

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

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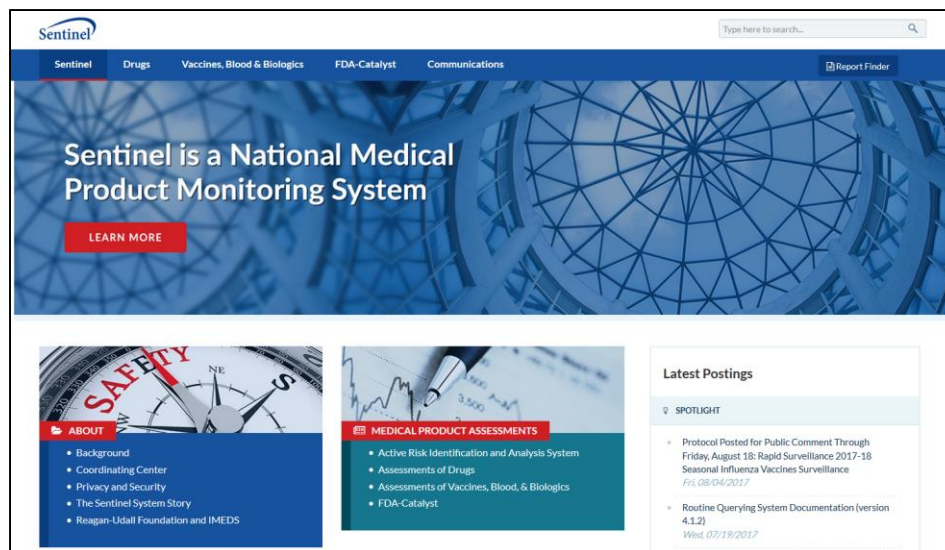
Disclosure

- 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

February 3, 2016

The logo for the U.S. Food and Drug Administration (FDA), consisting of the letters "FDA" in white on a blue square background.

“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.”



Janet Woodcock, MD
Director, Center for Drug Evaluation & Research
8th Annual Sentinel Initiative Public Workshop

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

Section 905

Mandates creation of ARIA



Section 901

New FDAAA PMR authority

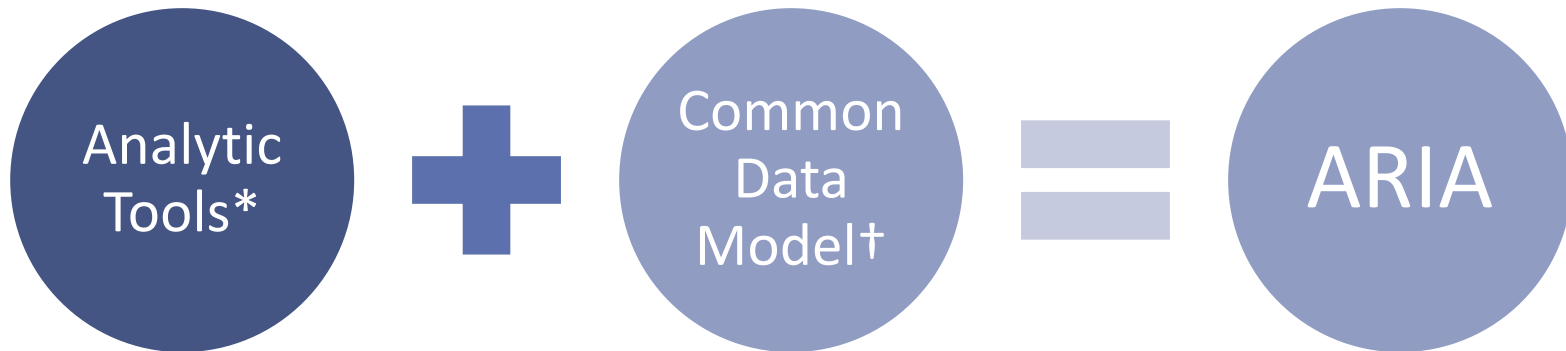
“The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the **active postmarket risk identification and analysis system** as available under subsection (k)(3) will not be **sufficient**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

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

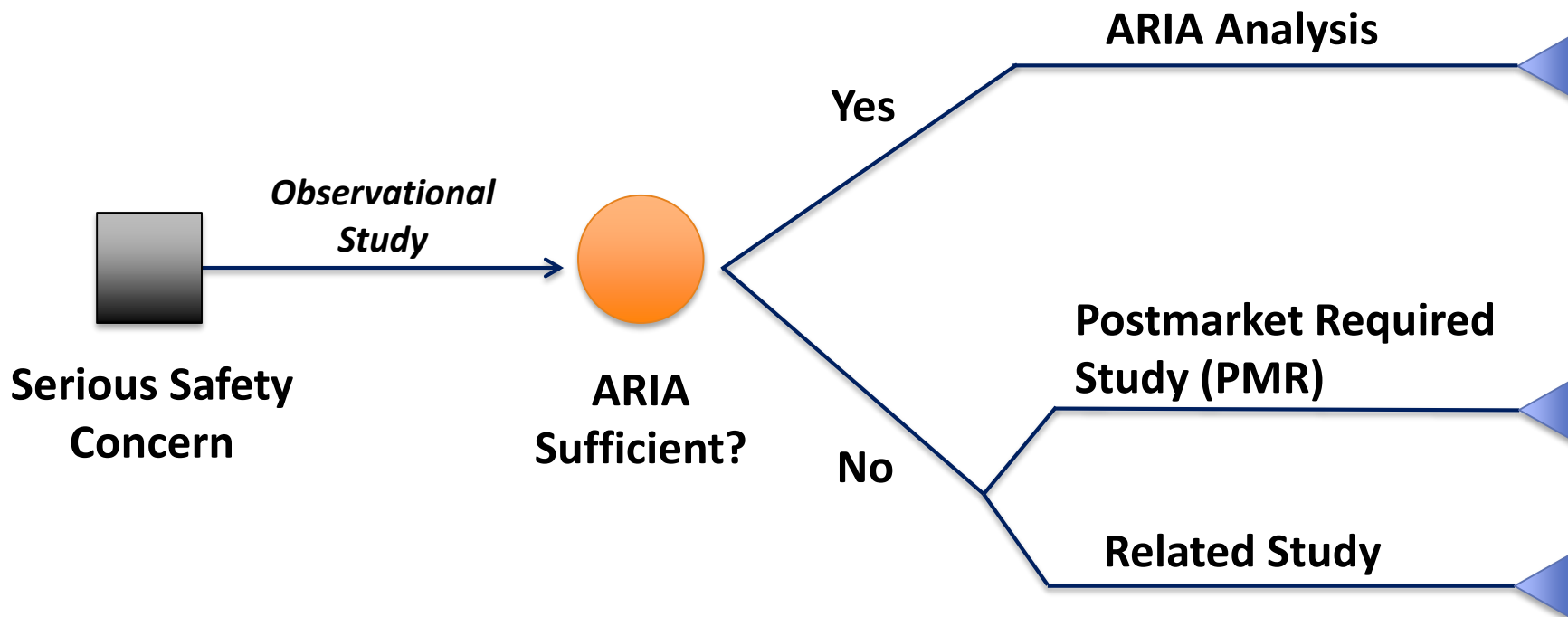
ARIA is a subset of Sentinel's full capabilities



