An Assessment of the Sentinel System:

Focus on the Active Risk Identification and Analysis (ARIA) System

Prepared by the Sentinel Operations Center

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number 75F40119D10037.

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1. Introduction

In the US Food and Drug Administration Amendments Act of 2007, the Food and Drug Administration (FDA) was mandated to establish a postmarket active risk identification and analysis (ARIA) system that contained data from 100 million patient lives to monitor risks associated with drug and biologic products using data from disparate sources to complement the FDA's existing postmarket capabilities. In response, FDA established the Sentinel Initiative. Within the Sentinel Initiative, a core program is the Sentinel System, a national medical product safety surveillance system with one of the largest curated multi-site distributed databases dedicated to medical product safety in the world. The Sentinel System supports the FDA's mission to protect public health and monitor the safety of FDA-regulated medical products. The objectives of this report are to review the activities conducted within the Sentinel System spanning federal fiscal years 2018-2022, which align with the period of the sixth term of the Prescription Drug User Fee Act (PDUFA VI). In this report, unless otherwise noted, "Sentinel" will refer to the Sentinel System.

Sentinel System Overview

The Office of Surveillance and Epidemiology within the Center for Drug Evaluation and Research oversees Sentinel. In 2019, Sentinel implemented a structure of three distinct centers, each with areas of specialty, that collaborate to advance regulatory science:

- The Operations Center is led by Harvard Pilgrim Health Care Institute and primarily focuses on maintaining Sentinel's core data resources and analytic tools. They also support FDA in executing regulatory-grade analyses, including those performed within Sentinel's Active Risk Identification and Analysis (ARIA) system (described in further detail below).
- The Innovation Center is led by four lead hubs, each focusing on a particular area of innovation, in collaboration with Harvard Pilgrim Health Care Institute. The Innovation Center serves as a test bed to identify, develop, and evaluate innovative methods to study drug safety and effectiveness.
- The Community Building and Outreach Center is led by Deloitte Consulting LLP. The primary function is to develop and engage the Sentinel community and expand Sentinel's user base outside of the FDA.

Data Resources and Analytic Tools

The cornerstone of Sentinel is the Sentinel Distributed Database. The Sentinel Distributed Database provides FDA access to a network of Sentinel Data Partners providing administrative claims and claims-linked electronic health record (EHR) data, as well as Medicare fee-for-service claims data, and Medicaid claims data in the Sentinel Common Data Model format. The Sentinel Common Data Model design emphasizes transparency and usability by various stakeholders and preserves data elements as close as possible to how they appear in the original record, preventing the loss of detail that can occur with mapping. Over time, the Sentinel Common Data Model has expanded to broaden Sentinel's study capabilities.

As of 2021, the Sentinel Distributed Database contained over 788 million person-years of data covering over 360 million unique patient identifiers between 2000 and 2021.[1] A significant accomplishment in the past five years was the addition of 100% Medicare fee-for-service data. This data source includes more than 70 million patient lives and constitutes approximately 15% of the total Database, offering important insights into the population 65 years of age and older.

[1] A unique patient identifier is not equivalent to a unique patient life. If patients move between health plans, they may have more than one patient identifier. However, most patients would only appear in one database at a given calendar time.

In response to the COVID-19 pandemic, Sentinel established a version of the Sentinel Distributed Database with a subset of existing partners with "fresher", more up-to-date adjudicated data, referred to as the Rapid Distributed Database. This resource also includes COVID-19 diagnostic laboratory test results. Participating Data Partners refresh their data every 1-2 months rather than the standard refresh timing for the Sentinel Distributed Database of every 3-12 months (varies by Data Partner). The Rapid Distributed Database is a resource available to FDA for both COVID-19-related analyses and regulatory analyses that benefit from fresher adjudicated data.

Sentinel's standardized analytic tools enable a range of pharmacoepidemiologic study designs to be performed on any data in the Sentinel Common Data Model format. These analytic tools are standardized SAS® statistical software code packs and may be parameterized for custom analyses. Sentinel's use of standardized tools enables faster and reproducible analyses in a multi-site setting. Sentinel's analytic tools are publicly available and accompanied by user documentation. Over time, Sentinel has continued to enhance its analytic tools. Two critical developments over the past five years were 1) enabling the capability to conduct comparative inferential analyses for infant outcomes following medical product exposure in pregnancy and 2) analytic ability to conduct signal identification studies.

While medical claims data is the backbone of the Sentinel Distributed Database, Sentinel also has access to multiple large EHR data sources. Sentinel worked with several EHR-based Data Partners during the COVID-19 pandemic. In May 2020, Sentinel began collaborating with TriNetX, which includes EHR data from approximately 110 million patients from 70 health care organizations in 29 states. Sentinel also engaged with the National Patient-Centered Clinical Research Network (PCORnet) to enable FDA to run analyses within their EHR data network. Another key partner is HCA Healthcare, which provides a rich source of inpatient EHR from 140 hospitals that capture approximately 35,000 weekly hospitalizations. Each data source has unique benefits and contributions, allowing Sentinel to triage study questions to the most appropriate data source available.

Sentinel Innovation Center

Sentinel continues to develop its data resources and analytic tools to meet FDA's needs. One key area of expansion is growing Sentinel's ability to use EHR data for medical product safety and effectiveness assessment. Established in 2019, the Sentinel Innovation Center works to identify, develop, and evaluate innovative methods to study drug safety and effectiveness using real-world data. It was created to address some of the strategic goals described in the Sentinel Five-Year Strategy and supports FDA's Medical Data Enterprise Initiative to build a system containing EHRs from ten million lives. Projects are focused in the following strategic priority areas:

1. Data Infrastructure: The Innovation Center is developing a principled approach to include new data elements from structured and unstructured EHR data into the Sentinel Common Data Model. The Innovation Center is also investigating approaches to detect and mitigate data inconsistencies and to harmonize data across multiple EHR data sources.

2. Feature Engineering: A vast amount of potentially useful information is stored as unstructured data in visit notes, radiology reports or images, and discharge summaries. Initiatives are underway to develop feature extraction methods assisted by natural language processing and tools and to improve generalizability and transportability of these approaches across systems.

3. Causal Inference: To clarify challenges in developing and applying causal methods that leverage both claims and EHR data sources, the Innovation Center is developing a causal analysis framework and developing and testing advanced statistical methods to improve causal inference and expand the acceptance of use of real-world data for regulatory decision making.

4. Detection Analytics: EHRs offer a potentially promising complementary source of information for medication safety signal detection but may require tailored approaches to account for and leverage

differences in data content and structure compared to administrative claims. The Innovation Center is developing a methodological framework and is conducting empirical evaluations to identify and test the most promising approaches for EHR-based signal detection.

FDA's Utilization of Sentinel to Protect Public Health

FDA has utilized Sentinel to monitor and assess drug safety and utilization, provide support for FDA's COVID-19 response, and support the work of other FDA offices outside of the Center for Drug Evaluation and Research.

Monitoring and Assessing Drug Safety and Utilization

A central function of Sentinel is implementation of the ARIA system for drug safety surveillance. In the FDA Amendments Act of 2007, the FDA was required to establish a postmarket active risk identification and analysis (ARIA) system that contained data from 100 million patient lives for monitoring risks associated with drug and biologic products using data from disparate sources to complement the FDA's existing postmarket capabilities. The ARIA system is currently defined by its component parts of data in the Sentinel Common Data Model, the Sentinel Distributed Database, and Sentinel's analytic tools.

Two core uses of the ARIA system are to:

1) Investigate a safety concern under section 505(o)(3) of the Federal Food, Drug, and Cosmetic (FD&C) Act, in lieu of a postmarket requirement (PMR) to drug sponsors. If FDA is considering requiring a sponsor to conduct a postmarket study to evaluate a safety concern, FDA must first assess whether that safety concern can be studied in the FDA Adverse Event Reporting System and the ARIA system. If FDA determines that the ARIA system is sufficient to evaluate the safety concern, FDA is obligated to conduct that study in the ARIA system rather than require a post-marketing study.

2) As part of FDA's routine pharmacovigilance, conduct studies to address identified safety concerns or other regulatory questions to support FDA's decision-making. This includes analyses that may support Drug Safety-related Labeling Changes or the issuance of Drug Safety Communications, among other regulatory activities.

Safety concerns evaluated in the ARIA system are tracked and defined as unique medical product and health outcome pairs. From 2016 to 2021, 133 unique safety concerns have been or are being assessed in the ARIA system. Of those, 22 safety concerns are being assessed in Sentinel in place of a PMR. Assessments have been completed for 54 of the 133 safety concerns assessed in the ARIA system while the remainder are still being assessed at the time of this report. FDA documents the regulatory impacts of completed ARIA system assessments, a summary of which is displayed in Figure 1 below.

The Center for Drug Evaluation and Research has also used Sentinel to support regulatory work not directly related to evaluating postmarket safety signals. The Office of Surveillance and Epidemiology used the ARIA system infrastructure to support the Risk Evaluation and Mitigation Strategies (REMS) drug safety program and has analyzed several medical products associated with a REMS program. The Office of Generic Drugs has utilized the ARIA system for multiple analyses assessing utilization and switching patterns of generic and brand name products. The Office of Medical Policy engaged with Sentinel in 2018 to perform a series of demonstration projects in support of the 21st Century Cures Act and oversees the FDA-Catalyst program, which combines data collected from interactions with patients or providers with the Sentinel data infrastructure. A key FDA-Catalyst project was the Implementation of a Randomized Controlled Trial to Improve Treatment with Oral Anticoagulants in Patients with Atrial Fibrillation (IMPACT-AFib) project, in which the FDA used a subset of the Sentinel Distributed Database to identify patients with atrial fibrillation who were

provided with an educational intervention aimed at increasing the use of oral anticoagulants in accordance with guideline-based best practices.[1]

FDA records instances where the ARIA system is found insufficient to address an identified safety concern and a sponsor is required to conduct an observational PMR study. This is done to promote transparency and inform Sentinel program development priorities. From 2016 through 2021, the top reasons for ARIA system insufficiency included lack of clinical data, absence of validated algorithms for clinical outcomes, lack of linkage to required data sources, and the inability of Sentinel's analytic tools to perform the required analysis. The latter is largely driven by a need to detect unspecified adverse outcomes among pregnant women exposed to a drug – i.e., data mining methods. There is ongoing work within Sentinel to build and validate signal identification methods in direct response to this gap.

