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REVIEW ARTICLE

Update on Biosimilar Insulins: A US Perspective

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Abstract
The development of biosimilar insulin products has slowly evolved with only two follow-on biologics currently available to patients in the US. Both Basaglar® (insulin glargine) and Admelog® (insulin lispro) have undergone extensive testing, and have gained significant use by patients in the US. Despite the availability of these follow-on products, the price of insulin has remained stubbornly high. New regulatory guidance under the Biologics Price Competition and Innovations Act that came into effect in March 2020 introduced an abbreviated pathway for the approval of biosimilar insulins and introduced the option to apply for interchangeability of the biosimilar insulin with the reference product. This abbreviated clinical testing may open the doors for numerous follow-on insulin products, with unknown supply-chain and fiscal ramifications. This review will highlight the development process of biosimilar insulin in the US and the recent regulatory changes that can aid this process. We will also discuss challenges for prescribers and patients who are navigating this ever-changing landscape. These new regulations for biosimilar insulins will have ramifications for patients, healthcare providers, and third-party payers, though the direction and scope of these changes is unclear.

Key Points

Biosimilar insulin development will change with the Biologics Price Competition and Innovations Act.

Physician and patient education will assist the transition to biosimilar insulins.

The cost-saving effect of biosimilar insulins to patients remains to be seen.

1 Introduction

According to the Centers for Disease Control National Diabetes Statistics Report, about 34.2 million patients or 10.5% of the US population had diabetes mellitus in 2018 [1]. Insulin is a crucial therapy for millions of people who have partial or complete insulin deficiency. Since its isolation by Banting, Best, and Macleod from purified dog pancreata in 1922, many modifications have improved the purity, safety, and pharmacokinetics of insulin used for therapeutic purposes. The efficacy of insulin was initially demonstrated when the extract lowered the blood glucose of severely hyperglycemic children, for which Banting and Macleod received the Nobel prize in 1923 [2]. Generous collaboration with Eli Lilly allowed large-scale manufacturing of bovine and porcine insulins, which were sufficiently close in structure to human insulin to provide reliable efficacy, albeit with occasional antibody development. Animal-sourced insulins were used until the mid-1980s when the manufacturing process shifted to the use of plasmid vectors in bacteria or yeast capable of producing human insulin in large quantities. This technology paved the way for the development of insulin analogs with different structures, absorption, and pharmacokinetic properties. Modifications of the peptide structure of the insulin molecule produced insulins with more rapid onset and shorter duration, or insulins with longer duration, slower absorption, and flatter profiles. Further modifications to the tertiary and quaternary structure or even to the excipients have contributed to the availability of multiple insulin products with different pharmacokinetic characteristics.

Insulin is the prototypical biologic drug and the most widely used biologic medication worldwide. Since the

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discovery of insulin, the industry grew to US $24 billion dollars globally by 2014, with an expected expansion to US $48 billion globally by 2020 [3]. The estimated national cost attributed to diabetes healthcare in the US was US $237 billion in 2017, with US $15 billion due to insulin [4]. The average price of insulin increased from US $4.34 per milliliter (mL) to US $12.92 per mL, which represents a 197% increase in the cost from 2002 to 2013. The amount of healthcare dollars spent on insulin in 2013 was higher than the cost of all oral diabetes medications combined [5]. Insulin pricing is complex and not transparent. In the US, manufacturers set a wholesale price that is further negotiated between the pharmaceutical companies and 'middlemen' including distributors, health plans, pharmacy chains, pharmacy benefit managers, and drug wholesalers [3]. Negotiations determine which insulin products are available to patients and at which 'tier' for purposes of setting patient co-payments. Patients are often responsible for paying a significant percentage of insulin costs if insured and struggle to pay for insulin if uninsured. The high price of insulin affects patients across the age spectrum, including the elderly. This review will highlight the development process of biosimilar insulin in the US and the recent regulatory changes that have aided this process. We will also discuss challenges for prescribers and patients who are navigating this ever-changing landscape.