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

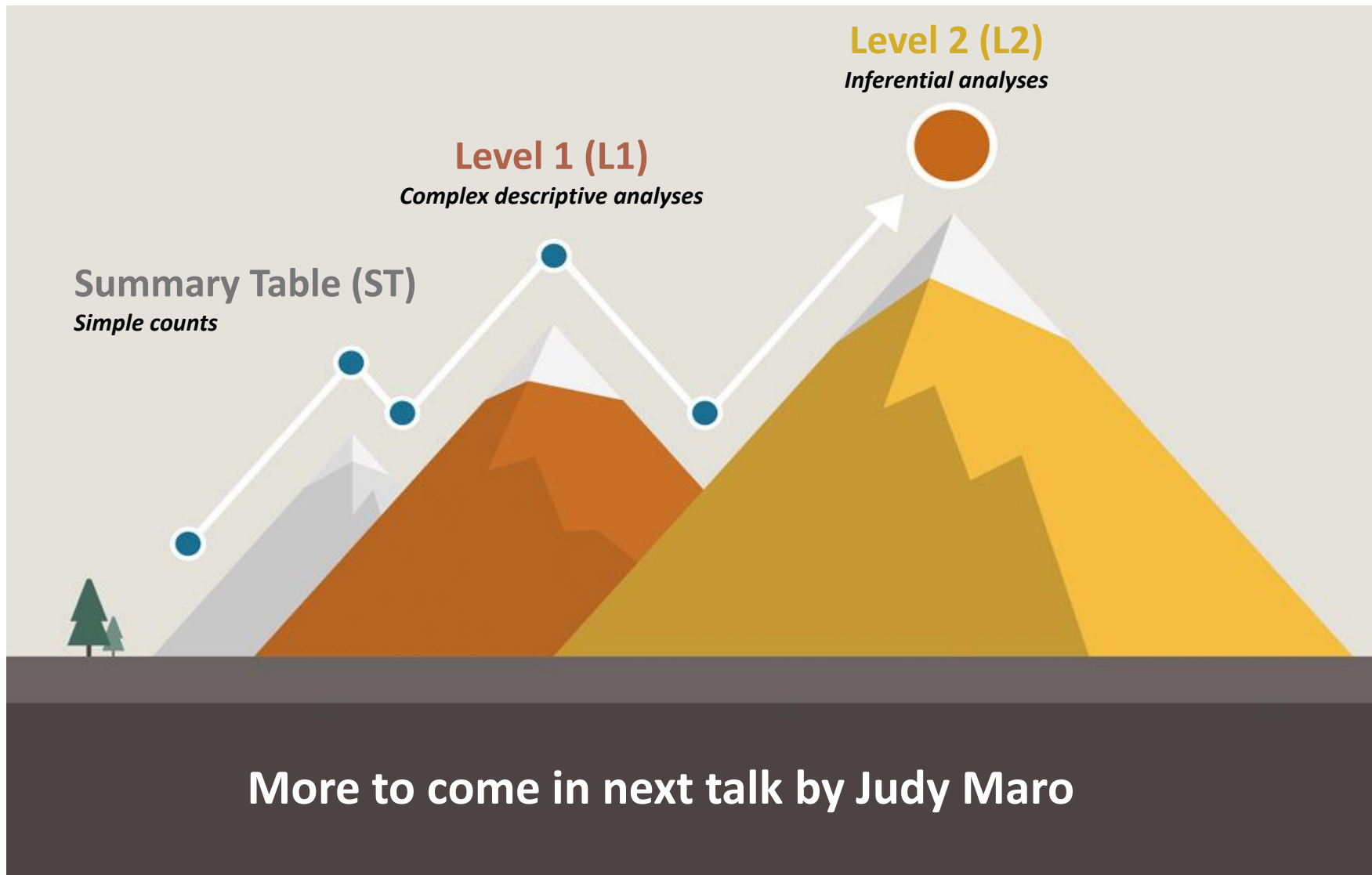
† Electronic claims data, without manual medical record review

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)

