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4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-N-1845]

Risk Evaluation and Mitigation Strategy Assessment Summary for Web Posting; Establishment of a Public Docket; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing the establishment of a docket to solicit public comment on a proposal to publish a summary of FDA's review of Risk Evaluation and Mitigation Strategy (REMS) assessments. The purpose of the docket establishment is to increase Agency transparency and promote exchange of information regarding the assessment of REMS programs.

DATES: Submit either electronic or written comments by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

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-2020-N-1845 for "Risk Evaluation and Mitigation Strategy Assessment Summary for Web Posting; Establishment of a Public Docket; Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), 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, 240-402-7500.

- 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.govinfo.gov/content/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, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Claudia Manzo, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 2418, Silver Spring, MD 20993, 301-796-0182, Claudia.Manzo@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Section 505-1(g)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) specifies that a REMS assessment shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each

element, is meeting the goal or whether one or more of the goals or elements should be modified. Information from a REMS assessment can be used to understand whether certain REMS requirements or specific tools are effective in mitigating a serious risk.

Every proposed REMS for a new drug application (NDA) and biologics license application (BLA) must have a timetable for submission of REMS assessments that fulfills the two parameters below:

- Includes assessments submitted to FDA by the dates that are: (1) 18 months after the strategy is initially approved; (2) 3 years after the strategy is initially approved; and (3) in the seventh year after the strategy is so approved, and
- Submitted at a frequency specified in the strategy and can be increased or reduced in frequency under certain circumstances and eliminated under certain circumstances.

REMS assessments are also required under the following conditions:

- When the applicant[1] is submitting a supplemental application for a new indication for use
- When required by the strategy
- Whenever FDA determines that an assessment is needed to evaluate whether the strategy should be modified (to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system when complying with the strategy)

Additionally, assessments of approved REMS may be submitted voluntarily by the applicant at any time.

All approved REMS for NDA and BLA products are required to include a timetable for submission of assessments of the REMS and applicants must submit their REMS Assessment Reports according to this timetable. The applicant's REMS Assessment Report is the document that contains information generated from the analysis of the metrics outlined in the REMS Assessment Plan. The REMS Assessment Plan is a specific plan for how the applicant intends to assess the performance of the REMS in meeting its risk mitigation goals and objectives. The

[1] For the purpose of this notice, applicant includes any person that holds an application approved under section 505-1 of the FD&C Act or a license issued under section 351 of the Public Health Service Act (42 U.S.C. 262) for such product, or who submits an NDA, an abbreviated new drug application (ANDA), a BLA, or an amendment or supplement to an NDA, an ANDA, or a BLA, to obtain FDA approval.

REMS Assessment Plan is outlined in the REMS approval letter for NDAs and BLAs and described in detail in the REMS Supporting Document.[2]

FDA conducts a review of the applicant's REMS Assessment Report to determine if the REMS is meeting its goals. These FDA reviews are archived in the Agency's electronic archival record system. Some of FDA's reviews of applicants' REMS Assessment Reports have been shared publicly at FDA advisory committee meetings. An applicant's REMS Assessment Report and FDA's review of this report may also be requested under the Freedom of Information Act (FOIA); these requests are reviewed by FDA staff, and any information exempt from disclosure must be redacted prior to fulfilling the FOIA request. An applicant's confidential commercial information (CCI), including specific information on stakeholder participation in REMS (e.g., number of certified prescribers, healthcare settings, or the number of enrolled patients), may be redacted from FOIA-released documents following FDA's determination that such information is non-public sales and usage information. Specific information on stakeholder participation in shared system REMS,[3] however, may be released following FDA's determination that such information is aggregate for all the applicants in the shared system REMS and is not considered CCI.

FDA has received feedback from healthcare providers, healthcare systems, industry members, researchers, professional organizations, and other Federal Agencies, indicating that it would be beneficial to make both the applicant's REMS Assessment Report and FDA's review

[2] The REMS Supporting Document provides additional information about the REMS, such as the rationale for, and supporting information about, the design, implementation, and assessment of the REMS.

[3] A shared system REMS encompasses multiple prescription drug products and is developed and implemented jointly by two or more applicants.

of this report available in the public domain for a number of purposes.[4,5,6,7,8] For example, industry members may consider the effectiveness of a particular strategy as they develop a new REMS; healthcare providers may have an interest in the assessment of a REMS that they participate in; and academics can use the information for research purposes.

