

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**FDA LACKS COMPREHENSIVE DATA
TO DETERMINE WHETHER RISK
EVALUATION AND MITIGATION
STRATEGIES IMPROVE DRUG SAFETY**



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EXECUTIVE SUMMARY: FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER REMS IMPROVE DRUG SAFETY, OEI-04-11-00510

WHY WE DID THIS STUDY

The Food and Drug Administration (FDA) requires manufacturers to submit structured plans, known as Risk Evaluation and Mitigation Strategies (REMS), for drugs associated with known or potential risks that may outweigh the drugs' benefits. If FDA does not properly monitor REMS' performance, it cannot ensure that the public is provided maximum protection from a drug's known or potential risks. However, FDA does not have the authority to require, but may request, drug manufacturers (i.e., sponsors) to submit specific information regarding REMS' effectiveness.

HOW WE DID THIS STUDY

We reviewed approved REMS since program inception in 2008 through 2011 and conducted structured interviews with FDA officials about FDA's efforts to evaluate REMS components. We also reviewed 49 sponsors' REMS assessments and FDA's reviews of these assessments to determine the extent to which sponsors' assessments were complete, were submitted to FDA within required timeframes, and indicated that REMS were meeting their goals. We also determined whether FDA evaluated the elements to assure safe use (ETASU) of one drug in each year of the program, as required by Federal law.

WHAT WE FOUND

FDA approved 199 REMS between 2008 and 2011, 99 of which were still required in 2012. Nearly half of sponsor assessments for the 49 REMS we reviewed did not include all information requested in FDA assessment plans, and 10 were not submitted to FDA within required timeframes. FDA determined that 7 of the 49 REMS we reviewed met all of their goals. However, FDA has not identified reliable methods to assess the effectiveness of REMS. Finally, FDA's assessment review times exceeded its goal of 60 days for all but one sponsor assessment, which reduces sponsors' time to make suggested changes before submitting subsequent assessments.

WHAT WE RECOMMEND

Our findings raise concerns about the overall effectiveness of the REMS program. To address these concerns, we made seven recommendations regarding FDA's evaluation and assessment of REMS and its review of sponsors' REMS assessments. FDA concurred with six of our recommendations. For the remaining recommendation, to seek legislative authority to make FDA assessment plans enforceable, FDA did not state whether it concurred or did not concur. However, FDA agreed that this recommendation should be considered if another opportunity arises to pursue legislative changes to the statutory provisions that describe the requirements for REMS assessments.

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OBJECTIVES

1. To describe the Risk Evaluation and Mitigation Strategies (REMS) the Food and Drug Administration (FDA) approved for drugs between program inception in 2008 and 2011.
2. To determine the extent to which sponsors' REMS assessments indicate that REMS are complete, are meeting their goals, and are submitted to FDA within required timeframes.
3. To determine the extent to which FDA has evaluated the effectiveness of REMS.
4. To determine the extent to which FDA reviews sponsors' REMS assessments within its goal of 60 days.

BACKGROUND

The Federal Food, Drug, and Cosmetic Act (FDCA), as amended by the Food and Drug Administration Amendments Act of 2007 and the Food and Drug Administration Safety and Innovation Act of 2012, authorizes FDA to require REMS for certain drugs and biological products (hereinafter referred to as drugs) to assure that their benefits outweigh their risks.^{1, 2} REMS are structured plans to manage specific risks of drugs that are effective but associated with known or potential risks (e.g., death, injury) that, without REMS, may outweigh benefits. When FDA requires a REMS, the drug manufacturer (i.e., sponsor) must develop, implement, and assess it.³ FDA reviews and approves each REMS.

¹ Biological products include vaccines, blood and blood products, gene therapies, and allergenic extracts. Therapeutic biological products generally fall under the definition of "drugs," which include substances intended for the diagnosis, cure, mitigation, treatment, or prevention of disease and which meet certain other requirements. FDA, *Drugs@FDA Glossary of Terms*. Accessed at <http://www.fda.gov/Drugs/informationondrugs/ucm079436.htm#B> on June 15, 2012.

² The Food and Drug Administration Amendments Act (P.L. 110-85, Sept. 27, 2007) added § 505-1 to the FDCA. The Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144, July 9, 2012) further amended FDCA § 505-1.

³ Under FDCA § 505-1, the responsible person submitting a covered application to market a drug or the holder of such approved application is required to submit, implement, and assess REMS. In this report, we refer to the "responsible person" as the sponsor. Generally, a drug manufacturer submits and holds a drug's application and is the drug's sponsor. FDA, *Drug Development and Review Definitions*. Accessed at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm> on April 24, 2012.

FDA has the authority to, among other things, deem a drug misbranded or impose civil monetary penalties on sponsors that violate approved REMS.^{4, 5}

Structure of REMS

Each REMS includes one or more overall goals to achieve a particular safety-related health outcome or understanding by patients and/or health care providers of a drug's risks.⁶ Examples of REMS goals include preventing fetal exposure to a drug and informing prescribers, patients, and pharmacists of the serious risks and safe-use conditions for a drug.

REMS include one or more strategies to provide additional safety in the usage of certain drugs. For example, REMS may require sponsors to create additional safety information for patients or to ensure that health care providers that prescribe the drug are specially certified.⁷

For brand-name drugs, each REMS must include a timetable for sponsors to submit REMS assessments.^{8, 9} The standard timetable requires sponsors to submit assessments of REMS' effectiveness by 18 months, 3 years, and 7 years after approval of the REMS.¹⁰ FDA may require sponsors to submit assessments at different intervals specified in the REMS or eliminate the timetable after 3 years if it determines that a drug's risks

⁴ A drug may be deemed to be misbranded if it is subject to a REMS and the sponsor fails to comply with a requirement of the REMS. FDCA § 502(y). Misbranded drugs may not be introduced into, delivered, or received into interstate commerce. FDCA § 301 (a) and (c).

⁵ Sponsors that violate REMS requirements may be subject to civil monetary penalties of up to \$250,000 per violation. Civil monetary penalties are not to exceed \$1 million in a single proceeding. Civil monetary penalties may increase to \$10 million for continued violations. FDCA § 303(f)(4)(A). Additionally, a sponsor may not introduce or deliver for introduction into interstate commerce an approved drug if a REMS is required for the drug and the sponsor fails to maintain compliance with the requirements of the approved REMS or with other requirements of § 505-1 of FDCA. FDCA § 505(p).

⁶ FDA, *Draft Guidance for Industry: Format and Content of Proposed REMS, REMS Assessments, and Proposed REMS Modifications*, p. 9. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> on June 23, 2011. This draft guidance will represent FDA's current thinking on this topic when finalized, but will not bind FDA or the public.

⁷ FDCA §§ 505-1(c)(2), 505-1(e)(2), and 505-1(f)(3)(A).

⁸ FDCA §§ 505-1(c)(1) and (d). The timetable for assessments specifies when sponsors will submit the assessment to FDA, not when the assessment will be performed.

⁹ REMS for drugs subject to abbreviated new drug applications (i.e., generics) do not require a timetable for assessments. FDCA § 505-1(i)(1)(A–B).

¹⁰ FDA often requires more frequent assessments (e.g., at 6-month intervals or annually) for drugs associated with the most serious risks.

have been adequately identified and assessed and are being adequately managed.¹¹

FDA may require one or more of the following components in addition to the timetable for assessments: medication guide or patient package insert, a communication plan, or elements to assure safe use (ETASU).¹² FDA determines which of these additional components to require according to a drug's risks.

Medication Guides and Patient Package Inserts. Medication guides are paper handouts that include FDA-approved information about the safe and effective use of a drug. Medication guides are not unique to REMS; FDA oversees their content and format under separate regulations and may require them without requiring a REMS.¹³ Some REMS may require patient package inserts, which also contain drug safety information, in addition to medication guides.^{14, 15}

Communication Plans. Communication plans describe how sponsors will inform health care providers about a drug's risks and/or the components of a REMS. These plans may describe how a sponsor will send letters to health care providers and disseminate information through professional societies about a drug's risks.¹⁶

¹¹ FDCA §§ 505-1(d)(4)(A) and (C). When FDA eliminates a REMS' timetable for assessments, it may continue to require the REMS but the sponsor is no longer required to submit assessments.