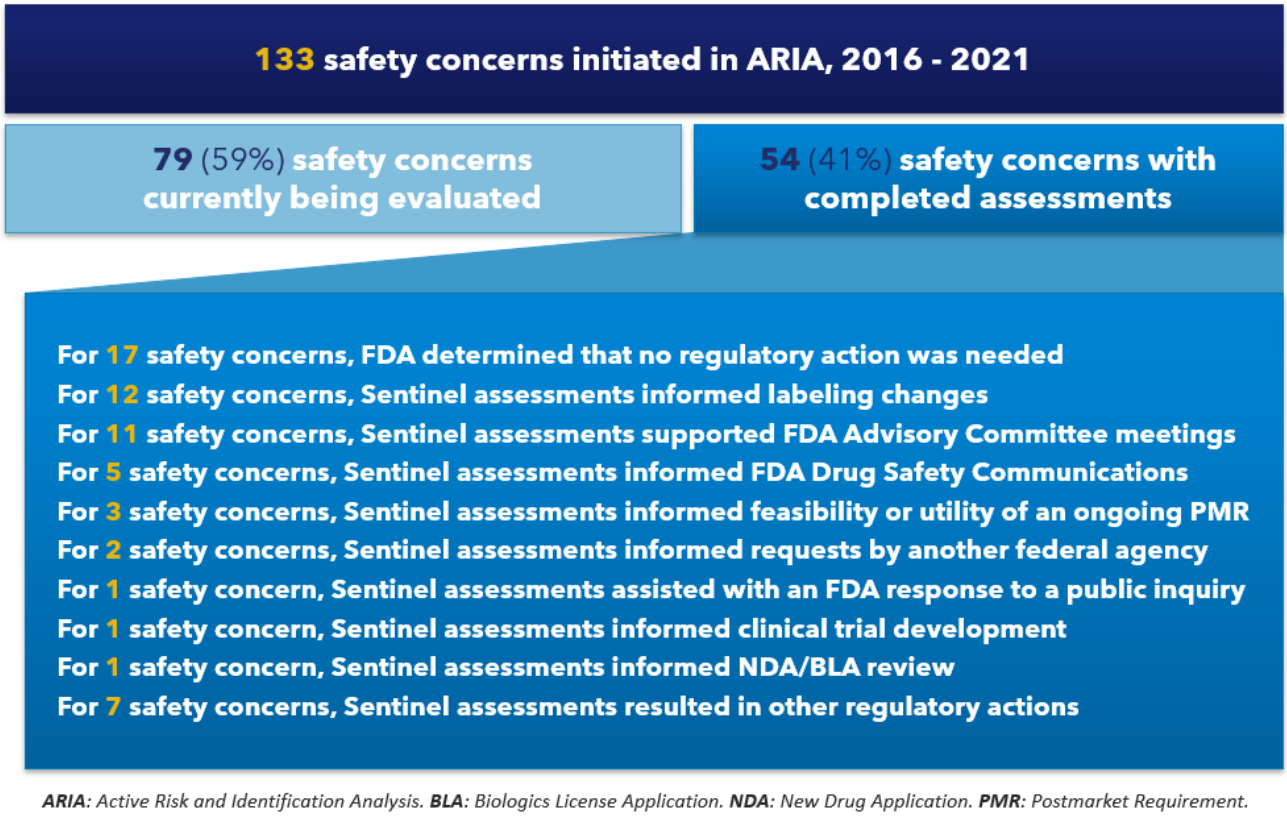


Figure 1: Regulatory Impacts of ARIA Assessments as of December 31, 2021. *This graphic depicts the impacts of Sentinel ARIA assessments. A single safety concern may result in one or more regulatory impact(s).*

COVID-19 Response

FDA was able to use Sentinel's established data sources, collaborations, and processes to support their COVID-19 response. Sentinel implemented a multi-pronged data approach and conducted numerous studies to support the FDA's response to COVID-19.[2] Highlights of COVID-19 related projects include developing validated claims-based algorithms for identifying hospitalized COVID-19 patients, creating a master protocol for assessing the natural history of COVID-19, describing the national history of coagulopathy among COVID-19 patients, and assessing the association between race and ethnicity and critical COVID-19 and in-hospital death. Sentinel brought on new data resources to enable these projects, including increasing the refresh frequency of existing data sources to provide

fresher data and bringing on new Sentinel Data Partners to provide inpatient and ambulatory electronic health record (EHR) data. These data sources have diversified the real-world data available to FDA for regulatory decision-making.

Uses of Sentinel Outside of the Center for Drug Evaluation and Research

The Sentinel infrastructure has also been leveraged by offices outside of the Center for Drug Evaluation and Research. The Office of Counterterrorism and Emerging Threats engaged with Sentinel as part of the Medical Countermeasures Initiative. Three activities were conducted to understand the potential contribution of Sentinel to study medical countermeasure safety and effectiveness and develop capacity for response during a public health emergency. Influenza served as the use case in these three studies.[3,4,5] In March of 2020, Sentinel was able to leverage the prior work conducted under one of the activities with HCA Healthcare and pivot to conduct analyses on hospitalized COVID-19 patients at the FDA's request.[2]

The Center for Biologics Evaluation and Research also collaborated with Sentinel to support postmarket surveillance of biological products including using the Sentinel Distributed Database for more than 45 analyses through 2021. The Center for Devices and Radiological Health also has engaged with Sentinel. Of note is a series of analyses investigating the safety of a permanently implanted birth control device for women.

Sentinel as a National Resource

Sentinel is a repository of curated longitudinal data for a large, geographically diverse population. Sentinel's data are the largest resource of its kind. Therefore, Sentinel strives to be a national resource through its partnerships with organizations external to the FDA and through efforts to make its tools and resources accessible to the field. A key example is the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program, launched by the Reagan-Udall Foundation for the Food and Drug Administration. IMEDS has completed or has ongoing work with nine projects from five industry sponsors[6]. The National Institutes of Health (NIH) Pragmatic Trials Collaboratory is another mechanism that enables investigators funded by the NIH and other not-for-profit sponsors to collaborate with Sentinel Data Partners. It fully leverages Sentinel's data, methods, tools, and querying infrastructure, but can also support direct contact with providers and payors to collect new information in support of randomized clinical trials.[7,8,9,10] The Biologics & Biosimilars Collective Intelligence Consortium is another institution that has leveraged Sentinel's infrastructure to evaluate the real-world safety and effectiveness of biologics, including biosimilars.[11,12,13,14] Finally, FDA collaborated with the Centers for Disease Control and Prevention (CDC) to utilize Sentinel to answer public health questions. Analyses have included utilization of single-dose doxycycline for Lyme disease prophylaxis, incidence and prevalence Type 1 and Type 2 diabetes, and identification of latent tuberculosis.

Sentinel is committed to transparency of the design and results of all regulatory analyses. The Sentinel Initiative website serves as a key mechanism for the public to engage with Sentinel. A key feature is the Drug Studies page, a central repository of studies led by the Center for Drug Evaluation and Research, and a page on FDA Safety Communications & Labeling Changes to highlight the ARIA system's regulatory impacts. Sentinel also maintains a Git website to make analytic code and documentation available to the public. Both Sentinel's Git website and main website support the FDA's applicant notification[15] process by providing access to analytic code and results from assessments performed in response to a safety concern. As of December 31, 2021, 30 analytic packages from completed analyses were available for download and reports from 245 analyses are available on the Sentinel website. Sentinel also organizes annual public training sessions, held online and in-person, that provide opportunities for interested parties to learn more about the tool capabilities, with attendance increasing annually.

Sentinel contributes to the field of pharmacoepidemiology and informatics through publication of peer-reviewed journals and attendance at scientific conferences. Sentinel has published 200 papers in more

than 50 distinct peer-reviewed journals, including New England Journal of Medicine, Journal of the American Medical Association, Annals of Internal Medicine, Journal of the American Medical Association Internal Medicine, and Diabetes Care. Since 2016, Sentinel has delivered 162 presentations and posters at scientific conferences.

