Evidence from real-world data
Sentinel Initiative of US FDA

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February 20, 2019
Disclaimer

- The views expressed in this presentation are mine and do not represent the official views or policies of the U.S. Food and Drug Administration.
Timeline

2007
Congress passes Food and Drug Administration Amendments Act (FDAAA)

2008
FDA launches Sentinel Initiative

2009
FDA launches Mini-Sentinel Pilot

2011
Mini-Sentinel distributed dataset reaches 100 million lives mark mandated by FDAAA

2012
Mini-Sentinel has suite of reusable programming tools for routine queries

2016
FDA launches Sentinel System
Sentinel partner organizations

Lead – HPHC Institute

Data & scientific partners

Scientific partners
Data snapshot

- 293 million patient identifiers in 2000-2018
- 67 million individuals currently accruing data
- Well-defined population with longitudinal data
- 13 billion medical encounters
- 14 billion dispensings

https://www.sentinelinitiative.org/sentinel/data/snapshot-database-statistics
Harmonizing multiple databases

Individual data partners

Site 1
Site 2
Site 3
Site 4

Data standardization

Site 1
Site 2
Site 3
Site 4

Data accessible to surveillance projects

• Surveillance projects
• Programs written against common data model

Data quality improvement feedback loop

Adapted from: http://www.hcsrn.org/asset/b9efb268ebp86-400e-8c74-2d42ac57fa4F/VDW.Infographic031511.jpg
Sentinel data quality assurance and characterization

Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

Sentinel Data Quality Assurance Practices

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Sentinel Data Quality Assurance Practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Posted</td>
<td>Thursday, March 23, 2017</td>
</tr>
<tr>
<td>Deliverables</td>
<td>Sentinel Data Quality Assurance Practices</td>
</tr>
<tr>
<td>Description</td>
<td>The Food and Drug Administration (FDA) set forth its current recommendations for data quality assurance (QA) in the following document: “Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data” (Guidance), section I.E. “Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC),” in May 2013. This Guidance describes best practices that particularly apply to observational studies designed to assess the risk associated with a drug exposure using electronic healthcare data. The SOC has drafted a document describing the ways in which SOC data quality assurance procedures align with FDA’s standards.</td>
</tr>
</tbody>
</table>

### Sentinel Common Data Model

#### Administrative Data

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Demographic</th>
<th>Dispensing</th>
<th>Encounter</th>
<th>Diagnosis</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Enrollment Start &amp; End Dates</td>
<td>Birth Date</td>
<td>Dispensing Date</td>
<td>Service Date(s)</td>
<td>Service Date(s)</td>
<td>Service Date(s)</td>
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<tr>
<td>Drug Coverage</td>
<td>Sex</td>
<td>National Drug Code (NDC)</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
</tr>
<tr>
<td>Medical Coverage</td>
<td>Zip Code</td>
<td>Days Supply</td>
<td>Encounter Type and Provider</td>
<td>Encounter Type and Provider</td>
<td>Procedure Code &amp; Type</td>
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<tr>
<td>Medical Record Availability</td>
<td>Etc.</td>
<td>Amount Dispensed</td>
<td>Facility</td>
<td>Diagnosis Code &amp; Type</td>
<td>Etc.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Etc.</td>
<td>Principal Discharge Diagnosis</td>
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</table>

#### Clinical Data

<table>
<thead>
<tr>
<th>Lab Result</th>
<th>Vital Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Result &amp; Specimen Collection Dates</td>
<td>Measurement Date &amp; Time</td>
</tr>
<tr>
<td>Test Type, Immediacy &amp; Location</td>
<td>Height &amp; Weight</td>
</tr>
<tr>
<td>Logical Observation Identifiers Names and Codes (LOINC®)</td>
<td>Diastolic &amp; Systolic BP</td>
</tr>
<tr>
<td>Tobacco Use &amp; Type</td>
<td>Etc.</td>
</tr>
</tbody>
</table>

