Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sandra Benton 301-796-1042.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2019
Biosimilars

Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2019
Biosimilars

TABLE OF CONTENTS

Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products

Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to applicants regarding whether and when comparative clinical immunogenicity studies may be needed to support licensure of proposed biosimilar and interchangeable recombinant human insulins, recombinant human insulin mix products, and recombinant insulin analog products that are intended for the treatment of patients with Type 1 or Type 2 diabetes mellitus (collectively described as "insulin products"). The recommendations in this guidance are applicable only to proposed biosimilar and interchangeable insulin products seeking licensure under section 351(k) of the Public Health Service Act (PHS Act) in biologics license applications (BLAs).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. The Pathway for Biosimilar and Interchangeable Insulin Products

Section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) requires that on March 23, 2020, an approved 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 PHS Act (42 U.S.C. 262). Although the majority of therapeutic biological products have been licensed under section 351 of

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

the PHS Act, some protein products historically have been approved under section 505 of the FD&C Act.[2]

This transition provision affects the insulin products to which this guidance is applicable. On March 23, 2020, the approved new drug applications (NDAs) for insulin products will be deemed to be licenses under section 351(a) of the PHS Act. Products with deemed BLAs will then be available to be used as reference products by applicants seeking licensure of proposed biosimilar and interchangeable insulin products under section 351(k) of the PHS Act.[3]

Section 351(k) of the PHS Act (42 U.S.C. 262(k)) sets forth the requirements for the licensure of biosimilar and interchangeable products. Section 351(i) defines "biosimilarity" to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" (referred to hereafter as "highly similar") and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (referred to hereafter as "no clinically meaningful differences").[4] To be licensed as a biosimilar, an application submitted under section 351(k) must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies demonstrating that the proposed biosimilar is highly similar to the reference product, animal studies, and a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) (see section 351(k)(2)(A)(i)(I) of the PHS Act). FDA has the discretion to determine that an element described in section 351(k)(2)(A)(i)(I) is unnecessary in a 351(k) application (see section 351(k)(2)(A)(ii) of the PHS Act).

To be licensed as an interchangeable, an applicant must provide sufficient information to demonstrate biosimilarity to the reference product, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). The terms "interchangeable" or "interchangeability" mean that the biological product may be substituted

---

[2] The BPCI Act also clarified the statutory authority under which certain protein products will be regulated by amending the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)" and describing procedures for submission of a marketing application for certain "biological products." As amended by the BPCI Act, a "biological product" is defined, in relevant part, as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings" (see section 351(i) of the PHS Act).

[3] Guidance for industry *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (December 2018).

[4] Section 351(i)(2) of the PHS Act; *see also*, guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015) for recommendations on demonstrating biosimilarity, including considerations for demonstrating that a proposed product is highly similar to its reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency.

for the reference product without the intervention of the health care provider who prescribed the reference product (see section 351(i)(3) of the PHS Act).

B. Scientific Considerations for Proposed Biosimilar and Interchangeable Insulin Products

FDA has approved many insulin products in NDAs submitted pursuant to section 505(b)(1) of the FD&C Act. FDA also has approved "follow-on" insulin products in NDAs submitted pursuant to the abbreviated approval pathway described in section 505(b)(2) of the FD&C Act. 505(b)(1) and 505(b)(2) NDAs must meet the same statutory requirements regarding safety and substantial evidence of effectiveness.[5] In the past, FDA generally has advised that clinical studies to evaluate potential risks from immunogenicity associated with proposed insulin products may be necessary to support NDA approval.

In addition, FDA previously has taken the position that data from a comparative clinical immunogenicity study would likely be needed to evaluate the potential risk and clinical impact of immunogenicity of proposed biosimilar and interchangeable insulin products in 351(k) BLAs. This recommendation was consistent with general principles set forth in guidances for industry on proposed biosimilar and interchangeable products in 351(k) BLAs generally,[6] and recommendations historically given in the context of applications submitted pursuant to section 505 of the FD&C Act.