In response to this feedback, FDA is proposing to post to the Approved REMS web page (https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm) a summary of FDA's review of the applicant's REMS Assessment Report (hereafter referred to as Summary of the REMS Assessment) submitted according to the timetable specified in the approved REMS. The Summary of the REMS Assessment is intended to provide a general understanding of what has been learned from specific REMS programs. The Summary of the REMS Assessment will include a high-level summary of the data included in the applicant's REMS Assessment Report and will include a summary of the FDA review of whether the REMS is meeting its risk mitigation goals. FDA will notify the applicant prior to posting the Summary of the REMS Assessment to the web page. Although the Agency acknowledges that information on specific stakeholder participation in REMS might be useful, this information would not be provided in the summaries of individual REMS[9] because, as mentioned above, it is considered CCI. Information on participation in shared system REMS would be provided in aggregate (e.g., number of prescribers, pharmacies, and/or patients enrolled in the shared system program).

II. Summary of the REMS Assessment for Web Posting

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[4] See The Pink Sheet, After REMS: An Interview With Amgen's Paul Seligman; posted July 7, 2014, and available at https://pink.pharmaintelligence.informa.com/PS056230/After-REMS-An-Interview-With-Amgens-Paul-Seligman.

[5] Fain, K., K. Nachman, and L. Rutkow, 2015, "An Analysis of FDA's Drug Safety Authorities: Challenges and Opportunities Under a New Regulatory Framework," *Legislation and Public Policy*, 17:1-36.

[6] See International Society of Pharmacoepidemiology comments (Docket No. FDA-2018-D-4628-0006) on the 2019 draft guidance for industry "Risk Evaluation and Mitigation Strategies Assessment: Planning and Reporting," (84 FR 1153, February 1, 2019) (Docket No. FDA-2018-D-4628), available at https://www.fda.gov/media/119790/download. When finalized, this guidance will represent the FDA's current thinking on these issues.

[7] Id., see Pfizer comments (Docket No. FDA-2018-D-4628-0011).

[8] Comments of Tracy Rupp, PharmD, MPH, RD, Senior Fellow at the National Center for Health Research, (Docket No. FDA-2013-N-0502-0069) submitted for Docket No. FDA-2013-N-0502, "Risk Evaluation and Mitigation Strategies: Understanding and Evaluating Their Impact on the Health Care Delivery System and Patient Access," available at http://www.center4research.org/nchr-statement-fda-meeting-risk-evaluation-mitigation-strategies-rems/.

[9] An individual REMS encompasses one or more prescription drug products and is developed and implemented by one applicant.

This *Federal Register* notice provides an example of a Summary of the REMS Assessment that would be publicly available. The Summary of the REMS Assessment would include the following sections: A. Introduction; B. Background; C. Key Findings; D. Conclusions; and E. Next Steps. Section A. Introduction will include a brief paragraph that includes the reporting time point (e.g., 2-Year Drug X REMS Assessment Report), the reporting period (e.g., November 28, 2017, through November 27, 2018), and the FDA submission date. Section B. Background will include a summary of the approved indication, the safety issue warranting a REMS, the date the REMS was approved, the goals and objectives of the REMS, the REMS requirements, and the timetable for submission of assessments. Section C. Key Findings will include the brief summary of the results of data used to inform each objective. Section D. Conclusions will include both the applicant's and FDA's conclusion about whether the REMS is meeting its goals. Section E. Next Steps will include whether modifications to the REMS program or to the REMS Assessment Plan is warranted.

III. Example of the Summary of the REMS Assessment for Web Posting

For the purpose of this example, we are using a fictitious product referred to as "Drug X."

A. Introduction

This is a summary of the FDA evaluation of the 2-Year REMS Assessment Report (Third Assessment Report) of the Drug X REMS from the reporting period of November 28, 2017, through November 27, 2018, submitted to FDA on January 27, 2019.

B. Background

Drug X is approved to treat the symptoms of a genetic, progressive, neurodegenerative disorder for which there are limited approved therapies. Drug X is an injectable medication given at a dose of 500 milligrams (mg) intravenously over 60 minutes weekly for 4 weeks, and monthly thereafter. A REMS was required at initial approval to mitigate the risk of anaphylaxis, which occurred in clinical trials in approximately 10 percent of patients within 30 minutes of receiving a dose of Drug X. The risk of anaphylaxis occurred with any dose and patients

appeared to be at higher risk if they experienced a prior event (e.g., hypersensitivity, allergic events). The Drug X REMS was approved on January 28, 2016.

