CDER Office of Surveillance and Epidemiology: 2016 Update

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FDA/CMS Summit
December 14, 2016
Adverse Event Data
Adverse Event Reports

Number of Adverse Event Reports

- Non-Expedited
- 15-Day
- Direct
Sentinel
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.sentinelsystem.org/sentinel/about
Summary Description

- **Sentinel System Characteristics**
  - 193 million individuals in 18 data partners
  - Access to laboratory, pharmacy and medical records
  - Primarily insured population
  - Adding Medicare and a large hospital network with EMR

- **Distributed system ensures privacy and security**
  - Data not pooled into single database
  - Data partners retain physical control
  - Analytic programs run against common data model

[https://www.sentinelsystem.org/](https://www.sentinelsystem.org/)
Bob's Story

- **Lives in Boston, MA**
- **2011**
  - **Encounter**
    - Office Visit Diagnosis: Influenza with pneumonia
- **Dispensings**
  - Prescription: Antibiotic
  - Hospital: Inpatient stay

- **2012**
  - **Encounters**
    - Emergency Department Procedure: Appendectomy
  - **Dispensings**
    - 3/15/2012 - 3/18/2012

- **2013**
  - **Encounter**
    - Office Visit Diagnosis: Hypertension
  - **Dispensings**
    - Prescription: Anti-hypertensive
    - 12/11/2012

- **2014**
  - **Encounter**
    - Office Visit Diagnosis: Hypertension
    - 10/31/2013

https://www.sentinelsystem.org/sentinel/data
Requirement to Consider Sufficiency of ARIA before PMR

“The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).”

ARIA = active risk identification and analysis system
Defining ARIA
(active risk identification and analysis system)

ARIA is a subset of Sentinel’s full capabilities

* Pre-defined, parameterized, and re-usable tools (in contrast to protocol based assessments with customized programming)

† Electronic claims data, without manual medical record review
ARIA is Used to Investigate Serious Safety Concerns
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

*L1+ and L2+ are analyses using the baseline L1/L2 tools with some modification to better fit the regulatory question.
Sentinel and PDUFA

PDUFA V Commitments

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

PDUFA VI (tentative) 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
Ninth Annual Sentinel Initiative Public Workshop

February 2, 2017 - 9:00 am to 4:30 pm
Barbara Jordan Conference Center
1330 G St NW, Washington, DC 20005

Description
On February 2, 2017, the Duke-Margolis Center for Health Policy will host the Ninth Annual Sentinel Initiative Public Workshop at the Barbara Jordan Conference Center at the Kaiser Family Foundation. This annual workshop serves as a forum to bring together leading experts and interested stakeholders to discuss the ongoing development of the Sentinel Initiative. With the passage of the Food and Drug Administration Amendments Act of 2007, Congress mandated that the U.S. Food and Drug Administration (FDA) develop a national electronic system to track the safety of regulated medical products. In response to this charge, FDA launched the Sentinel Initiative in 2008 with the goal of utilizing electronic health care data for post market risk identification and analysis of medical product safety. Since its inception, Sentinel has continued to refine and expand its data infrastructure and capabilities. In recent years, new analytical tools and enhancements to data methods have unlocked access to more diverse sources of data to improve the quality of evidence for safety surveillance operations.

The workshop will feature a keynote from Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research. Other key FDA officials and leadership presenting their perspective on sentinel.

Speaker
Key speakers include:
- Keynote: Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research
- Dr. Steven Anderson, Director, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research
- Dr. Gerald Dal Pan, Director of the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research
- Dr. Gregory Pappas, Associate Director for National Device Surveillance, Center for Devices and Radiological Health
- Dr. Richard Platt, Principal Investigator of the Sentinel Coordinating Center

https://healthpolicy.duke.edu/events/ninth-annual-sentinel-initiative-public-workshop
Human Factors Studies
Definition of Human Factors (HF)

Ergonomics (or human factors) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human well-being and overall system performance.

International Ergonomics Association (IEA)
Increasing Safe Use through HF

- Optimized design
- Original design
- Reduce risk through Human Factors

Low risk product
High risk product
Draft Guidance

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

– Issued February 2016

Scope

• Describes Agency recommendations regarding HF information in a combination product investigational or marketing application
  – Focuses on HF issues related to combination products that are comprised of a drug or biological product and a device

• Clarifies:
  – the different types of HF studies;
  – the recommended timing and sequencing of HF studies;
  – and how HF studies are part of the process to maximize the likelihood that the combination product user interface is safe and effective for use by the intended users, for intended uses and environments.