2 Biosimilar Regulatory Pathway

Biologic medications, in contrast to small molecule drugs, are composed of peptides of varying sizes that either act as endogenous hormones or interfere with immunologic and other disease processes. Due to the complexity of the amino acid structure, the manufacturing process and testing required for approval of biologic products in the US were historically protected from generic competition even after the original patent had expired. This de facto protection was addressed by the Affordable Care Act in the US, which provided a pathway for the development of follow-on biologic products manufactured by competitor companies under the Biologics Price Competition and Innovations Act of 2009 [6]. The reference product is "the single biological product already approved by the FDA against which a proposed biosimilar product is compared" [7]. Typical generic drugs are the same as the reference product in active ingredients, dosage, safety, strength, route, duration of action, and indication, though they can differ in inactive ingredients [8]. Biosimilar drugs are not identical to but are similar enough to the reference product to produce no 'clinically meaningful differences' and were previously approved via two pathways in the US. Non-insulin biosimilars were approved under the Public Health Services (PHS) Act section 351 Biologics License Application [6] while follow-on biologics such as insulin were approved through the Federal Food, Drug, and Cosmetics (FFDC) Act section 505(b)(2) [9]. Applications for biosimilar drugs were allowed 12 years after licensing of the reference product.

The development of a biosimilar is complex and requires multiple types of studies to demonstrate therapeutic equivalence of the biosimilar to the reference product according to FDA regulations. Because differences in the manufacturing process of a biosimilar biologic medication can lead to changes in the protein structure that may induce alterations in function, potency, and safety, the FDA requires studies of purity, pharmacokinetics, and clinical efficacy in intended populations. Steps in the process include comparative structural and functional assays to evaluate the analytical similarity of the biosimilar to the originator, animal studies including evaluation of toxicity, and pre-clinical studies for safety and efficacy. Finally, clinical studies are required to 'demonstrate safety, purity, and potency' of the biosimilar product. Human studies that demonstrate equivalence in pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and immunogenicity profiles are required for the approval of biosimilar medications [6]. Applications under this policy include change of dosage form, strength, route of administration, or substitution of an active product in a combination product. Despite the similarities between the biosimilar and reference product, the biosimilar development process under FFDC 505(b) was costly and time consuming due to the requirement for clinical trials.

New regulations to streamline this process were enacted in the Patient Protection and Affordable Care Act, which created an amendment to the PHS Act allowing the approval of a biosimilar product under section 351(k) if only minor differences exist in the inactive ingredients and there are no significant differences between the biosimilar and reference product for safety, purity, and potency. This new abbreviated pathway, which came into effect in the US on March 23, 2020, requires the biologic product to be biosimilar to the reference product via analytical, chemical, and PK/PD studies without conducting longer term clinical trials [6]. Additionally, studies on immunogenicity are "generally unnecessary" if an analytical assessment demonstrates similarity of the biosimilar to the reference product. Justification is required for why further immunogenicity studies are not required and for some biosimilar insulin products, "a comparative immunogenicity study may still be needed" if uncertainties remain, including 'novel excipients' or certain 'impurities' [10]. This new guidance is based on the low risk of immunogenicity of insulin, and aligns FDA guidelines with European Medicines Agency guidelines. A new biosimilar insulin will still require chemistry, manufacturing, and control information, a comparative analytical assessment to demonstrate that it is 'highly similar' to the originator, and a

clinical pharmacology study assessing 'time-concentration' and 'time-action' profiles [10]. Furthermore, the regulation allows biosimilar drugs to seek approval for interchangeability under section 351 (k)(4)(A). Interchangeability means that the biosimilar drug can be substituted for the reference product by the pharmacy without physician approval, if the drug achieved biosimilar approval and can "be expected to produce the same clinical results as the reference product in any given patient". This may require identification of differences in analytical, mechanism of action, PK or PD, immunogenicity, or toxicity of the biosimilar compared with the reference product. Switching studies may not be required if the product is "highly similar to the reference product with very low residual uncertainty about immunogenicity" [11]. The FFDC 505(b) pathway will no longer be available for follow-on biologic insulin applications, and future applications will be approved or denied under section 351 of the PHS Act and will be deemed biosimilars to the reference product. These modifications are expected to hasten biosimilar insulin approval and may aid in decreasing insulin cost. A timeline of biosimilar development is outlined in Fig. 1.