#### Registry Data

<table>
<thead>
<tr>
<th>Death</th>
<th>Cause of Death</th>
<th>State Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Death Date</td>
<td>Cause of Death</td>
<td>Vaccination Date</td>
</tr>
<tr>
<td>Source</td>
<td>Source</td>
<td>Admission Date</td>
</tr>
<tr>
<td>Confidence</td>
<td>Confidence</td>
<td>Vaccine Code &amp; Type</td>
</tr>
<tr>
<td>Etc.</td>
<td>Etc.</td>
<td>Provider Etc.</td>
</tr>
</tbody>
</table>

#### Inpatient Data

<table>
<thead>
<tr>
<th>Inpatient Pharmacy</th>
<th>Inpatient Transfusion</th>
</tr>
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<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Administration Date &amp; Time</td>
<td>Administration Start &amp; End Date &amp; Time</td>
</tr>
<tr>
<td>Encounter ID</td>
<td>Encounter ID</td>
</tr>
<tr>
<td>National Drug Code (NDC)</td>
<td>Transfusion Administration ID</td>
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<tr>
<td>Route</td>
<td>Transfusion Product Code</td>
</tr>
<tr>
<td>Dose</td>
<td>Blood Type</td>
</tr>
<tr>
<td>Etc.</td>
<td>Etc.</td>
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</tbody>
</table>

#### Mother-Infant Linkage Data

<table>
<thead>
<tr>
<th>Mother-Infant Linkage</th>
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</thead>
<tbody>
<tr>
<td>Mother ID</td>
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<tr>
<td>Mother Birth Date</td>
</tr>
<tr>
<td>Encounter ID &amp; Type</td>
</tr>
<tr>
<td>Admission &amp; Discharge Date</td>
</tr>
<tr>
<td>Child ID</td>
</tr>
<tr>
<td>Child Birth Date</td>
</tr>
<tr>
<td>Mother-Infant Match Method</td>
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<tr>
<td>Etc.</td>
</tr>
</tbody>
</table>
1. User creates and submits query
2. Data Partners retrieve query
3. Data Partners review and run query against their local data
4. Data Partners review results
5. Data Partners return results via secure network
6. Results are aggregated and returned

https://www.sentinelinitiative.org/privacy-and-security
Sentinel Initiative

Sentinel Infrastructure

Sentinel System
Routine queries and other activities that use pre-existing data
- PRISM
- BloodSCAN
- ARIA

FDA-Catalyst
Routine queries + interventions and interactions with members and/or providers
ARIA: Active Risk Identification and Analysis System

- Routine queries and other activities that use pre-existing data
  - PRISM
  - BloodSCAN
  - ARIA

- Routine queries + interventions and interactions with members and/or providers

https://www.sentinelinitiative.org/sentinel/about
“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).”
Sentinel and FDA’s mandate

ARIA: Active Risk Identification and Analysis System
ARIA

Summary Tables
- Simple Code Counts

Level 1
- Descriptive Analyses, Unadjusted Rates

Level 2
- Adjusted Analyses with Sophisticated Confounding Control

Level 3
- Sequential Adjusted Analyses with Sophisticated Confounding Control

Current Capabilities

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate the use of dehydrated alcohol in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel’s Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the following serious risks: heart failure, ventricular fibrillation, atrioventricular block with and without permanent pacemaker insertion, subsequent septal myectomy, and death.