The goal of the Drug X REMS is to mitigate the risk of negative outcomes associated with Drug X-induced-anaphylaxis. Objectives of the REMS include:

(1) Ensuring prescribers are educated on the risk of anaphylaxis associated with the use of Drug X, that the risk may occur with any dose, and that all patients need be observed for 30 minutes following each dose

(2) Ensuring that Drug X is dispensed only in certified healthcare settings that have immediate access onsite to equipment, emergency medication, and personnel trained to manage anaphylaxis

(3) Ensuring that healthcare providers observe patients for at least 30 minutes after each injection

(4) Informing patients about the risk of anaphylaxis associated with Drug X and the importance of remaining at the healthcare setting for 30 minutes after each injection

The Drug X REMS includes the following key requirements: (1) the sponsor must implement a communication plan including sending a REMS letter to all potential prescribers of Drug X outlining the risks and REMS requirements (communication plan completed January 2019); (2) healthcare providers that prescribe Drug X must become certified, which includes completing REMS training, successfully completing a knowledge assessment, and enrolling in the Drug X REMS; (3) certified prescribers must counsel patients prior to administration of the first dose; (4) healthcare settings that order and dispense Drug X must become certified, which includes completing REMS training, successfully completing a knowledge assessment, enrolling in the Drug X REMS, and attesting to having immediate access onsite to equipment, emergency medication, and personnel trained to manage anaphylaxis; and (5) certified healthcare setting must observe patients for a minimum of 30 minutes after each injection and complete and submit a completed post-injection form to the Drug X REMS.

The Drug X REMS assessment reporting frequency is 6 months, 12 months, and annually after initial approval of the REMS.

C. Key Findings Informing REMS Goals and Objectives

Goal: To mitigate the risk of negative outcomes associated with Drug X-induced anaphylaxis.

Objective 1: Ensuring that prescribers are educated on the risk of anaphylaxis associated with the use of Drug X, that the risk may occur with any dose, and that all patients need be observed for 30 minutes following each dose.

Data evaluated: Number and recipients of REMS letter; successful completion of prescriber knowledge assessment, surveys of prescribers' knowledge.

Key findings:

- REMS letters were distributed to likely prescribers of Drug X during the reporting period; about 75 percent of the letters were emailed to neurologists with an email open rate of 14 percent, which is consistent with the email open rate of other REMS programs.
- All enrolled prescribers completed the knowledge assessment with a score of 100 percent; only 15 percent of prescribers required two attempts to achieve this score.
- Prescriber survey respondents demonstrated knowledge of the risks and safe use conditions with a mean knowledge rate of 88 percent.[10]

Conclusion: FDA concluded that this objective is being met because the applicant notified the appropriate prescriber population with information about the Drug X REMS and certified prescribers successfully completed the training program and the knowledge assessment prior to enrollment. In addition, prescriber survey respondents demonstrated knowledge of the risks and the safe use conditions necessary for Drug X.

Objective 2: Ensuring that Drug X is dispensed only in certified healthcare settings that have immediate access onsite to equipment, emergency medication, and personnel trained to manage anaphylaxis.

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[10] The knowledge rate is the proportion of subjects who know the key message out of all subjects; the target knowledge rate for this prescriber survey was 80 percent.

Data evaluated: Shipment of Drug X only to certified healthcare settings; surveys of healthcare settings, audits of healthcare settings.

Key findings:

No shipments of Drug X were sent to non-certified healthcare settings during the reporting period. Audits of 10 percent of certified healthcare settings found that all were in compliance with the requirement to have immediate access onsite to equipment, emergency medication, and personnel trained to manage anaphylaxis after receiving Drug X.

Conclusion: FDA concluded that this objective is being met because Drug X is being dispensed in certified healthcare settings.

Objective 3: Ensuring that healthcare settings observe patients for at least 30 minutes following Drug X dosing.

Data evaluated: Completed post-injection forms, surveys of healthcare settings, and audits of healthcare settings.