The goal of these regulatory changes is to streamline the biosimilar insulin development process and encourage the approval of more biosimilar products to lower the cost of insulin. Prior to March 23, 2020, follow-on biologic insulins (trade names Basaglar® and Admelog®) reduced the cost of insulin by 10–15% from the originator product. In the following sections, we will review two follow-on biologic insulins, Basaglar® and Admelog® and discuss prescribing issues associated with these insulins from the US perspective.

3 Long-Acting Insulin: Basaglar®

Insulin glargine, manufactured by Sanofi as Lantus®, is a long-acting insulin developed to cover basal insulin requirements in persons with type 1 (T1DM) or type 2 diabetes mellitus (T2DM). It was approved by the US FDA in 2000 and is the originator product for follow-on insulin products. Since the development of Lantus®, it has become widely used due to its prolonged duration of action up to 24 h, lower variability, and lower risk of hypoglycemia compared with human NPH insulin [12]. The efficacy of the originator product, Lantus®, was shown in The Treat-to-Target Trial, in which a higher percentage of patients using Lantus® achieved the primary endpoint of HbA1c < 7% without symptomatic hypoglycemia compared with human NPH insulin users (33.2% vs 26.7%, $p < 0.05$) [13]. Due to the improved safety profile of Lantus®, it became the most widely prescribed basal insulin. After the patent on the parent molecule expired, a follow-on insulin product, trademarked Basaglar® (Eli Lilly), was tested and approved via section 505(b)(2) of the FFDC Act in 2015.

Both Lantus® and Basaglar® are recombinant human insulin analogs created by replacing asparagine with glycine at position 21 of the alpha chain and adding two arginines to the C-terminus of the beta chain of the insulin peptide. Both insulins are soluble at pH 4 and are dissolved in a clear, aqueous fluid [14, 15].

A phase I, three-site, randomized, double-blind, two-treatment, four-period crossover replicate euglycemic clamp study in 211 healthy subjects compared 0.5 units per kg of Basaglar® versus EU Lantus®, EU Lantus® versus US Lantus®, or US Lantus® versus Basaglar®. The PK study of Basaglar® versus US-approved Lantus® demonstrated similar PK parameters between treatments with 90% CI least squares means (LSM) difference for AUC [0–24 h] within the prespecified interval (Table 1). There were no statistically significant differences in PK parameters (maximum concentration [C_{max}], time to maximum concentration [T_{max}]). PD parameters showed similar glucose infusion rate (GIR) profiles and 90% CI for ratios of LSM for total glucose infusion during clamp (G_{tot}), and maximum glucose infusion rate (R_{max}) were contained within the prespecified interval of 0.80–1.25 [16].

In order to meet the requirements of the FFDC 505(b) Act, clinical trials showing equivalent efficacy and safety were required (Table 1). The phase III study "Efficacy and Safety of LY2963016 Insulin Glargine compared with Insulin Glargine (Lantus®) in Patients with T1DM" (ELEMENT 1) trial was a randomized, multicenter, active control, open-label, parallel study of 535 patients with T1DM stratified to once-daily Basaglar® or Lantus® with prandial insulin Humalog® for 52 weeks. Basaglar® was non-inferior to Lantus® for change in HbA1c over 24 weeks (−0.35 vs −0.46%, LSM difference 0.108%, 95% CI −0.002 to 0.219; $p > 0.05$). There was no difference in the proportion achieving HbA1c < 7%, daily mean glucose, daily basal

