Integrating Sentinel into Routine Drug Review: A Snapshot of the First Year

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Disclosure

• Nothing to disclose

• This presentation reflects the views of the author only and should not be construed to represent FDA’s official views or policies
FDA Sentinel System

- National medical product monitoring system
- 17 data partners with 178 million members with pharmacy and medical coverage
- Distributed system where data partners retain physical control of data to protect privacy and security

https://www.sentinelinitiative.org/
Data Partners

1. Aetna
2. Blue Cross Blue Shield of Massachusetts
3. HealthCore, Inc.
4. Harvard Pilgrim Health Care Institute
5. HealthPartners Institute
6. Humana Comprehensive Health Insights, Inc.
7. Marshfield Clinic Research Foundation
8. Meyers Primary Care Institute
9. Hospital Corporation of America
10. Kaiser Permanente Colorado
11. Kaiser Permanente Hawaii
12. Kaiser Permanente Mid-Atlantic
13. Kaiser Permanente Northern California
14. Kaiser Permanente Northwest
15. Kaiser Permanente Washington Health Research Institute
16. Optum: Optum Epidemiology
17. Vanderbilt University Medical Center

https://www.sentinelinitiative.org/data-partners
“Since our launch in 2008, we’ve been committed [to building the Sentinel Initiative]. We’ve had a successful Mini-Sentinel pilot and we have now transitioned – I can declare – Mini-Sentinel to a fully functioning Sentinel System, which was the vision and body that Congress directed us to do.”
Four L2 Analyses in this Symposium

Propensity Score Matching L2 tool

Venous thromboembolism after oral contraceptives
By David Moeny

Stroke after antipsychotics medications
By Lockwood Taylor

Self-controlled L2 tool

Seizures after ranolazine
By Efe Eworuke

Seizures after gadolinium based contrast agents
By Steve Bird
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).”

FDAAA = FDA Amendments Act 2007
Defining 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
Defining ARIA

ARIA is a subset of Sentinel’s full capabilities

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

† Electronic claims data, without manual medical record review
ARIA Must Be Considered Before a PMR Can be Issued

- ARIA is now integrated into the overall framework for drug safety in CDER
- ARIA sufficiency is assessed whenever further characterization of a safety issue is needed (i.e., for tracked safety issues)
Reaching the Goal with the Right Tools

Summary Table (ST)
Simple counts

Level 1 (L1)
Complex descriptive analyses

Level 2 (L2)
Inferential analyses

More to come in next talk by Judy Maro
ARIA Analyses by Quarter, FDA-wide

By date of distribution to data partners

N=162
Sentinel is a National Medical Product Monitoring System

Learn More

About
- Background
- Coordinating Center
- Privacy and Security
- The Sentinel System Story
- Reagan-Udall Foundation and IMEDS

Medical Product Assessments
- Active Risk Identification and Analysis System
- Ongoing ARIA Assessments
- Assessments of Drugs
- Assessments of Vaccines, Blood, & Biologics
- FDA-Catalyst

DATA & SURVEILLANCE TOOLS
- Distributed Database and Common Data Model

Communications
- FDA Safety Communications

Latest Postings

Spotlight
- Ongoing ARIA Assessments
  Wed, 08/23/2017
- Routine Querying System Documentation (version 4.1.2)
  Wed, 07/19/2017
- Sentinel Common Data Model v6.01
  Wed, 04/26/2017

ONGOING PROJECTS
- Inverse Probability of Treatment Weighting Functional Specifications and Prototype Development
  Thu, 08/24/2017
Where to Find Results

https://www.sentinelinitiative.org/drugs/assessments
Where to Find Ongoing Analyses

https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments
Where to Find Ongoing Analyses

### ARIA Analyses for Safety Issues Identified During Review of New Applications and Supplements

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Outcomes Being Assessed</th>
<th>Date Posted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siliq (brodalumab)</td>
<td>• Neutopenia&lt;br&gt;• Serious infections&lt;br&gt;• Myocardial infarction and stroke&lt;br&gt;• Lymphoma</td>
<td>8/23/2017</td>
</tr>
<tr>
<td>Stelara (ustekinumab)</td>
<td>• Serious Infections</td>
<td>8/23/2017</td>
</tr>
</tbody>
</table>

