DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–D–3235]

M4E(R2): The Common Technical Document—Efficacy; International Conference on Harmonisation; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance entitled ''M4E(R2): The CTD—Efficacy'' (M4E(R2)). The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). In August 2001, FDA made available guidance on preparing the efficacy components of an application file in the common technical document (CTD) format (''M4E: The CTD—Efficacy'' (M4E guidance)). This draft guidance revises the M4E guidance. The revised draft guidance standardizes the presentation of benefit-risk information in regulatory submissions, providing greater specificity on the format and structure of benefit-risk information. This revision is intended to facilitate communication among regulators and industry.

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on any guidance at any time (see 21 CFR 10.115 (g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by December 1, 2015.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10001 New Hampshire Ave.,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 (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 the office in processing your requests. The draft guidance may also be obtained by mail by calling CBER at 1–800–835–4709 or 240–402–7800. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to *http://www.regulations.gov.* Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: *Regarding the guidance:* Pujita Vaidya, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 1144, Silver Spring, MD 20993–0002, 301–796–0684; 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.

Regarding the ICH: Michelle Limoli, Center for Drug Evaluation and Research, International Programs, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7212, Silver Spring, MD 20993–0002, 301–796–8377.

SUPPLEMENTARY INFORMATION:

I. Background

In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based and harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and reduce differences in technical requirements for drug development among regulatory Agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from other interested stakeholders. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: Europe, Japan, and North America. The eight ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; the Japanese Pharmaceutical Manufacturers Association; CDER and CBER, FDA; the Pharmaceutical Research and Manufacturers of America; Health Canada; and Swissmedic. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers such as the World Health Organization. In August 2015, the ICH Steering Committee agreed that a draft guidance entitled ''M4E(R2): The CTD—Efficacy'' should be made available for public comment. The draft guidance is the product of the M4E(R2) Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Expert Working Group.

ICH M4E(R2) revises the M4E guidance (made available in August 2001), which covers the Clinical Overview and Clinical Summary of Module 2 of the CTD and the Clinical Study Reports of Module 5. The revised draft guidance provides more specific guidance regarding the format and structure of the benefit-risk assessment in section 2.5.6; it also revises other sections of the guidance for clarification, given the proposed revisions in section 2.5.6. In addition, the revised draft guidance changes the numbering and the section headings for consistency.

Regulatory authorities approve drugs that are demonstrated to be safe and effective for human use. The meaning of ''safe'' has historically been interpreted to mean that the benefits of the drug outweigh its risks. This benefit-risk assessment of pharmaceuticals is the fundamental basis of regulatory decision-making. In the last several years, providing greater structure for the benefit-risk assessment has been an important topic in drug regulation. The M4E guidance directs applicants to include their conclusions on benefits and risks in the Clinical Overview of Module 2 of the CTD under section 2.5.6. Although general guidance is provided in the M4E guidance regarding the expected content of section 2.5.6, no further structure is suggested to aid industry in developing the benefit-risk assessment. As a result, regulators observe a high degree of variability in the approaches taken by applicants in presenting this information. This variability may not facilitate efficient communication of industry views to regulators. Although regulators and industry have developed approaches for structured benefit-risk assessment and these approaches may take different forms, there is a common thread evident that can inform harmonization of the format and structure of benefit-risk

assessments provided by applicants in their regulatory submissions.

Recognizing that there are many reasonable approaches for conducting a benefit-risk assessment, M4E(R2) does not specify a particular approach to be used by industry. However, the document does offer specific guidance on the major elements that should be included in the benefit-risk assessment. Furthermore, consistent with the concept paper that laid the groundwork for the Expert Working Group, the revised draft guidance does not dictate an approach used by a regulator in conducting a benefit-risk assessment.

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 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.

II. Comments

Interested persons may submit either electronic comments regarding this document to *http://www.regulations.gov* or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

III. Electronic Access

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

Dated: *September 28, 2015.*

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0418]

An Evaluation of the Prescription Drug User Fee Act Workload Adjuster; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for public comment on an assessment of the Prescription Drug User Fee Act (PDUFA) Workload Adjuster conducted by an independent consulting firm. This assessment was conducted to fulfill FDA performance commitments made as part of the fifth authorization of PDUFA in section XV, ''Improving FDA Performance Management,'' subsection B, which was reauthorized by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). Independent consulting firms conducted two assessments during PDUFA V. This is the second assessment to evaluate whether the adjustment reasonably represents actual changes in workload volume and complexity in the human drug review program and to present options to discontinue, retain, or modify any elements of the adjustment. After review of the report and receipt of public comment, FDA can adopt appropriate change to the workload adjustment methodology, if warranted.

DATES: Submit electronic or written comments by November 2, 2015.

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–2013–N–0418 for ''An Evaluation of the Prescription Drug User Fee Act Workload Adjuster; Request for Comments.'' 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