Regulatory Approaches to Distributed Analyses of Medical Product Safety in the FDA’s Sentinel System

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2007 FDA Amendments Act (FDAAA)

- Post Marketing Requirements
- Safety Labeling Changes
- Risk Evaluation and Mitigation Strategies (REMS)
- Required Safety Reviews (“915” and “921”)
- Active Post-market Risk Identification and Analysis System
  - FDA Sentinel Initiative
About

Sentinel is an active surveillance system sponsored by the U.S. Food and Drug Administration (FDA) to monitor the safety of regulated medical products using pre-existing electronic healthcare data from multiple sources. The Sentinel System is part of the FDA’s Sentinel Initiative, a long-term effort to improve the FDA’s ability to identify and assess medical product safety issues.

https://www.sentinel-system.org/sentinel/about
Mini-Sentinel Accomplishments

• Established Coordinating Center and Distributed Data Network
  ▪ > 30 Collaborating institutions (17 Data Partners)
  ▪ Common Data Model
  ▪ Secure querying behind data partners’ firewall
  ▪ Access to quality checked, electronic healthcare data of over 178 million patients

• Developed and demonstrated value of reusable modular programs for foundation of an active medical product safety surveillance system
Post-Market Safety Assessment

Signal Identification:
Potential safety concern identified

Signal Refinement:
Initial evaluation of safety concerns

Signal Evaluation:
Detailed assessment

Data Mining (e.g. TreeScan)

Modular Programs

>Level 2 Modular Programs/Protocol-based Assessments
Future of Sentinel Initiative

- FDA has moved from “Mini-Sentinel” pilot to a sustained active surveillance system, the Sentinel System
  - Active Risk Identification and Analysis (ARIA) system consists of modular programs and the common data model
  - Additional Sentinel System capabilities available to FDA including Protocol-based Assessments
  - Continue to expand capabilities
- FDA Catalyst
- Opening Sentinel System to other stakeholders

Sentinel Initiative

Sentinel Infrastructure

Sentinel System
- PRISM
- BloodSCAN
- ARIA

FDA-Catalyst
Sentinel Initiative Involves Multiple Centers
Where do Sentinel System Analyses Come Into Play?

**Primary focus for CDER is ARIA:**
- During the review of new applications, as part of the PMR process
- During the evaluation of postmarket drug safety issues

**Primary focus for CBER is Protocol Based Assessments (PBA):**
- When applicable, consider use of PBA or PMR for new applications
- May use PBAs, ARIA to evaluate potential postmarket safety concerns or signals
- Transitioning to more use of ARIA tools in lieu of PBAs when possible

**Other potential Sentinel System uses:**
- Identification of new safety issues (i.e. “datamining”)
- Drug use questions
- Medication error detection
- Generic drug bioequivalence
- REMS evaluation
Defining ARIA

ARIA uses a subset of Sentinel System’s full capabilities to fulfill the FDAAA mandate

* Pre-defined, parameterized, and re-usable modular programs to enable faster safety surveillance in Sentinel (in contrast to protocol based assessments with customized programming)

† Electronic claims data, without manual medical record review
Types of ARIA Analyses

Level 1
- Descriptive Analyses, Unadjusted Rates

Level 2
- Adjusted Analyses with Sophisticated Confounding Control

Level 3
- Sequential Adjusted Analyses with Sophisticated Confounding Control

Capabilities Currently in ARIA

Future ARIA Capabilities

What is ARIA Sufficiency?

• Adequate data
  – Drug of interest and comparator
  – Health outcome of interest
  – Confounders and covariates

• Appropriate methods

• To answer the question of interest
  – assess a known serious risk related to the use of the drug
  – assess signals of serious risk related to the use of the drug
  – identify an unexpected serious risk when available data indicate the potential for a serious risk

• To lead to a satisfactory level of precision
ARIA Analyses by Quarter, FDA-wide

By date of distribution to data partners
Highlights from CDER Activities

Widespread Adoption & Integration ARIA

- Implementation of new processes for routine integration of ARIA into CDER review activities
- Routine use of ARIA in majority of therapeutic areas regulated by CDER

New Tools

- Evaluating confounding control tools and methods and developing new tools for signal identification, generic drug switching, REMS evaluation, and medication errors

New Data Sources, Tough Outcomes

- Continuing to add new data partners
  - Expanding the CDM to capture Hospital Corporation of America’s EMR data elements
  - Add Medicare Virtual Research Data Center
- Assess new approaches for detecting health outcomes of interest
Highlights from CBER Activities

Widespread Adoption & Use of Sentinel, ARIA

- Integrated and regular use of Sentinel in pre- and postmarket regulatory review processes
- Sentinel use in all product areas in CBER

PBAs, Methods and Tool Development

- Use of PBA studies to conduct general safety studies and to evaluate safety of vaccines during pregnancy
- Conduct signal identification in vaccines using TreeScan
- Conduct Rapid Cycle Analyses of annual influenza vaccine
- HOIs to support pandemic preparedness

New Data Sources, Tough Outcomes

- Development of HCA and Kaiser-Permanente EHR data to evaluate AEs for blood and blood products to enhance biovigilance capabilities
- Evaluation of vaccine effectiveness outcomes
Opening the Sentinel System
Innovation in Medical Evidence Development and Surveillance

- IMEDS is offered by the Reagan-Udall Foundation for the FDA which was established by the U.S. Congress to advance regulatory science
  - Sentinel Data Partners are invited to participate
  - The analytic/coordinating center utilized by the FDA through the Sentinel System also participates

- Public and Private sector sponsors are able to access modular programs, customized studies, or a blended approach that complements the Active Risk Identification and Analysis system

- Organizations interested in partnering with IMEDS should email IMEDS@reaganudall.org
Sentinel System and PDUFA

PDUFA V Commitments

• Public stakeholder meeting ✓
• Fund 4 – 6 activities ✓
• Interim Sentinel assessment ✓
• Final Sentinel assessment ✓

PDUFA VI Commitments

• Expand data sources and core capabilities
• Enhance communications with sponsors and public
• Evaluate additional ways to facilitate public and sponsor access to Sentinel
• Hold public stakeholder meeting
• Establish MAPPS and SOPPs for sponsor communication
• Integrate Sentinel into drug review
• Develop a comprehensive training program for review staff
• Report impact of Sentinel expansion and integration by FY2022
Summary

• FDA and partners have successfully implemented the Sentinel System to meet the requirements for an **Active Post-market Risk Identification and Analysis** system

• **Reusable tools, highly curated data, and structured approach for application**, lead to timely results that address regulatory questions about medical product safety

• FDA is committed to continued improvement of the Sentinel System’s capabilities, and opening the Sentinel System to more stakeholders
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