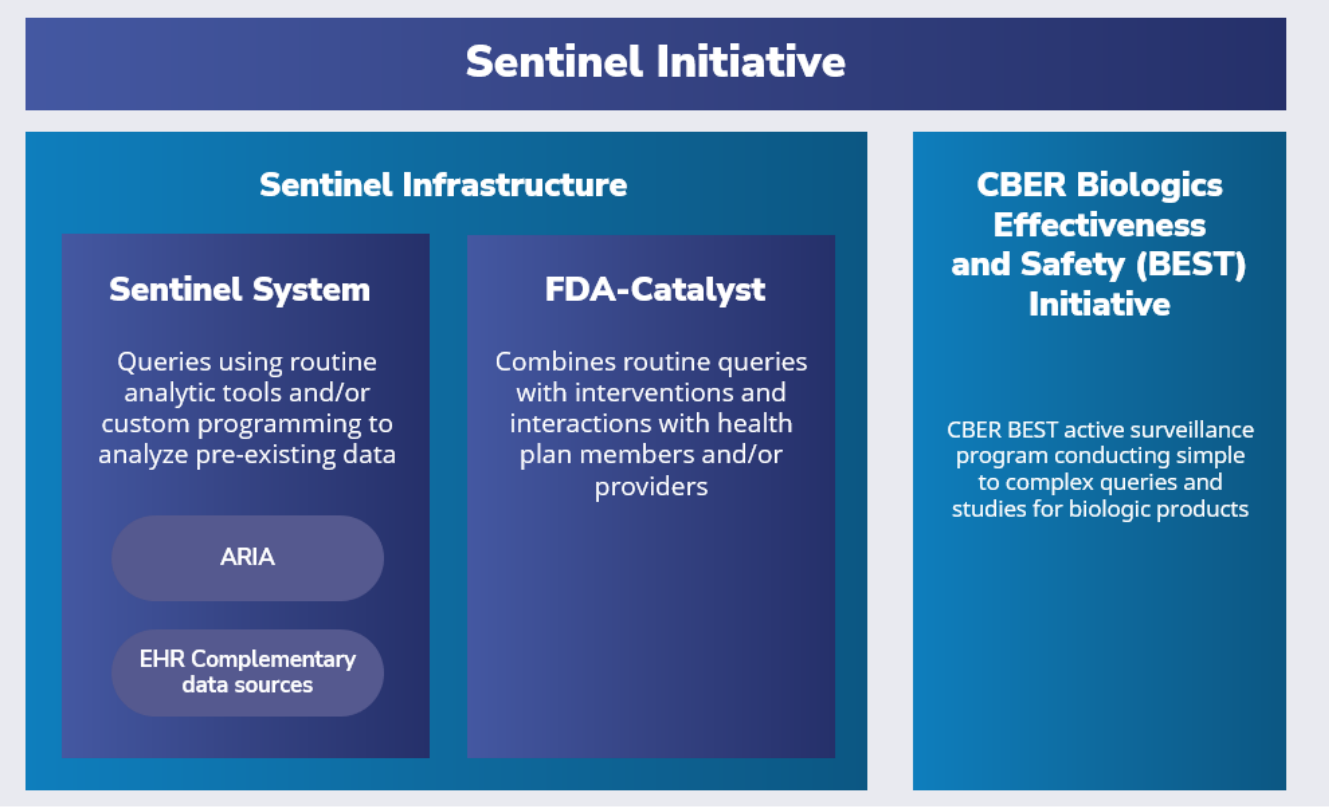
Summary

FDA's investment in and utilization of Sentinel directly supports their mission of protecting public health through robust drug safety surveillance. The ARIA system has been a central component of this work, but FDA has also leveraged the data and resources of Sentinel for other work within FDA (including their COVID-19 response) and made these resources available to other stakeholders, furthering the vision of Sentinel becoming a national resource. The following report provides more detail on the activities of Sentinel to illustrate the various ways FDA has made use of the program.

2. Sentinel System Overview

2.1. Structure and Background

The FDA Amendments Act of 2007 mandated FDA to establish a program to monitor and assess medical product safety in the postmarket environment. In response to this legislation, FDA established the Sentinel Initiative in 2008 (Figure 2). The Sentinel Initiative encompasses activities performed by Sentinel (i.e., the Sentinel System and FDA-Catalyst, which largely rely upon common data and analytic tool infrastructure), and activities performed by the Biologics Effectiveness and Safety Initiative overseen by the Center for Biologics Evaluation and Research. In Sentinel specifically, scientific analyses are conducted using standardized analytic tools to analyze pre-existing data. A key component of Sentinel is the ARIA system, a postmarket surveillance system based on a large, distributed dataset of electronic healthcare data. This report will cover activities performed in the Sentinel over the past five years.



ARIA: Active Risk Identification and Analysis

Figure 2: Sentinel Initiative Structure: *The Sentinel Initiative represents activities using Sentinel's infrastructure through the Sentinel System and FDA-Catalyst, in addition to the Biologics Effectiveness and Safety (BEST) System. In this report, "Sentinel" will refer to the Sentinel System, unless otherwise stated.*

In 2019, the Sentinel System implemented a structure of three distinct centers, each with areas of specialty, that collaborate to advance regulatory science:

- Sentinel Operations Center is led by Harvard Pilgrim Health Care Institute. The primary functions of the Operations Center are to maintain and enhance core data sources and tools, including the Sentinel Distributed Database and Sentinel's standardized analytic tools, and support FDA in

designing and distributing regulatory-grade analyses to monitor and assess medical product safety. The Operations Center implements the ARIA system.

- Sentinel Innovation Center is led by the Division of Pharmacoepidemiology and Pharmacoeconomics of Brigham and Women's Hospital and Harvard Medical School, Duke Clinical Research Institute, Vanderbilt University Medical Center Department of Biomedical Informatics, and Kaiser Permanente Washington Health Research Institute & University of Washington School of Public Health, in collaboration with Harvard Pilgrim Health Care Institute. The Innovation Center serves as a test bed to identify, develop, and evaluate innovative methods to study drug safety and effectiveness. A core goal of the Innovation Center is to supplement Sentinel's existing data infrastructure with a new system containing electronic health records from ten million lives in support of FDA's Medical Data Enterprise Initiative.
- Community Building and Outreach Center is led by Deloitte Consulting LLP. The primary function of the Community Building and Outreach Center is to develop and engage the Sentinel community and expand the Sentinel System's user base outside of the FDA. This is accomplished by understanding end-user needs and deepening relationships with stakeholders.

Figure 3 presents a timeline of these key Sentinel Initiative milestones.

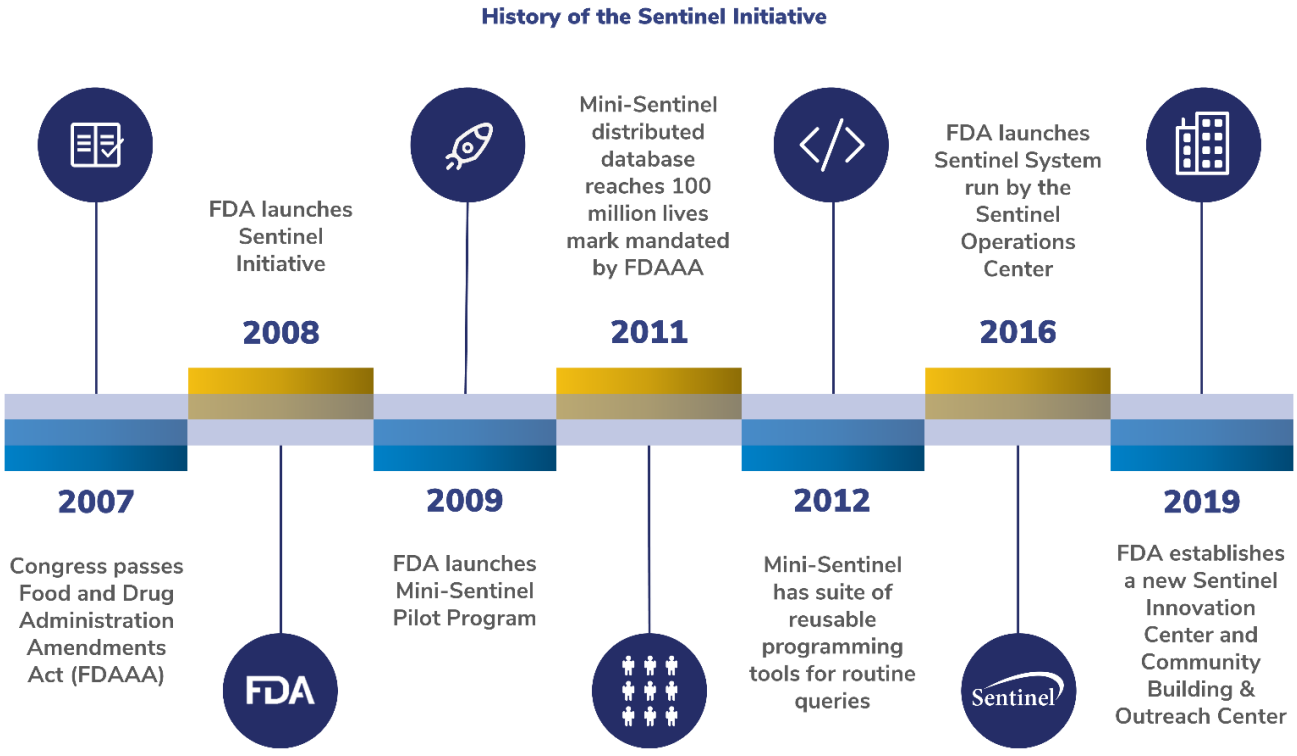


Figure 3: History of the Sentinel Initiative. *The Sentinel Initiative has grown over time and been enhanced to meet FDA's evolving needs.*

2.2. Data Resources and Analytic Tools

2.2.1. Sentinel Distributed Database

As mentioned in the introduction, the cornerstone of the Sentinel System is the Sentinel Distributed Database. The Database provides FDA access to a network of partners providing administrative healthcare claims, claims-linked-to-electronic health record (EHR) data, Medicare fee-for-service claims data, and Medicaid claims data, all formatted into the Sentinel Common Data Model. As of December 2021, the Sentinel Distributed Database contained over 788 million person-years of data covering over 360 million unique patient identifiers with over 15.7 unique medical encounters between 2000 and 2021. The Sentinel Distributed Database contains around 5.8 million linked deliveries. Additional characteristics of the Sentinel Distributed Database are included in routinely refreshed Key Database Statistics.

