REMS Platform Standards Initiative: Needs Assessment

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1 About This Document

In 2015, the Food and Drug Administration (FDA) announced the creation of the REMS Platform Standards Initiative. This initiative is intended to encourage and support the development of data standards, called *REMS platform standards*, to help standardize risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU) and better integrate them into the increasingly electronic health care system. Under the initiative, FDA seeks to encourage the development of electronic data standards that may be used to facilitate communication between REMS and their participants. Once the standards are developed, FDA would maintain a list of REMS platform standards and encourage their use in REMS.

The purpose of this document is to provide REMS stakeholders, standards developers, and health information technology (IT) systems developers with specific, detailed information on the areas in which standards development is needed and the information that the data standards would need to communicate.

The first section of this document introduces REMS and the REMS Platform Standards Initiative. The next section describes the parties involved in the REMS Platform Standards Initiative, provides an overview of the REMS activities supported by the platform, and describes how information is exchanged in aREMS. The final section details the areas in which REMS platform standards can support REMS communication and the specific information that should be communicated using these standards.

2 Introduction to REMS and the REMS Platform Standards Initiative

REMS are programs that use specific tools beyond FDA-approved labeling to mitigate serious risks associated with the use of a drug. FDA requires the manufacturers (referred to as *sponsors*) of certain drugs to put REMS in place to ensure that the benefits of the drug outweigh its risks. FDA can require a REMS at the initial approval of a new drug, or, should FDA become aware of new safety information and make a determination that a REMS is necessary, after the drug has been approved and is on the market.

REMS development involves multiple parties and steps. FDA first determines whether a REMS is necessary to ensure that the benefits of a drug outweigh its risks and then determines the required elements of the REMS to ensure safe use of the drug. Sponsors are notified by FDA of the REMS requirement and then design the REMS and submit their proposal for FDA review. This proposal includes requirements the sponsor must meet to carry out the REMS and, in some cases, may include requirements for health care providers or patients. Certain REMS, called REMS with ETASU, may restrict prescribing, dispensing, or distribution of a drug to health care providers, settings, and patients who have met the REMS requirements and completed certain activities to ensure the safe use of the drug.

As part of the REMS development process, FDA and sponsors may reach out to stakeholders (health professionals, professional organizations, etc.) for input on the drug delivery and care processes for patients with the condition the drug is intended to treat or to obtain feedback on how a REMS with ETASU can be designed to minimize the burden to the health care delivery system.

Following FDA approval of the REMS, sponsors are responsible for implementing the REMS requirements. They may administer the REMS themselves or hire third-party vendors to do so. The sponsor submits assessments of

its REMS to FDA based on a predetermined timetable. FDA reviews these assessments to determine whether the REMS is meeting its goals.

The requirements of a given REMS are specific to the goals and objectives of the REMS. Because the sponsors are responsible for developing and implementing these programs and because the risks that are mitigated vary, standardization across different REMS has been limited. Similar tools are often used to meet REMS requirements; however, to date, the tools may have different names, use different terminology, or require different processes, and in general, they are not well-integrated into health system workflows or health information technology (IT) systems, which creates burdens for providers and barriers to efficient communication about the risks of the drug and the REMS requirements. This challenge is particularly acute for REMS with ETASU, where the programs may place specific requirements on health care providers and patients in order for them to be able to use the drug.

In response to these challenges, FDA has taken steps to standardize REMS and better integrate them into the health care system. Among these efforts is FDA's REMS Platform Standards Initiative. The goal of this initiative is to leverage electronic health data standards to standardize certain activities in REMS with ETASU and integrate them into health IT systems. Under the initiative, FDA seeks to encourage the development of electronic data standards that may be used to facilitate communication between REMS and their participants. Once the standards are developed, FDA would maintain a list of REMS platform standards, encourage their use in REMS with ETASU, and encourage the development of tools that use these standards to integrate REMS into healthcare providers' existing systems.