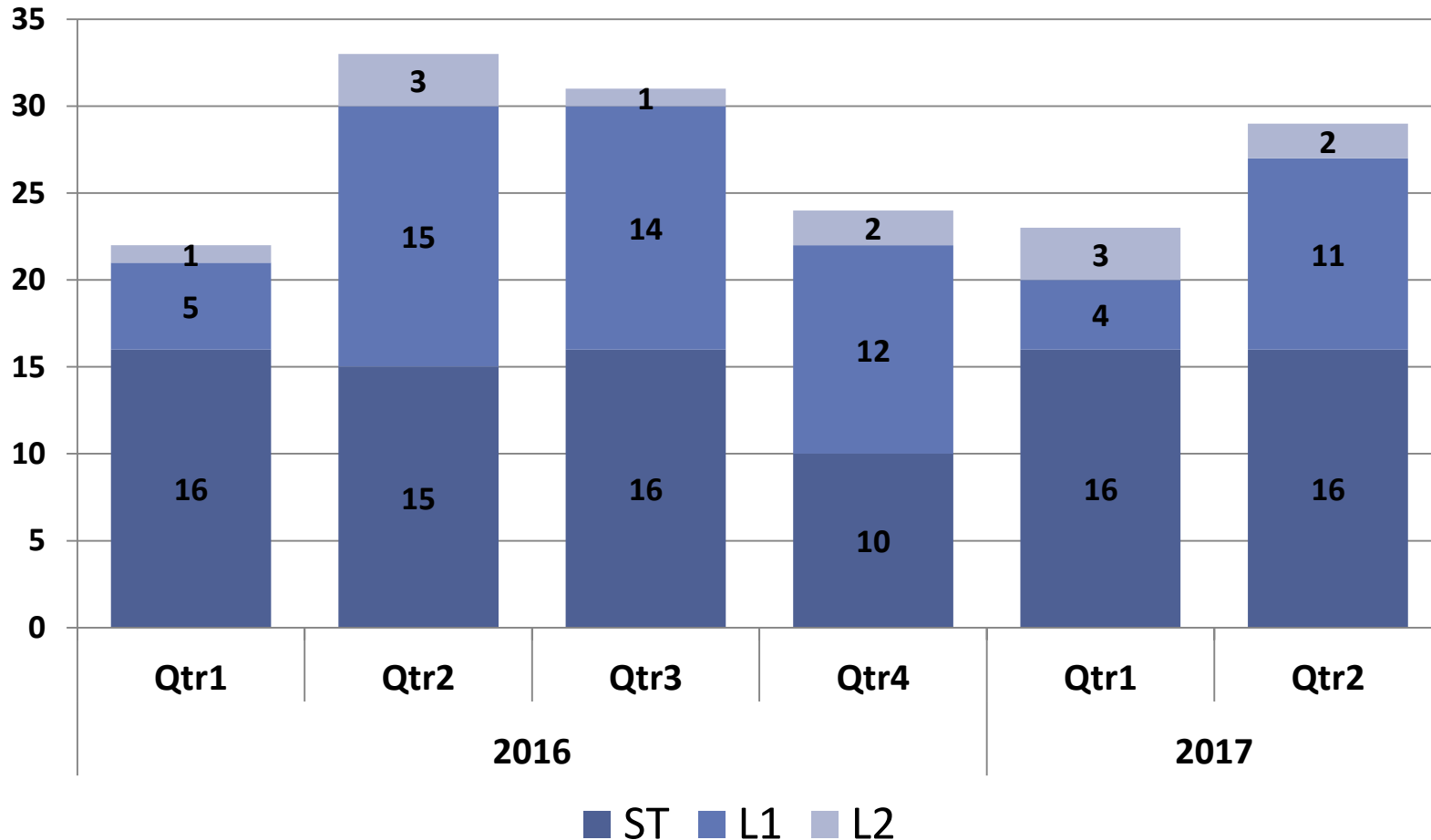
Reaching the Goal with the Right Tools



ARIA Analyses by Quarter, FDA-wide



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

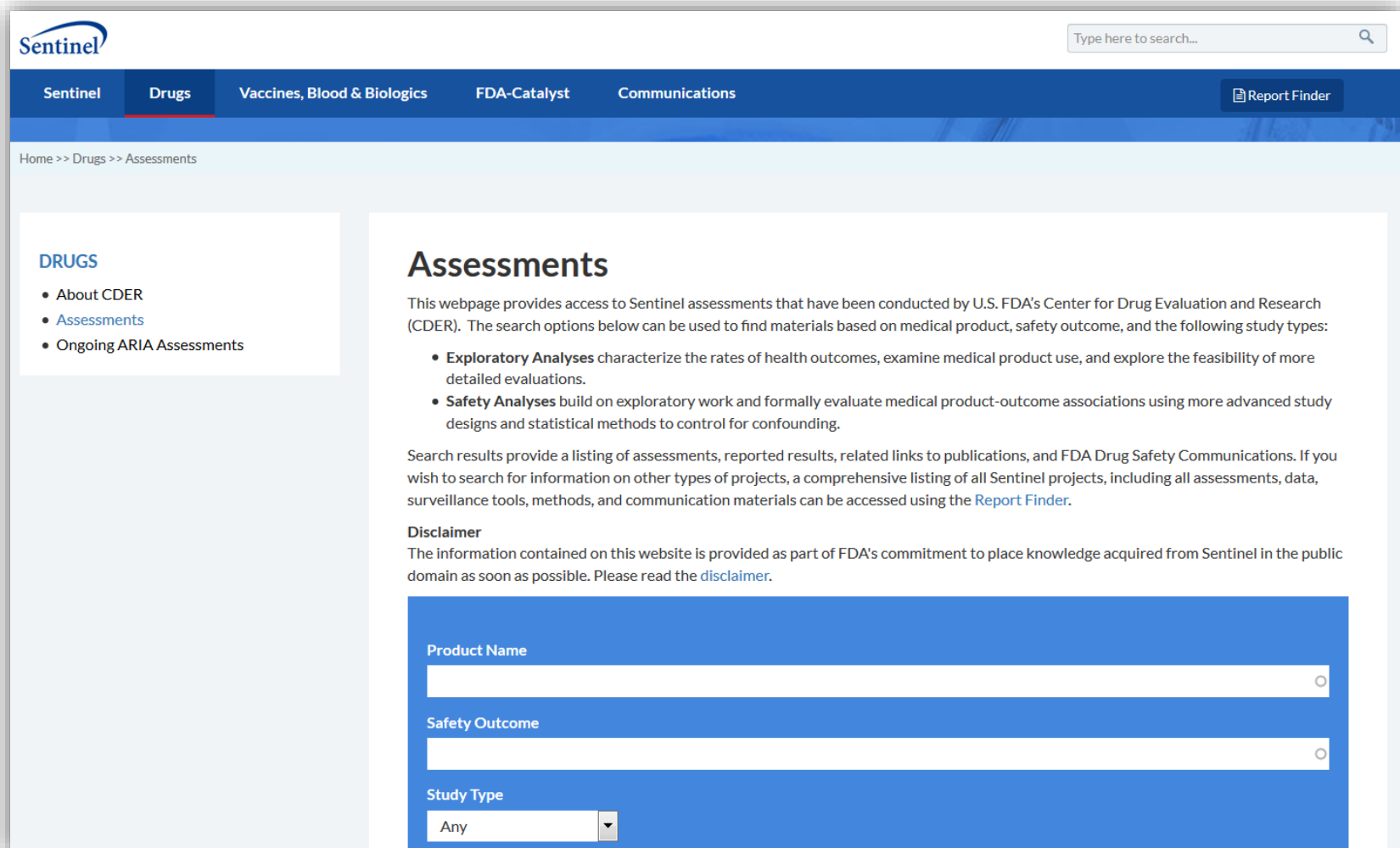
SPOTLIGHT

- 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



Home >> Drugs >> Assessments

DRUGS

- About CDER
- [Assessments](#)
- Ongoing ARIA Assessments

Assessments

This webpage provides access to Sentinel assessments that have been conducted by U.S. FDA's Center for Drug Evaluation and Research (CDER). The search options below can be used to find materials based on medical product, safety outcome, and the following study types:

- **Exploratory Analyses** characterize the rates of health outcomes, examine medical product use, and explore the feasibility of more detailed evaluations.
- **Safety Analyses** build on exploratory work and formally evaluate medical product-outcome associations using more advanced study designs and statistical methods to control for confounding.

Search results provide a listing of assessments, reported results, related links to publications, and FDA Drug Safety Communications. If you wish to search for information on other types of projects, a comprehensive listing of all Sentinel projects, including all assessments, data, surveillance tools, methods, and communication materials can be accessed using the [Report Finder](#).

Disclaimer
The information contained on this website is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Please read the [disclaimer](#).

Product Name

Safety Outcome

Study Type
Any ▼

Where to Find Ongoing Analyses

Sentinel | **Drugs** | Vaccines, Blood & Biologics | FDA-Catalyst | Communications | Report Finder

Home >> Drugs >> Ongoing ARIA Assessments

DRUGS

- About CDER
- Assessments
- Ongoing ARIA Assessments

Ongoing ARIA Assessments

CDER's Medical Product Assessments in Sentinel's Active Risk Identification and Analysis (ARIA) System

This page describes FDA's active and ongoing analyses in the Sentinel System as part of the implementation of section 505(o) of the Federal Food, Drug, and Cosmetic Act, added by section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). FDA uses the Sentinel System to conduct active surveillance of the safety and effectiveness of the products FDA regulates. FDA conducts safety assessments in [ARIA](#) for the following purposes, as described in Section 505(o)(3)B):

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk


