REMS Assessment: Planning and Reporting
Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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REMS Assessment: Planning and Reporting

Guidance for Industry

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TABLE OF CONTENTS

REMS Assessment: Planning and Reporting Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document provides guidance to industry on the assessment of risk evaluation and mitigation strategies (REMS) for prescription drug products, including biological products.[2,3] This guidance describes how to develop a REMS Assessment Plan[4], specifically, how the REMS program goals, objectives[5] and REMS design may impact the selection of metrics[6] and data sources, which will be used to assess whether the program is meeting its risk mitigation goals. The guidance also discusses considerations for assessing the impact of REMS on patient access to the drug and its burden to the healthcare delivery system. Finally, this guidance provides

[1] This guidance has been prepared by the Division of Risk Management, Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with other divisions and offices within CDER and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For purposes of this guidance, unless otherwise specified, references to "drugs" and "drug products" include drugs approved under the FD&C Act and biological products licensed under the Public Health Service (PHS) Act, other than biological products that also meet the definition of a device in section 201(h) of the Federal Food, Drug and Cosmetic (FD&C) Act (21 U.S.C. 321(h)).

[3] This is one of several guidance documents being developed to fulfill performance goals under the fifth authorization of the prescription drug user fee program, the Prescription Drug User Fee Act V (PDUFA V), PDUFA V Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, Section XI.A.1

[4] For purposes of this guidance, a *REMS Assessment Plan* is a specific plan for how the applicant intends to assess the performance of the REMS in meeting its risk mitigation goals and objectives. The REMS Assessment Plan is outlined in the REMS approval letter for NDAs and BLAs and described in detail in the REMS Supporting Document.

[5] For purposes of this guidance, *REMS goals* are the overall, safety-related health outcome(s) that the REMS are designed to achieve. *REMS objectives* are the metrics that indicate that the program is meeting its goals when the risk mitigation goal cannot be measured directly.

[6] For purposes of this guidance, *REMS metrics* are the measures (such as quantity, quality, duration, size, or frequency) of an aspect of the program that provide a systematic basis for assessing how well a program has performed.

recommendations on a standardized approach for reporting REMS assessment findings to FDA using the REMS Assessment Report.[7]

This document does not address the design or development of REMS, methods for designing, conducting, and reporting surveys, pharmacoepidemiologic safety studies, or other studies when used as a component of a REMS assessment; however, in relevant sections, it references available FDA guidances that address these issues.

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 (FD&C Act) (21 U.S.C. 355(b) or 355(j)), or section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), that are required by FDA to have REMS. These applications are considered "covered applications" and include new drug applications (NDAs), abbreviated new drug applications (ANDAs) and biologics license applications (BLAs).

In general, FDA's guidance documents 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 cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 505-1 of the FD&C Act (21 U.S.C. 355-1), as added by the Food and Drug Administration Amendments Act of 2007 (FDAAA) and later amended by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), authorizes FDA to require REMS for certain drugs[8] if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[9, 10, 11]

[7] For purposes of this guidance, the *REMS Assessment Report* is the document applicants submit that contains information generated from the analysis of the metrics outlined in the REMS Assessment Plan.

[8] Section 505-1 of the FD&C Act applies to applications for prescription drugs submitted or approved under subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications) of the FD&C Act and to applications submitted or approved under section 351 (i.e., biologics license applications) of the Public Health Service Act (42 U.S.C. 262). For the purposes of this document, unless otherwise specified, the term *drug* refers to human prescription drugs, including those that are licensed as biological products (biologics).

[9] Public Law 110-85, September 27, 2007, available at https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm, accessed November 19, 2018.

[10] Public Law 112-144, July 9, 2012, available at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf, accessed November 19, 2018.

[11] See Section 505-1(a) of the FD&C Act.

REMS may include a Medication Guide, a patient package insert, and/or a communication plan.[12] FDA also may require certain elements to assure safe use (ETASU) as part of REMS for a drug.[13]

Every proposed REMS for an NDA and BLA must have a timetable for submission of REMS assessments,[14] that:

- includes assessments submitted to the FDA by the dates that are 1)18 months, 2) 3 years after the strategy is initially approved, and 3) in the 7th year after the strategy is so approved, and

- is at a frequency specified in the strategy and can be increased or reduced in frequency under certain circumstances and eliminated under certain circumstances.

With limited exceptions, REMS assessments are also required when submitting a supplemental application for a new indication for use, when required by the strategy, and whenever FDA determines that an assessment is needed to evaluate whether the strategy should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the strategy.[15] In addition to the required assessments, an applicant may voluntarily submit an assessment of an approved REMS at any time.[16]

Section 505-1(g)(3) of the FD&C Act specifies that a REMS assessment shall include, with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified. The FD&C Act does not specifically describe how an applicant should conduct this assessment.

III. REMS ASSESSMENT—OVERVIEW

The development of the REMS Assessment Plan should begin during the REMS design phase, with the development of a clear risk mitigation goal (i.e., REMS goal). The risk mitigation goal is the safety-related health outcome that the REMS will be designed to achieve. Because risk mitigation goals cannot always be measured directly, it is important to include one or more intermediate measurable objectives that, if achieved, indicate that the program is meeting its goals. For example, a REMS for a drug with a risk of renal toxicity may include a goal to mitigate the risk of renal failure, the success of which may be measured by the objectives that all patients undergo periodic testing of serum creatinine and that appropriate management steps are undertaken when laboratory values are out of range.

[12] Section 505-1(e)(2)-(3) of the FD&C Act.

[13] See Section 505-1(f)(1) of the FD&C Act.

[14] See Section 505-1(c)-(d) of the FD&C Act.

