May 23, 2019

Dr. Norman E. Sharpless  
Acting Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Room 600E  
Silver Spring, MD 20993

Submitted electronically to: www.regulations.gov

RE: The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Biosimilar and Interchangeable Insulin Products; Public Hearing; Request for Comments (Docket No. FDA-2019-N-1132)

Dear Acting Commissioner Sharpless:

Kaiser Permanente appreciates the opportunity to respond to the U.S. Food and Drug Administration’s (FDA) request for comments on increasing access to insulin. We commend FDA’s attention to insulin affordability and continued focus on increasing biosimilar competition.

As the largest private integrated health care delivery system in the United States, Kaiser Permanente\(^1\) delivers health care to more than 12.2 million members in eight states and the District of Columbia. Within that footprint, we maintain a primarily internalized pharmacy system, including over 550 outpatient, hospital, infusion, specialty and mail order pharmacy sites staffed by over 14,000 pharmacy personnel. Kaiser Permanente spends approximately $10 billion annually on pharmaceuticals. Our Permanente Medical Group (PMG) physicians prescribe and our pharmacies dispense over 90 million prescriptions annually. We are committed to providing high-quality, affordable care and improving the health of our members and communities we serve.

Kaiser Permanente is deeply concerned about the crippling burden high drug prices impose on our members and the impact they have on our ability to carry out our mission. Pharmaceutical companies continue to raise prices to unaffordable levels, forcing many patients and families to choose between paying their rent or mortgage, or paying for their medications. It is time for a new framework for drug pricing that rewards innovation and discoveries, but also provides medicines at prices patients can afford.

Rising insulin prices are particularly troubling, as insulin is a vital, life-sustaining drug and a mainstay of treatment for many patients with diabetes. Given the sheer volume of insulin prescribing, any increase in price has significant financial implications for our system. Unfortunately, the three manufacturers that dominate the U.S. insulin market routinely raise prices.

\(^1\) Kaiser Permanente comprises Kaiser Foundation Health Plan, Inc., the nation’s largest not-for-profit health plan, and its health plan subsidiaries outside California and Hawaii; the not-for-profit Kaiser Foundation Hospitals, which operates 39 hospitals and over 650 other clinical facilities; and the Permanente Medical Groups, self-governed physician group practices that exclusively contract with Kaiser Foundation Health Plan and its health plan subsidiaries to meet the health needs of Kaiser Permanente’s members.
For example, the U.S. list price of a vial of Humalog® (insulin lispro) increased from $35 in 2001 to $234 in 2015, with list prices for Novolog® (insulin aspart) and Lantus® (insulin glargine) increasing from $289 to $540 and $244 to $431, respectively, over the same period.2 Primarily due to these price increases, average insulin spending in the U.S. doubled on a per patient basis between 2012 and 2016.3 These price increases are unsustainable, and we applaud FDA’s efforts to make insulin more affordable by injecting more competition into this market.

I. Kaiser Permanente’s Unique Approach to Insulin

Maintaining insulin affordability is a priority for Kaiser Permanente. Our integrated structure, evidence-driven formulary and ability to commit to shifting market share to preferred drugs often enables us to negotiate significant discounts, including on insulin. These discounts, however, tend to be outpaced by regular insulin list price increases. Thus, our system continues to absorb more costs as manufacturers raise insulin prices year-over-year.

Our integrated model and commitment to letting evidence drive the treatment decisions also empowers us to implement various programs and initiatives that generate savings while maintaining and improving clinical outcomes. For example, our approach to treating patients with type 2 diabetes—which constitute the vast majority of the diabetes patient population—often involves earlier initiation of insulin therapy and caution before switching members to newer, more expensive insulins when longstanding, more affordable options work just as well.

Kaiser Permanente’s unique approach to insulin appears to be slowing down spending growth in our system relative to the rest of the market. The Kaiser Family Foundation recently estimated that total spending on insulin under Medicare Part D increased 840 percent between 2007 and 2017.4 At Kaiser Permanente, our total spending on insulin in California increased by approximately 300 percent over the same period. Thus, while climbing insulin prices are a burden on our system, our efforts to contain costs while preserving high-quality care have reduced the negative impact of insulin price increases on member access and systemwide costs.