The appearance of a drug on this page does not mean that FDA has concluded that the drug has the listed risk. It means that FDA has identified a potential safety issue, but it does not mean that FDA has identified a causal relationship between the drug and the listed risk. FDA is not suggesting that healthcare providers should not prescribe the drug or that patients taking the drug should stop taking the medication while an evaluation of the potential safety issue is being conducted. Patients who have questions about their use of the identified drug should contact their health care provider.

All final results will be posted in the [Assessments](#) section after the analysis is completed. Data obtained through Sentinel are intended to complement other types of data, such as adverse event reports, published study results, and clinical trials to inform regulatory decisions. Any public health actions taken by FDA regarding products involved in Sentinel analyses are communicated through existing channels.

Resources

- FDA Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Drug Safety, April 2011)
- FDA Information by Drug Class
- FDA Index to Drug Specific Information

Where to Find Ongoing Analyses



Sentinel

Home >> Drugs >

DRUGS

- About C...
- Assessm...
- Ongoing

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

Drug Name	Outcomes Being Assessed	Date Posted
Siliq (brodalumab)	<ul style="list-style-type: none"> • Neutropenia • Serious infections • Myocardial infarction and stroke • Lymphoma 	8/23/2017
Stelara (ustekinumab)	<ul style="list-style-type: none"> • Serious Infection 	8/23/2017

ARIA Analyses for Safety Issues Identified Post-Approval

Drug Name	Outcomes Being Assessed	Date Posted
Ranexa (ranolazine)	<ul style="list-style-type: none"> • Seizures 	8/23/2017
Antipsychotic drugs	<ul style="list-style-type: none"> • Stroke • Use as adjuvant therapy 	8/23/2017
Continuous or extended cycle oral contraceptives	<ul style="list-style-type: none"> • Venous thromboembolism 	8/23/2017
Gadolinium-based contrast agents	<ul style="list-style-type: none"> • Seizures 	8/23/2017
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	<ul style="list-style-type: none"> • Stroke 	8/23/2017

Making Sentinel Available to Others

The screenshot shows the Sentinel website interface. At the top left is the Sentinel logo. A search bar on the top right contains the text "Type here to search...". A navigation menu below the search bar includes "Sentinel", "Drugs", "Vaccines, Blood & Biologics", "FDA-Catalyst", and "Communications". A "Report Finder" button is located on the right side of the navigation bar. The breadcrumb trail reads "Home >> Sentinel >> Reagan-Udall Foundation and IMEDS".

