4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-D-1747]

Risk Evaluation and Mitigation Strategies: Modifications and Revisions; 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 "Risk Evaluation and Mitigation Strategies: Modifications and Revisions." This guidance provides information on how FDA will define and process submissions for modifications and revisions of risk evaluation and mitigation strategies (REMS), as well as information on what types of changes to approved REMS will be considered modifications or revisions of the REMS. The guidance also provides instructions to application holders related to procedures for submission of REMS modifications and revisions to FDA as well as different timeframes for FDA's review of and action on such changes. The definitions of REMS modifications and revisions apply to all types of REMS. This guidance updates the guidance of the same name, issued April 7, 2015, including finalizing the portion that sets forth the submission procedures for REMS revisions.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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-2014-D-1747 for "Risk Evaluation and Mitigation Strategies: Modifications and Revisions." 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 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, 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 guidance document.

FOR FURTHER INFORMATION CONTACT: Vaishali Jarral, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6480, Silver Spring, MD 20993-0002, 301-796-4248; 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 "Risk Evaluation and Mitigation Strategies: Modifications and Revisions." This guidance provides information

on what types of changes to approved REMS will be considered modifications of the REMS and what types of changes will be considered revisions. (See section 505-1(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1(h)).) This guidance also provides information on how REMS modifications and revisions should be submitted to FDA and how FDA intends to review and act on these submissions.

If FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks, FDA is authorized to require a REMS for such drugs under section 505-1 of the FD&C Act.[1] Section 505-1(g) and (h) of the FD&C Act include provisions for the assessment and modification of an approved REMS. Section 505-1(h) of the FD&C Act requires FDA to review and act on proposed *minor modifications*, as defined in guidance, within 60 days.[2] It also requires FDA to establish, through guidance, that "certain modifications" can be implemented following notification to FDA. (See section 505-1(h)(2)(A)(iv) of the FD&C Act.) In addition, FDA is required to review and act on REMS modifications to conform the REMS to approved safety labeling changes, or to a safety labeling change that FDA has directed the application holder to make pursuant to section 505(o)(4) of the FD&C Act within 60 days. (See section 505-1(h)(2)(A)(iii) of the FD&C Act.) Finally, section 505-1(g)(4)(A) of the FD&C Act specifies that proposed REMS modifications no longer require submission of a REMS

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[1] Section 505-1 of the FD&C Act applies to applications for prescription drugs submitted under subsection 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications) of the FD&C Act (21 U.S.C. 355(b) or (j), respectively) and applications under section 351 of the Public Health Service Act (i.e., biologics license applications).

[2] See section 505-1(h)(2)(A)(ii) of the FD&C Act. Section 1132(c) of the Food and Drug Administration Safety and Innovation Act also provides that FDA will issue guidance that, for purposes of section 505-1(h)(2)(A) of the FD&C Act, describes the types of modifications to approved risk evaluation and mitigation strategies that are considered to be minor modifications of such strategies.

assessment; instead, proposed modifications must include an adequate rationale for the proposed changes.

This guidance updates the guidance of the same name, issued April 7, 2015 (80 FR 18629), and finalizes the portion that sets forth the submission procedures for REMS revisions. FDA carefully considered all comments received, including comments on the submission procedures portion, and revised the guidance as appropriate.

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 "Risk Evaluation and Mitigation Strategies: Modifications and Revisions." 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 final guidance refers to previously approved collections of information found in FDA regulations. These collections of information 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). REMS modifications are submitted to FDA as supplements to approved new drug applications (NDAs) under 21 CFR 314.70 and for abbreviated new drug applications (ANDAs) under 21 CFR 314.97, and for approved biologics license applications (BLAs) under 21 CFR 601.12. Burden hours for NDAs and ANDAs are approved by OMB under control number 0910-0001, and for BLAs under control number 0910-0338. REMS revisions are submitted to FDA as application correspondence and are also approved by OMB under control numbers 0910-0001 and 0910-0338.

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/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances, or https://www.regulations.gov.

Dated: July 3, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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