Formulary Design

Kaiser Permanente’s approach to formulary design focuses on the comparative clinical performance of different therapeutic options and strives to maintain optimal insulin affordability for our members. New, expensive versions of insulin and other diabetes medications (e.g., quick

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pen combination products, once and twice daily formulations, new oral agents) come to market regularly, but do not always offer meaningful clinical advantages for all patients that justify often significantly higher prices. Kaiser Permanente’s evidence-driven approach ensures a focus across our system on the highest-value products, which helps us maintain affordable access to insulin and other drugs for our members.

The core of our evidence-driven approach is the establishment and management of our own formularies through a rigorous process in close collaboration with PMG physicians and clinical pharmacists. On an ongoing basis, our pharmacists review and develop an objective, evidence-based analysis of a drug or therapeutic class. Pharmacist and physician experts then review the evidence associated with each drug and make recommendations to our clinician-led Pharmacy & Therapeutics (P&T) committees. Prescribers within our system trust our formularies because they are grounded in clinical evidence and built in partnership with their peers. Therefore, they tend to prescribe consistently with them in the vast majority of cases.

Kaiser Permanente makes best efforts to insulate our members from rising insulin prices, including by where we place insulin on pharmacy benefit tiers on our formularies. While we prefer certain insulin products, our members can access any insulin, including off-formulary products, as long as their physician believes it is the right product to meet their medical needs. Any insulin product is therefore accessible to our members when needed.

Kaiser Permanente is also able to negotiate deep discounts on certain insulin products through our standard approach to pharmacy contracting. We strongly prefer securing upfront discounts from manufacturers instead of rebates. These upfront discounts are recognized in premiums and the development of our member pricing, which is what determines cost-sharing in the deductible and Medicare Part D coverage gap benefit phases. These discounts therefore help us keep insulin more affordable for our members across different benefit phases. Nevertheless, even our significant discounts generally do not fully offset constant insulin price increases.

Drug Use Management

To maintain quality and access, Kaiser Permanente also uses an evidence-driven approach to insulin use management that prioritizes therapies that deliver positive clinical outcomes at a lower cost. The exact approach taken varies from patient-to-patient depending on their individual medical and personal needs. There may also be slight variance in specific approaches to drug use management across our regions. Relative to the rest of the health care system, however, we have greater utilization of neutral protamine Hagedorn (NPH) insulins and tend to start type 2 patients on insulin therapy earlier. These best practices help us mitigate the impact of ever-increasing insulin prices to the greatest extent possible while still delivering high-quality care.

Use of NPH Insulin

Kaiser Permanente prefers use of NPH insulin for most patients with type 2 diabetes over more expensive, newer analogs. For the vast majority of patients with type 2 diabetes, NPH insulins are just as safe and effective as newer insulin analogs. Kaiser Permanente has extensively studied and reviewed the performance of NPH insulin among our members. Specifically, the Kaiser Permanente Division of Research received a grant from the National Institutes of Health (NIH) to
conduct a ten-year observational study of 25,000 patients with type 2 diabetes, comparing clinical outcomes between those who used insulin analogs and those who used NPH insulin. The study found that the patients on insulin analogs did not have substantially better blood sugar control or lower risk of hypoglycemia than those on NPH insulin.\(^5\)

While NPH insulin and insulin analogs perform similarly, NPH insulins tend to be significantly less expensive. Newer insulin analogs can cost up to ten times more. As a result, NPH insulin has long been the standard of care within Kaiser Permanente for most patients with type 2 diabetes. Over 90 percent of our members with type 2 diabetes are started on NPH insulin. In the rest of the market, approximately 90 percent of patients with type 2 diabetes use higher price insulin analogs.\(^6\)

Where our members have a clinical need for an analog, they can still access them. For example, analogs are commonly used across our system for patients with type 1 diabetes and type 2 patients with glycemic variability.

