



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA-2018-D-2456]**

**Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Results From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies; 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 “Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Results From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.” This document provides guidance to sponsors on the evidence necessary to demonstrate the effectiveness of investigational new drugs or new drug uses intended for slowly progressive, low-prevalence rare diseases that are associated with substrate deposition and are caused by single enzyme defects. This guidance applies only to those low-prevalence rare diseases with a well-characterized pathophysiology and in which changes in substrate deposition can be readily measured in relevant tissue or tissues. This guidance incorporates the comments received for and finalizes the draft guidance of the same name issued on July 27, 2018.

**DATES:** The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

**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-2018-D-2456 for “Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Results From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.” 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.govinfo.gov/content/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 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:** Hylton Joffe, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6300, Silver Spring, MD 20993-0002, 301-796-1954; 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 final guidance for industry entitled “Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Results From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.” This document provides guidance to sponsors on the evidence necessary to demonstrate the effectiveness of investigational new drugs or new drug uses intended for slowly progressive, low-prevalence rare diseases that are associated with substrate deposition and are caused by single enzyme defects. This guidance applies only to those low-prevalence rare diseases with a well-characterized pathophysiology and in which changes in substrate deposition can be readily measured in relevant tissue or tissues.

This guidance finalizes the draft guidance of the same name issued on July 27, 2018 (83 FR 35653). FDA considered comments received on the draft guidance in devising this final guidance. Changes from the draft to the final guidance include the following: clarification that a “low prevalence” condition may be defined as one affecting a very small population (e.g., approximately a few thousand persons or fewer in the United States); clarification that, in the absence of nonhuman data to guide a potentially efficacious dose, animal toxicology data can inform a safe starting human dose; and removal of language regarding assay versus intrasubject variability--approaches to manage intrasubject variability within specific drug development programs can be addressed via formal sponsor meetings with the relevant division at FDA.

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 “Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Results From Single Enzyme

Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.” 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.

## II. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 50 have been approved under OMB control number 0910-0755. The collections of information for expedited programs in the guidance for industry entitled “Expedited Programs for Serious Conditions--Drugs and Biologics” (available at <https://www.fda.gov/media/86377/download>) have been approved under OMB control number 0910-0765.

## III. Electronic Access

Persons with access to the internet may obtain the guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics>, or <https://www.regulations.gov>.

**Dated:** March 10, 2020.

**Lowell J. Schiller,**

*Principal Associate Commissioner for Policy.*

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