Implementation of Signal Detection Capabilities in the Sentinel System

Bethesda Hyatt Regency
December 3, 2018

Join the conversation with #sentinelinitiative
Welcome and Introductions

Join the conversation with #sentinelinitiative
Presentation: Signal Identification in the Sentinel System: Past, Present, and Future
Signal Identification in the Sentinel System: Past, Present, and Future

Michael D. Nguyen, MD
FDA Sentinel Program Lead
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

December 3, 2018
Plan for Talk

• Motivation for initiating signal identification in Sentinel
• Approach to building a signal identification program in Sentinel
• Signal identification operational pilot
• Establishing a scientific community

Workshop goal: Obtain scientific input
4.2: The committee recommends that in order to facilitate the formulation and testing of drug safety hypotheses, CDER

(a) Increase their intramural and extramural programs that access and study data from large automated healthcare databases and
(b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest, and
(c) develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings.

FDA Amendment Act 2007

SEC. 905. ACTIVE POSTMARKET RISK IDENTIFICATION AND ANALYSIS.

(a) In General.—Subsection (k) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended by adding at the end the following:

“(3) ACTIVE POSTMARKET RISK IDENTIFICATION.—

“(A) Definition.—In this paragraph, the term ‘data’ refers to information with respect to a drug approved under this section or under section 351 of the Public Health Service Act, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

“(B) Development of Postmarket Risk Identification and Analysis Methods.—The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities—

“(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C);

“(ii) develop validated methods for the establishment of a postmarket risk identification and analysis

FDA Amendment Act 2007

FDAAA 2007

Early Goals Defined in the Mini-Sentinel Pilot

“The system being created under the auspices of the Sentinel Initiative (the Sentinel System) will help FDA identify and investigate postmarket safety signals, a concern about an excess of adverse events compared with what is expected to be associated with a product’s use, through the processes of signal generation, signal refinement, and signal evaluation.”
Testing & Evaluation of Signal Identification

<table>
<thead>
<tr>
<th>Foundational Methods</th>
<th>Shorter Term Exposures</th>
<th>Longer Term Exposures</th>
</tr>
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<tbody>
<tr>
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**Foundational Methods**

Evaluation with simulated data, creation of different methods, infrastructure for alert follow-up

**Shorter Term Exposures**

Tested on vaccines, antibiotics

**Longer Term Exposures**

Tested on statins, long acting reversible contraceptives, diabetes drugs

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**Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic**

Shirley V. Wang, Judith C. Mauro, Elhamde Barro, Rita Izem, Inna Dashkevsky, James R. Rogerson, Michael Nguyen, Joshua J. Gagne, Elisabeta Paterno, Krista P. Hagbrecht, Jacqueline M. Majors, Esther Zlom, Megan Reedy, Austin Congreve, Sebastian Schneeweiss, and Martin Kulldorff

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**MINI-SENTINEL CBER/PRISM SURVEILLANCE**

INFRASTRUCTURE FOR EVALUATION OF STATISTICAL ALERTS ARISING FROM VACCINE SAFETY DATA MINING ACTIVITIES IN MINI-SENTINEL

Prepared by: David V. Celie, BM, Martin Kulldorff, PhD, Meghan Baker, MD, ScD, Grace Lee, MD, MPH, Judith C. Maro, PhD, MS, Inna Dashkevsky, MS, W. Katherine Yih, PhD, MPH, Carolyn Balsbaugh, MPH, Estelle Russek-Cohen, PhD, David Martin, MD, MPH, Michael Nguyen, MD
Testing & Evaluation of Signal Identification

Foundational Methods
- Evaluation with simulated data, creation of different methods, infrastructure for alert follow-up

Shorter Term Exposures
- Tested on vaccines, antibiotics

Longer Term Exposures
- Tested on statins, long acting reversible contraceptives, diabetes drugs

Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic

MINI-SENSITEL CBER/PRISM SURVEILLANCE

INFRARSTRUCTURE FOR EVALUATION OF STATISTICAL ALERTS ARISING FROM VACCINE SAFETY DATA MINING ACTIVITIES IN MINI-SENSITEL
Prepared by: David V. Cole, BM,1 Martin Kulldorff, PhD,2 Meghan Baker, MD, ScD,3 Grace Lee, MD, MPH,1 Judith C. Maro, PhD, MS,4 Inna Dashevsky, MS, W. Katherine Yih, PhD, MPH,5 Carolyn Balsbaugh, MPH,5 Estelle Russek-Cohen, PhD,6 David Martin, MD, MPH,7 Michael Nguyen, MD7