**Initiating Insulin Therapy at Earlier Stages of Type 2 Diabetes**

Kaiser Permanente’s protocols also generally encourage prescribers and patients with type 2 diabetes to move to insulin therapy at earlier disease stages instead of continuing to rely on oral agents. Before starting insulin, patients with type 2 diabetes typically use oral hypoglycemic agents. Many of these oral agents (particularly newer, brand products), however, tend to be more expensive than insulin while providing fewer clinical benefits as the patient’s condition progresses. At the latest, patients with type 2 diabetes should initiate insulin therapy as soon as they fail to achieve glycemic control using first-line oral agents.\(^7\) However, insulin is often delayed until absolutely necessary, due to a fear of needles and for other reasons, which can worsen outcomes.\(^8\)

PMG physicians and clinical pharmacists at Kaiser Permanente work together to educate prescribers about the appropriate timing for insulin initiation for type 2 patients. While our specific approach varies from region-to-region, this process often involves preparing talking points, FAQ documents and other user-friendly educational materials for physicians and care teams to guide conversations with patients. We also utilize clinical pharmacists to manage chronic care through collaborative practice agreements, which focus on improving patient outcomes.

**Internal Provider Education**

Physicians and pharmacists within Kaiser Permanente also work together to limit the influence of potentially biased pharmaceutical industry marketing within our system. Throughout the United

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\(^5\) Lipska, K. et al. (June 2018). Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin with Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and with Glycemic Control in Patients with Type 2 Diabetes. JAMA. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29936529.


States, pharmaceutical companies heavily market newer insulin analogs, combination products and other expensive diabetes medications directly to physicians, pharmacists and care teams through various detailing tactics and provision of free samples. In many cases, industry detailing focuses on higher price products even when lower price, equally effective options exist. These marketing tactics are often successful at steering prescribers toward newer, more expensive products.

Kaiser Permanente is relatively insulated from industry marketing practices due to the extensive steps we take to ensure PMG physicians, care teams and pharmacists across our system have access to the best available, unbiased evidence. Pharmaceutical sales representative access to physicians and care teams is very controlled within Kaiser Permanente. The PMGs in each of our regions also strongly discourage acceptance and use of free samples from pharmaceutical companies. Clinical pharmacist experts at Kaiser Permanente work with PMG physicians in our quality departments to build and routinely update guidelines for diabetes treatment. Instead of relying on information from the pharmaceutical industry, we generally use and disseminate our own materials to educate our providers, including through peer-to-peer education, direct visits, convening meetings at our facilities and other activities.

Pharmaceutical sales representatives can meet with our Drug Information Services, Pharmacy Contracting and other departments within our pharmacy operations to share evidence about their drugs and receive orientation about what they can and cannot discuss with Kaiser Permanente. We closely scrutinize information provided by pharmaceutical companies to maintain our strict focus on evidence. We believe our internal education policies and practices have played a significant role in empowering prescribers in our system to make appropriate decisions regarding outcome-based therapy for our members.

II.  Policy Recommendations to Promote Biosimilar Competition

Kaiser Permanente strongly supports FDA’s interest in fostering favorable conditions for biosimilar insulin development and approval. While others have been slow to transition to biosimilars, Kaiser Permanente embraces them. Within our system, the biosimilar Inflectra® (infliximab-dyyb) is used over 80 percent of the time instead of Remicade® (infliximab), the reference biologic. Inflectra® utilization in the rest of the market is 2.3 percent. Our experience with the biosimilar Zarxio® (filgrastim-sndz) and the reference product Neupogen® (filgrastim) has been similar, resulting in use of Zarxio® in approximately 95 percent of cases.

Based on our experience with insulin and success with biosimilars, we believe biosimilar insulins could help make the market more competitive and ultimately have a net lowering effect on prices. But brand manufacturers must believe that new entrants pose a genuine threat to their market shares. In order to create these conditions, we encourage FDA to continue its work to breakdown broader barriers to biosimilar market entry that could prevent biosimilar insulins from gaining a meaningful foothold in the United States. With that context in mind, we offer the following policy recommendations.