[15] See Section 505-1(g)(2) of the FD&C Act.

[16] See Section 505-1(g)(1) of the FD&C Act.

Once the goals and objectives have been determined, the design of the REMS can begin, including the REMS requirements[17] and REMS materials[18], and if applicable an implementation system, that align with the goals and objectives. For example, if the REMS includes a goal to mitigate the risk of a drug and an objective to inform or educate patients about the safe use of that drug, prescribers could be required to counsel their patients using a REMS material such as a patient-prescriber agreement.

While a comprehensive discussion regarding REMS design is beyond the scope of this guidance, it is important to consider how the REMS design corresponds to the goals and objectives of the REMS and to the development of the REMS Assessment Plan.

When designing a REMS program, applicants should consider:

- The characteristics of the risk associated with the drug that the REMS is intended to mitigate (e.g., risk factors, timing, detectability, reversibility)

- Any information demonstrating the effectiveness of the proposed strategy in mitigating the risk (e.g., results from premarket testing with stakeholders, effectiveness demonstrated during clinical trials or from the published literature, findings from qualitative or quantitative human factors studies, previous experience with similar REMS programs).

- Which stakeholders within the existing healthcare delivery system may require additional support to effectively mitigate the risk, as well as the type and extent of the support that may be required (e.g., training about how to manage the risk, verification that laboratory monitoring was conducted).

- The feasibility of implementing the proposed strategies, the potential burden of the proposed mitigation strategies on the healthcare delivery system, and the potential impact of the proposed strategies on patient access to the drug (e.g., strategies that have the potential to result in treatment interruption or delays, particularly where patients have serious or life-threatening conditions).

Applicants should document the rationale for their proposed REMS design in the REMS Supporting Document.[19] The rationale should include how the REMS requirements, REMS materials, and implementation system were selected or designed to achieve the goals and objectives.

[17] For purposes of this guidance, the term *REMS requirements* refers to the activities that both REMS participants (e.g., healthcare providers, patients, health care settings) and applicants must undertake in a REMS.

[18] For purposes of this guidance, the term *REMS materials* is used to describe any materials, processes, or system designed to operationalize one or more REMS requirements.

[19] For purposes of this guidance, the *REMS Supporting Document* provides additional information about the REMS, such as the rationale for, and supporting information about, the design, implementation, and assessment of the REMS.

The REMS Assessment Plan should include the metrics, data sources, and methodologies that the applicant intends to use to assess the performance of the REMS. It should also include a plan for assessing the impact of the REMS on the healthcare delivery system and patient access to the drug.

The data sources, methodologies, and metrics used to assess the effectiveness of REMS continue to evolve. As with any method or data source used to support program evaluation, there are limitations that should be considered with REMS assessments. For example, for a REMS that is established at the time of initial drug approval, there may not be relevant baseline data for comparison, such as the incidence of the risk associated with the drug or drug use patterns. Also, many safety-related health outcomes that are the focus of the REMS may occur rarely and thus be challenging to measure and accurately evaluate using available data sources. Additionally, for drugs that are infrequently prescribed some commonly used data sources may not have sufficient drug utilization information to make study of program impact possible. Finally, it is often difficult to distinguish the effect of the REMS from other healthcare or public health initiatives. Applicants should make every effort to develop a REMS Assessment Plan that enables them to assess the effectiveness of the REMS, while acknowledging these limitations.

Considering their limitations, no single metric, data source, or methodology should be relied upon to assess the effectiveness of REMS. Instead, several metrics, data sources, and methodologies should be considered, as appropriate. Each REMS Assessment Plan should include discussion of any anticipated challenges with conducting the assessment and limitations, if any, of the data that will be used.

FDA encourages applicants and the research community to develop novel methods for assessing REMS. Robust collaborations between FDA and other regulatory agencies, applicants, and the research community can help advance the science of post-market assessment of effectiveness of risk mitigation strategies.

IV. DEVELOPING THE REMS ASSESSMENT PLAN

A. Assessment Categories

The REMS Assessment Plan should include assessment of all aspects of program performance, including the individual REMS requirements (e.g., prescriber certification), REMS materials (e.g., prescriber-patient agreement), and the overall impact of the program.[20,21] REMS can be assessed using both process indicators[22] and the intended outcomes (e.g., reduction in inappropriate prescribing), but can also include the unintended outcomes (e.g., barriers to patient access) of the program. Below is a set of assessment categories that are intended to capture both

[20] Gaglio B, Shoup JA, Glasgow RE. The RE-AIM Framework: A Systematic Review of Use Over Time. *Am J Public Health.* 2013;103(6):e38-e46.

[21] Practical Approaches to Risk Minimisation for Medicinal Products: Report of CIOMS Working Group IX; August 2014.

[22] For purposes of this guidance, *process indicators* directly measure the extent of compliance with required REMS processes, such as processes used to comply with REMS requirements, such as distribution of REMS materials.

REMS program processes and outcomes. There may be some overlap between these categories, and each category may include both process and outcome metrics.

- *Program Outreach and Communication*—Measures of the extent to which the REMS materials reached the intended stakeholders.

- *Program Implementation and Operations*—Measures of the extent to which the intended stakeholders are participating in the program; how effectively the REMS program is being implemented, including the extent of use of REMS materials and compliance with REMS requirements; and any unintended consequences that could affect patient access or potential burden to the healthcare system related to the program operations.

- *Knowledge*—Measures of the extent of stakeholders' (e.g., patient/caregiver, prescriber, pharmacist) knowledge about the REMS-related risk or knowledge of any safe use conditions that are needed in order to mitigate the risk.[23]

- *Safe Use Behaviors*—Measures of the extent to which safe use conditions are being adopted or followed (e.g., how often a required laboratory test is conducted prior to dispensing of the medication).

