4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-D-0154]

Considerations in Demonstrating Interchangeability With a Reference Product; 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 final guidance for industry entitled "Considerations in Demonstrating Interchangeability With a Reference Product." This guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product is interchangeable with a reference product for the purposes of submitting a marketing application or supplement under the Public Health Service Act (PHS Act). This guidance is one in a series of guidances that FDA has developed to implement the Biologics Price Competition and Innovation Act of 2009 (BPCI Act).

DATES: The guidance was posted to the Agency's website on May 10, 2019.

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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-2017-D-0154 for "Considerations in Demonstrating Interchangeability With a Reference Product." 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 this 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 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 guidance for industry entitled "Considerations in Demonstrating Interchangeability With a Reference Product." This guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product (proposed interchangeable product) is interchangeable with a reference product for the purposes of submitting a marketing application or supplement under section 351(k) of the PHS Act (42 U.S.C. 262(k)).

Section 351(k) of the PHS Act sets forth the requirements for an application for a proposed biosimilar product and for an application or a supplement for a proposed interchangeable product. Specifically, section 351(k)(4) provides that upon review of an application submitted under section 351(k), or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application (or supplement) is sufficient to show that the biological product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient; and for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between 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. Section 351(i) of the PHS Act states that the term interchangeable or interchangeability, in reference to a biological product that is shown to meet the standards described in section 351(k)(4), means that the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.

This guidance gives an overview of important scientific considerations in demonstrating interchangeability with a reference product, including:

- The data and information recommended to support a demonstration of interchangeability
- Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability
- Considerations regarding the comparator product in a switching study or studies
- Abbreviated considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products

This guidance finalizes the draft guidance issued on January 18, 2017. Changes made to the guidance took into consideration the comments received. FDA provided changes to clarify its recommendations for demonstrating interchangeability with the reference product. FDA intends to provide more detailed recommendations on the data and information recommended to support the proposed interchangeable product's presentation and related issues in a separate guidance.

In the *Federal Register* of January 18, 2017 (82 FR 5579), FDA announced the availability of the draft guidance for industry "Considerations in Demonstrating Interchangeability With a Reference Product." FDA requested comment on the following questions: (1) are there considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products and (2) how, if at all, should the Agency consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed. The comments submitted in response to these questions are being considered; FDA will address these topics in future guidance, as appropriate.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "Considerations in Demonstrating Interchangeability With a Reference Product." 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. 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 under 21 CFR part 312 have been approved under OMB control number 0910-0014; the collections of information under 21 CFR part 601 have been approved under OMB control number 0910-0338; and the collections of information under section 351(k) of the PHS Act have been approved under OMB control number 0910-0719.

III. Electronic Access

Persons with access to the internet may obtain the 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 10, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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