ABOUT

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- Collaborators
- Coordinating Center
- Privacy and Security
- ▶ The Sentinel System Story
- Reagan-Udall Foundation and IMEDS

Reagan-Udall Foundation and IMEDS

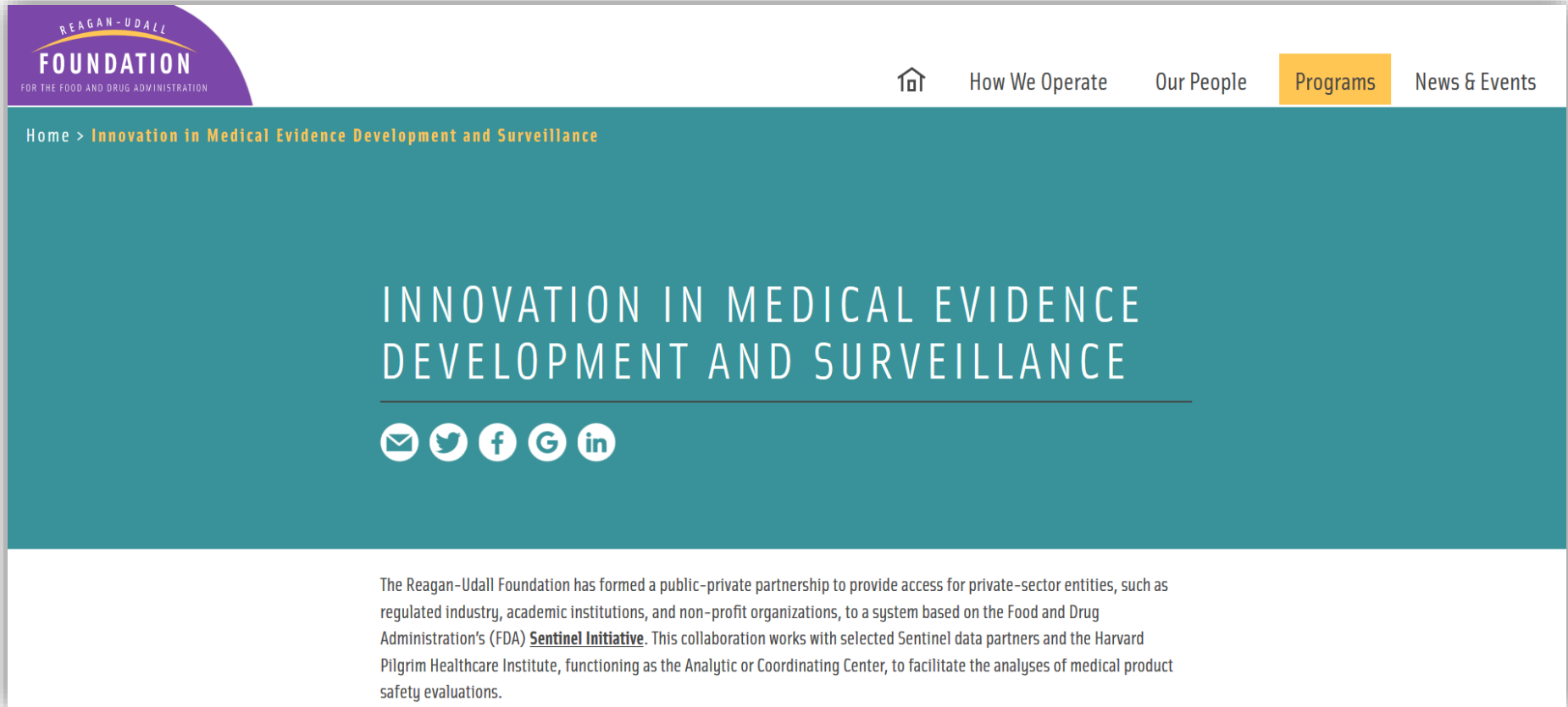
FOR THE FOOD AND DRUG ADMINISTRATION

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](#).

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IMEDS and Sentinel



The screenshot shows the website for the Reagan-Udall Foundation. The top navigation bar includes a home icon, "How We Operate", "Our People", "Programs" (highlighted in orange), and "News & Events". The main content area has a teal background with the title "INNOVATION IN MEDICAL EVIDENCE DEVELOPMENT AND SURVEILLANCE" in white. Below the title are social media icons for email, Twitter, Facebook, Google+, and LinkedIn. A paragraph of text describes the foundation's partnership with the FDA's Sentinel Initiative.

REAGAN-UDALL
FOUNDATION
FOR THE FOOD AND DRUG ADMINISTRATION

Home > [Innovation in Medical Evidence Development and Surveillance](#)

INNOVATION IN MEDICAL EVIDENCE DEVELOPMENT AND SURVEILLANCE

[✉](#) [🐦](#) [f](#) [G](#) [in](#)

The Reagan-Udall Foundation has formed a public-private partnership to provide access for private-sector entities, such as regulated industry, academic institutions, and non-profit organizations, to a system based on the Food and Drug Administration's (FDA) **Sentinel Initiative**. This collaboration works with selected Sentinel data partners and the Harvard Pilgrim Healthcare Institute, functioning as the Analytic or Coordinating Center, to facilitate the analyses of medical product safety evaluations.

