# Guidance for Industry

# Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

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For questions regarding this draft document contact (CDER) Kathleen Frost 301-796-2380, or (CBER) the Office of Communication, Outreach, and Development (OCOD) at 301-827-1800 or 800-835-4709.

**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 2009**
**Drug Safety**

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**U.S. Department of Health and Human Services**
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## TABLE OF CONTENTS

# Guidance for Industry[1]
# Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. INTRODUCTION

This document provides guidance to industry on:

- The format and content of a proposed risk evaluation and mitigation strategy (REMS), including REMS supporting documentation;
- The content of assessments and proposed modifications of approved REMS;
- What identifiers to use on REMS documents; and
- How to communicate with FDA about a REMS.

This guidance applies to certain drug and biological products submitted for approval or approved under sections 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), or section 351 of the Public Health Service Act (PHS Act), that are required by FDA to have a REMS. The information on the content of a proposed REMS submission (section III of this document) also applies to proposed REMS that are voluntarily submitted by applicants or holders of approved applications (see section II.A of this document).

This guidance will address REMS elements and provisions that are broadly applicable to proposed REMS and to assessments and modifications of approved REMS. Other provisions, such as those that pertain only to abbreviated new drug applications (ANDAs), or expanded information about REMS assessments and proposed modifications, will not be fully addressed, but will be the subject of future guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the FDAAA Title IX Working Group in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## II. BACKGROUND

### A. FDAAA and REMS: Initial Approval and Postapproval Requirements

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85).[2] Title IX, Subtitle A, section 901 of this statute created new section 505-1 of the FDCA, which authorizes FDA to require persons submitting certain applications (applicants) to submit a proposed REMS as part of such application if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.[3] Section 505-1 applies to applications for approval of prescription drugs submitted under FDCA subsections 505(b) or (j) and applications submitted under section 351 of the Public Health Service Act. These applications are termed *covered applications* and refer to new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs). Please note that the term "drug" is used in this guidance to refer to prescription drug and biologic products for which there are pending or approved applications.

Section 505-1 also authorizes FDA to require holders of covered applications approved without a REMS to submit a proposed REMS if the FDA becomes aware of new safety information as defined in 505-1(b)(3) and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug. Once the holder of an approved covered application is notified by FDA that a REMS is necessary, the holder must submit a proposed REMS within 120 days, or within such other reasonable time as FDA requires to protect the public health (section 505-1(a)(2)(B)).

In addition, persons with certain covered applications that were approved before the effective date of Subtitle A, March 25, 2008, were deemed to have in effect an approved REMS and were also required to submit a proposed REMS. See section II.C of this document, Products Deemed to Have in Effect an Approved REMS.

An applicant may voluntarily submit a proposed REMS without having been required to do so by FDA. For instance, without having been notified by FDA to submit a proposed REMS, an applicant may include a proposed REMS in an original application or in a supplemental application, or in an amendment to an existing original or supplemental application, if the applicant believes a REMS would be necessary to ensure that the benefits of the drug outweigh its risks and the other relevant statutory criteria in section 505-1 are met. Section V of this document describes submission types and document identification. If FDA determines that a

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

[3] Subtitle A took effect on March 25, 2008, 180 days after enactment of FDAAA.

REMS is necessary to ensure that the benefits of the drug outweigh the risks, FDA will determine which elements of a REMS are necessary and will approve the REMS once the Agency has determined that the proposed REMS will ensure that the benefits of the drug outweigh the risks, and the other relevant statutory criteria in section 505-1 are met. An approved REMS that was voluntarily submitted is subject to the same requirements and enforcement as a REMS that was originally submitted as a required proposed REMS. If an applicant voluntarily submits a proposed REMS, it will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria. Proposed REMS that are not approved are not subject to the requirements and enforcement of an approved REMS. FDA will notify applicants who voluntarily submit a proposed REMS whether the REMS will be required. If the FDA determines that a REMS is not required, an applicant may undertake voluntary risk management measures that would be performed outside of a REMS.

### B. Relationship Between REMS and RiskMAPs

Before FDAAA was enacted, FDA approved a small number of drug and biological products with risk minimization action plans (RiskMAPs). A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required safety reporting. For the majority of approved products, labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits. In a small number of cases, when additional measures were needed to ensure that the benefits of a drug outweigh the risks of the drug, FDA approved the drug with a RiskMAP. In 2005, FDA issued a guidance for industry on *Development and Use of Risk Minimization Action Plans*[4] (the RiskMAP guidance), that described how to develop RiskMAPs, select tools to minimize risks, evaluate and monitor RiskMAPs and monitoring tools, and communicate with FDA about RiskMAPs.

Now that FDAAA has given FDA the authority to require REMS when necessary to ensure that the benefits of a drug outweigh the risks, FDA anticipates that:

- A product that would previously have been approved with a RiskMAP will, instead, be approved with a REMS if statutory requirements for a REMS are met.[5]
- Products that would previously have been approved with a Medication Guide or patient package insert that meet the statutory requirements for a REMS will now be required to have a REMS.
- While certain products approved with RiskMAPs that included certain types of risk management tools have been deemed to have in effect an approved REMS (see section II.C of this document), all other approved RiskMAPs and approved Medication Guides and patient package inserts that were in place when Subtitle A took effect will continue to be in effect, unless they are replaced by or included in a REMS. They will be

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf
[5] Unless it is an ANDA based on a reference listed drug with an approved RiskMAP.

replaced by or included in a REMS if FDA determines, based on new safety information identified after approval of the product, that a REMS is necessary to ensure that the benefits of the drug outweigh the risks.

- ANDAs for which the reference listed drug has an approved RiskMAP will be approved with a comparable RiskMAP that includes the same essential elements.
- ANDAs for which the reference listed drug has a REMS will be approved with the elements of that REMS applicable to ANDAs.
- Revisions of existing Medication Guides or patient package inserts that meet REMS requirements will be approved as part of a REMS.

Many of the principles that were included in the RiskMAP guidance are embodied in the FDAAA REMS provisions as implemented by FDA. Many of those principles pertaining to REMS are included in this guidance, and others will be included in future guidance documents related to REMS. The RiskMAP guidance continues to apply to products with existing RiskMAPs (e.g., products with RiskMAPs that were not deemed to have in effect an approved REMS) and to products with new RiskMAPs (e.g., ANDAs for which the reference listed drug has a RiskMAP).

### C. Products Deemed to Have in Effect an Approved REMS

Section 909(b)(1) of FDAAA addresses products approved before the effective date of Subtitle A that have been deemed to have in effect an approved REMS.

> A drug that was approved before the effective date of this Act is . . . deemed to have in effect an approved risk evaluation and mitigation strategy under section 505-1 of the Federal Food, Drug, and Cosmetic Act . . . if there are in effect on the effective date of this Act elements to assure safe use—
>
> (A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or
>
> (B) otherwise agreed to by the applicant and the Secretary for such drug.

Section 909(b)(2) states that the REMS for a drug deemed to have an approved REMS consists of the timetable required under section 505-1(d) and any additional elements under subsections 505-1(e) and (f) in effect for the drug on the effective date of FDAAA.

Section 909(b)(3) of FDAAA states:

> Not later than 180 days after the effective date of this Act, the holder of an approved application for which a risk evaluation and mitigation strategy is deemed to be in effect . . . shall submit to the Secretary a proposed risk evaluation and mitigation strategy. Such proposed strategy is subject to section 505-1 of the Act as if included in such application at the time of submission of the application to the Secretary.[6]

[6] 121 Stat. 951.

On March 27, 2008, FDA published in the *Federal Register* a list of drugs that were identified as deemed to have an approved REMS, and directed holders of approved applications for those products to submit a proposed REMS by September 21, 2008.[7] For most of these drugs, the elements of the existing RiskMAPs or restricted distribution and risk management programs were or will be simply converted to the new content and format of a REMS in the proposed REMS. FDA generally does not intend to make substantial changes to these programs during this conversion unless new safety or effectiveness information identified since the drug was approved (including an evaluation of the program identifying deficiencies) suggests that the existing REMS should be modified to ensure that the benefits of the product outweigh the risks. In those cases, FDA has or will require modifications to the REMS.

