Low-Frequency Molecular Subsets of a Disease.'' This guidance is intended to assist sponsors in designing drug development programs to generate the evidence needed to demonstrate efficacy of a targeted therapy across molecular subsets within a disease where some molecular alterations may occur at low frequencies.

In recent years, advances in our understanding of the molecular pathology of many diseases have led to the development of targeted therapies. Although variability in drug response has long been recognized in drug development, targeted therapies present new challenges in addressing the heterogeneity in drug response because the pharmacological effect of a targeted therapy is often related to a particular molecular alteration (*e.g.,* a mutation, gene fusion, epigenetic change, etc.). Many clinically defined diseases are influenced or caused by a range of different molecular alterations, some of which may be rare, that impact a common target protein or pathway involved in the disease pathogenesis. This heterogeneity in the molecular etiology of a given disease can result in differential effects of a targeted therapy among patients with the same disease but who have different molecular alterations. Therefore, the type and quantity of evidence that is needed to demonstrate efficacy across molecular subsets within a disease needs to be clearly specified.

This guidance addresses the following important topics in evaluating the benefits and risks of targeted therapeutics within a disease where some molecular alterations may occur at low frequencies:

- Identification of patients for inclusion in clinical trials
- Interpretation of study results and generalizability of findings to the study population
- Benefit-risk determination and therapeutic product labeling
- Refining the indicated population after the initial approval

This final guidance incorporates public comments to the draft guidance published in December of 2017 and includes minimal revisions for clarity.

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 ''Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease.'' 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. 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: October 10, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–22437 Filed 10–15–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–D–3268]

Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings; 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 ''Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings.'' The purpose of this draft guidance is to assist sponsors of drug and biological products for the treatment of rare diseases in planning and conducting more efficient and productive pre-investigational new drug application (pre-IND) meetings. Drug development for rare diseases has many challenges related to the nature of these diseases. This draft guidance is intended to advance and facilitate the development of drugs and biological products for the treatment of rare diseases.

DATES: Submit either electronic or written comments on the draft guidance by December 17, 2018 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–2018–D–3268 for ''Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings; Draft Guidance for Industry.'' 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 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: Lucas Kempf, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6460, Silver Spring, MD 20993–0002, 301–796–1140; 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 ''Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings.'' This guidance is intended to assist sponsors of drug and biological products for the treatment of rare diseases in planning and conducting more efficient and productive pre-IND meetings through a discussion of selected issues commonly encountered in the early phases of rare disease drug development. Although these issues are encountered in other drug development programs, the issues are frequently more difficult to address in the context of a rare disease than in the context of a common disease, of which there is often greater and more widespread medical experience. A rare disease is defined in section 526(a)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb(a)(2)) as a disease or condition that affects fewer than 200,000 people in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Most rare diseases affect far fewer than 200,000 people.

Most rare disorders are serious conditions with no approved treatments, and rare disease patients often have considerable unmet medical needs. Collectively, rare diseases are highly diverse. FDA is committed to helping sponsors of drugs for rare diseases have successful pre-IND meetings that address the particular challenges posed by each drug.

This guidance addresses the following important topics related to pre-IND meetings:

- Regulatory considerations across various FDA disciplines including chemistry, manufacturing, and controls; nonclinical; clinical pharmacology; and clinical.
- Additional considerations, including expedited programs for serious conditions, companion diagnostics, orphan drug incentives, pediatric studies, and data standards.

Early consideration of these issues allows sponsors to efficiently and adequately plan for a productive pre-IND meeting with FDA.

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 ''Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings.'' 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. The 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. 3501–3520). The collections of information in 21 CFR parts 312 and 314 have been approved under OMB control numbers 0910–0014 and 0910–0001, respectively. The collection of information resulting from the draft guidance for industry ''Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products'' (available at *https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm590547.pdf*) has been approved under OMB control number 0910–0429. The collection of information resulting from the guidance for industry ''Expedited Programs for Serious Conditions—Drugs and Biologics'' (available at *https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm358301.pdf*) has been approved under OMB control number 0910–0765.

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/default.htm,* or *https://www.regulations.gov.*

Dated: October 10, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–22435 Filed 10–15–18; 8:45 am]

BILLING CODE 4164–01–P