¹² FDCA §§ 505-1(e)(1-3) and 505-1(f)(1-3).

¹³ If FDA requires a medication guide not as a component of a REMS, sponsors are not required to assess them. See 21 CFR 208.

¹⁴ Patient package inserts are required for some prescription drugs, including estrogens and oral contraceptive products and are considered to be part of a drug's labeling. Manufacturers of other drugs may voluntarily provide patient package inserts. Required patient package inserts must be dispensed to patients with the drug. 21 CFR 310.501, 21 CFR 310.515. See also, FDA, *Guidance: Drug Safety Information – FDA's Communication to the Public*, p. 10. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072281.pdf> on December 19, 2012.

¹⁵ FDA does not expect to require both patient package inserts and medication guides frequently. FDA may allow sponsors to include an existing patient package insert in a REMS instead of a medication guide or require sponsors to convert a patient package insert into a medication guide, if it meets medication guide requirements. FDA, *Guidance for Industry: Format and Content of Proposed REMS, REMS Assessments, and Proposed REMS Modifications*, p. 10. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> on June 23, 2011.

¹⁶ FDCA § 505-1(e)(3).

ETASUs. FDA may require ETASUs for drugs that are associated with a serious adverse drug experience if, without the ETASUs, FDA would not approve the drug or would withdraw the drug's approval.^{17, 18} If drugs were initially approved without ETASUs, FDA must determine that other REMS components are not sufficient to mitigate risks before it requires ETASUs.¹⁹

FDA can require one or more of the following ETASUs:

- health care providers who prescribe the drug have certain training, experience, or certification;
- pharmacies, practitioners, and/or other health care settings that dispense the drug are specially certified;
- the drug is dispensed only in certain health care settings (e.g., hospitals, appropriately equipped physicians' offices);
- the drug is dispensed only to patients with evidence or documentation (e.g., laboratory test results, signed acknowledgement of risks) that they can safely use the drug;
- each patient using the drug is subject to monitoring (e.g., patients must periodically contact the prescriber or undergo laboratory tests); and
- each patient using the drug is enrolled in a registry.²⁰

Each ETASU must (1) correspond to the specific serious risk listed in the labeling of a drug; (2) considering such risk, not be unduly burdensome on patient access to a drug, particularly considering patients with serious or life-threatening conditions and patients who have difficulty accessing health care; and (3) to the extent practicable, minimize the burden on the health care delivery system.²¹

¹⁷ A serious adverse drug experience is an adverse event associated with the use of a drug that results in death, the immediate risk of death, inpatient hospitalization or prolonging existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or a medical or surgical intervention to prevent these outcomes. FDCA § 505-1(b)(4).

¹⁸ FDCA § 505-1(f)(1)(A).

¹⁹ FDCA § 505-1(f)(1)(B).

²⁰ FDCA § 505-1(f)(3)(A–F).

²¹ FDCA §§ 505-1(f)(2)(A), (C), and (D). Specifically, to minimize the burden on the health care system, ETASUs should conform with the ETASUs of drugs with similar serious risks and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs. FDCA § 505-1(f)(2)(D). Additionally, each ETASU must be posted publicly by the Secretary within 30 days with an explanation of how it will mitigate the safety risk. FDCA § 505-1(f)(2)(B).

When FDA requires certain ETASUs, the REMS may also include an implementation system.²² Sponsors may use implementation systems to take reasonable steps to monitor, evaluate, and improve the implementation of ETASUs.²³ Examples of implementation systems include requiring sponsors to conduct periodic audits of health care settings that use the drug or to maintain a database of all certified entities to ensure that certification requirements are met.²⁴

REMS components are not exclusive. For example, REMS that require ETASUs generally also require a communication plan and/or a medication guide. FDA refers to three types of REMS according to the most intensive (i.e., primary) required component: medication guide, communication plan, and ETASU REMS. See Table 1 for examples of drugs that require the various REMS components.

²² ETASUs that may include an implementation system are: requiring special certification for pharmacies, practitioners, or other health care providers that dispense the drug; dispensing the drug in certain settings; and dispensing the drug only to patients with certain evidence or documentation. FDCA § 505-1(f)(4).

²³ FDCA § 505-1(f)(4).

²⁴ FDA, *Guidance for Industry: Format and Content of Proposed REMS, REMS Assessments, and Proposed REMS Modifications*, pp. 14–15. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> on June 23, 2011.

Table 1: Examples of Drugs Requiring REMS

Drug	Approved Indication	Risks	Required REMS Components*	Primary REMS Component
Chantix	Smoking cessation	Neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts and actions	Timetable for assessments, medication guide	Medication guide
Vibativ	Treatment of adult patients with complicated skin and skin structure infections caused by susceptible Gram-positive bacteria	Unintended exposure of pregnant women resulting in teratogenicity	Timetable for assessments, medication guide, communication plan	Communication plan
OxyContin controlled-release tablets	Management of moderate to severe pain when a continuous, around-the-clock, opioid analgesic is needed for an extended period	Potential for abuse, misuse, overdose, and addiction	Timetable for assessments, medication guide, ETASUs	ETASU
Avandia	Management of type II diabetes	Myocardial infarction	Timetable for assessments; medication guide; communication plan; ETASUs, including an implementation system	ETASU

Source: Office of Inspector General (OIG) analysis of approved REMS, 2011.

* The required components of these REMS may change over time. This table includes REMS components required as of December 31, 2011.

Criteria for Requiring REMS

FDA may require a REMS before approving an application to market a drug (i.e., preapproval REMS) or after a drug is on the market (i.e., postapproval REMS).²⁵ FDA must consider the following factors to determine whether a preapproval REMS is necessary:

- the estimated size of the population likely to use the drug,
- the seriousness of the disease or condition that the drug treats,
- the expected benefit of the drug,
- the duration of treatment,

²⁵ FDCA § 505-1(a).

- the seriousness of any known or potential adverse events related to the drug and the background incidence (i.e., frequency) of these events in the population likely to use the drug, and
- whether the drug is a new molecular entity.^{26, 27}

FDA may require a postapproval REMS if it becomes aware of new safety information after a drug is on the market and determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks.^{28, 29} For example, FDA required a postapproval REMS for the drug Wellbutrin in response to reports of suicide-related events in patients using the drug for smoking cessation.³⁰

REMS Approval Process

When FDA requires a REMS, it notifies the drug's sponsor in a REMS notification letter. The REMS notification letter instructs the sponsor to submit a proposed REMS containing the components FDA determines are necessary. FDA reviews the proposed REMS and approves it after an interactive process with the sponsor.³¹ After FDA approves a proposed REMS, it notifies the drug's sponsor in a REMS approval letter.

FDA works with sponsors to develop an FDA assessment plan for each REMS, which is included in the REMS approval letter. Assessment plans describe the information that FDA requests sponsors to collect to complete a valid assessment of whether a REMS is meeting its goals.³² For example, FDA may request that a sponsor's assessment include the

²⁶ A new molecular entity is an active ingredient that has never been marketed in the United States in any form. FDA, *Drugs@FDA Glossary of Terms*. Accessed at <http://www.fda.gov/Drugs/informationondrugs/ucm079436.htm#N> on September 2, 2011.

²⁷ FDCA § 505-1(a)(1)(A–F).

²⁸ FDCA § 505-1(a)(2)(A). New safety information is derived from scientific data (e.g., clinical trials, adverse event reports) about serious or unexpected risks associated with a drug that FDA has become aware of since the drug was approved, since the REMS was required, or since the last assessment of the approved REMS. These scientific data may be based on a new analysis of existing information. FDCA § 505-1(b)(3).

