

# The Future of Biosimilar Insulins

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■ **IN BRIEF** Biosimilar insulins are available in many countries and will be made available in the United States in the near future. Some concerns associated with biosimilar insulins include potential differences in the efficacy and safety between a biosimilar product and its reference insulin, the ramifications of having the same name or different names for a biosimilar and its reference insulin, the prospects of and limitations to substituting insulin products, and the proper implementation of pharmacovigilance. Still, health care providers will have the opportunity, with continued appropriate monitoring, to offer alternative, and possibly more individualized, therapy for diabetes management with the introduction of biosimilar insulins.

Insulin was first discovered by surgeon Frederick Grant Banting and medical student Charles Herbert Best at the University of Toronto in a happenstance moment in 1921. In January 1922, the first patient with diabetes (14-year-old Leonard Thompson) was treated with insulin (originally termed “isletin”) that was successfully extracted from whole fresh animal pancreas. The insulin product was patented by the academic team in 1923, but they sold the patent for \$1 per discoverer to the University of Toronto, which contracted with Eli Lilly to mass-produce purified insulin (1). The question that follows is why no generic version of insulin was marketed until 2015 (available in other countries; technically, there are no biosimilar insulins yet available in the United States).

Once a patent is issued for a biological drug product, the manufacturer has exclusivity rights for 12 years (2). Nevertheless, insulin products have maintained market exclusivity for 93 years. The life of a patent can technically, and unfortunately commonly, be extended by a

manufacturer by developing a similar but improved version of the soon-to-expire drug and obtaining a new patent of another 12 years of exclusivity. To seal the deal, manufacturers may also decide to discontinue manufacturing the older drug and thus force the market share to shift to the new version (2). Examples of such exploitation of the market system include memantine to memantine extended-release, filgrastim to pegfilgrastim, and insulin to short-acting and long-acting insulin. With a series of improved insulin products over many years, the market opportunity for generic insulins was made impossible—until today. For example, the patent for insulin glargine (sold by Sanofi under the trade name Lantus) expired in February 2015 (3).

Recently, Basaglar (marketed under the name Abasaglar in Europe [4]) was approved by the U.S. Food and Drug Administration (FDA) on 16 December 2015, after having received tentative FDA approval on 18 August 2014. Table 1 summarizes the clinical trial results used to support the approval of Basaglar (5–12).

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TABLE 1. Basaglar (Insulin Glargine; LY2963016) Clinical Trials