A major accomplishment in the Prescription Drug User Fee Act (PDUFA VI) period was the addition of 100% Medicare fee-for-service data to the Sentinel Data Partner network. This data source includes more than 70 million individuals and constituted approximately 15% of the total Sentinel Distributed Database as of December 2021. These data offer FDA increased insights into a population 65 years of age and older. The Sentinel Distributed Database also includes and is expanding access to data on Medicaid recipients. Current sources of Medicaid claims data include Tennessee's Medicaid program TennCare via the Department of Health Policy at Vanderbilt University Medical Center and includes over four million patient lives. These data also include birth certificates to link mothers and infants and death registry data.

In early 2020 in response to the COVID-19 pandemic, Sentinel established a version of the Sentinel Distributed Database called the Rapid Distributed Database. This resource also included the addition of COVID-19 diagnostic laboratory results data. The Rapid Distributed Database is comprised of a subset of existing partners that provide more frequent data refreshes, therefore decreasing the standard Sentinel Distributed Database data lag. This supports time-sensitive analyses related to the rapidly evolving COVID-19 pandemic. Participating Data Partners refresh their datasets every 1-to-2-months rather than the 3-to-12-month schedule of Data Partners in the Sentinel Distributed Database. For efficiency, the Rapid Distributed Database only includes data from 2017 and on (compared to 2000 and on in the routine Sentinel Distributed Database) and includes a subset of patients with records in the COVID-19 era. This lighter data footprint enabled a nimble response with rapid refreshes. The Rapid Sentinel Distributed Database is also available to FDA for analyses not related to COVID-19 to support projects where freshness of data is more important than overall patient volume or a long observation period.

2.2.2. Sentinel Common Data Model

The Sentinel Common Data Model represents a standard data structure and format for electronic healthcare data. Data stored in the Sentinel Common Data Model may be analyzed by the same analytic code when distributed across multiple sites. The design of the Sentinel Common Data Model emphasizes transparency, comprehensive documentation, and usability by a variety of stakeholders including FDA, academia, and industry. Sentinel Data Partners actively contributed to its development during the Mini-Sentinel phase of the project, providing on-the-ground input and expertise.

The Sentinel Common Data Model preserves data elements as close as possible to how they appear in the original record. This prevents the loss of detail that can occur with data mapping and is the best analogue to primary data collection like that in clinical trials. This provides the FDA with flexibility in designing studies using Sentinel data and ensures full understanding of the underlying data contributing to studies used for regulatory decision making. The Sentinel Common Data Model allows for use of many coding terminologies, including ones used by international collaborators, to enable native data streams to maintain their original data format. It is also firmly grounded in a concept of

enrollment in a health system to enable longitudinal studies that require complete capture of patient information over time. FDA's requirement for complete capture of exposures and adverse outcomes in observational data highlights the rigorous requirements of data declared fit for purpose for pharmacoepidemiologic studies grounded in causal inference.

The initial focus of the Sentinel Common Data Model centered on structured data that was highly interoperable and could achieve the necessary 100 million lives requirement set forth by Congress in the FDA Amendments Act of 2007. Administrative claims data best met these requirements as these data are heavily audited to ensure accurate payment and rely on existing well-documented code structures, such as the World Health Organization's International Classification of Diseases (ICD) standard.

Over time, the Sentinel Common Data Model has expanded to broaden Sentinel's study capabilities. Figure 4 provides a visual of enhancements to the Sentinel Common Data Model as they have been released over time, with additional detail on development milestones provided in Appendix B: Implementation of the Sentinel Distributed Database. A major focus has been incorporating semi-structured data elements such as laboratory test results, vital signs, and inpatient pharmacy data derived from EHRs and clinical laboratory records. Another major initiative was developing the capability to link mothers and their infants in support of assessments of neonatal outcomes following medical product exposure in pregnancy. More recently, the Sentinel Common Data Model added a prescribing table to capture prescriptions distinct from dispensed medications. There are plans to expand the Sentinel Common Data Model to include a patient-reported measures tables to capture information from patient surveys and physician-administered clinical instruments (e.g., Columbia-Suicide Severity Rating Scale).

Beginning in 2018, Sentinel collaborated with the United Kingdom's Clinical Practice Research Datalink to transform a sample of its Aurum primary care medical record data into the Sentinel Common Data Model. Sentinel has since also worked with organizations in Canada and Denmark to transform host country databases into the Sentinel Common Data Model. These datasets were used for an international study on nitrosamine impurities in losartan, valsartan, and other angiotensin receptor blockers. These collaborations have catalyzed Sentinel Common Data Model improvements to expand the types of data that can be incorporated to accommodate international data sources.

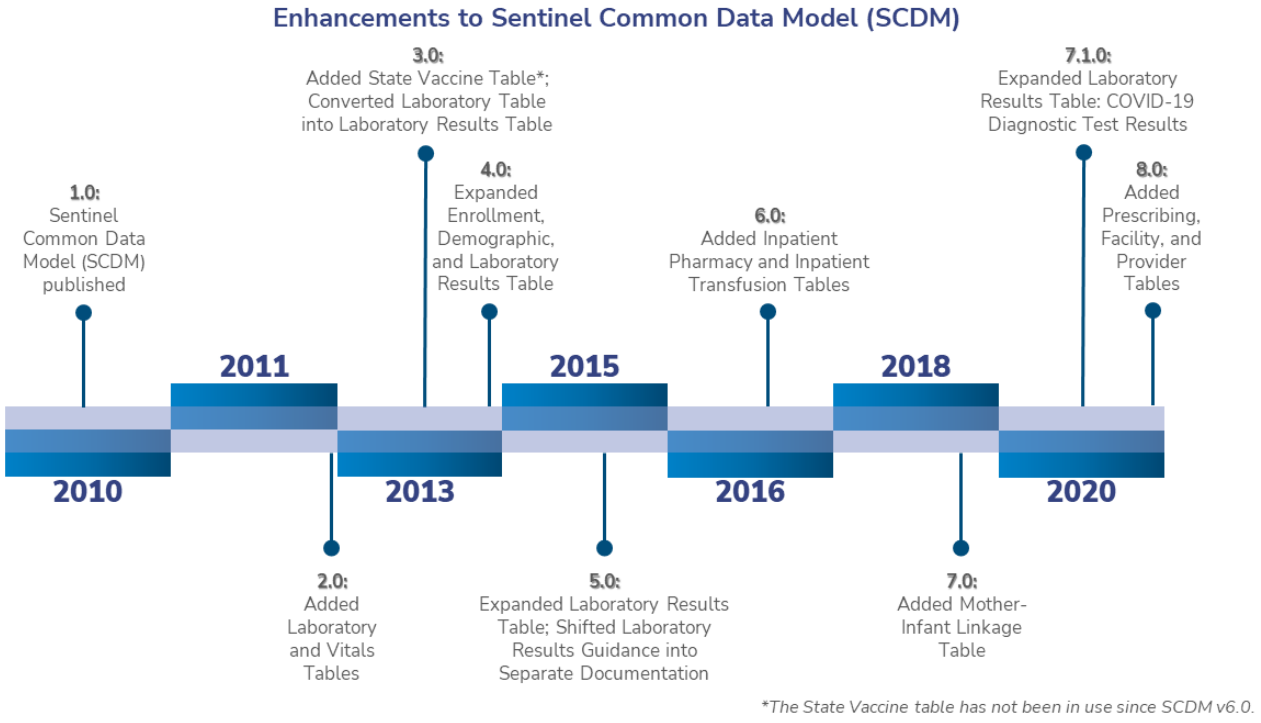


Figure 4: Enhancements to Sentinel Common Data Model. *The Sentinel Common Data Model has evolved over time to support Sentinel's data infrastructure. Releases prior to 2016 took place in the Mini-Sentinel pilot program.*

2.2.3. Sentinel's Analytic Tools

Sentinel's suite of analytic tools allows FDA investigators and other users to efficiently design and implement medical product safety analyses. Sentinel's analytic tools are reusable and can parameterize a wide range of pharmacoepidemiologic study designs (Figure 5). Level 1 analyses are descriptive analyses, Level 2 analyses are comparative analyses, and Level 3 analyses are for prospective sequential surveillance. More detail on the capabilities of Sentinel's analytic tools can be found in Appendix C: Sentinel's Analytic Tools. The SAS code for Sentinel's analytic tools are publicly available and complemented by documentation to support users within and outside of Sentinel.

