

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-2017-D-6528 for “Refusal of Inspection by a Foreign Food Establishment or Foreign Government.” 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 the guidance to the Compliance Policy Staff/Office of Compliance, Center for Food Safety and Applied Nutrition (HFS-605), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740. Send two self-addressed adhesive labels to assist that office in processing your request. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance.

FOR FURTHER INFORMATION CONTACT: Yinqing Ma, Center for Food Safety and Applied Nutrition (HFS-605), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-2479.

SUPPLEMENTARY INFORMATION:

I. Background

We are announcing the availability of a guidance for industry entitled “Refusal of Inspection by a Foreign Food Establishment or Foreign Government.” We are issuing this guidance consistent with our good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on this topic. 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.

In the **Federal Register** of December 12, 2017 (82 FR 58410), we made available a draft guidance for industry entitled “Refusal of Inspection by a Foreign Food Establishment or Foreign Government” and gave interested parties an opportunity to submit comments by February 26, 2018, for us to consider before beginning work on the final version of the guidance. We received several comments on the draft guidance and have modified the final guidance where appropriate. Changes to the guidance include: provided additional information on FDA’s inspection authority; clarified that the investigator will inform the owner, operator, or agent in charge of the establishment when they consider their action to be a refusal and will explain the consequences of the refusal; and clarified that the Agency will make the final decision regarding refusal and listing on Import Alert 99-32. In addition, we made editorial changes to improve clarity. The guidance announced in this notice finalizes the draft guidance dated December 2017.

II. Electronic Access

Persons with access to the internet may obtain the guidance at either

<https://www.fda.gov/FoodGuidances> or <https://www.regulations.gov>. Use the FDA website listed in the previous sentence to find the most current version of the guidance.

Dated: October 17, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022-22884 Filed 10-20-22; 8:45 am]

BILLING CODE 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA 2016-D-4460]

Multiple Endpoints in Clinical Trials; 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 “Multiple Endpoints in Clinical Trials.” This guidance provides sponsors and review staff with the Agency’s thinking about the problems posed by multiple endpoints in the analysis and interpretation of study results and how these problems can be managed in clinical trials for human drugs, including drugs subject to licensing as biological products. This guidance finalizes the draft guidance of the same title issued on January 13, 2017.

DATES: The announcement of the guidance is published in the **Federal Register** on October 21, 2022.

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 2016-D-4460 for “Multiple Endpoints in Clinical Trials.” 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, 240-402-7500.

- 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, 240-402-7500.

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 to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), 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:

Scott N. Goldie, Center for Drug Evaluation and Research, Office of Biostatistics, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-796-2055, 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 guidance for industry entitled “Multiple Endpoints in Clinical Trials.” This guidance describes various strategies for grouping and ordering endpoints for analysis of a drug’s effects and applying some well-recognized statistical methods for managing multiplicity within a clinical trial to control the chance of making erroneous conclusions about a drug’s effects. FDA’s International Conference on Harmonization (ICH) guidance for industry “E9 Statistical Principles for Clinical Trials” is a broad-ranging guidance that includes discussion of

multiple endpoints. This guidance provides greater detail on the topic of multiple endpoints.

Failure to account for multiplicity when there are several clinical endpoints evaluated in a clinical trial can lead to false positive conclusions regarding the effects of the drug. The regulatory concern regarding multiplicity arises principally in the evaluation of clinical trials intended to demonstrate effectiveness and support drug approval; however, this issue is important throughout the drug development process.

The focus of this guidance is control of the Type 1 error rate for the planned primary and secondary endpoints of a clinical trial so that the major findings are well supported. Multiplicity adjustments provide a means for controlling the Type 1 error rate when there are multiple analyses of the drug’s effects. The issues of multiplicity and methods to address them are illustrated in the guidance with examples of different study endpoints. Both the issues and methods that apply to multiple endpoints also apply to other sources of multiplicity, including multiple doses, time points, or study population subgroups.

This guidance finalizes the draft guidance of the same title that published January 13, 2017 (82 FR 4353). FDA considered comments received on the draft guidance as the guidance was finalized. Changes from the draft to the final guidance include clarifications for some of the potential issues caused by including multiple endpoints in clinical trials and clarifications for some of the strategies for handling these issues. In addition, editorial changes were made to improve clarity by reducing redundancies in the text.

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 “Multiple Endpoints in Clinical Trials.” 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

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of

information are subject to review by OMB under the PRA. The collections of information in 21 *CFR* 312.23 for the content and format of investigational new drug applications have been approved under OMB control number 0910-0014. The collections of information in 21 *CFR* part 314 for submitting applications for FDA approval to market a new drug have been approved under OMB control number 0910-0001. The collections of information in 21 *CFR* 201.56 and 201.57 for preparing and submitting labeling have been approved under OMB control number 0910-0572.

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/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

Dated: October 17, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-D-1061]

Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Healthcare; Draft 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 the draft guidance entitled “Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Healthcare.” FDA has developed this draft guidance to propose select updates to the guidance that clarify how the program may be applicable to certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions in populations impacted by health and/or healthcare disparities. This draft guidance is not final nor is it for implementation at this time.

DATES: Submit either electronic or written comments on the draft guidance by December 20, 2022 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-2022-D-1061 for “Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Healthcare.” 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, 240-402-7500.

- **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>.

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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 draft guidance document entitled “Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Healthcare” to the Office of Policy, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5431, Silver Spring, MD 20993-0002; or the Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and