## D. Content of a REMS

A REMS for an NDA or BLA product must have a timetable for submission of assessments of the REMS (505-1(d)). In addition, a REMS may include any or all of the other REMS elements, if specified criteria are met. These additional elements are listed below and described in more detail in section III of this document:

### *1. Timetable for Submission of Assessments*

Section 505-1(d) requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. FDAAA specifies that the timetable for submission of assessments of the REMS must include an assessment by the dates that are 18 months and 3 years after the strategy is approved, and an assessment in the 7th year after the strategy is approved, or at another frequency specified in the strategy (see section III.A.6 of this document for additional information).

### *2. Additional Potential Elements*

Section 505-1(e) lists "Additional Potential Elements" of a REMS that may include the following (see section III.A.3 of this document for additional information):

- A Medication Guide as provided for under part 208 of title 21, Code of Federal Regulations
- A patient package insert if such insert may help mitigate a serious risk of the drug
- A communication plan to health care providers if the plan may support implementation of an element of the strategy

### *3. Elements to Ensure Safe Use (ETASU)*

[7] See *Federal Register* Notice "Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (REMS) for Purposes of the Food and Drug Administration Amendments Act of 2007" (73 FR 16313, March 27, 2008).

Section 505-1(f)[8] lists certain *Elements to Assure Safe Use* that may be required if the drug has been shown to be effective, but is associated with a serious adverse event and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate the specific serious risk(s) listed in the labeling of the product. Elements to assure safe use may be required for approved products when an assessment and Medication Guide, patient package insert, or communication plan are not sufficient to mitigate these risks. The elements to assure safe use must include one or more goals to mitigate the specific serious risk(s). If a REMS includes certain elements to assure safe use, the REMS may also include required implementation systems to enable the applicant to monitor, evaluate, and improve the implementation of the elements (see section III.A.4 of this document for additional information).

This guidance document uses the word *tool* to describe a process or system designed to implement one or more REMS elements. In some cases, an element itself, such as a Medication Guide, may be viewed as a tool. In other cases, such as for an ETASU that requires that a drug be dispensed to patients with evidence or other documentation of safe-use conditions (505-1(f)(3)(D)), specific tools are used to implement a REMS element; for example, systems to ensure that certain laboratory test result outcomes are obtained before a drug may be dispensed.

## E. Assessments and Modifications of Approved REMS

FDAAA includes provisions for the assessment and modification of an approved REMS in section 505-1(g). Additional information on assessments and modifications is included in sections III.B.4 and IV of this document.

### *1. Voluntary Assessments and Proposed Modifications (505-1(g)(1) and (4))*

In addition to required assessments of an approved REMS described below, an applicant may voluntarily submit an assessment of, and propose modifications to, an approved REMS at any time. Proposed modifications may enhance or reduce the approved REMS, and may include additions to or modifications of the timetable for submission of assessments, including a proposal to eliminate assessments, and/or the addition, modification, or removal of a Medication Guide, patient package insert, communication plan or ETASUs.

### *2. Required assessments (505-1(g)(2))*

REMS assessments are **required** under the following circumstances:

- When submitting a supplemental application for a new indication for use, unless the approved REMS for the drug includes only a timetable for submission of assessments. FDA anticipates rarely requiring a REMS that includes only a timetable for submission of assessments.

[8] FDA is considering the implications of section 505-1(f) on the restricted distribution provisions under 21 CFR 314 Subpart H (drugs) – 314.520, and 21 CFR 601 Subpart E (biologics) – 601.42 and will address this in a future guidance.

- When required by the approved REMS, as provided for in the timetable for submission of assessments
- When required by the FDA, within a time period to be determined by the FDA, if the FDA determines that new safety or effectiveness information indicates that the timetable for submission of assessments should be modified and/or that a Medication Guide, patient package insert, communication plan, or ETASUs should be added, modified, or removed
- Within 15 days when ordered by the FDA, if the FDA determines that there may be a cause for withdrawal or suspension of approval under section 505(e) of the FDCA

### F. REMS Are Enforceable

REMS required under section 505-1 are subject to inspection and are enforceable under the FDCA as amended by FDAAA.[9] A drug is misbranded under section 502(y) if the responsible person for that drug[10] fails to comply with a requirement of the approved strategy. Also, under section 303(f)(4)(A) of the FDCA, a responsible person who violates a REMS requirement is subject to civil monetary penalties of up to $250,000 per violation, not to exceed $1 million in a single proceeding. These penalties increase if the violation continues more than 30 days after FDA notifies the responsible person of the violation. The penalties double for the second 30-day period, and continue to double for subsequent 30-day periods, up to $1 million per period and $10 million per proceeding. In imposing a monetary penalty, FDA will consider the responsible person's efforts to correct the violation. In addition, under 505(p), a person may not introduce or deliver for introduction into interstate commerce an approved drug that is the subject of a covered application, if a REMS is required with respect to that drug, and the person fails to maintain compliance with the requirements of the approved REMS or with other requirements under 505-1, such as requirements regarding assessments of approved REMS.

## III. CONTENT OF A PROPOSED REMS SUBMISSION TO FDA

A proposed REMS submission to FDA should include two parts: a *proposed REMS*, which is a concise document that describes the proposed goals and elements of the REMS and, once approved, will be the basis for enforcement; and a *REMS supporting document*, that expands on information included in the proposed REMS and provides additional information not included in the proposed REMS, including a thorough explanation of the rationale for, and supporting information about, the content of the proposed REMS. These two parts of a proposed REMS submission are described below.

### A. Content of the Proposed REMS

The proposed REMS should include concise information describing the goal(s) of the REMS and the REMS element(s) proposed for inclusion in the approved REMS for the specified product.

[9] See FDAAA Title IX, section 902.

[10] The term 'responsible person' means the person submitting a covered application or the holder of the approved such application. Section 505-1(b)(7).

All proposed materials that are included as part of the REMS (e.g., proposed communication and education materials, Medication Guide, patient package insert, enrollment forms, prescriber and patient agreements) should be appended to the proposed REMS. The proposed REMS should be written to clearly describe the responsibilities of the applicant in implementing the REMS; for example, statements will generally begin with, "[Name of the applicant] will…" The proposed REMS should include the date by which each of the REMS elements will be implemented.

A template for the proposed REMS is available on the FDA's "Postmarket Drug Safety Information for Patients and Providers" Web site, at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm. Attachment A provides an example of a completed proposed REMS for a fictitious product that an applicant would submit to FDA for review. The preferred template may be periodically updated as we gain more experience with REMS; therefore, applicants should check the Web site for the latest version. Questions should be directed to the FDA contacts described in section V.C of this document.

Prior to approving a REMS, FDA may require applicants to revise a proposed REMS to ensure that the benefits of the drug will outweigh the risks.

FDA will append any REMS materials that will be included in the approved REMS, as described above, to the final REMS. The final REMS and appended documents will be referenced in and appended to the approval letter for the application or supplement that contains the proposed REMS, and the approval letter and appended documents will be posted on the following FDA Web sites:

For products regulated by CDER:

- The Drugs@FDA Web site at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
- The Postmarket Drug Safety Information for Patients and Providers Web site (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm). This Web site also includes a list of approved REMS (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm). The list of approved REMS includes links to the REMS document and REMS materials, excluding Medication Guides.
- Medication Guides can be accessed on the Drugs@FDA Web site and on the Postmarket Drug Safety Information for Patients and Providers Web site through the link to approved Medication Guides (http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm).

For products regulated by CBER:

- The Biologics Products and Establishments Web site at http://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm
- The Postmarket Drug Safety Information for Patients and Providers Web site (see link above)

The elements of an approved REMS are enforceable under FDAAA, Title IX, section 902 (see section II.F of this document), and any changes to the REMS, including to the appended documents, must be submitted as a proposed modification of an approved REMS and approved by FDA before being implemented (see section IV).

The proposed REMS should contain the following sections as appropriate to manage the risks of the particular product; if an applicant is not proposing one of the elements, the proposed REMS should include a statement that the element is not necessary.