The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.
# Ongoing ARIA assessments (selected)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Outcome Assessed</th>
<th>ARIA Analysis</th>
<th>Related Links</th>
<th>Date Posted</th>
</tr>
</thead>
</table>
| Ablilsinol (Dehydrated alcohol)                                           | • Number of percutaneous transluminal septal myocardial ablation procedures  
  • Ventricular arrhythmia  
  • Heart failure  
  • Atrioventricular block  
  • Septal myectomy  
  • Death                                                                    | Level 2                             | • Approval letter           | 10/22/2018  |
| Anovora (progesterone acetate and ethinyl estradiol vaginal system)       | • Early detection of a large increase in the risk of non-fatal venous thromboembolism or arterial thromboembolism in the United States population | Level 3 (Sequential safety monitoring) | • Approval letter       | 9/24/2018   |
| Ilumyta (tilALKzumab)                                                     | • Lymphoma                                                                        | TBD                                |                        | 5/25/2019   |
| Sinuva (mononatone furoate)                                               | • Cataracts  
  • Glaucoma  
  • Nasal perforation                                                          | Level 1                             | • Approval letter           | 12/18/2017  |
| Tremfya (guselkumab)                                                      | • Short term lymphoma e.g., within 1-3 years                                        | TBD                                |                        | 9/29/2017   |
| Stelara (ustekinumab)                                                     | • Serious Infection                                                                | TBD                                |                        | 8/23/2017   |
| Siliq (brodolumab)                                                        | • Neutropenia  
  • Serious infections  
  • Myocardial Infarction and stroke                                           | TBD                                |                        | 8/23/2017   |

[https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments](https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments)
How Sentinel has been used by FDA (selected)

**The NEW ENGLAND JOURNAL of Perspective**

**Dabigatran and Postmarketing Reports of Bleeding**

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Events</td>
</tr>
<tr>
<td><strong>Gastrointestinal hemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,599</td>
<td>16</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,195</td>
<td>19</td>
</tr>
<tr>
<td><strong>Intracranial hemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,587</td>
<td>8</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,182</td>
<td>10</td>
</tr>
</tbody>
</table>

How Sentinel has been used by FDA (selected)

FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran)

The FDA has issued new information about this safety issue, see the FDA Drug Safety Communication issued 05-13-2014.

This update is a follow-up to the FDA Drug Safety Communication of 12/7/2011: Safety review of postmarket reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
References

Safety Announcement

[11-02-2012] The U.S. Food and Drug Administration (FDA) has evaluated new information about the risk of serious bleeding associated with use of the anticoagulants (blood thinners) dabigatran (Pradaxa) and warfarin (Coumadin, Jantoven, and generics). Following the approval of Pradaxa, FDA received a large number of postmarketing reports of bleeding among Pradaxa users. As a result, FDA investigated the actual rates of gastrointestinal bleeding (occurring in the stomach and intestines) and intracranial hemorrhage (a type of bleeding in the brain) for new users of Pradaxa compared to new users of warfarin. This assessment was done using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).1 (see Data Summary). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, M.D., M.P.H., Tracy A. Leo, M.D., M.P.H., Martin Kuller, Ph.D., David Martin, M.D., M.P.H., Cheryl M. Madsen-Willem, M.S.W., Ph.D., Richard Platt, M.D., Nandita Selam, Ph.D., M.P.H., Marco Selvas, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Figure, M.D.

Figure 1. Attributable Risk of Intussusception after the First Dose of RotaTeq (RV5) Rotavirus Vaccine.

The attributable risk of intussusception after dose 1 of the RV5 vaccine, shown as the number of excess cases of intussusception per 100,000 recipients, was calculated for two study designs — a self-controlled risk-interval (SCRI) design and a cohort design — with the original age-adjustment method (based on the rates from Tate et al.25 in the SCRI design and the quadratic risk function from the unexposed person-time in the cohort design) and an alternative age-adjustment method (based on the quadratic risk function from the unexposed cohort person-time in the SCRI design and the rates from Tate et al.25 in the cohort design). For dose 1 of RV5, age adjustment with the use of the quadratic risk function obtained from the study population results in only slightly lower attributable risks than age adjustment with the use of hospital-discharge data from Tate et al.25

How Sentinel has been used by FDA (selected)

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RotaTeq safely and effectively. See full prescribing information for RotaTeq.

**RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent)**

**Oral Solution**

**Initial U.S. Approval:** 2006

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**RECENT MAJOR CHANGES**

<table>
<thead>
<tr>
<th>Indications and Usage</th>
<th>02/2017</th>
</tr>
</thead>
</table>

**INDICATIONS AND USAGE**

RotaTeq is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9. (1)

RotaTeq is approved for use in infants 6 weeks to 32 weeks of age. (1)

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**DOSEAGE AND ADMINISTRATION**

- FOR ORAL USE ONLY. NOT FOR INJECTION. (2)
- The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age.

