnering with ProSciento, an experienced, therapeutically focused CRO, can provide valuable support in terms of study design, including selection of subjects; technical expertise, especially in euglycemic clamp studies; and preparation of regulatory submissions. The EMA guidance is regularly used as a starting reference point for the design of clinical studies as it is both rigorous and has been widely applied.

Study design considerations in insulin time-action profile studies: Selection of study populatio

Type 1 diabetes	Advantage of having no/negligible interference from endogenous insulin secretion
Type 2 diabetes	Largest clinically relevant population. However, variable endogenous insulin secretion may confound results. 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 and Pharmacodynamic Studies

In order to meet regulatory requirements for insulin biosimilars, appropriate biosimilar-specific assays must be used to determine pharmacokinetic and pharmacodynamic properties. While various methods are available for quantifying insulin action and assessing the clinical equivalence of a biosimilar product to a licensed reference insulin, the euglycemic clamp procedure is recognized as the method of choice.

Clamp-Derived Time-Concentration and Time-Action Profiles

The FDA and EMA recognize the euglycemic glucose clamp technique as the most reliable method for quantifying the pharmacokinetic and pharmacodynamic properties of a novel or biosimilar insulin. The glucose clamp technique can be used to rapidly attain the required blood glucose level and maintain it at target according to the objectives of the experiment. Ancillary techniques such as isotopic tracer methodology or indirect calorimetry can be combined with a clamp to provide additional information about substrate utilization.

In the context of glucose clamp studies, deviations in blood glucose from the pre-specified target are undesirable. Thus, when evaluating clamp services provided by a clinical research organization (CRO), the accuracy with which the blood glucose concentration is maintained at target becomes an important quality consideration. While no universal definition of clamp quality has been established a coefficient of variation of <5% is regarded as optimal.

Manual vs. Automated Euglycemic Clamp Procedures

Unless otherwise specified, it should be assumed that manual glucose clamp methodology is being employed by a CRO. Manual glucose clamps are open-loop systems that comprise measurement of blood glucose at the bedside and estimation of the glucose infusion rate required to reach and maintain the glucose target guided by the human clamp operator.
While the manual clamp method is versatile, the skill of the operator is a factor in the quality of each clamp study. There is a well-recognized learning curve associated with acquiring the requisite expertise for high quality, reproducible clamp studies. This brings the potential for variability between individual clamp operators. This consideration is especially important when change from baseline in response to a therapeutic intervention is measured.

An alternative technique applied by ProSciento scientists is the Automated Glucose Clamp. This specialized approach utilizes a closed-loop system in which the variable of inter-operator proficiency is removed. The automated glucose clamp technology determines, and in a closed-loop or semi closed-loop setting infuses, the required amount of exogenous glucose to maintain the target glucose level. A published algorithm calculates glucose requirements based on glucose measurements obtained minute-by-minute or at five-minute intervals, depending on the particular technology employed. In this scenario, the operator is not required to make frequent judgments about the glucose infusion rate required to maintain the target glucose concentration. Thus, the potential for unconscious human operator bias is largely eliminated along with the issue of inter-operator variability.

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	Manual method is labor intensive; requires skilled technical staff; assessment of ultra-long acting insulins has limitations. **Automated clamp method** removes these barriers.	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, Quantification of Insulin Action in Human Subjects, In: Krentz AJ, Weyer C, Hompesch M (Eds). *Translational Research Methods in Diabetes, Obesity, and Nonalcoholic Fatty Liver Disease: A Focus on Early Phase Clinical Drug Development.* Springer 2019.

Current Landscape of Biosimilar Insulins

The current landscape of biosimilar insulins approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) are listed below. Per recent FDA guidance, as of March 23, 2020, any approved drug application for a follow-on biological product is now "deemed" to have a biologics license (BLA) instead of a New Drug Application (NDA) approval and will be interchangeable with the reference product.

Biosimilar product	Active substance	Reference product	Authorization date
Semglee® (Biocon Biologics)	Insulin glargine	Lantus (Sanofi	2018 EMA
Admelog® (Sanofi Insulin lispro Sanofi®	Insulin lispro	Humalog (Lilly)	2017 FDA 2017 EMA
Lusduna® (Merck)	Insulin glargine	Lantus (Sanofi	2016 EMA
Abasaglar® (Eli Lilly and Boehringer Ingelheim)	Insulin glargine	Lantus (Sanofi	2016 FDA 2104 EMA

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. A comprehensive clinical development program that incorporates the required pharmacokinetic/pharmacodynamic and safety studies is required. The general agreement is that the euglycemic clamp technique is the best available method to investigate the pharmacokinetic and pharmacodynamic characteristics of novel and biosimilar insulins. Clamp studies can be performed manually or by using an automated procedure. While both methods require substantial experience, the manual method is prone to inconsistent results, inter-operator variability and requires frequent blood draws. An alternative technique applied by ProSciento scientists is the Automated Glucose Clamp method. This specialized approach utilizes a closed-loop system in which the variable of inter-operator proficiency is removed. The Automated Glucose Clamp technology determines and infuses the required amount of exogenous glucose to maintain the target glucose level. 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.

Partnering with ProSciento

ProSciento is a specialty clinical research organization (CRO) exclusively focused on diabetes, NASH, obesity and related metabolic diseases. We provide scientific and operational expertise in the design and management of all facets of early phase clinical and regulatory development for biologics, small molecules, and devices. ProSciento has conducted more than 350 clinical projects for metabolic drugs and devices and more than 130 clinical trials in biologics, including novel and biosimilar insulins. To learn more about ProSciento's clinical R&D services for single and multi-site studies, contact bd@prosciento.com or visit www.prosciento.com.

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Similar Publications Co-Authored by ProSciento Scientists

- Krentz AJ, Weyer C, Hompesch M (Eds). Translational Research Methods in Diabetes, Obesity, and Nonalcoholic Fatty Liver Disease: A Focus on Early Phase Clinical Drug Development. Springer 2019.
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