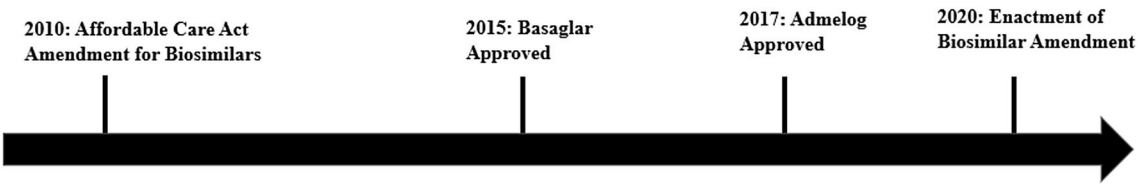

Fig. 1 Timeline of the US biosimilar pathway

Table 1 Basaglar® studies

Study	Study design	Type of diabetes and subjects	Intervention	Outcomes
PK, PD study [16]	Phase I: Randomized, double-blind, two-treatment, four-period crossover, replicate euglycemic clamp studies	211 Healthy subjects	Healthy subjects 0.5 units per kg of Basaglar® vs US Lantus®, US vs EU Lantus®, Basaglar® vs EU Lantus®	PK/PD parameters similar between treatments
ELEMENT 1 [17]	Phase III: Multicenter, randomized, open-label parallel study Duration: 52 weeks	535 T1DM	Once daily Basaglar® or Lantus® with prandial insulin Humalog®	Basaglar® noninferior to Lantus® for change in HbA1c from baseline to 24 weeks No difference in proportion achieving HbA1c < 7, daily mean glucose, daily insulin doses No difference in total, symptomatic, nocturnal, or severe hypoglycemia
ELEMENT 2 [18]	Phase III: Multicenter, randomized, double-blind, parallel study Duration: 24 weeks	756 T2DM	Insulin-naive or prior Lantus® and ≥ 2 orals randomized to Lantus® or Basaglar®	Basaglar® noninferior to Lantus® for HbA1c change from baseline No difference in fasting glucose proportion of patients reaching HbA1c <7, or insulin dose. No difference in total, symptomatic, nocturnal, or severe hypoglycemia
ELEMENT 5 [19]	Phase III: Multicenter, randomized, open-label, treat-to-target Duration: 24 weeks	493 T2DM (48% Asian, 46% White)	Insulin-naive or prior basal insulin all on ≥ 2 orals randomized to Basaglar® or Lantus®	Basaglar® noninferior to Lantus® in change in HbA1c from baseline Superior fasting glucose change from baseline with Lantus® vs Basaglar® No difference in proportion of patients achieving HbA1c < 7 or insulin dose No difference in hypoglycemia

PD pharmacodynamics, *PK* pharmacokinetics, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

insulin doses, or hypoglycemia [17]. Another phase III, double-blind, parallel 24-week trial in 756 patients with T2DM stratified to Lantus® or Basaglar® with doses titrated to achieve fasting blood glucose to < 100 mg/dL showed Basaglar® was noninferior to Lantus® in HbA1c reduction from baseline (− 1.29 vs − 1.34%, LSM difference 0.052%, 95% CI − 0.070 to 0.175); $p > 0.05$). There was no difference in fasting glucose, proportion of patients achieving HbA1c < 7% at 24 weeks, or hypoglycemia [18]. These findings were also consistent in a population of 493 patients with T2DM either on basal insulin or insulin-naïve on more than two oral antihyperglycemic drugs who were randomized to Lantus® or Basaglar®. Basaglar® also demonstrated noninferiority to Lantus® for change in HbA1c or hypoglycemia, but Lantus® was superior in LSM change in fasting glucose control from baseline (0.32 mmol, 95% CI 0.09, 0.55; P= 0.007) [19].

Basaglar® is approved for use in adults and pediatric patients ≥ 6 years of age with T1DM and adults with T2DM [15]. Basaglar® is formulated as 100 units per mL in a 3-mL Basaglar Kwikpen® device. The excipients include zinc, metacresol, glycerin, and water.

4 Short-Acting Insulin: Admelog®

Admelog®, the trade name for insulin lispro manufactured by Sanofi, became the first short-acting insulin follow-on product to be approved by the US FDA in December 2017 via the 505(b)(2) pathway. The originator product, Humalog®, received initial US approval in 1996. Admelog® is an aqueous, clear, and colorless solution like its originator product with a pH of 7.0–7.8 and each mL containing insulin lispro 100 units [20]. The primary structure of Admelog® is identical to that of Humalog®. Admelog® and Humalog® have lysine and proline at locations 28 and 29 of the beta chain compared with proline and lysine in the corresponding positions in human insulin [20, 21]. The similarity between the PK and PD of Admelog® to both US- and EU-approved Humalog® was demonstrated in a phase 1 trial by Kapitza et al. [22]. This was a single-center, randomized, double-blind, three-treatment, three-period, six-sequence, crossover, euglycemic clamp study. 30 male patients with T1DM were randomized to receive 0.3 unit per kg of Admelog® compared with US- and EU-approved Humalog® with 28 subjects completing all three periods. PK parameters and PD parameters were similar in all comparisons. The point