²⁹ FDA also considers the factors listed in FDCA § 505-1(a)(1)(A–F) when requiring a postapproval REMS.

³⁰ FDA, *NDA 018644/S-041, NDA 023858/S-048 Approval Letter*, February 26, 2010. Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/018644s041,020358s0481r.pdf on November 1, 2011.

³¹ FDA, *CDER 21st Century Review Process Desk Reference Guide*, p. 53. Accessed at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf> on May 3, 2012.

³² FDA, *Guidance for Industry: Format and Content of Proposed REMS, REMS Assessments, and Proposed REMS Modifications*, p. 18. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> on June 23, 2011.

number of patients enrolled in a user registry or an evaluation of patients' understanding of a drug's risks.

Sponsors' Assessments of REMS

Sponsors of brand-name drugs must submit their assessments of REMS for FDA's review according to the timetable in the approved REMS.³³ FDCA requires FDA to review sponsors' assessments but does not require FDA to perform its own assessments of each REMS.³⁴ FDA may require sponsors to submit an additional assessment if one is needed to evaluate whether the REMS should be modified.³⁵ Sponsors may also submit voluntary assessments of REMS at any time.³⁶ Sponsors' assessments must include information required by FDCA and should also include information requested in FDA assessment plans.

Requirements for Sponsors' Assessments. At the time of our review, assessments of REMS with ETASUs were required to include an evaluation of the extent to which each ETASU is meeting the goal stated in the REMS in addition to complying with the approved timetable. Under current amendments to FDCA, all REMS assessments must include, with respect to each goal of the REMS, an assessment of the extent to which REMS are meeting the goals or of whether the goals or REMS should be modified.³⁷ FDCA does not require sponsors to include additional information about the effectiveness of REMS in assessments. FDA may take enforcement actions (e.g., deem a drug misbranded, impose civil monetary penalties) if sponsors fail to meet the assessment requirements outlined in FDCA.³⁸ However, FDA does not have authority to take enforcement actions if sponsors' assessments do not include information requested in FDA assessment plans.

FDA's Reviews of Sponsors' Assessments. Multidisciplinary teams made up of staff in FDA's Division of Risk Management within the Office of Surveillance and Epidemiology, the respective drug review division(s) in the Office of New Drugs, and the Office of Compliance review sponsors' REMS assessments. Staff in the Division of Risk Management complete review memorandums that summarize the teams' findings. The teams

³³ FDCA § 505-1(d). Sponsors of generic drugs are not required to submit REMS assessments according to a timetable.

³⁴ FDCA § 505-1(h)(1). FDA's requirement to assess the ETASUs of at least one drug each year is distinct from its responsibility to review sponsors' assessments.

³⁵ FDCA § 505-1(g)(2)(C).

³⁶ FDCA § 505-1(g)(1).

³⁷ FDCA § 505-1(g)(3). Because this was not required at the time of our review, we determined only whether assessments of REMS with ETASUs included assessments of the extent to which each ETASU was meeting the stated goal in the REMS.

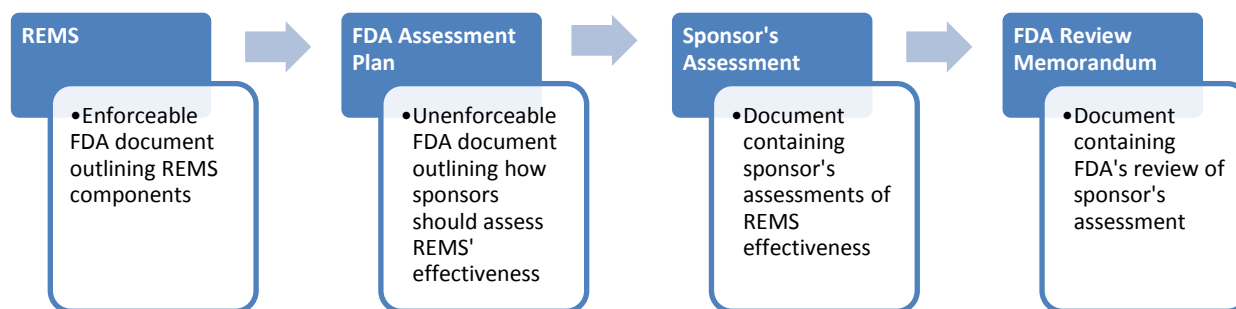
³⁸ FDCA §§ 502(y) and 303(f)(4)(A).

review assessments for completeness and determine whether REMS are meeting their goals or whether modifications to the REMS or FDA assessment plans are required. A Division of Risk Management review memorandum documents whether a sponsor’s assessment (1) is complete, (2) indicates the REMS is meeting its goals or needs modifications, and (3) identifies any deficiencies that may affect a REMS’s ability to mitigate risks.³⁹

The Office of Compliance also completes review memorandums, which document whether sponsors submit complete assessments according to the approved timetable. However, the Office of Compliance defers the analysis of assessment data and of whether REMS are meeting their goals to the Division of Risk Management.⁴⁰

FDCA requires FDA to promptly review sponsors’ assessments.⁴¹ Although FDA does not define “promptly,” FDA officials indicated that their goal is to complete all assessment reviews within 60 days of submission if it does not discuss REMS modifications with sponsors.⁴² Figure 1 illustrates the relationship of the REMS, FDA assessment plan, sponsor’s assessment, and FDA review memorandum.

Figure 1: Relationship of REMS Documents



Source: OIG analysis of REMS documents, 2012.

FDA’s Evaluation of REMS

Federal law (i.e., FDCA) requires FDA to evaluate the ETASUs of at least one REMS each year to determine whether the ETASUs (1) assure safe

³⁹ Federal regulations and FDA policy do not define a complete assessment. “Complete” is defined later for the purposes of this study.

⁴⁰ Based on OIG review of Office of Compliance review memorandums.

⁴¹ FDCA § 505-1(h)(1).

⁴² Since FDA set this goal, some FDCA provisions regarding the review of sponsors’ assessments have changed because of FDASIA. Before FDASIA was enacted, FDA opened a 90-day discussion period to work with sponsors to determine whether REMS modifications were necessary and to discuss possible modifications. FDASIA removed the provision regarding the 90-day discussion period, but FDA may still discuss REMS modifications with sponsors and is still required to promptly review sponsors’ assessments.

use of the drug; (2) are unduly burdensome on patient access to the drug; and (3) to the extent practicable, minimize the burden on the health care delivery system.⁴³

In 2008, FDA issued a 5-year plan (2008–2012) to enhance and modernize its drug safety activities. In the 5-year plan, FDA states that it will develop a plan to identify, develop, validate, and assess the effectiveness of REMS components.⁴⁴

METHODOLOGY

Scope

We reviewed and described the REMS that FDA approved between program inception in 2008 and 2011. Additionally, we reviewed sponsors' most recent assessments to determine whether they were complete. We reviewed FDA's review memorandums for each of the sponsor assessments to determine whether FDA notified sponsors about incomplete assessments, concluded that REMS were meeting their goals, and completed its reviews within 60 days. We also determined the extent to which FDA has evaluated REMS with ETASUs, as required by Federal law.

Our review included 199 REMS. We reviewed sponsors' assessments and FDA review memorandums for the 49 REMS that required assessments according to their approved timetables as of December 31, 2011.⁴⁵ We also reviewed the second most recent assessment (i.e., prior assessment) and FDA review memorandums for the 14 REMS that required multiple assessments during our timeframe.⁴⁶ See Appendix A for a list of REMS and associated review memorandums provided by FDA.

We limited our review of sponsors' assessments to those required by the timetable in each REMS. We did not include REMS for generic drugs in our review because sponsors of these drugs are not required to submit

⁴³ FDCA § 505-1(f)(5)(B). FDA has been required to complete this evaluation for one drug with an ETASU REMS each year since 2008.

⁴⁴ FDA, *PDUFA Drug Safety 5-year Plan 2008–2012*, December 2008, p. 8. Accessed at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM119244.pdf> on September 23, 2011. The 5-year plan is distinct from FDA's required evaluation and is not specific to ETASUs.

