DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–D–2818]

Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled ''Rare Diseases: Common Issues in Drug Development.'' This draft guidance assists sponsors of drug and biological products intended to treat or prevent rare diseases in conducting more efficient and successful development programs through discussions of selected issues commonly encountered in rare disease drug development. This draft guidance addresses the following important aspects of drug development: Adequate description and understanding of the disease's natural history, adequate understanding of the pathophysiology of the disease and the drug's proposed mechanism of action, nonclinical pharmacotoxicology considerations to support the proposed clinical investigation or investigations, reliable endpoints and outcome assessment, standard of evidence to establish safety and effectiveness, drug manufacturing considerations during drug development, participation of patients, caretakers, and advocates in development programs, and interactions with the Agency. This guidance revises and replaces the draft guidance of the same name issued on August 17, 2015.

DATES: Submit either electronic or written comments on the draft guidance by April 2, 2019 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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–2015–D–2818 for ''Rare Diseases: Common Issues in Drug Development; 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 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.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled ''Rare Diseases: Common Issues in Drug Development.'' This draft guidance assists sponsors of drug and biological products intended to treat or prevent rare diseases in conducting more efficient and successful development

programs through a discussion of selected issues commonly encountered in rare disease drug development. This draft guidance addresses the following important aspects of drug development:

- Adequate description and understanding of the disease's natural history
- Adequate understanding of the pathophysiology of the disease and the drug's proposed mechanism of action
- Nonclinical pharmacotoxicology considerations to support the proposed clinical investigation or investigations
- Reliable endpoints and outcome assessment
- Standard of evidence to establish safety and effectiveness
- Drug manufacturing considerations during drug development

This guidance revises and replaces the draft guidance for industry of the same name issued on August 17, 2015 (80 FR 49246). This revision includes the following:

- Updates to the natural history section
- Inclusion of issues for evaluation of biomarkers for consideration as surrogate endpoints
- Description of nonclinical flexibility
- Additional information on historical (external) controls and early randomization
- Addition of safety section
- Retitled Chemistry, Manufacturing, and Controls section to Pharmaceutical Quality Considerations
- Additional information on changes to drug substance or manufacturing process with clarification on areas of flexibility
- Addition of a considerations section addressing several topics including participation of patients, caretakers, and advocates; consideration of pediatric issues; and interactions 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: Common Issues in Drug Development.'' 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 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 following collections of information in the draft guidance have been approved under OMB control number 0910–0001:

- Submitting under 21 CFR 314.50(c)(1)(iv) and (d)(3) (§ 314.50(c)(1)(iv) and (d)(3)) a summary of the nonclinical pharmacology and toxicology section and the human pharmacokinetics and bioavailability section of new drug application (NDAs);
- Submitting under § 314.50(d)(1)(i) chemistry, manufacturing, and controls information, including the drug substance, for the content and format of a NDA for rare diseases; and
- Submitting under § 314.50(d)(5) and (d)(5)(iv) clinical data of a drug, including a description of any other data information relevant to an evaluation of the safety and effectiveness of a drug.

The following collections of information in the draft guidance have been approved under OMB control number 0910–0014:

- Submitting under 21 CFR 312.23(a)(6)(i) (§ 312.23(a)(6)(i)) a protocol for the duration of a trial and the criteria to enter a trial and under § 312.23(a)(6)(i), (a)(6)(iii)(d) and (g) a description of an estimate of patients that will be involved in a trial, including a description of the safety exclusions and a description of clinical procedures, laboratory, or other methods;
- Submitting under § 312.23(a)(3)(i) a brief introductory statement and general investigational plan, including the route of administration of a drug;
- Submitting under § 312.23(a)(7) and (a)(7)(iv)(a) chemistry, manufacturing, and controls information for the content and format of an investigational new drug application (IND) and the safety and effectiveness of such information;
- Submitting under § 312.23(a)(8) and (a)(8)(i) pharmacology, toxicology, and drug disposition information for rare diseases;
- Submitting under 312.23(a)(10)(iii) plans for assessing pediatric safety and effectiveness;
- Submitting under § 312.32(c)(1) IND safety reports;
- Submissions under §§ 312.305(b) and 312.310(b) for expanded access uses and treatment of an individual patient.

The collections of information in 21 CFR part 316 for submitting the content and format of NDAs for orphan drugs have been approved under OMB control number 0910–0167.

The collections of information under § 314.80 for submitting postmarketing reporting of adverse drug experiences have been approved under OMB control number 0910–0230.

The collections of information under §§ 312.47 and 312.82 for requesting meetings with FDA about drug development programs have been approved under OMB control number 0910–0429.

The following collections of information have been approved under OMB control number 0910–0765: (1) Requests under 21 CFR part 314, subpart H to grant accelerated approval for INDs to treat rare diseases that are serious or life threatening and (2) as a basis for accelerated approval requests, submissions of evidence to support that an endpoint reasonably likely to predict clinical benefit.

III. Electronic Access

Persons with access to the internet may obtain the guidance at *https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, https://www.fda.gov/Biologics;BloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm,* or *https://www.regulations.gov.*

Dated: January 16, 2019.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–D–1387]

Safety and Performance Based Pathway; Guidance for Industry and Food and Drug Administration Staff; 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 entitled ''Safety and Performance Based Pathway,'' which was previously issued in draft version entitled ''Expansion of the Abbreviated 510(k) Program: Demonstrating Substantial Equivalence Through Performance Criteria.'' This final