

# Biosimilar and Follow-on Insulin: The Ins, Outs, and Interchangeability

John White, PA-C, PharmD<sup>1,2</sup>  
and Jennifer Goldman, PharmD, CDE, BC-ADM, FCCP<sup>1</sup>

Journal of Pharmacy Technology  
2019, Vol. 35(1) 25–35  
© The Author(s) 2018



Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/8755122518802268  
journals.sagepub.com/home/pmt



## Abstract

**Objective:** To provide an overview of the differences between biosimilars and generics, and to summarize regulatory requirements and outstanding issues related to biosimilar insulins in the United States, including the issue of interchangeability. **Data Sources:** References were obtained using MEDLINE searches, the bibliographies of articles identified during the searches, review articles, and general Internet searches. Key words included the following: diabetes, insulin, biosimilar, regulatory, follow-on, and interchangeability. **Study Selection and Data Extraction:** Articles, studies, regulatory documents, and opinion pieces that addressed issues around biosimilar/follow-on insulins and interchangeability of insulins in people with diabetes were selected for inclusion in this narrative review. **Data Synthesis:** There is understandable interest in the potential for new *copies* of existing insulins—termed biosimilar insulins or follow-on insulins—to reduce the substantial and growing costs associated with managing the diabetes epidemic and to improve access, as has been achieved with conventional generic drugs. However, biosimilars or follow-on insulins are not generics. There are critical differences between biologic products and conventional chemical drugs, which present specific challenges to manufacturers, regulators, and clinicians. **Conclusions:** Health care providers and payers need to be aware of the issues surrounding biosimilar and follow-on insulins as they become more widely available in the coming years. In particular, in the face of limited data on comparative safety and efficacy, careful consideration needs to be given when interchanging between originator and biosimilar drugs, when switching patients from one biosimilar drug to the other.

## Keywords

diabetes, insulin, biosimilar, regulatory, follow-on, interchangeability

## Introduction

The recent and upcoming expiration of patent protection for a number of insulin preparations will open up the insulin market worldwide to manufacturers of insulin copies or biosimilars, or as they are currently called due to US Food and Drug Administration (FDA) regulations, follow-on insulins (Table 1). The potential attraction of these new insulins is clear, especially with the US health care system facing extra costs associated with managing the increasing number of patients with diabetes. In 2017, it was estimated that health care expenditures on insulin alone for people with diabetes costs were almost \$15 billion.<sup>1</sup> The hope is that these new insulin biosimilars or copies will deliver savings similar to those achieved with generic drugs (small molecules). However, biosimilars are not generic copies but are biologic products found to be highly similar to the brand (often termed the “originator product”; Table 1). This has important implications for their regulation and use. Overall, there are currently 11 biosimilar products approved in the United

States, none of which are yet considered interchangeable with their originator product.<sup>2</sup> With regard to insulins, there are currently none approved as biosimilars in the United States. Basaglar (U100 insulin glargine; Eli Lilly, Indianapolis, IN; Boehringer Ingelheim, Ingelheim, Germany) is classified as a “follow-on” to the basal insulin Lantus (Sanofi-Aventis, Paris, France), as it was approved pursuant to Section 505(b)(2) of the Food, Drug, and Cosmetic Act (“FD&C Act”), and as will be discussed in further detail, biologics approved under this pathway are not classified as biosimilar (Table 2).<sup>3</sup> Lusduna (Merck & Co, Kenilworth, NJ), another follow-on insulin to Lantus, has received tentative approval from the FDA.<sup>4</sup> Admelog

<sup>1</sup>MCPHS University, Boston, MA, USA

<sup>2</sup>Washington State University, Spokane, WA, USA

### Corresponding Author:

John White, Department of Pharmacotherapy, Washington State University, PBS Building Suite 120, Pullman, WA, USA.  
Email: whitej@wsu.edu

**Table I.** Terminology.

Term	Definition
Biologic products	Generally large, complex molecules that are often produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell.
Biosimilar	A biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. Approved under the Public Health Service Act pathway (see Table 2).
Interchangeable product	A biosimilar product that meets additional requirements outlined by the Biologics Price Competition and Innovation Act, with evidence that it will: <ul style="list-style-type: none"> <li>• Produce the same clinical result as the reference product in any given patient.</li> <li>• For products administered to a patient more than once that the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product has been evaluated.</li> </ul>
Follow-on product	“Copies” of biologic products approved under the Food, Drug, and Cosmetic Act 505(b)(2) pathway (see Table 2).
Reference product	The single biologic product, already approved by the FDA, against which a proposed biosimilar product is compared.
Originator product	FDA-approved, branded biologic used as a reference product during approval.

Abbreviation: FDA, US Food and Drug Administration.

(Sanofi-Aventis, Paris, France), a follow-on to the short-acting insulin Humalog (Eli Lilly, Indianapolis, IN), was also recently approved by the FDA through the Section 505(b)(2) pathway.<sup>5</sup>

Traditional chemical drugs are generally stable, small-molecule (typically between 100 and 1000 Da<sup>18</sup>) compounds. They have well-defined, completely characterized structures, which are identical even when produced by different synthetic pathways.<sup>11</sup> As such, identical copies can be easily manufactured using controlled and predictable chemical processes.<sup>4</sup> When the composition patents for these drugs expire, the generic manufacturer must show that the generic drug contains the same active ingredients as the originator drug. They must be identical in strength, dosage form, and route of administration. They must also have the same use indications, be bioequivalent, and meet the same batch requirements (for large molecules) for identity, strength, purity, and quality. Furthermore, they must be manufactured under the same strict standards as that of the FDA's Good Manufacturing Practice regulations required for originator products (no animal or clinical studies are required).<sup>19</sup> Meeting such requirements is generally straightforward for completely chemically characterized drugs manufactured using standard chemical synthetic processes. However, biologic products are less straightforward. In general, biologic products are large (commonly ranging from 18 000 to 145 000 Da<sup>18</sup>), unstable compounds (eg, hormones, interferons, antibodies) with complex, heterogeneous structures that are difficult to fully characterize. The precise structure as well as the spatial orientation of the molecule is closely related to function.<sup>11,12</sup> The structures of biologic products are highly dependent on the complex biological processes used to create them, usually involving the production of a recombinant