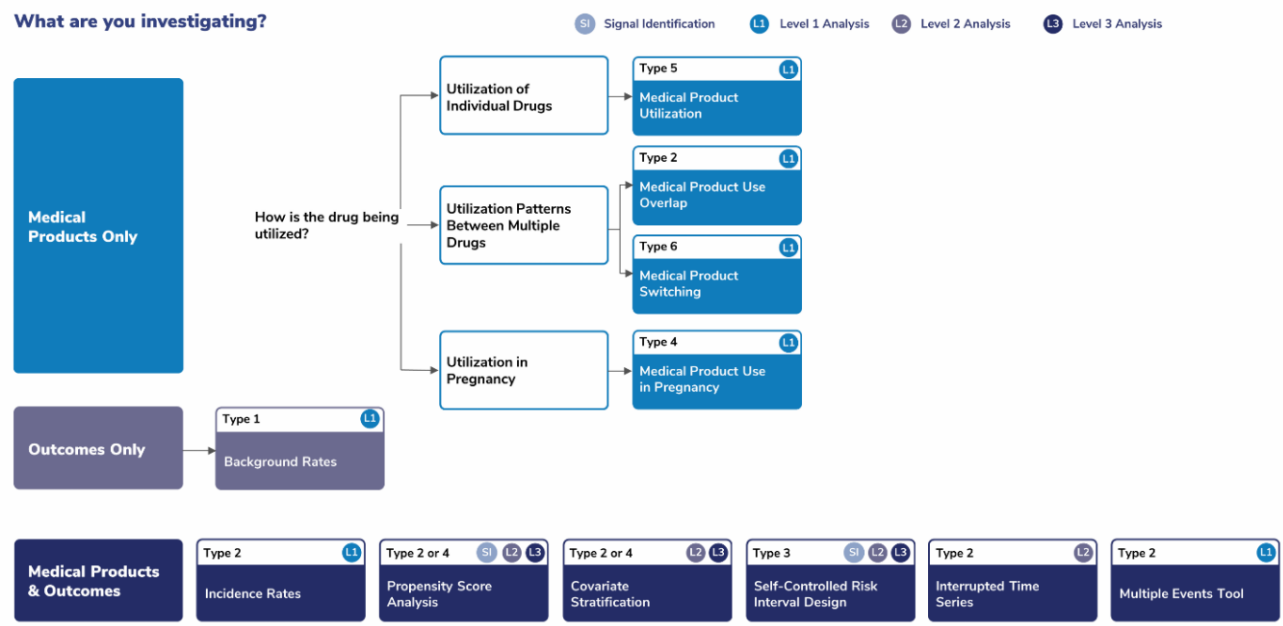


Figure 5: Sentinel's Analytic Tools. *Selection of a Sentinel analytic modules depends on what you are investigating. Use this flow chart to determine which study design type is applicable.*

Table 1 summarizes utilization of Sentinel's analytic modules in analyses distributed to Sentinel Data Partners over three years. A full mapping of the types of modules used in analyses leading to regulatory impacts can be found in Appendix D: Detailed List of Sentinel ARIA Studies and Their Analyses, Safety Concerns, and Regulatory Impacts. In addition, over 30 exploratory analyses using descriptive modules were performed using Merative™ MarketScan® Research Databases data to aid study design.

Table 1: Summary of Sentinel Analyses* by Sentinel Analytic Tool Module; January 1, 2018, through December 31, 2021.

Module Category	Analytic Module	Number of Analyses
Descriptive Analytic Modules	Background Rates	80
	Incidence Rates, Medical Product Overlap, Concomitant Use, Multiple Events	56
	Medical Product Use in Pregnancy	10
	Medical Product Utilization	18
	Medical Product Switching	6
Comparative Analytic Modules	Self-Controlled Risk Interval Design	0
	Propensity Score Analysis Modules	30
	Incidence Rates	1
	Signal Identification	0
Patient-Level Line Lists	Patient Episode Profile Retrieval (PEPR) Tool	7

**This table includes analyses conducted by the following FDA centers and offices: Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER); Center for Devices and Radiologic Health (CDRH); and Office of the Commissioner/Office of Counterterrorism and Emerging Threats (OCET).*

Sentinel has continued to enhance its analytic tools over time. Figure 6 below presents a timeline of these enhancements. Newer capabilities enable study designs grounded in causal inference principles to be completed in a multi-site, privacy preserving fashion with minimal transfer of patient-level information. Outside of Sentinel, many complex and resource-intensive pharmacoepidemiologic designs have been created and optimized to run in single database settings with complete access to all patient-level variables. In Sentinel's ARIA system, these same designs must be adapted to produce the same results using summary-level data returned from multiple Sentinel Data Partner sites with a wide variety of technical environments. While this can present challenges, the distributed nature of the database offers protection of patient privacy and therefore enables contribution of many patient lives from Data Partners. The ARIA system's growth over time reflects the continual adaptation of classical study designs to enable more pharmacoepidemiologic study questions to be addressed within Sentinel's distributed data structure using Sentinel's analytic tools.

Another critical development was the introduction of the analytic ability to conduct signal identification in 2019 following a Sentinel public workshop on the topic in 2018. Signal identification detects statistically higher numbers of adverse health outcomes than expected after exposure to a medical product, thereby enabling detection of potential safety concerns without pre-specifying outcomes. It is a hypothesis generating technique and is typically followed by additional approaches to further investigate potential safety signals, such as a clinical review or targeted pharmacoepidemiology safety study.[16] Sentinel has incorporated TreeScan™ into signal identification work, which is a free data-mining software available in the public domain that allows users to analyze large data sets using different versions of the tree-based scan statistic. Developing signal identification methods in Sentinel is of particular importance due to the high proportion of safety concerns for which the ARIA system was found insufficient due to lack of broad-based signal detection capabilities, as noted in the Analysis of ARIA Insufficiency section of this report. The analytic approach is currently being validated in a project identifying signals of adverse infant outcomes following maternal perinatal medication use.[17]

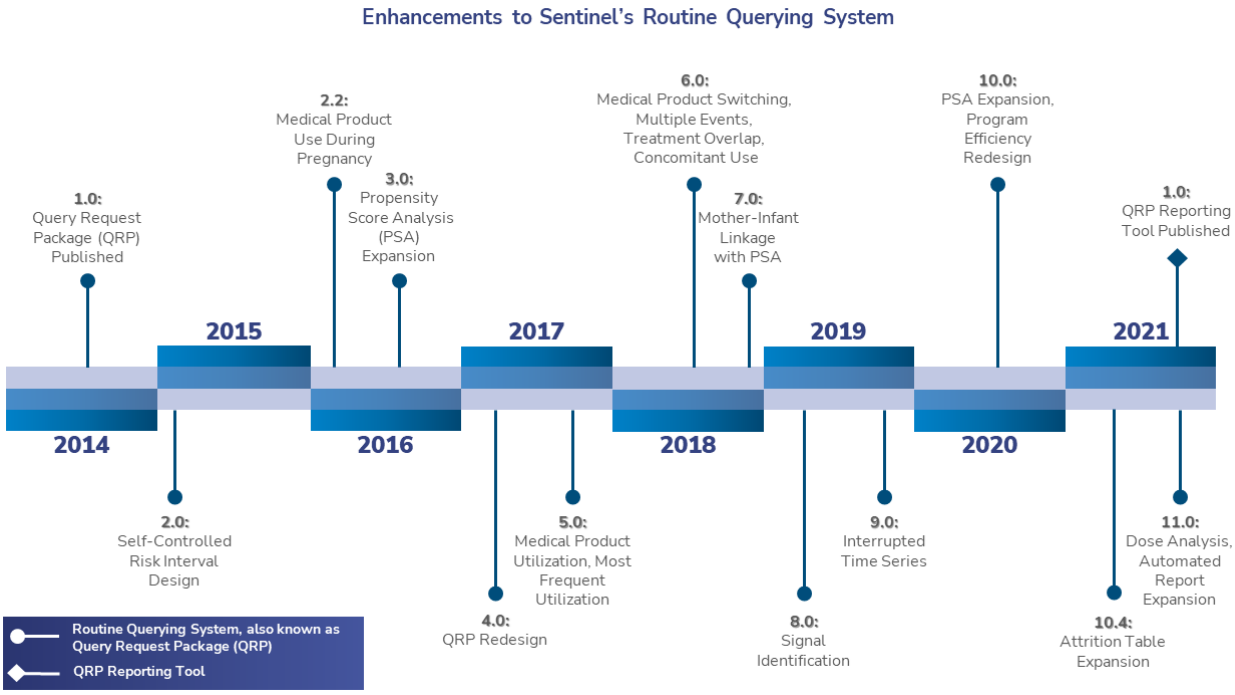


Figure 6: Enhancements to Sentinel's Analytic Tools. *Sentinel's analytic tools have evolved over time to expand Sentinel's ability to evaluate safety concerns identified by the FDA.*

2.2.4. Supplemental Analytic Tools

In addition to Sentinel's core analytic tools, Sentinel enhances the design and execution of medical product safety analyses through a suite of supplemental tools.

Sentinel released the inaugural version of the Code Lookup Tool in 2015 to further support operational efficiencies in study design. The Code Lookup Tool is a web-based application accessible to the Sentinel Operations Center, and recently FDA, that provides centralized access to a variety of medical terminologies with advanced search features, allowing users to search for medical codes reliably and consistently.

Sentinel released a Query Builder web application in 2019 to enable FDA to independently develop medical product utilization analyses using Sentinel's analytic tools. FDA may design analyses directly on the Query Builder application through an interactive user interface. They are then run on Merative™ MarketScan® Research Databases by Sentinel Operations Center staff within one week. This workstream enables expedited assessment of sample size, coding practices, and drug use trends to inform the design of more complex regulatory analyses supported by the Sentinel Operations Center. The Query Builder standalone application is also available to the public, enabling broad use of the application for users outside of FDA.

In response to the growth of its analytic capabilities, Sentinel developed Sentinel Views, a data visualization application that allows FDA users and the general public to better navigate and visualize results. The goal of Sentinel Views is to make results from Sentinel analyses more accessible—a key tenet to promote the growth of Sentinel as a national resource. As of January 2022, Sentinel Views supports several interactive visualizations such as propensity score diagrams, Kaplan-Meier curves, attrition tables, and forest plots, to illustrate results from comparative analyses. Highlights of Sentinel Views are captured in Figure 7.

