

# How Similar Are Biosimilars? What Do Clinicians Need to Know About Biosimilar and Follow-On Insulins?

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**■ IN BRIEF** As more patents on biological medicines expire, increased numbers of biologic copies, referred to as “biosimilars,” will likely become available in the United States in the coming years. With greater availability and the drive for health care savings, the use of biosimilars and of “follow-on” biological products is likely to increase in routine clinical practice. Health care practitioners need to be fully aware of these products and accompanying considerations if they are to make informed decisions together with their patients.

In the past 20–30 years, biological drugs or “biologics” have influenced disease management across multiple therapeutic areas. The high cost of drug development and innovation, and the potential for a share in the large and growing market in biologics, has led to an interest in developing drugs that are biologically similar to products already approved by the U.S. Food and Drug Administration (FDA). These drugs, known as “biosimilars,” are specific drug entities that were given their own regulatory pathway as part of the Biologics Price Competition and Innovation Act of 2010. Copies of biologics may also be approved under the same pathway as a generic drug, via a New Drug Application (NDA) or the abbreviated approval pathways (abbreviated NDA [ANDAs]), although this is set to change in 2020. However, products approved in this way are not classed as “biosimilars” but rather as “follow-on” products, a difference in terminology that has implications not only for their regulation but also for their use in practice.

The distinction between biosimilars and generics is an important one. Biosimilars have been erroneously

described as generic versions of biologic agents; however, it is important to understand that biosimilars have unique differences from their reference products, which means they cannot be considered conventional generics (Table 1).

Conventional drugs are generally stable, small (low molecular weight) chemical compounds with well-defined, completely characterized structures that are manufactured using defined chemical reactions (1). When the patents for such drugs expire, a generic manufacturer only needs to show that the generic drug contains the same active ingredient as the original drug and is identical in strength, dosage form, and route of administration and is manufactured under the same stringent conditions (2). There is no need for a manufacturer to carry out animal or clinical studies for generics, because they are essentially the same as the original drug.

Biological products are different from conventional chemical drugs; they are generally large (high molecular weight) compounds with complex, heterogeneous structures that are difficult to fully character-

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**TABLE 1. Key Differences Between Generic Drugs and Biosimilar Drugs**

	Generics	Biosimilars
FDA definition	A generic drug is identical (bioequivalent) to a branded drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use	A biosimilar is highly similar to its U.S.-licensed reference biological product and has no clinically relevant differences to the reference product in terms of safety, purity, and potency
Size	Low molecular weight	High molecular weight
Structure	Simple, well defined	Complex, potential for structural variation
Complexity	Easy to fully characterize	Difficult to characterize
Manufacturing	Produced by chemical synthesis	Produced by specialized biological process
Stability	In general, relatively stable	Sensitive to storage and handling conditions
Immunogenicity	Lower potential	Higher potential
FDA approval process	ANDA; preclinical (animal) and clinical (human) data to establish safety and effectiveness are generally not required	351(k) of the PHS Act; preclinical (animal) and clinical (human) data to establish safety and effectiveness are generally required

ize (1). Importantly, these structures are not created by chemical synthesis, but rather by complex, multistep processes in biological systems such as plant or animal cell cultures or microorganisms. Biologics are highly dependent on the process used to create them, and even small changes in the manufacturing process can alter their structure and potentially affect their efficacy and safety (1). The obstacle facing biosimilar manufacturers is that specific manufacturing processes for existing biologics, including insulins, are the proprietary information of the originating pharmaceutical company and therefore cannot be duplicated, even if the exact processes were known (3). Because manufacturers must develop their own processes, which may introduce changes relative to the product they are attempting to copy (known as the “reference” or “originator” product), biosimilars have a potential for variation from their reference product. This is generally not seen for chemical drugs.

