

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 This draft guidance addresses the following important aspects of drug development: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This guidance revises and replaces the draft guidance for industry of the same name issued on August 17, 2015 (80 FR 49246).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This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Rare Diseases: Common Issues in Drug Development."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This draft guidance refers to previously approved collections of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The following collections of information in the draft guidance have been approved under OMB control number 0910–0001: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/BiologicsBloodVaccines/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

guidance provides FDA's current thinking on using performance criteria to demonstrate substantial equivalence for premarket notification (510(k)) submissions. The intent of the final guidance is to describe an optional program for certain well understood device types, where a submitter could demonstrate that a new device meets FDA-identified performance criteria instead of directly comparing the performance of the new device to a specific, submitter-identified predicate device as part of a demonstration of substantial equivalence.

**DATES:** The announcement of the guidance is published in the **Federal Register** on February 1, 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-2018-D-1387 for "Safety and Performance Based Pathway; Guidance for Industry and Food and Drug Administration Staff." 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)).

An electronic copy of the guidance document is available for download from the internet. See the **SUPPLEMENTARY INFORMATION** section for

information on electronic access to the guidance. Submit written requests for a single hard copy of the guidance document entitled "Safety and Performance Based Pathway" to the Office of the Center Director, Guidance and Policy Development, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5431, 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 request.

**FOR FURTHER INFORMATION CONTACT:** Sonja Fulmer, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5451, Silver Spring, MD 20993-0002, 240-402-5979; 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, 240-402-7911.

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Background**

FDA has explained and clarified, through the guidance entitled "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)],"<sup>1</sup> how it makes substantial equivalence decisions under section 513(i)(1)(A) of the Federal, Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360c(i)(1)(A)). Substantial equivalence is rooted in comparisons between new devices and predicate devices. However, the FD&C Act does not preclude FDA from using performance criteria to facilitate this comparison. If a legally marketed device performs at certain levels relevant to its safety and effectiveness, and a new device meets those levels of performance for the same characteristics, FDA could find the new device as safe and effective as the legally marketed device. Instead of reviewing data from direct comparison testing between the two devices, FDA could support a finding of substantial equivalence with data demonstrating the new device meets the level of performance of an appropriate predicate device(s). Under the approach expanded in this guidance, a submitter could

<sup>1</sup> Available at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443>.

satisfy the requirement to compare its device with a legally marketed device by, among other things, independently demonstrating conformance to all performance criteria necessary to support a finding of substantial equivalence for a device type established in FDA guidance, rather than using direct predicate comparison testing for some of the performance characteristics.

Use of objective performance criteria developed for this approach may promote predictability and consistency in the review of 510(k) submissions, thereby reducing burdens on the Agency and possibly review times on individual submissions. At the same time, this approach satisfies the statutory standard for demonstrating substantial equivalence. The reviews of Safety and Performance Based Pathway 510(k) submissions remain subject to the same timeframes as Traditional 510(k) submissions, but FDA anticipates that faster review timeframes may be possible for the Safety and Performance Based Pathway 510(k) submissions. As a result, this pathway is intended to promote the public health by helping patients gain more timely access to new medical devices that are high quality, safe, and effective. Moreover, as FDA stated in its April 2018 Medical Device Safety Action Plan,<sup>2</sup> this approach would provide an opportunity for device developers to demonstrate that their product meets these modern performance criteria as well as the ability to do so in a more straightforward and efficient manner than under the traditional 510(k) Pathway. Through this more transparent approach, FDA may drive greater market competition to develop safer devices. Manufacturers would be able to demonstrate that their products meet established performance criteria (including those related to safety), and thus, may be able to more readily demonstrate that their products perform equivalent to or better than other devices on the market (including that they are safer).

FDA considered comments received on the draft guidance entitled “Expansion of the Abbreviated 510(k) Program: Demonstrating Substantial Equivalence Through Performance Criteria” that appeared in the **Federal Register** of April 12, 2018 (83 FR 15847). FDA has changed the name of this draft guidance to the “Safety and

Performance Based Pathway” and revised it as appropriate in response to the comments received. Among others, FDA received comments requesting additional clarity on the device types that will be appropriate for the Safety and Performance Based Pathway and how the performance criteria will be developed. FDA intends to maintain a list of device types appropriate for the Safety and Performance Based Pathway on the FDA website. Additionally, industry and other stakeholders may suggest device types for which FDA should consider establishing performance criteria, by for example, identifying products for which there are comprehensive FDA-recognized consensus standards. FDA also welcomes evidence-based suggestions on what the performance criteria should be for such device types. FDA intends to develop performance criteria for appropriate device types through guidance in accordance with the good guidance practices regulation (§ 10.115), which includes an opportunity for FDA to receive input from stakeholders.

## II. Significance of Guidance

This guidance is being issued consistent with FDA’s good guidance practices regulation (§ 10.115). The guidance represents the current thinking of FDA on the “Safety and Performance Based Pathway.” 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.

## III. Electronic Access

Persons interested in obtaining a copy of the guidance may do so by downloading an electronic copy from the internet. A search capability for all Center for Devices and Radiological Health guidance documents is available at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>. This guidance document is also available at <https://www.regulations.gov> or <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>. Persons unable to download an electronic copy of “Safety and Performance Based Pathway” may send an email request to [CDRH-Guidance@fda.hhs.gov](mailto:CDRH-Guidance@fda.hhs.gov) to receive an electronic copy of the document. Please use the document number 17046 to identify the guidance you are requesting.

## IV. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information. 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 in 21 CFR 807, subpart E have been approved under OMB control number 0910–0120.

Dated: January 15, 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–4629]

#### Survey Methodologies To Assess Risk Evaluation and Mitigation Strategies Goals That Relate to Knowledge; 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 “Survey Methodologies to Assess REMS Goals That Relate to Knowledge; Draft Guidance For Industry.” This draft guidance provides recommendations to industry on conducting risk evaluation and mitigation strategies (REMS) assessment surveys used to evaluate respondent knowledge of REMS-related information. Most applicants use surveys to evaluate patients’ and healthcare providers’ understanding of the serious risks associated with, and safe use of, their drugs to assess REMS knowledge goals. The draft guidance discusses general principles and recommendations related to conducting REMS assessment knowledge surveys, including study design, survey instrument development, survey data collection and processing, and data analysis.

**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:

<sup>2</sup> “Medical Device Safety Action Plan: Protecting Patients, Promoting Public Health,” April 2018, available at <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM604690.pdf>.