- *Health Outcomes and/or Surrogates of Health Outcomes*—Measures of the safety-related health outcome of interest (e.g., a reduction in the number of serious outcomes associated with a particular adverse event) or a surrogate of a health outcome (e.g., a reduction in the number or proportion of patients at greatest risk of an adverse event who are prescribed a drug).

B. Selecting Metrics

REMS assessment metrics should be identified for all assessment categories that are relevant to the REMS program and that are feasible. Applicants should provide a rationale for all metrics selected and state whether the metric has been validated. The metrics should fall within the categories described above in section IV.A. More than one metric may be selected for each assessment category. Example metrics for the above assessment categories are provided below.

- Metrics in the *Program Outreach and Communication* assessment category may include numbers of specific REMS materials that were distributed to, and the proportion of these that were subsequently opened or read by, the targeted audiences.

[23] See the draft guidance for industry, *Survey Methodologies to Assess REMS Goals That Relate to Knowledge*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page (available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm) or Biologics guidances web page (available at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm). When final, this guidance will represent FDA's current thinking on this topic.

- Metrics in the *Program Implementation and Operations* assessment category may include the number of prescribers, health care settings, and/or pharmacies that have certified or undergone training in the REMS program; the number of contacts to the call center and a summary of the reason for the contact; number and results of audits of certified health care settings; and the number of shipments of the drug to non-certified settings.

- Metrics in the *Knowledge* assessment category may include stakeholder understanding of the risks and safe use of the drug. The draft guidance for industry *Survey Methodologies to Assess REMS Goals that Relate to Knowledge* provides further recommendations on using surveys to evaluate knowledge of REMS risks and safe use conditions.[23]

- Metrics in the *Safe Use Behaviors* assessment category can include an evaluation of prescribing patterns and the proportion of patients who were counseled prior to initiating a drug, as evidenced by the use of a REMS material such as a patient counseling tool or patient-provider agreement form.

- Metrics in the *Health Outcomes and/or Surrogates of Health Outcomes* assessment category can include numbers and/or rates of a specific adverse event of interest such as rates of serious bleeds or severe neutropenia. Surrogate metrics could include the number of inadvertent fetal exposures or the number of prevented fetal exposures to the teratogenic drug.

The metrics that are selected within each assessment category will depend on the goals and objectives of the program, the REMS requirements (e.g., education, dispensing requirements) and REMS material (e.g., prescriber-patient agreement), and the feasibility of the measurement.

See Appendix 1 for additional examples of some potential metrics for the different assessment categories and Appendix 2 for an example of how the development of a REMS Assessment Plan may be linked to the REMS goals, objectives, and requirements. Applicants may also consider other healthcare program assessment frameworks to help identify and organize REMS metrics.

C. Selecting Sources of Assessment Data

Applicants are encouraged to identify complementary data sources that provide a combination of qualitative and quantitative information about the REMS and should select sources that provide data supporting the REMS assessment starting from the initial REMS implementation.

In selecting the sources of data, applicants should take into consideration how accurately and completely each data source can capture the relevant population and important components necessary for the assessment. Some data sources may be used to assess multiple identified metrics. For example, drug utilization data may be used to assess changes in prescribing behaviors as well as to inform potential barriers to patient access that would require additional analyses. In other cases, multiple data sources may be needed to assess a single metric.

A detailed description of the data sources and methodological approaches, as well as the applicant's evaluation of the adequacy of these in assessing the specific REMS requirement or REMS materials, should be provided in the REMS Supporting Document. For all studies, a protocol and statistical analysis plan should be submitted to FDA for review and comment prior to study initiation. If applicable, timelines for the submission of study protocol and interim and final reports should be provided by the applicant and agreed upon by FDA.

Described below are examples of data sources that may be used to inform REMS assessments. This list is not meant to be comprehensive, and additional sources or approaches may be appropriate.

1. *Applicant's REMS Data*

REMS with ETASU may include a requirement that the applicant maintain a database of certified/enrolled prescribers, dispensers, healthcare settings, distributors, or patients. This database can be a rich source of data for metrics that apply to several assessment categories. Applicants should carefully consider what data need to be collected for REMS assessment purposes when they design and develop REMS databases.

As an example, an applicant's REMS database can collect program participation metrics, including the number of stakeholders or healthcare settings enrolled or certified in the program when an ETASU requires such enrollment or certification. Depending on what data are captured, the database might help to provide information about patient access to the drug, geographic location of prescribers, numbers of prescriptions dispensed, and prescriber specialties. The database can also include data that inform program operations and safe use conditions, such as the number of prescriptions dispensed with and without the proper authorization when the ETASU require such authorization. It may provide information about burden to the healthcare system through categorizing data from general complaints received through a call center or instances of delays in patient access that may be associated with the REMS. For REMS that require a post-training knowledge assessment, the database can capture poor performance on knowledge assessment questions, which can prompt a revision of the training program content to address knowledge gaps. The database may also collect information related to health outcomes of interest or results of laboratory monitoring (e.g., absolute neutrophil counts, pregnancy test results).

Many applicants also collect other REMS operations data, such as the results of audit findings. Applicants are encouraged to collect data across a wide range of program processes and functions to the extent it facilitates their assessment of their REMS.

2. Surveys

When a REMS includes an objective to inform or educate patients or health care professionals about a serious risk associated with a drug, or about the safe use of a drug, the assessment plan should include an assessment of these stakeholders' knowledge. The key messages for each targeted stakeholder should be defined prior to REMS approval (and documented in the REMS Supporting Document), should be consistent with the key messages in the counseling, education, or communication materials, and should relate to the REMS objective. Surveys are often used to assess knowledge of these key messages and the related safe use actions to be taken by various stakeholders.