All of these considerations have affected the way biosimilars are regulated and approved compared to conventional generic products. Such considerations may also affect the way these agents are prescribed, with issues involving their interchangeability with and use as a substitute

for their originator product. Given the drive to cut costs, such issues are important in bringing biosimilars into routine practice. Biosimilars in other areas of medicine are usually offered for a lower price than the originator product, and, given the huge and growing insulin market, this is clearly a major potential benefit in the diabetes area. Increased competition is generally welcome, and keener market pricing may improve access. New insulin products, including biosimilars and follow-on products, are likely to become increasingly available in the coming years. Therefore, health care professionals (HCPs) need to be aware of these products, the terminology for describing them, and the considerations related to their use.

**Defining Biosimilarity: the FDA Approval Process**

The FDA defines a biosimilar as “a type of biological product that is licensed (approved) by the FDA because it is highly similar to an already FDA-approved biological product (the reference product) and has been shown to have no clinical differences from the reference product” (Table 2). The key consideration driving regulation is that, for all the reasons discussed previously, biosimilars are similar, but not identical, to their reference product. Therefore, they require a specific regulatory ap-

proach distinct from that for generics. Initially, copies of biologics were approved in the United States under the same pathway as generic drugs, namely via NDAs or ANDAs under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under this act, copy biologic products could rely on data generated by the reference product to support their application, similar to generics, without the need to repeat some of the studies, such as extensive clinical trials, that were needed for the approval of the reference product. An important consideration for this is that copy biosimilars approved under this pathway are not called “biosimilars” by the FDA, but rather are described as “follow-on” products. This has implications for the way they can be prescribed and dispensed.

Biosimilars as a drug class were first addressed specifically by the Affordable Care Act, signed into law in 2010. As part of this, the Biologics Price Competition and Innovation Act created an abbreviated licensure pathway in section 351(k) of the Public Health Service (PHS) Act for biological products (4). This new pathway is set to replace the FD&C pathway in the coming years; the 10-year transition period will end on 23 March 2020. After this date, all biosimilars (including those submit-

TABLE 2. Terminology

Term	Definition
Generics Generic drugs	Generic drugs are identical (or bioequivalent) to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.
Biologics Biological products	Biological products are made from a variety of natural sources and are used to either treat or cure diseases and medical conditions, prevent diseases, or diagnose diseases. Biological products can be made of sugars, proteins, nucleic acids, or complex combinations of these substances or may be living entities such as cells and tissues.
Biosimilars Biosimilar products	Biosimilars are a type of biological product that is licensed (approved) by the FDA under section 351(k) of the PHS Act because they are highly similar to an already FDA-approved biological reference product and have been shown to have no clinically meaningful differences from the reference product. Minor differences in clinically inactive components are allowed, but there must be no clinically meaningful differences between the biosimilar and the reference product it was compared to in terms of the safety, purity, and potency of the product.
Follow-on biologics	This term is used to describe biological products designed to be similar to a biological reference product that has been approved under a pathway other than 351(k) of the PHS Act.
Reference products Reference biologics	These terms describe biological products approved by the FDA under section 351(k) of the PHS Act.
Interchangeable products	Interchangeable products are both biosimilar to their reference product and expected to produce the same clinical result as the reference product in any given patient. In addition, for a biological product that is administered more than once to an individual, the risk in alternating or switching between the biological product and the reference product in terms of safety or diminished effectiveness will not be greater than the risk of using the reference product without alternating or switching.
Automatic substitution	An interchangeable product that may be substituted for the reference product without the intervention of the HCP who prescribed the reference product (depending on local regulations).
Originator insulin Innovator insulin	These terms refer to the original, branded formulation of an insulin.
Noninferiority study	This term describes a study that aims to demonstrate that a biosimilar is not inferior to a reference insulin by more than a small prespecified amount.

ted but not yet approved under the FD&C Act) must be submitted under the PHS pathway.