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9 Please see Kaiser Permanente’s comments on *Facilitating Competition and Innovation in the Biological Products Marketplace* (Docket No. FDA-2018-N-2689-0001) for a more detailed explanation of our experience with biosimilars and policy recommendations about how to build a more robust market for biosimilar competition.
Interchangeability

Kaiser Permanente supports FDA’s efforts to facilitate the development of interchangeable insulins and applauds the recent finalization of guidance for industry entitled “Considerations in Demonstrating Interchangeability With a Reference Product.” To date, there are no licensed interchangeable biosimilars in the United States. The final guidance may provide clearer standards on how manufacturers can obtain interchangeability designations for insulin, creating certainty for manufacturers that may increase competition and lower costs.

Access to Data

Timely access to data is crucial to Kaiser Permanente’s formulary development process and helping providers evaluate when biosimilars are appropriate for their patients. We appreciate FDA’s efforts to make more information about biosimilars, including review materials, available to the public through its website. The relatively robust data for Inflectra® and Zarxio® provided the information our physicians and pharmacists needed to evaluate whether individual patients were good candidates for conversions.

Unfortunately, review materials are not always made public, particularly when the product is not subject to Advisory Committee review or is not the first licensed biosimilar in its class. Even when such resources are public, posting is often delayed, sometimes by over a year. We encourage FDA to make review materials for all licensed biosimilars available on its website within two months of approval. Making data more accessible will help facilitate successful conversions for insulin and other biosimilar products in the future.

Instilling Confidence in Biosimilars

Kaiser Permanente’s success with biosimilar utilization reflects a concerted effort across our system to instill prescriber confidence by providing reliable, evidence-based information about biosimilars to physicians, pharmacists and care teams. Our experience creating educational tools and resources for prescribing biosimilars suggests that prescribers would benefit from FDA making additional educational tools and resources publicly available. FDA should ensure that education efforts include the entire care team, including physicians, nurses, pharmacists, physician assistants, and other health care professionals that communicate with patients. FDA should also consider how it can encourage health care system stakeholders to access reliable information about biosimilars from sources other than the pharmaceutical industry, including by encouraging adoption of counter-detailing policies or similar restrictions on marketing to Kaiser Permanente.

Most importantly, more must be done to increase patient confidence in biosimilars. No patient wants to feel like she is receiving an “inferior” medicine. Unfortunately, these misperceptions about biosimilar products are common. Because physicians and other practitioners are a trusted resource for patients, improving prescriber education about biosimilars should also enhance patient education and comfort. FDA can help by continuing to aggressively use its platform to assure the public that biosimilars are safe and effective alternatives to reference products, including through consumer-focused statements and public awareness campaigns.
Overcoming Market Entry Barriers

There are many barriers for potential entrants into the insulin market that make it risky to invest in developing a biosimilar insulin. For example, the insulin market in the United States has long been concentrated among three manufacturers, whose marketing strategies have created considerable brand loyalty. While overall insulin spend is high, net unit costs are low. Therefore, biosimilar entrants would need to gain substantial market share to make a profit, which could require them to launch products at very low prices. This is a significant market barrier that may explain the near absence of appetite amongst manufacturers to develop generic and biosimilar insulins.

There are steps, however, that the federal government could take to encourage more investment in biosimilar insulin development. For example, FDA user fees or other sources of funding could be set aside to pay for the costs of biosimilar applications over the near-term until the market becomes more competitive and prices decline. Increased access to tax credits could also be used to help offset costs associated with studies needed to demonstrate biosimilarity and interchangeability. Such investments could help reduce deterrents and financial risks for manufacturers capable of developing biosimilar insulins.

Reducing Anticompetitive Behavior

Kaiser Permanente is deeply concerned about anticompetitive “lifecycle management” tactics reference product manufacturers use to delay market entry of biosimilar products. FDA has approved 19 biosimilars to date. But only a handful of those are actually available to patients, primarily due to excessive patenting and related legal disputes. Insulin products are already subject to over-patenting and evergreening, which occurs when repeated incremental improvements that often do not constitute significant clinical advancements are made to a drug and patented. Moving forward, we are concerned that reference product manufacturers may try to leverage evergreening strategies to interfere with interchangeability determinations on biosimilar insulins.