Published online 20 March 2013 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3423

Drug safety data mining with a tree-based scan statistic
Martin Kulldorff2,2a, Inna Dashevsky1, Talizer R. Avery1, Arnold K. Chan1,3, Robert L. Davis2, David Graham6, Richard Platt2,2b, Susan E. Andrade2,2, Denise Hoodenoud2,2, Margaret J. Gunter2,2b, Lim J. Herrin2,2a, Parnala A. Pawloski2,2a, Marsha A. Raebel2,2a, Douglas Roblin2,2 and Jeffrey S. Brown2,2a
Public Training on Signal Identification

Discuss Challenges of Implementation

Presentation: Key Statistical Considerations for Implementing Signal Identification in the Sentinel System
Mark Levenson, U.S. Food and Drug Administration
Panelist: Darren Toh, Harvard Medical School
Panelist: Juhaeri Juhaeri, Sanofi
Panelist: Mary Beth Ritchey, RTI International
Panelist: Simone Pinheiro, U.S. Food and Drug Administration

Presentation: Potential Processes for Communicating Result Uncertainty
Theresa Toigo, U.S. Food and Drug Administration
Panelist: Stephen Evans, The London School of Hygiene & Tropical Medicine
Panelist: Joanne Waldstreicher, Johnson & Johnson
Panelist: Mary Frances Schubert, Merck & Company, Inc
Panelist: Diana Zuckerman, National Center for Health Research

Next Steps

Next steps: conduct pilot of signal identification, learn in action, grow and enhance toolkit, and establish a best practices framework

Plan for Talk

- Motivation for initiating signal identification in Sentinel
- **Approach to building a signal identification program in Sentinel**
- Signal identification operational pilot
- Establishing a scientific community
Signal Detection Approaches Available in Sentinel

- **Pre-Specified Panel of Select Outcomes**
  - Prospective sequential surveillance tool (Level 3)

- **One Product, All Outcomes**
  - TreeScan

- **One Outcome, All Products**
  - DrugScan

- **All Products, All Outcomes**
  - No existing tool in Sentinel
No One Best Method: Need for Broad Toolkit

Inferential Analyses in Sentinel System, 2016-2018

All FDA Medical Product Centers

- Self-Controlled: 40%
- Propensity Score: 60%

Varieties of TreeScan

Tree-temporal

Propensity Score Matched

Self-controlled
**Foundation for Signal Identification**

**Data Quality Review and Characterization**

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**1. Preparation**
- **Sentinel Operations Center** prepares quality review and characterization package for new ETL.

**2. Transformation**
- **Data Partner** transforms source data into the Sentinel Common Data Model.

**3. Distribution**
- **Sentinel Operations Center** distributes quality assurance package to Data Partners.

**4. Model Compliance**
- **Data Partner** runs quality review and characterization package completing the following:
  - Level 1 checks
  - Level 2 checks
  - > 900 different checks

  Quality review and characterization package outputs list of errors or anomalies (flags) identified during data checks.

  **Data Partner** resolves these flags and sends a detailed report to the Sentinel Operations Center.

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**5. Review & Characterization**
- **Sentinel Operations Center** receives output from Data Partner and reviews.

  **Sentinel Operations Center** runs additional quality assurance checks:
  - Level 2 checks
  - Level 3 checks
  - Level 4 checks
  - > 500 different checks

  **Sentinel Operations Center** evaluates any additional flags and creates issue report for Data Partner to address.

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*On average, there are 44 flags identified by the program and 10 additional flags identified by the Sentinel Operations Center per ETL.*

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Plan for Talk

• Motivation for initiating signal identification in Sentinel
• Approach to building a signal identification program in Sentinel
• **Signal identification operational pilot**
• Establishing a scientific community
Proposed Sentinel Signal Identification Process

Integrated Safety Summary

Clinical Trial Data

Prescribing Information

1. Select 1 product
2. Choose study design(s) or tool
3. Conduct analysis
4. Review and classify statistical alerts
5. Integrate results with other sources of information

Identify Outcome for Further Evaluation (if any)

Signal identification led by Divisions of Pharmacovigilance and Sentinel Program Team

Follow up investigations to be conducted by Divisions of Epidemiology
Adapting Lessons Learned to a New Program

Active Risk Identification and Analysis System (ARIA)

- Serious safety concern
- Determined by statistical power and study design considerations
- Established roles, templates, processes across FDA divisions
- Established templates, webpages to share ongoing analyses, results, regulatory outcomes