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### WARNINGs AND PRECAUTIONS

- No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised (e.g., HIV/AIDS). (8.2)
- In a post-marketing study, cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. (5.3, 6.2)
- No safety or efficacy data are available for the administration of RotaTeq to infants with a history of gastrointestinal disorders (e.g., active acute gastrointestinal illness, chronic diarrhea, failure to thrive, history of congenital abdominal disorders, and abdominal surgery). (5.4)
- Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient contacts. (5.5)

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### ADVERSE REACTIONS

Most common adverse events included diarrhea, vomiting, irritability, otitis media, nasopharyngitis, and bronchopneumonia. (6.1)

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### Post-Marketing Observational Safety Surveillance Studies

The temporal association between vaccination with RotaTeq and intussusception was evaluated in the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program, an electronic active surveillance program comprised of 3 US health insurance plans.

More than 1.2 million RotaTeq vaccinations (507,000 of which were first doses) administered to infants 5 through 36 weeks of age were evaluated. From 2004 through 2011, potential cases of intussusception in either the inpatient or emergency department setting and vaccine exposures were identified through electronic procedure and diagnosis codes. Medical records were reviewed to confirm intussusception and rotavirus vaccination status.

The risk of intussusception was assessed using self-controlled risk interval and cohort designs, with adjustment for age. Risk windows of 1-7 and 1-21 days were evaluated. Cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. Based on the results, approximately 1 to 1.5 excess cases of intussusception occur per 100,000 vaccinated US infants within 21 days following the first dose of RotaTeq. In the first year of life, the background rate of intussusception hospitalizations in the US has been estimated to be approximately 34 per 100,000 infants.3

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Label change

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How Sentinel has been used by FDA (selected)

NDA approval letter

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

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https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/207987Orig1s000ltr.pdf
EXECUTIVE SUMMARY

Febuxostat (Uloric®), a selective inhibitor of xanthine oxidase, lowers serum uric acid levels by inhibiting the conversion of xanthine to uric acid. It was approved by the FDA in February 2009 for the management of chronic hyperuricemia in patients with gout. Preliminary results from a post-approval safety trial (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidity (CARES)) showed an increased risk of cardiovascular-related death and all-cause death in febuxostat users. As a result, FDA issued a drug safety communication in November 2017. An advisory committee (AC) meeting is scheduled for January 11, 2019 to discuss potential regulatory action to address the safety of febuxostat. For context, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested the Division of Epidemiology (DEPI) to investigate the characteristics of the gout population and use of febuxostat and allopurinol in real-world settings using the Sentinel Distributed Database (SDD), since the CARES trial was enriched for patients with CVD.
## How ARIA has been used by FDA (selected)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Outcome Assessed</th>
<th>ARIA Analysis</th>
<th>Regulatory Determination / Use</th>
<th>Date Posted</th>
</tr>
</thead>
</table>
| Ranexa (ranolazine)                | Seizures                          | Level 1, Level 2| Combined with evidence from the Centers for Medicare & Medicaid Services, risk of seizure was determined to be driven primarily by underlying comorbidities. FDA decided that no action is necessary at this time, based on available information.  
  - Results  
  - 2017 ICPE Symposium            | 01/03/2019                        |
| Multiple sclerosis (MS) drugs      | Exposure before, during, and after pregnancy | Level 1         | Contextualized enrollment and recruitment in MS pregnancy registries. Described patterns of drug use before, during, and after pregnancy.  
  - Results  
  - 2018 ICPE Presentation        | 12/6/2018                          |
| Interleukin-1/6 inhibitors         | Pulmonary arterial hypertension and interstitial lung disease | Level 1         | Feasibility assessment of ARIA to conduct a postmarket safety study. FDA decided that no action is necessary at this time, based on available information.  
  - Results                           | 12/3/2018                          |
| Forteo (teriparatide)              | Duration of use                    | Level 1         | Contributed to the decision regarding continuation of sponsor Postmarket Requirement for teriparatide  
  - Results  
  - Approval Letter with PMR/PMC Commitments  
  - Supplemental Approval Letter with PMR/PMC Commitments | 11/30/2018                          |
# Transparency