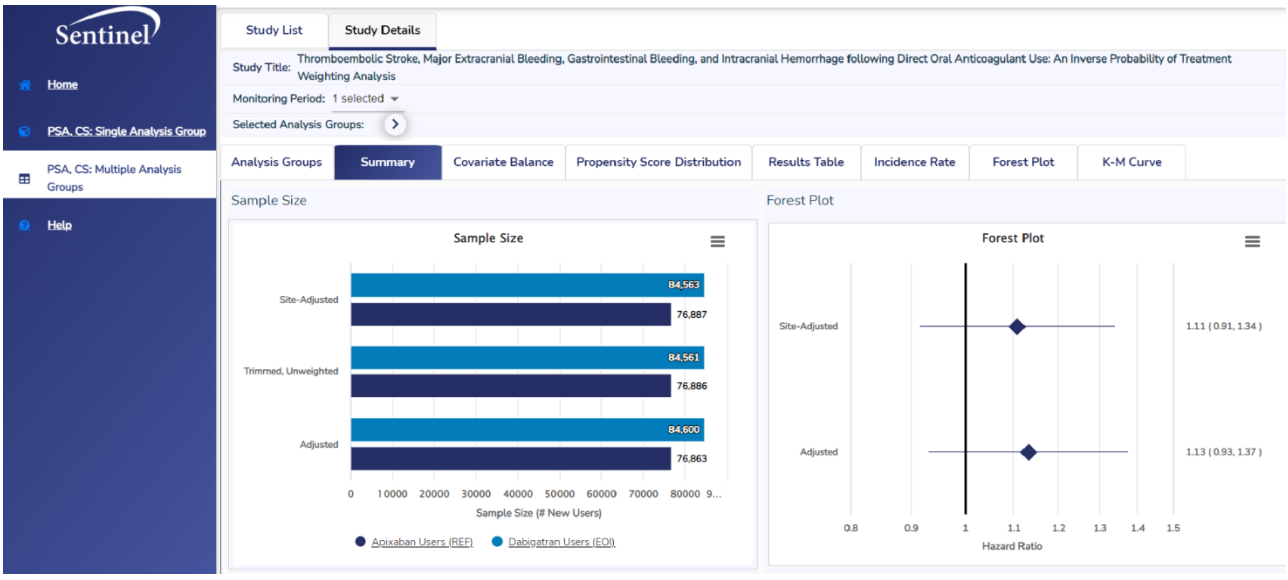


Figure 7: Sentinel Views: A Data Visualization Application. *This figure highlights various functionality available in Sentinel Views including propensity score distributions and forest plots.*

2.2.5. Electronic Healthcare Record Data in Sentinel

Sentinel has worked with several providers of EHR data to supplement the primarily claims-based Sentinel Distributed Database. This has allowed Sentinel to leverage a multi-modal response system to triage study questions to the most appropriate data source (Figure 8).

Sentinel worked with several providers of EHR data during the COVID-19 pandemic to enable access to additional laboratory and inpatient data. Sentinel leveraged an existing relationship with the National Patient-Centered Clinical Research Network (PCORnet) to perform COVID-19 related analyses. In May 2020, Sentinel began collaboration with TriNetX to provide up to date EHR data for urgent COVID-19 questions. TriNetX offers access to records from around 110 million patients from 70 health care organizations in 29 states, of which approximately 90% have more than ten years of data. Sentinel also worked with the IBM® Explorys Network, which consists of 39 health system partners comprising 71 million unique patients.

A final key partner is HCA Healthcare. HCA Healthcare provides a rich source of inpatient electronic health data. The current Sentinel HCA Healthcare resource includes inpatient data from 140 hospitals that capture around 35,000 inpatient hospitalizations weekly. HCA Healthcare data was used to support FDA's Office of Counterterrorism and Emerging Threats in a study of seasonal influenza hospitalizations and select complications that aimed to understand how Sentinel could be used to respond to a potential pandemic (see the Medical Countermeasures Initiative section of this report). This work standardized and structured HCA's data and enabled Sentinel to quickly pivot the HCA Healthcare data structure towards the COVID-19 response as soon as the pandemic began.

Highlights of how each of these EHR data contributors supported FDA's response to the COVID-19 pandemic are described in the COVID-19 Response section of this report. A key contribution of Sentinel to FDA's COVID-19 pandemic response was quick engagement with new partners to provide FDA access to fit-for-purpose data was a key contribution of Sentinel to the COVID-19 pandemic response.

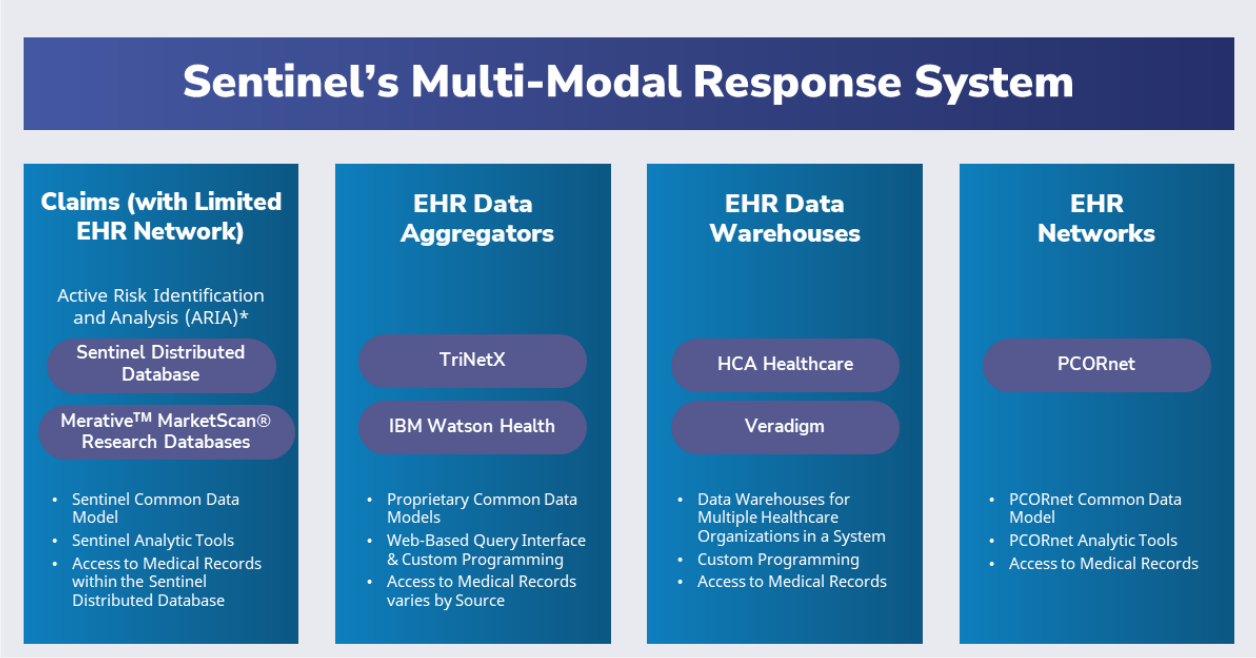


Figure 8: Sentinel's Multi-Modal Response System. *Sentinel leverages a multi-modal response system to triage a regulatory question from the FDA to a relevant data source.*

2.2.6. Methods and Characterization Work to Strengthen the Sentinel System

Sentinel has also supported FDA's regulatory science efforts through dedicated projects to validate outcome algorithms for use in epidemiologic studies. Outcome algorithm validation for serious infections[18] and lymphoma[19] made it possible to study six safety concerns with the ARIA system analyses in place of a PMR. Additional algorithm validations for stillbirth deliveries,[20] anaphylaxis, and acute pancreatitis are aimed at enabling further analyses in Sentinel to inform regulatory questions.

Another example supported FDA's COVID-19 response. In the early stages of the COVID-19 pandemic, no claims-based International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code was available to capture COVID-19 hospitalizations, until code U07.1 was released in April 1, 2020. Due to fluctuating guidelines in medical coding, and fluidity of diagnostic test availability and guidance, Sentinel pursued an effort to determine the ICD-10-CM code(s) that best defined the most valid and complete cohort of patients hospitalized with COVID-19.[21]

2.3. Sentinel Innovation Center

Health insurance claims data currently form the backbone of Sentinel; however, lack of deep clinical information limit Sentinel's ability to address important drug safety questions. Linking EHRs, containing detailed clinical information stored as structured and unstructured data to insurance claims can address gaps in the Sentinel's data infrastructure. As previously described, several current Sentinel Data Partners are integrated delivery systems that provide access to claims-linked-to-EHR data, including laboratory and vitals data. Sentinel has also taken steps to enable broader access to EHR data for drug safety analyses for the COVID-19 pandemic response.

Sentinel continues to expand its use of EHR data through several ongoing activities within the Sentinel Innovation Center. Established in 2019, the Sentinel Innovation Center works to identify, develop, and evaluate innovative methods to study drug safety and effectiveness using real-world data. The Innovation Center was created to address some of the strategic goals described in the Sentinel Five-Year Strategy and support FDA's Medical Data Enterprise Initiative to build a new system containing EHRs from ten million lives. As described in the Innovation Center Master Plan, the Innovation Center's focuses are in the following strategic priority areas:

1. Data Infrastructure: There is a need to develop Sentinel's data infrastructure to support claims linked EHR data. Ongoing work within the Sentinel Innovation Center is aimed at developing a principled approach to extend the Sentinel Common Data Model to include new data elements from structured and unstructured EHR data. Additionally, to address the challenge of semantic interoperability across sites, the Sentinel Innovation Center is conducting projects to investigate approaches to detect and mitigate data consistency issues and to harmonize data across multiple EHR data sites. Finally, the Innovation Center developed a set of data quality metrics and approaches for integration of structured and unstructured data elements from EHR into the Sentinel Common Data Model to facilitate reliable analyses of medical product outcomes using these data. These learnings will improve the ability to leverage the Sentinel System for analyses supporting regulatory questions. Finally, there has been substantial progress made to develop a set of open-source algorithms to augment the assessment of mortality in EHR data through probabilistic linkages to additional mortality data sources, including state registry data, the Centers for Disease Control's National Death Index and publicly available social media data (Augmenting Date of Death & Cause of Death Ascertainment in Sentinel).