With these concerns in mind, Kaiser Permanente encourages FDA to work with the Federal Trade Commission (FTC) to address these competition-delaying tactics. Further coordination between FDA and FTC would foster greater understanding about how FDA processes are abused for anticompetitive purposes. Specifically, FDA and FTC should jointly review issues related to patent thickets, interchangeability determinations, settlements between reference product and biosimilar manufacturers, product hopping and evergreening through “biobetter” reformulations and misleading communications about biosimilars by reference product manufacturers.

Kaiser Permanente appreciates the opportunity to provide feedback in response to FDA’s request for comments on insulin. We would be pleased to discuss these comments and our experience with

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10 Biosimilar Product Information. FDA. Available at: [https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm](https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm)

insulin and biological products in our integrated delivery system. If you have questions, please contact me (510.271.6835; anthony.barrueta@kp.org) or Polly Webster (202.216.1900; polly.f.webster@kp.org).

Sincerely,

Anthony A. Barrueta
Senior Vice President, Government Relations
May 27, 2019

The Insulin Club
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852


Dear Sir/Madam:

On behalf of The Insulin Club, thank you for the opportunity to comment and participate in the discussion regarding the future of insulin biosimilars: increasing access and facilitating the efficient development of biosimilar and interchangeable insulin products.

The Insulin Club is dedicated to producing a new, low-cost, biosimilar version of analogue insulins. We will be structured as a membership club. In exchange for a small annual fee, we will guarantee a supply of insulin at a low, fixed net margin.

One of our core values is complete, radical price transparency. We plan to disclose to our members our total costs in developing, manufacturing, and marketing our products, so that they may be able to make informed, rational decisions about their own health care. Our initial goal is to bring to market a biosimilar version of glargine insulin at a price point of $20 a vial within 3 years.

Three manufacturers currently control 99% of the US insulin market, resulting in a severe lack of competition and the potential for continued price hikes. At this moment, the regulatory structure makes it difficult for new companies to develop insulin. A new regulatory framework for bringing insulin products to market is on the horizon, which has the potential to increase competition in the marketplace and to facilitate new entrants such as ourselves. Starting in 2020, insulin will be regulated as a biologic product under the 351(k) FDA pathway. However, development times for biosimilar drugs remain lengthy and costly, which forms the basis for our comments below:

1. REQUIREMENTS FOR SUBMISSION OF 351(K) APPLICATION

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) requires that on March 23, 2020, an approved marketing application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) will be deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) and regulated under the PHS Act. The Food and Drug Administration (FDA or the Agency) states that these statutes will create an abbreviated licensure pathway for biosimilar products such as insulin. However, under these current guidelines, the standards for evaluating biosimilarity are not abbreviated and are in fact lengthy, costly, and rigorous, creating a barrier to entry for follow-on products.
2. **SCIENTIFIC STANDARDS FOR EVALUATING BIOSIMILARITY AND INTERCHANGEABILITY OF AN INSULIN PRODUCT**

Current regulations will require companies developing or planning to develop biosimilar insulin to undergo large and expensive Phase III clinical trials. There are often lengthy, costly, and unable to detect clinical differences between biosimilar and originator products.\(^1\) It is well known that proteins have unique structural components that are used to characterize their purity, potency and safety. While concerns have been raised regarding structural folding differences and post-translational modifications (PTMs) and their effect on bioequivalence, the development of sophisticated analytical models has allowed for comparability assessments between originators and biosimilars that are more sensitive and meaningful than clinical testing.\(^2\) Based on the current analytical methods that are available, The Insulin Club believes that a robust chemistry, manufacturing and controls (CMC) package combined with a Phase I clinical trial should be sufficient in demonstrating bioequivalence of a follow-on insulin product when compared to its reference product.

