DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–D–0449]

Integrated Summary of Effectiveness; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a guidance for industry entitled ''Integrated Summary of Effectiveness.'' This guidance describes how an integrated summary of effectiveness (ISE) should be prepared by industry for new drug applications (NDAs) and biologics license applications (BLAs). This guidance is intended to improve the quality of drug applications by describing what efficacy information should be submitted so that FDA can make a regulatory decision on an application. This guidance finalizes the draft guidance issued August 28, 2008.

DATES: Submit either electronic or written comments on Agency guidances at any time.

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–2008–D–0449 for Integrated Summary of Effectiveness; 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 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 the Office of Communication, Training, and Manufacturers Assistance, Center for Biologics Evaluation and Research, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993–0002. The guidance may also be obtained from the Center for Biologics Evaluation and Research by mail by calling 1–800–835–4709 or 240–402–7800. 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: Helen Sile, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6462, Silver Spring, MD 20993–0002, 301–796–4123; 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 ''Integrated Summary of Effectiveness.'' This guidance describes how an ISE should be prepared by industry for NDAs and BLAs. The ISE has been required as part of an NDA submission since 1985 (21 CFR 314.50(d)(5)(v)), but the regulation does not describe the specific components of the ISE. The guidance for industry ''Guideline for the Format and Content of the Clinical and Statistical Sections of an Application'' (Clin-Stat guidance) provides a description of what FDA recommends for inclusion in an ISE. However, since the Clin-Stat guidance was published, several International Conference on Harmonisation guidances, including the ICH guidances for industry ''E3 Structure and Content of Clinical Study Reports,'' ''E10 Choice of Control Group and Related Issues in Clinical Trials,'' and ''M4E The CTD—Efficacy,'' have

provided additional recommendations for describing individual trials and providing results of efficacy analyses.

This guidance supersedes section II.G., Integrated Summary of Effectiveness Data, of the Clin-Stat guidance to reflect FDA's current thinking regarding the format and content of the ISE to provide a truly integrated analysis, rather than a summary of efficacy results from individual clinical trials, and to satisfy FDA regulatory requirements. This guidance also incorporates the conceptual framework of section 2.7.3, Summary of Clinical Efficacy, from ICH M4E. Although there are no corresponding regulations requiring an ISE for BLA submissions, applicants are encouraged to provide these analyses.

The focus of the ISE is not on the detailed results of individual studies, which are described in individual study reports, but a comprehensive, detailed, integrated analysis that goes beyond individual study results to examine all sources of information concerning effectiveness to provide further insight into the efficacy of the study drug. Integrated analyses included in an ISE generally fall into two broad categories: (1) Comparing the individual studies to better understand the overall results; and (2) using the greater power of pooled analyses to gain insight into the nature of the drug's effectiveness in demographic (*e.g.,* age, sex, race, and ethnicity) and other subpopulations, dose-response, and onset and duration of effect, among others.

A draft of this guidance was published for comment in the **Federal Register** on August 28, 2008 (73 FR 50825). Comments received on the draft guidance have been considered and the guidance has been revised as follows: (1) Clarification on the difference between the document included in Module 2, section 2.7.3, Summary of Clinical Efficacy, from ICH M4E, and the ISE has been provided; (2) the definition of integrated analyses has been revised and the components that constitute an integrated analyses have been clarified; (3) pooled analyses has been defined; and (4) the recommendations for when it is appropriate to pool data has been included.

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 preparing an ISE. 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. The Paperwork Reduction Act of 1995

This 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 part 314 have been approved under OMB control number 0910–0001. The collections of information for submission of data in a BLA under 21 CFR 601.2 have been approved under OMB control number 0910–0338.

III. Electronic Access

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

Dated: October 2, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2014–D–2138]

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing the availability of a final guidance for industry entitled ''Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act.'' Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), an outsourcing facility must submit adverse event reports to FDA. This guidance explains FDA's current thinking on adverse event reporting for these outsourcing facilities.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: You may submit comments as follows:

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- 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–2014–D–2138 for Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act; 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