



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-4460]

Multiple Endpoints in Clinical Trials; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Multiple Endpoints in Clinical Trials.” This draft guidance provides sponsors and review staff with the Agency’s thinking about the problems posed by multiple endpoints in the analysis and interpretation of study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. Most clinical trials performed in drug development contain multiple endpoints to assess the effects of the drug and to document the ability of the drug to favorably affect one or more disease characteristics. The purpose of this guidance is to describe various strategies for grouping and ordering endpoints for analysis and applying some well-recognized statistical methods for managing multiplicity within a study to control the chance of making erroneous conclusions about a drug’s effects.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://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 <http://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): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, 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; Draft Guidance for Industry; Availability." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management 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 <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. 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:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://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 Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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 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 draft guidance document.

FOR FURTHER INFORMATION CONTACT: Scott Goldie, Center for Drug Evaluation and Research, 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 draft guidance for industry entitled “Multiple Endpoints in Clinical Trials.” This guidance describes various strategies for grouping and ordering endpoints for analysis and applying some well-recognized statistical methods for managing multiplicity within a study. 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 draft guidance provides greater detail on the topic of multiple endpoints. The issuance of this draft guidance represents partial fulfillment of an FDA commitment under the Food and Drug Administration Amendments Act of 2007. (Title I of the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85)). Under section XI (Expediting Drug Development) of the Prescription Drug User Fee Act (PDUFA) Performance Goals, FDA agreed to develop and publish for comment draft guidance on “Multiple Endpoints in Clinical Trials,” and to complete the final guidance within one year of the close of the public comment period of the PDUFA Performance Goals (see <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm>).

Failure to account for multiplicity when there are several clinical endpoints evaluated in a study 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 draft 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 Type 1 error when there are multiple analyses of the drug’s effects. The issues of multiplicity and methods to address them are

illustrated in the draft 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.

Once a trial is successful (demonstrates effectiveness or “wins” on the primary endpoint(s)), there are many other attributes of a drug’s effects that may be described. Analyses that describe these other attributes of a drug can be informative and are often included in physician labeling. Such descriptive analyses are not the subject of this draft guidance and are not addressed in detail.

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 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. Electronic Access

Persons with access to the Internet may obtain the draft guidance at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, or <http://www.regulations.gov>.

Dated: January 10, 2017.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2017-00695 Filed: 1/12/2017 8:45 am; Publication Date: 1/13/2017]