In addition to the analytical methods available, insulin is a small, well understood protein that has been studied for nearly 100 years. Unlike large, complex biologics such as monoclonal antibodies (mAbs) that are difficult to characterize and copy, insulin has an extensive historical database and pharmacodynamic markers to support its efficacy, safety and immunogenicity among regulators, patients and physicians. In September of 2017, the FDA issued a draft guidance titled “Statistical Approaches to Evaluate Analytical Similarity—Guidance for Industry.”\(^3\) The Insulin Club believes that this guidance should be considered in future guidelines related to biosimilar insulin development strategies.

It is a common belief among clinicians that reference products never change, even though multiple reports demonstrate extensive post-approval changes in the manufacturing processes of reference products in Europe.\(^4\) While these changes have the potential to affect the biologic activity of the protein, analytical comparisons have shown no adverse impact on quality factors and all products have remained on the market, without having undergone extensive clinical testing.\(^5\) The scientific standards used by the EMA and other regulatory bodies acknowledge that “the demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.”\(^6\) This concept

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\(^2\) Ibid


\(^6\) Supra note 2
applies to both reference products and biosimilars in the EU and should be applied to the development of biosimilar insulin products in the U.S.\(^7\)

Biosimilar Phase III clinical trials have many limitations and challenges:\(^8\)

- They are not powered to detect meaningful differences in safety profiles.
- Differences in adverse events that are within safety parameters are often difficult to interpret due to the cohort size.
- There is a low probability of detecting differences in efficacy.

The challenges associated with these studies reinforce the proposal to utilize CMC/PK data as a basis for confirming biosimilarity for follow-on insulin products and utilizing post marketing studies to generate “real world evidence” data.

In an effort to reassure the healthcare community, multiple studies have been conducted on the risk of immunogenicity-related safety concerns and diminished efficacy of biosimilar products.\(^9,10\) These studies have been on much larger and complex biologic products, enrolling tens of thousands of patients and have failed to show any clinically meaningful effects of switching between a biologic and a biosimilar. Therefore, one can assume that given the size and simplicity of insulin, forgoing a Phase III clinical trial and relying on extensive analytical and Phase I clinical data should be sufficient in demonstrating bioequivalence.

Phase III clinical trials are extremely burdensome, time consuming and expensive. Typical studies require 200 – 400 plus patients per group at a cost exceeding $44,100 per patient.\(^11\) Based on current ICH Good Clinical Practice (GCP) Guidelines, many have even ventured to call Phase III clinical trials unethical as “without scientific validity, there is no ethical validity.”\(^12,13\)

In general, if the evaluation of a biosimilar and its reference product on an analytical and functional basis are deemed similar, there should be little residual uncertainty regarding a product’s bioequivalence, leaving little to be addressed through extensive clinical studies. Therefore, The Insulin Club proposes that

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\(^8\) Supra note 1


\(^10\) Biosimilar infliximab (CT-P13) is not inferior to originator infliximab: results from a 52-week randomized switch trial in Norway. ACR Meet Abstr. 2016.


the FDA waive the Phase III clinical trial requirement for the development of biosimilar insulin and utilize a comprehensive CMC data package and Phase I clinical trial as sufficient evidence to deem an insulin product bioequivalent.

In addition, a robust Phase I clinical trial could potentially contain additional endpoints to evaluate immunogenicity and efficacy.

After working in conjunction with consulting biostatistician Munish Mehra, PhD, MS, Msc, we feel a trial of around 150 subjects can establish efficacy

From: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743680/

We estimate the drop in HbA1c will be 0.5% over 12 weeks with the drop in the placebo group of 0.0%. Assuming a standard deviation of 0.9% from the referenced article, at 90% power and with a 2-sided hypothesis test at $\alpha=0.05$ with 1-1 randomization we would need 69 subjects per treatment arm. Recognizing the important of intercurrent events and missing data we would work with the agency to reach agreement on an appropriate estimate in accordance with ICH E9 (R1) addendum.

In addition, The Insulin Club believes that it would be acceptable to require post market surveillance studies following a product approval.