Assessment of stakeholder understanding of REMS requirements may also be useful to determine whether safe use behaviors are being adopted and whether stakeholders adhere to certain REMS requirements. For example, if a REMS requires prescribers to counsel patients before prescribing the drug, prescribers may be surveyed on whether they did so with the initial and any subsequent prescriptions. Patients, in turn, may be surveyed on whether they received counseling from their provider before they were prescribed the drug.

In addition to the use of surveys to assess self-reported adherence with program requirements, surveys may also be designed to assess attitudes and beliefs and the potential burden associated with REMS program requirements. FDA's draft guidance, *Survey Methodologies to Assess REMS Goals That Relate to Knowledge*, provides recommendations to industry on conducting REMS assessment surveys to assess respondent knowledge of REMS-related information.[23]

3. Drug Utilization Data

Drug utilization data not only provide descriptive information on the patterns of drug use but can also provide useful information on overall disease treatment patterns and healthcare market dynamics. Studies incorporating drug utilization data may be able to measure patient and provider characteristics; reasons for use; rates of drug uptake; concomitant drug use; and, in some cases, more detailed information such as duration of use and drug switching patterns. Finally, drug utilization studies may, in combination with other studies, inform barriers to patient access to the drug (see section V.B.).

If a REMS Assessment Plan includes a drug utilization study, it should describe the drug utilization data source, the rationale for the data source, and the data collection methodology, design and analytical approaches, and any limitations. The drug utilization study protocol should also describe the national representativeness of the utilization data analyzed, as well as the representativeness of the population evaluated in the drug utilization study relative to the overall patient population receiving the drug product, comprehensiveness of the capture of drug utilization across all settings of care, any linkages to other data sources as relevant/appropriate, and any relevant data projection methodologies employed.

For all drug utilization studies, a study protocol should be submitted to FDA for review and comment prior to study initiation. In some cases, a statistical analysis plan may also be necessary.

4. Postmarketing Adverse Event Data

Adverse event data can provide qualitative information on adverse events and outcomes related to the risk that the REMS is intended to mitigate. A number of factors affect spontaneous adverse event reporting, including the nature and severity of the adverse event and length of time the product has been on the market.

The quality of the adverse event reports is critical for appropriate assessment of the REMS; therefore, we recommend collection of targeted information about specific adverse events of interest. The information collected should focus on further characterizing the risk, and capturing patient outcomes, as well as determining whether safe use conditions were met. The type of data the applicant plans to collect to further characterize the adverse event should be included in the REMS Assessment Plan. If feasible, it is helpful to link patient information in the applicant's REMS database, when one exists, to adverse event reports in the applicant's adverse event database.

A well-recognized limitation of spontaneous adverse event reporting is underreporting. It is possible that the extent of underreporting for products with REMS with ETASU is not as extensive as products without REMS, particularly when there is a mechanism to monitor patients for adverse events as part of a REMS requirement. However, because spontaneous adverse event reporting systems do not capture all adverse events, even adverse events for drugs with an approved REMS, the data from those reporting systems cannot be used to calculate the incidence of a particular adverse event.

Postmarketing adverse event data can be used to compare reporting rates of an adverse event before and after a REMS have been implemented. In certain circumstances, however, it may not be appropriate to do so because there may be differences in the way the adverse event information was obtained. For example, prior to the implementation of a REMS, adverse event information may be collected solely from spontaneous reports. If the REMS includes a prescriber attestation to report adverse events experienced by patients taking the drug, the number of reported events may be higher after REMS implementation (stimulated reporting).

To the extent possible, several sources should be employed to obtain information on adverse events and outcomes related to the risk that the REMS was intended to mitigate. Adverse event reports received or identified through REMS are still required to be evaluated and must be submitted to FDA per the regulations for postmarketing adverse event reporting.[24]

[24] 21 CFR 314.80, 314.98, and 600.80.

5. Observational/Epidemiology Data

Studies analyzing observational data to evaluate outcomes associated with use of drug products (i.e., pharmacoepidemiology studies) can be considered to evaluate various aspects of REMS including safe use behaviors, prescribing patterns, barriers to patient access, and safety-related health outcomes or surrogates of those outcomes.

When designing epidemiology studies to assess a REMS, applicants may consider various population data sources and study designs. FDA has published best practices for conducting and reporting pharmacoepidemiology safety studies using electronic health care data.[25] Additionally, the published literature contains guidelines for planning, conduct, analysis, and reporting of epidemiologic studies of drug safety, which could be used to assess the performance of REMS.[26,27]

There may be unique challenges in using pharmacoepidemiology data to assess the effectiveness of a REMS. In most instances, existing databases may not adequately capture important data elements, such as the outcome of interest and covariates, therefore limiting the adequacy of a pharmacoepidemiology study to evaluate the metrics of interest. In those instances, studies employing prospective data collection will need to be considered. Additionally, the utility of pharmacoepidemiology data is limited when a REMS is implemented at the time of approval and therefore no data are available on the use of the drug without a REMS. Nevertheless, the optimal design and methodology of studies using observational/epidemiologic data to assess the impact of REMS or specific REMS requirements on certain outcomes are evolving. FDA intends to exercise a flexible approach with regard to such studies.

This guidance does not recommend a specific pharmacoepidemiology study design or type for REMS assessments, nor does it address the specific population or data sources to be considered. The decision to use a pharmacoepidemiology study should be guided by the questions of interest, and the feasibility of the selected data to adequately evaluate the question of interest. A discussion of the challenges of conducting a proposed assessment and limitations of the data used should be included in the study proposal.