Sentinel Signal Identification Program

- Use risk-based approach, need to determine if system is “fit for purpose” for drug of interest
- Balance desire for timeliness with statistical power
- Develop and pilot roles, templates, processes across FDA divisions. Build upon existing ARIA process
- Build upon existing ARIA framework
Plan for Talk

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• Establishing a scientific community
New Investigators in Sentinel Projects

SENTINEL METHODS PROTOCOL

Evaluation of Three Self-Controlled Methods for Signal Detection: TreeScan, Information Component Temporal Pattern Discovery, and Sequence Symmetry Analysis

Prepared by: Judith C. Maro, PhD, MS,1 Shirley V. Wang, PhD, ScM,2 Inna Dashevsky, MS,1 David Cole, BM,1 Joshua J. Gagne, PharmD, ScD,2 Sai Dharmarajan, PhD,3 Esther H. Zhou, MD, PhD,4 Sandra DeLuccia, MPH,1 Ella Pestine, MPH,1 Monica Munoz, PhD, MS,4 Danijela Stojanovic, PharmD, PhD,4 Jesper Hallas, MD, DrMedSc,5 G. Niklas Norén, PhD,6 Martin Kulldorff, PhD,2 Michael D. Nguyen, MD4

Public Engagement Through Posting of Study Protocols for Comment

B. RESPONSES TO PUBLIC COMMENT

This study was posted for public comment from August 10, 2018 to September 7, 2018. We received one set of comments and have responded to each question individually below. We have minimally rephrased the questions slightly to a more general format but the content and intent remains the same.

Question 1: Given the large number of available empirical approaches for model selection, it could be helpful to provide motivation for why high dimensional propensity score (hdPS) was chosen for this evaluation as opposed to other options. For instance, Karim et al. (Epidemiology 2018 Mar; 29(2): 191-198) recently showed that a machine learning with hdps hybrid often outperforms hdps alone.

Response: This paper found that machine learning based approaches such as LASSO and ElasticNet in combination with hdPS performed marginally better than hdPS alone in the context of selection based on potential for bias for a single outcome. The machine learning component of the hybrid empirical variable selection methods worked to further reduce the dimensionality of variables identified with hdPS.

In our context, we are scanning across thousands of potential outcomes. It would not be feasible to apply a hybrid approach which selects variables based on association with outcome. Furthermore, it may be helpful in our scanning context to include a slightly broader base of variables to provide proxy adjustment for confounders on a wider range of outcomes.

We will include this citation and a brief explanation as above in the background.

Question 2: Similarly, it could be useful to motivate why the TreeScan methodology was selected as opposed to other scan statistics (or, minimally, to provide its major advantages and limitations in this

Planned Future Projects

- Development of sequential TreeScan to enable multiple looks over time
- Evaluation of TreeScan for pregnancy outcomes
Advancing the Sentinel System

Explore opportunities to leverage advances in machine learning, natural language processing, artificial intelligence

Expand the Sentinel Common Data Model

Enhance existing data sources, particularly with electronic health records

https://healthpolicy.duke.edu/events/improving-efficiency-outcome-validation-sentinel-system
https://healthpolicy.duke.edu/events/public-webinar-planned-next-steps-advance-sentinel-system
Summary

• Establishing a Sentinel signal identification program fulfills a congressional mandate and expands the utility of the system

• Sentinel signal identification program can build upon prior experience using the Sentinel System
  – Will be integrated into existing regulatory processes

• Next steps include a pilot program, and establishing durable processes and best practices

• FDA will continue to engage the scientific community, expand its analytic toolkit, and disseminate lessons learned

• FDA is interested in obtaining input from this meeting
Presentation: Integrating Signal Identification into FDA’s Pharmacovigilance Framework
Integrating Signal Identification with Sentinel into FDA’s Pharmacovigilance Framework

CDR Monica Muñoz, PharmD, MS
Deputy Director
Division of Pharmacovigilance I
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research
December 3, 2018
Current Signal Management

Signal Identification

- Identification of potential safety concern
- Ongoing surveillance:
  - FDA Adverse Event Reporting System (FAERS)
  - Published literature
  - Sponsor’s periodic safety reports
- Review of other sources:
  - Regulator exchanges
  - Sponsor communications
  - Clinical trials
  - Study output
  - Other inputs

Signal Refinement

- Initial evaluation of safety concerns for triage and prioritization
- Preliminary consideration of:
  - Potential causal association
  - Potential public health impact
  - All available quantitative data about the safety concern

