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

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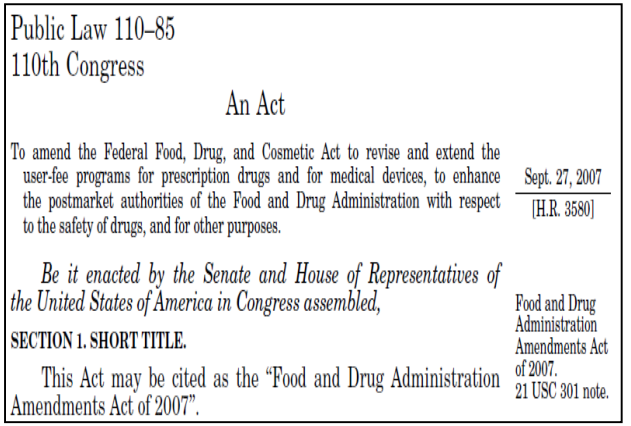
2007 FDA Amendments Act (FDAAA)

- 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**



Public Law 110–85
110th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Sept. 27, 2007
[H.R. 3580]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

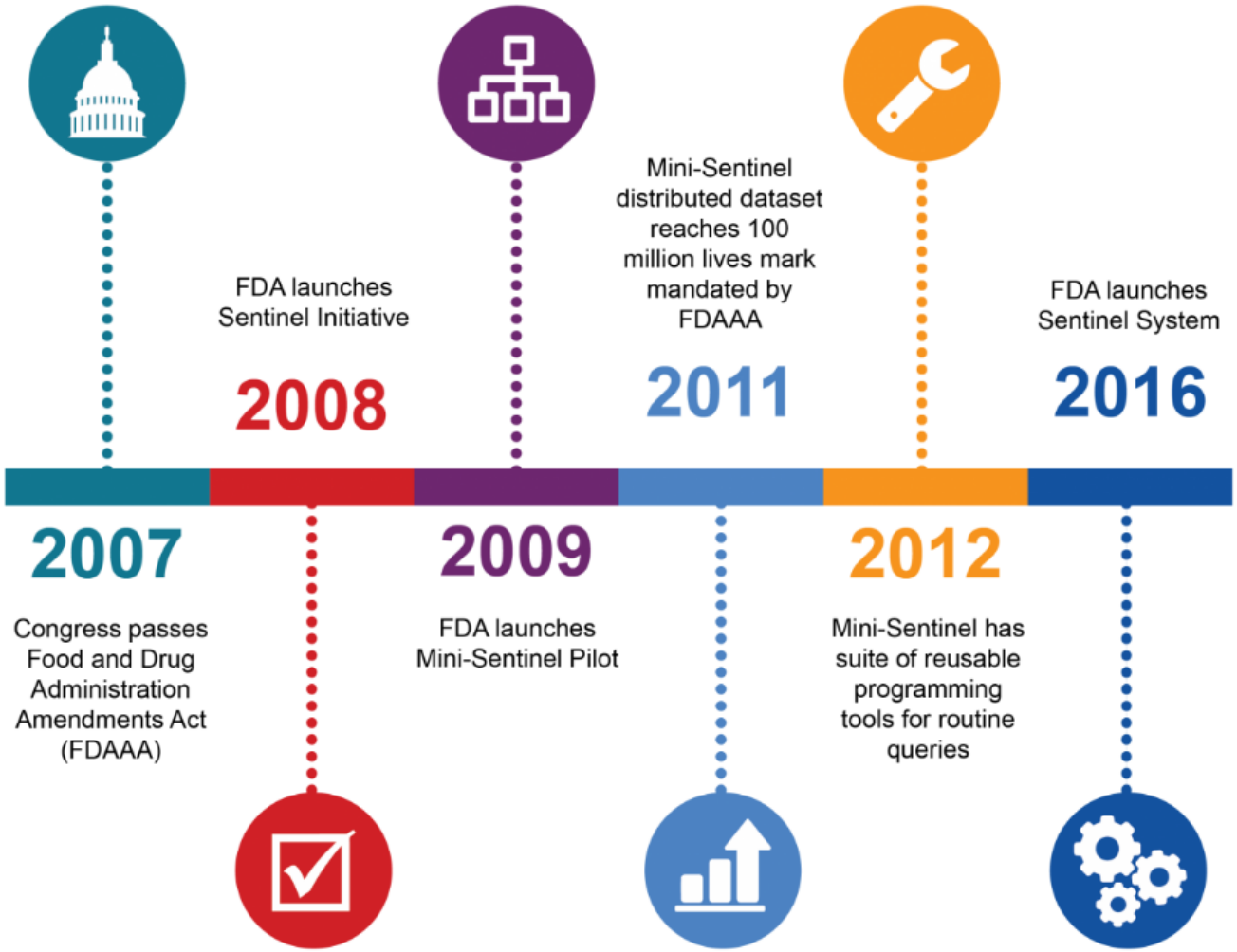
SECTION 1. SHORT TITLE.

