



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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

Considerations in Demonstrating Interchangeability With a Reference Product; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Considerations in Demonstrating Interchangeability With a Reference Product.”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 or proposed 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: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments 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): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, 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; Draft Guidance for Industry; Availability.” 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 Division of Dockets Management 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 Division of Dockets Management. 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: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

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 Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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. 51, rm. 6340, 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 “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 or proposed 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)). The BPCI Act amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act Of 2010 (Affordable Care Act) (Pub. L. 111-148)).

Section 351(k) of the PHS Act sets forth the requirements for an application for a proposed biosimilar product and 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 an 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 subsection 351(k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

This guidance gives an overview of important scientific considerations in demonstrating interchangeability, including:

- The data and information needed to support a demonstration of interchangeability;
- Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability;
- Recommendations regarding the use of U.S.-licensed reference products in a switching study or studies; and
- Considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products.

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 topics sponsors should consider when seeking to demonstrate that a proposed therapeutic protein product is interchangeable with a reference product. It does not establish any rights for any person and is not binding on FDA or the public.

## II. Topics for Comment

In addition to comment on the draft guidance, we also invite general comments on interchangeability, including comments on regulation of an interchangeable product over its lifecycle, as well as comments on the following topics:

1. Since the mid-1990s, FDA has approved manufacturing changes for biological products based on data from comparability assessments comparing the pre-change and post-change product using comparative analytical, and, when necessary, animal and/or clinical (e.g., pharmacokinetic, immunogenicity) studies. A demonstration of comparability between pre- and post-change product supports a determination that the safety and efficacy profile remains

the same for the product. With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products? Your comments should include the scientific rationale and justification for your recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.

2. As explained in the guidance “Considerations in Demonstrating Interchangeability With a Reference Product,” FDA expects that sponsors seeking an interchangeability determination will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product’s licensed conditions of use. 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? Your comments should include the scientific rationale and justification for your recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.

### III. Paperwork Reduction Act of 1995

This draft 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.

#### IV. Electronic Access

Persons with access to the Internet may obtain the draft guidance at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>,

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>,

or <https://www.regulations.gov>.

Dated: January 12, 2017.

Leslie Kux,

Associate Commissioner for Policy.

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