### *1. Product and Contact Information*

The proposed REMS should include the application number, proprietary and established names, dosage form of the product, the drug class as described in the product's label, and the applicant's name and address. The proposed REMS should also include contact information, including position titles, for those responsible for the REMS policy, management, and implementation.

### *2. Goals*

All REMS should include a statement of one or more overall goals. In addition, if the REMS has one or more elements to assure safe use (505-1(f)), the REMS must include one or more goals to mitigate a serious risk listed in the labeling of the drug for which the ETASUs are required. Even when ETASUs are not part of a REMS (e.g., a REMS with a Medication Guide or communication plan only), the goals of the REMS should be identified. Assessments of approved REMS should measure whether the goals are being met.

As used in this document, a proposed REMS goal is the desired safety-related health outcome or the understanding by patients and/or health care providers of the serious risks targeted by the use of specified REMS elements. REMS goals should target the achievement of particular health outcomes or knowledge related to known safety risks and should be stated in a way that aims to achieve maximum risk reduction. The following are examples of REMS goals: "Patients taking W drug should be aware of the serious risks relative to the potential benefits," "Patients on X drug should not also be prescribed Y drug," or "Fetal exposures to Z drug should not occur." Goals should be stated in absolute terms. Although it might not be possible to ensure that the goal can be met for every patient (i.e., no one on X drug receives Y drug), FDA believes that a goal, as the term implies, is a statement of the ideal outcome of a REMS.

REMS goals should be associated with pragmatic, specific, and measurable program objectives that result in processes or behaviors leading to achievement of the REMS goals. Objectives can be thought of as intermediate steps to achieving the overall REMS goal. A REMS goal can be associated with more than one objective, depending upon the frequency, type, and severity of the specific risk or risks being minimized. For example, a goal may be the elimination of occurrences of a serious adverse event caused by an interaction of the drug with another drug. The objectives could include lowering physician co-prescribing rates and/or pharmacist co-dispensing rates for the specific drugs.

*3. Additional Potential REMS Elements*

(a) Medication Guide and/or Patient Package Insert

As one element of a REMS, the FDA may require the development of a Medication Guide, as provided for under 21 CFR part 208, which sets forth requirements for patient labeling for human prescription drug products, including biological products, that the FDA determines pose a serious and significant public health concern requiring the distribution of FDA-approved patient information. Medication Guides will be required if the FDA determines that one or more of the following circumstances exist:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Under 21 CFR part 208 and in accordance with 505-1 of the FDCA, the applicant is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed the drug. This section of the REMS should describe the mechanisms the applicant intends to use for distribution of the Medication Guide.

In addition, FDA may require a patient package insert as part of a REMS if the FDA determines that the patient package insert may help mitigate a serious risk of the drug. Having both a required patient package insert and a Medication Guide for the same drug is not expected to occur frequently. In most instances, FDA anticipates requiring a Medication Guide (or requiring conversion of an existing PPI to a Medication Guide) if FDA is requiring patient labeling that meets Medication Guide requirements.

The following types of changes to a PPI would **not** ordinarily trigger the need to convert a PPI to a Medication Guide:

- Editorial changes
- Changes related to how to use a product (e.g., how to inject the product subcutaneously) *unless* these changes have the potential to mitigate a serious risk, such as overdose

Copies of Medication Guides and patient package inserts that are part of a REMS should be appended to the proposed REMS.

(b) Communication Plan

FDA may determine that a communication plan targeted at health care providers is a necessary element of a REMS if it may support implementation of the REMS. The communication plan may include sending letters to health care providers; disseminating information about REMS elements to encourage implementation by health care providers or to explain certain safety protocols, such as medical monitoring by periodic laboratory tests; or disseminating information to health care providers through professional societies about any serious risks of the drug and any protocol to assure safe use (section 505-1(e)(3)).

Copies of communication plan materials should be appended to the proposed REMS.

If an NDA has been approved with a REMS with a communication plan, and subsequently an abbreviated new drug application (ANDA) is approved with that NDA product as the reference listed drug, then FDA must undertake the communication plan (section 505-1(i)(2)(A)). Neither the holder of the NDA that is the reference listed drug nor the ANDA holder has to undertake a communication plan once an ANDA is approved. However, many tools that have previously been considered part of a communication plan, such as training materials, specified procedures, patient/physician agreements or other informed consent, patient educational materials, safety protocols, medical monitoring procedures, and data collection forms may fit under one or more elements to assure safe use (ETASU) if specified criteria are met. Both NDA holders and ANDA holders are required to implement ETASUs.

*4. Elements to Assure Safe Use*

Elements to assure safe use are intended to provide safe access for patients to drugs with known serious risks that would otherwise be unavailable. Required ETASUs are put in place to mitigate a specific serious risk listed in the labeling of a drug. Before requiring one or more ETASUs, the FDA must make the following determinations (505-1(f)(1)):

- That the drug, which has been shown to be effective but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements were required; and
- That for a drug initially approved without ETASUs, other possible elements of a REMS are not sufficient to mitigate such serious risk.

This subsection of the proposed REMS should describe the ETASUs included in the proposed REMS and any tools designed to implement one or more elements to assure safe use. Copies of all relevant materials should be appended to the proposed REMS. Examples of relevant materials include health care provider attestations; pharmacy, practitioner, health care setting, and patient enrollment forms; training materials; specified procedures; patient/physician agreements or other informed consent; patient educational materials; safety protocols; medical monitoring procedures; and data collection forms.

The following lists the elements to assure safe use that may be included in the REMS. Note that some of the tools designed to implement the elements to assure safe use may appear in more than one category:

A. Health care providers who prescribe the drug have particular training or experience, or are specially certified.

In general, section 505-1(f)(3)(A) pertains to prescribers of the drug. Elements under this category might require certification of training, or attestation of specific experience or knowledge, before the health care provider is enrolled in a program that allows that provider to prescribe the product.

For example, in order to be certified, a health care provider may be required to demonstrate that he or she:

- Can diagnose the condition for which the product is indicated
- Understands the risks and benefits of the product and has read the educational materials for prescribers
- Can diagnose and treat potential adverse reactions associated with the product

The program may require periodic recertification and reenrollment.

The opportunity to obtain this training or certification must be available to any willing provider, for example through an on-line or mail course, at reasonable cost to the provider (505-1(f)(3)(A)).

B. Pharmacies, practitioners, or health care settings that dispense the drug are specially certified.

In general, section 505-1(f)(3)(B) pertains to how the drug is dispensed. Elements under this category might require certification of training or attestation of specific experience or knowledge before the pharmacy, practitioner, or health care setting is enrolled in a program that allows the practitioner or staff at the pharmacy or health care setting to dispense the product.

For example, to be certified, practitioners and staff at pharmacies, hospitals, and infusion sites may be required to demonstrate that they:

- Understand the risks and benefits of the product and have read the educational materials before the drug is dispensed
- Agree to fill a prescription and dispense the drug only after receiving prior authorization
- Agree to check laboratory values, or check for the presence of stickers that providers affix to prescriptions for specified products to indicate that the patient has met all criteria for receiving the product (“qualification stickers”), before dispensing a drug
- Agree to fill a prescription and dispense the drug only within a specified period of time after the prescription is written
- Agree to fill prescriptions only from enrolled prescribers

The program may require periodic recertification and reenrollment.

The opportunity to obtain this certification must be available to any willing provider (505-1(f)(3)(B)).

C. The drug be dispensed to patients only in certain health care settings, such as hospitals.

In general, section 505-1(f)(3)(C) pertains to restrictions on dispensing the product to patients in specific health care settings.

For example, the applicant may be required to

- Ensure the drug is dispensed only to patients in hospitals that have met certain conditions
- Ensure the drug is dispensed only to physicians' offices equipped to treat the potential risks associated with the drug following administration of the drug (e.g., access to medication and equipment necessary to treat a serious allergic reaction)

D. The drug be dispensed only to patients with evidence or other documentation of safe-use conditions, such as laboratory test results.

In general, section 505-1(f)(3)(D) pertains to ensuring that patients meet specified criteria before drug exposure.