This Act may be cited as the “Food and Drug Administration Amendments Act of 2007”.

Food and Drug Administration Amendments Act of 2007.
21 USC 301 note.

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.

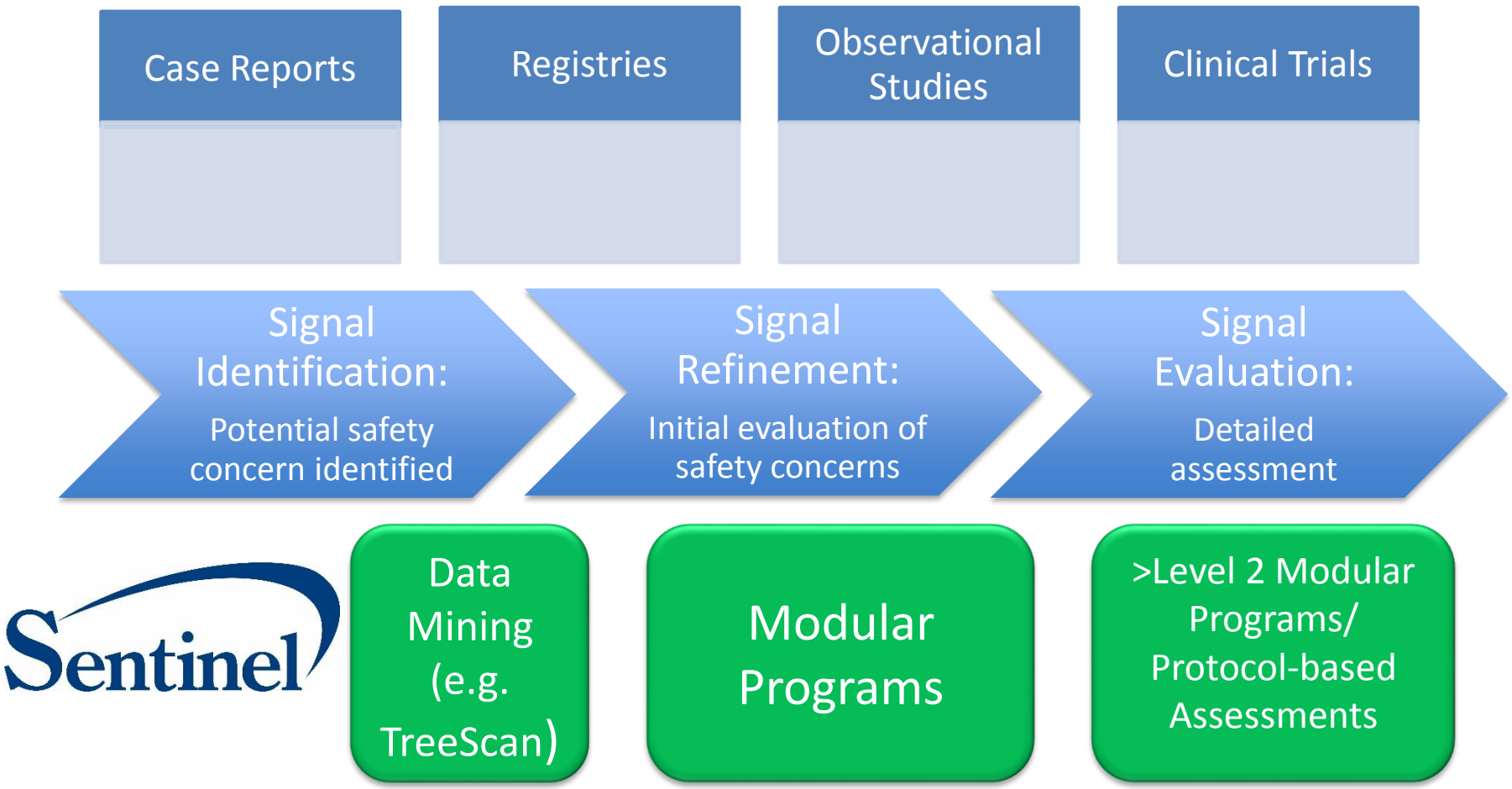


https://www.sentinelsystem.org/sentinel/about

Mini-Sentinel Accomplishments

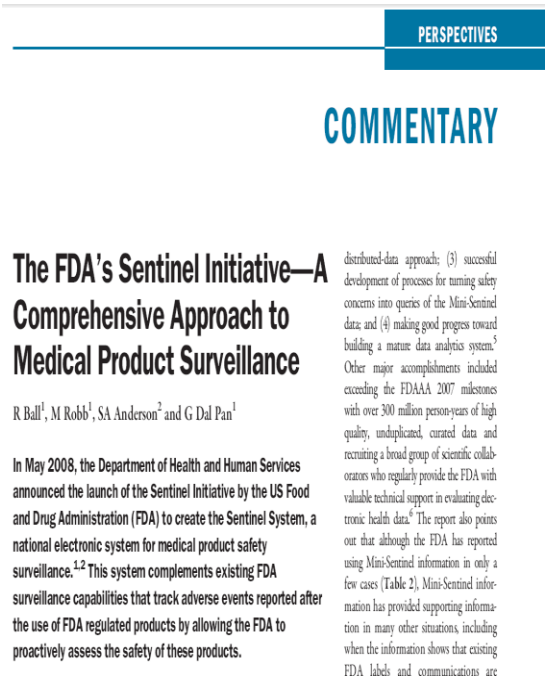
- Established Coordinating Center and Distributed Data Network
  - > 30 Collaborating institutions (17 Data Partners)
  - Common Data Model
  - Secure querying behind data partners' firewall
  - Access to quality checked, electronic healthcare data of over 178 million patients
- Developed and demonstrated value of reusable modular programs for foundation of an active medical product safety surveillance system