<http://reaganudall.org/innovation-medical-evidence-development-and-surveillance>

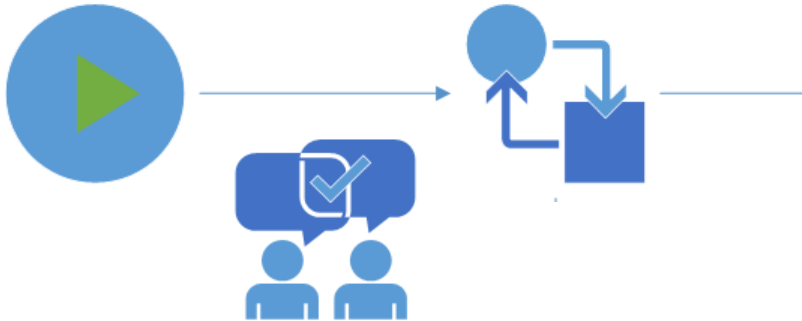
Query Development Process

Step 1

Step 2

Concept Brief

Test Specifications



Translate Analysis Plan
to ARIA Tools

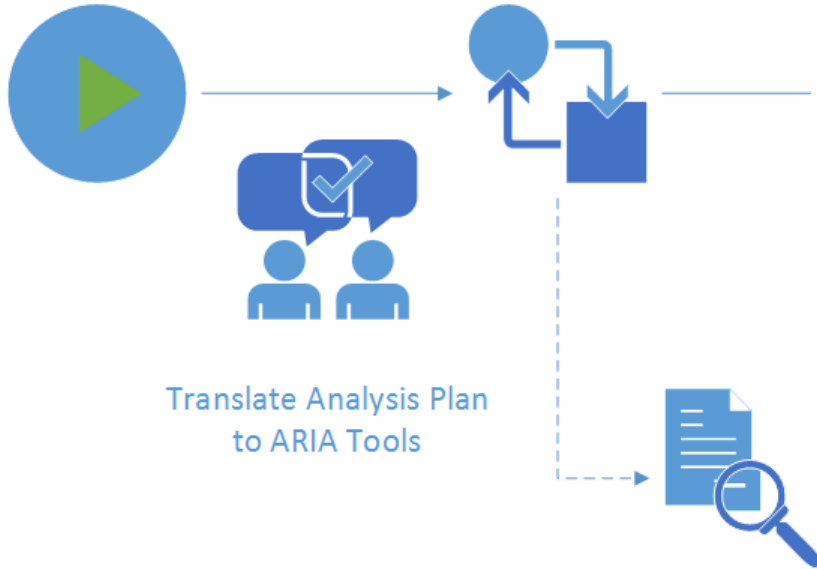
Query Development Process

Step 1

Step 2