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[25] FDA guidance for industry *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets*. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm243537.pdf.

[26] Von Elm E, Altman DG, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007; 335:806-808.

[27] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 1) [Internet]. London (UK): European Medicines Agency. EMA/95098/2010. Available at http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_2.pdf

6. Data from Root Cause Analysis

A root cause analysis (RCA) is a structured method used to analyze adverse events or root causes of program deficiencies and focuses on improving systems and processes to enhance patient safety.[28] An RCA may need to be conducted to better understand the observed findings from a specific REMS assessment. RCAs may be conducted after a REMS assessment has been completed if it is unclear whether certain aspects of the program are performing as intended. RCAs can help identify determinants and underlying causes of REMS failure to meet its goals. RCAs can also help identify the factors responsible for a particular type of failure of the REMS, as well as burden of the program on the healthcare delivery system, and barriers to patient access to the drug. This analysis may help inform any necessary modifications to the REMS program goals and requirements.

RCA best practices include the development and use of a predefined protocol and a team-based reconstruction of each issue via retrospective review and interviews. The applicant should then assess the sequence of steps that led to each type of program failure (e.g., inadequate prescriber knowledge, lack of compliance) or unintended effect and determine how and why that event occurred. RCAs can also help assess other adverse events or unfavorable effects that may occur as an unintended consequence of the REMS requirements.

7. Data from Stakeholder Outreach

Applicants should consider seeking input from the key stakeholders affected by the REMS, including prescribers, pharmacists, other healthcare professionals, and patients. Input from marketing research surveys, focus groups, and interviews could also inform the applicant and the Agency about the impact of the program on the healthcare delivery system and on patient access to the drug, as well as opportunities for program improvement.

D. Specifying Thresholds for REMS Effectiveness

An additional consideration in REMS assessment planning is specifying performance thresholds for determining the effectiveness of the REMS. The specification of performance thresholds or performance levels over time provides criteria to help determine if REMS program performance is acceptable or if modifications to the REMS are needed. For example, a proposal and justification for a performance threshold should be provided in study protocols for knowledge surveys. In this case, the threshold would be the minimum knowledge rate that, if achieved, demonstrates that the REMS has met its goals of communicating the REMS key messages.[23]

The REMS Assessment Plan should specify a performance threshold for a health outcome of interest, if feasible. If the health outcomes of interest for the REMS are difficult to measure directly, performance thresholds should be specified for surrogate metrics.

[28] Patient safety primers: root cause analysis [Internet]. Rockville (MD): Department of Health and Human Services (US). Agency for Healthcare Research and Quality. Available from: http://psnet.ahrq.gov/primer.aspx?primerID=10. See also Root Cause Analysis [Internet]. Washington (DC): Department of Veterans Affairs (US). National Center for Patient Safety. Available from: https://www.patientsafety.va.gov/professionals/onthejob/rca.asp

Applicants should describe potential limitations or challenges with selected performance thresholds. In cases in which prespecifying a performance threshold is deemed infeasible, applicants should explain the issues and considerations that resulted in this determination.

In lieu of prespecifying performance thresholds, applicants could consider providing alternatives such as: (1) a comparison of an adverse event for a drug with a REMS to a similar drug without a REMS, (2) a comparison of the reporting rate of an event from data obtained in a REMS registry to a background rate of that event in a similar patient population from a representative database, or (3) a comparison of the reported rate or the event rate from observational studies to the rate that was observed in the clinical trials. Each of these comparisons has limitations and should be interpreted with caution.

V. CONSIDERATIONS FOR MEASURING BARRIERS TO PATIENT ACCESS AND BURDEN ON THE HEALTH CARE DELIVERY SYSTEM

Including ETASU in REMS allows patients safe access to drugs with known serious risks that would otherwise not be approved or would be withdrawn. Section 505-1(f)(2) of the FD&C Act states that such ETASU shall, considering the risk, not be unduly burdensome on patient access, and, to the extent practicable, minimize the burden on the health care delivery system.

A. Assessing Burden on the Health Care Delivery System

In the context of REMS with ETASU, burden reflects the additional effort that healthcare professionals and other stakeholders expend in complying with the REMS requirements beyond what is required for good clinical care.[29] This may include, for example, the effort expended to comply with program requirements to complete certification and training or to implement a process in a healthcare system for verifying documentation of laboratory monitoring as required by a REMS. Burden may also result when information on REMS requirements is not easily found or stakeholder roles and responsibilities under REMS are communicated in ways that stakeholders find confusing.

Identifying potential REMS burdens should begin during the REMS design phase, and applicants should make efforts to minimize potential burdens at this stage. When proposed REMS with ETASU are submitted, applicants should provide supportive information that demonstrates that they have considered the ways in which ETASU may introduce additional burden and that they have attempted to minimize that burden to the extent practicable. Applicants may use a range of methods to identify burdens and opportunities to reduce them, including interviews with stakeholders or use of focus groups, as well as assessing the workflows associated with implementing REMS requirements in various health care settings. For example, workflows may vary based on the outpatient or inpatient setting and, for the latter, whether the medication is formulary, nonformulary, or supplied by the patient. An analysis of workflow during the REMS design phase will also provide opportunities to identify postimplementation inefficiencies and

[29] FDA Background Document: Impact of REMS on the Healthcare Delivery System and Patient Access. Public Meeting, October 5-6, 2015. Available from: https://www.fda.gov/Drugs/NewsEvents/ucm441308.htm

make program improvements to reduce burden. Applicants are encouraged to explore additional methods to identify burdens associated with REMS with ETASU and describe these in their proposed REMS submission. For example, a time and motion study could potentially be used to evaluate the time required to complete a REMS activity and identify a more efficient operation thus reducing healthcare delivery burden. [30,31]

The REMS Assessment Plan should describe the metrics, data sources, and analytical tools that applicants intend to use to assess REMS burdens following program implementation. Applicants should submit protocols for all studies assessing REMS burden to the Agency for review and comment prior to conducting the assessment (see section IV.C above).