Post-Market Safety Assessment



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



PERSPECTIVES

COMMENTARY

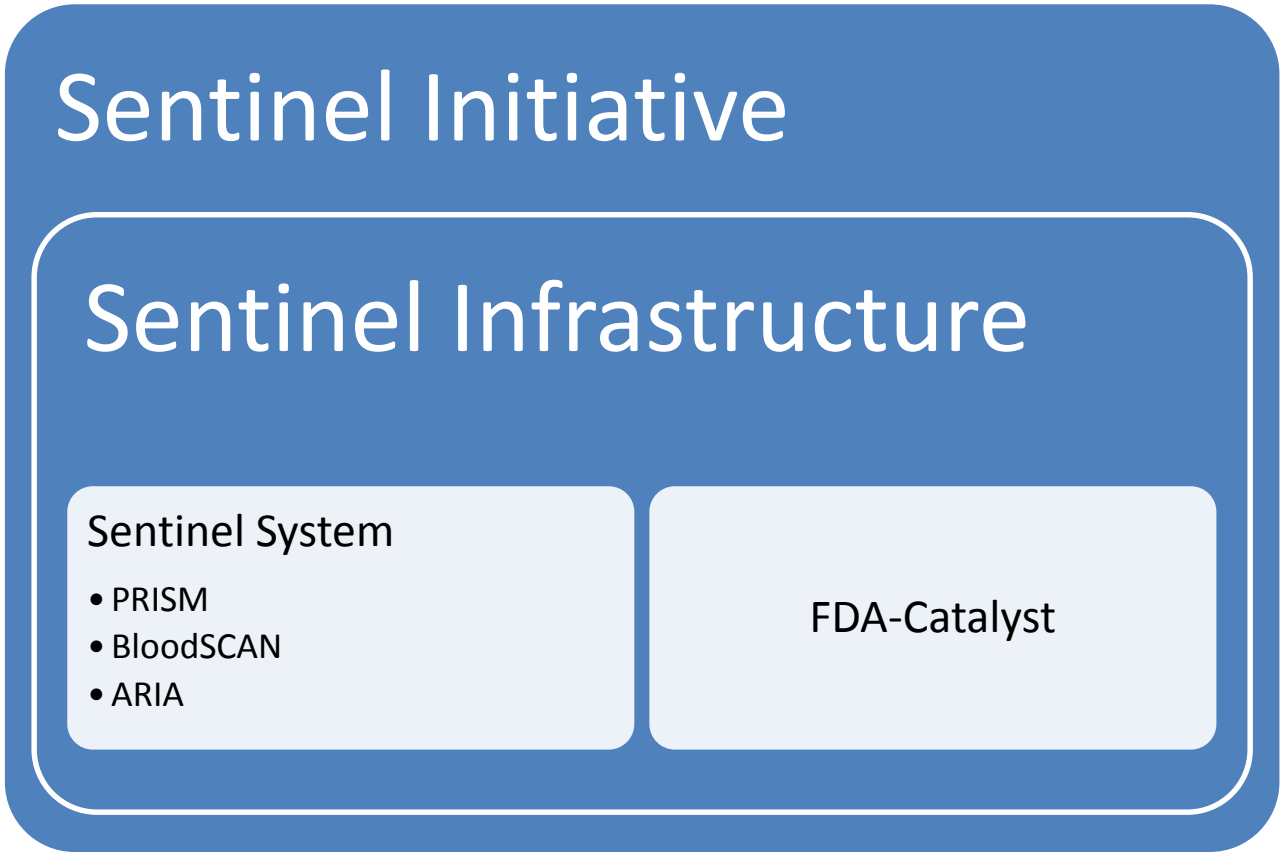
The FDA’s Sentinel Initiative—A Comprehensive Approach to Medical Product Surveillance

R Ball[1], M Robb[1], SA Anderson[2] and G Dal Pan[1]

In May 2008, the Department of Health and Human Services announced the launch of the Sentinel Initiative by the US Food and Drug Administration (FDA) to create the Sentinel System, a national electronic system for medical product safety surveillance.[1,2] This system complements existing FDA surveillance capabilities that track adverse events reported after the use of FDA regulated products by allowing the FDA to proactively assess the safety of these products.

distributed-data approach; (3) successful development of processes for turning safety concerns into queries of the Mini-Sentinel data; and (4) making good progress toward building a mature data analytics system.[5] Other major accomplishments included exceeding the FDAAA 2007 milestones with over 300 million person-years of high quality, unduplicated, curated data and recruiting a broad group of scientific collaborators who regularly provide the FDA with valuable technical support in evaluating electronic health data.[6] The report also points out that although the FDA has reported using Mini-Sentinel information in only a few cases (Table 2), Mini-Sentinel information has provided supporting information in many other situations, including when the information shows that existing FDA labels and communications are

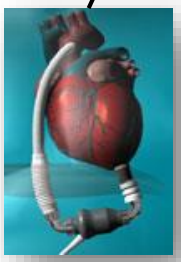
Ball R, Robb M, Anderson SA, Dal Pan G. FDA's Sentinel Initiative - A Comprehensive Approach to Medical Product Surveillance. *Clinical Pharmacology & Therapeutics.* 99:265-268, 2016.


