4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-D-2102]

Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations." This draft guidance describes the Agency's recommendations on the design and evaluation of comparative analytical studies intended to support a demonstration that a proposed therapeutic protein product is biosimilar to a reference product licensed under the Public Health Service Act (PHS Act). Additionally, this draft guidance is intended to provide recommendations to sponsors on the scientific and technical information for the chemistry, manufacturing, and controls (CMC) portion of a marketing application for a proposed product submitted under the PHS Act. This draft guidance revises the guidance entitled "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" that was published on April 30, 2015.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure

that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2019-D-2102 for "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469,

September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Sandra Benton, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 6522, Silver Spring, MD 20993-0002, 301-796-1042; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations." This draft guidance describes the Agency's recommendations on the design and evaluation of comparative analytical studies intended to support a demonstration that a proposed therapeutic protein product is biosimilar to a reference product licensed under section 351(a) of the PHS Act (42 U.S.C. 262(a)). Additionally, this draft guidance is intended to provide recommendations to sponsors on of the scientific and technical information for the CMC portion of a marketing application for a proposed product submitted under section 351(k) of the PHS Act. Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products.

The Biologics Price Competition and Innovation Act of 2009 was enacted as part of the Patient Protection and Affordable Care Act (Pub. L. 111-148) on March 23, 2010, and created an abbreviated licensure pathway under section 351(k) of the PHS Act for biological products demonstrated to be biosimilar to, or interchangeable with, a reference product. Under this abbreviated licensure pathway, FDA will license a proposed biological product submitted under section 351(k) of the PHS Act if, among other things, FDA determines that the information submitted in the application is sufficient to show that the biological product is biosimilar to the reference product.

In the *Federal Register* of February 15, 2012 (77 FR 8884), FDA announced the availability of the draft guidance entitled "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product." FDA received a number of comments on the draft guidance. In response to these comments, FDA provided further clarification on the general principles described through a final guidance entitled "Quality Considerations in Demonstrating

Biosimilarity of a Therapeutic Protein Product to a Reference Product," which was announced in the *Federal Register* of April 30, 2015 (80 FR 24257).

In the *Federal Register* of September 22, 2017 (82 FR 44425), FDA announced the availability of the draft guidance entitled "Statistical Approaches to Evaluate Analytical Similarity." FDA received a number of comments on the draft guidance. Comments submitted to the docket addressed a range of issues that could impact the cost and efficiency of biosimilar development, including the number of reference product lots the draft guidance would have recommended that biosimilar developers sample in their evaluation of high similarity and the statistical methods for this evaluation. After considering the public comments that FDA received, FDA determined it would withdraw the draft guidance to give further consideration to the scientific and regulatory issues involved. FDA announced the withdrawal of the draft guidance on June 21, 2018, with the intention of issuing future draft guidance on the evaluation of analytical data to support a demonstration that a proposed biosimilar product is highly similar to a reference product.

This draft guidance revises the guidance issued on April 30, 2015. FDA has adjusted the title of this draft guidance to more clearly communicate that this draft guidance includes the Agency's recommendations on the design and evaluation of comparative analytical studies intended to support a demonstration that a proposed therapeutic protein product is biosimilar to a reference product. In addition to editorial and clarifying edits, the draft guidance includes a section that fulfills the Biosimilar User Fee Act II commitment to publish a revised draft or final guidance, describing statistical considerations for the analysis of analytical similarity data intended to support a demonstration of "highly similar" for biosimilar biological products within

18 months after the close of the public comment period for the withdrawn guidance, "Statistical Approaches to Evaluate Analytical Similarity."

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations." 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. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information found in FDA regulations, which are not expected to change as a result of the guidance. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information related to the submission of: (1) an investigational new drug application, which is covered under 21 CFR part 312 and approved under OMB control number 0910-0014; (2) a new drug application, which is covered under 21 CFR 314.50 and approved under OMB control number 0910-0001; (3) a biologics license application (BLA) under section 351(a) of the PHS Act, which is covered under part 601 (21 CFR part 601) and approved under OMB control number 0910-0338; and (4) a BLA under section 351(k), which is covered under part 601 and approved under OMB control number 0910-0719.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, or https://www.regulations.gov.

Dated: May 16, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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