



## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **Food and Drug Administration**

**[Docket No. FDA-2018-D-3710]**

### **Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products; Draft Guidance for Industry; Availability**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**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products.” This document, when finalized, will provide guidance to applicants submitting investigational new drug applications, new drug applications, biologics license applications, or supplemental applications on the use of meta-analyses of randomized controlled clinical trials (RCTs) to evaluate the safety of human drugs or biological products within the framework of regulatory decision-making.<sup>1</sup> This draft guidance is also intended for FDA reviewers and for third-party entities that prepare or evaluate meta-analyses assessing the safety of drug products. Specifically, this guidance describes the factors FDA intends to consider when evaluating the strength of evidence provided by a meta-analysis studying the safety of drugs.

**DATES:** Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure

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<sup>1</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and biologic products unless otherwise specified.

that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-3710 for “Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products: 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., Hillendale Building, 4th Floor, Silver Spring, MD 20993-0002; or to 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 N. Goldie, Office of Biostatistics, 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 “Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products.” Evaluating the safety of drug products, both before approval and after marketing, is a fundamental responsibility of the FDA. This evaluation often requires combining and integrating information from multiple sources, and meta-analysis is a useful tool for this purpose.

This draft guidance describes general principles of design, conduct, and reporting that FDA intends to apply to meta-analyses conducted by the Agency, and to use as benchmarks when evaluating meta-analyses conducted by sponsors or third parties. The focus of the draft guidance is on the evaluation of safety. This draft guidance is not intended to be a reference guide on how to conduct a meta-analysis. Rather, this draft guidance document discusses the important principles underlying best practices for safety meta-analyses and the way that FDA intends to factor adherence to those principles into its decision-making process.

This draft guidance is being issued to fulfill a commitment made under the Prescription Drug User Fee V agreement (section IX.B.3 of the document entitled “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017”) to promote a better understanding and increased consistency among the Agency, industry and other stakeholders regarding meta-analyses and their role in regulatory decision-making.

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 “Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products.” 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. Paperwork Reduction Act of 1995

This draft 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, 314, and 601 have been approved under OMB control numbers 0910-0014, 0910-0001, and 0910-0338 respectively.

## 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/Guidances/default.htm>, or <https://www.regulations.gov>.

Dated: November 1, 2018.

**Leslie Kux,**

*Associate Commissioner for Policy.*

[FR Doc. 2018-24316 Filed: 11/6/2018 8:45 am; Publication Date: 11/7/2018]