FOCUS PAPER



Development Considerations for Biosimilar Insulin Delivery Devices

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Key Focus Points

- Companies developing biosimilar insulins are entering a crowded marketplace where the device used to deliver the biosimilar insulin can have a substantial impact on patient preference.
- "Biosimilar" insulin delivery devices should not fundamentally differ from "originator" devices to preserve safety features and dosing accuracy, but there is substantial space to customize insulin devices for target populations.
- Device development can take a variety of approaches from designing a novel product in house to licensing an existing product for use, but regardless of the route taken all new devices are subject to the same regulatory requirements, including clinical and user testing.





Introduction

Insulin therapy has been a mainstay of effectively managing diabetes mellitus for nearly a century. A growing number of companies are entering the marketplace with insulin biosimilars (also called follow-on biologics), which are modified insulin molecules intended to be clinically equivalent to an originator insulin that has reached the end of its patent life. An aspect of development that receives less attention is the device used to deliver the biosimilar insulin. From a patient's perspective, the device is their interface with the insulin; a device that is cumbersome or has safety concerns runs the risk of patients rejecting the product. In this article we consider the design features of biosimilar insulin delivery devices and an overall approach to device design, focusing on insulin pens.

Insulin Delivery Devices - Old and new

For most patients treated with insulin, an insulin pen - or needle-based injection system (NIS) - becomes a way of life, Patients readily see differences in aspects of the devices used to administer the insulins. The first insulin pen developed by NovoNordisk (NovoPen, 1985) contained a short visible needle. Much more recently, an NIS developed by Eli Lily in 2014 to deliver Trulicity® (dulaglutide, the first ready-to-use, once weekly glucagon-like receptor-1 receptor agonist) has a hidden needle. While this may seem like a small differentiator, fear of needles is a commonly cited concern for patients that leads to non-adherence to the prescribed insulin regimen. It is unlikely the traditional (visible needle) insulin pens will be replaced short-term since they still have a very strong market presence.

What distinguishes a biosimilar device from the originator device?

Biosimilar insulins are by definition as close to the originator insulins as possible in function so that they can be substituted for the originator insulin in a clinical setting. Thus, the means of delivery may offer a way for a biosimilar insulin to stand out in a crowded market place.

It is important to note that all biosimilar insulin devices should adhere to the established best practices for NISs, including tamper resistance and dose management strategies, to ensure that all patients have access to a safe, reliable, and effective product.

Virtually all of the insulin pens in use today follow a "dial-up, dial-down, press to inject" format that was originally pioneered by NovoNordisk with the NovoPen 2. In the biosimilar arena, Abasaglar/Basaglar (insulin glargine) is the only biosimilar approved for use in the United States and Europe and is marketed in the Eli Lilly KwikPen format and as cartridges for Lilly's refillable Savvio pen. Among the locally produced biosimilars being developed in emerging markets, all manufacturers utilize insulin pens for delivery, although three of the manufacturers have chosen to develop their own devices rather than utilize existing pens.

One area in which some biosimilar insulin delivery devices differ from the originator devices is their adherence to the requirements in ISO 11608-1, which is the applicable international standard for NISs. While major manufacturers in Europe comply fully with ISO 11608-1, some of the insulin pens produced by suppliers in emerging markets have applied the ISO 11608-1 standard less rigorously. One potentially important example is the way that different manufacturers have addressed Section 5.5 of ISO 11608-1, which regulates how the NIS performs when the insulin vial is near empty, or contains an insufficient quantity of insulin to administer a selected dose. Section 5.5 of the General design requirements, section j of 11608-1 2012 states that the design of the variable multi-dose NISs must prevent the user from presetting, or attempting to deliver, a larger dose than that remaining in the container. Alternatively, the design must make the user aware of the amount of drug delivered, or the "shortfall", i.e., the amount of the preset dose not delivered. While insulin pens available in Western markets include a range of features to address these issues, at least one of the insulin pens produced by a supplier from an emerging market was





capable of delivering less than the insulin dose selected when the device approaches empty and did not alert the patient that there was a dosing shortfall. Thus, choosing the manufacturer of an insulin device and verifying that the device is performing to consistently deliver the pharmacokinetic and pharmacodynamic profiles expected for a biosimilar insulin are important considerations.

On a more positive note, biosimilar insulins have the opportunity to differentiate themselves from the originator by specifically targeting the design of their delivery device to specific patient subgroups. Patient populations that may be of particular interest include:

- Seniors who are visually and hearing impaired and often lack dexterity
- Pediatric patients requiring smaller or even half unit doses of insulin
- Adolescent and young adult patients who may value style and discretion in a device

Including delivery device design features that appeal to specific patient subgroups may improve adherence and give the biosimilar insulin an advantageous market position.

Choosing to develop a novel device or use an existing device

Given the importance of a biosimilar insulin delivery device and the potential advantages of customizing the device to target markets, manufacturers of insulin biosimilars are confronted with the choice of making their own insulin pen or utilizing an existing pen. In reality, these choices exist along a spectrum of options.

Figure 1: Options for Developing an Insulin Pen. Adapted from Fry A et al. 2016.



Each of the options have risks and benefits.

- Licensing an existing device unchanged or with minimal modification has the fewest risks and can often be accomplished quickly with minimal cost. However, this option provides very little opportunity to customize beyond marketing (e.g., color and labeling).
- Licensing and extensively adapting or developing an existing product is an attractive intermediate.
 Depending on the extent of customization desired, this can be almost as expensive as designing new.
 Using this hybrid option, it is possible to customize core technology and licensed intellectual property to meet the needs of a specific patient group.
- Developing a new device requires the largest investment of capital and time, and is the riskiest option. The learning curve can be surprisingly steep and the patent landscape is crowded. However, successful development allows a pharmaceutical company to design exactly the device they want.