In their REMS Assessment Reports, applicants should include the results of the assessment of REMS burden and evaluate the degree to which the observed burden compares to the expected burden across different categories of stakeholders or settings. The report should also include any additional areas of potential burden that may have been identified during program implementation. For example, applicants could demonstrate that they have assessed how REMS burden was reduced in certain settings by integrating verification of safe use requirements into electronic systems such as pharmacy practice management systems. The report could also include the settings that were unable to employ compatible electronic systems. Finally, the report could identify areas of opportunity and potential strategies for further reducing known or newly identified burdens.

B. Assessing Barriers to Patient Access

Despite efforts during the REMS development to minimize barriers to patient access, certain patients may still find it difficult to access a drug that is subject to a REMS with ETASU. Assessing the impact of REMS with ETASU on barriers to patient access to the medication is an important part of the overall REMS performance assessment.

Identifying potential barriers to patient access should begin during the REMS design phase, and applicants should try to minimize any identified potential barriers to access. For example, when REMS place significant burdens on healthcare systems, some providers (e.g., prescribers, pharmacies, or clinics) may choose not to prescribe the drug because they may be unwilling to participate in the REMS; or, it may be difficult for a patient to find a participating prescriber in their geographical area, affecting the patient's access to the drug. REMS program requirements may result in delays to patient access of a drug in ways that were not anticipated during the design phase.

The REMS Assessment Plan should describe the metrics, data sources, and methodologies that applicants intend to use to assess barriers to patient access that are related to the REMS

[30] Time and Motion Studies Database US Department of Health and Human Services (US) Agency for Healthcare Research and Quality National Resource Center; Health Information Technology Available at: https://healthit.ahrq.gov/health-it-tools-and-resources/evaluation-resources/time-and-motion-studies-database

[31] Lo HG, Newmark LP, Yoon C, et al. Electronic Health Records in Specialty Care: a Time-Motion Study. JAMIN 2007;14(5): 609-615. Available at: https://academic.oup.com/jamia/article/14/5/609/721654

following implementation. This may be particularly challenging when a new product is approved with a REMS with ETASU, as uptake of the product may be slow. Patient interviews and focus groups may again be useful to identify any negative impact on patient access of REMS with ETASU.

Drug utilization data may be used to evaluate REMS impact on patient access. However, the use of these data should be planned carefully, because drug utilization data alone cannot be relied upon to fully describe the impact of REMS on patient access. For example, drug utilization data may show a reduction in the use of a drug product if a REMS with ETASU is imposed post-approval. However, additional analysis may be needed to determine whether the reduction in use is consistent with the goals of the REMS or whether it suggests a reduction in the use of the product in patients for whom the benefit outweighs the risks. As with any data sources and methodologies used to assess REMS, protocols should be submitted to the Agency for review and comment prior to the assessment (see section IV.C above).

Applicants should include the results of the assessment of access as specified in the REMS Assessment Plan and the degree to which the observed barriers to access compare to those expected across different categories of stakeholders or settings. The assessment should also include any additional barriers to patient access that may have been identified during program implementation. Finally, the assessment could identify areas of opportunity and potential strategies for further reducing barriers to access.

VI. REMS ASSESSMENT SUBMISSIONS

A. REMS Assessment Plan

1. Overview

The REMS Assessment Plan should be presented in a separate section in the REMS Supporting Document and submitted to the Agency with the proposed REMS submission.

The REMS Assessment Plan should include an overview that depicts the REMS goals and objectives, REMS requirements and the REMS materials, and how each requirement is going to be assessed, including the assessment category, selected metrics, related data sources, analytical tools, and the frequency of assessment. The overview may be in a tabular format, as shown in Appendix 2A. An additional column could be added that maps the assessment plan metric, data source, or analytical tool to the location in the REMS Supporting Document where the details of the methodology or protocol are described further.

The REMS Assessment Plan described in the FDA approval letter will include only the REMS assessment categories and their corresponding metrics.

2. Methodology or Protocols Describing Sources of Data and Analytical Tools

The REMS Assessment Plan should also include a thorough description of and rationale for each of the various data sources that will be used to collect data for the REMS assessment.

Additionally, the metrics used to measure each objective, the types of data that will be analyzed, the analytical tools that the applicant intends to use, and the rationale for the selection of the types and source of data should be provided. The assessment plan should include as much detail as possible at the time the REMS Supporting Document is submitted.

If the assessment instruments and methodology have not been determined prior to approval of the REMS and are not included in the REMS Supporting Document, the applicant should include a timeline for submission of the methodology or the study protocol in the REMS Supporting Document. For example, if the applicant is planning a drug utilization study or pharmacoepidemiology study to assess an aspect of the REMS but has not fully developed the study protocol, the planned timeframe for protocol submission should be indicated. Applicants are encouraged to submit a full protocol for specific studies (e.g., surveys, pharmacoepidemiology studies, RCA) at least 90 days before the assessments will be conducted to allow for Agency review and feedback.