protein in unicellular (eg, bacteria, yeast, or mammalian cells) or multicellular (eg, transgenic animals) organisms. Even small changes in the biological manufacturing processes may result in structural alterations (eg, aggregation or oxidation) and so affect their efficacy and safety.<sup>11,12</sup> The possible differences in posttranslational modifications between a biosimilar and the originator product may have obvious and less obvious implications for safety and efficacy, as the specific tissue, cell line, or organism in which a biosimilar is produced can differ from that used to produce the originator product.<sup>18</sup> The manufacturing protocols for existing biologic products, including insulins, are the proprietary information of the originator pharmaceutical company, and therefore other manufacturers may not duplicate the production process. Because of the sensitivity of biologic products to the manufacturing process, it is impossible for other manufacturers to produce copies that are identical to the originator biologic product, hence the term biosimilar is used and not biogeneric or bioidentical.<sup>12</sup> Biosimilars are defined as biologic products that are approved by the FDA on the basis that they are highly similar to an already FDA-approved originator biologic product, known as the reference product. They have been shown to have no clinically meaningful differences from the reference product in terms of safety, purity, and potency.<sup>10</sup> Given the complexity of biologic products and their manufacturing process, biosimilars are expensive to develop compared with traditional drugs.<sup>20</sup> However, they are often used to treat chronic conditions requiring long-term, often life-long, therapy, making them an attractive area for development by the pharmaceutical industry. Additionally, they offer the potential of end-user savings.<sup>21</sup> However, once the complexity of their manufacturing process has been overcome, biosimilar insulins still

**Table 2. Approval Pathways, Terminology, and Requirements.**

Approval Pathway	FDCA Approval Pathways		PHSA Act Approval Pathways <sup>6</sup>			
	Full NDA 505(b)(1) <sup>7</sup>	AND A 505(i) <sup>8</sup>	NDA-Approved via 505(b)(2) <sup>6</sup>	Full BLA 351(a) <sup>9</sup>	Biosimilar 351(k) <sup>10</sup>	Interchangeable Biosimilar <sup>10</sup>
Type of agent	Small molecule drugs and some drugs of biologic origin <sup>11</sup>	Mostly small molecules with some exceptions <sup>12</sup>	Multiple possibilities that include follow-on of reference drug approved through 505(b)(1)	Biologics as defined by FDA	Biosimilar of biologic as defined by FDA	BLA that includes information under Section 351(k)(4) of the PHSA
Term	Reference product	Generic	Follow-on biologic	Biologic reference product	Biosimilar	Interchangeable biosimilar
Approval requirements	Safety and efficacy must be demonstrated	Bioequivalence and “sameness” must be demonstrated	Provide new data for any proposed change to the reference product	Safety, purity, and potency must be demonstrated	High similarity and lack of clinically meaningful differences compared with the reference product	Biosimilar; can be expected to produce the same clinical results as the reference product, and there is no additional risk related to switching
Pertinent example	Lantus, Toujeo, Tresiba, and Levemir		Basaglar (no TE rating) <sup>15</sup>	Neupogen (filgrastim), Remicade (infliximab), Enbrel (etanercept), and Praluent	Zarxio (filgrastim-sndz), Inflectra (infliximab-dyyb), and Erelzi (etanercept-szss)	None yet approved as interchangeable
“Substitution” reference	Orange Book <sup>16</sup>	Orange Book <sup>16</sup>	Orange Book <sup>16</sup>	Purple Book <sup>17</sup>	Purple Book <sup>17</sup>	Purple Book <sup>17</sup>
“Substitution” terminology	Therapeutically equivalent.	Therapeutically equivalent. Equivalence ratings in the form of “A” and “B” code letters	Therapeutically equivalent. Equivalence ratings in the form of “A” and “B” code letters	Designated as “B”	Designated as “B”	Interchangeable, designated as “1”

Abbreviations: ANDA, Abbreviated New Drug Application; BLA, Biologics License Application; FDA, US Food and Drug Administration; FDCA, Food, Drug, and Cosmetic Act; NDA, New Drug Application; PHS, Public Health Service; S/E, safety/efficacy; TE, therapeutically equivalent.

face a range of hurdles before they become widely available to patients.

## Data Sources

References were obtained using MEDLINE searches, the bibliographies of articles identified during the searches, review articles, and general Internet searches. Key words for searches included the following: diabetes, insulin, biosimilar, regulatory, FDA, follow-on, interchangeability, and delivery devices.

## The Approval Process

The regulation of biosimilars has evolved over recent years in the United States and is still an ongoing process. Initially, there was no abbreviated approval process for the vast majority of biologic drugs approved under the Public Health Service (PHS) Act. Only those few biologics approved under the FD&C Act were eligible for abbreviated approval under Section 505(b)(2), the paper New Drug Application (NDA) route (Table 1). Under this pathway, the follow-on biologics (which are not referred to as biosimilars) have to be shown to be bioequivalent to the reference biologic, and can rely on safety and efficacy data from published studies for the reference biologic to support their application. Although the implications of this are that the follow-on biologic does not have to undergo the usual multiple phases of clinical trials required for approval of a novel biologic drug, some clinical trials (although not strict interchangeability trials) are required for this type of submission.

The FDA has acknowledged that abbreviated pathways for biologics present particular challenges not usually faced by standard generic drugs due to the scientific and technical complexities associated with their production.<sup>12</sup> Biosimilars became a specific entity under the Biologicals Price Competition and Innovation (BPCI) Act of 2009 and signed into law through the Patient Protection and Affordable Care Act (Affordable Care Act) on March 23, 2010. The BPCI Act created an abbreviated licensure pathway in Section 351(k) of the PHS Act for biologic products that are demonstrated to be biosimilar to or interchangeable with an FDA-licensed (approved) biologic product (Table 2). Proof of biosimilarity under Section 351(k) of the PHS Act is more challenging, requiring a step-wise series of studies beyond those required under Section 505(b)(2) of the FD&C Act. Currently, the FDA provides guidance as to the type of studies it expects for biosimilar applications. Study requirements for approval of an individual biosimilar are provided by the FDA<sup>22</sup>: analytical studies (structural analyses and in vitro and/or in vivo functional assays) that demonstrate that the biologic product is highly similar to the reference product; animal studies (where appropriate and where there is a suitable animal species in which the biologic activity of the

product mimics the human response), including the assessment of toxicity; and a range of clinical studies. For clinical studies, comparative human pharmacokinetic (PK) and pharmacodynamic (PD) studies are considered to be fundamental components of the submission package. Immunogenicity is a particular concern with biologic products, where even subtle differences in their composition or structure may affect their immunogenic potential. This is particularly true where a biosimilar is administered over time, such as is the case with insulin. Immunogenicity assessment is therefore also considered a key element in demonstrating biosimilarity, with the study duration depending on the frequency and duration of the biosimilar dosing regimen. Comparative efficacy and safety is based on analytical, animal, PK/PD, and immunogenicity studies. These studies are considered necessary if there is residual uncertainties surrounding clinically meaningful differences between the biosimilar and the reference product. The requirement is that the biosimilar sponsor designs these studies specifically to address the uncertainties identified.