⁴⁵ Fifty-seven REMS required at least one assessment by December 31, 2011. We did not include eight REMS in this analysis because FDA did not provide review memorandums for them. This does not necessarily indicate that FDA failed to review these assessments. These assessments may have been under FDA review during our data collection period.

⁴⁶ Twenty REMS required multiple assessments by December 31, 2011. We did not include six REMS in this analysis because FDA did not provide prior review memorandums for four REMS and did not provide the most recent review memorandums for two.

REMS assessments according to a timetable.⁴⁷ We did not review sponsors' assessments for which FDA did not provide review memorandums. Additionally, we did not independently determine the extent to which REMS are meeting their goals and relied on FDA statements in review memorandums.

Data Collection and Analysis

We reviewed relevant statutes, policies, and guidance documents related to REMS. We conducted structured interviews with and requested documentation from FDA officials. Finally, we analyzed REMS, FDA assessment plans, sponsors' assessments, and FDA review memorandums.

Describing REMS Approved Between 2008 and 2011. We used FDA's online list of REMS to calculate the number of REMS that FDA approved between March 25, 2008, when FDA's authority to require REMS began, and December 31, 2011, when we collected our data. We described the components of these REMS and determined how many REMS were no longer required as of December 31, 2011.

Determining Completeness and Timeliness of Sponsors' Assessments. We analyzed the 49 most recent sponsor assessments to determine whether sponsors included information requested in FDA assessment plans and required by Federal law. We based our determination on an independent review of sponsor assessments and FDA assessment plans. We did not rely on statements in FDA review memorandums to determine whether assessments were complete. However, if FDA review memorandums indicated that FDA no longer requested sponsors to submit certain pieces of information, we did not consider the information to be missing. To determine whether sponsors submitted their assessments according to the approved timetable, we compared assessment submission dates to the timetable in each approved REMS. We also requested documentation of any enforcement actions FDA has taken in response to sponsor assessments that did not comply with Federal requirements.

Determining Whether REMS Were Meeting Goals. We analyzed FDA review memorandums associated with the 49 most recent sponsor assessments to determine whether FDA concluded that REMS were

⁴⁷ Our review includes the drug isotretinoin, which was approved as an acne treatment and marketed as Accutane. FDA required a single, shared-system REMS for Accutane and its generic equivalents but Accutane's approval was withdrawn at the request of its sponsor. Several of its generic equivalents remain on the market and are under the originally approved single, shared-system REMS. Sponsors of these generic drugs have submitted assessments in accordance with the timetable included the Accutane REMS.

meeting their goals.⁴⁸ We considered determinations of whether REMS were meeting their goals to be in four categories: (1) the REMS was meeting its goals, (2) the REMS was not meeting its goals, (3) FDA reviewers could not determine whether the REMS was meeting its goals, and (4) FDA reviewers did not determine whether the REMS was meeting its goals.

We did not independently determine whether REMS were meeting their goals; instead, we relied on statements from FDA reviewers in review memorandums. For example, a review memorandum for a REMS that FDA determined was not meeting its goals states that "... we find that the goals are not being met." A review memorandum for a REMS for which FDA could not determine was meeting its goals states that "... due to a lack of valid data, we cannot comment on whether the REMS is meeting its educational goals." We considered REMS to be in the fourth category if review memorandums did not contain a statement from the reviewer regarding whether the REMS was meeting all of its goals.

For the 14 REMS that required at least one prior assessment, we analyzed the prior review memorandums to determine whether reviewers stated that the assessments identified deficiencies that may affect the REMS' ability to mitigate risks.⁴⁹ If reviewers noted deficiencies in prior assessments, we determined whether the reviewers noted the same deficiencies in the most recent sponsor assessments. We also compared FDA's determinations about whether REMS were meeting their goals in review memorandums for the prior assessments to determinations in the most recent review memorandums.

Determining the Extent of FDA's Evaluation of REMS. We conducted structured interviews with FDA officials regarding (1) the evaluation of ETASUs, as required by FDCA; and (2) FDA's plan to identify, develop, validate, and assess the effectiveness of REMS components, as described in its 5-year plan (2008–2012) to enhance and modernize drug safety activities.

Determining FDA's Assessment Review Times. We determined FDA's review times for sponsor assessments for which FDA did not discuss REMS modifications with sponsors. For these 29 sponsor assessments, we used the submission dates on the assessments and the dates on the

⁴⁸ Reviewers' determinations regarding whether REMS are meeting each goal are found in the discussion section of review memorandums. Only Division of Risk Management review memorandums include this determination; however, the memorandums reflect the reviews of a multidisciplinary team.

⁴⁹ Reviewers note deficiencies in the discussion and recommendations sections of review memorandums.

associated FDA review memorandums to determine whether FDA completed reviews within its goal of 60 days.⁵⁰

Limitations

We did not review FDA communication with sponsors regarding their assessment reviews. We based reports of actions that FDA took after assessment reviews (e.g., discussing REMS modifications with sponsors) on the recommendations stated in FDA's Division of Risk Management review memorandums, not on FDA communication with sponsors.

Standards

This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

⁵⁰ For Division of Risk Management review memorandums, we used the dates of review as the review completion dates. For Office of Compliance review memorandums, with one exception, we used the electronic signature dates for the review completion dates.

FINDINGS

FDA approved 199 REMS between 2008 and 2011, 99 of which were still required in 2012

FDA requires REMS to manage specific risks of drugs that are effective but associated with known or potential risks (e.g., death, injury) that, without REMS, may outweigh the drugs' benefits. Of the 199 approved REMS, 119 required medication guides only and 48 required communication plans. For drugs with the most serious risks, FDA approved 32 REMS with ETASUs.⁵¹ These drugs would not be approved or their approval would be withdrawn without the ETASUs.⁵² Of the 199 approved REMS, FDA approved 74 preapproval REMS in response to information in drug applications. The remaining 125 postapproval REMS were required in response to new safety information discovered after the drugs were already on the market or for drugs with ETASUs already in effect before REMS program initiation.⁵³

As of December 31, 2011, FDA no longer required 100 of the 199 approved REMS. Ninety-two of the REMS that are no longer required included medication guides only, seven required communication plans, and one required ETASUs. Medication guides existed prior to REMS and may be required for drugs without REMS. Following program inception, FDA required REMS for all drugs that required medication guides. However, in November 2011, FDA published a guidance document describing when medication guides would be required without also requiring REMS. It also provided sponsors of REMS requiring only medication guides with information about how to submit proposals to eliminate the REMS.⁵⁴

⁵¹ REMS components are not exclusive. The 48 REMS that required communication plans may have also required medication guides, and the 32 REMS that required ETASUs may have also required communication plans and/or medication guides. We categorized the REMS according to their primary component as of December 31, 2011.

⁵² Of the 32 REMS with ETASUs, 28 also required implementation systems.

⁵³ FDA worked with sponsors to implement ETASUs for certain drugs prior to the REMS program. After REMS program initiation, FDA required sponsors of these drugs to submit REMS proposals in accordance with § 909(b)(3) of the Food and Drug Administration Amendments Act (P.L. 110-85, Sept. 27, 2007).

⁵⁴ FDA, *Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in REMS*, pp. 7–8, November 2011. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf> on August 2, 2012. This guidance states that it represents FDA's current thinking on this topic but does not bind FDA or the public.