If there are changes to a previously submitted assessment instrument or methodology, the REMS Supporting Document should be updated and submitted for review and comment at least 90 days before the assessments will be conducted. Updates to the REMS Supporting Document may be included in a new document that references previous REMS Supporting Document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS Supporting Document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA/ANDA [assigned #] REMS CORRESPONDENCE (insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

B. REMS Assessment Reports

Submit the REMS Assessment Report to FDA according to the timetable for submission of assessments in the approved REMS. FDA suggests that the REMS Assessment Report include the following sections:

Cover Page
Table of contents
1. Executive summary
2. Introduction
3. Background
    (a) REMS goals and objectives, REMS requirements, and REMS materials
    (b) REMS history[32]

[32] The REMS history outlines all changes made to the REMS since its approval. The REMS history should be similar in format to the summary that application holders include in labeling supplements that provides the history of changes made to the product label. The REMS history should be in a tabular format as described in the guidance for

(c) Pending supplements

4. REMS Assessment Plan
   (a) An overview in tabular format (see Appendix 2A) or other format
   (b) Details of the information summarized in the overview of the REMS Assessment Plan (see section VI.A above). Methodology used to support REMS assessment (e.g., survey, other methodology) can be included or referenced to prior submission
5. Brief summary of previous assessments
6. Results or summary of findings of each assessment metric
7. Discussion: overall assessment of whether the REMS goals and objectives are being met
8. Proposed modifications to the REMS or revisions to the REMS Assessment Plan

The cover page should include the reporting time point (e.g., 18-month assessment), the date of the REMS Assessment Report, and the assessment reporting period (e.g., September 30, 2015, reporting period August 1, 2014, to July 31, 2015). Following the table of contents, the report should include an executive summary of the findings and conclusions. This should be followed by the introduction, background section, which includes the REMS goals and objectives, REMS requirements, and REMS materials that were in place during the assessment reporting period, a REMS history, and any pending supplements.

If survey results are included in the REMS Assessment Report, the survey instruments should be included in the report or reference the submission in which these instruments were provided. Any new methodologies or protocols, as well as those not previously submitted to the Agency, should be included in the REMS Assessment Report. The REMS Assessment Report should also include a brief summary of the previous assessments, including the key results and the overall conclusions.

The results section should include the aggregate data collected for each metric, a written summary of the data that was analyzed, key results, and a description of limitations. When appropriate, the data should be reported for the reporting period and cumulatively, and trends in performance compared to previous periods should be reported and discussed.

The discussion section should provide an evaluation of whether each individual goal or objective is being met as well as an overall evaluation and conclusion as to whether the REMS is meeting its goals and objectives. In some REMS Assessment Reports, it may be clear that one goal or objective is being met while others are not, leading to the conclusion that the REMS is only partially meeting its goals. If data are not robust enough to determine whether a goal or objective is being met this should be stated along with recommendations for additional data sources or analyses that would allow a conclusion to be made in a future assessment. In addition, for REMS with ETASU, a conclusion should be made regarding whether the burden on the healthcare

industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions.* Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM441226.pdf

delivery system is being minimized to the extent practicable, whether the ETASU are unduly burdensome on patient access to medication, and an explanation for these conclusions.

The final section should include any proposed modifications to the REMS, as well as the basis for the proposed modifications (e.g., address REMS' compliance issues, reduce burdens, overcome barriers to patient access, improve efficiencies). Any considerations to address reducing burdens that are identified through the REMS assessment should focus on how burden could be reduced without adversely affecting the overall impact of the program on the safe use of the drug. For example, if a laboratory test is required as part of a safe use condition, burden could be potentially minimized if issues identified in the ordering, scheduling, and reporting of the results are addressed. In this example, the requirement for testing would remain; however, the processes surrounding it might be reevaluated to reduce inefficiency. Recommendations for proposed REMS modification or elimination should be supported by an analysis of the expected impact or a plan to assess the impact of any proposed modification or elimination on the future safe use of the drug.

The applicant should also consider proposed revisions to the REMS Assessment Plan if additional information is needed to determine whether the goal of the REMS is being met or if there are aspects of the REMS that are no longer necessary to assess.

On the first page of the submission of a REMS Assessment Report of 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 Report 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.

APPENDIX 1: EXAMPLE - ASSESSMENT CATEGORY AND METRICS

The following table lists the two REMS assessment categories and examples of associated metrics for a REMS whose objective is to ensure that safe use conditions are documented prior to administration of a drug; and which requires that the drug can only be dispensed by in a certified healthcare setting after completion of a checklist by a health care provider confirming safe use conditions.

REMS Assessment Category	Example Metrics
Program implementation and operations	• Number and geographical location of certified healthcare settings that are able to dispense the drug • Number of certified healthcare settings that have administered drug at least once during the reporting period • Number of healthcare settings that were unable to become certified and reasons why • Summary of regions in the United States that do not have certified healthcare settings that are able to dispense drug • Summary of audit findings including the number of certified settings that lacked protocols or order sets or policies to ensure completion of the checklist prior to administering drug • Analysis of call center data indicating: o Difficulty locating a certified healthcare facility o Number of and reason for delays in drug dispensings
Safe use behavior	• Number and percent of doses not administered because safe use condition on checklist was not performed • Number of patients for whom prescribers were contacted because of an issue identified by the pre-infusion/pre-administration checklist and subsequent outcome of contact • Number of counseling visits before or during initiation of treatment (claims database) • Number of patients receiving a concomitant medication known to potentiate risk being mitigated (drug utilization database)

APPENDIX 2: EXAMPLE REMS ASSESSMENT PLAN OVERVIEW

Appendix 2A shows a REMS Assessment Plan overview in tabular format. The overview is for a fictitious REMS and illustrates the relationship among the REMS program (goals, objectives, stakeholder requirements and materials) and the REMS Assessment Plan (data sources, metrics, methodologies, performance thresholds).