2. Feature Engineering: While EHR-based data such as administrative data, medication orders, and most laboratory testing results are recorded in structured or semi-structured fields, a vast amount of potentially useful information is stored as unstructured data in visit notes (e.g., narrative descriptions of a patient's signs and symptoms, family history, social history), radiology reports or images, and discharge summaries. Substantial engineering is needed to identify features, or data elements, from unstructured data that can be extracted and organized as structured data. Natural language processing and automated feature extraction are essential mechanisms to support use of computer-readable clinical definitions from EHRs in signal detection and signal refinement activities. Development of automated feature extraction workflows that allow for time-contextualization is critical to enable determination of temporality in confounder, exposure, and outcome assessment in Sentinel queries. Initiatives are underway to develop natural-language-processing-assisted feature extraction methods, using anaphylaxis as a case study for how machine learning and natural language processing techniques can improve the identification algorithms for health outcomes of interest that may be used in Sentinel. Another ongoing project aims to advance Sentinel's computable phenotyping strategy for EHR data by using NLP for identifying incident (versus prevalent) conditions. The use case of suicidality was used, which relies on unstructured EHR data and is lacking a clearly defined reference standard.

3. Causal Inference: As regulatory decisions are predicated on observed causal relationships between a medical product exposure and adverse outcomes, non-randomized studies using secondary data must be robust enough to allow for causal inference. To support the application of causal methods that leverage both claims and EHR data sources, the Sentinel Innovation Center is currently developing a causal analysis framework proposing a stepwise process that systematically considers key choices with respect to design and analysis that influence validity of studies conducted with non-randomized data. The Innovation Center also completed a project evaluating the potential use of Targeted Learning methods on linked claims-EHR data.

4. Detection Analysis: EHRs offer a potentially promising complementary source of information for signal detection of unexpected potential safety concerns but may require tailored approaches to account for and leverage differences in data content and structure compared to health insurance claims. Specifically, unstructured clinical narratives recorded in EHRs may provide more complete capture of subtle adverse events that may not trigger formal coding or medical interventions, aspects that are observable in claims data. The addition of detailed information from EHRs presents an opportunity to expand signal detection efforts that are currently used in Sentinel. While natural-language-processing-based identification of adverse events from unstructured clinical notes has been proven feasible in the broader scientific community with currently available methods, relational identification of newly occurring adverse events in a temporal sequence to specific medication exposures is complex and the subject of active research. The Sentinel Innovation Center has completed a scoping review to evaluate Existing Approaches to EHR-based Signal Identification which will guide future empiric activities to test the most promising approaches for EHR-based signal detection.

Sentinel Innovation Center projects are available to reference on the Methods webpage of the Sentinel Initiative website, among other methods initiatives.

3. FDA's Utilization of Sentinel to Protect Public Health

FDA uses Sentinel to further their mission to protect public health. This section outlines the ways in which FDA has utilized Sentinel with a focus on the following three areas:

- **Monitoring and assessing medical product safety**: A core pillar of Sentinel is to support the monitoring and assessment of medical product safety, centered around Sentinel's ARIA system.
- **Responding to the COVID-19 pandemic**: FDA used Sentinel's existing infrastructure and collaborations to respond to the COVID-19 pandemic.
- **Using Sentinel outside of the Center for Drug Evaluation and Research**: Throughout the past five years, Sentinel's infrastructure and expertise has been used by a variety of FDA offices outside of the Center for Drug Evaluation and Research for assessing the safety of biologics, medical devices, and other purposes.

3.1. Monitoring and Assessing Drug Safety

The Center for Drug Evaluation and Research's core use of the Sentinel System is to monitor and assess medical product safety. Most of the Center's work is within the ARIA system, though the Center has also leveraged the Sentinel System infrastructure to support medical product monitoring and regulation outside of the ARIA system. This section will describe how the Center has used the ARIA system as well as how the Center has leveraged Sentinel's infrastructure outside of the ARIA system to support their mission.

3.1.1. FDA's Utilization of the Active Risk Identification and Analysis (ARIA) System

A key component of Sentinel is the ARIA system. In the FDA Amendments Act of 2007, FDA was mandated to establish a postmarket risk identification and analysis system that contained 100 million patient lives for monitoring risks associated with drug and biologic products using data from disparate sources, to complement the FDA's existing postmarket capabilities. The ARIA system fulfills that requirement and is a key tool for FDA drug safety surveillance.

The ARIA system is used by FDA to:

1. Investigate a safety concern when FDA is considering issuing a postmarket requirement (PMR) to drug sponsors. If during the drug approval process, FDA is considering requiring a sponsor to conduct a postmarket study to evaluate a potential safety concern, FDA must first assess whether that safety concern can be studied in the ARIA system under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)). If FDA determines that the ARIA system's capabilities are sufficient to evaluate the safety concern, FDA must conduct that study in the ARIA system.

2. Conduct studies to address identified safety concerns or other regulatory questions to support FDA's decision-making as part of FDA's pharmacovigilance. The ARIA system capabilities enable inferential comparative analyses and signal identification. These analyses may inform discussions that lead to issuance of Drug Safety-related Labeling Changes or Drug Safety Communications, among other regulatory activities.

Sentinel curates and maintains data sets tracking FDA's utilization of the ARIA system and regulatory impacts. A Sentinel study may include multiple analyses investigating one or more safety concerns, defined as a medical product and health outcome pair. For example, a Sentinel study on the association between the novel oral anticoagulants apixaban, dabigatran, and rivaroxaban with severe uterine bleed assesses three distinct safety concerns:

- Apixaban and severe uterine bleed

- Dabigatran and severe uterine bleed
- Rivaroxaban and severe uterine bleed

This study evaluated these three safety concerns through two descriptive analyses followed by a comparative propensity score-based analysis. The regulatory impact of this Sentinel study was a class-wide labeling change for oral anticoagulants (more information available in the Regulatory Impacts of Assessed Safety Concerns section.) Figure 9 demonstrates how Sentinel describes and tracks components of an ARIA system study.

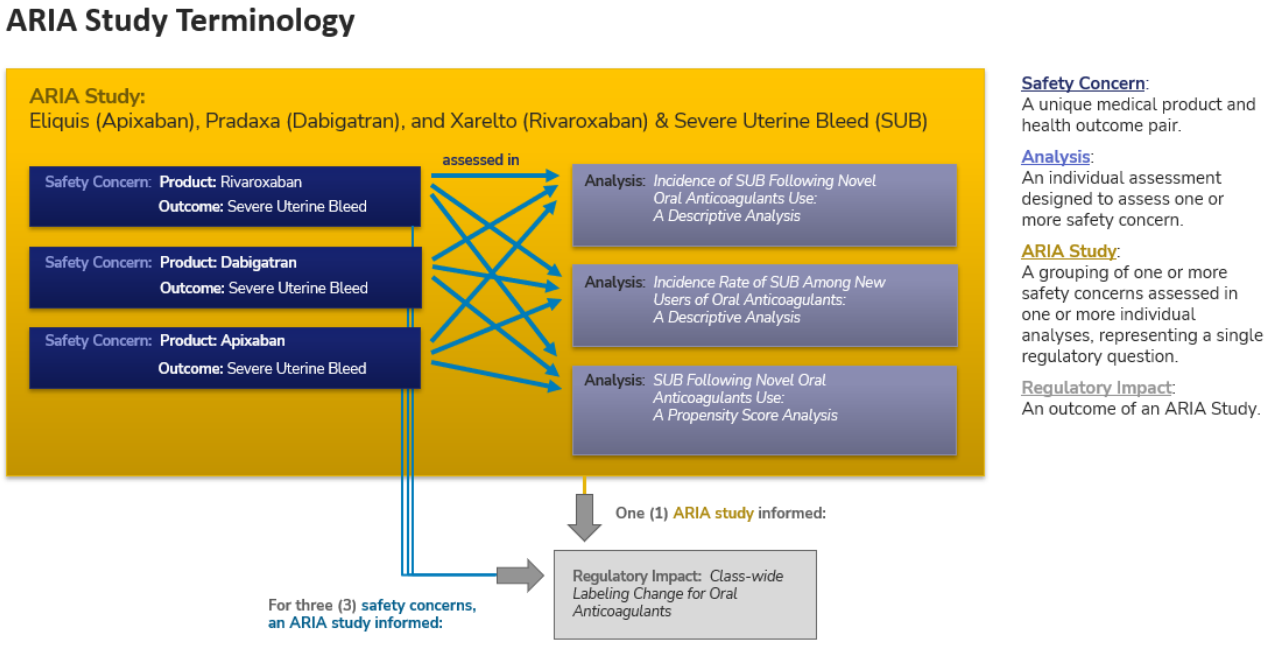


Figure 9: ARIA Study Terminology. *This graphic defines four key terms used in this report and depicts how these terms interact. Learn more about the featured example here.*

In addition to tracking utilization of the ARIA system, Sentinel also documents safety concerns for which the ARIA system was deemed insufficient and reasons for insufficiency. This is a requirement for safety concerns identified during the review of a New Drug Application (NDA) or Biologics License Application (BLA) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act referenced above, and the reasons for insufficiency inform future program development. Memos for each safety concern that outline why the ARIA system was found to be insufficient are included in the action package for NDA and BLA approvals and are linked on Sentinel's website.