## Analytic Request Packages Available for Download

<table>
<thead>
<tr>
<th>Request ID</th>
<th>Summary</th>
</tr>
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<tbody>
<tr>
<td>cder_mpl2p_wp001</td>
<td>Venous Thromboembolism after Continuous or Extended Cycle Contraceptive Use</td>
</tr>
<tr>
<td>cder_mpl2p_wp002</td>
<td>Ranexa (Ranolazine) and Seizures, Report 2</td>
</tr>
<tr>
<td>cder_mpl2p_wp006</td>
<td>Ranexa (Ranolazine) and Seizures, Report 3</td>
</tr>
</tbody>
</table>
Table 1: Incident Ranolazine Use with Either Concomitant Beta Blocker, Calcium Channel Blocker, or Nitrate Use and Seizures in the Sentinel Distributed Database (SDD) between January 1, 2006 and September 30, 2015, by Strength of Ranolazine and Concomitant Exposure among All Individuals

<table>
<thead>
<tr>
<th>Ranolazine (500 mg strength)</th>
<th>New Users</th>
<th>New Episodes</th>
<th>Dispensings</th>
<th>Days Supplied</th>
<th>Amount Supplied</th>
<th>Episode Duration</th>
<th>Years at Risk</th>
<th>Episodes with Events</th>
<th>Episodes with Events per 10K Years at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranolazine With or Without Concomitant Use</td>
<td>49,256</td>
<td>49,256</td>
<td>199,812</td>
<td>7,344,143</td>
<td>15,257,873</td>
<td>7,634,313</td>
<td>20,902</td>
<td>32</td>
<td>15.31</td>
</tr>
<tr>
<td>With Concomitant Beta Blocker Use</td>
<td>30,679</td>
<td>30,679</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>3,698,827</td>
<td>10,127</td>
<td>23</td>
<td>22.71</td>
</tr>
<tr>
<td>With Concomitant Calcium Channel Blocker Use</td>
<td>2,476</td>
<td>2,476</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>268,127</td>
<td>734</td>
<td>1</td>
<td>13.62</td>
</tr>
<tr>
<td>With Concomitant Nitrates Use</td>
<td>26,853</td>
<td>26,853</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>2,569,997</td>
<td>7,036</td>
<td>18</td>
<td>25.58</td>
</tr>
<tr>
<td>Ranolazine (1000 mg strength)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ranolazine With or Without Concomitant Use</td>
<td>5,618</td>
<td>5,618</td>
<td>16,988</td>
<td>639,582</td>
<td>1,294,857</td>
<td>667,033</td>
<td>1,826</td>
<td>4</td>
<td>21.91</td>
</tr>
<tr>
<td>With Concomitant Beta Blocker Use</td>
<td>3,394</td>
<td>3,394</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>321,790</td>
<td>881</td>
<td>2</td>
<td>22.70</td>
</tr>
<tr>
<td>With Concomitant Calcium Channel Blocker Use</td>
<td>233</td>
<td>233</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>18,781</td>
<td>51</td>
<td>1</td>
<td>196.08</td>
</tr>
<tr>
<td>With Concomitant Nitrates Use</td>
<td>2,719</td>
<td>2,719</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>203,253</td>
<td>556</td>
<td>2</td>
<td>35.97</td>
</tr>
</tbody>
</table>