| Clinical trials. gov Identifier | Comparative Agent   | Study Population   | Trial Type  | Primary Objective(s)                        | Results   |
|---------------------------------|---|--|---|---|---|
| NCT01634165 (5)                 | Insulin glargine (Lantus)                                     | Healthy subjects (n = 24)  | Randomized, double-blind, active-controlled, cross-over study   | AUC and C <sub>max</sub> (pharmacokinetics) | No statistical analysis, but the PK of LY2963016 0.3–0.6 units/kg in healthy volunteers appear to be similar to the PK of Lantus (same dose range)  |
| NCT01600950 (6)                 | Insulin glargine (Lantus)                                     | Type 1 diabetes (n = 20)   | Randomized, double-blind, active-controlled, cross-over study   | Duration of action (pharmacodynamics)       | No statistical analysis, but the PD of duration of action appear similar between LY2963016 0.3 units/kg and Lantus (same dose)  |
| NCT01476345 (7)                 | Insulin glargine (Lantus)                                     | Diabetes mellitus (n = 80)                                       | Randomized, double-blind, active-controlled, cross-over study   | AUC and C <sub>max</sub> (pharmacokinetics) | No statistical analysis, but PK of LY2963016 0.5 units/kg in patients with diabetes mellitus appear to be similar to the PK of Lantus (same dose)   |
| NCT01688635 (8)                 | Insulin glargine (Lantus)                                     | Healthy subjects (n = 91)  | Randomized, double-blind, active-controlled, cross-over study   | AUC and C <sub>max</sub> (pharmacokinetics) | No statistical analysis, but AUC and C <sub>max</sub> of LY2963016 0.5 units/kg appears to be similar to those of Lantus (same dose)  |
| NCT01374178 (9)                 | Insulin glargine (Lantus)                                     | Diabetes mellitus (n = 16)                                       | Randomized, open-label, active-controlled, cross-over study     | AUC (pharmacokinetics)                      | No statistical analysis, but AUC of LY2963016 0.5 units/kg appears to be similar to the AUC of Lantus (same dose)   |
| NCT01421459 (10)                | Insulin glargine (Lantus); oral antihyperglycemic medications | Type 2 diabetes mellitus (n = 756; 376 LY2963016 and 380 Lantus) | Randomized, double-blind, active-controlled, parallel-arm study | Change in A1C from baseline to 24 weeks     | LY2963016 + oral antihyperglycemic agents was noninferior to Lantus + oral antihyperglycemic agents: <ul style="list-style-type: none"> <li>• A1C decreased by 1.286 (SE 0.06) in the LY2963016 arm and by 1.338 (SE 0.06) in the Lantus arm after 24 weeks of therapy</li> <li>• Mean difference was 0.052 (95% CI –0.07 to 0.175, P = 0.403); analyzed by ANCOVA</li> </ul> |
| NCT01421147 (11)                | Insulin glargine (Lantus); insulin lispro                     | Type 1 diabetes mellitus (n = 535; 268 LY2963016 and 267 Lantus) | Randomized, open-label, active-controlled, parallel-arm study   | Change in A1C from baseline to 24 weeks     | LY2963016 + insulin lispro was noninferior to Lantus + insulin lispro: <ul style="list-style-type: none"> <li>• A1C decreased by 0.352 (SE 0.053) in the LY2963016 arm and by 0.460 (SE 0.054) in the Lantus arm after 24 weeks of therapy</li> <li>• Mean difference was 0.108 (95% CI –0.002 to 0.219, P = 0.055); analyzed by ANCOVA</li> </ul>                            |
| NCT02302716 (12)                | Insulin glargine (Lantus); oral antihyperglycemic medications | Type 2 diabetes mellitus   | Randomized, open-label, prospective, parallel-arm study         | Change in A1C from baseline to 24 weeks     | Study is ongoing; no results are available  |

ANCOVA, analysis of covariance; AUC, area under the curve; C<sub>max</sub>, maximum plasma concentration; PK, pharmacokinetics; PD, pharmacodynamics; SE, standard error.

**TABLE 2. Biological Drug Terms and Definitions (19–21)**

|                                 |  |
|---------------------------------|--|
| <b>Biologics</b>                | Products composed of sugars, proteins, nucleic acids, and/or cells or tissues used to prevent, treat, or cure a disease or condition in humans. Products include vaccines, blood and blood components, allergenic products, and recombinant therapeutic proteins.  |
| <b>Originators (References)</b> | First biologics approved against which future related biologics are evaluated.   |
| <b>Biosimilars</b>              | Biologic that is highly similar to a reference product (i.e., originator) with no clinically meaningful difference in purity, potency, and safety.   |
| <b>Interchangeables</b>         | Biologics that meet the requirements of biosimilars and produce the same clinical result as the originator in any patient. The risk of reduced efficacy or increased adverse events from switching to the interchangeable or alternating between the interchangeable and the originator should be no greater than the risk associated with continuous use of the originator. |

Basaglar, manufactured by Eli Lilly and Company, is another version of Sanofi's insulin glargine product (Lantus) (13). Technically, Basaglar is not a biosimilar biological drug product because insulin products and new versions of insulin products are regulated and approved under the Food, Drug, and Cosmetic Act (FD&C Act), section 505(b)(2), new drug application pathway (13,14). In all essence, however, Basaglar is a biosimilar. As such, the Biologics Price Competition and Innovation Act, under the Patient Protection and Affordable Care Act that was passed in 2010, created an amendment to the Public Health Service Act (PHSA) section 351(k), which will require all biosimilars of biological drug products (including insulin) to be regulated under PHSA section 351(k) by 2020 (15–17). Thus, for the purposes of this article, similar versions of insulins will be referred to as “biosimilars.”