For example, evidence or other documentation of safe use conditions may include the following:

- Patients have been counseled about the risks and benefits of the product and have signed an acknowledgment that they understand the risks and benefits of the product
- Patients have been provided a copy of patient educational materials and demonstrated that they understand the risks and benefits of the product
- Patients receive drug only after specified authorization is obtained and verified by the pharmacy. Examples of authorizations include checking laboratory values and checking for physician qualification (stickers) on the prescription

E. Each patient using the drug be subject to certain monitoring.

Elements under 505-1(f)(3)(E) might require that patients be monitored or that specific follow-up should occur at specific time points.

Examples include the following:

- Patients' laboratory tests are monitored on a specified periodic basis to prevent the serious risk
- Patients are required to contact the prescriber within a specified period of time after beginning treatment with the drug to ensure they are still appropriate candidates for treatment
- Patients are required to contact their prescriber periodically during and following treatment to ensure they did not experience the serious risk associated with the use of the drug

F. Each patient using the drug be enrolled in a registry.

In general, section 505-1(f)(3)(F) pertains to enrolling patients into a program as part of an overall strategy to mitigate a specific serious risk listed in the labeling of the drug. The use of a registry may be combined with other ETASUs, such as when a registry is used to document that the drug is dispensed to patients with evidence or other documentation of safe-use conditions; or to document that each patient using the drug is subject to certain monitoring.

Drug access may be contingent on patient enrollment. The types of information that may be collected on enrolled patients include:

- Information on clinical outcomes
- Clinical and laboratory data
- Safety information
- Data on compliance with prescribed management and prescribing protocols
- Data on the impact of tools on ensuring compliance and outcomes

Registries that are established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug would be required under a REMS. Registries may also serve as a repository for clinical data and allow for case finding and follow-up. These registries are not considered PMRs, but studies conducted using the data may be.[11]

*5. Implementation System*

Section 505-1(f)(4) of the FDCA gives the FDA authority to require an implementation system for a REMS that includes the ETASUs described under 505-1(f)(3)(B), (C), and (D). Through the implementation system, the applicant may be expected to take reasonable steps to monitor and evaluate implementation by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing those elements, and to work to improve their implementation.

[11] See the draft guidance for industry on *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act*, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

FDA may require the implementation system to include a description of how applicable products will be distributed. In addition, as part of the implementation system, FDA may require the certification of wholesalers and/or distributors who distribute the product to ensure that the product is distributed only to certified or otherwise specified pharmacies, practitioners, or health care settings that dispense the drug, or only to patients who meet the requirements of the REMS.

Other examples of methods used to monitor and evaluate implementation of REMS with ETASUs described under 505-1(f)(3)(B), (C), and (D) include the following:

- The applicant maintains a validated and secure database of all certified entities (pharmacies, practitioners, and health care settings) to ensure any certification requirements or other requirements for pharmacies, practitioners, or health care settings are met
- The applicant conducts periodic audits of pharmacies, practitioners, and health care settings to ensure compliance with ETASUs (e.g., documentation of safe-use conditions prior to dispensing drug)
- If the ETASUs include limits on where and how a drug may be dispensed, the applicant conducts periodic audits of wholesale shipment or distribution systems to determine that the drug is only being distributed to authorized entities

#### *6. Timetable for Submission of Assessment of the REMS*

This subsection of the proposed REMS should describe the proposed timetable for submission of assessments of the REMS as required by section 505-1(d) of the FDCA. REMS for NDAs and BLAs must include a timetable for submission of assessments of the REMS. REMS for ANDAs do not include a timetable for submission of assessments. Additional information on REMS and ANDAs will be included in future guidance.

Under section 505-1(d), each timetable for submission of assessments of a REMS must at a minimum include assessments submitted by 18 months and by 3 years after the REMS is initially approved, and in the 7th year after the REMS is initially approved, with additional dates if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. Factors that may influence the need for more frequent assessments of the REMS include, among others, the estimated size of the population likely to use the drug, the seriousness of known or potential risks that may be related to the drug, and knowledge about the effectiveness of REMS elements to mitigate the risks. The requirements for the assessments submitted by 18 months and by 3 years may be met through assessments submitted at specified earlier dates; for example, assessments required in an approved REMS to be submitted at 12 months and 24 months would meet the requirements for the assessments submitted by 18 months and 3 years.

The timetable specifies when the assessment will be submitted to FDA, not when the assessment will be performed. This subsection should specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an

assessment that is to be submitted by July 31 should conclude no earlier than June 1. The assessment is to be received by the FDA on or before the due date.

Requests for modification of the timetable for submission of assessments, including eliminating assessments, may be made after approval of the REMS (see 505-1(g)(4)). After the assessment due by 3 years after the REMS is initially approved is submitted, all further assessments, including the 7th-year assessment, may be eliminated if the FDA determines that serious risks of the drug have been adequately identified and assessed and are being adequately managed.

## B. Content of the REMS Supporting Document

The REMS supporting document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS. A template for the REMS supporting document is available on the FDA's "Postmarket Drug Safety Information for Patients and Providers" Web site, at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm. The REMS supporting document should include the sections listed in the template for the applicable proposed REMS elements for the specified product, as well as a table of contents. The REMS supporting document should include a description of how and when each REMS element will be implemented and should specify the rationale for the overall timelines and milestones. If any REMS activity will not be implemented at the time of REMS approval, the REMS supporting document should include the rationale for the implementation schedule. For example, the document should address the rationale for whether a communication plan would be implemented before, or concurrently with, other elements. Additional information on each section of the REMS supporting document is described below.

### *1. Background*

The Background section of the REMS supporting document should explain why a REMS is necessary and provide a concise summary of how the proposed REMS would ensure that the benefits of the drug outweigh the risks. For a new REMS that is proposed for an already-approved product, the Background section should also include the description of the new safety information that suggests a REMS is necessary.

The Background section should describe what is known about the risk to be minimized by the REMS, including the magnitude, severity, and frequency of the adverse events, whether there are particular populations at risk, the background incidence of the risk in the population likely to use the product, whether the adverse event can be prevented or is reversible, and the benefits that would be preserved by the implementation of the REMS. It should also describe the factors that FDA considers when determining whether a REMS is necessary to ensure that the benefits of the drug outweigh the risks: the estimated size of the population likely to use the product, the seriousness of the disease or condition that is to be treated with the product, the expected benefit of the product with respect to such disease or condition, the expected or actual duration of treatment with the drug, the risks and benefits of alternative therapies, and whether the drug is a new molecular entity. The statute specifically requires these factors to be considered for REMS

required at initial approval (505-1(a)(1)), but FDA will also consider these factors in making determinations about postapproval REMS.

The Background section of the REMS supporting document should include a discussion, if pertinent, about the successes and failures of actions by regulatory authorities, systems of health care, or applicants in mitigating the risks of concern for this product or similar products. Information on risk management plans submitted to other regulators, such as the European Union's EU Risk Management Plan,[12] should be included, with a clear description of how that information supports the proposed REMS, along with reasons for any differences between the proposed REMS and other risk management plans for the product.

Information provided by the applicant regarding relevant past experiences, domestically or in other countries, will assist in the development of REMS that are compatible with established distribution, procurement, and dispensing systems within the health care delivery system, and that avoid the cost of implementing REMS tools already determined to be unsuccessful. In addition, we encourage applicants to provide applicable information or evaluations from past experiences with products or programs that are similar to the proposed REMS. Brief descriptions of the available evidence regarding the effectiveness of each element and tool included in the proposed REMS may be mentioned in the Background section. Thorough descriptions should be included in the "Supporting Information on Proposed REMS Elements" section.

### *2. Goals Section*

This section of the REMS supporting document should describe the rationale for the proposed goals of the REMS and summarize how each proposed element and stated objectives will individually and collectively contribute to achieving the goals. All REMS should include a statement of one or more overall goals. In addition, if the REMS has one or more elements to assure safe use (505-1(f)), the REMS must include one or more goals to mitigate a serious risk listed in the labeling of the drug for which the elements to assure safe use are required. Even if a REMS does not contain elements to assure safe use (e.g., a REMS that includes a Medication Guide or communication plan only), the goals of the REMS should be identified. Additional information about how each particular element and tool will contribute to achieving the goals of the REMS should be included in the "Supporting Information About Proposed REMS Elements" section described immediately below. REMS goals are described in more detail in section III.A.2 of this document.