Drug X REMS:

Drug X is a fictitious new medication shown in clinical trials to improve survival and function in patients with a rare progressive cardiac condition for which there are no FDA-approved therapies. However, up to 10 percent of patients experienced an acute, serious neurologic adverse reaction within 30 minutes of dosing that, if detected could be rapidly treated with a corticosteroid injection. The likely prescribers of Drug X are cardiologists and the medication is to be administered by intravenous infusion once a month. No risk factors were identified to help predict which patients were at risk of experiencing the acute neurologic adverse event.

The sponsor filed a new drug application with a proposed REMS including a communication plan and elements to assure safe use, because of the importance of educating cardiologists and other Drug X prescribers about detecting acute neurologic symptoms, the need to ensure early observation and detection and access to corticosteroid treatment, and the possibility of long-term sequelae if the adverse event is not promptly treated.

The goal of the Drug X REMS is to mitigate the risk of developing long-term adverse neurologic effects. Objectives of the REMS include: (1) ensuring healthcare providers are educated about the risk (including that prior exposure with an associated adverse event is a risk factor), the neurologic symptoms they need to monitor following dosing, and how to treat the acute neurologic symptoms should they occur; (2) ensuring healthcare providers observe patients for at least 30 minutes following Drug X dosing and that the treatment setting has corticosteroid injection readily available; and (3) ensuring healthcare providers enroll all patients who experience the adverse event into a patient registry to avoid re-exposure.

The Drug X REMS program includes the following requirements and REMS materials: (1) a REMS letter, (2) healthcare provider training, (3) certification of the healthcare setting to ensure that the setting has corticosteroid treatment available (i.e., as a safe use condition), and (4) a registry for enrolling patients who experience the acute neurologic adverse event. The Drug X REMS assessment reporting frequency is 6 months, 12 months, and annually after initial approval of the REMS.

Appendix 2A: Drug X REMS Assessment Plan

Objective	Requirement	REMS Materials	Assessment Plan Category/ Domain	Metrics	Data Sources/ Analytical Tools	REMS Assessment Report: Frequency of metric reporting	Performance Threshold	Methodology/ Protocol Location and Date Submitted
Goal: Mitigate the risk of long-term adverse neurological events								
Ensure healthcare providers are educated about the risk, the neurologic symptoms that must be monitored following dosing, and how to treat acute neurologic symptoms should they occur	Communication plan	-REMS letter -REMS website	Outreach and communication	-Number and date of REMS letters sent/opened/ returned -Website access statistics	-Sponsor REMS database -Sponsor REMS website	In 6 and 12 month reports	—	REMS letters list obtained by [organization]
	Prescriber certification	-Prescriber training program	Implementation and operations	-Date of product launch -Number and specialty of certified prescribers - Number of prescription orders written by noncertified prescribers and disposition	-Sponsor REMS database - Successful completion of Post-Training Knowledge assessment - Evaluation of healthcare provider knowledge (e.g., surveys of knowledge)	In 6 month, 12 month, and annual reports	100% of prescribers trained -Score 100% on post training knowledge assessment -80% knowledge rate on evaluation of healthcare provider knowledge (e.g., surveys of knowledge)	-Healthcare provider knowledge survey protocol (submitted mo, day, year) -
Ensure healthcare setting has corticosteroid injection available	Pharmacy and Healthcare facility certification	Pharmacy and Healthcare setting attestation of safe use conditions (authorized representative enrollment form)	Implementation and operations	Number and type of pharmacy and healthcare facilities enrolled	-Sponsor REMS database	In 12 month and annual reports	100% pharmacies and healthcare settings that receive and administer drug are certified	
	Safe use conditions		Evaluation of safe use conditions	-Results of audits of healthcare facility including summary of	Audit protocol	In 12 month and annual reports	-100% of audited healthcare settings have policies and procedures in	-Audit plan submitted [month/day/year]

Objective	Requirement	REMS Materials	Assessment Plan Category/ Domain	Metrics	Data Sources/ Analytical Tools	REMS Assessment Report: Frequency of metric reporting	Performance Threshold	Methodology/ Protocol Location and Date Submitted
Goal: Mitigate the risk of long-term adverse neurological events								
				findings and any corrective actions taken -Results of surveys of certified prescribers, pharmacies and healthcare settings regarding need for and availability of corticosteroids			place to ensure corticosteroids are available -80% overall knowledge score on survey	-Survey methodology submitted [month/day/year]
Ensure healthcare providers observe patients for at least 30 minutes following Treatocil dosing	Safe use conditions	Postinjection observation form	Evaluation of safe use conditions	-Number of patients who received the drug -Number of completed forms documenting observation period of 30 minutes -Reports of adverse events with and without observation	-Sponsor REMS database -FAERS	In 6 month, 12 month, and annual reports	100% of observation forms completed 100% of audited healthcare settings have policies and procedures in place to ensure patients are monitored for 30 minutes following infusion	
Ensure healthcare providers enroll all patients who experience acute neurologic adverse event following dosing into a registry	Safe use conditions	-Post-injection observation form -Neurologic event registry	-Program infrastructure and performance -Evaluation of safe use conditions -Adverse event surveillance	-Total number of patients who received the drug -Number of cases of acute neurologic events following dosing	-Sponsor REMS database -Sponsor registry -Surveys of certified prescribers, pharmacies, and healthcare facilities	In 12 month and annual reports		Registry protocol

Objective	Requirement	REMS Materials	Assessment Plan Category/ Domain	Metrics	Data Sources/ Analytical Tools	REMS Assessment Report: Frequency of metric reporting	Performance Threshold	Methodology/ Protocol Location and Date Submitted
Goal: Mitigate the risk of long-term adverse neurological events								
					-Sponsor's adverse event database/ FAERS			