The FDA's approach to the designs of these clinical studies is the demonstration of biosimilarity between the biosimilar and the reference product, not to independently establish the safety and effectiveness of the proposed product.<sup>23</sup> A biosimilar product that is shown to be highly similar to an FDA-approved reference product may rely on data supporting the reference product's safety and effectiveness, as included in the FDA-approved prescribing information. Sponsors are not required to generate a full profile of biosimilar-specific nonclinical and clinical data.

Two different approval pathways exist in the United States for biosimilars and follow-on biologics: Section 351(k) of the PHS Act and Section 505(b)(2) of the FD&C Act, respectively (Table 2). In the future, however, the less stringent FD&C Act pathway will not be open to biosimilar developers. The FDA has released a proposed interpretation of part of the BPCI Act that states any approved application for a biologic under Section 505(b)(2) of the FD&C Act "shall be deemed to be a license for the biologic product under Section 351 of the PHS Act,"<sup>24</sup> meaning that an application for a biosimilar product must include a reference product also approved under Section 351 of the PHS Act (Table 2). However, when this requirement was introduced, there was a caveat that it was subject to certain exceptions during a 10-year transition period, which will end on March 23, 2020.<sup>24</sup> The exception was for a biologic product with a reference product that was approved under Section 505 of the FD&C Act no later than March 23, 2010, with the provision that there was no other biologic product approved under Section 351 of the PHS Act that could be used as a reference product. Therefore, up until the end of the BPCI transition period in 2020, submissions for follow-on biologics under the less stringent Section 505(b)(2) of the FD&C Act can still be made, but not under the name of a biosimilar. There

are no insulin products currently licensed under the PHS Act, so there is no reference product for a proposed biosimilar insulin using this pathway.<sup>13</sup> This was the case for Eli Lilly's insulin (U100) glargine Basaglar, which was approved by the FDA in December 2015.<sup>13</sup> Basaglar was approved through the abbreviated approval pathway under the FD&C Act with a Section 505(b)(2) application that relied, in part, on the FDA's finding of safety and effectiveness for Lantus (U100 insulin glargine injection). Comparative PK/PD to Lantus,<sup>14,25</sup> clinical trials in type 1 diabetes mellitus (T1DM)<sup>26</sup> and in type 2 diabetes mellitus (T2DM),<sup>27</sup> and evaluation of immunogenicity<sup>28</sup> also supported approval. These trials did not evaluate or address interchangeability of this insulin with Lantus. While the FDA submission did rely on previously submitted Lantus data, Basaglar is not approved as a Lantus biosimilar but is referred to as a follow-on product, and marketed as such, because it was not approved under the PHS Act (Table 2).

Approvals for biologics that are pending, or even tentatively approved, at the end of the transition period in March 2020 will need to be resubmitted under the PHS Act,<sup>29</sup> and the time taken for FDA review can extend to several years. This potentially puts manufacturers in a difficult situation whereby they are unable to submit a biosimilar application under the PHS Act because the reference product has not yet been deemed licensed, but are also unable to submit a Section 505(b)(2) application because there may not be enough time to guarantee approval by the cutoff date.<sup>29</sup> For those manufacturers with biosimilar insulins in the later stages of development, however, there is likely still time to gain approval under Section 505(b)(2) of the FD&C Act. As for Basaglar, in the United States this will be as a follow-on biologic, not a biosimilar insulin.

## The Question of Delivery Devices

While regulatory guidelines cover aspects such as the structure, PK/PD, efficacy, safety, and immunogenicity of a biosimilar, one aspect that is equally important is the delivery device. Delivery devices are key factors in the patient experience with insulin administration, where regular use becomes part of the patient's life.<sup>30</sup> While the precision of dosing is a key concern, ease of use, comfort, and convenience of the device are important factors that could potentially influence patient adherence and so have an impact on efficacy. Familiarity and comfort with a particular delivery device may encourage patients to remain loyal to a specific branded insulin, even if less expensive biosimilars are available.<sup>31</sup> It is likely that biosimilar insulins or follow-on insulins produced by companies who 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; however, while the maximum dose of Humalog

delivered is 60 units, the maximum dose of Basaglar delivered by the KwikPen is 80 units. Sanofi's Admelog is administered using the SoloStar pen, developed for administration of Lantus. Both devices contain 3 mL of 100 units/mL insulin solution. The dosing windows displays number of insulin units, and doses can range from 1 unit to a maximum of 80 units. Conversely, if patients are required to change to a different manufacturer's product, a new or different device may discourage switching.<sup>31</sup> It cannot necessarily be assumed that an insulin biosimilar will be compatible with an existing administration device, because the combinations of insulin and device may differ widely in their dosing characteristics.<sup>32</sup> The FDA has produced guidelines describing the technical and scientific data it expects in a marketing application for pen, jet, and related injectors for use with any biologic products (not only biosimilars). These cover aspects such as design features, performance testing, and labeling,<sup>9</sup> and any new pen-injector will have to meet these quality standards. In the case of biosimilars, the FDA has stated that a biosimilar product may have some design differences in the delivery device compared with the reference product. For example, the biosimilar may be licensed in a prefilled syringe or an auto-injector if the reference product was administered using the same method. This is providing that the proposed product meets the statutory standard for biosimilarity, and adequate performance data for the delivery device or container closure system are provided.<sup>33</sup> For a proposed biosimilar product in a different delivery device, compatibility with the final formulation must be shown through appropriate studies (eg, extractable/leachable studies and stability studies), and performance testing and human factors studies may be needed for certain (unspecified) design differences in the delivery. The FDA also states that a proposed biosimilar product in a delivery device will be considered a combination product and may, in some instances, require a separate application for the device.