In this guidance, FDA describes its updated thinking that, generally, if a comparative analytical assessment based on state-of-the-art technology supports a demonstration of "highly similar" for a proposed biosimilar or interchangeable insulin product, there would be little or no residual uncertainty regarding immunogenicity; in such instances, the proposed biosimilar or interchangeable insulin product, like the reference product, would be expected to have minimal or no risk of clinical impact from immunogenicity. In such instances, a comparative clinical immunogenicity study generally would be unnecessary to support a demonstration of biosimilarity or interchangeability. For some proposed biosimilar or interchangeable insulin products, a comparative clinical immunogenicity study may still be needed to address residual uncertainty regarding immunogenicity. For example, such a study would be needed to address uncertainty raised by, among other things, differences in certain impurities or novel excipients, but that would be a case-by-case scientific determination in the context of individual applications.

This updated recommendation is based on an extensive multidisciplinary evaluation involving several considerations, including:

- the relatively small, structurally uncomplicated[7] and well-characterized nature of insulin

[5] See section 505(b)-(d) of the FD&C Act.

[6] See e.g., guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015); guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019).

[7] Given their relatively small size among biologics and few post-translational modifications, insulin products are described herein as "structurally uncomplicated."

products in comparison to the vast majority of biologics, which generally allows for a comprehensive analytical evaluation, leaving little or no residual uncertainty regarding risk of clinical impact from immunogenicity;

- extensive experience and literature survey that confirm minimal or no clinical relevance of immunogenicity with insulin product use; and

- scientific thinking on the lack of clinical impact of immunogenicity with insulin product use, as reflected in:

    - Decades of clinical experience with approved insulin products, including the lack of a correlation between immunogenicity and safety or effectiveness as reflected in approved product labeling for insulin products.

    - Public comments received by FDA in response to the May 2019 public meeting, "The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Biosimilar and Interchangeable Insulin Products." FDA held that public meeting in order to receive input from stakeholders on, among other things, the development process for biosimilar and interchangeable insulin products. FDA carefully considered the presentations given at that meeting and comments submitted to the docket, many of which asserted that comparative clinical immunogenicity studies are unnecessary for licensure of biosimilar or interchangeable insulin products.[8]

    - Updated recommendations from the European Medicines Agency, which published a revised guideline in 2015 that no longer recommends a clinical immunogenicity study to support a biosimilar marketing application.[9]

    - Published literature, including reports of clinical trial results in adults and pediatric patients with diabetes and retrospective reviews, which indicated a poor correlation between immunogenicity in insulin-treated patients and clinical impact on safety and efficacy and confirmed minimal or no risk of clinical impact from immunogenicity.[10]

[8] Docket FDA-2019-N-1132, "The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Biosimilar and Interchangeable Insulin Products." Additional comments to the docket discussed concerns about immunogenicity when alternating or switching between medications, including comments regarding the type and amount of data FDA should expect for licensure of products under section 351(k). FDA carefully considered all relevant comments in developing the recommendations contained in this guidance.

[9] European Medicines Agency, Guideline on nonclinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. EMEA/CHMP/BMWP/32775/2005_Rev. 1 (2015)

[10] See, e.g., Richter B and G Neises, 2005, 'Human' insulin versus animal insulin in people with diabetes mellitus, Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD003816; Fineberg, SE, et al, 2007, Immunological Responses to Exogenous Insulin, Endocr Rev, 28(6):625-652; Thalange N, et al, 2016, Development of Insulin Detemir/Insulin Aspart Cross-Reacting Antibodies Following Treatment with Insulin Detemir: 104-week Study in Children and Adolescents with Type 1 Diabetes Aged 2–16 Years, Diabetes Ther 7:713-724; Ilag LL, et al, 2016, Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus® insulin glargine in patients

The science and technology of protein manufacturing has advanced considerably over time. As described in the draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019),[11] improvements in manufacturing processes, process controls, materials, and product testing, as well as characterization tests and studies, have led to evolution in the understanding and extensive characterization of protein products. This is particularly true of insulin products, which, in contrast to other biologics, are relatively small, structurally uncomplicated proteins that are well-understood and well-characterized.[12]

In addition, decades of experience with the development and wide clinical use of insulin products has contributed to scientific understanding of insulin products. There are numerous new drug applications for insulin products listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). Under the guidance of health care practitioners, both short- and long-acting insulin products are used by patients with type 1 and type 2 diabetes, with changes in doses and insulin products over time. To date, this extensive clinical experience with approved insulin products has identified no meaningful clinical impact of immunogenicity on the safety or efficacy of insulin product use. This scientific understanding, as well as better purification methods developed over time, has resulted in diminished concerns about the risk of clinical impacts from immunogenicity for currently approved insulin products.

