Providing Regulatory Submissions in Electronic Format — Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 180 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Adam Kroetsch, 301-796-3842, Aaron Sherman, 240-402-0493, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2017
Electronic Submissions

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Guidance for Industry

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Guidance for Industry[1]

I. INTRODUCTION

Under section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379k-1(a)), beginning no earlier than 24 months after the issuance of a final guidance in which the Food and Drug Administration (FDA or Agency) has specified the electronic format for submitting certain submission types to the Agency, the content of such submission types must be submitted electronically and in the format specified by FDA. This draft guidance and the Structured Product Labeling (SPL) implementation guide[2] describe the requirements for the electronic submission of the content of a risk evaluation and mitigation strategy (REMS) document[3] under section 745A(a) of the FD&C Act. This draft guidance describes how FDA plans to implement the requirements for the electronic submission of REMS documents as part of submissions under new drug applications (NDAs), abbreviated new drug applications (ANDAs), and certain biologics license applications (BLAs). Pursuant to section 745A(a), beginning 24 months after this guidance is finalized, REMS documents that are not submitted electronically in accordance with the final guidance will not be filed or received.

In section 745A(a) of the FD&C Act, Congress granted explicit authorization to FDA to implement the statutory electronic submission requirements in guidance. Accordingly, as indicated by the use of the words *must* or *required*, this draft guidance is not subject to the usual restrictions in FDA's good guidance practices (GGP) regulation, such as the requirement that guidances not establish legally enforceable responsibilities (see 21 CFR 10.115(d)).[4]

To comply with the GGP regulations and make sure that regulated entities and the public understand that guidances are nonbinding, FDA guidances ordinarily contain standard language explaining that guidances should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in this guidance because the language is not an accurate description of the effects of this guidance. Insofar as this guidance specifies the format for electronic submission of REMS documents under section 745A(a) of the FD&C Act, it will have binding effect, 24 months after the publication of the final guidance in the Federal Register.

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[1] This guidance has been prepared by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] Available at: https://www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM321876.pdf.

[3] See page 3 for more detail on which component of a REMS submission needs to be submitted in SPL format.

[4] See also guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs Guidance Web site at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

FDA engaged stakeholders over a 3-year time frame and analyzed their feedback regarding REMS standardization. The agency's findings were published as a report: "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)."[5] As the report describes, some stakeholders expressed concern about the clarity and consistency with which information about REMS materials and requirements are communicated to stakeholders. They told FDA that REMS materials and requirements may be difficult to locate, and that specific activities and requirements of various stakeholders (e.g., prescriber, pharmacist) are not always clearly outlined. Some stakeholders expressed the need to have better ways to integrate REMS materials and procedures into their existing health information systems and health care delivery processes. Stakeholders also expressed the desire to avoid spending excessive time trying to locate, understand, and comply with different REMS requirements while ensuring safe use of drugs with REMS. To help address these concerns, FDA intends to require applicants of NDAs, ANDAs, and BLAs to submit the content of their REMS documents in Structured Product Labeling (SPL) format. SPL can be used to capture and present REMS information in a format that is easily shared with stakeholders and readily incorporated into health information technology. For more general background information on REMS, as well as a more comprehensive discussion of the issues mentioned in this paragraph, please refer to the "Background Materials" for the July 2013 REMS Standardization and Evaluation Public Meeting.[6]

III. REQUIREMENT TO SUBMIT ELECTRONICALLY UNDER THIS GUIDANCE

Twenty-four months after the final version of this guidance is published in the Federal Register, applicants must submit REMS documents in electronic format consistent with the requirements set forth below.

A. Types of Submissions That Must Adhere to the Electronic Submission Requirement Described in This Guidance

Section 745A(a) of the FD&C Act applies to submissions under section 505(b), (i), or (j) of the FD&C Act (21 U.S.C. 355(b), (i), or (j)) and under section 351(a) or (k) of the Public Health Service Act (42 U.S.C. 262(a) or (k)). For the purposes of this guidance, these submissions include the following types:

- NDAs
- ANDAs

[5] Available at: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf.
[6] Available at: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM362078.pdf.