## The Biosimilar Insulin Landscape

As mentioned, to date, no insulin has been approved as a biosimilar by the FDA. Given that potential reference insulins were approved under Section 505(b)(2) of the FD&C Act and not under Section 351 of the PHS Act, this is not likely to change until the BPCI "deemed to be a license" comes into effect in 2020. Until then, any biosimilar insulins in the United States will be approved under the FD&C Act as follow-on insulins. However, they will be described as biosimilars in the European Union (EU), if approved there, as is the case for Basaglar, which is marketed in the EU as a biosimilar insulin glargine under the trade name of Abasaglar. Basaglar underwent a series of clinical studies to demonstrate similarity (not interchangeability) to the reference insulin glargine (Lantus). These included PK/PD studies in

healthy individuals<sup>14</sup> and in patients with T1DM<sup>25</sup> and assessments of immunogenicity in patients with T1DM and T2DM.<sup>28</sup> Furthermore, 2 phase 3 three noninferiority studies in patients with T1DM (ELEMENT 1)<sup>26</sup> and T2DM (ELEMENT 2)<sup>27</sup> were conducted.

Looking to the future, a number of potential follow-on/biosimilar insulins are undergoing or have recently completed clinical trials in the United States (Table 3). Of these, 3 have completed phase 3 clinical trials, which will be discussed below as they are furthest along in the approval process: 2 insulin glargine U100 (Lantus) products, Lusduna and Mylan's insulin glargine approved in Europe under the trade name of Semglee (Biocon, Bengaluru, India; Mylan, Canonsburg, PA), and 1 rapid-acting U100 insulin lispro (Humalog) Admelog.

Lusduna was found to be bioequivalent to both US- and EU-approved Lantus based on a double-blinded, randomized, 3-period, balanced crossover euglycemic clamp study in healthy males<sup>46</sup> and a 2-treatment, 4-period replicate crossover study in T1DM patients (Table 3).<sup>47</sup> Data from 2 phase 3 studies were determined to show noninferiority of Lusduna to Lantus in terms of change from baseline in glycated hemoglobin after 24 weeks of treatment in both T1DM (least square mean difference [LSM] = 0.04%; 95% confidence interval [CI] = -0.11 to 0.19) and T2DM (LSM = 0.03%; 95% CI = -0.12 to 0.18), with a similar efficacy and safety profile and final insulin dose.<sup>48,49</sup> After a total of 52 weeks, LSM treatment difference in change from baseline in A1C was -0.02 (95% CI = -0.18 to 0.14) in patients with T1DM.<sup>48</sup> Lusduna has been approved in the EU as a Lantus biosimilar as the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use concluded that it had been shown to have comparable quality, safety, and effectiveness to Lantus.<sup>50</sup> In the United States, Lusduna received tentative approval from the FDA in July 2017 for use to "improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus."<sup>51</sup>

For Mylan's insulin glargine, it has been reported that a phase 3 noninferiority study (INSTRIDE-1)<sup>52</sup> and an extension study<sup>53</sup> versus Lantus have been completed in the United States for T1DM (Table 3). It has been further reported that a phase 3 noninferiority study has also been completed in the United States for T2DM (INSTRIDE-2).<sup>41</sup> In January 2018, the EMA recommended that Mylan's insulin glargine should be granted marketing authorization.<sup>51</sup> This was approved by the European Commission in March 2018.<sup>54</sup> Mylan's insulin glargine has not been launched in the United States, where Sanofi has brought claims that Mylan's proposed product infringes Sanofi's patent rights. The PK and PD of Admelog have been shown to be bioequivalent to both US-approved and EU-approved insulin lispro (Humalog) in a phase 1, single-center, randomized, double-blind, 3-treatment, 3-period, 6-sequence, crossover,

euglycemic clamp study in 30 male patients with T1DM (Table 3).<sup>55</sup> Phase 3 noninferiority studies are completed in T1DM (SORELLA-1)<sup>38,56</sup> and in T2DM (SORELLA-2).<sup>39</sup> The EMA approved insulin lispro (Admelog in the United States) in July 2017 for the "treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis" and "for the initial stabilization of diabetes mellitus."<sup>57</sup> In December 2017, Admelog received approval from the FDA for "improving glycemic control in adults and pediatric patients 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus."<sup>55</sup>

## Interchangeability

Interchangeability for new insulin products is a key consideration for patients, health care providers, and payers. It is important to understand that being described as biosimilar or follow-on does not mean products are interchangeable. Basaglar, for instance, has not been given a "therapeutic equivalence rating" by the FDA and thus is not deemed "automatically substitutable."<sup>13</sup> Regardless, the US pharmacy benefit management company CVS Caremark, and others, have dropped Lantus from their formularies and replaced it with Basaglar. A product approved as a biosimilar can be prescribed in lieu of the FDA-approved reference product. However, it must be prescribed by a health care professional and the prescriber must write the specific name of the biosimilar on the prescription.<sup>10</sup> Currently, there are no biosimilar insulins or follow-on insulins approved as an interchangeable drug. An interchangeable biologic product must meet all the criteria for biosimilarity to an FDA-approved reference product and must also include data or information to show that the proposed interchangeable biologic product is expected to produce the same clinical result as the reference product in any given patient (Table 2).<sup>10</sup> Additional considerations are needed for a product that will be administered more than once to an individual, and where patients may be switched between drugs, possibly on more than one occasion. This may have potential implications in terms of immunogenicity. The FDA has stated that applications for interchangeability must "include information that demonstrates that the risk in terms of safety or diminished effectiveness of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without alternating or switching." The type of studies the FDA will require to prove interchangeability and the safety of switching are currently undefined, with only draft guidance currently in place.<sup>58</sup> There has been some discussion regarding the form these studies should take, with some authors proposing specifically designed crossover/switching studies. For example, double-blind, randomized, crossover studies with single/multiple switches over an

