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.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a 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 to risk evaluation and mitigation strategies (REMS), as well as 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 of the REMS. There are different procedures for submission of REMS modifications and revisions to FDA as well as different timeframes for FDA review and action of such changes. In addition, this guidance provides information on how REMS modifications and revisions should be submitted to FDA and how FDA intends to review and act on these submissions. The definitions of REMS modifications and revisions apply to all types of REMS.

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 guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit either electronic or written comments concerning the proposed collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit written requests for single copies of the 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.

Submit electronic comments on the 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: Kristen Everett, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 6484, Silver Spring, MD 20993-0002, 301-796-0453; 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 and what types of changes will be considered revisions. See section 505-1(h) of the Federal Food, Drug, and Cosmetic Act (the 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] added by section 901 of the Food and Drug Administration Amendments Act of

[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) and applications under section 351 of the Public Health Service Act (i.e., biologics license applications).

2007 (Public Law 110-85).[2] Section 505-1(g) and (h) of the FD&C Act include provisions for the assessment and modification of an approved REMS.

In 2009, FDA issued draft guidance on the format and content of REMS, REMS assessments, and proposed REMS modifications. In that guidance, based on the language of section 505-1(g) and (h) of the FD&C Act before the amendments made by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144) (FDASIA), FDA stated that any proposed modification to an approved REMS, including proposed changes to materials that are appended to the REMS document, must be submitted as a proposed REMS modification in the form of a prior approval supplement and must include a REMS assessment. The guidance stated that the proposed modification(s) may not be implemented until approved by FDA.

FDASIA amended the REMS modification provisions under section 505-1(g) and (h) of the FD&C Act. Section 505-1(h), as amended by FDASIA, requires FDA to review and act on proposed "minor modifications," as defined in guidance, within 60 days.[3] It also requires FDA to establish, through guidance, that "certain modifications" can be implemented following notification to FDA.[4] In addition, FDASIA requires FDA to review and act on REMS modifications due to approved safety label changes, or to a safety label change that FDA has directed the

---

[2] See http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm.

[3] See section 505-1(h)(2)(A)(ii) of the FD&C Act.

[4] See section 505-1(h)(2)(A)(iv) of the FD&C Act.

application holder to make pursuant to section 505(o)(4) of the FD&C Act within 60 days.[5] Finally, FDASIA specifies that proposed REMS modifications no longer require submission of a REMS assessment; instead, proposed modifications must include an adequate rationale for the proposed changes. This guidance is issued pursuant to section 505-1(h)(2)(A)(ii), (h)(2)(A)(iii), and (h)(2)(A)(iv) of the FD&C Act.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). This guidance, except for the portion setting forth the submission procedures for REMS revisions, is being implemented without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (21 CFR 10.115(g)(2)). The Agency made this determination because, consistent with the requirements of FDASIA, FDA is issuing this guidance to establish a less burdensome policy and process for submitting certain changes to REMS that is consistent with public health. Although the guidance document is immediately in effect, except for the submission procedures for REMS revisions, it remains subject to comment in accordance with the Agency's good guidance practices. Insofar as this guidance establishes the modifications to an approved REMS that may be implemented following notification to the Secretary under section 505-1(h)(2)(A)(iv)--here referred to as REMS revisions--it has binding effect, except for the portion of the guidance setting forth the submission procedure for REMS revisions, which will, when final, have binding effect.

---

[5] See section 505-1(h)(2)(A)(iii) of the FD&C Act.

II. Paperwork Reduction Act of 1995

This guidance contains information collection provisions 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 title, description, and respondent description of the information collection are given under this section with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

We invite comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Guidance for Industry on Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Description: The guidance provides information on submitting to FDA modifications and revisions to approved REMS for approved new drug applications (NDAs), abbreviated new drug applications (ANDAs), or biologics license applications (BLAs).

REMS modifications are submitted to FDA as supplements to approved NDAs under 21 CFR 314.70 and for ANDAs under 21 CFR 314.97, and as supplements to approved BLAs under 21 CFR 601.12. The burden hours for preparing and submitting supplements to NDAs and ANDAs is approved by OMB under control number 0910-0001, and for BLAs under control number 0910-0338.

Concerning REMS revisions, application holders should include the following information in each submission: (1) A full description of the changes to the REMS and/or appended materials, the date the changes will be implemented, and a REMS history that outlines all changes made to the REMS since its approval; (2) a clean Word version of the revised REMS and all appended REMS materials; (3) a redlined (tracked changes) Word version of the revised REMS and revised appended REMS materials that shows the changes from the previous versions; (4) an updated REMS supporting document, if needed; and (5) Form FDA 356h indicating that the submission is a REMS revision. (Form FDA 356h is approved by OMB under control number 0910-0338.) Each REMS revision that is submitted to FDA should also be documented in the next annual report for the application under 21 CFR 314.81(b)(2) (the burden hours for preparing and submitting annual reports for NDAs and ANDAs is approved by OMB under control number 0910-0001, and for BLAs under control number 0910-0338). All subsequent REMS submissions (i.e., proposed modifications or additional REMS revisions) should include previously implemented REMS revisions in the REMS document and appended materials, and should be noted in the REMS history.

Currently, there are 117 application holders with approved REMS that include 152 drugs. Based on FDA's current review of REMS submissions for approved NDAs, ANDAs, and BLAs, and anticipating an average of 1 REMS revision across the entire group of REMS, we estimate that annually a total of approximately 117 application holders ("Number of Respondents" in table 1) will submit to FDA approximately 152 REMS revision submissions ("Total Annual Responses" in table 1) as described in this document and in the guidance. We also estimate that it will take an application holder approximately 30 hours to prepare and submit to FDA each REMS revision ("Average Burden per Response" in table 1).

The total estimated reporting burden for the guidance is as follows:

Table 1.--Estimated Annual Reporting Burden[1]

Guidance for Industry on Risk Evaluation and Mitigation Strategies: Modifications and Revisions	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
REMS revisions	117	1	152	30	4,560

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

III. 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.

IV. Electronic Access

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

Dated: April 2, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015-08015 Filed: 4/6/2015 08:45 am; Publication Date: 4/7/2015]