- Certain BLAs[7,8]

As stated in the guidance, *Providing Regulatory Submissions in Electronic Format –Submissions Under Section 745A(a) of The Federal Food, Drug, and Cosmetic Act Guidance for Industry*[9], "Section 745A(a) also applies to all subsequent submissions, including amendments, supplements, and reports, to the submission types identified above." Because they are part of a drug's approval, REMS submissions are submissions under section 505(b), (i), or (j) of the FD&C Act (21 U.S.C. 355(b), (i), or (j)) or under section 351(a) or (k) of the Public Health Service Act (42 U.S.C. 262(a) or (k)). Therefore, REMS submissions fall within the scope of requirements set forth in section 745A(a).

Applicants must submit the content of their REMS document electronically using the format described in this guidance beginning 24 months after this guidance is finalized. A submission that is not in the electronic format(s) described in the final guidance will not be filed or received.

B. Requirements That Must Be Followed for Electronic Submission of the Content of REMS Documents

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." This guidance addresses electronic submission requirements for certain documents that are part of a REMS. A *REMS document*, which is part of the REMS that is approved by FDA, concisely describes the goals and requirements of the REMS. FDA has determined that the content of a REMS document must be submitted electronically in SPL format, using specifications outlined in the FDA Data Standards Catalog.[10] *REMS materials* are all materials that are included as part of the REMS (e.g., communication and educational materials, enrollment forms, prescriber and patient agreements) that are also approved and enforceable, and are appended to the REMS document. REMS materials must be referenced in the SPL file. REMS supporting documents[11] should <u>not</u> be submitted in SPL format. The table below shows which components of a REMS will be required to be filed in SPL format. Additional details for creating REMS document SPL files for submission to FDA can be found in the "Structured Product Labeling (SPL) Implementation Guide with Validation Procedures" (SPL Implementation Guide) on FDA's SPL Web site (available at

[7] This guidance does not apply to those devices that are regulated by CBER as biological products under section 351 of the PHS Act, including those that do not require the submission of an IND prior to the submission of a BLA. Although a discussion of which devices CBER regulates as biological products under section 351 of the PHS Act is outside the scope of this guidance, as a general matter, this category would include those reagents used in determining donor/recipient compatibility in transfusion medicine.

[8] Specifically, this guidance is not applicable to submissions for blood and blood components, including Source Plasma.

[9] Available at: https://www.fda.gov/downloads/drugs/guidances/ucm384686.pdf.

[10] The most current version of the catalog is available at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls.

[11] For purposes of this guidance, a *REMS supporting document* is a document that expands on information in the REMS document and provides additional information about the REMS, such as the rationale for, and supporting information about, the design, implementation, and assessment of the REMS.

https://www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM321876.pdf).

Component of a REMS Submission	Submitted in SPL Format?
REMS Document	Yes
REMS Supporting Document	No
REMS materials	Referenced in SPL file[12]

In addition to the requirements outlined in this guidance, we recommend that applicants also continue to submit the .DOC or .DOCX version of the REMS document and all REMS materials for the product. These file formats facilitate the exchange of REMS comments and changes between the applicant and FDA.

C. Types of Submissions That Are Exempt From the Electronic Submission Requirement Described in This Guidance

Section 745A(a) of the FD&C Act allows FDA to establish exemptions from the electronic submission requirements. Currently, FDA does not intend to grant exemptions to the requirement that REMS documents be submitted electronically in SPL format.

D. SPL Specifications

Applicants must submit electronic submissions using the version of SPL currently supported by FDA at the time this guidance is finalized. The version of SPL currently supported is specified in the FDA Data Standards Catalog[13] and is further described in the SPL Implementation Guide.

E. Contact Information

For questions about providing electronic submissions according to the requirements in this guidance, you should contact FDA's REMS Web site management team at FDAREMSWebsite@fda.hhs.gov. Specific questions about the content of applications should be directed to the appropriate review division or office.

[12] See SPL Implementation Guide for more information.
[13] Available at: https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls.