A PDUFA VII Preview: Enhancement and Modernization of the FDA Drug Safety System

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REdI Annual Conference – June 6-10, 2022

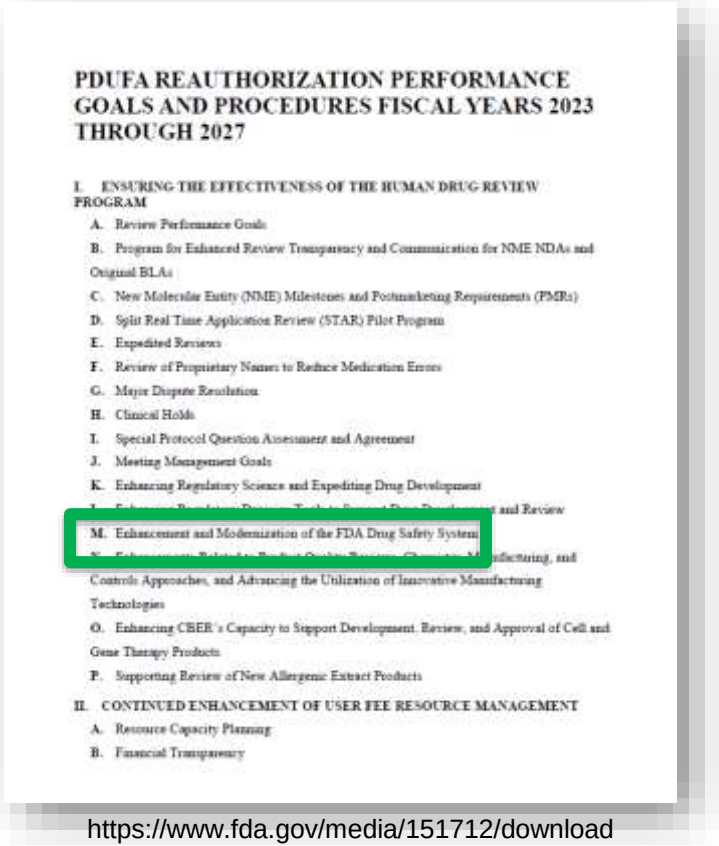
Learning Objectives

- Review the PDUFA VII related commitments related to FDA's drug safety system
- Identify the two postmarket drug safety initiatives under this section of the commitment letter to be modernized and enhanced
- Recognize high-level milestones and opportunities for external stakeholders to provide input over the next five years starting October 1, 2023

PDUFA VII Commitment Letter

Section M. Enhancement and Modernization of the FDA Drug Safety System

1. Modernization and Improvement of REMS Assessments
2. Optimization of the Sentinel Initiative



PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027

I. ENSURING THE EFFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM

A. Review Performance Goals

B. Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs

C. New Molecular Entity (NME) Milestones and Postmarketing Requirements (PMRs)

D. Split Real Time Application Review (STAR) Pilot Program

E. Expedited Reviews

F. Review of Proprietary Names to Reduce Medication Errors

G. Major Dispute Resolution

H. Clinical Holds

I. Special Protocol Question Assessment and Agreement

J. Meeting Management Goals

K. Enhancing Regulatory Science and Expediting Drug Development

M. Enhancement and Modernization of the FDA Drug Safety System

Controls Approaches, and Advancing the Utilization of Innovative Manufacturing Technologies

O. Enhancing CBER's Capacity to Support Development, Review, and Approval of Cell and Gene Therapy Products

P. Supporting Review of New Allergenic Extract Products

II. CONTINUED ENHANCEMENT OF USER FEE RESOURCE MANAGEMENT

A. Resource Capacity Planning

B. Financial Transparency

https://www.fda.gov/media/151712/download

Modernizing and improving REMS assessments

- Add new REMS review performance goals for review of methodological approaches and study protocols for REMS assessments
- Update relevant guidances to incorporate REMS assessment planning into the design of REMS
- Update existing policies and procedures for reviewing methodological approaches and study protocols used to assess a REMS program
- Develop draft guidance regarding the format and content of a REMS assessment report, including the type of data that can support elimination of a REMS.
- Issue new or update existing policies and procedures to determine if modifications to the REMS or revisions to the REMS assessment plan are needed

Milestones & dates specified

Milestone	Date
For *REMS assessment methods and study protocols*, FDA will: • **Update relevant guidances** to incorporate REMS assessment planning into the design of the REMS. • Issue **new or update existing policies and procedures** for reviewing methodological approaches and study protocols used to assess a REMS program For *REMS assessment reports*, FDA will: • Issue **new or update existing policies and procedures** to systematically determine, as part of the review of the REMS assessment reports, if modifications to the REMS or revisions to the REMS assessment plan are needed	By March 31, 2024 .
For *REMS assessment reports*, FDA will: • Develop **draft guidance** regarding the format and content of a REMS assessment report.	By March 31, 2026

PDUFA VII performance goals

Goal	Fiscal Year
Review and notify sponsor with concurrence or comments within 90 days of receipt for **50%** of REMS assessment methods and protocols	**FY 2024** (Oct. 1, 2023 – Sep. 30, 2024)
Review and notify sponsor with concurrence or comments within 90 days of receipt for **70%** of REMS assessment methods and protocols	**FY 2025** (Oct. 1, 2024 – Sep. 30, 2025)
Review and notify sponsor with concurrence or comments within 90 days of receipt for **90%** of REMS assessment methods and protocols	**FY 2026** (Oct. 1, 2025 – Sep. 30, 2026)

Optimizing the Sentinel Initiative

1. Continued support for the Sentinel Initiative maintenance, training, and transparency.
2. Enhancement of the analytic capabilities of the Sentinel Initiative to address questions of product safety and advance the understanding of how real-world evidence can be used for studying effectiveness

Continued support for the Sentinel Initiative

- Maintain the quality and quantity of data available through the Sentinel Initiative (Sentinel and BEST) and processes and tools for determining when and how those data are utilized
- Support comprehensive training of review staff on the use of Sentinel
- Communicate with sponsors and the public regarding general methodologies for Sentinel queries and post study results, study parameters, and analysis code online
  - Report on the use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, postmarket requirement (PMR)s, or postmarket commitment (PMC)s.
  - Report on spending for the Sentinel Initiative in important categories (e.g., data infrastructure, analytical capabilities).

Milestones & dates specified

Milestone	Date
FDA will: • Publish **report** on its website an update on facilitation of public and sponsor access to Sentinel's distributed data network to conduct safety surveillance. • Analyze, and **report** on the use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, PMRs, or PMCs.	By September 30, 2025
FDA will report its obligations for updated PDUFA VI commitments for PDUFA VII Sentinel Initiative annually in the **PDUFA Financial Report**.	Each fiscal year

Enhancement of the analytic capabilities of the Sentinel Initiative

FDA will advance the analytic capabilities of the Sentinel Initiative related to:

- Regulatory decision making to address questions of drug and biologic **product safety in pregnancy**
- Advance our understanding of how real word evidence can be used for studying effectiveness with **negative controls**

Enhancement of the analytic capabilities of the Sentinel Initiative: pregnancy safety

Support for the development of a consistent approach for assessing the outcomes of pregnancies in women exposed to drugs and biological products

- Develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used
- Hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s)
- Conduct 5 demonstration projects to address knowledge gaps about performance characteristics of different study designs
- Develop a guidance or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.

Milestones & dates specified

Milestone	Date
FDA will hold a **public workshop** on post-market safety studies in pregnant women	By September 30, 2023
FDA will: • Publish a **workshop report** describing the proposed framework. • Initiate the following **demonstration projects** which may be modified as needed	By September 30, 2024
FDA will, based on the results of the demonstration projects: • Update the proposed **framework** • Develop a **guidance or MAPP/SOPP** as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.	By September 30, 2027

Enhancement of the analytic capabilities of the Sentinel Initiative: negative controls

Support for development of new methods to support causal inference for product safety questions and advance our understanding of how real world evidence (RWE) may be used for studying effectiveness through the use of negative controls

- Hold a public workshop on use of negative controls for assessing the validity of non-interventional studies of treatment and the proposed Sentinel Initiative projects.
- Conduct two methods development projects
- Publish a report on the results of the development projects.

Milestones & dates specified

Milestone	Date
FDA will hold a **public workshop** on use of negative controls for assessing the validity of non-interventional studies of treatment and the proposed Sentinel Initiative projects.	By September 30, 2023
FDA will 1) **develop an empirical method** to automate the negative control identification process in Sentinel and integrate it into the Sentinel System tools; and 2) **develop a method** to use a double negative control adjustment to reduce unmeasured confounding in studying effectiveness of vaccines.	By September 30, 2024
FDA will **publish a report** on the results of the development projects.	By September 30, 2027

Challenge Question #1

What two initiatives will be FDA's primary focus to modernize and enhance drug safety under this section M of the commitment letter?

A. Sentinel Initiative and FAERS

B. REMS Assessments and PMRs

C. REMS Assessments and Sentinel Initiative

D. Pregnancy safety and negative controls

Challenge Question #2

When would an external stakeholder NOT have the opportunity to comment or provide feedback on a milestone specified in the commitment?

A. Public workshop on use of negative controls

B. An annual financial report for Sentinel

C. Draft guidance for a REMS assessment reports

D. Draft framework for pregnancy safety

Summary

- FDA commits to modernizing and enhancing REMS assessments and optimizing the Sentinel Initiative under these PDUFA VII commitments
- Many opportunities for external stakeholders to provide feedback and comments to help shape the final deliverables

Questions?

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