* Years at Risk stop accumulating when first event during episode is encountered

## Public Repositories

<table>
<thead>
<tr>
<th>Name</th>
<th>Sentinel Repository Path</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Analytic Development</strong> / qrp</td>
</tr>
<tr>
<td></td>
<td><strong>Sentinel Analytic Packages</strong> / Sentinel Analytic Packages</td>
</tr>
<tr>
<td></td>
<td><strong>Sentinel Common Data Model</strong> / sentinel_common_data_model</td>
</tr>
<tr>
<td></td>
<td><strong>Sentinel Documentation</strong> / Sentinel Routine Querying Tool Documentation</td>
</tr>
</tbody>
</table>

[https://dev.sentinelsystem.org/repos?visibility=public](https://dev.sentinelsystem.org/repos?visibility=public)
Sentinel Initiative

Sentinel Infrastructure

Sentinel System
Routine queries and other activities that use pre-existing data
- PRISM
- BloodSCAN
- ARIA

FDA-Catalyst
Routine queries + interventions and interactions with members and/or providers

https://www.sentinelinitiative.org/sentinel/about
What is TreeScan?

- A signal detection / data mining method
- Automatically adjusts for multiple hypothesis testing
- Scans electronic health data that are grouped into hierarchical tree structures
Evaluating impacts of FDA actions

Figure 2. Percentage of LABA product initiation before, between and after the 2005 and 2010 FDA regulatory activities for LABA-containing agents in children and adults with asthma and no history of a LABA dispensing in 180 days.
Medication exposure during pregnancy

Sentinel Initiative

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https://www.sentinelinitiative.org/sentinel/about
Pragmatic trial in Sentinel

MEMBER LETTER

According to our records, you may have been diagnosed with atrial fibrillation. We know that managing your health can be a challenge, and hope this information about your treatment risk to stroke will help.

People who have the heartbeat irregularity known as "atrial fibrillation" are at an increased risk of having a stroke.

Please visit www.IMPACT-AFib.org, to learn more about atrial fibrillation, stroke risk, and anticoagulant medications. More information about the IMPACT-AFib Initiative is available by calling (800-000-0000) or emailing [email protected]

You can lower your risk of stroke:

1. Bring this letter and pocket card to your next doctor's appointment.
2. Talk to your doctor about the use of anticoagulant medications to prevent stroke.

Talk to your doctor about anticoagulant medications.

This packet contains information about the benefits of taking anticoagulant medications, also called blood thinners, to lower your risk of having a stroke. We recommend that you bring this information packet to your next doctor's appointment. We also ask that your doctor discuss these medications with you.

Anticoagulant medications may not be right for everyone, but they might be right for you. Even if you have talked about this with your doctor in the past, we encourage you to have another conversation about these medications. Your anticoagulant medications are safe and effective options for many patients.

Protecting your health information

We respect your privacy and confidentiality. None of your personal information has been shared with other health organizations. Only you and your doctor were sent this information.

Sincerely,

Chief Medical Officer

If you have any questions, please contact [name] at [phone number] or [email]

PROVIDER LETTER

As part of our effort to improve the use of oral anticoagulants medications for stroke prevention in patients with atrial fibrillation (AFib), we would like to introduce you to the IMPACT-AFib Initiative. The objective of the IMPACT-AFib initiative is to increase awareness and education among patients and you. This FDA-sponsored initiative is being conducted by [HEALTH PLAN] in collaboration with researchers at Harvard and Duke.

Educational materials were sent to patients who appear to have atrial fibrillation, have high stroke risk (CHA2DS2-VASc score 2), and have no record available to us of having filled a prescription for an anticoagulant in the past year. Please see the next page for a list of patients who received these materials.

Facts about atrial fibrillation

- Patients with AFib have a five times higher stroke risk relative to patients without AFib (Circulation 2011;123;13:2629-2635). More than 40% of strokes caused by AFib are preventable with anticoagulation (Annals of Internal Medicine 2016;165;303-317).
- 30% of patients with AFib and high-stroke risk have not filled an anticoagulant prescription (Circulation 2014;129;1570-1576).

Common misperceptions about stroke prevention

Aspirin is good enough

- Aspirin reduces stroke by <20%, if at all, compared with 70% reduction with anticoagulation; therefore, aspirin is not sufficiently effective for stroke prevention.