According to the approved timetable in each REMS, 57 REMS required sponsors to submit at least 1 assessment by December 31, 2011.⁵⁵ FDA provided review memorandums for 49 of these REMS.⁵⁶ Of these 49 REMS, 11 required medication guides only, 19 required communication plans, and 19 required ETASUs.⁵⁷

Nearly half of the 49 sponsor assessments we reviewed did not include all information requested in FDA assessment plans, and 10 were not submitted to FDA within required timeframes

FDA assessment plans request sponsors to submit specific information to enable FDA to determine whether REMS are meeting their goals. FDA reviewed 49 sponsor assessments as of December 31, 2011. Almost half (23 of 49) of the sponsor assessments did not include all of the information requested in FDA assessment plans. See Table 2 for the number of assessments that lacked information requested in assessment plans by primary REMS component. For example, one sponsor did not include the number of pharmacies that were deauthorized to dispense the drug because of noncompliance with the REMS, as requested in the assessment plan. The same sponsor also did not include the amount of the drug shipped to health care providers compared to actual patient orders, as requested. In review memorandums for the 23 assessments that did not include information requested in assessment plans, reviewers recommended that FDA notify the sponsors of 6 that their assessments were incomplete. FDA review memorandums for the remaining 17 assessments did not indicate that FDA no longer requested sponsors to submit the missing information.

⁵⁵ This number does not include REMS that were no longer required as of December 31, 2011, or REMS for generic drugs, which are not subject to a timetable for assessments.

⁵⁶ For the remaining eight assessments, FDA had not completed assessment reviews as of December 31, 2011. As of December 31, 2011, FDA's assessment reviews did not meet its goal of 60 days for three of these eight assessments.

⁵⁷ Of the 19 REMS with ETASUs, 12 required implementation systems.

Table 2: Sponsors' Assessments Lacking Information Requested in Assessment Plans

Primary REMS Component	Number of Assessments Lacking Information Requested in Assessment Plans
ETASU	10
Communication plan	8
Medication guide	5
Total	23

Source: OIG analysis of sponsor assessments.

Sponsors and health care providers have expressed concerns about the challenges associated with collecting data on the compliance of third parties (e.g., patients, pharmacies, drug distributors). Specifically, concerns about patient confidentiality and the lack of a standardized format for sponsor assessments may contribute to the lack of data in some assessments.⁵⁸

FDA does not have authority to take enforcement actions against sponsors that do not include requested information in their REMS assessments.

Some items requested in FDA assessment plans are also required by Federal law. An assessment of the extent to which the ETASUs met the goal stated in the approved REMS was required by Federal law, but was missing from seven assessments.⁵⁹

Further, 10 of 49 of sponsor assessments were not submitted to FDA by the dates specified in the approved timetables, as required by FDCA. These assessments were submitted between 3 and 70 days after the dates specified in the timetables, with a median of 17 days. FDA has the authority to take enforcement actions against sponsors that do not meet Federal requirements for REMS assessments. However, since program inception in 2008, FDA has not done so.

FDA determined that 7 of the 49 REMS we reviewed met all of their goals

Using limited information in sponsor assessments, FDA determined that 7 of the 49 REMS we reviewed were meeting all of their goals and that 21

⁵⁸ FDA, *Transcript of REMS Public Meeting*, July 28, 2010, pp. 208 and 284. Accessed at <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM224950.pdf> on July 3, 2012.

⁵⁹ Assessments of the extent to which the ETASUs met the goals stated in the approved REMS were required only for the 19 REMS with ETASUs. FDASIA changed this requirement to no longer apply specifically to ETASUs. According to FDCA § 505-1(g)(3), all sponsor assessments must now include, with respect to each goal of the REMS, assessments of the extent to which the REMS are meeting the goals or of whether the goals or REMS should be modified.

were not. FDA review memorandums indicated that FDA could not determine whether 17 REMS were meeting all of their goals. FDA review memorandums did not contain statements regarding whether the remaining four REMS were meeting all of their goals.⁶⁰

As shown in Table 3, FDA determined that 1 of 19 REMS with ETASUs, which are required for the riskiest drugs, was meeting all of its goals. In review memorandums, FDA reviewers stated that eight REMS with ETASUs were not meeting all goals and that they could not determine whether eight others were meeting all goals. FDA did not determine whether two REMS with ETASUs were meeting their goals.

Table 3: Determinations of Whether REMS Were Meeting Goals

Primary REMS Component	Meeting All Goals	Not Meeting All Goals	Unable To Determine	Did Not Determine	Total
ETASU	1	8	8	2	19
Communication plan	2	10	5	2	19
Medication guide	4	3	4	0	11
Total	7	21	17	4	49

Source: OIG analysis of FDA review memorandums, 2012.

FDA most often determined that REMS were not meeting their goals because of deficiencies in patient and prescriber awareness of drug risks

When FDA determined that REMS were not meeting all of their goals, it most often identified deficiencies related to patient awareness of risks (14 of 21 assessments) and/or prescriber awareness of risks (12 of 21 assessments). For example, because a survey showed that patients had a low understanding of key risk messages, FDA determined that one REMS was not meeting its goal to inform patients of a drug’s risks. FDA discussed REMS modifications with sponsors for 16 of the 21 REMS it determined were not meeting all of their goals.

FDA did not discuss REMS modifications with sponsors of the remaining five REMS it determined were not meeting their goals.⁶¹

⁶⁰ If an FDA review memorandum did not contain a statement from the reviewer regarding whether the REMS was meeting its goals, we concluded that FDA did not make that determination.

⁶¹ In some cases, FDA may have suggested that sponsors modify REMS assessments or education materials rather than modifying the REMS. FDA indicated that these suggestions were not consistently included in review memorandums.

Nearly all deficiencies identified by prior FDA assessment reviews were still present in the sponsors' most recent assessments

FDA identified 22 deficiencies that may affect a REMS' ability to mitigate risks.⁶² In 11 prior assessments we reviewed, 19 of 22 deficiencies identified by FDA's prior assessment reviews were identified again in reviews of the most recent assessments. Reviewers identified deficiencies that included low patient exposure to medication guides, low understanding of risk messages among patients and/or prescribers, and poor compliance with the REMS among health care providers.

FDA could not determine whether REMS were meeting their goals most often because of incomplete information in assessments

For 8 of 17 assessments, FDA could not determine whether REMS were meeting their goals because of a lack of information included in the sponsors' assessments. For example, FDA could not determine whether one REMS was meeting its goal to inform patients of the drug's risks because the sponsor did not include an assessment of patients' understanding of risks in the assessment. FDA could not determine whether an additional three REMS were meeting their goals because assessments were required too early in the implementation of the REMS to draw conclusions.⁶³

FDA could not determine whether five REMS were meeting their goals because of concerns about the quality of the surveys used in the sponsor assessments.⁶⁴ FDA's concerns generally related to small sample sizes or the use of surveys that did not meet FDA's standards. However, FDA does not specify in its assessment plans the sample size that would enable it to determine whether a REMS is meeting its goals.

FDA has not identified reliable methods to evaluate the effectiveness of REMS

FDA has not developed a plan to identify, develop, validate, and assess the effectiveness of REMS components, as stated in its 5-year plan (2008–2012) to enhance and modernize drug safety activities.

⁶² A sponsor's second most recent assessment is considered the prior assessment. FDA provided review memorandums for 14 prior assessments and identified deficiencies in 11.

⁶³ Two of these assessments were required 6 months after REMS approval. The third assessment was required 12 months after approval, but the drug's introduction to the market was delayed, which delayed data collection for the assessment.

⁶⁴ Two of these five REMS assessments also lacked information. FDA reviewers did not explain why they were unable to determine whether REMS were meeting their goals for the remaining sponsors' assessments.

Additionally, FDA has not met the Federal requirement to evaluate the ETASUs of one REMS each year. Further, FDA has identified limitations in methods used to evaluate the effectiveness of REMS.

FDA has evaluated the ETASUs of one REMS since program inception in 2008

According to FDCA, FDA must evaluate the ETASUs for at least one drug each year to determine whether they (1) assure safe use of the drug; (2) are unduly burdensome on patient access to the drug; and (3) to the extent practicable, minimize the burden on the health care delivery system. Between 2008 and 2011, FDA approved 32 REMS with ETASUs to address drugs with the most serious risks. As of December 31, 2011, FDA had completed an evaluation for one drug with an ETASU.