### *3. Supporting Information About Proposed REMS Elements*

This section should include a description of why particular elements and tools were chosen for the proposed REMS and how each particular element and tool will contribute to achieving the goals of the REMS. Each subsection about elements included in the proposed REMS should include a thorough description of the element(s) proposed for mitigating the risk or risks targeted by the proposed REMS; any tools proposed to be implemented under each element; how the

[12] GUIDELINE ON RISK MANAGEMENT SYSTEMS FOR MEDICINAL PRODUCTS FOR HUMAN USE, Doc. Ref. EMEA/CHMP/96268/2005 http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf.

elements or tools will mitigate the risk; how the elements or tools conform with elements or tools for other products with similar risks; and whether the elements or tools are compatible with established distribution, procurement, and dispensing systems.

A thorough description of the available evidence regarding the effectiveness of each element or tool should be provided, including, where applicable, results from pretesting of proposed elements or tools or a time frame for when these will be submitted. These subsections should also note whether the applicant sought input from patient or health care interests, and if so, a description of the feedback received regarding the feasibility of its REMS.

*Elements to Assure Safe Use*. Section 505-1(f)(2) requires that FDA consider how to ensure access and minimize the burden of a REMS that includes ETASUs. Therefore, for a proposed REMS that includes ETASUs, the Elements to Assure Safe Use subsection of the REMS supporting document should include the following:

- An explanation of how the proposed ETASUs correspond to the specific serious risks listed in the labeling
- An explanation of how the proposed ETASUs will mitigate the observed serious risk
- Verification that the proposed elements are not unduly burdensome on patient access to the drug considering the risk being mitigated. Include particular consideration of patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care.
- A description of how, to the extent practicable, the proposed ETASUs will minimize the burden on the health care delivery system: how the proposed ETASUs conform to those required for other drugs with similar serious risks, and how the proposed elements are designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

*Implementation System.* This subsection should include the rationale and supporting information for the proposed implementation system, including each method used to monitor and evaluate implementation of the REMS and any planned ways to improve its implementation.

*Timetable for Submission of Assessments of the REMS.* This subsection should include the rationale and supporting information for the proposed timetable for submission of assessments of the REMS. This subsection should also include the rationale for the interval that each assessment will cover and for the planned date the assessment will be submitted to the FDA.

### *4. REMS Assessment Plan*

This section should describe the rationale and supporting information for the proposed plan to assess the REMS. Section 505-1(g) of the FDCA describes the requirements for REMS assessments. REMS assessments should include an evaluation of the extent to which each of the REMS elements are meeting the goals and objectives of the REMS, and whether or not the goals, objectives, or REMS elements should be modified. Plans to obtain this information should be included in the REMS supporting document to ensure that sufficient information will be collected to do a valid assessment of the REMS.

In accordance with section 505-1(g)(3)(A), for a REMS that includes one or more ETASUs, the REMS assessment shall include an assessment of the extent to which the ETASUs are meeting the goal (see section III.A.2), or whether the goal or such elements should be modified.

This subsection should describe the proposed REMS assessment plan, including the following:

- The proposed evaluation methods (including measurements or measures) for assessing the overall effectiveness of the REMS and the effectiveness of each of the REMS elements and tools (e.g., claims-based data systems, surveys, registries) and the rationales for the chosen measures.
- Targeted values for each measure and the timeframe for achieving them. Include interpretations of expected results under best- and worst-case scenarios. In addition, this section should specify what values of measures at specific time points will trigger consideration of REMS modification.
- The type of data that will be collected, and the nature and timing of data collection, analyses, audits, or monitoring that will be used to assess the performance of each individual REMS element or tool in achieving the REMS's objectives and goals.
- Where applicable and possible, this section should discuss plans to assess unintended and/or unfavorable consequences of the REMS following implementation.

For example, a REMS may indicate that the following data will be collected to support an assessment:

- A survey to evaluate knowledge of a labeled serious adverse event to determine whether patients are using the product correctly to prevent the adverse event, or to evaluate use of the product as labeled, particularly when the indicated use is for a restricted population or when numerous contraindications exist.

- Information about use patterns of the drug including:
    - Use by prescriber specialty
    - Patient-level data (age, gender, race)
    - Length of therapy
    - Indication

- Population-based administrative or claims-based data that capture service or payment claims to measure rates of specified serious adverse events.

- Active surveillance using sentinel reporting sites to determine rates of specified serious adverse events.

Whenever possible, specific assessment instruments (e.g., surveys) and methodology should be included in the REMS supporting document. If the assessment instruments and methodology are not available when the proposed REMS is submitted to FDA, at least 90 days before the assessments will be conducted, the applicant should update the REMS supporting document to include specific assessment instrument and methodology information. Updates to the REMS

supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions of the REMS, or updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. See section V.B.3 for information on how to identify the submission that includes specific assessment instruments when they are submitted after the REMS is approved.

For a REMS that includes a Medication Guide, information needed for assessment of the REMS should include but may not be limited to the following:

(a) Survey of patients' understanding of the serious risks of the drug
(b) Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
(c) Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

If a product is distributed in unit-of-use packaging that includes a Medication Guide with a quantity of product dispensed to a single patient and not divided, the reports in (b) and (c) above would not be necessary.

This subsection of the REMS supporting document might also include information describing the rationale for, and a description of, all elements proposed to be included in the assessments of the REMS, such as the following:

- Narrative summary and analysis of serious adverse events of interest
- Summary of data that will be tracked in a REMS-related database
- Summary of wholesaler shipment data
- Summary of surveys conducted
- Summary of data on drug use
- Summary of registry data
- Refill frequency and amount

The assessment should include sufficient detail to identify the need for changes to the REMS. For example, an applicant may be required to assess reports of adverse events associated with the effectiveness of the REMS, each known occurrence of prescriptions written by health care providers who do not have required certification, or dispensing of the product by a pharmacy, practitioner, or health care setting that does not have the required certification. The assessment should also describe any corrective actions taken for these occurrences.

### *Requirements for Information on the Status of Any Postapproval Study or Clinical Trial Required Under Section 505(o) or Otherwise Undertaken to Investigate a Safety Issue*

In accordance with section 505-1(g)(3)(B) and (C), all REMS assessments shall include certain information about any postapproval study or clinical trial required under section 505(o) or otherwise undertaken by the applicant to investigate a safety issue.

- For *postapproval studies*, the REMS assessment shall include the status of each study, including whether any difficulties completing the study have been encountered.
- For *postapproval clinical trials,* the REMS assessment shall include
  (a) The status of each clinical trial, including whether enrollment has begun,
  (b) The number of participants enrolled,
  (c) The expected completion date,
  (d) Whether any difficulties completing the clinical trial have been encountered, and
  (e) Registration information with respect to registry and results databank requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. This includes information on whether the data have been submitted to clinicaltrials.gov, and proper certifications have been submitted to the FDA.

The REMS assessment can satisfy the requirements in section 505-1(g)(3)(B) and (C), for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue, by referring to relevant information included in the most recent annual report required under section 506B of the FDCA and 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70, and including any updates to the status information since the annual report was prepared, as long as the information required about postapproval studies and clinical trials described above was provided in the annual report. Failure to submit a complete REMS assessment under 505-1(g)(3) could result in enforcement action.

*5. Other Relevant Information*

This subsection should include information on the positions within the applicant's company responsible for REMS policy, management, and implementation, including organizational chart(s) that include these REMS-related positions.

In addition, this subsection should include any other information relevant to the proposed REMS not included elsewhere.

## C. Foreign Language REMS

Foreign-language versions of REMS, including any materials appended to the REMS such as Medication Guides, patient package inserts, communication and education materials, enrollment forms, prescriber and patient agreements, and others, are not considered part of the approved REMS. FDA will not review foreign-language versions of REMS.