Patients with AFib are at greater risk of bleeding than stroke

- 30% of elderly patients fall in a year, but a patient would need to fall nearly every day before the risk of intracranial bleeding outweighs the benefits of anticoagulation.
- The risk of recurrent GI bleeding averages 1.2% per year, but would have to exceed 10% before the risk of GI bleeding outweighs the benefits of anticoagulation.

There are appropriate reasons for patients to not take an anticoagulant, including pregnancy and history of intracranial hemorrhage. A response message is enclosed for you to share these reasons, should they exist for your patient(s).
Collecting patient-reported information

https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
Developing the Sentinel System — A National Resource for Evidence Development

Rachel E. Behrman, M.D., M.P.H., Joshua S. Benner, Pharm.D., Sc.D., Jeffrey S. Brown, Ph.D., Mark McClellan, M.D., Ph.D., Janet Woodcock, M.D., and Richard Platt, M.D.


The FDA Sentinel Initiative — An Evolving National Resource

Richard Platt, M.D., Jeffrey S. Brown, Ph.D., Melissa Robb, M.S., Mark McClellan, M.D., Ph.D., Robert Ball, M.D., M.P.H., Michael D. Nguyen, M.D., and Rachel E. Sherman, M.D., M.P.H.

“Opening up” Sentinel

INNOVATION IN MEDICAL EVIDENCE DEVELOPMENT AND SURVEILLANCE

http://reaganudall.org/innovation-medical-evidence-development-and-surveillance
https://www.sentinelinitiative.org/sentinel/reagan-udall-foundation-and-imeds
Do FDA label changes work? Assessment of the 2010 class label change for proton pump inhibitors using the Sentinel System's analytic tools

Rachel E. Sobel¹ | Andrew Bate¹ | James Marshall² | Kevin Haynes³ | Nandini Selvam³ | Vinit Nair⁴ | Gregory Daniel⁵ | Jeffrey S. Brown² | Robert F. Reynolds¹
Lilly's Olumiant Resubmission Includes Safety Data From US FDA's Sentinel Network

22 Feb 2018 | ANALYSIS
Sentinel System 5-year strategic plan

A sustainable national resource to monitor the safety of marketed medical products, and expand real-world data sources used to evaluate medical product performance

Sentinel System 5-year strategic plan

Enhance the foundation of the Sentinel System
- Expand data sources and linkages
- Improve data infrastructure and methods development
- Enable more effective use through operational improvements

Further enhance safety analysis capabilities
- Increase ARIA sufficiency
- Leverage advances in data science and signal detection

Accelerate access to and broader use of real-world data
- Enable new avenues for generating real-world evidence by investing in access to and approaches to use of electronic health records
- Conduct specific real-world data-driven demonstration projects to explore the universe of addressable effectiveness questions

Create a national resource by broadening the Sentinel user base
- Improve operations and procedures for accessing tools, methods, and results
- Evolve the Sentinel System operating model
- Engage directly with potential users and develop a Sentinel scientific community

Disseminate knowledge, and advance regulatory science
- External outreach and convening across the learning healthcare ecosystem
- Provide transparency, and encourage innovation and collaboration

A sustainable national resource to monitor the safety of marketed medical products, and expand real-world data sources used to evaluate medical product performance

RWD/RWE and regulatory science

- Using trials or studies with RWD/RWE for effectiveness decisions
- Assessing fitness of RWD for use in regulatory decisions
- Potential for study designs using RWD to support effectiveness
- Regulatory consideration for study design using RWD
- Data standards – appropriate data standards for integration and submission to FDA

Specifically, FDA’s RWE Program will evaluate the potential use of RWE to support changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information.
Developing the Sentinel System — A National Resource for Evidence Development

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A national infrastructure for evidence generation

- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, analytics, lessons, security, software
Adapted from a slide by Dr. Janet Woodcock, CDER, FDA; https://healthpolicy.duke.edu/sentinel
Darren_Toh@harvardpilgrim.org
@darrentoh_epi
https://www.distributedanalysis.org