### ARIA Analyses for Safety Issues Identified Post-Approval

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Outcomes Being Assessed</th>
<th>Date Posted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranexa (ranolazine)</td>
<td>• Seizures</td>
<td>8/23/2017</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>• Stroke&lt;br&gt;• Use as adjuvant therapy</td>
<td>8/23/2017</td>
</tr>
<tr>
<td>Continuous or extended cycle oral contraceptives</td>
<td>• Venous thromboembolism</td>
<td>8/23/2017</td>
</tr>
<tr>
<td>Gadolinium-based contrast agents</td>
<td>• Seizures</td>
<td>8/23/2017</td>
</tr>
<tr>
<td>Sodium-glucose cotransporter-2 (SGLT-2) inhibitors</td>
<td>• Stroke</td>
<td>8/23/2017</td>
</tr>
</tbody>
</table>

[https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments](https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments)
Making Sentinel Available to Others

Reagan-Udall Foundation and IMEDS

The Innovation in Medical Evidence Development and Surveillance (IMEDS) program offered by the Reagan-Udall Foundation for the Food and Drug Administration (FDA) supports the FDA's vision of providing the Sentinel Initiative as a broader resource for public health and medical evidence generation.

By partnering with the Harvard Pilgrim Health Care Institute as the Analytic Center and select Data Partners contributing data to the Distributed Database, the Foundation is in the unique position of being able to offer industry, academia, and researchers access to a system similar to Sentinel for evaluating safety signals, implementing post-market studies, and assessing the impact of risk management actions. Learn more about the IMEDS program here.

https://www.sentinelinitiative.org/sentinel/reagan-udall-foundation-and-imeds
IMEDS and Sentinel

http://reaganudall.org/innovation-medical-evidence-development-and-surveillance
Query Development Process

Step 1
Concept Brief

Step 2
Test Specifications

Translate Analysis Plan to ARIA Tools
Query Development Process

Step 1: Concept Brief
- Translate Analysis Plan to ARIA Tools

Step 2: Test Specifications
- Review Test Results and Adjust
Query Development Process

Step 1: Concept Brief
Step 2: Test Specifications
Step 3: Final Specifications
Step 4: Analysis Results

Translate Analysis Plan to ARIA Tools
Review Test Results and Adjust
Example Timeline: Oral Contraceptives

- **5/23/2016** L1 Start
- **7/12/2016** L1 Results
- **9/13/2016** L2 Start
- **4/24/2017** L2 Results

**Timeline Events:**
- **50 days**
- **223 days, (7 mo.)**
- **336 days (11 mo.)**
Detailed Timeline: L1

- **5/23/2016**: L1 Start
- **7/12/2016**: L1 Results
- **9/13/2016**: L2 Start
- **4/24/2017**: L2 Results

**Timeline Details**

- **5/23/2016** - **30/Jul-16**: 32 days (planning)
- **6/23/2016** - **6/24/2016**: 18 days (computation)

**Key Dates**

- **5/23/2016**: L1 Start
- **6/23/2016**: Test Specs
- **6/24/2016**: Final Specs
- **7/12/2016**: L1 Results
- **16-May-16**: L1 Start
- **1-May-16**: L1 Start
- **1-Jun-17**: L1 Start
- **30-Jul-16**: L1 Results
# Total Time to Assess Safety Issue

<table>
<thead>
<tr>
<th>Safety Issue</th>
<th>Type and No. Analyses</th>
<th>Total Time, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranexa (ranolazine)</td>
<td>ST, L1, L2</td>
<td>302 (10 mo.)</td>
</tr>
<tr>
<td>Gadolinium contrast agents</td>
<td>L1, L2</td>
<td>741 (24 mo.)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>L1, L2</td>
<td>277 (9 mo.)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>L1, L2</td>
<td>336 (11 mo.)</td>
</tr>
</tbody>
</table>

- **ST** = Summary table, simple counts
- **L1** = Level 1, complex descriptive analysis
- **L2** = Level 2, inferential analysis
ARIA: A Snapshot of the 1st Year

• Since activation in 2016, ARIA has been used robustly in CDER to evaluate the safety of FDA approved drugs
• Evaluating ARIA sufficiency informs strategic development of Sentinel System
• Each safety analysis relies upon the full complement of ARIA tools and can be completed in <12 months
• ARIA tools accelerate computation time, but do not abbreviate study design or planning process
• ARIA tools are a flexible, efficient analytic platform to meet FDA’s mission