The reason why biosimilar insulins are not considered generic products is because the term “generic” is reserved for copies of nonbiologics or small-molecule drugs because these copies contain the exact same active ingredient as their respective proprietary reference drugs. Generic manufacturing companies are able to identically replicate active ingredients of small-molecule drugs despite the fact that manufacturers do not divulge proprietary composition information or manufacturing protocols (17). In contrast, insulin is a large-protein, biological product that

cannot be exactly replicated because of the greater complexity involved in manufacturing biologics. Biosimilar insulins are manufactured in living organisms (e.g., yeast and bacteria) to produce large quantities of the desired large-protein product, which limits the ability to manufacture exact replicas of original biological medications (15,18). In fact, there is inevitable variability among different lots of a single reference biologic and even within a single lot. Any difference in the manufacturing process (e.g., organism type, culture media, protein extraction, and purification) or equipment can ultimately contribute to differences between biosimilars and their respective reference biologic (i.e., “originator”) (14). Table 2 distinguishes the differences among common terms for biological drugs (19–21).

Minor changes observed between a new biosimilar insulin and its respective originator may not only be a result of differences in the manufacturing processes, but also may be a result of differences in delivery devices. Manufacturers are permitted to create a delivery device that is different from the delivery device patented for the corresponding originator insulin. Thus, the proposed delivery devices for biosimilar insulins must be studied to show that the delivery devices do not alter the stability of the insulin products and deliver the correct intended dose in a safe and dependable manner. Although biosimilar insulins do not have to be delivered in the exact

same device as their corresponding originators, they must be delivered by the same route of administration (19,22). For example, Basaglar is to be administered subcutaneously via Eli Lilly's KwikPen device similar to Sanofi's subcutaneous delivery of Lantus via the Solostar pen device (23,24).

Thus, the word “generic” is reserved for exact replicas of the active ingredients of small-molecule drugs, and the term “biosimilar” was coined to address the fact that biological medications are not exact duplicates of their originator but are highly similar with no clinically meaningful differences in efficacy or safety (18). Nevertheless, there are concerns that these subtle differences may potentially alter the efficacy or safety of a biosimilar insulin compared to its originator insulin.

Current practice allows pharmacists to automatically substitute original reference drugs with their respective small-molecule generic drugs without having to contact the prescriber if the products have been deemed interchangeable by the FDA (i.e., have A ratings in the FDA's Orange Book listing of approved drug products with therapeutic equivalence evaluations) (21,25). By FDA definition, interchangeability status similarly allows a biosimilar to be substituted without first contacting the prescriber (26). The FDA's Purple Book lists all biologics with notations on which medications are originators, biosimilars, or interchangeables. Thus, the Purple Book

**TABLE 3. Advantages of the Two Proposed Naming Systems for Interchangeable Biologics (29–31)**

| Same Four-Letter Suffix   | Different Four-Letter Suffix   |
|---|--|
| <ul style="list-style-type: none"> <li>• Less confusion; can mitigate medication errors</li> <li>• Less resistance to substitution; easier to accept designated status of interchangeability</li> <li>• Current tracking and safety alert systems can recognize new products</li> </ul> | <ul style="list-style-type: none"> <li>• Easier to track and associate adverse events and/or change in disease to correct product</li> <li>• Facilitates having accurate records of automatic substitutions (e.g., insurance-mediated switch)</li> <li>• Lower costs due to marketing competition of different products</li> </ul> |

is the Orange Book for biologics and can be used similarly to determine which biologic is biosimilar to or interchangeable with an originator (19,27).

There is debate, however, about whether pharmacists should be able to automatically substitute interchangeable biosimilars without contacting the prescriber. Surveys indicate that, although health professionals would be interested in prescribing biosimilars, they would prefer to be notified of any switches. Of 376 physicians, 85.9% indicated they would like to be notified prior to their patients being switched to a biosimilar insulin, and an additional 6.4% expressed wanting to be made aware of a switch within 24 hours (17).