Signal Evaluation

- Detailed assessment of the evidence
- May include:
  - Case review
  - Literature review
  - Drug utilization analyses
  - Epidemiologic analyses
  - Clinical trials
  - Other pertinent data sources

Regulatory Action

- Determination of action
- May include:
  - Labeling modifications
  - Communication
  - Sponsor or FDA led studies
  - Compliance actions
  - Risk Evaluation and Mitigation Strategies (REMS)
  - Continued surveillance
Current Signal Identification Practices

• Screening FAERS, published literature
  – Review of individual reports/articles
  – Disproportionality analyses

• Cumulative analyses
  – Cumulative review of FAERS, literature, and Sponsor’s periodic safety reports
  – Risk-based approach* to frequency and product selection

Current Signal Sources

- 57% of FDA Drug Safety Communications were informed by FAERS data

- Most common evidence sources:
  - Spontaneous reports (52%)
  - Clinical trials (16%)
  - Pharmacokinetic studies (11%)
FAERS as a Signal Source

• FAERS is a valuable source of safety information
  – Good for detecting rare and acute events
  – Captures all products and settings of use
  – Can provide a patient perspective
FAERS as a Signal Source

• FAERS has important limitations
  – Unknown denominator, underreporting, stimulated reporting, variable information quality, etc.

• Difficult to identify and evaluate signals associated with long latency, worsening disease, or high background rates

• Limitations preclude quantifying risks
Sentinel as a Signal Source

• Leverages the following advantages:
  – Exposure denominator
  – Exposure/event capture not dependent on voluntary process
  – Longitudinal data
  – Ability to control for confounding variables
Signal Identification Opportunities

- Surveillance activities currently reliant on passive data sources
- Active hypothesis-free signal identification in Sentinel can complement current surveillance tools
Future Signal Identification Practices

• Sentinel signal identification output integrated into surveillance
  – FDA to pilot Sentinel signal identification

• Continue other pharmacovigilance practices to identify new postmarket safety issues
Session I: Statistical Considerations for Implementing Signal Identification in the Sentinel System
Statistical Considerations for Implementing Signal Identification in the Sentinel System

December 3, 2018

Mark Levenson, Ph.D.
Office of Biostatistics
Center for Drug Evaluation and Research
Goals

• Propose the use case for signal identification followed by signal refinement or evaluation (both in Sentinel)
• Clarify objectives of use case
• Set the stage for panel discussion with concepts and terminology
Signal Identification and Refinement/Evaluation (In Sentinel)

- **Approval**
  - Integrate Sentinel into FDA’s risk-based pharmacovigilance

- **Signal Identification**
  - Depending on drug uptake, conduct signal identification in Sentinel

- **Signal Refinement/Evaluation**
  - Follow-up signals in Sentinel
Some Details

• Address case where Sentinel is used for both signal identification and signal refinement/evaluation

• Propose to use all or some of the same data for both signal identification and signal refinement/evaluation (Data Reuse)
  – Maximizes use of available data

• Objective of refinement/evaluation: Strengthen evidence for or against signal by reducing bias and confounding
  – Not seeking independent replication/reproduction
Typical Biases

Sources
• Difference in prognostic factors between comparator groups (confounding)
• Errors in outcome ascertainment

Remedies
• Careful consideration of confounding and adjustment
• More specific outcome definition or chart review
• Narrower analysis population
What Is the Concern With Data Reuse?

Worrisome, but not in scope
• Fabricating or misreporting research data
• Inappropriate research and statistical methods
• Failure to properly document and preserve research results
• Etc.

Concerns about data reuse
• Analyzing data in enough different ways to observe an association
• Selectively focusing on analyses that are statistically significant
• Not properly accounting for multiple statistical testing
• Variations of above
What Is the Concern With Data Reuse?

**Worrisome, but not in scope**
- Fabricating or misreporting

**Concerns about data reuse**
- Analyzing data in enough different ways to observe an association
- Selectively focusing on analyses that are statistically significant
- Not properly accounting for multiple statistical testing
- Variations of above

**Remedies:**
1. Prespecification and transparency of analysis plan and results
2. Proper attention to statistical testing and errors
Type 1 and 2 Errors

• Type 1 (false positive): Concluding there is a signal when there is not one
  – Usually attempt to probabilistically bound at e.g., $\alpha = 0.01$ or 0.05

• Type 2 (false negative): Concluding there is no signal when there is one
Type 1 Error Consideration

No True Signal

All outcomes considered in signal identification

Outcomes that imply signal (known probability bound $\alpha$)