Table 2 Admelog® studies

Study	Study design	Type of diabetes and subjects	Intervention	Outcomes
Kapitza et al [22]	Phase 1: Randomized double-blind, euglycemic clamp study	28 T1DM	Admelog® vs Humalog® US vs Humalog® EU	Similar PK and PD parameters Adverse events were similar for all 3 products
SORELLA 1 [23]	Phase 3: Randomized, open-label, multicenter, two-arm, parallel-group study	507 T1DM	Admelog® vs Humalog®	Non-inferior efficacy Similar safety profile with no difference in hypoglycemia Similar prevalence and incidence of antibodies
SORELLA 2 [24]	Phase 3: Randomized, open-label, multicenter, two-arm, parallel-group study	505 T2DM	Admelog® vs Humalog®	Non-inferior efficacy Similar safety profile with no difference in hypoglycemia Similar prevalence and incidence of antibodies

PD pharmacodynamics, *PK* pharmacokinetics, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

estimates of treatment ratios were 0.95–1.03 for PK parameters and 1.00–1.07 for PD parameters with 90% confidence intervals within the pre-specified bioequivalence limit (0.80–1.25) (Table 2).

The phase III study, "Comparison of SAR342434 to Humalog as the Rapid Acting Insulin in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine" (SORELLA 1) was a randomized, open-label, multicenter, two-arm, parallel-group study to evaluate efficacy, adverse effects, and immunogenicity of Admelog® versus Humalog®. Admelog® plus insulin glargine were compared with Humalog® plus insulin glargine in 507 patients with T1DM. At 26 weeks, HbA1c reduction was similar in both treatment groups (−0.42% vs −0.47%; LSM difference 0.06%, [95% CI −0.087 to 0.197]). Fasting glucose, seven-point glucose profiles, hypoglycemic events, and adverse events were similar in the two groups. The prevalence and incidence of anti-insulin antibodies in the two groups was also similar at week 52 [23]. Additionally, "The Efficacy and Safety of Biosimilar SAR342434 Insulin Lispro in Adults with Type 2 Diabetes Also Using Insulin Glargine" (SORELLA 2) study was a 26-week, phase III, randomized, open label, multicenter, two-arm parallel-group study comparing Admelog® and Humalog® in patients with T2DM also using insulin Lantus®. A total of 505 patients with T2DM were randomized to multiple daily injections of Admelog® or Humalog® plus once-daily glargine injections. At week 26, HbA1c reduction from baseline was similar in both treatment groups (−0.92% vs −0.85%; LSM difference −0.07% [95% CI −0.215 to 0.067]). Fasting glucose, seven-point self-monitored plasma glucose profiles, hypoglycemic events, and treatment-emergent adverse events were similar in the two groups. Prevalence and incidence of anti-insulin antibodies in the two groups was similar at week 26 [24] (Table 2).

Admelog® is approved for use in adults and children > 3 years of age with T1DM and adults with T2DM. There are no clinical trials for the use of Admelog® in pregnancy or lactation [21]. Data is extrapolated from efficacy and safety data available for Humalog® [20]. Admelog® is available in vials (each vial contains 10 mL) and in prefilled delivery devices (disposable 3-mL pens). It can be administered subcutaneously via pens, injections, insulin pumps, or through intravenous infusions.

5 Future Products

Several new biosimilar insulins are in development in the US including Semglee® (MYL-1501D, insulin glargine) produced by Mylan and Biocon, which has approval in Europe and Australia but is awaiting approval in the US [25]. Semglee® demonstrated noninferiority compared with insulin glargine in phase III studies in both T1DM [26] and T2DM [27] for HbA1c, safety, immunogenicity, and hypoglycemia. Lusduna® (insulin glargine), produced by Merck, was approved by the FDA in 2017 but has not been released to market [28]. Several generic manufacturers are developing insulin aspart and human insulin products for the US and European markets. Some of these products are expected to be approved under the new FDA guidance with only analytical, preclinical, pharmacokinetic, and pharmacodynamic data, but without clinical trials.