Biosimilars submitted for approval to the FDA under this PHS pathway can rely on some of the scientific data developed to support the application of their reference biologic. In general, for approval, biosimilars must undergo analytical studies (structural analyses and *in vitro* and/or *in vivo* functional assays); animal studies, including the assessment of toxicity; and a range of clinical studies, including pharmacokinetic (PK) and pharmacodynamic (PD) studies, immunogenicity assessment, and comparative efficacy and safety studies that demonstrate that the biological product is highly similar to

the reference product. Although the FDA states that clinical studies may only be needed in certain circumstances in which the results of the previous studies are not conclusive, follow-on insulins in development are undergoing or have undergone head-to-head clinical trials with their reference insulin.

An important consideration of the FDA's approach to biosimilars is that the goal is to demonstrate similarity between the biosimilar and the reference product, not to independently establish the safety and effectiveness of the biosimilar (5). Therefore, the clinical studies performed by biosimilar manufacturers do not need to be as extensive as those performed for the reference product. This may

introduce the potential to miss rare events such as immunogenic adverse events. Therefore, postmarketing pharmacovigilance is a key aspect of the approval process for biosimilars, and HCPs are likely to find such data in real-world patients particularly beneficial (6).

One important consideration for biosimilars that clearly sets them apart from generics is that approval of a drug as a biosimilar does not automatically mean it is interchangeable with its reference product. According to the FDA, a biosimilar product cannot be substituted at the pharmacy level without the intervention of the prescribing HCP. For biosimilars to be approved as interchangeable, they must meet further criteria during

the approval process. In addition to meeting all of the criteria to prove biosimilarity, they must also show that they can be expected to produce the same clinical result as the reference product in any given patient. Also, if they are to be administered more than once, the risk, in terms of safety or diminished effectiveness, of alternating or switching between use of the proposed interchangeable product and the reference product must be no greater than the risk of using the reference product without alternating or switching (7). Although the FDA has stated these requirements, they have not yet specified the type of studies required to prove them and, to date, no interchangeable biosimilar products have been approved in the United States. Because decisions about interchangeability are made at the state rather than the federal level, it is possible that this situation may differ among states. To date, most states that have ruled on biosimilar interchangeability have included the proviso that the biosimilar must have been approved as interchangeable by the FDA (8). Such products will be listed in the FDA “Purple Book,” the equivalent for biologics of the FDA “Orange Book” for generic products.

### Biosimilar Insulins in the United States: Present and Future

To date, only one follow-on insulin (not a biosimilar) has been approved in the United States: Eli Lilly’s insulin glargine Basaglar (9). Unlike in the European Union, where it is approved as a biosimilar insulin glargine, Basaglar is classified as a “follow-on” insulin in the United States because it was approved under the 505 NDA pathway and not under the 351(k) biosimilar pathway of the PHS Act, as discussed previously. Although relying in part on data from its reference product, insulin glargine (Lantus), Basaglar underwent a range of studies and clinical trials only to establish its similarity to Lantus. These included PK and PD studies that showed that Basaglar had similar, although not identical, PK

properties to Lantus. Any differences were within the FDA’s prespecified acceptance limits and were not considered to be clinically relevant (10). In addition, two phase 3 clinical trials were carried out comparing Basaglar and Lantus: one in 535 patients with type 1 diabetes (ELEMENT 1) (11) and one in 756 patients with type 2 diabetes (ELEMENT 2) (12). The trials showed that Basaglar was noninferior to Lantus in terms of the main endpoint of the study (change in A1C from baseline) and was similar to Lantus in other glycemic measures and in its safety profile. Again, it is worth mentioning that, because Basaglar could rely on clinical data generated for its reference product, its trials were considerably smaller than those carried out for Lantus (13). Postmarketing surveillance for follow-on biologics or biosimilars is important.

Three other follow-on insulins are undergoing clinical trials in the United States. It is likely that most, if not all, of these will be submitted under the FD&C Act before the end of the transition period in March 2020. If approved, they will therefore be classified as follow-on, not biosimilar, insulins similar to Basaglar.