Sentinel Initiative
Sentinel Infrastructure
Sentinel System
• PRISM
• BloodSCAN
• ARIA
FDA-Catalyst

Sentinel Initiative Involves Multiple Centers

Center for **F**ood **S**afety & **A**pplied **N**utrition **(CFSAN)**

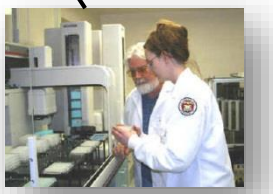
Center for **V**eterinary **M**edicine **(CVM)**



Center for **D**evices & **R**adiological **H**ealth **(CDRH)**

Center for **B**iologics **E**valuation & **R**esearch **(CBER)**

Center for **D**rug **E**valuation & **R**esearch **(CDER)**



Center for **T**obacco **P**roducts **(CTP)**

Office of **R**egulatory **A**ffairs **(ORA)**

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

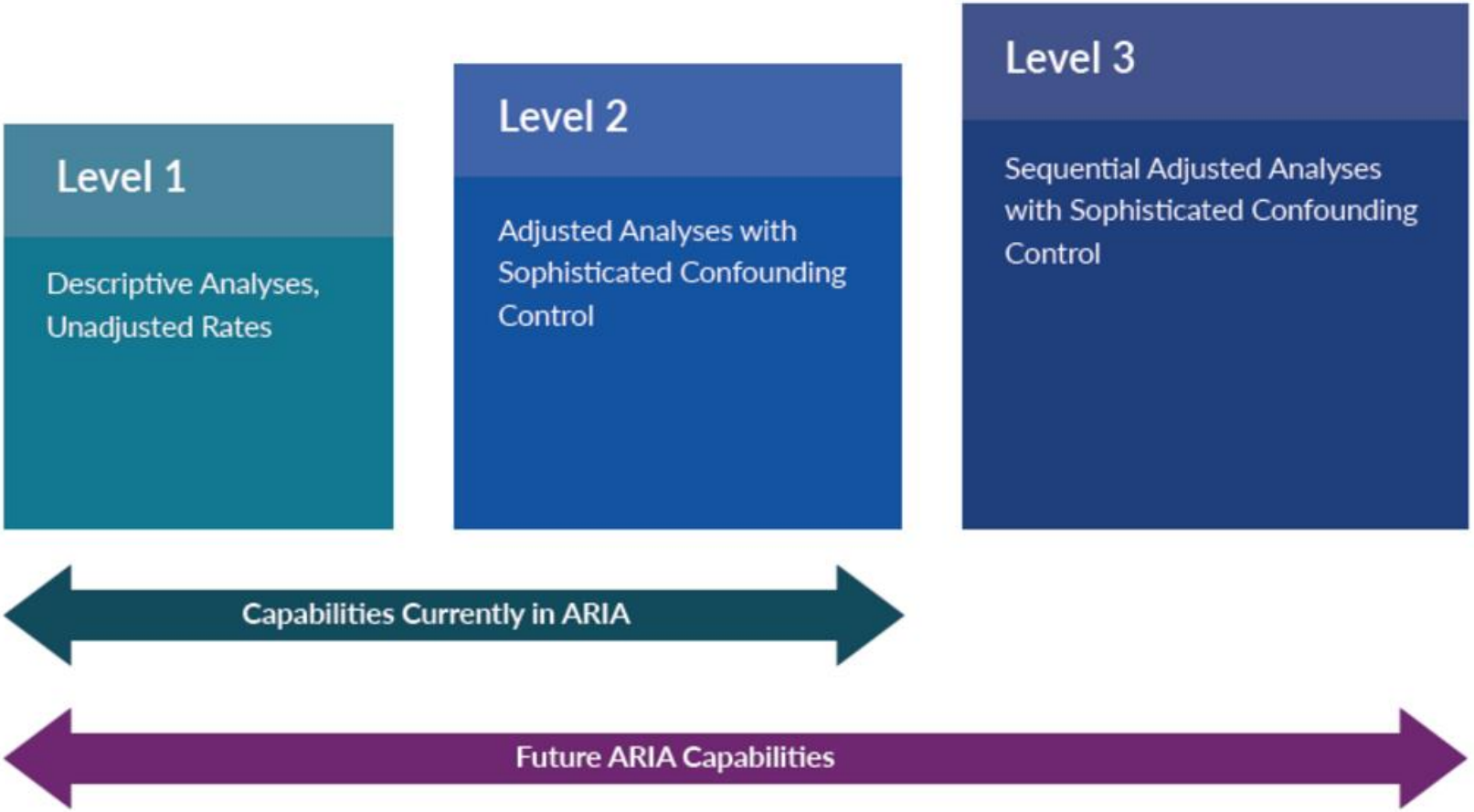
Defining ARIA

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

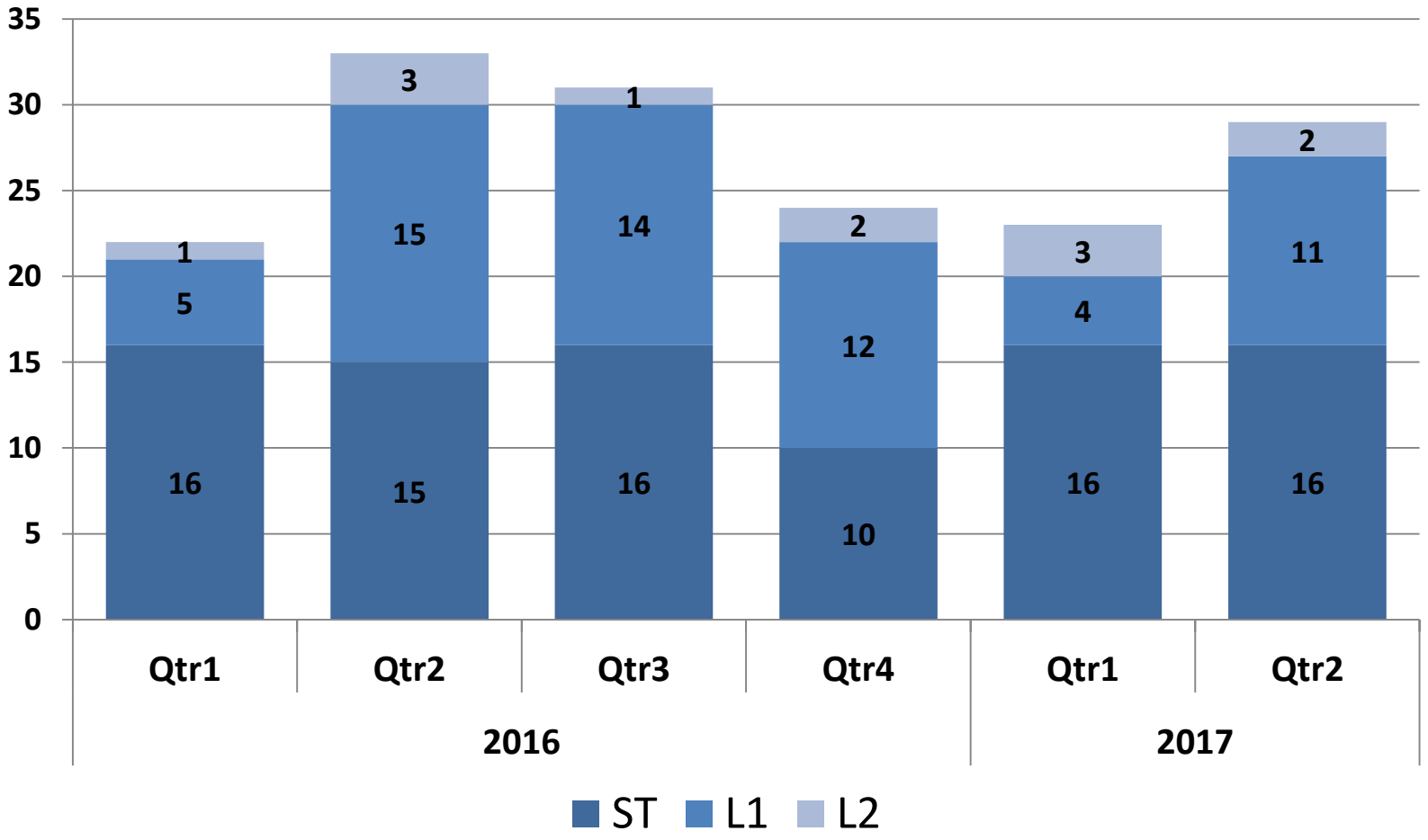


https://www.sentinelsystem.org/active-risk-identification-and-analysis-aria

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

Acknowledgements

- At FDA, Gerald Dal Pan, Michael Nguyen, Melissa Robb, Steve Anderson, David Martin, and Sentinel Team
- Sentinel Operations Center and Sentinel Partners

Thank you