**Table 3.** Biosimilar Insulins in Clinical Trials.

Manufacturer	Product	Reference	Clinical Trial Phase, clinicaltrials.com Identifier	Subjects	Proposed Enrollment	Status		
Merck (USA)	Lusduna	Lantus	Phase I	Normal		Completed <sup>33</sup>		
			Phase I, NCT02059174 <sup>34</sup>	T1DM	76	Completed		
			Phase 3, NCT02059161 <sup>35</sup>	T1DM	730	Completed		
			Phase 3, NCT02059187 <sup>36</sup>	T2DM	536	Completed		
Sanofi (France)	Admelog	Humalog	Phase I, NCT02273258 <sup>37</sup>	T1DM	30	Completed <sup>31</sup>		
			Phase I, NCT02603510	T1DM	27	Completed		
			Phase 3, SORELLA-1, NCT02273180 <sup>38</sup>	T1DM	480	Completed <sup>33</sup>		
			Phase 3, SORELLA-2, NCT02294474 <sup>39</sup>	T2DM	505	Completed		
Biocon-Mylan (India)	Mylan insulin glargine	Lantus	Phase 3, INSTRIDE-1, NCT02227862 <sup>40</sup>	T1DM	500	Completed		
			Phase 3, INSTRIDE-2, NCT02227875 <sup>41</sup>	T2DM	600	Completed		
			Phase 3 extension, NCT02666430 <sup>42</sup>	T1DM	138	Active, not recruiting		
			Phase 3, NCT03376789	T1DM	202	Recruiting		
Julphar Gulf Pharmaceutical Industries (United Arab Emirates)	Julphar insulin R	Humulin R	Phase I, NCT02634515 <sup>43</sup>	Normal	26	Completed		
			Julphar insulin N Basal	Huminsulin Basal	Phase I, NCT02634528	Normal	85	Active, not recruiting
					Julphar insulin 30/70	Huminsulin Profil III	Phase I, NCT02631928	Normal
Gan and Lee (China)	Basalin <sup>a</sup>	Gan and Lee insulin glargine	Phase I, NCT02506647	T1DM	40	Recruiting, completion Q2 2016		
			Phase 3, NCT03371082	T1DM	522	Recruiting, completion Q1 2020		
			Phase 3, NCT03371108	T2DM	544	Recruiting, completion Q1 2020		
Wockhardt (India and USA)	Glaritus	Lantus	Phase I, NCT01357603 <sup>44</sup>	T1DM	111	Completed		
			Phase 3, NCT01352663 <sup>45</sup>	T1DM	500	Not yet recruiting		

Abbreviations: Q, quarter; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

<sup>a</sup>Already available in China, Japan, and India.

appropriate period of time, ideally in patients most likely to switch.<sup>59</sup>

Delivery devices may also require additional considerations for patients to be safely alternated or switched between the reference product and the interchangeable product without the intervention of the prescribing health care provider.<sup>9</sup> Additional performance data about the delivery device may also be necessary.

In principle, once a biosimilar achieves interchangeable status it may be substituted for the reference product by a pharmacist without the consent of the health care provider who prescribed the reference product. In the United States, laws passed by individual state legislature provide the legal mechanism and requirements for the substitution of an originator biologic with the biosimilars. A number of states have already adopted or are considering laws related to the legislation around substitution, which will guide substitution of originator insulins with interchangeable biosimilar

insulin at the retail pharmacy level.<sup>60</sup> All states in the United States to date that have accepted interchangeability should rely on the biosimilar being deemed interchangeable by the FDA. However, there are differences between states in factors such as the time frame for informing the physician of any substitution and the patient record retention period.<sup>60</sup> Details of the regulatory status of biosimilars are available in the FDA Purple Book,<sup>17</sup> the biologic equivalent of the Orange Book<sup>16</sup> for drugs approved under the FD&C Act. The Purple Book lists biologic products, including any biosimilar and interchangeable biologic products licensed by the FDA under the PHS Act, and shows whether a biologic product licensed under Section 351(k) has been determined by the FDA to be biosimilar to or interchangeable with a reference biologic product. As mentioned, there are no biosimilar insulins or interchangeable insulins in the market, only follow-ons, and this will not change until the new legislation goes into effect in 2020.

Interchangeability, and potentially substitution, is likely to be a key factor in the uptake of biosimilars, including biosimilar insulin, in the United States.<sup>61</sup> A recent survey on the pharmacist perceptions of biosimilar naming conventions showed that pharmacists' willingness to interchange a product relied on the use of a naming convention for biosimilars that includes a nonproprietary proper name with a designated suffix.<sup>15</sup> In January 2017, the FDA finalized its guidance for the naming of biologic products.<sup>62</sup> They state that the names of products should comprise a nonproprietary name and "a distinguishing suffix that is devoid of meaning and composed of 4 lowercase letters." For example, Sandoz, Inc's Zarxio is biosimilar to Amgen Inc's Neupogen (filgrastim), a bone marrow stimulant. Zarxio's nonproprietary name is filgrastim-sndz.

Payers are also likely to promote uptake of the less expensive option through the use of a tiered formulary to steer patients and physicians toward biosimilars and the current available follow-ons.<sup>61</sup> In the absence of automatic substitution, the decision to prescribe a biosimilar lies with the physician, and survey evidence suggests that most clinicians (around 70%) are comfortable with prescribing FDA-approved biosimilars to new patients, with a similar proportion also reporting they would be likely to switch existing patients.<sup>61</sup> Efficacy and safety are the 2 most important considerations for physicians; however, price of treatment also has influence on their decision.<sup>61</sup> Recent draft guidance from the FDA regarding biosimilar labeling may mean that not all efficacy and safety data will be included on a biosimilar product label. In fact, the draft guidance states that the label should include only relevant data and information from the FDA-approved labeling for the reference product, along with any appropriate modifications specific to the biosimilar product.<sup>22</sup> The FDA's view is that the label should generally not include information and data from clinical studies of the biosimilar itself.<sup>22</sup> Comparative data supporting the demonstration of biosimilarity should not be included in biosimilar product labeling unless necessary. According to the FDA, these are "not likely to be relevant to a health care 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." Although this is in line with how the FDA labeled the first approved biosimilar in the United States, Zarxio (filgrastim-sndz), there is a suggestion that the consensus among physicians is for full disclosure of all relevant data for the biosimilar when possible.<sup>63</sup> However, the FDA's position has been supported by health care stakeholders. In a letter to the FDA, a group of leading pharmaceutical supply chain organizations stated that "including a biosimilar product's biosimilarity data in addition to that of the reference product would only provide unnecessary information and create confusion for prescribers and patients."<sup>64</sup>

There are considerations beyond efficacy and safety with regard to interchangeability, which will impact health care providers. Switching insulins requires additional monitoring, and, with a change in the delivery device, patients will need support and retraining. In addition, automatic substitution without appropriate record control and information sharing between the pharmacy and physicians may make evaluation of causality of adverse events, such as hypersensitivity or other immune-mediated reactions, difficult. In addition, according to the FDA, interchangeable biologic products can be substituted by the pharmacist "without the intervention" of the prescriber. Some physicians comment that the wording allowing for a switch "without the intervention" of the prescriber will allow the pharmacist to switch the biologic even if the prescriber wrote "dispense as written." Currently all 50 states in the United States are addressing this issue individually. For instance, a law was passed in Arizona<sup>65</sup> that states that an electronic record is created of the substitution, which is accessible by the prescriber. However, there is no direct contact between the pharmacist and the prescriber. This point of no direct communication as well as the need for close pharmacovigilance will need to be further monitored and possibly adjusted in the future as currently there are only follow-on insulins on the market, which are not interchangeable.