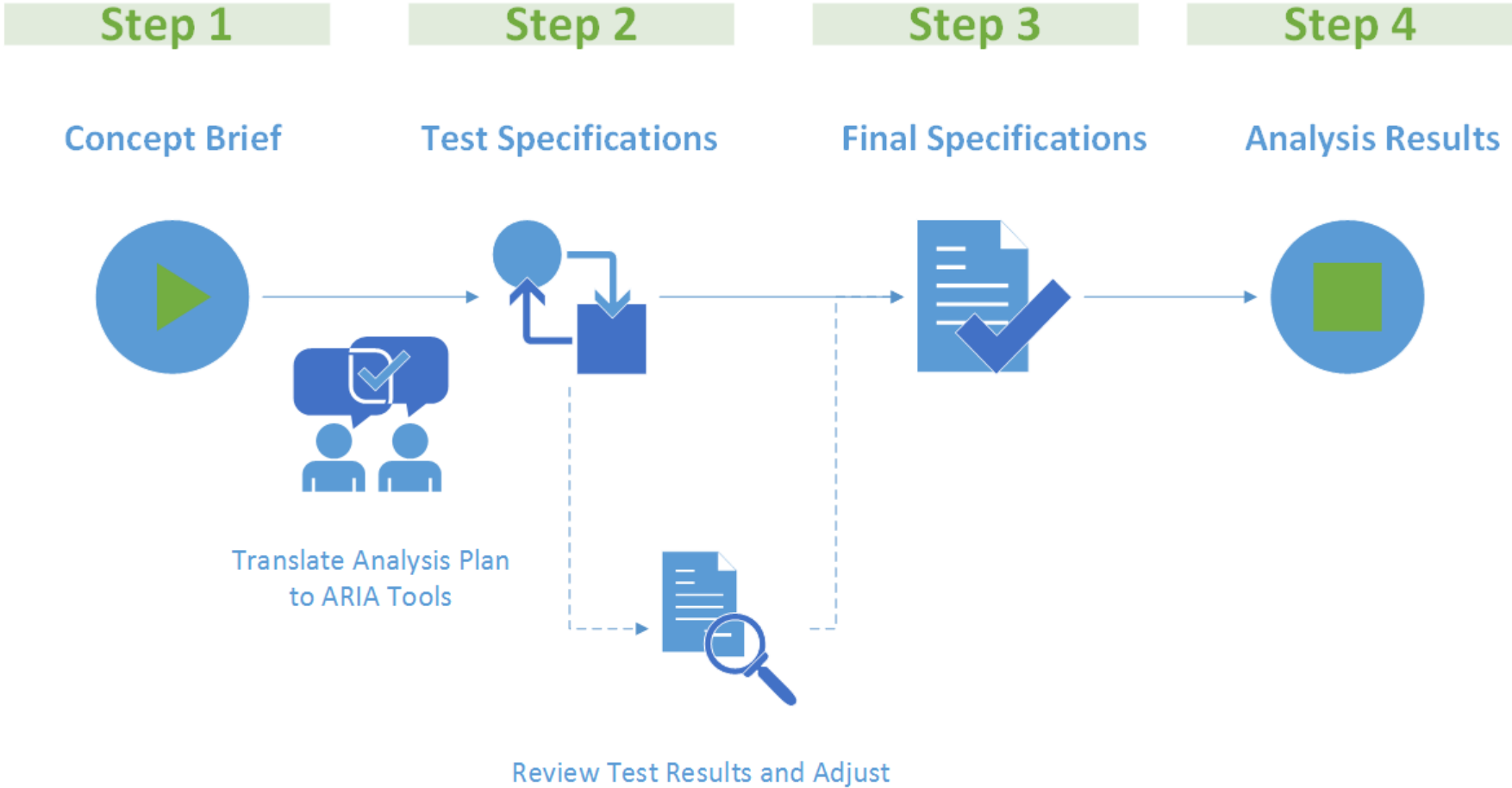
Concept Brief

Test Specifications

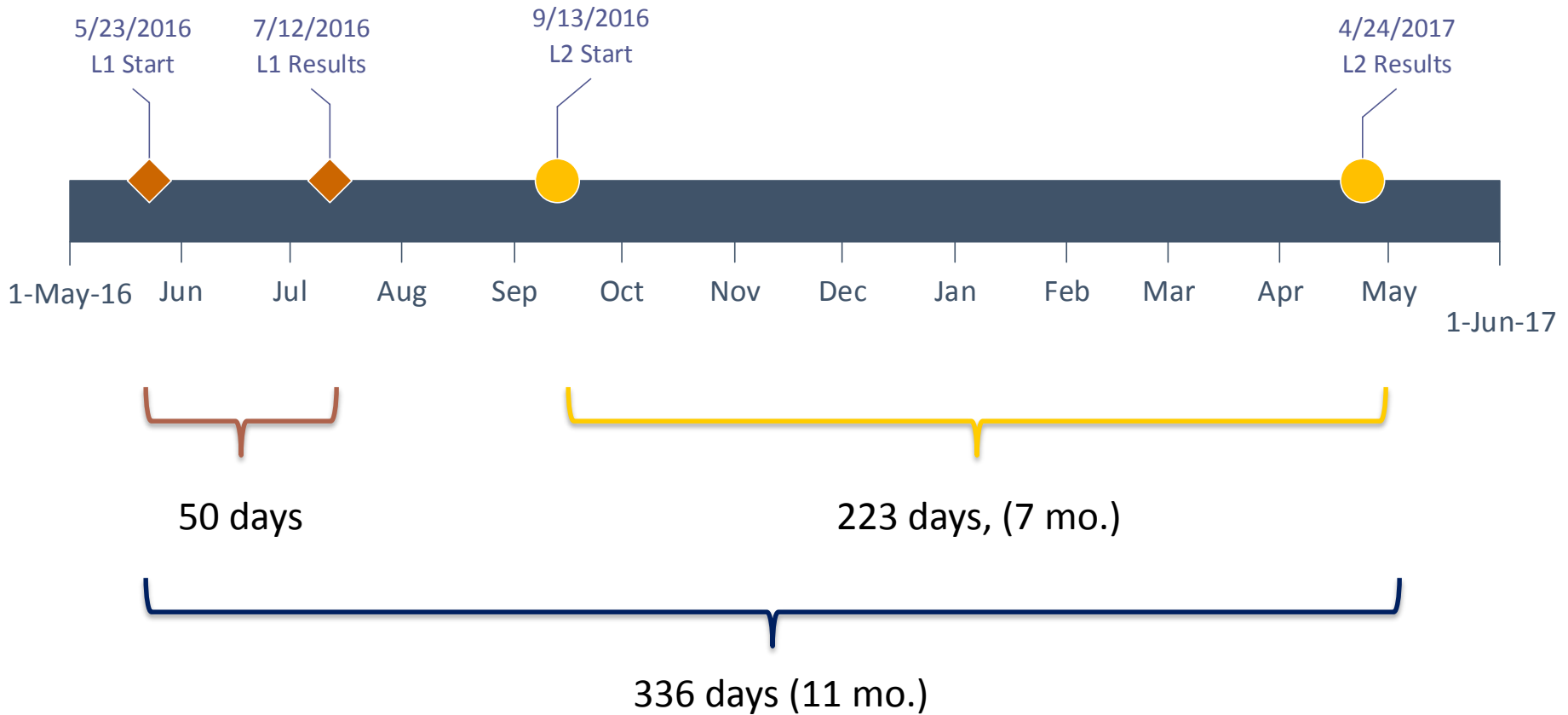


Review Test Results and Adjust

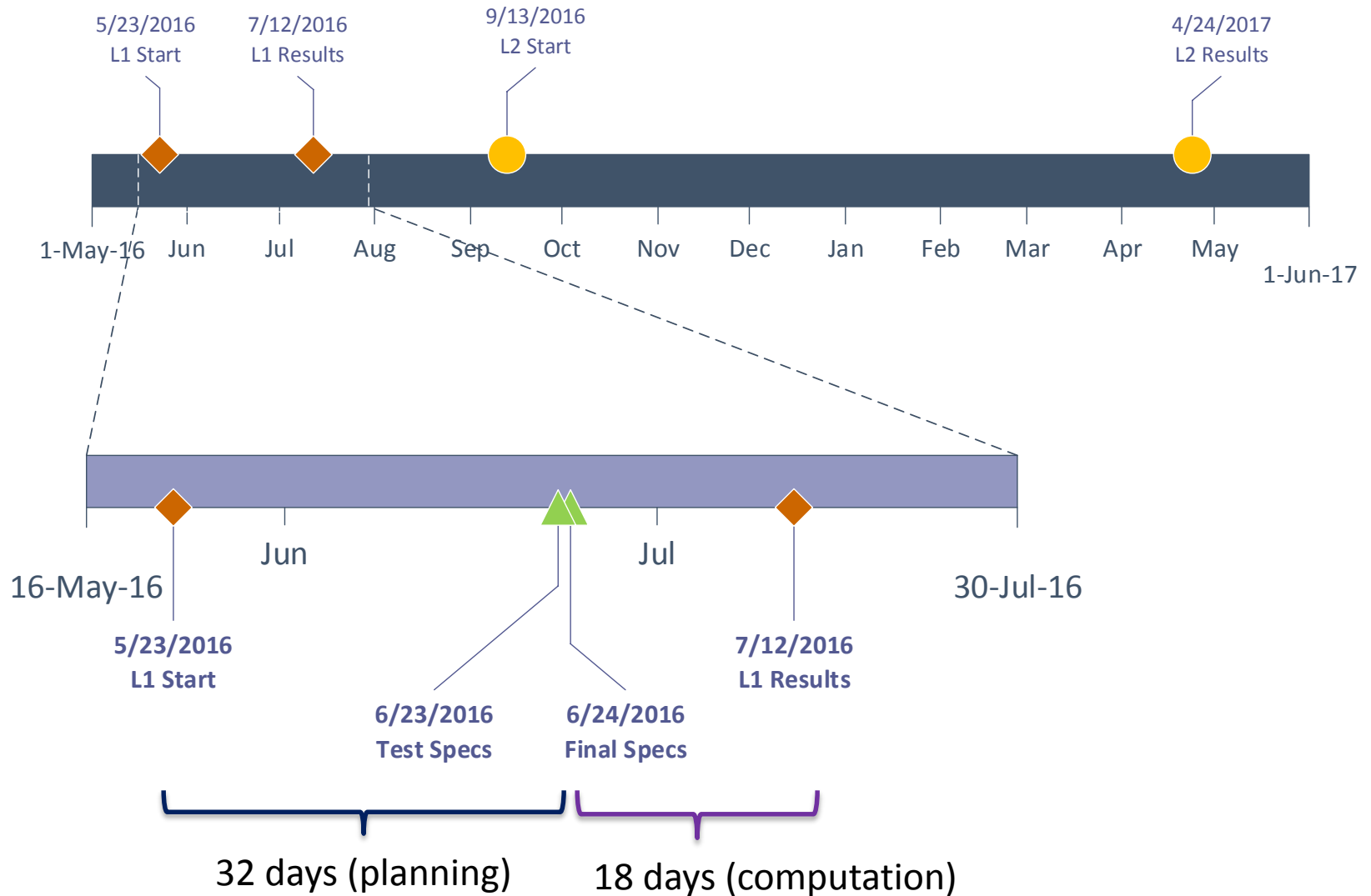
Query Development Process



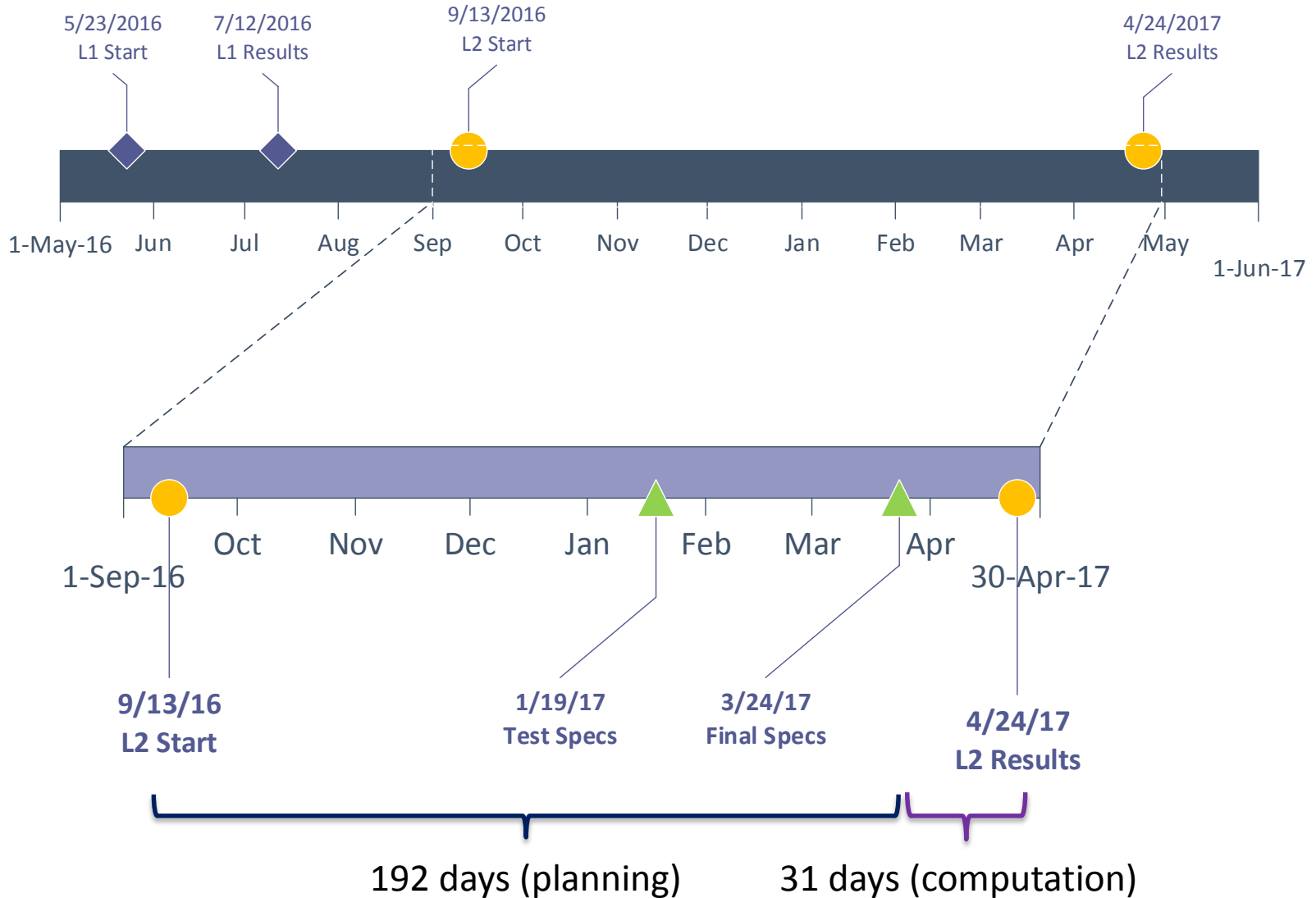
Example Timeline: Oral Contraceptives



Detailed Timeline: L1



Detailed Timeline L2





Total Time to Assess Safety Issue

Safety Issue	Type and No. Analyses	Total Time, days
Ranexa (ranolazine)	ST, L1, L2	302 (10 mo.)
Gadolinium contrast agents	L1, L2	741 (24 mo.)
Antipsychotics	L1, L2	277 (9 mo.)
Oral contraceptives	L1, L2	336 (11 mo.)

- 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