Key Findings:

- Certified healthcare facility personnel survey respondents demonstrated knowledge of the risk of anaphylaxis following Drug X infusion with a knowledge rate of 87 percent. When asked about their facilities' compliance with post-injection observation, 90 percent reported that patients are observed for 30 minutes following each injection at their facility.
- Audits of 10 percent of healthcare settings found that 75 percent of healthcare settings had policies and procedures in place to ensure that patients were observed for 30 minutes following each injection.
- Of the post-injection forms that were received:
    - Less than 0.1 percent of the forms noted that the patient did not stay for 30 minutes; each facility reporting this was sent a warning letter; future non-compliance may result in decertification as outlined in the non-compliance action plan.

- Less than 0.1 percent of the forms documented anaphylaxis; no events occurred more than once in a given patient.
    - The majority of patients who experienced anaphylaxis, were treated and observed at the healthcare facility and discharged once stable.
    - A small number were transported to a hospital for additional monitoring; outcome for these three patients is outstanding and will be reported in the next assessment report.

Conclusion: FDA concluded that this objective is being partially met. While survey findings were acceptable (exceeding the prespecified acceptable knowledge rate of >80 percent) and healthcare setting personnel indicated by survey that patients were being observed for 30 minutes, 25 percent of healthcare settings audited did not have policies and procedures to ensure patient observation.

Objective 4: Informing patients about the risk of anaphylaxis associated with Drug X and the importance of remaining at the healthcare setting for 30 minutes after each injection.

Data evaluated: Surveys of patients.

Key Findings:

Patient survey respondents showed high knowledge of the risk of anaphylaxis (92 percent) and the need to remain at the facility for 30 minutes after each injection of Drug X (95 percent).

Conclusion: FDA determined that this objective is being met because the patient knowledge rate exceeded the prespecified acceptable knowledge rate of >80 percent.

D. Conclusions About Whether the REMS Goals and Objectives Are Being Met

Sponsor conclusion: The Drug X sponsor concluded that the goal and objectives of the Drug X REMS were being met and did not propose any changes to the REMS as a result of the REMS assessment findings.

FDA conclusion: FDA concluded that while not all objectives are fully met, the overall goals of the program are being met. Appropriate outreach to likely prescribers was completed

via REMS letters and the open rate for email letters is consistent with communications for other REMS. Surveys of a sample of enrolled prescribers showed that they understood the risks of Drug X, the need to monitor following dosing, and how to treat anaphylaxis. Patients surveyed were also aware of the risk and the need to be observed for 30 minutes following each dose. No Drug X was shipped to facilities that were not enrolled. Audits of facilities were in compliance with the need to have access onsite to equipment, emergency medication, and personnel trained to manage anaphylaxis; however, findings did reveal that 25 percent did not have specific policies and procedures in place to ensure that patients are observed 30 minutes following each injection of Drug X. Certified healthcare facility personnel surveyed were also aware of the risk and stated that they ensure all patients are observed for 30 minutes following each injection. Facilities reporting patient non-compliance with the 30-minute observation period were warned and will be followed in subsequent assessment reports. Although patients experiencing anaphylaxis were treated appropriately, three did require transport to a hospital and their outcome was not provided in this report.

E. Next Steps

Based on our review of the findings in the third REMS Assessment Report, modifications to the Drug X REMS are not warranted.

On May 1, 2019, FDA sent a letter to the applicant to acknowledge our completion of the third REMS assessment report review. In the letter the applicant was instructed to ensure that the audited healthcare settings that were out of compliance are fully compliant within 3 months of the date of issuance of the letter and that the outcome for the three patients that were transferred to a hospital must be provided to FDA as soon as possible. The applicant was also encouraged to use probability random sampling and recruit a larger sample of prescribers in subsequent prescriber surveys.

IV. Additional Issues for Consideration

FDA is soliciting comment from stakeholders regarding the information that would be posted in the Summary of the REMS Assessment. In addition to any other aspects of or issues

concerning FDA's proposal to publicly post a Summary of the REMS Assessment, FDA is interested in comments on the following topics:

(1) whether the information contained in the Summary of the REMS Assessment example would be beneficial to the public, and if so, why it would be beneficial

(2) whether the Summary of the REMS Assessment would be useful to a wide range of stakeholders, including healthcare providers, patients, the pharmaceutical industry, and academics, and if so, why it would be beneficial

(3) whether any additional information should be included in the Summary of the REMS Assessment

(4) possible negative impacts of posting the Summary of the REMS Assessment

Dated: October 30, 2020.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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