## Future Perspectives

Despite the developmental, regulatory, and commercial hurdles facing them, biosimilar or follow-on insulins are likely to become widely available in the coming years and are expected to have a major impact on diabetes care. A number of pivotal issues remain to be fully clarified, such as defining and regulating interchangeability, as well as questions around delivery devices and product labeling; for instance, the availability of biosimilar data is lacking. As the number of available insulin formulations increases, there is the potential for increased confusion among patients, clinicians, and payers; education and support will be key to ensure biosimilar insulins gain acceptance. Experience from first-generation biosimilars such as epoetin, filgrastim, and somatotropin suggest that penetration of biosimilar insulins into routine care may not be a rapid process, and may rely on specific legislation to promote their use.<sup>30</sup> In the United States this could potentially lead to further confusion, with differences in formulary preferred product status and legislation around interchangeability and automatic substitution between states.<sup>66</sup> Existing state legislation around generic drugs also has the potential to cause confusion and cause delays, and it is essential that biosimilars and interchangeable biologics are clearly distinguished from generic drugs.

Postmarketing surveillance will be an essential component in ensuring the safety and effectiveness of biosimilar insulins. Therefore, it is essential that mechanisms are in



place to differentiate between the adverse events associated with a biosimilar (immunogenicity) and those associated with the reference product and, if automatic substitution is allowed, to ensure that prescribers and other pertinent clinicians are aware of the exact insulin or biosimilar insulin a patient is receiving.

While the ever-increasing overall costs of health care will make medication pricing a strong driver for biosimilars, it remains to be seen whether biosimilar insulin will provide the anticipated benefits in terms of costs and availability. Low manufacturing and development costs will likely result in price reductions, which are expected to be much less than those experienced for generic drugs. However, with the significant and growing prevalence of diabetes in the United States, even small savings relative to originator insulins may be important to clinicians, patients, and payers trying to find ways to efficiently allocate health care resources.

In conclusion, although there are currently few biosimilar products approved in the United States, there are many more in development, including several insulin biosimilars. These are likely to become available in the coming years, meaning it is essential that health care providers and payers are aware of the issues surrounding these products.

### Author's Note

The contents of the article and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: John White: Advisory board—Sanofi, Novo Nordisk, Becton Dickinson. Jennifer Goldman: Speakers bureau—Novo Nordisk, Sanofi; Consultant—Becton Dickinson.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors received writing/editorial support in the preparation of this article, which was provided by Michael van der Veer, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

### References

1. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41:917-928. doi:10.2337/dci18-0007
2. Food and Drug Administration. Center for Drug Evaluation and Research. List of licensed biological products with (1) reference product exclusivity and (2) biosimilarity or interchangeability evaluations to date. <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf>. Accessed March 2, 2018.
3. Food and Drug Administration. Approval package for Basaglar. [www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/205692Orig1s000Approv.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205692Orig1s000Approv.pdf). Published December 16, 2015. Accessed April 24, 2018.
4. Food and Drug Administration. Tentative approval letter for Lusduna. [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2017/208722Orig1s000TAltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/208722Orig1s000TAltr.pdf). Accessed April 24, 2018.
5. Food and Drug Administration. NDA approval for Admelog. [www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2017/209196Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/209196Orig1s000ltr.pdf). Accessed April 24, 2018.
6. Food and Drug Administration. Abbreviated new drug application (ANDA). [www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/). Accessed May 4, 2017.
7. Food and Drug Administration. New drug application (NDA). [www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/newdrugapplicationnda/default.htm](http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/newdrugapplicationnda/default.htm). Accessed May 4, 2017.
8. Food and Drug Administration. Applications covered by Section 505(b)(2). [www.fda.gov/downloads/Drugs/.../Guidances/ucm079345.pdf](http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079345.pdf). Published October 1999. Accessed May 4, 2017.
9. Food and Drug Administration. Guidance for industry and FDA staff: technical considerations for pen, jet, and related injectors intended for use with drugs and biological products. [www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf). Published June 2013. Accessed May 4, 2017.
10. Food and Drug Administration. Biosimilar and interchangeable products. <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm>. Accessed May 4, 2017.
11. Declerck P. Biologicals and biosimilars: a review of the science and its implications. *Gabij*. 2012;1:13-16. doi:10.5639/gabij.2012.0101.005
12. Ventola CL. Biosimilars: part 1: proposed regulatory criteria for FDA approval. *P T*. 2013;38:270-287.
13. Food and Drug Administration. FDA approves Basaglar for diabetes, the first "follow-on" insulin glargine product to treat diabetes.
14. Linnebjerg H, Lam EC, Seger ME, et al. Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and EU- and US-approved versions of Lantus insulin glargine in healthy subjects: three randomized euglycemic clamp studies. *Diabetes Care*. 2015;38:2226-2233. doi:10.2337/dc14-2623
15. Tomaszewski D. Biosimilar naming conventions: pharmacist perceptions and impact on confidence in dispensing biologics. *J Manag Care Spec Pharm*. 2016;22:919-926. doi:10.18553/jmcp.2016.22.8.919
16. Food and Drug Administration. Approved drug products with therapeutic equivalence evaluations (Orange Book). <https://www.fda.gov/drugs/informationondrugs/ucm129662.htm>. Accessed September 4, 2018.
17. Food and Drug Administration. Purple Book: lists of licensed biological products with reference product exclusivity