Refine/evaluate only outcomes in blue box
Bias Consideration

- Analysis with little or no control for biases (confounding and outcome ascertainment)
- Bias remaining after signal identification
- Bias remaining after focused signal refinement/evaluation
End Result After
Signal Identification and Refinement/Evaluation

- Understanding of probability of false positives
- Reduction of biases and some understanding of residual biases
Other Considerations

• Type 1 and 2 errors can be tuned to achieve sensitivity (finding true signals) and specificity (not finding false signals)
  – May need to delay analyses until sufficient data are available

• Assessment signals after identification and refinement/evaluation will require clinical, epidemiological, and statistical review
  – Biological plausibility
  – Magnitude and uncertainty of findings
  – Residual confounding
Conclusion

• Signal identification and signal refinement/evaluation may use the same data source IF
  – Goal is to reduce bias and not to provide replication
  – There is control of Type 1 and 2 errors at both signal identification and signal refinement/evaluation stages
  – Prespecification and transparency of plans and results are prescribed
Session I: Statistical Considerations for Implementing Signal Identification in the Sentinel System
BREAK

Join the conversation with #sentinelinitiative
Session II: Effectively Communicating Sentinel Signal Identification Information

Join the conversation with #sentinelnitiative
Effectively Communicating Sentinel Signal Identification Information

December 3, 2018

Theresa (Terry) Toigo, M.B.A., R.Ph.
Associate Director for Drug Safety Operations
Center for Drug Evaluation and Research
Overview

- Drug Safety Transparency Initiatives
- Transparency and Sentinel Signal Identification
- Signal Identification and Regulatory Processes
- Pilot Framework for Communicating Signal Identification Information
Select FDA Transparency Initiatives

• 1993: Launched MedWatch Program
  – Facilitates reporting by providers; also informs providers about FDA regulatory actions.

• 2005: Launched Drug Watch webpage
  – Posted significant emerging safety information FDA received about certain drugs (or classes of drugs) while the agency continues to actively evaluate the information.

• 2007: Replaced Drug Watch with Index to Drug-Specific Information webpage
  – Includes drugs that have been the subject of a drug safety communication.

• 2008: Launched Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) webpage
  – Section 921 of FDAAA requires quarterly posting on the FAERS website of potential signals of serious risks and new safety information.
Sentinel Transparency Initiatives

Analysis Tools and Use Counts
- SAS tools available online
- Synthetic public use dataset
- FDA use metrics

Study Design and Parameters
- Executable SAS programs that can run on other datasets formatted in Sentinel CDM
- Contains study design, parameters, algorithms

Study Results
- Full analytic results organized in tabular format
- Publication

Regulatory Outcomes
- Brief description of how Sentinel data contributed to a decision, regulatory outcome, or action

https://dev.sentinelssystem.org

Sentinel Transparency Initiatives

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How ARIA Analyses Have Been Used by FDA
The page summarizes how selected analyses conducted in Sentinel's Active Risk Identification and Analysis (ARIA) system have been used by FDA since Sentinel's official launch in February 2016. ARIA can contribute to FDA's regulatory process in a variety of ways, such as contributing evidence to support a label change, respond to a Citizens' Petition, or become part of an Advisory Committee's considerations. Information from ARIA can also provide evidence that alleviates concerns about a particular safety issue and might help FDA determine that no regulatory action is necessary based on the available information.

Each ARIA analysis listed below contributed in some manner to a recent or ongoing regulatory discussion or action. FDA notes decisions about drug safety issues based upon the totality of evidence. The listing of an ARIA analysis in this table means that Sentinel's ARIA system was one important source of evidence considered.
Sentinel Signal Identification
Transparency Goals

• Communicate FDA efforts to proactively monitor the safety of newly approved medications in Sentinel

• Balance desire for transparency with preliminary nature of results from signal identification studies
  – Represents possibility of new concern (not an actual new risk)
  – Results alone don’t constitute actionable evidence for a patient or FDA
  – Statistical alerts require further study and clinical correlation
  – May later be refuted, refined, or strengthened upon further investigation
Challenges to Transparency

DESIRABLE ENDPOINTS

• Demonstrating proactive efforts of FDA signal identification studies
• Sharing valuable knowledge gained from Sentinel to patients, consumers, and industry
• Enabling a robust FDA signal identification program by addressing the need to carefully adjudicate data before dissemination