6 Interchangeability

One of the hallmarks of generic drugs is pharmacy substitution for the originator product or other generic equivalent. This process requires the generics to be designated as interchangeable with the originator. The ability for pharmacies to interchange biosimilar insulins for the originator product depending on insurance coverage has been evaluated by individual US states. New regulations on interchangeability under 351 (k)(4)(A) of the PHS Act may provide states with greater leverage for consideration of insulin interchangeability when future biosimilar insulins achieve an interchangeability designation. Interchangeable medications such as generics are provided a therapeutic equivalence designation (TE) found in the Orange Book [29]. Neither Admelog® nor Basaglar®, found in the Purple Book, have a TE designation compared to the originators. However, this may not pose a significant issue given the lack of significant differences in immunogenicity in the clinical trials for either drug compared with their originators. In a real-world study, switching from Lantus® to Basaglar® did not create a difference in dose at 12 months or change in HbA1c; however, the insulin cost was reduced for patients with both T1DM and T2DM [30]. At the state level, several forms of regulations exist. Many states currently permit pharmacists to substitute a follow-on insulin product for the reference, but require pharmacists to communicate with the prescriber through notes in the electronic health record or pharmacy records to allow for the substitution. Prescribers can prevent substitutions if they prescribe the insulin via use of 'dispense as written' or 'brand name necessary'. In 20 states, patients are required to be notified of substitutions and some require patient's consent prior to substitution [31].

Pharmacy-driven substitutions for insulin products can pose several issues. If the substitution occurs with products with a different name or in a delivery device unfamiliar to the patient, there is potential for errors in dosing or administration that may pose unforeseen risk to the patient. Biosimilars with unfamiliar names may lead to patient confusion and affect adherence. Healthcare providers who do not recognize the insulin name may offer the wrong advice about dosing. Patient and provider education are crucial for successful transitions between the biosimilar and reference products. Alternatively, if interchangeability is prohibited and substitutions are not allowed, healthcare providers are challenged with responding to frequent requests for prescription changes that may delay refills for patients. In reality, the choice may not always lie in the hand of the physician as many insurance companies have tiered formularies and may prefer a less expensive biosimilar drug. Whether additional labeling or other safeguards will be put into place is yet to be determined.

Biosimilar insulins are projected to reduce acquisition costs by 10–40% in the US [32]. Currently, the Medicaid national average acquisition cost for Lantus® is US $27.23 per mL compared with US $20.92 per mL for its follow-on biologic insulin, Basaglar®, while the price of insulin lispro is US $33.94 per mL and US $16.19 per mL for Admelog® [33]. Despite the potential cost savings of biosimilar insulins, there are several roadblocks that may deter significant cost savings. Approval and production costs may be reduced with the new simplified regulatory process and overseas manufacturing; however, bundled price negotiations between payers and manufacturers, rebates, and other pricing considerations may affect biosimilar insulin selection in the formulary. An example of formulary exclusion was seen with the exemption of biosimilar drugs from the Medicare coverage gap discount. Based on a projected cost study of Medicare part D plans, the lack of gap discounts would have increased the out-of-pocket cost of the biosimilar infliximab-dyyb by US $1700 to beneficiaries compared with the reference product in 2017 [34]. Medicare has since changed its policy to allow biosimilars to be subject to 70% of the manufacturer's rebate in the Part D coverage gap [35]. Whether these projected financial benefits of biosimilar insulins will be passed along to patients remains to be seen.

7 Conclusion

The advent of biosimilar insulins has provided options for patients and third-party payers, but has added complexities to insulin prescribing by physicians. Biosimilar insulins available thus far have been shown to have equivalent efficacy and safety to the originator product, given rigorous testing procedures and approval requirements. While the availability of additional insulin products has provided choice, the added products have not substantially lowered the price of insulin at the time of writing. Whether these substitutions will significantly lower costs in the future is unclear. Understanding the biosimilar development process, efficacy compared with the originator, and interchangeability is necessary for prescribers and pharmacists to provide optimal patient care. The updated FDA guidance may contribute to many more approvals of biosimilar insulin products and delivery devices starting in 2020 and continuing for years after. Healthcare providers will need information about new biosimilar insulins and delivery devices; however, there is no clearly defined pathway for dissemination of such information. The development and approval of competing biosimilar insulins will increase the need for physicians to stay updated on this rapidly changing field.

Compliance with Ethical Standards

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