On December 1, 2011, FDA's Drug Safety and Risk Management Advisory Committee met to evaluate the ETASUs of isotretinoin.⁶⁵ At the meeting, FDA and stakeholders discussed the impact of the isotretinoin REMS on patients and the health care delivery system. FDA and industry representatives noted several challenges associated with completing the required evaluation, including the lack of baseline (pre-REMS) utilization data and the inability to account for changes in utilization because of factors not related to the REMS.

FDA stated that it had not formally evaluated a REMS with ETASUs in the first 3 years of the REMS program because it was focused on developing REMS and implementing the program. Additionally, FDA stated that REMS must be implemented for a sufficient period of time before they can be properly evaluated.⁶⁶

Because FDA has completed this evaluation for just 1 of 32 drugs with ETASUs, it has limited data to demonstrate that the remaining REMS with ETASUs effectively ensure safe use of drugs or meet statutory requirements to minimize burdens on patients and the health care system.

⁶⁵ Isotretinoin was originally approved as an acne treatment and marketed as Accutane. Accutane is no longer on the market, but its generic equivalents remain on the market under a single, shared-system REMS for isotretinoin. The ETASUs require that prescribers and pharmacies be specially certified, patients have evidence of safe-use conditions, and sponsors maintain pregnancy registries. Minutes of the Advisory Committee meeting are available to the public. Accessed at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm250295.htm> on July 19, 2012.

⁶⁶ Prior to the use of REMS, FDA used Risk Minimization Action Plans (RiskMAPs) to manage risks of certain drugs. The ETASUs for isotretinoin were fully implemented in 2006 under a RiskMAP. Claudia Karwoski, *Opening Remarks for Drug Safety and Risk Management and Ophthalmic Advisory Committee Meeting*, December 1, 2011. Accessed at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM285047.pdf> on September 20, 2012.

FDA has identified limitations with using survey data to assess REMS

FDA often requests that sponsors include results of surveys regarding patients' and/or health care providers' knowledge of risks in REMS assessments.⁶⁷ FDA made such requests in each of the 49 sponsor assessments we reviewed. Of these 49 sponsor assessments, 40 included survey data in response to this request and 9 did not.

However, in a White Paper issued in June 2012, FDA identified several limitations in some sponsors' surveys. These included sample sizes too small to draw conclusions, survey populations that do not reflect the demographics of the target population, bias caused by convenience samples, and the lack of objective standards to measure knowledge of risks.⁶⁸ FDA states that because of these limitations, surveys may not always be the best method for assessing the effectiveness of REMS educational components.⁶⁹

FDA's assessment review times exceeded its 60-day goal for all but one sponsor assessment

FDCA requires FDA to promptly review sponsor assessments.⁷⁰ Although FDA does not define "promptly," FDA officials indicated that their goal is to complete all assessment reviews within 60 days of a sponsor's assessment submission if FDA does not discuss REMS modifications with sponsors. FDA did not discuss REMS modifications with sponsors for 29 of the 49 sponsor assessments we reviewed.⁷¹ FDA's assessment review times exceeded 60 days for 28 of these 29 sponsor assessments. FDA's average assessment review time was 73 days and the median review time was 69 days.⁷² Reviews of three sponsor assessments were completed at least 120 days after the sponsor submitted them.⁷³ If FDA

⁶⁷ FDA, *Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge*, pp. 1–2. Accessed at <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM301966.pdf> on September 13, 2012.

⁶⁸ Convenience samples are selected on the basis of what is most feasible for the researcher and are therefore not always representative of the larger population.

⁶⁹ *Ibid*, pp. 5–6.

⁷⁰ FDCA § 505-1(h)(1).

⁷¹ FDA's 60-day goal for reviewing sponsors' assessments does not apply to the remaining 20 assessments for which it discussed REMS modifications with sponsors.

⁷² The average and median review times do not include reviews that were not complete as of December 31, 2011.

⁷³ The FDA review memorandum for one of these REMS indicated that it is included in the opioid class REMS, which was under development at the time of the review and may have contributed to delays in review completion. The FDA review memorandums for the remaining two REMS do not indicate a reason for delays.

does not review sponsor assessments in a timely manner, sponsors may have limited time to implement suggested changes to a REMS before submitting the next assessment.

CONCLUSION AND RECOMMENDATIONS

FDA requires REMS for drugs associated with known or potential risks that, without REMS, may outweigh the drugs' benefits. REMS are enforceable, structured plans to manage specific risks associated with drugs. However, FDA does not have the authority to take enforcement actions against sponsors that do not include all information requested in FDA assessment plans. If FDA does not have comprehensive data to monitor the performance of REMS, it cannot ensure that the public is provided maximum protection from a drug's known or potential risks.

Between program inception in 2008 and 2011, FDA approved 199 REMS, 99 of which were still required in 2012. However, FDA does not have comprehensive data from sponsor assessments to determine whether REMS are meeting their goals because many sponsor assessments are incomplete or include data that do not meet FDA's standards.

Additionally, using the limited information in sponsor assessments, FDA determined that 7 of 49 REMS were meeting all of their goals and that 21 were not, raising questions about the effectiveness of REMS.

Further, FDA has completed the federally required evaluation for 1 of 32 drugs with ETASUs since program inception. Therefore, FDA has limited data to demonstrate that the remaining REMS with ETASUs effectively ensure safe use of drugs or meet statutory requirements to minimize burdens on patients and the health care system. Additionally, FDA has not identified reliable methods for evaluating REMS.

Finally, FDA's assessment review times exceeded 60 days for all but one sponsor assessment, which may limit sponsors' ability to implement suggested changes to the REMS before submitting the next assessment.

In conclusion, our findings raise concerns about the overall effectiveness of the REMS program. To address these concerns, we recommend that FDA:

Develop and implement a plan to identify, develop, validate, and assess REMS components

This plan should fulfill FDA's commitment in its 5-year plan and outline ways that FDA will assess the effectiveness of REMS beyond reviewing sponsors' assessments.

FDA should also identify and implement reliable methods to assess the effectiveness of REMS. FDA should decrease its reliance on survey data in sponsors' assessments and work with sponsors and health care providers to develop more accurate evaluation methods.

Additionally, FDA should continue to hold discussions with stakeholders, similar to the public meetings held in 2010 and 2012, about the issues and challenges associated with assessing the effectiveness of REMS components.⁷⁴

Identify REMS that are not meeting their goals and take appropriate actions to protect the public health

FDA should consistently discuss potential REMS modifications with sponsors when it determines that a REMS is not meeting its goals. FDA should work with sponsors to determine the most appropriate modifications to address the REMS' deficiencies. If a REMS undergoes multiple modifications and continues not to meet its goals, FDA should consider removing the drug from the market.

If FDA cannot determine whether a REMS is meeting its goals, it should work with sponsors to obtain any additional information that it needs to make this determination. FDA should not wait until it reviews the next sponsor assessment to determine whether a REMS is meeting its goals.

Evaluate the ETASUs of one REMS each year as required by Federal law

FDA should determine whether the ETASUs (1) assure safe use of the drug; (2) are unduly burdensome on patient access to the drug; and (3) to the extent practicable, minimize the burden on the health care delivery system. FDA fulfilled this requirement for the first time in 2011 and should continue to conduct formal evaluations of at least one REMS with ETASUs each year.

Through these evaluations, FDA can determine how effective various ETASUs are, whether ETASUs cause barriers to patient access, and which ETASUs are the most burdensome for health care providers. Evaluations would also inform FDA's decisions about the most effective ETASUs for mitigating specific risks. FDA should use this information to change or eliminate any ETASUs that are both burdensome and ineffective in assuring safe use of a drug.

Identify incomplete sponsor assessments and work with sponsors to obtain missing information

FDA should consistently notify sponsors that their assessments are incomplete and request that sponsors provide the missing information as soon as possible. FDA should also work with sponsors to obtain the missing information.

⁷⁴ 75 Fed. Reg. 34453 (June 17, 2010) and 77 Fed. Reg. 26292 (May 3, 2012).