The rapid-acting insulin lispro (Humalog) biosimilar SAR342434 (Sanofi) has been shown to have similar PK and PD properties to both the FDA- and European Medicines Agency (EMA)-approved Humalog (14). Results of the phase 3 study SORELLA 1 trial in type 1 diabetes patients (NCT02273180) showed that SAR342434 was as effective and well tolerated as Humalog, with a similar safety profile. The results of another phase 3 study, SORELLA 2 in type 2 diabetes patients (NCT02294474), are expected soon. Both studies compared the immunogenicity of SAR342434 and Humalog (i.e., antibody status and titers and relationship of anti-insulin antibodies with efficacy and safety), rates of hypoglycemia, safety, and a range of secondary efficacy parameters,

including the percentage of patients achieving A1C targets, change in fasting plasma glucose, postprandial glucose excursions, and 24-hour plasma glucose concentrations.

Merck’s insulin glargine (MK-1293) has demonstrated similar PK and PD properties to EMA-approved Lantus (15). It has been shown to be noninferior to Lantus in terms of change in A1C from baseline and to have a similar safety profile in two phase 3 studies, which included 508 patients with type 1 diabetes (NCT02059161) and 531 patients with type 2 diabetes (NCT02059187) (16–18). Merck submitted results for approval to the FDA in August 2016 (19) under 505(b)(2) of the FD&C Act, which means that MK-1293 will also be made available as a follow-on insulin glargine.

Finally, Mylan’s insulin glargine (Biocon-Mylan) is undergoing phase 3 studies (INSTRIDE-1 [NCT02227862] and INSTRIDE-2 [NCT02227875]) aiming to demonstrate noninferiority to Lantus. It has been submitted to the EMA for approval in November 2016 (20).

### Biosimilar Insulins Outside of the United States

Although insulins classified as “biosimilar” have been available for many years in a number of countries, including China, India, Pakistan, Peru, Thailand, and Mexico, in most cases, these countries had little or no biosimilar-specific regulatory procedures in place when they were approved, raising concerns regarding their safety and effectiveness compared to their reference products (21). Given that such products have generally not been compared and analyzed against a licensed reference biological product under comprehensive biosimilar regulations, it has been suggested that they should be termed “noninnovator copy biologics” rather than biosimilars (21).

Where available, uptake of these biosimilar insulins has not been rapid. In India, for example, biosimilar

insulins have gained only a relatively small market share to date, possibly related to mistrust by clinicians after past problems with quality, which led to withdrawal of a biosimilar insulin from the market (22). For these products to be approved for use in more controlled markets such as the United States and the European Union, they will have to prove biosimilarity under the stringent conditions required in these regions (e.g., Biocon/Mylan's insulin glargine, mentioned above, is already approved in India and Japan, but is currently undergoing additional clinical trials to support approval in the United States).

The European Union has been ahead of the United States in terms of regulation of biosimilars and has specific guidance in place for biosimilar insulins. Currently, only one biosimilar insulin is approved in the European Union: Eli Lilly's insulin glargine biosimilar Abasaglar. (In the United States, Basaglar will be marketed as a follow-on insulin.) Abasaglar is approved for the treatment of diabetes in adults, adolescents, and children  $\geq 2$  years of age and can be prescribed like any approved insulin preparation. As with all new biologics, including biosimilars, it carries a "black triangle" requirement for additional monitoring (23). Black triangle labeling in the European Union is not the same as a boxed warning on prescription drugs in the United States, which highlights risk of serious or life-threatening adverse events. Black triangle labeling aims to encourage reporting of adverse events, but does not warn of them. Although the EMA is responsible for the approval of biosimilars such as Abasaglar, it does not make recommendations regarding whether a biosimilar should be used interchangeably with its reference product. Such decisions are made at a national level, and local regulations vary (24).