Current analytical tools used to evaluate quality attributes for insulin products can support a comprehensive analytical comparison thorough enough to support a conclusion that a particular proposed biosimilar insulin product that is "highly similar" to its reference product generally would have little or no residual uncertainty regarding immunogenicity and would be expected, like the reference product, to have minimal or no risk of clinical impact from immunogenicity. In such cases, a comparative clinical immunogenicity study would generally not be necessary to support licensure of a proposed biosimilar or interchangeable product.

III. DATA EXPECTATIONS FOR PROPOSED BIOSIMILAR AND INTERCHANGEABLE INSULIN PRODUCTS

A comparative clinical immunogenicity study generally would be considered unnecessary to

---

with type 1 or type 2 diabetes mellitus, Diabetes Obes Metab 18(2):159-168; Home P, et al, 2018, Anti-Insulin Antibodies and Adverse Events with Biosimilar Insulin Lispro Compared with Humalog Insulin Lispro in People with Diabetes, Diabetes Technol Ther 20(2):160-170. See also Yamada T, et al, 2018, Biosimilar vs. originator insulins: Systematic review and meta-analysis, Diabetes Obes Metab, 20(7):1787-1792; Heinemann L, 2012, Biosimilar insulins, Expert Opin Biol Ther, 12(8):1009-1016; Kuhlmann M and A Schmidt, 2014, Production and manufacturing of biosimilar insulins: implications for patients, physicians, and health care systems, Biosimilars, 4:45-58; Heinemann L and M Hompesch, 2014, Biosimilar Insulins: Basic Considerations, J Diabetes Sci Technol, 8(1):6-13.

[11] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

[12] Regular human insulin is comprised of two non-glycosylated alpha amino acid polymers with a specific, defined sequence consisting of amino acid chain subunits with 21 amino acids and 30 amino acids that form a disulfide-bonded heterodimer, respectively, totaling more than 40 amino acids. All currently approved insulin analogs differ minimally in their amino acid sequence from "regular" human insulin.

support a demonstration of biosimilarity in a 351(k) BLA for a proposed insulin product seeking licensure as a biosimilar or interchangeable if the BLA contains a robust and comprehensive comparative analytical assessment demonstrating that the proposed insulin product is "highly similar" to its proposed reference product with very low residual uncertainty regarding immunogenicity and the application otherwise meets the standards for licensure under section 351(k) of the PHS Act.[13]

FDA recommends that a 351(k) BLA for a biosimilar or interchangeable insulin product contain, among other things:

- Adequate chemistry, manufacturing, and control (CMC) information to fulfill product quality-related requirements described in 21 CFR 601.2, including a validated manufacturing process,[14] and to support an inspection of the facility that is the subject of the application (i.e., a facility in which the proposed biological product is manufactured, processed, packed, or held);[15]

- A comprehensive and robust comparative analytical assessment between the proposed insulin product and the proposed reference product demonstrating that the proposed insulin product is "highly similar" to the reference product;[16]

- A comparative clinical pharmacology study between the proposed insulin product and the reference product that provides a time-concentration profile and a time-action profile

[13] See section 351(i)(2) of the PHS Act; see also, guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015) for recommendations on determining biosimilarity, including considerations for demonstrating that a proposed product is highly similar to its reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency.