PITFALLS TO AVOID

• Sharing premature information that might lead to drug discontinuation or drug avoidance with consequent loss of drug’s beneficial effects
• Inadvertently contributing to patient anxiety with uncertain information
• Not distinguishing between actionable information and preliminary data in communications
• Alert fatigue
Sentinel Signal Identification
General Principles

• FDA goal to strengthen an already robust pharmacovigilance framework
  – Sentinel is a new analytic tool that will augment, not replace, existing systems
• Signal identification activities will be integrated into existing regulatory processes, e.g.
  – Sponsor communication will continue through existing processes, such as 21st Century review, safety labeling changes, tracked safety issue notification
  – Public risk communication will leverage existing Drug Safety Communication approaches
• Build on the existing transparency initiatives in Sentinel
Signal Identification Builds on Existing Sentinel Transparency Initiatives

<table>
<thead>
<tr>
<th>Information about the analysis tool itself</th>
<th>Sentinel ARIA</th>
<th>Signal Identification</th>
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<tbody>
<tr>
<td>- SAS code, worked examples online</td>
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<tbody>
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<td>✔️</td>
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</table>
Information About the Tool

SAS Code Hosted on GitHub Site

Sentinel Analytic Packages

Overview
Sentinel's analytic request packages are intended to run on data formatted in accordance with the Sentinel Common Data Model (SCDM). Note that data must be in SAS® datasets to use these analytic programs.

Analytic Request Packages Available for Download

<table>
<thead>
<tr>
<th>Request ID</th>
<th>Summary</th>
</tr>
</thead>
<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</td>
</tr>
</tbody>
</table>

To View Analytic Request Packages
- Click the drop-down menu in the top left-hand corner
- Choose the Request ID representing the analysis of interest
- Click the "..." button
- Select "Download" from the menu that appears

https://dev.sentinelsystem.org
Information About
When FDA Uses Signal Identification

Signal Identification Will Be Added to Existing Sentinel Use Summaries Available Online
Information About Results and Outcomes

**FAERS**

Signal Identification Using Spontaneous Reports

- All Reports Downloadable
- Online Query Tool / Public Dashboard
- Post Potential Safety Concerns
- Update When FDA Action is Taken
Information About Results and Outcomes (cont.)

How ARIA Analyses Have Been Used by FDA

This page summarizes how select analyses conducted in Sentinel’s Active Risk Identification and Analysis (ARIA) system have been used by FDA since Sentinel’s official launch in February 2016. ARIA can contribute to FDA’s regulatory process in a variety of ways, such as contributing evidence to support a label change, respond to a Citizens Petition, or become part of an Advisory Committee deliberation. Information from ARIA can also provide evidence that alleviates concerns about a particular safety issue and might lead FDA to determine that no regulatory action is necessary based on the available information.

Each ARIA analysis listed below contributed in some material way to inform an important regulatory discussion or action. FDA makes decisions about drug safety issues based upon the totality of evidence. The listing of an ARIA analysis in the table means that Sentinel’s ARIA system was one important source of evidence considered.

<table>
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<tr>
<th>Drug Name</th>
<th>Outcome Assessed</th>
<th>ARIA Analysis</th>
<th>Regulatory Determination / Use</th>
<th>Date Posted</th>
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</table>
| Medications for attention deficit hyperactivity disorder | Heart failure and cardiomyopathy | Level 1       | Follow up investigation of case reports of cardiac events after long term stimulant use. FDA decided that no action is necessary at this time, based on available information.  
• Results  
• Presentation at February 2017 Sentinel Public Workshop  
• Publication | 8/30/2018   |
# Pilot Framework for Communicating Signal Identification Information

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</table>
| Drug A    | Signal identification of multiple outcomes | TreeScan | FDA will further investigate outcomes A and B in a Level 2 analysis.  
• [Results](#) | Date |
| Drug A    | • Outcome A  
• Outcome B | Level 2 | Outcome A was added to Warnings and Precautions. Following further investigation of outcome B, FDA decided that no action is needed at this time based on available information.  
• [Level 2 Results](#)  
• [Revised Label](#) | Date + 10 months |
Summary

• Sentinel is a new signal identification tool that will augment, not replace, existing systems

• FDA goal
  – strengthen an already robust pharmacovigilance framework
  – integrate signal identification activities into existing regulatory processes
    • Sentinel-specific processes
    • General regulatory processes for all marketed drugs
  – post results in a meaningful but not misleading manner

• FDA plans to pilot a framework for communicating signal identification information and evaluate the pilot
Session II: Effectively Communicating Sentinel Signal Identification Information

Join the conversation with #sentinelinitiative