Regardless of the route taken, all of the devices are subject to the same regulatory requirements.

Structuring a development program for a biosimilar device

Numerous agencies have written standards that provide comprehensive guidance for companies interested in insulin delivery device development (Table 1).

Table 1: Considerations and associated risks when selecting patients with type 2 diabetes for early phase clinical trials

Reference Number	Document Title
ISO 11608 series of standards	Particularly: ISO 11608-1-2012 and ISO 11608-1-2014; there are 5 parts to the series
ISO 10993-1	Biological evaluation of medical devices – part 1: evaluation and testing within a risk management process
ISO 13485:2003	Medical devices-quality management systems – requirements for regulatory purposes
ISO 14253-1	Geometrical product specifications (GPS) – inspection by measurement of workpieces and measuring equipment – part 1: decision rules for proving conformance or nonconformance with specifications
ISO 14971	Medical devices – application of risk management to medical devices
ISO/IEC Guide 98-3	Uncertainty of measurement – part 3: guide to the expression of uncertainty in measurement (GUM:1995)
IEC 60068-2-6:2007	Environment testing – part 2-6: tests – test Fc: vibration (sinusoidal)
IEC 60068-2-30:2005	Environmental testing – part 2-30: tests-test Db: damp, heat, cyclic (12 + 12 h cycle)
IEC 60601-1-2:2007	Medical electrical equipment – part 1-2: general requirements for basic safety and essential performance – collateral standard: electromagnetic compatibility – requirements and tests.
IEC 62366	Medical devices – application of usability engineering to medical devices

In 1997, the Food and Drug Administration issued their design control guidance for medical device manufacturers. This included the well-known "waterfall" diagram capturing the various interconnected and necessary documents for a successful device development program. A version of the diagram is shown in Figure 2.

In its most basic form, device development is a series of tests to determine whether the output of the design process meets the specifications set at earlier stages. The highest level document is the technical product profile (TPP), which describes the patient needs that the device is intended to meet. Through an iterative process, the TPP gives rise to increasingly technically focused documents such as the user requirements specification (URS) that defines what the user will get from the device, the product requirements specification (PRS) that defines what the device will do, and the detailed design specification (DDS) that defines what the device is and serves as the reference for production validation.







Figure 2: Waterfall model of the device development process. Adapted from Fry A et al. 2016.

As the iterations progress the device design is refined. At each stage of development, the output (models, prototypes etc.) are assessed against the relevant specification (URS, DDS, etc.) and any revisions required are based on such assessments. For example, the URS is typically validated through user trials and Phase III clinical trials. The PRS and DDS are generally validated as part of the overall design verification process. Well run clinical and user trials are vital for establishing the efficacy of the final medical device design.

Conclusions

The design of a biosimilar insulin delivery device is potentially highly relevant to the market success of a novel biosimilar insulin. While all best practices in design should be adhered to so that patients have access to a safe, reliable, and effective insulin delivery device, there is substantial opportunity to position biosimilar insulins advantageously in the market by customizing the delivery device to specific patient populations. To achieve customization of their delivery devices, pharmaceutical companies have a range of options from licensing an "off the shelf" existing pen to designing a completely novel product. Regardless of the design option chosen, the insulin delivery device will be subject to stringent regulatory requirements and clinical and user testing to ensure it delivers the expected pharmacokinetic and pharmacodynamic profiles for the biosimilar insulin.

Looking Ahead

While this article has focused primarily on insulin pens, other insulin delivery devices that are being used in clinical settings range from continuous pumps to inhalers. When considering device design, the primary container (or Container Closure System) and any related parts that come into contact with the drug are particularly important given the sensitive nature of insulin. For example, the therapeutic efficacy of the delivery system would be impaired if the insulin were to adsorb onto a part of the device. In the future, careful consideration must be given to alternative insulin delivery devices and demonstrating their safe, reliable, and effective use.





Further Reading

Anderson BJ and Redondo MJ. What can we learn from patient-reported outcomes of insulin pen devices? 2011 J Diabetes Sci Technol 5(6):1563-71

Fry AR, Krentz AJ, Hompesch M. Considerations in biosimilar insulin device development. 2016 Biosimilars 6:1-7 Fry A. Insulin delivery device technology 2012: where are we after 90 years? 2012. J Diabetes Sci Technol. 6(4):947-53

About the Authors



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Mr. Fry is the founder of Team Consulting Ltd. A mechanical engineer by profession, he has over 25 years' experience in medical device development, specializing in drug delivery. He is an active member of several pharmaceutical industry associations including the PDA and Aerosol Society and is also a UK accredited representative sitting on ISO committees developing the ISO 11608 series of standards. He is a regular speaker at industry conferences, author of a number of journal

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As Senior Research Fellow at ProSciento, Prof. Krentz's research involves investigator-initiated research in diabetes and cardiometabolic therapies. In addition to original articles, reviews and book chapters he has authored or edited a number of 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*

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Dr. Hompesch's is a highly regarded expert in early phase clinical trial design for diabetes, obesity and related metabolic drug and device development. He is also a founder of ProSciento, the leading CRO exclusively focused on metabolic diseases and one of the few CROs actively conducting clinical research and biomarker validation studies using imaging and biopsy methods to detect progressive NASH in NAFLD and diabetes patients for therapeutic development. Dr.

Hompesch is the author of more than 85 peer-reviewed publications and editorials and is a

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