Consistent with CDER's approach to foreign-language labeling, when applicants distribute foreign-language versions of a currently approved REMS, they are responsible for ensuring that such materials are complete and accurate.[13] Supplemental applications for foreign-language REMS are not required and should not be submitted.

[13] Note that applicants are required to comply with the requirements regarding distribution of labels and labeling under 21 CFR 201.15(c).

## IV. REMS ASSESSMENT AND PROPOSED REMS MODIFICATION SUBMISSIONS TO FDA

REMS assessments must be submitted according to the timetable for submission of assessments included in the REMS, and as otherwise required (see section II.E of this document and 505-1(g)). Applicants may also voluntarily submit an assessment of, and propose a modification to, an approved REMS at any time. An applicant's proposal for modification of an approved REMS must include an assessment of the REMS.

Under section 505-1(g)(2)(C), when FDA determines that new safety information indicates that an element of the REMS, such as a Medication Guide, should be modified, the application holder is required to assess the REMS. Where the application holder agrees with the Agency's proposed modification to a REMS that consists solely of a Medication Guide and/or a communication plan, that assessment may consist of a statement that the Medication Guide and/or communication plan would be adequate with the proposed modifications to achieve its/their purpose.

Proposed modifications may include an enhancement or reduction to the approved REMS, and may include additions or modifications to the timetable for submission of assessments, including a proposal to eliminate assessments (after the 3-year period described in 505-1(d)), and/or the addition, modification, or removal of a Medication Guide, patient package insert, communication plan, or ETASU.

A proposed modification of an approved REMS that is not associated with an existing supplemental application should be submitted as a new prior-approval supplemental application as described in section V of this document.

Any proposed modification to the approved REMS, including any proposed changes to materials that are included as part of the REMS (e.g., communication and education materials, enrollment forms, prescriber and patient agreements), must be submitted as a proposed modification to an approved REMS in a new prior-approval supplemental application, as described in section V of this document, and must not be implemented until the modified REMS is approved by FDA.

Each proposed modification submission should include a new proposed REMS (based on the proposed REMS template described in section III.A) that shows the complete previously approved REMS with all proposed modifications highlighted. In addition, the submission should include an update to the REMS supporting document that includes the rationale for and description of all proposed modifications and any impact the proposed modifications would have on other REMS elements. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions of the REMS, or updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. The content of the proposed REMS and REMS supporting document are described in section III of this document. Additional information on assessments and modifications to approved REMS is included in section II.E of this document. More complete information on assessments and modifications of approved REMS will be the subject of future guidance.

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966 **V. COMMUNICATING WITH FDA REGARDING REMS**
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968 **A. Submission Type**
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970 A proposed REMS may be included in the initial submission of an original or supplemental
971 application, or may be submitted as an amendment to an existing original or supplemental
972 application. All supplemental applications that include a proposed REMS or proposed
973 modifications to an approved REMS should be submitted as prior-approval supplements, not as
974 changes being effected supplements (see 21 CFR 314.70 and 601.12).
975
976 A proposed REMS submitted after approval and not associated with an existing supplemental
977 application should be submitted as a new supplemental application.
978
979 Assessments of approved REMS may be submitted voluntarily at any time and must be
980 submitted as required in the timetable for submission of assessments of the REMS and as
981 otherwise required (see sections II.E and IV of this document). A REMS assessment alone (i.e.,
982 not proposing a modification) is not considered a supplemental application.
983
984 REMS assessments that include a proposed modification to the approved REMS should be
985 submitted either as a new supplemental application or included in a related supplemental
986 application. They can be included in a related supplemental application either at the time of
987 submission or as an amendment to the supplemental application.
988
989 A supplemental application for a new indication for use for a product with an approved REMS
990 must include a REMS assessment unless the drug is not subject to section 503(b) and the REMS
991 for the drug includes only the timetable for submission of assessments (505-1(g)(2)(A)). The
992 supplemental application for the new indication should include the required REMS assessment
993 and may propose modifications to the REMS.
994
995 A proposed REMS and proposed modifications to an approved REMS should be submitted using
996 the format in the template for a proposed REMS described in section III.A, and, to facilitate the
997 review process, the submission should include electronic versions of the proposed REMS or
998 proposed modifications to an approved REMS as an Adobe Acrobat pdf document and in a
999 document generated using a word processing program.
1000
1001 As described in section III.C, supplements for foreign-language REMS are not required and
1002 should not be submitted.
1003
1004 Send requests for current information on where REMS-related documents should be included
1005 when submitted as part of an electronic common technical document (eCTD) and questions
1006 about electronic submissions to FDA to the following email address: esub@fda.hhs.gov.
1007
1008 **B. Document Identification**
1009

### *1. Proposed REMS*

Regardless of when or how a proposed REMS is submitted, it is critical to provide identifying information on the submitted REMS document so that it can be tracked, routed, and reviewed appropriately. In each case, the first page of the submission should prominently identify the submission as providing a **PROPOSED REMS** in bold capital letters at the top of the page. This wording on the first page of the submission should be combined with any other applicable content identification, for example:

When the proposed REMS is submitted as part of an original application:

**NEW ORIGINAL APPLICATION FOR <name of drug>**
**PROPOSED REMS**

When the original proposed REMS is submitted as an amendment to an existing original or supplemental application:

**NDA/BLA/ANDA [assigned #]**
**PROPOSED REMS**

**NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]**
**PROPOSED REMS**

When the original proposed REMS is submitted postapproval as a new supplemental application:

**NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]**
**PROPOSED REMS**

When the original proposed REMS is submitted postapproval with a new supplemental application:

**NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]**
< other applicable content identification >
**PROPOSED REMS**

On the first page of subsequent submissions related to an already-submitted proposed REMS, prominently identify the submission by including this wording in bold capital letters at the top of the letter:

**NDA/BLA/ANDA [assigned #]**
**PROPOSED REMS-AMENDMENT**

**NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]**
**PROPOSED REMS-AMENDMENT**

*2. Assessments and Modifications of Approved REMS*

On the first page of the submission of an assessment of an approved REMS, prominently identify its content in bold capital letters at the top of the page:

**NDA/BLA/ANDA [assigned #]**
**REMS ASSESSMENT**

If a REMS assessment is submitted as a part of another submission, it is critical to provide complete identifying information on the submission so that it can be tracked, routed, and reviewed appropriately. In each case, the first page of the submission should prominently identify the submission as providing a **REMS ASSESSMENT** in bold capital letters at the top of the page. This wording on the first page of the submission should be combined with any other applicable content identification.

The first page of the submission of an assessment of an approved REMS submitted with a supplemental application for a new indication for use should prominently identify the content in bold capital letters at the top of the page. The submission may include proposed modifications to the approved REMS. This wording on the first page of the submission should be combined with any other applicable content identification, for example:

**NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]**
< other supplement identification >
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

The first page of the submission of proposed modifications to an approved REMS submitted as a stand-alone new supplemental application or included with another new supplemental application should prominently identify the content in bold capital letters at the top of the page. This wording on the first page of the submission should be combined with any other applicable content identification, for example:

**NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]**
< other supplement identification >
**PROPOSED REMS MODIFICATION**
**REMS ASSESSMENT**

The first page of the submission of proposed modifications to an approved REMS submitted as an amendment to a pending supplemental application should prominently identify the content in bold capital letters at the top of the page:

**NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]**
**PROPOSED REMS MODIFICATION**
**REMS ASSESSMENT**

The first page of subsequent submissions related to a proposed modification to an approved REMS should prominently identify the submission by including this wording in bold capital letters at the top of the page:

**NDA/BLA/ANDA [assigned #] SUPPLEMENT [assigned #]**
**PROPOSED REMS MODIFICATION -AMENDMENT**

*3. Other REMS Submissions*

An applicant may submit REMS submissions that are not proposed REMS, proposed modifications to an approved REMS, amendments to proposed REMS, proposed modifications to an approved REMS, or REMS assessments. Such submissions may include a request for information about what to include in a proposed REMS, information about the REMS assessment plan for an approved REMS (e.g., assessment instruments and methodology), general correspondence about an approved REMS that does not include a proposed modification, amendment to a proposed modification, or a REMS assessment, or other submissions that do not fall into the categories described above. On the first page of such submissions, prominently identify its content with the words, "**REMS - OTHER**" followed by a concise description of the content in bold capital letters at the top of the page. For example:

**NDA/BLA/ANDA [assigned #]**
**REMS-OTHER**
**SURVEY METHODOLOGY**

The first page of a submission requesting Agency input on the content of a proposed REMS that has **not** yet been submitted should include the following wording in bold capital letters at the top of the page:

**NDA/BLA/ANDA [assigned #]**
**REMS-OTHER**
**REQUEST FOR GUIDANCE ON CONTENT OF PROPOSED REMS**

If the proposed REMS has already been submitted, such a request should be identified as a proposed REMS amendment – see section V.B.1.