### HCPs' Perspectives on Biosimilar Insulins

Despite the fact that conventional ge-

nerics have been available for decades and are often widely substituted for branded products, many HCPs (and their patients) may still have concerns about them, with many viewing generics as less effective or of poorer quality than proprietary drugs (25). Experience in other fields has reinforced this belief (e.g., the long controversy around the bioequivalence and pharmacy switching of generic levothyroxine in patients with hypothyroidism and studies that showed marked differences between generic [approved as interchangeable] products and their reference products) (26). The greater complexity of biosimilars compared to generics is likely to raise similar concerns that must be addressed if these products are to be accepted in routine practice.

A survey of 222 U.S. HCPs directly involved with biological therapies (55% physicians, 26% pharmacists, 8% nurses, 7% nurse practitioners, and 4% other HCPs) showed that there was an interest in prescribing, dispensing, or administering biosimilars across a number of therapeutic areas (6). Yet, their knowledge of these products was not optimal. Confidence in knowledge of biosimilars was relatively low; 45% of survey respondents said they had a "great need to learn more" about biosimilars, with an additional 43% saying they had a basic understanding but would like to learn more. In addition to their own comfort level with prescribing biosimilars, HCPs may also be influenced by patient preference; patients with diabetes, particularly those with type 1 diabetes, consider the quality of their insulin to be of utmost importance and may be highly resistant to switching from a brand they trust (27).

Head-to-head studies directly comparing the clinical efficacy and safety of biosimilars and their reference products were considered to be the most important factor in helping to make informed decisions about biosimilar use; cost differences were relatively less important (27).

Confidence in the regulatory process for biosimilars and in the ability of related studies to address HCP concerns is therefore key to improving confidence in prescribing biosimilar insulins. In connection with this, new draft labeling guidelines from the FDA do not require data from studies specifically carried out with the biosimilar to be included in prescribing information, but rather only data from studies using the reference product, in line with generic labeling (4). The reason given by the FDA for this is that data from comparative studies are "not likely to be relevant to a healthcare practitioner's considerations regarding safe and effective use of the biosimilar product and potentially may cause confusion, resulting in an inaccurate understanding of the risk-benefit profile of the product" (4). However, this has raised concerns from originator manufacturers, HCPs, and patient advocates. Organizations have called for labeling that clearly shows that a drug is a biosimilar, that includes data from tests and trials of the specific drug, that clearly identifies the source of the data provided and clearly describes the specific conditions in which the biosimilar was tested, and that states whether any indications have been extrapolated from the reference product but not tested directly.

### Impact of Delivery Devices

Delivery devices are key factors in clinician, nurse, and, particularly, patient experiences with insulin administration, for which regular use becomes a part of the patient's life (28). Although precision of dosing is a key concern, ease of use, comfort, and convenience of the device are important factors that could potentially influence patient acceptance and adherence and could thus affect efficacy. Although cost is certainly a consideration, familiarity and comfort with a particular delivery device may make patients less likely to want to switch insulins, even if less expensive biosimilars are available (29).

It is likely that biosimilar insulins produced by companies that already manufacture originator insulins will be delivered using the company's existing devices; Eli Lilly's Basaglar, for example, is administered using the KwikPen, developed for administration of Humalog. Familiar devices are likely to contribute to patient comfort and acceptance; conversely, the use of a new or different device for a biosimilar may discourage switching (29). However, a biosimilar insulin will not necessarily be compatible with an existing administration device; combinations of insulins and devices may differ widely in their dosing characteristics (30).

Any new devices will have to meet the FDA's normal quality standards (31). For biosimilars, the FDA has stated that a biosimilar product may have "some design differences" in delivery device compared to the reference product provided that the proposed product meets the statutory standard for biosimilarity supported by performance data (32). For a proposed biosimilar product in a different delivery device, compatibility with the final formulation must be shown through performance testing, and human studies may be needed for certain (unspecified) design differences in the delivery. Overall, a proposed biosimilar product in a delivery device will be considered a combination submission product (insulin and device) and may, in some instances, require a separate application for the device.