Although FDA seeks to encourage the development of platform standards, it does not intend to create them. Instead, FDA wishes to work with established standards development organizations (SDOs). All of the standards currently in place in health care are developed by these parties, including groups such as the National Council for Prescription Drug Programs (NCPDP), Health Level 7 International, and Integrating the Healthcare Enterprise. These SDOs have been set up to incorporate a wide range of stakeholder input when developing their standards.

3 REMS Stakeholders and Information Exchange Model

The purpose of REMS platform standards is to facilitate the exchange of information among REMS stakeholders as they carry out and verify the completion of certain REMS activities needed to meet requirements specified in REMS with ETASU. The following section presents more detailed information about the individual REMS stakeholders who exchange information, the REMS activities the platform may support, and how REMS stakeholders would exchange information about these activities using the REMS platform.

3.1 REMS Stakeholders

REMS platform standards are designed to facilitate information exchange among the following REMS stakeholders.

REMS administrators are the parties who implement REMS. A REMS administrator may be the sponsor of a new drug application, abbreviated new drug application, or biologics license application, or a third party acting on the sponsor's behalf. The REMS platform can help REMS administrators provide REMS participants with materials,

work with health care providers to help ensure that they can complete REMS activities, and verify that REMS activities are completed.

Health care providers are those who are involved in the care of patients who are prescribed a drug that is subject to a REMS requirement, including prescribers, pharmacists, nurses, and other practitioners who dispense or administer the drug or who monitor patients using a drug with a REMS requirement. The REMS platform standards can help health care providers exchange information about a range of REMS activities, including training, enrolling in a REMS, counseling, screening, and monitoring of patients.

DailyMed is a repository operated by the National Library of Medicine (NLM) that provides information about drugs, including their labeling, in structured product labeling (SPL) format. FDA will soon be providing REMS information on DailyMed in SPL format, enabling the availability of standardized, machine-readable information that can be used by health care providers and health IT systems to identify which products have REMS, what each REMS requires, and which REMS platform standards those REMS use.

Patients who are prescribed a drug that is subject to a REMS would not be expected to use REMS platform standards. They may share relevant information with their health care providers that may subsequently be exchanged by the health care provider using the REMS platform standards.

FDA would not be expected to use REMS platform standards to exchange information with health care providers or sponsors, but the information collected by the sponsor using these standards may inform the assessments of the REMS that are submitted to FDA.

3.2 REMS Activities

The REMS platform standards are designed to facilitate the exchange of information to help REMS stakeholders carry out certain REMS activities that may be required under the REMS. These activities may take place at several points during the medication use process.

First, there are activities that prescribers, health care settings, or pharmacies may be required to complete in order to prescribe, dispense, administer, or order a drug. Collectively, these activities form a process known as **Certification**. For example, a practitioner wishing to prescribe a drug may be required to provide identifying, descriptive, and contact information to a REMS administrator; complete certain training questions; and agree to carry out certain activities to ensure the safe use of the drug. For health care settings or pharmacies, some of these activities may be carried out by an authorized representative on behalf of the setting rather than by individual health care providers.

Second, there are activities that health care providers may be required to complete at the **Initiation of Treatment** with a patient. For example, a practitioner may be required to counsel the patient, provide the patient with certain materials, or evaluate the results of a specific laboratory test to ensure the patient is an appropriate candidate to receive the drug.

Third, there are activities that health care providers may be required to complete **During and After Treatment**, including when the drug is prescribed, dispensed, or discontinued or at regular intervals thereafter. For example, a practitioner may be required to check to make sure that certain safe use conditions are met before

dispensing a drug, monitor patients when the drug is administered, and report serious adverse events of interest or patient outcomes to the REMS.[1]

3.3 REMS Information Exchange

Although REMS administrators oversee implementation of the REMS and ensure that REMS activities are completed, health care providers must carry out most key REMS activities. Therefore, for REMS to be carried out effectively, information must regularly be exchanged between health care providers and REMS administrators. The REMS platform is designed to support this exchange by establishing standards by which information will be shared.