Sincerely,

Alex Oshmyansky, MD, PhD
President and CEO
The Insulin Club
IQVIA Conceptual Proposal for Development of Insulin Biosimilar

1. Scientific standards for evaluating the biosimilarity and interchangeability of an insulin product.

a. What considerations should FDA take into account when evaluating data and other information submitted by an applicant, including from analytical and clinical studies, to determine whether an insulin product is biosimilar to a reference product?

IQVIA Conceptual Proposal for Development of Insulin Biosimilar

Background and Proposed Prerequisites

On March 30, 2020, insulin products that are currently approved under the FD&C Act will be transitioned to be regulated under the PHS Act. This will allow development of insulin biosimilar products under the abbreviated 351(k) pathway. These products will have to meet all applicable statutory standards, such as demonstration of biosimilarity, and could rely on certain existing knowledge about the safety and effectiveness of a reference product. As such, prerequisites to the initiation of a clinical program for insulin biosimilar products should be:

1. Demonstration of high degree of analytical similarity of proposed biosimilar product to the US-licensed reference product by developing and executing an extensive analytical similarity study that will incorporate state of the art analytical techniques.
2. Generation of comparative animal data between proposed biosimilar and US-licensed product to demonstrate high degree of similarity in toxicity, immunogenicity and pharmacokinetics (PK) using an appropriate animal model.

Proposed insulin biosimilars that meet all prerequisites could proceed to a clinical program.

Insulin Biosimilar Clinical Program

Clinical development is the most time-consuming and expensive step of any product development, including clinical development of biosimilars. Despite the overall expectations that biosimilar product development
could rely on certain existing knowledge about the safety and effectiveness of a reference product, there is an opportunity to further optimize the biosimilar clinical program.

Based on IQVIA’s experience, the average time for the execution of a clinical program for an insulin biosimilar product is approximately 3 - 5 years. While IQVIA always strives to optimize the time of clinical study execution, it is not always possible to reduce the clinical program timelines without introducing innovative approaches. Accordingly, we propose one such approach for the agency’s consideration, i.e., the use of a comparator arm in the Phase III clinical study.

The current clinical program for biosimilar of insulin usually comprises of the following studies:

1. Phase I randomized, double-blind, controlled, cross over, euglycemic clamp study to evaluate Pharmacokinetic (PK) and Pharmacodynamic (PD) equivalence of proposed biosimilar versus reference product in patients. Usually, the study is in patients with Type 1 diabetes mellitus.

2. Phase III Randomized, open-label, parallel-group, multi-center clinical trial comparing the efficacy and safety of proposed biosimilar versus reference product in patients. Often the study is in patients with Type 1 diabetes mellitus. Supportive Phase III study could be conducted in patients with Type 2 diabetes.

The Phase III study is the most costly and time-consuming, as it requires recruitment of at least 500 patients, treatment and follow-up periods. A high-level outline of the typical Phase III insulin biosimilar study is presented in Table 1 below.