- and biosimilarity or interchangeability evaluations. [www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418). Accessed May 4, 2017.
18. Schellekens H. Biosimilar therapeutics—what do we need to consider? *NDT Plus*. 2009;2(suppl 1):i27-i36. doi:10.1093/ndtplus/sfn177
  19. Food and Drug Administration. Generic drugs: questions and answers. [www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100](http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100). Accessed May 16, 2016.
  20. Blackstone EA, Fuhr JP Jr. Innovation and competition: will biosimilars succeed? The creation of an FDA approval pathway for biosimilars is complex and fraught with hazard. Yes, innovation and market competition are at stake. But so are efficacy and patient safety. *Biotechnol Healthc*. 2012;9:24-27.
  21. DeVries JH, Gough SC, Kiljanski J, Heinemann L. Biosimilar insulins: a European perspective. *Diabetes Obes Metab*. 2015;17:445-451. doi:10.1111/dom.12410
  22. Food and Drug Administration. Clinical pharmacology data to support a demonstration of biosimilarity to a reference product. Guidance for industry. [www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf). Published December 2016. Accessed May 4, 2017.
  23. Food and Drug Administration. Labeling for biosimilar products. Guidance for industry. [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf). Published July 2018. Accessed September 4, 2018.
  24. Food and Drug Administration. Implementation of the “deemed to be a license” provision of the Biologics Price Competition and Innovation Act of 2009. Guidance for industry. [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf). Published March 2016. Accessed May 4, 2017.
  25. Heise T, Zhang X, Chen E, et al. Duration of action of 2 insulin glargine products, LY2963016 and Lantus, in subjects with type 1 diabetes mellitus (T1DM). *Diabetes*. 2015;63(suppl 1):A228. doi:10.1111/dom.12759
  26. Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab*. 2015;17:726-733. doi:10.1111/dom.12496
  27. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes Obes Metab*. 2015;17:734-741. doi:10.1111/dom.12482
  28. Ilag LL, Deeg MA, Costigan T, et al. Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus® insulin glargine in patients with type 1 or type 2 diabetes mellitus. *Diabetes Obes Metab*. 2016;18:159-168. doi:10.1111/dom.12584
  29. Brennan Z. Pharma companies warn of regulatory “dead zone” with FDA’s interpretation of BPCIA. [www.raps.org/Regulatory-Focus/News/2016/05/27/25031/Pharma-Companies-Warn-of-Regulatory-%E2%80%98Dead-Zone%E2%80%99-With-FDA%E2%80%99s-Interpretation-of-BPCIA/](http://www.raps.org/Regulatory-Focus/News/2016/05/27/25031/Pharma-Companies-Warn-of-Regulatory-%E2%80%98Dead-Zone%E2%80%99-With-FDA%E2%80%99s-Interpretation-of-BPCIA/). Published May 27, 2016. Accessed May 4, 2017.
  30. Fry AR, Krentz AJ, Hompesch M. Considerations in biosimilar insulin device development. *Biosimilars*. 2016;6:9-15. doi:10.2147/BS.S77034
  31. Polimeni G, Trifirò G, Ingrassiotta Y, Caputi AP. The advent of biosimilars for the treatment of diabetes: current status and future directions. *Acta Diabetol*. 2015;52:423-431. doi:10.1007/s00592-015-0771-7
  32. Kramer I, Sauer T. The new world of biosimilars: what diabetologists need to know about biosimilar insulins. *Br J Diabetes Vasc Dis*. 2010;10:163-171. doi:10.1177/1474651410369234
  33. Food and Drug Administration. Guidance for industry on biosimilars: Q&As regarding implementation of the BPCI Act of 2009: questions and answers part I.
  34. ClinicalTrials.gov. A study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of MK-1293 compared with a basal insulin in participants with type 1 diabetes (MK-1293-005). [www.clinicaltrials.gov/ct2/show/NCT02059174](http://www.clinicaltrials.gov/ct2/show/NCT02059174). Accessed May 4, 2017.
  35. ClinicalTrials.gov. A study of the safety and efficacy of MK-1293 compared to Lantus™ in participants with type 1 diabetes mellitus (T1DM) (MK-1293-003). [www.clinicaltrials.gov/ct2/show/NCT02059161](http://www.clinicaltrials.gov/ct2/show/NCT02059161). Accessed September 14, 2016.
  36. ClinicalTrials.gov. The safety and efficacy of MK-1293 versus Lantus™ in participants with type 2 diabetes mellitus (MK-1293-006). [www.clinicaltrials.gov/ct2/show/NCT02059187](http://www.clinicaltrials.gov/ct2/show/NCT02059187). Accessed May 4, 2017.
  37. ClinicalTrials.gov. A study to compare pharmacokinetics and pharmacodynamics of SAR342434 to insulin lispro in subjects with type 1 diabetes. [www.clinicaltrials.gov/ct2/show/NCT02273258](http://www.clinicaltrials.gov/ct2/show/NCT02273258). Accessed May 4, 2017.
  38. ClinicalTrials.gov. Comparison of SAR342434 to humalog as the rapid acting insulin in adult patients with type 1 diabetes mellitus also using insulin glargine (SORELLA 1). [clinicaltrials.gov/ct2/show/NCT02273180](http://clinicaltrials.gov/ct2/show/NCT02273180). Accessed May 4, 2017.
  39. ClinicalTrials.gov. Comparison of SAR342434 to humalog as the rapid acting insulin in adult patients with type 2 diabetes mellitus also using insulin glargine (SORELLA 2). [clinicaltrials.gov/ct2/show/NCT02294474](http://clinicaltrials.gov/ct2/show/NCT02294474). Accessed May 4, 2017.
  40. ClinicalTrials.gov. Non-inferiority study to compare the efficacy and safety of Mylan’s insulin glargine with Lantus® in type 1 diabetes mellitus patients (INSTRIDE 1). <https://clinicaltrials.gov/ct2/show/NCT02227862>. Accessed April 24, 2018.
  41. ClinicalTrials.gov. Non-inferiority study to compare the efficacy and safety of Mylan’s insulin glargine with Lantus® in type 2 diabetes mellitus patients (INSTRIDE 2). [clinicaltrials.gov/ct2/show/NCT02227875](http://clinicaltrials.gov/ct2/show/NCT02227875). Accessed May 4, 2017.
  42. ClinicalTrials.gov. Extension study to assess safety and efficacy of Mylan’s insulin glargine and Lantus® in type 1 diabetes mellitus patients. [www.clinicaltrials.gov/ct2/show/NCT02666430](http://www.clinicaltrials.gov/ct2/show/NCT02666430). Accessed May 4, 2017.
  43. ClinicalTrials.gov. Pharmacokinetic (PK) bioequivalence and pharmacodynamics of Julphar insulin R and Huminsulin® normal. [www.clinicaltrials.gov/ct2/show/NCT02634515](http://www.clinicaltrials.gov/ct2/show/NCT02634515). Accessed May 4, 2017.
  44. ClinicalTrials.gov. Comparative glucose clamp study of Wockhardt’s recombinant insulin analog glargine (Glaritus)