The table below outlines a few major types of information exchange that take place in REMS, although the specifics of the information exchange will vary depending on the REMS.

Information Exchange in REMS

REMS Administrators…	**Health Care Providers…**
Inform health care providers about the REMS activities they must carry out.	Carry out REMS activities and provide evidence that the activity has been completed.
Provide health care providers with the relevant REMS materials, including forms.	Review relevant REMS materials and complete and submit REMS forms.
Inform health care providers whether relevant REMS requirements have been met.	Check with the REMS administrator to confirm that they have met relevant REMS requirements.
Inform health care providers if an important REMS activity has not been completed.	Work to resolve issues in meeting REMS requirements and communicate to the REMS administrator that an issue has been resolved.

REMS use two basic approaches to the exchange of information between REMS administrators and health care providers: (1) In some cases, the REMS may require *predispense authorization* from the REMS administrator; (2) In other cases, the REMS may require the tracking of certain information through *periodic reporting and audits*.

If predispense authorization is required, a drug may not be dispensed to a patient until the REMS administrator has verified that all of the necessary REMS activities have taken place. The REMS most likely to require the REMS administrator to carry out such an authorization are those in which REMS activities are carried out across multiple health care providers and settings. A REMS with a predispense authorization requirement may necessitate frequent exchanges of information between the REMS administrator and health care providers, dispensers, settings, and patients to ensure that each participant is aware of what requirements the other participants have completed. For example, consider a REMS in which a patient must undergo a laboratory test and have the test results confirmed before a prescription is dispensed. If the laboratory test is obtained at a prescriber's office, but the prescription is filled at an outpatient pharmacy, it can be difficult for the pharmacy to

[1] Any specific reporting requirements under an approved REMS would not obviate an application holder's requirements for postmarket safety reporting for human drugs and biological products under 21 CFR 310.305, 314.80, and 314.98 and section 600.80 of the Federal Food, Drug, and Cosmetic Act.

In some cases, participants receive feedback on incorrect answers, explaining why their answer was incorrect and presenting additional training material relevant to that question.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the health care provider to send the following information to the REMS Administrator.

- Information needed to identify and track the health care provider
- Answers to multiple-choice questions

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the health care provider.

- General instructions for completing the training questions
- Knowledge assessment questions and answer choices
- Confirmation of whether specific questions were answered correctly or not
- Confirmation of whether or not the health care provider successfully answered the training questions

4.1.4 Enroll in the REMS

Enrollment is used to enable REMS administrators to collect basic identifying information about prescribers, pharmacies, and health care settings participating in the program and to track which participants have been certified and communicate with them.

Successful enrollment in a REMS may serve as evidence that a health care provider has met all requirements for certification and is therefore able to prescribe, dispense, administer, or distribute the drug. For this reason, the terms *enrolled* and *certified* are often used interchangeably within REMS. However, it is possible for health care providers to be enrolled in a REMS without being certified if they have not yet completed other requirements for certification.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the health care provider to send the following information to the REMS Administrator.

- Information needed to identify, track, and contact the health care provider
- Requests for information about a health care provider's enrollment status

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the health care provider.

- Confirmation of receipt of enrollment information
- Documentation that can be used by the health care provider as evidence of certification, if the enrollment culminates in certification, including the date of certification and the name of the REMS for which they were certified

4.2 Initiation of Treatment

4.2.1 Complete Prescriber Acknowledgments and Agreements for Initiation of Treatment

REMS with ETASU may require prescribers to attest to various acknowledgments before initiating treatment for a patient. The REMS acknowledgments that are made at the initiation of treatment vary significantly across REMS but are typically used to confirm that the prescriber has met the necessary prerequisites for prescribing the drug to a particular patient, including the following:

- The prescriber understands the risks of the drug and how to use the drug safely.
- The prescriber has ensured that the patient is an appropriate candidate for treatment.
- The prescriber has counseled the patient on the risks of the drug and how to use the drug safely.
- The prescriber has provided the patient with necessary materials.
- The prescriber has conducted necessary laboratory tests or screening.