### Cost Implications of Biosimilar Insulins

In 2008, the U.S. Congressional Budget Office calculated that biosimilars, in general, had the potential to reduce total expenditures on biologics by ~\$25 billion over the 2009–2018 period—roughly 0.5% of national spending on prescription drugs during the 10-year period (33). According to market research, the global insulin market was valued at nearly \$24 billion in 2014, with

an increase to ~\$48 billion expected by 2020 (34). In the United States alone, the already large insulin market is expected to grow by nearly 12% between 2015 and 2020 (35). Generic drugs in the United States cost on average ~80–85% less than branded drugs, and it is estimated that the use of FDA-approved generics saved \$158 billion in 2010 alone—an average of \$3 billion per week (36).

However, it is unlikely that biosimilar insulins will result in similar reductions in costs in the treatment of diabetes. Because of the complexity of biosimilar insulins and their manufacturing processes, they are considerably more expensive to develop and manufacture than generic products. In addition, the need for clinical and immunogenicity studies means that the process of gaining approval for biosimilars is much more expensive than for generic drugs. Finally, approval of biosimilars also requires the implementation of postmarketing pharmacovigilance programs, which again adds to the costs of producing biosimilar insulins. Because of these factors, the price differential between a biosimilar and its originator insulin is not expected to be as great as that seen with conventional generics (3).

In the United States, price reductions with biosimilar insulins have been predicted to be ~20–40%, considerably less than that seen with conventional generics (22). Other analyses have suggested that long-acting biosimilar insulins may be ~15% less expensive than their originator drugs (22), which is the case in the United Kingdom, where Abasaglar (the E.U. name for Basaglar) has a list price 15% lower than Lantus (37). Nevertheless, because daily insulin use is lifelong for patients with type 1 diabetes and for many patients with type 2 diabetes, the absolute cost savings from adoption of biosimilars are potentially considerable, even with relatively small cost differentials.

Clearly, many patients struggle with the cost of insulin, which has

risen 200% in the past 10 years (38). However, there are considerations for costs beyond the basic price of the insulin preparation, including potential effects on HCP and patient workload. For example, switching from originator to biosimilar insulin glargine would require a managed approach, with increased blood glucose monitoring during the transition period. Because the biosimilar insulin may be administered using a different device from its originator, time will also be required for patient education and support. The cost and time implications of this for HCPs are unknown but are likely to be substantial.

### Summary

Biosimilars are not the same as generics; they are similar, but not identical, to their reference drug, meaning that they may have small differences that could potentially affect both safety and efficacy. Time will tell as follow-on insulins and biosimilar insulins become increasingly available during the next few years. A decision in August 2016 by a large provider to include the follow-on insulin Basaglar in its formulary and drop current (branded) insulins may have a significant effect on the biosimilar insulin market; however, this, too, remains to be seen. The European experience with biosimilar products to date has been generally positive, although long-term information is lacking.

Biosimilar or follow-on insulins have the potential to offer several advantages in terms of an increased range of treatment options to choose from and increased patient access to treatment. However, their introduction may raise concerns with HCPs and patients, and many HCPs feel they do not have the knowledge they need to make informed decisions. There is a general need for information regarding the safety and efficacy of biosimilars compared to their reference insulins; therefore, it is crucial that a robust postapproval surveillance program be in place and that the approval process include

sufficient and appropriate studies to ensure HCPs' and patients' ability to make informed choices.

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## Duality of Interest

C.T. is a consultant for Novo Nordisk and Sanofi and a speakers bureau member for Boehringer Ingelheim and Novo Nordisk. D.H. is a consultant and speaker for Eli Lilly, Novo Nordisk, and Sanofi. V.V. sits on advisory boards for Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, CeQur, Eli Lilly, Intarcia, Janssen, and Novo Nordisk; is a consultant for Abbott Diabetes Care, Adocia, CeQur, and Eli Lilly; and is a speaker for Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, and Pamlab.

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