- with Lantus in T1DM. [www.clinicaltrials.gov/ct2/show/NCT01357603](http://www.clinicaltrials.gov/ct2/show/NCT01357603). Accessed May 4, 2017.
45. ClinicalTrials.gov. Immunogenicity safety study of Wockhardt's recombinant insulin analogue in type 1 diabetic patients. [www.clinicaltrials.gov/ct2/show/NCT01352663](http://www.clinicaltrials.gov/ct2/show/NCT01352663). Accessed May 4, 2017.
  46. Palcza J, Mostoller K, Mahon C, et al. A single dose euglycemic clamp study in healthy subjects demonstrating pharmacokinetic and pharmacodynamic equivalence between MK-1293 and Lantus. *Diabetes*. 2015;63(suppl 1):A262.
  47. Crutchlow M, Palcza J, Mostollera K, et al. A Single-dose euglycemic clamp study in subjects with type 1 diabetes demonstrating pharmacokinetic and pharmacodynamic similarity between MK-1293 insulin glargine and originator insulin glargine (lantus). *Diabetes*. 2016;65(Suppl 1):A221.
  48. ClinicalTrials.gov. A study of the safety and efficacy of MK-1293 compared to Lantus™ in participants with type 1 diabetes mellitus (T1DM) (MK-1293-003). [www.clinicaltrials.gov/ct2/show/NCT02059161](http://www.clinicaltrials.gov/ct2/show/NCT02059161). Accessed September 14, 2016.
  49. ClinicalTrials.gov. The safety and efficacy of MK-1293 versus Lantus™ in participants with type 2 diabetes mellitus (MK-1293-006). <https://clinicaltrials.gov/ct2/show/results/NCT02059187>. Accessed April 24, 2018.
  50. European Medicines Agency. EPAR summary for the public. Lusduna, insulin glargine. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Summary\\_for\\_the\\_public/human/004101/WC500219589.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004101/WC500219589.pdf). Accessed September 4, 2018.
  51. Blevins TC, Barve A, Sun B, Ankersen M. Efficacy and safety of MYL-1501D versus insulin glargine in patients with type 1 diabetes after 52 weeks: results of the phase 3 INSTRIDE 1 Study. *Diabetes Obes Metab*. 2018;20:1944-1950. doi:10.1111/dom.13322
  52. ClinicalTrials.gov. Extension study to assess safety and efficacy of Mylan's insulin glargine and Lantus® in type 1 diabetes mellitus patients. <https://clinicaltrials.gov/ct2/show/study/NCT02666430>. Accessed April 24, 2018.
  53. European Medicines Agency. Summary of opinion (initial authorisation). Semglee, insulin glargine. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Summary\\_of\\_opinion\\_-\\_Initial\\_authorisation/human/004280/WC500242403.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004280/WC500242403.pdf). Accessed April 24, 2018.
  54. Mylan NV. Mylan and Biocon receive approvals from the European Commission and TGA Australia for Semglee™, biosimilar insulin glargine. <https://www.prnewswire.com/news-releases/mylan-and-biocon-receive-approvals-from-the-european-commission-and-tga-australia-for-semglee-bio-similar-insulin-glargine-300620737.html>. Published March 27, 2018. Accessed April 24, 2018.
  55. Nowotny I, Kapitzka C, Lehmann A, et al. Comparative PK and PD of the rapid-acting insulin lispro product SAR342434, and US- and EU-approved Humalog® in subjects with T1DM. *Diabetes*. 2015;63(suppl 1):A261.
  56. Garg SK, Wernicke-Panten K, Rojas M, Pierre S, Kirchheiner Y, Jedynasty K. Efficacy and safety of biosimilar SAR342434 insulin lispro in adults with type 1 diabetes also using insulin glargine-SORELLA 1 Study. *Diabetes Technol Ther*. 2017;19:516-526. doi:10.1089/dia.2017.0117
  57. European Medicines Agency. Summary of product characteristics. Insulin lispro Sanofi. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/004303/WC500235294.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004303/WC500235294.pdf). Accessed July 12, 2018.
  58. Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product. Guidance for industry. <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm537135.pdf>. Published January 2017. Accessed September 4, 2018.
  59. Dowlat HA, Kuhlmann MK, Khatami H, Ampudia-Blasco FJ. Interchangeability among reference insulin analogues and their biosimilars: regulatory framework, study design and clinical implications. *Diabetes Obes Metab*. 2016;18:737-746. doi:10.1111/dom.12676
  60. Thimmaraju PK, Rakshambikai R, Farista R, Juluru K. Legislations on biosimilar interchangeability in the US and EU—developments far from visibility. <http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility>. Published January 6, 2015. Accessed July 17, 2018.
  61. Cohen JP, Felix AE, Riggs K, Gupta A. Barriers to market uptake of biosimilars in the US. *GaBi J*. 2014;3:108-115. <http://gabi-journal.net/barriers-to-market-uptake-of-biosimilars-in-the-us.html>
  62. Food and drug administration. Nonproprietary naming of biological products. Guidance for industry. <https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf>. Published January 2017. Accessed May 4, 2017.
  63. Brennan Z. FDA releases long-awaited draft guidance on biosimilar labeling. [www.raps.org/Regulatory-Focus/News/2016/03/31/24681/FDA-Releases-Long-Awaited-Draft-Guidance-on-Biosimilar-Labeling/](http://www.raps.org/Regulatory-Focus/News/2016/03/31/24681/FDA-Releases-Long-Awaited-Draft-Guidance-on-Biosimilar-Labeling/). Published March 31, 2016. Accessed May 4, 2017.
  64. Generic Pharmaceutical Association. Healthcare stakeholders call on FDA to support patient access to biosimilars by avoiding unnecessary labeling statements. <https://www.biosimilardevelopment.com/doc/healthcare-fda-patient-access-to-biosimilars-unnecessary-labeling-statements-0001>. Accessed September 13, 2018.
  65. House of Representatives HB 2310: biological products; prescription orders. [www.azleg.gov/legtext/52leg/2r/summary/hb2310\\_01-22-16\\_caucuscow.pdf](http://www.azleg.gov/legtext/52leg/2r/summary/hb2310_01-22-16_caucuscow.pdf). Accessed May 4, 2017.
  66. Carter AW. In the biosimilar marketplace will there be 50 ways to leave your insulin? *J Diabetes Sci Technol*. 2016;10:1188-1191. doi:10.1177/1932296816629488