Clarify expectations for sponsors' assessments in FDA assessment plans

FDA should make assessment plans as specific as possible to ensure that data included in sponsors' assessments will enable FDA to determine whether REMS are meeting their goals. For example, FDA should specify sample sizes needed to complete valid surveys. FDA should use assessment plans to establish quality standards for data to be submitted in sponsors' assessments. If FDA cannot determine whether a REMS is meeting its goals because of the quality of data in a sponsor's assessment, it should notify the sponsor of this concern and, if necessary, clarify data standards for future assessments.

Seek legislative authority to enforce FDA assessment plans

FDA currently does not have authority to take enforcement actions when sponsors do not submit all information requested in assessment plans. FDA should work with the appropriate stakeholders to seek legislative authority to enforce assessment plans. This would allow FDA to take regulatory actions when a sponsor's assessment did not include all items requested in the FDA assessment plan. Further, enforcement authority should encourage sponsors to submit the amount and quality of information FDA needs to determine whether REMS effectively mitigate risks.

Ensure that assessment reviews are timely

FDCA requires FDA to promptly review sponsor assessments. FDA officials indicated that their goal is to complete all assessment reviews within 60 days of sponsors' assessment submissions if FDA does not discuss REMS modifications with sponsors. Since FDA set this goal, some FDCA provisions regarding the review of sponsors' assessments have changed because of FDASIA. If FDA chooses to change this goal of 60 days, it should define "promptly" as it pertains to reviewing sponsor assessments and complete assessment reviews within this timeframe. FDA should identify ways to complete assessment reviews within its goal of 60 days or the newly established timeframe. This would allow time for informed discussions with sponsors about REMS modifications, if necessary. This would also enable sponsors to make timely changes to REMS and/or REMS assessments in response to FDA's review. To maximize review resources, FDA could prioritize assessment reviews for REMS with ETASUs as these REMS are required for drugs with the most serious risks and generally require more frequent assessments.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

In its comments on the draft report, FDA concurred with six of our recommendations and, for the remaining recommendation, agreed that seeking legislative change should be considered if another opportunity arises to do so. FDA agreed with the need to improve future REMS assessments but stated that there would always be challenges in measuring the impact of REMS. FDA provided historical context to describe the evolving nature of pharmaceutical risk management. FDA also provided information about the REMS Integration Initiative which was created in 2011.

With regard to our first recommendation, FDA noted that the REMS Integration Initiative will include contributions from key stakeholders on the development, implementation, and effectiveness of REMS tools.

With regard to our second recommendation, FDA stated that it has worked and will continue to work with sponsors to determine the best response when it determines that a REMS is not meeting its goals. Additionally, FDA stated that it plans to develop draft guidance concerning how to write REMS goals and the metrics for determining whether these goals have been met.

With regard to our third recommendation, FDA noted that it faced challenges, including insufficient experience in evaluating REMS and insufficient assessment data available, in meeting the Federal requirement to evaluate the ETASUs of at least one drug each year. FDA also noted that while it did not formally meet this requirement until 2011, it discussed certain REMS with ETASUs at various advisory committees prior to 2011.

With regard to our fourth recommendation, FDA stated that it has worked and will continue to work with sponsors to obtain information missing from assessments if that information is necessary to determine whether a REMS is meeting its goals. If FDA determines that the information is not necessary to determine whether a REMS is meeting its goals, it will reevaluate the need for the information.

With regard to our fifth recommendation, FDA stated that it is committed to holding public workshops to gather stakeholder input. FDA plans to issue draft guidance on methodologies for assessing whether REMS are meeting their goals and the impact of REMS on patient access and burden on the health care system. Additionally, FDA noted that it has reviewed and will continue to review proposed assessment protocols if sponsors submit them prior to initiating the REMS assessment.

FDA did not explicitly concur with our sixth recommendation but agreed that it should be considered if another opportunity arises to pursue legislative changes to the statutory provisions that describe REMS assessment requirements.

Finally, with regard to our seventh recommendation, FDA stated that it is examining the internal assessment review process for ways to improve the timeliness of FDA assessment reviews.

We support FDA's efforts to address these issues and encourage it to continue making progress in these areas. For the full text of FDA's comments, see Appendix B. We made minor changes to the report based on FDA's technical comments.

APPENDIX A

Assessment Review Memorandums Provided by FDA			
Name of Drug	Division of Risk Management Review Memorandum	Office of Compliance Review Memorandum	Prior Assessment and Review Memorandum(s)*
ETASU			
Abstral sublingual tablets	X	X	
Erythropoiesis stimulating agents	X	X	X
Butrans transdermal system	X		
Caprelsa tablets	X	X	
Entereg capsules	X	X	X
Exalgo extended-release tablets	X	X	X
Isotretinoin	X	X	
Letairis tablets	X	X	
Lumizyme	X		X
Nplate for subcutaneous injection	X	X	X
Onsolis buccal soluble film	X		
Oxycontin controlled-release tablets	X		X
Promacta tablets	X	X	X
Revlimid capsules	X	X	X
Sabril tablets and oral solution	X		X
Soliris injection	X	X	X
Suboxone sublingual film	X	X	X
Thalomid capsules	X		
Tracleer tablets	X	X	
Communication Plan			
Actemra injection	X	X	
Ampyra extended-release tablets	X		
Botox and Botox Cosmetic injection	X	X	
Dulera inhalation aerosol	X	X	
Dysport injection	X	X	
Effient tablets	X	X	

continued on next page

Appendix A, continued

Assessment Review Memorandums Provided by FDA			
Name of Drug	Division of Risk Management Review Memorandum	Office of Compliance Review Memorandum	Prior Assessment and Memorandum(s)
Communication Plan			
Embeda extended-release tablets	X	X	X
Forteo injection	X	X	
Kalbitor injection	X	X	
Krystexxa injection	X	X	
Multaq tablets	X	X	X
Myobloc injection	X	X	
Samsca tablets	X		
Stelara injection	X	X	
Tasigna capsules	X		
Vibativ injection	X		
Xenazine tablets	X	X	X
Xiaflex injection	X	X	
Zortress tablets	X	X	
Medication Guide			
Actoplus Met tablets	X		
Actoplus Met XR extended-release tablets	X		
Actos tablets	X		
Duetact tablets	X		
Androgel 1.62% gel	X	X	
Chantix tablets	X	X	
Nucynta immediate release tablets	X		
Testim gel	X	X	
Venlafaxine hydrochloride extended-release tablets	X	X	
Vivitrol extended-release injectable suspension	X		
Zyban sustained-release tablets, Wellbutrin, Wellbutrin sustained-release tablets, and Wellbutrin extended-release tablets	X	X	
Total	49	33	14

*Some REMS had not required multiple assessments as of December 31, 2011. A blank in this column does not necessarily indicate that a sponsor did not complete a required assessment.

APPENDIX B

Agency Comments



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

DATE: December 10, 2012

TO: Daniel R. Levinson
Inspector General

FROM: Peter Lurie, MD, MPH
Acting Associate Commissioner for Policy and Planning

SUBJECT: **Food and Drug Administration's Response to Office of Inspector General
Draft Report: *FDA Lacks Comprehensive Data to Determine Whether REMS
Improve Drug Safety (OEI-04-11-00510)***

FDA is providing the attached response to the Office of Inspector General's draft report.

FDA appreciates the opportunity to comment on this draft report.

/s/

Peter Lurie
Acting Associate Commissioner for Policy and Planning

Attachment

**Food and Drug Administration's General Comments to
Office of Inspector General Draft Report:
*FDA Lacks Comprehensive Data to Determine
Whether REMS Improve Drug Safety (OEI-04-11-00510)***

The Food and Drug Administration (FDA) appreciates the Office of Inspector General's (OIG) draft report, *FDA Lacks Comprehensive Data to Determine Whether REMS Improve Drug Safety*, and welcomes the opportunity to comment on and respond to the recommendations included in this draft report.