## C. Questions about REMS

In the Center for Drug Evaluation and Research (CDER), the primary contact about a proposed REMS for a product under an NDA or BLA is the regulatory project manager in the Office of New Drugs (OND) review division assigned to that product. The primary contact about a proposed REMS for a product under an ANDA is the Director of the Division of Labeling and Program Support in the Office of Generic Drugs (OGD). The Office of Surveillance and Epidemiology, and other program offices as needed, will work with OND and OGD in the review and development of a proposed REMS.

In the Center for Biologics Evaluation and Research (CBER), the primary contact about a proposed REMS is the regulatory project manager in the office with product responsibility. The Office of Biostatistics and Epidemiology, and other program offices as needed, will work with the product office in the review and development of a proposed REMS.

**GLOSSARY** – applicable to terms as used in this document

**Assessment**: An assessment of the approved REMS as described in section II.E and III.B.4 of this document.

**Changes Being Effected Supplement**: Also called a "changes being effected supplemental application." A supplement that includes changes that do not require supplement submission and approval prior to the changes being implemented; the application holder may commence distribution of the drug product involved upon receipt by the agency of a supplement for these changes. A "Changes Being Effected in 30 days" supplement includes changes that do not require approval prior to the changes being implemented, but requires supplement submission at least 30 days prior to distribution of the drug product made using the change. If, after review, FDA disapproves a changes being effected supplement or a changes being effected in 30 days supplement, FDA may order the manufacturer to cease distribution of the drug products made using the disapproved change (21 CFR 314.70(c) and 601.12(c)). See section V.A of this document.

**Goal**: The desired safety-related health outcome or the understanding of serious risks targeted by the use of specified REMS elements. See section III.A.2 of this document.

**Objective**: An intermediate step to achieving the overall goals of the REMS. Objectives should be pragmatic, specific, and measurable. Objectives may use one or more elements or tools that result in processes or behaviors leading to achievement of the REMS goals. A REMS goal can be translated into different objectives, depending upon the frequency, type, and severity of the specific risk or risks being minimized. See section III.A.2 of this document.

**Prior-approval Supplement:** Also called a "prior-approval supplemental application." A supplemental application that includes changes requiring supplement submission and approval prior to the distribution of the product made using the change. (21 CFR 314.70(b) and 601.12(c)). See section V.A of this document.

**Qualification Stickers:** Stickers given by the applicant to providers to affix to prescriptions for specified products to indicate that the patient has met all criteria for receiving the product.

**REMS**: Stands for "Risk Evaluation and Mitigation Strategy," and is the enforceable document that describes the elements that an applicant is required to implement. See section III.A of this document.

**REMS Supporting Document**: A document that includes a thorough explanation of the rationale and supporting information for the content of the proposed REMS. See section III.B of this document.

**Tool**: A process or system designed to implement one or more REMS elements. In some cases an element itself, such as a Medication Guide, may be viewed as a tool. In other cases, such as for an ETASU that requires that a drug be dispensed to patients with evidence or other documentation of safe-use conditions (505-1(f)(3)(C)), specific tools are used to implement a

REMS element. Examples of such tools include systems that ensure certain laboratory test result outcomes are obtained before a drug may be dispensed.

# ATTACHMENT A: EXAMPLE OF A REMS DOCUMENT FOR A FICTITIOUS DRUG

**NDA ##-### Drug X**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

Class of Product as per label

**ABCD Pharmaceuticals**

123 Fake Street
City, State Zip
Contact Information for those responsible for
REMS policy, management, and implementation

(555)-xxx-xxxx
www.emailaddress.xxx

## I. GOAL

To minimize the risk of drug exposure during pregnancy in women of child-bearing potential taking Drug X. Because Drug X is teratogenic, ABCD Pharmaceuticals (ABCD) will mitigate this risk by:

- Ensuring that only females of childbearing potential with a negative pregnancy test begin therapy with Drug X and only females of childbearing potential with a monthly negative pregnancy test continue therapy with Drug X.
- Ensuring that females of childbearing potential understand the risks to the fetus and know what precautions are necessary to prevent pregnancy.
- Ensuring that all patients and health care providers understand the risks associated with Drug X.

This drug is contraindicated in female patients who are or may become pregnant.

## II. REMS ELEMENTS

### A. Medication Guide (FDCA Section 505-1(e)(2))

A Medication Guide will be dispensed with each Drug X prescription. To ensure compliance with 21 CFR 208.24, ABCD will attach a Drug X Medication Guide to each unit-of-use package of Drug X to ensure that the Medication Guide is given to each patient with each new prescription and refill. A copy of the Medication Guide is appended to the REMS Document. The Medication Guide will be available on the ABCD Web site within 10 days of approval of the Medication Guide.

### B. Communication Plan (FDCA Section 505-1(e)(3))

ABCD will implement a communication plan to health care providers to support implementation of this REMS:

1. The audience for this communication plan is health care professionals (HCPs)—especially neurologists, endocrinologists, and pharmacists.

2. ABCD will provide physicians and pharmacists with educational materials listed below that describe the key risks and benefits of Drug X:

   a. Prescriber Materials — Dear Health Care Professional Letter
   b. Pharmacist Materials — Dear Pharmacist Letter
   c. Additional Resources — Drug X REMS Program Internet Site

   The printed communication and educational materials listed above are appended.

3. Distribution of materials: Communication plan materials will be distributed within 60 days of approval of the Drug X REMS.

   a. At the time the Drug X REMS elements to assure safe use are implemented, ABCD will send the Dear Health Care Professional Letter by mass mailing to targeted Drug X prescribers to announce the REMS program and the requirements of the program. The mailing will include the materials listed in 2a above. Copies of these materials will be available through the product Web site.

   b. At the time the Drug X REMS elements to assure safe use are implemented, ABCD will send the Dear Pharmacist Letter by mass mailing to targeted pharmacies who currently order Drug X, to announce the REMS program and the requirements of the program. The mailing will include the materials listed in 2b above. Copies of these materials will be available through the product Web site.

### C. Elements To Assure Safe Use (FDCA Section 505-1(f)(3))

ABCD will implement the following elements to ensure safe use to mitigate the risk of drug exposure during pregnancy by women of child-bearing potential. The elements to assure safe use will be implemented within 60 days of approval of the Drug X REMS.

1. Drug X will be prescribed only by prescribers who are specially certified under 505-1(f)(3)(A) by enrollment in the Drug X REMS program.

   a. ABCD will ensure that physicians and other appropriately licensed health care providers who prescribe Drug X are specially certified. ABCD will ensure that, to become certified, each prescriber, on the prescriber enrollment form, attests to the following:

- To have read and understood the communication and educational materials for prescribers regarding the risks and benefits of Drug X, including the Drug X Prescriber Guide and the Prescriber Contraception Counseling Guide
- To have knowledge of the high risk of severe birth defects associated with Drug X
- To know the risk factors for unplanned pregnancy and the effective measures to avoid pregnancy
- To prescribe Drug X after ensuring documentation of safe use conditions described below
- To submit information about any pregnancy they learn about to the pregnancy registry
- To monitor patients treated with Drug X as described below

b. ABCD will maintain a list of all certified prescribers and will provide the list to those needing to verify that a prescriber has obtained the required certification.

c. ABCD will ensure that prescribers will be recertified in the Drug X REMS program annually.