Thus, when interchangeable insulins are approved in the future, pharmacists may legally, automatically substitute an insulin product with another interchangeable. However, pharmacists may be asked to keep track of substitutions (for cost or insurance reasons, for example) and report them back to prescribers. Such open, interdisciplinary communication between health professionals can help facilitate good pharmacovigilance practice, as further discussed below. It is important to note that, if desired, there is still the option of prescribing insulin products under a “dispense as written” notation to avoid automatic substitutions when interchangeable insulins become available.

The FDA is in the process of creating a final naming system for biosimilars and their corresponding reference drugs (and a naming system for interchangeable biosimilars).

The FDA has proposed a naming system that is similar to the naming process for biologics established by the World Health Organization (28). For biosimilars, the FDA has proposed that a unique four-letter suffix be added to the nonproprietary name (e.g., filgrastim-sndz). For interchangeables, essentially, the debate is between having the same name or a different name compared to the original reference biological drug. The FDA proposed two options for naming interchangeable biologics: 1) same name, in which the interchangeable would assume the same 4-letter suffix as the originator, or 2) different names, in which the interchangeable could create a unique four-letter suffix distinct from the originator (19). Advocates of each option have argued the advantages of each, as shown in Table 3 (29–31).

What is tied closely to the future approved naming system of biosimilars and interchangeable biologics is pharmacovigilance. Pharmacovigilance is the tracking of marketed drug products in a way that allows adverse events (AEs) to be attributed to the correct drug product. A good pharmacovigilance system is necessary to appropriately link observed postmarketing AEs to the correct corresponding biologic (19).

There is a risk of immunogenicity with any biologic. Immunogenicity refers to the development of antibodies against the drug (i.e., antidrug antibodies). The possible repercussions from having anti-insulin antibodies, occurring at any time after starting therapy, include hypersensitivity reactions, mild decreases in insulin effectiveness, and severe insu-

lin resistance (rare). Rarely observed, but theoretically possible, immunogenicity may be clinically evidenced by a need to adjust therapy (e.g., increase insulin dose or switch insulin products) to reestablish optimal therapy (32). As switches are made among biosimilar insulins and/or future interchangeable insulins, it will be important to have a good pharmacovigilance system in place to associate the correct insulin product with an observed AE or decrease in effectiveness—particularly when there is the potential for multiple substitutions (e.g., because of change in insurance plans or formularies). However, because immunogenicity can occur at any time, it may prove to be difficult to always keep accurate records of what product caused which effect.

An ongoing study is being conducted in Norway to verify that switching to a biosimilar infliximab does not result in significant differences in safety or effectiveness (33). It will be important for health professionals to await similar postmarketing studies on biosimilar insulins.

Despite these concerns, there are advantages to having biosimilar insulins such as Basaglar. The extent of cost savings may not be as drastic with biosimilars as they were with small-molecule generics because of the complex nature of biologics and their more complicated manufacturing processes. Nevertheless, the introduction of biosimilar products has the potential to lower costs by increasing market competition (34). Another advantage is the potential for enhanced individualized patient care with the availability of a greater

variety of biosimilars. With the introduction of biosimilar insulins, prescribers may find that certain individuals are more willing to subject themselves to using a particular biosimilar insulin delivery device or find that they respond better or present with fewer hypoglycemic events, for example, with one biosimilar compared to another.

In summary, health professionals should be aware of the concerns associated with biosimilar insulins such as Basaglar and should stay informed about the developments surrounding biosimilar insulins, which are expected to be official in 2020. In the meantime, the FDA can be relied on to require manufacturers to meet strict standards and ensure consistency in the final production of these highly similar biologics, and health professionals can continue to practice with due diligence by assessing the acceptability of biosimilar insulins for their specific patients' needs and wants and by closely monitoring patients at times of initiation of and transition to a biosimilar insulin.

## Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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