Pharmaceutical risk management is a relatively new and emerging scientific discipline. Accordingly, regulatory experience with pharmaceutical risk management is also evolving. In 2003, FDA issued three concept papers focused on (1) premarketing risk assessment, (2) risk management programs, and (3) postmarketing pharmacovigilance and pharmacoepidemiologic assessments. Following stakeholder input, FDA developed and issued three final guidance documents in 2005 describing its thinking on the principles and practices of risk management. One guidance, *Development and Use of Risk Minimization Action Plans*, addressed the development, implementation, and evaluation of Risk Minimization Action Plans (RiskMAPs) for prescription drug products.

In 2007, Congress passed new legislation, the FDA Amendments Act (FDAAA), authorizing FDA to require Risk Evaluation and Mitigation Strategies (REMS). In 2009, FDA issued draft guidance, *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*. The draft guidance describes elements that comprise REMS programs, the structure and content of submissions of proposed REMS, and the process for modifying an approved REMS, and includes limited information about REMS assessments, such as information about when assessments must be submitted. However, as REMS were still in their infancy at the time the draft guidance was issued, it does not describe information FDA now considers important to assess the effectiveness of REMS programs.

FDA's implementation of RiskMAPs and, more recently, REMS programs, has been adapted to accommodate the new regulatory authorities and requirements, as well as emerging risk management methods, tools, and metrics, which often need to be tested and refined. Additionally, FDA has sought and received stakeholder feedback, requesting comments and conducting a series of meetings and workshops on how such programs could be improved to make them less burdensome and more standardized.

Against this background of continuous evolution of both the science and statutory framework for pharmaceutical risk management, it is not surprising that data available to FDA for determining whether REMS programs are effective are incomplete. As the science evolves, FDA continues to learn more about various aspects of REMS, including

setting measurable goals, designing REMS programs that can be readily implemented and integrated into the existing healthcare system, assessing REMS effectiveness (i.e., to what extent the goals are being met), reporting assessment results, making decisions about REMS modifications, and minimizing the burden on patient access and the healthcare system.

The OIG draft report identifies several possible deficiencies in how REMS programs have historically been assessed by sponsors, and then reviewed and evaluated by FDA. Although OIG did not provide FDA with the evidence upon which OIG based its findings of these deficiencies, FDA agrees with the need to improve future REMS assessments given the evolving nature of pharmaceutical risk management. There will always be challenges in attempting to measure the impact of a REMS program (or individual REMS tools) on outcomes, since multiple concurrent REMS and non-REMS variables may contribute to an outcome. Although we can track and measure “system inputs” (such as how many prescribers are trained or how many medication guides are distributed), attempting to associate particular interventions with specific outcomes (for example, fewer emergency room visits) will continue to be difficult.

FDA has already identified a broader set of areas for improving this new science, and in 2011, created the REMS Integration Initiative, designed to evaluate and improve our implementation of REMS authorities. The goals of the REMS Integration Initiative include developing guidance on how to apply the statutory criteria to determine when a REMS is required, improved standardization and assessment of REMS, and improved integration of REMS into the existing and evolving healthcare system. This initiative will incorporate input from stakeholders on issues and challenges associated with the development, implementation and assessment of REMS.

To support the REMS Integration Initiative, the FDA Center for Drug Evaluation and Research (CDER) REMS Integration Steering Committee (RISC) oversees the activities of three subordinate work groups whose deliverables will fulfill commitments FDA has made under the reauthorized Prescription Drug User Fee Act (PDUFA V, reauthorized on July 9, 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012).

- The Policy Work Group is currently developing a draft guidance to provide more information about how FDA applies the statutory criteria to determine whether a REMS is necessary. FDA expects to publish this draft guidance by September 2013.
- The Design and Standardization Work Group is leading FDA’s efforts to identify best practices to incorporate into REMS design, as well as appropriate ways to standardize REMS tools and integrate REMS into the healthcare delivery system. This group will solicit stakeholder input within the next year and expects to develop a report of its findings by December 2013.
- The Evaluation Work Group is leading FDA’s efforts to develop an evidence-based approach to assessing the effectiveness and burden of REMS. In addition to a June 2012 public workshop on survey methodologies, the Evaluation Work

Group will obtain additional stakeholder input and expects to publish a draft guidance on evaluation methodologies by September 2014.

By March 2015, FDA intends to publish a report on what it has learned about REMS through the efforts of these groups.

FDA Responses to OIG Recommendations

Recommendation 1: *Develop and implement a plan to identify, develop, validate, and assess REMS components*

FDA concurs with this recommendation. As described above, in 2011 FDA launched the REMS Integration Initiative to evaluate implementation of our REMS authority. The initiative will include contributions from key stakeholders on questions and concerns pertinent to REMS development and implementation, including review and consideration of the functionality and effectiveness of REMS tools.

Recommendation 2: *Identify REMS that are not meeting goals and take appropriate actions to protect public health*

FDA concurs with this recommendation. When FDA determines that a REMS is not meeting one or more of its REMS goals, FDA has worked and will continue to work with sponsors to determine the best response including, when appropriate, modifications to address REMS deficiencies. In the future, we plan to develop draft guidance on how to write REMS goals and the metrics for determining if the goals have been achieved.

Recommendation 3: *Evaluate the Elements to Assure Safe Use (ETASU) of one REMS each year as required by Federal law*

FDA concurs with this recommendation. Section 505-1(f)(5)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA) requires FDA, at least annually, to evaluate the ETASU for a drug through the Drug Safety and Risk Management Advisory Committee (DSaRM). FDA faced challenges in meeting this requirement in the early years of REMS implementation. At the time, we had insufficient experience in evaluating REMS and insufficient assessment data available to inform a robust and meaningful discussion by the DSaRM committee.

FDA's first formal evaluation of the ETASU for a drug, through the DSaRM, occurred in 2011, when we discussed the iPLEDGE program for isotretinoin with the DSaRM. Although we faced difficulty formally meeting this requirement in the early years of REMS implementation, even prior to 2011 FDA did discuss REMS with ETASUs for certain drugs with various FDA advisory committees, including the DSaRM. On December 12-13, 2012, the DSaRM will meet to discuss various approaches to the management of drug-associated teratogenic risk. As part of that discussion, the committee will consider whether the risk management strategies for teratogenic drugs,

including several drugs that have REMS with ETASU, assure safe use of a drug, are not unduly burdensome on patient access to the drug and, to the extent practicable, minimize the burden on the healthcare delivery system.

Recommendation 4: *Identify incomplete sponsor assessments and work with sponsors to obtain missing information*

FDA concurs with this recommendation. FDA has worked and will continue to work with sponsors to obtain missing information if that information is needed to determine whether the REMS is meeting its goals. If we determine that the information is not necessary to determine if the REMS is meeting its goals, we will re-evaluate the need for the information.

Recommendation 5: *Clarify expectations for sponsors' assessments in FDA assessment plans*

FDA concurs with this recommendation. FDA is committed to holding workshops to gather stakeholder input and plans to issue draft guidance on methodologies for assessing whether REMS are meeting their goals, as well as the impact of REMS on patient access and burden on the healthcare delivery system.

Currently FDA includes in REMS approval letters a description of the information that should be in the REMS assessments. In addition, FDA has reviewed and will continue to review proposed assessment protocols if they are submitted by the sponsors prior to the sponsor initiating the REMS assessment for a product.

Recommendation 6: *Seek legislative change to make FDA assessment plans explicitly enforceable*

FDA's REMS authority, added to the FDCA by FDAAA, was amended recently, on July 9, 2012. FDA agrees that this recommendation should be considered if another opportunity arises to pursue legislative changes to the statutory provisions that describe the requirements for REMS assessments.

Recommendation 7: *Ensure that assessment reviews are timely*

FDA concurs with this recommendation. FDA will continue to promptly review sponsor assessments to determine whether the REMS is meeting its goals. We are currently re-examining our internal assessment review process for ways to further improve upon the timeliness of FDA reviews of REMS assessments.

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