The following materials are part of the REMS and are appended:

- Prescriber enrollment form,
- Prescriber Guide
- Prescriber Contraception Counseling Guide

2. Drug X will be dispensed only by pharmacies that are specially certified under 505-1(f)(3)(B) by enrollment in the Drug X REMS program.

a. ABCD will ensure that responsible pharmacy personnel from pharmacies that dispense Drug X are specially certified. ABCD will ensure that, to be certified, responsible pharmacy personnel will attest to the following:

- To have read and understood the communication and educational materials for pharmacists regarding the risks and benefits of Drug X, including the Drug X Pharmacist Guide
- To have knowledge of the high risk of severe birth defects associated with Drug X
- To train all pharmacists to fill and dispense Drug X only after ensuring documentation of safe-use conditions described below
- To ensure that all pharmacists who fill and dispense Drug X comply with required documentation of safe-use conditions described below
- To agree not to sell, borrow, lend, or otherwise transfer Drug X to or from another pharmacy

b. ABCD maintains a list of all certified pharmacies and will provide the list to those needing to verify that a pharmacy has obtained the required certification.

c. Drug X will be distributed to certified pharmacies.

d. Pharmacies will be recertified in the Drug X REMS program annually.

The pharmacy enrollment form and Pharmacist Guide are part of the REMS and are appended.

3. Drug X will only be dispensed to patients with documentation of safe-use conditions under 505-1(f)(3)(D)) described below:

a. ABCD will ensure that prescribers of Drug X will:

- Register each patient in the Drug X REMS program (patient enrollment form is appended)
- Determine the childbearing status of all female patients
- Counsel each female of childbearing potential (FCBP) before beginning therapy with Drug X and on a monthly basis to avoid pregnancy by using effective contraceptive forms or refer the patient for contraception counseling
  - Provide them with the following educational materials: Guide for Patients Who *Can* Become Pregnant (appended)
  - Confirm that FCBP have signed the appropriate informed consents — Informed consent for Patients Who *Can* Become Pregnant (appended)
- Counsel males and females not of child bearing potential about the risks and benefits of Drug X before beginning therapy with Drug X.
  - Provide them with the following educational materials: Guide for Patients Who *Cannot* Become Pregnant (appended)
  - Confirm that males and females not of childbearing potential have signed the appropriate informed consents — Informed consent for Patients Who *Cannot* Become Pregnant (appended)
- Complete for each patient either the Drug X Prescriber Checklist for Patients Who *Can* Become Pregnant, or the Drug X Prescriber Checklist for Patients Who *Cannot* Become Pregnant (appended)
- For female patients of childbearing potential prior to each prescription:
  - Indicate patient's chosen contraceptive forms each month by telephone or secure Internet Web site
  - Order CLIA-certified pregnancy test for each patient prior to each prescription and enter results of pregnancy test each month by telephone or secure Internet Web site

b. ABCD will ensure that pharmacies that dispense Drug X will:

- Obtain authorization from the Drug X REMS program by telephone or secure Internet Web site for every Drug X prescription and write the authorization number on each prescription
- Dispense only a 30-day supply
- Dispense within 7 days of a last negative pregnancy test
- Dispense the Drug X Medication Guide with each prescription

c. ABCD will ensure that Drug X is dispensed only to patients who have met the following conditions:

- All patients have:
  - Signed the informed consent prior to beginning therapy with Drug X
- Females of childbearing potential (before each prescription) have:
  - Obtained a CLIA-certified pregnancy test
  - Indicated chosen contraceptive forms each month by telephone or secure Internet Web site
  - Completed a questionnaire each month through a secure Internet Web site

4. ABCD will ensure that patients who are treated with Drug X are monitored by their prescribers monthly for the duration of Drug X therapy and for 1 month following Drug X discontinuation under section 505-1(f)(3)(E). Monitoring will include the following elements:

- Re-counseling all patients about the risks and benefits of Drug X therapy and determining whether they are still appropriate for Drug X therapy
- Determining whether the childbearing status of female patients has changed
- Obtaining a CLIA-certified pregnancy test prior to each Drug X prescription
- Ensuring FCBP are still on appropriate contraception and re-counseling FCBP of the importance of complying with contraceptive methods during and for 1 month following therapy with Drug X

5. ABCD will ensure that Drug X will only be dispensed to patients who are enrolled in the REMS program registry under 505-1(f)(3)(F) and who meet the following conditions:

- Patient must understand that severe birth defects can occur with the use of Drug X by female patients.
- Patient must be reliable in understanding and carrying out instructions.
- Patient must agree to not share Drug X with anyone.
- Patient must agree to not donate blood while on Drug X and for 1 month after Drug X discontinuation.
- Females of child-bearing potential (FCBP) must:
  - Not be pregnant and understand the importance of avoidance of pregnancy
  - Be capable of following mandatory contraceptive measures

The following information will be collected on enrolled patients:

- Age, gender, and childbearing status
- Documentation of counseling
- Prescription data (e.g., dates RX filled, quantity dispensed)
- For FCBP:
  - Baseline and monthly pregnancy test (dates and results)
  - Chosen methods of contraception
- For females who become pregnant
  - Maternal and fetal outcomes
  - Information on circumstances that led to failure to prevent pregnancy

## D. Implementation System (FDCA Section 505-1(f)(4))

The implementation system will include the following components:

1. ABCD will maintain a validated and secure database of all entities enrolled under 505-1(f)(3)(B) and (D) and 505-1(f)(4), including wholesalers/distributers, pharmacies and patients.
2. ABCD will ensure that wholesalers/distributers who distribute Drug X are specially certified. To become certified, wholesalers/distributers will be enrolled in the Drug X REMS program.

    a. The Drug X REMS Program wholesaler/distributor enrollment process is composed of the following three steps that must be completed prior to receiving Drug X inventory for distribution:

        i. The Distributor's Authorized Representative reviews the Wholesaler/Distributor Program Materials.

        ii. Prior to receiving Drug X, the Distributor's Authorized Representative completes and signs the Distributor Enrollment Form and faxes it to the Drug X REMS Program. In signing the Enrollment Form, the Representative is required to indicate they understand that Drug X is available only through the Drug X REMS Program, agree to comply with program requirements, and acknowledge that:

            A. I will ensure that relevant staff are trained about the Drug X REMS Program for Drug X procedures.

            B. I will ensure that relevant staff distribute Drug X only to Drug X REMS pharmacies that are active in the database.

            C. I will provide monthly records of Drug X shipments to each Drug X REMS pharmacy.

D. I will permit a program-related audit of our shipping records to corroborate that we are shipping Drug X only to Drug X REMS pharmacies.

iii. A Drug X REMS Program professional reviews the form, requests any missing or illegible information, and, when the form has been verified to be accurate and successfully completed, the distributor is notified of activation.

b. Upon initial activation, wholesalers/distributors remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

c. If a previously active wholesaler becomes inactive, the wholesaler/distributor can become active again by completing the standard wholesaler enrollment process in its entirety.

d. Wholesalers/distributors are re-educated and re-enrolled following substantial changes to the program or at least every 2 years. Substantial changes to the Drug X REMS Program are defined as changes that modify the operation of the Drug X REMS Program in a way that changes Drug X REMS Program procedures for distributors.

e. The Distributor Enrollment Form is part of the REMS and is appended.

3. ABCD will monitor wholesaler distribution data to ensure that only registered entities are dispensing Drug X.
4. ABCD will monitor pharmacies to ensure these entities are dispensing Drug X to patients only after receiving authorization.
5. ABCD will correct pharmacy noncompliance with program requirements.
6. ABCD will conduct periodic audits of registered pharmacies to determine whether the data collected is in the manner and frequency agreed upon with FDA.
7. ABCD will maintain a Call Center (1-800-ABCD411) to respond to questions from practitioners, pharmacists, and patients (FDAAA Section 505-1(f)(3)(B), and (D)).

E. **Timetable for Submission of Assessments**

ABCD will submit REMS Assessments to FDA every 6 months from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. ABCD will submit each assessment so that it will be received by the FDA on or before the due date.

[Attachments are not included in this example.]