In addition to acknowledgments at initiation of treatment, prescribers may also be asked to agree to meet REMS requirements for that patient, including those requirements described in sections 4.1 and 4.3 of this document. For example, prescribers may agree to counsel patients who are taking the drug or to report certain adverse events.

<u>Platform Standard Requirements</u>

A REMS platform standard that supports this activity should enable the prescriber to send the following information to the REMS administrator.

- Information needed to identify and track the prescriber
- Checkboxes or yes/no responses to indicate that the prescriber has read and confirmed each attestation statement
- Confirmation (e.g., a digital signature) that the prescriber has read and understood all of the attestation statements

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the prescriber.

- Confirmation of receipt of the prescriber's attestations
- A reminder to perform the necessary REMS activities

4.2.2 Complete Patient Acknowledgments and Agreements for Initiation of Treatment

In addition to the prescriber, the patient may also be required to complete certain acknowledgments and agreements when initiating therapy. Patients may, for example, be asked to acknowledge that they understand the risks of the drug, how to use it safely, and how to recognize and address potential adverse events.

Typically, the prescriber is responsible for ensuring that the patient completes the REMS acknowledgements and agreements and, when necessary, that documentation of their completion is sent to the REMS administrator.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the prescriber to send the following information to the REMS administrator.

- Information needed to identify and track the patient
- Information needed to identify and track the health care provider
- Checkboxes or yes/no responses to indicate that the patient has read and confirmed each acknowledgment and agreement
- Confirmation (e.g., a digital signature) that the patient has read and understood all of the acknowledgments and agreements

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the health care provider.

- Confirmation of receipt of acknowledgments and agreements
- Documentation that can be used by the health care provider as evidence that the patient has been certified, which includes the date of certification and the name of the REMS for which they were certified

4.2.3 Screen Patient

A number of REMS with ETASU require prescribers or other health care providers to screen patients and assess whether they are appropriate candidates for therapy before prescribing the drug. In these cases, the REMS may require the health care provider to document this screening and assessment by sending the REMS administrator information on the patient's condition, health status, or the completion of certain laboratory tests.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the health care provider to send the following information to the REMS administrator.

- Information needed to identify and track the health care provider
- Information needed to identify and track the patient
- Checkboxes or yes/no responses to acknowledge that a laboratory test was completed
- Information about the laboratory test, potentially including the date of the test, the time of the test, and the type of test conducted
- Results of the laboratory test
- Responses to questions about the patient's condition or health status

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the health care provider.

- Confirmation of receipt of information
- Confirmation of whether laboratory test result or other health information is acceptable

- If deemed necessary, alerts to authorize, order and/or change the monitoring frequency/dosing, or to discontinue treatment
- If deemed necessary, alerts about pending expiration of laboratory tests

4.2.4 Enroll Patient in the REMS

Enrollment allows REMS administrators to collect basic identifying information about patients, enabling REMS administrators to communicate with patients and track whether necessary safe use conditions have been met before the patient receives a drug.

Typically, the prescriber is responsible for ensuring that the patient is enrolled in the REMS and that the enrollment information is sent to the REMS administrator.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the health care provider to send the following information to the REMS administrator.

- Information needed to identify, track, and contact the patient
- Information needed to identify and track the health care provider
- Information relevant to the treatment with a drug. The information may include the indication for which the drug is being prescribed, concomitant medication(s), relevant medications, previous treatment(s), or patient category (e.g., child bearing status).

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the health care provider.