Table 1: Phase III insulin biosimilar study design.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, open-label, parallel-group, multi-center clinical trial comparing the efficacy and safety of proposed biosimilar versus reference product in patients with Type 1 diabetes mellitus</th>
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<tbody>
<tr>
<td>Objective</td>
<td>To compare the efficacy and safety of proposed biosimilar versus US-licensed reference product. Safety assessments included hypoglycaemia, adverse events (AEs) including hypersensitivity and injection site reactions and anti-insulin antibody (AIA).</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Change in hemoglobin A1c (HbA1c) from baseline to 24 weeks</td>
</tr>
</tbody>
</table>
| Secondary    | • Immunogenicity: Change from baseline in titer and incidence of AIA, for up to 52 weeks  
|              | • Safety: occurrence of hypoglycemia, local reactions, systemic reactions and other adverse events  
|              | • Insulin dose per body weight (U/kg)  
|              | • Device-related safety assessment  
|              | • Change in HbA1c from baseline during scheduled visits  
|              | • Change in fasting plasma glucose from baseline  
|              | • Change in 8-point SMBG profile from baseline  
<p>|              | • Proportion of participants with HbA1c &lt;7% at 24 weeks |
| Planned # of patients | A minimum of 500 patients with Type 1 diabetes |
| Patients enrolment period: | Not less than 12 months |
| Study Duration Screening/Wash out | 4-6 week(s) |</p>
<table>
<thead>
<tr>
<th>Treatment and Evaluation period</th>
<th>6-months (24 weeks) main study + 6-months (24 weeks) comparative safety extension period, for the collection of safety data, including immunogenicity data up to 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Drugs</td>
<td>Insulin Biosimilar and US-Licensed reference product</td>
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As presented in Table 1, the time for enrolment of the minimum number of patients for the study is about 12 months. Up to 50% of recruited patients will be assigned to the arm with US-licensed product and will have to undergo medical visits, testing and evaluations just for the generation of the comparative efficacy and safety data. This creates an inconvenience for these patients, who, otherwise, could have been taking an approved product without medical intervention. From the patient’s perspective, this could also be considered an ethical issue, because the patient could continue to use an approved product without participation in a clinical study and without being subjected to additional medical tests, in a study which is not intended to provide greater benefits to the patient in comparison to the standard of care. To address this potential concern as well as reduce the recruitment period and overall study duration, IQVIA suggests replacing the group of patients that would be administered US-licensed reference product with an external comparator arm derived from real-world data (RWD). This comparator arm approach is described in the next section.

**External Comparator Arm in Phase III Insulin Biosimilar Study**

The adjustment of the current design of the Phase III insulin biosimilar study to incorporate an external comparator arm derived from RWD would provide multiple benefits to patients and sponsors and, at the same time, would generate a level of evidence of efficacy and safety that has been accepted by the FDA in oncology and rare disease indications.

An external comparator is used to provide comparative context for clinical trial data, particularly when the clinical trial employs a single-arm design, where all trial participants are assigned to the treatment arm (e.g., insulin biosimilar). External comparators have been utilized in the past, predominantly in rare disease research, and usually in the form of a historical control from literature. Access to high-quality RWD enables external comparators that more closely match the trial population as certain inclusions/exclusion criteria can be ascertained through information documented in RWD. If appropriately designed, an external comparator from RWD that closely matches the trial population may provide sufficiently compelling information for decision-making.

An external comparator from RWD could be used to provide broadly generalizable comparative information on the real-world experience of patients using the comparator product. To develop the external comparator arm, a detailed feasibility of global RWD sources (both secondary and primary sources) would be performed to identify patients that closely match the inclusion and exclusion criteria of the Phase III insulin biosimilar study. This cohort of patients would then be followed prospectively (concurrently to the trial) through the appropriate RWD source, with trial endpoints measured based on real-world standard of care. Certain safety and efficacy endpoints, like HbA1c, could be captured through RWD sources. Depending on the RWD source selected, different approaches for data validation can be put in place to verify the data captured in the external comparator arm is fit for purpose.

There are inherent differences between the real-world setting and clinical trial setting that would need to be addressed in the design of any trial that incorporates an external comparator from RWD. These differences must be appropriately addressed in the analysis plan and design of the trial.

For example, based on IQVIA’s knowledge of RWD for insulin, there may be a need to adjust the design of both Phase I and Phase III insulin biosimilar studies in comparison with traditional studies as presented in this proposal. The Phase I study could include additional evaluation of safety and immunogenicity with some additional follow up. We understand that a very important aspect of insulin biosimilar evaluation is comparative immunogenicity. It would be challenging to use an external comparator for this evaluation, as such post approval safety study may be more appropriate.

IQVIA would be very interested in participating in further discussion with FDA and sponsors to evaluate the best applications of this concept.
Conclusion

In conclusion, IQVIA would like to thank FDA for conducting a public hearing and presenting questions that are extremely important for patients and sponsors with regards to insulin biosimilar development. IQVIA is committed to improving the lives of patients in the USA and across the globe. As such, we request that the implementation of external comparator in the Phase III biosimilar study for insulin products be considered as an alternative approach for biosimilar of insulin.

Best regards,
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