[14] All product applications should contain a complete and thorough CMC section that provides appropriate information (e.g., characterization, adventitious agent safety, process controls, and specifications) necessary to support that the manufacturing process consistently delivers a product with the intended characteristics. See e.g., 21 CFR Parts 210, 211, 314, 600 through 680, and 820; guidances for industry, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016); *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Questions and Answers* (April 2018); *Q11 Development and Manufacture of Drug Substances* (November 2012); *Q11 Development and Manufacture of Drug Substances—Questions and Answers (Chemical Entities and Biotechnological/Biological Entities)* (February 2018); *Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use* (August 1996); and *Process Validation: General Principles and Practices* (January 2011). See also draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019). This guidance, when finalized, will represent FDA's current thinking on that topic.

[15] Section 351(k)(2)(A)(i)(V) and (k)(3) of the PHS Act.

[16] See section 351(k)(2)(A)(i) of the PHS Act and guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015). As outlined in that guidance and in the draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019), this generally will include: (1) comprehensive, robust comparative physicochemical and functional studies (these may include biological assays, binding assays, and enzyme kinetics) to evaluate the proposed product and the reference product; and (2) side-by-side analyses of an appropriate number of lots (≥ 10 lots of the reference product and ≥ 6 lots of the proposed product), where results are evaluated using pre-specified criteria. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

over the duration of action of each product based on reliable measures of systemic exposure and glucose response (e.g., glucose infusion rate), using an euglycemic clamp procedure or other appropriate test;[17] and

- An immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity. This justification may reference other data and information in the application, e.g., the comparative analytical assessment with very low residual uncertainty described in the preceding section.

With regard to proposed interchangeable products, as described in the guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019), advances in analytics may allow for extended analytical characterization that affects the extent of other data and information needed to support a demonstration of interchangeability and may in certain circumstances lead to a more selective and targeted approach to clinical studies intended to support a demonstration of interchangeability. Consistent with these statements in the guidance and the recommendations in this section, a comprehensive and robust comparative analytical assessment between a proposed interchangeable insulin product and the reference product demonstrating that the proposed interchangeable product is "highly similar" to the reference product with very low residual uncertainty about immunogenicity generally would mean that an applicant would not need to conduct a comparative clinical immunogenicity study, e.g., a switching study, to support licensure under section 351(k)(4) of the PHS Act so long as the statutory criteria for licensure as an interchangeable are otherwise met.

Applicants should consult with the Division of Metabolism and Endocrinology Products (DMEP) in the Office of New Drugs before submitting a 351(k) BLA to discuss any data and information that may be needed. To determine whether a specific development program meets the criteria outlined in this guidance, an applicant should request a Biosimilar Biological Product Development (BPD) meeting, e.g., a Type 2 meeting for targeted advice based on substantive review of summary analytical data or a Type 3 meeting for an in-depth data review and recommendations regarding comprehensive analytical similarity data.[18]

IV. CLINICAL EVALUATIONS OF IMMUNOGENICITY

The recommendations described above with regard to the need for comparative clinical immunogenicity studies are applicable when a proposed biosimilar or interchangeable insulin product is demonstrated to be "highly similar," based upon a robust, comprehensive comparative analytic assessment to its proposed reference product such that there is little or no residual uncertainty related to clinical impact from immunogenicity. In other circumstances, there may

[17] See section 351(k)(2)(A)(i) of the PHS Act; see also guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016) for recommendations regarding exposure and response assessments to support a demonstration of biosimilarity.

[18] BsUFA II goals letter titled "BsUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022" available on the FDA website at https://www.fda.gov/downloads/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/UCM521121.pdf; draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic.

be residual uncertainty regarding immunogenicity and a comparative clinical immunogenicity study may be needed to support a demonstration of biosimilarity or interchangeability. For example, additional data, including possibly a comparative clinical immunogenicity study, may be necessary to support licensure of a proposed biosimilar or interchangeable insulin product for which differences in certain impurities or novel excipients give rise to questions or residual uncertainty related to immunogenicity.

If additional considerations relating to immunogenicity exist for a proposed product, licensure as a biosimilar or interchangeable under section 351(k) of the PHS Act may still be possible if such considerations are adequately addressed. Contact the DMEP in the Office of New Drugs to discuss your proposed development program and to request a BPD meeting, as appropriate.