- Acknowledgment of successful enrollment
- If necessary, a unique identification number for the patient to use during future interactions with the REMS

4.3 During and After Treatment

4.3.1 Monitor Patient Condition or Health Status

Some REMS with ETASU require regular patient monitoring, such as laboratory tests and periodic assessments by prescribers or other health care providers to facilitate earlier identification and treatment of serious risks that may result from the drug and to ensure that the benefits of the drug continue to outweigh the risks for the patient.

These REMS may require health care providers to provide REMS administrators with information about the patient's health status and conditions or about any screening or monitoring that has been done.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the health care provider to send the following information to the REMS administrator.

- Checkboxes or yes/no responses to acknowledge that a laboratory test was completed or other health information was collected
- Information about the laboratory test or information collection, potentially including the date, time, and type of test conducted or information collected
- Results obtained from the laboratory test
- Responses to questions about the patient's condition or health status

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the health care provider.

- Confirmation of receipt of information
- Confirmation of whether the result of laboratory test result or other clinical assessment is acceptable
- If deemed necessary, alerts to authorize, change the monitoring frequency/dosing, or discontinue treatment

4.3.2 Verify Safe Use Conditions When Prescribing

Certain REMS with ETASU may place limits on how drugs may be prescribed, including restricting the permitted days' supply or disallowing refills to ensure that patients are regularly monitored. These REMS may also use the prescribing step as an opportunity to verify that safe use conditions are in place before the prescription order reaches the dispenser.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the prescriber to send the following information to the REMS administrator.

- Information needed to identify the prescriber
- Information needed to identify the patient
- Information needed to identify the dispenser
- Additional information about the prescription, including the drug, days' supply, quantity prescribed, and whether refills are permitted

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the prescriber.

- Alert if the certain safe use conditions have not been met, including REMS refill restrictions and days' supply restrictions. The alert may be for informational purposes or may serve as a hard stop, preventing prescribing
- Alert if there are any pending REMS-related deadlines, such as the need to recertify the prescriber or patient or conduct additional monitoring

4.3.3 Obtain REMS Dispensing Authorization

In many REMS with ETASU, the REMS administrator tracks whether safe use conditions have been met, and the REMS may require dispensers to verify that these requirements are met by obtaining authorization from the REMS administrator before dispensing the drug.

In existing REMS, many retail pharmacies' predispensing authorization can be carried out electronically using NCPDP's telecommunications standard.[2]

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the dispenser to send the following information to the REMS administrator.

- Information needed to identify and track the prescriber
- Information needed to identify the patient
- Information needed to identify the dispenser
- Prescription information, including any information necessary to verify safe use conditions (e.g., National Drug Code, dosage, days' supply, number of refills)

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the dispenser.

- Authorization to dispense the medication (i.e., verification that safe use conditions have been met)
- Reminders to carry out certain actions, such as counseling the patient or dispensing a Medication Guide.
- Notification that safe use conditions were not met (i.e., not authorized to dispense) and corrections are necessary for authorization

4.3.4 Report Adverse Patient Outcomes or Adverse Events of Interest

REMS may collect information on specific adverse events that are the focus of the REMS that is more detailed than what might be obtained through standard adverse event reporting. In some cases, this information collection is associated with a patient registry required as part of the REMS.

Platform Standard Requirements

A REMS platform standard that supports this activity should enable the health care provider to send the following information to the REMS administrator.

- Patient demographic information
- Information about the event, including time to onset of event, signs and symptoms, relevant laboratory or other diagnostic results, potential risk factors, medication dispensing information, length of treatment, patient disposition/event outcome information, and concomitant medications

[2] NCPDP's Telecommunication Standard is used primarily for the adjudication of pharmacy claims, but is also used in REMS to permit electronic dispensing authorization. For more information about NCPDP standards, see https://www.ncpdp.org/Standards-Development/Standards-Information.

A REMS platform standard that supports this activity should enable the REMS administrator to send the following information to the health care provider.

- Confirmation of receipt of a reported adverse event