• Describes how HF studies relate to other clinical studies
HF Study Timeline Considerations

OSE/DMEPA involvement can be as early as pre-IND stage
HF Evaluation of Drug, Biologic, and Combination Products in CDER

OSE/DMEPA is the lead for review of human factors submissions (e.g., protocols, study reports, etc.) within CDER

- Evaluate HF submissions for drugs, biologics, and combination products regulated by CDER
- OSE/DMEPA will identify the need for and issue intra- and inter-center consults as appropriate to inform review
Prescription Opioid Abuse
The Opioid Epidemic

FIGURE 2. Drug overdose deaths* involving opioids, †,§ by type of opioid§ — United States, 2000–2014

Source: MMWR January 1, 2016 / 64(50);1378-82
Nationally Estimated Number of Prescriptions Dispensed for Selected* Opioid Analgesics Oral Solids and Transdermal products from U.S. Outpatient Retail Pharmacies

Source: National Prescription Audit (NPA). Extracted May 2015 (For 2005-2014 data) and November 2016 (For 2015 data).
Measuring abuse and related outcome rates: trends and comparing across products

• No single national surveillance system for opioid abuse, misuse, addiction, overdose, and death

• All data sources have significant limitations
  – Most not product/formulation specific
  – Product-specific data sources
    • Represent unknown proportion of actual abuse occurring—can change over time
    • May not be able to reliably identify formulation, brand/generic, etc.

• When comparing rates across products and time periods, denominator choice is critical
  – population vs. prescriptions or tablets dispensed?

• Methods and data sources continue to evolve: how to best make regulatory decisions based on imperfect data and uncertain methods?
Pathways to the Abuse/Misuse of Prescription Drugs and Related Adverse Outcomes

Drug manufactured → Drug distributed → Drug prescribed/dispensed → Patient supply

Drug diversion

Inappropriate use

Use as prescribed

Outcome captured in...

Abuse

Misuse

Addiction

Overdose

Death

Population Surveys (self-report)

Health Care Utilization data

Mortality Records

Nationally-representative household and school surveys

Treatment center surveys

Internet surveys

Poison Control Center data

Emergency Department Visit and Hospitalization data (in development)

Addiction treatment admissions

National Vital Statistics

Medical Examiner data (only some states, limited access)

National death certificate free text (in development)
FDA News Release

Califf, FDA top officials call for sweeping review of agency opioids policies

The FDA will:

- Re-examine the risk-benefit paradigm for opioids and ensure that the agency considers their wider public health effects;
- Convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties;
- Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved;
- Develop changes to immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to the extended-release/long-acting (ER/LA) opioid analgesics labeling that is currently required;
- Update Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations and review of existing requirements;
- Expand access to, and encourage the development of, abuse-deterrent formulations of opioid products;
- Improve access to naloxone and medication-assisted treatment options for patients with opioid use disorders; and
- Support better pain management options, including alternative treatments.
Communication and Outside Engagement: Public Meetings

• Committed to expanded use of public meetings to discuss FDA work in this area

• In 2016 OSE participated in 9 public meetings on opioids:
  – 7 Advisory Committee meetings
    • May 3-4 – ER/LA opioid analgesic REMS
    • May 5 – KP-201 (Apadaz)
    • June 7 – Troxyca
    • June 8 – Vantrela
    • August 4 – Arymo
    • Sept 15-16 – Pediatric use of opioid analgesics
    • Oct 5 – Naloxone dosing
  – 2 FDA Science Board meetings (March/Nov)
Regulatory Activities

• Review of the Extended-Release Long-Acting Opioids REMS

• Requiring post-marketing studies to assess impact of regulatory decisions
  – Studies required of ER-LA opioid manufacturers on quantitative estimates of the serious risks of opioids
  – Studies required of manufacturers of abuse-deterrent opioids to assess their real-world effects on abuse

• March, 2016: FDA requiring additional warnings on immediate-release (IR) opioids relabeling to match ER-LA opioids
  – Includes boxed warning about serious risks of misuse, abuse, addiction overdose and death
  – Includes additional warning about neonatal opioids withdrawal syndrome
  – Over 125 generic and over 75 brandname products

• August, 2016: FDA required additional warnings, including boxed warning, about concomitant use of benzodiazepines and opioids
Improved Science: Epidemiologic Assessment of Opioid Use/Abuse

- Office of Surveillance & Epidemiology (OSE)
  - Dedicated staff focused on identifying patterns of prescription drug use, misuse and abuse
  - 2016: New contracts allowing direct data access
    - Inflexxion, RADARS Treatment Center data
    - AAPCC (poison control centers)
  - 2016: Collaborating with CDC to develop new data sources/capabilities for measuring abuse and its sequelae
    - National Hospital Care Survey (“new DAWN”)
    - NEISS-CADES augmentation to monitor abuse
    - Gathering drug-specific information from death certificates