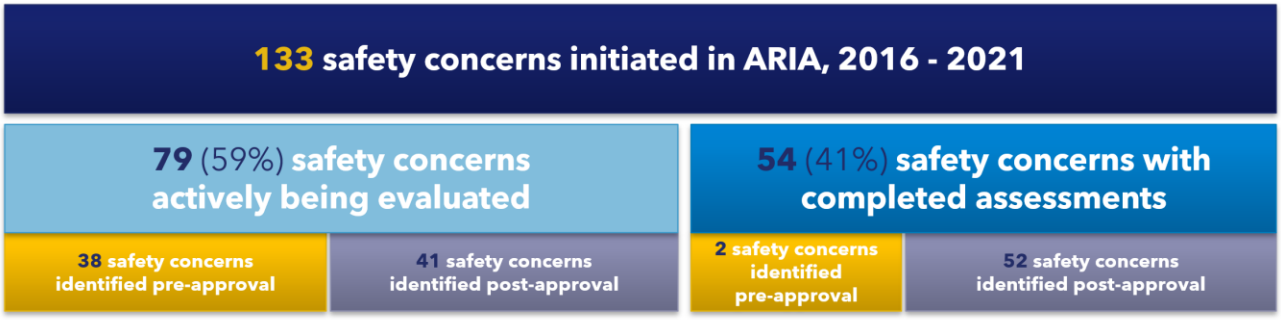
The content in this section includes metrics from January 1, 2016, when the Mini-Sentinel pilot program transitioned to a fully operational Sentinel System, through December 31, 2021. Safety concerns, the primary unit of analysis, are assigned years according to the date in which a safety concern was identified. Thus, safety concerns identified from 2016 to 2021 are included in this report.

Characteristics of Assessed Safety Concerns

A total of 330 safety concerns were examined for potential evaluation in the ARIA system since January 1, 2016. Of those, 133 were analyzed in the ARIA system. The ARIA system was not deemed sufficient to address the remaining 197 as it is currently defined. Some root causes of the ARIA system insufficiency are inherent to administrative claims data, while other driving factors could be

addressed through system enhancements. A root cause analysis characterizing these cases of insufficiency, along with system solutions to expand the ARIA system sufficiency, is later described in the Analysis of ARIA Insufficiency section of this report.

Of the 133 safety concerns undergoing assessment in the ARIA system, 79 are currently being evaluated, while 54 have completed assessments. Safety concerns follow different regulatory paths based on whether they are identified prior to the drug's approval, i.e., pre-approval, or whether the safety concern is identified after the drug is already on the market, i.e., post-approval. Safety concerns that are identified pre-approval often result in use of the ARIA system in lieu of FDA issuing a PMR, authorized by Section 505(o)(3) described above. They may also inform decisions around issuance of Risk Evaluation and Mitigation Strategies or simply provide more context for the application review. When a safety issue is identified post-approval, analyses results inform FDA discussions on regulatory actions. Results may be presented at Advisory Committee meeting(s), inform a label change or drug safety communication, or inform decisions on Risk Evaluation and Mitigations Strategies. The 133 safety concerns represent 40 total concerns identified prior to the approval of a medical product of interest (i.e., during the review of an application; pre-approval), while 93 concerns were identified in the post-approval setting (Figure 10).



ARIA: Active Risk Identification and Analysis.

Figure 10: Safety Concerns Initiated in ARIA from 2016 through 2021. *This graphic depicts the breakdown of Sentinel ARIA safety concerns by assessment status and associated regulatory approval phase.*

Table 2 and Table 3 show the distribution of medical products and health outcomes evaluated or currently undergoing evaluation in the ARIA system by regulatory approval phase. Medical product exposures are categorized using the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system. Table 2 presents safety concerns at the ATC 2nd Level, representing therapeutic subgroups. Appendix E: Detailed List of ARIA Safety Concerns lists all safety concerns evaluated in Sentinel, including their assigned ATC code(s).

Table 2: Distribution of Safety Concerns Evaluated or Being Evaluated in ARIA by Medical Product using ATC Therapeutic Subgroup Terminology and Regulatory Approval Phase *(N = 133 Safety Concerns*).*

Medical Product (ATC 2nd Level Therapeutic Subgroup)	Number of Safety Concerns Identified Pre-Approval	Number of Safety Concerns Identified Post-Approval	Total
Antithrombotic agents	0	22	22
Immunosuppressants	8	8	16
Drugs for obstructive airway diseases	4	5	9

Medical Product (ATC 2nd Level Therapeutic Subgroup)	Number of Safety Concerns Identified Pre-Approval	Number of Safety Concerns Identified Post-Approval	Total
Drugs used in diabetes	2	6	**8**
Psychoanaleptics	0	4	**4**
Sex hormones and modulators of the genital system	2	2	**4**
Diuretics	0	4	**4**
Drugs for acid related disorders	0	4	**4**
Drugs for functional gastrointestinal disorders	2	2	**4**
Endocrine therapy	0	4	**4**
Psycholeptics	0	4	**4**
Agents acting on the renin-angiotensin system	0	3	**3**
Analgesics	0	3	**3**
Antineoplastic agents	0	3	**3**
Antigout preparations	0	2	**2**
Antiobesity preparations, excluding diet products	0	2	**2**
Cardiac therapy	0	2	**2**
Contrast media	0	2	**2**
Antianemic preparations	0	1	**1**
Antibacterials for systemic use	1	0	**1**
Antiepileptics	0	1	**1**
Antifungals for dermatological use	0	1	**1**
Antivirals for systemic use	0	1	**1**
Beta blocking agents	0	1	**1**
Calcium homeostasis	0	1	**1**
Drugs for constipation	1	0	**1**
Ophthalmological and ontological preparations	0	1	**1**
Other dermatological preparations	1	0	**1**
Other[1]	17	1	**18**
N/A[2]	2	3	**5**
Total*	**40**	**93**	**133**

**A safety concern may be associated with one or more ATC code.*
[1] A recording of "Other" indicates that an appropriate ATC code is not yet assigned to the medical product of interest.
[2] A recording of "N/A" indicates that the safety concern does not assess a specific medical product of interest. For example, a safety concern may intend to evaluate the characteristics of a patient population and is therefore not assessing a pertinent medical product of interest.

Health outcomes are categorized using the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's Medical Dictionary for Regulatory Activities

(MedDRA) classification system. Table 3 presents health outcomes at the broadest classification category of MedDRA's classification hierarchy, System Organ Class. Appendix E: Detailed List of ARIA Safety Concerns lists all safety concerns evaluated in Sentinel, including their assigned MedDRA code(s).

Table 3: Distribution of Safety Concerns Evaluated or Being Evaluated in ARIA by Health Outcome using MedDRA System Organ Class Terminology and Regulatory Approval Phase *(N = 133 Safety Concerns*).*

Health Outcome (MedDRA System Organ Class)	Number of Safety Concerns Identified Pre-Approval	Number of Safety Concerns Identified Post-Approval	Total
Nervous system disorders	0	14	**14**
Cardiac disorders	4	6	**10**
Surgical and medical procedures	6	2	**8**
Gastrointestinal disorders	1	6	**7**
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	4	2	**6**
Injury, poisoning and procedural complications	1	4	**5**
Immune system disorders	4	0	**4**
Psychiatric disorders	0	4	**4**
Congenital, familial and genetic disorders	0	3	**3**
Eye disorders	3	0	**3**
Reproductive system and breast disorders	0	3	**3**
Skin and subcutaneous tissue disorders	0	3	**3**
Vascular disorders	2	1	**3**
General disorders and administration site conditions	1	1	**2**
Infections and infestations	0	2	**2**
Metabolism and nutrition disorders	1	1	**2**
Pregnancy, puerperium, and perinatal conditions	1	1	**2**
Product issues	0	2	**2**
Renal and urinary disorders	0	1	**1**
Blood and lymphatic system disorders	1	0	**1**
Investigations	0	1	**1**
Musculoskeletal and connective tissue disorders	0	1	**1**
Other[1]	3	2	**5**
N/A[1]	8	35	**43**
Total*	**40**	**95**	**135**

**A safety concern may be associated with one or more MedDRA code.*
[1] A recording of "Other" indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.
[2] A recording of "N/A" indicates that the safety concern does not assess a specific health outcome of interest. For example, a safety concern may intend to evaluate the utilization of a medical product and is therefore not assessing a pertinent health outcome of interest.

Safety Concerns Under Assessment in the ARIA system in Lieu of a Postmarket Requirement

A key benefit of Sentinel's ARIA system for industry is its ability to eliminate a PMR for the sponsor. As of December 31, 2021, 22 safety concerns for 11 medical products are undergoing assessment (Table 4). Assessment of six of these 22 safety concerns was made possible by Sentinel-led outcome algorithm validations for serious infections[18] and lymphoma.[19]

Table 4: Safety Concerns Under Assessment in Sentinel under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Medical Product	Health Outcome
Ablysinol (dehydrated alcohol)	Atrioventricular block
	Death
	Heart failure
	Septal myectomy
	Ventricular arrhythmia
Annovera (segesterone acetate and ethinyl estradiol vaginal system)	Arterial thromboembolism
	Venous thromboembolism
Gimoti (metoclopramide nasal spray)	Tardive dyskinesia and adverse central nervous system reactions
Ibsrela (tenapanor)	Inflammatory bowel disease
Ilumya (tildrakizumab)	Lymphoma
Invokana (canagliflozin)	Renal cell carcinoma
Siliq (brodalumab)	Hospitalized neutropenia
	Myocardial infarction and stroke
	Serious infections
Sinuva (mometasone furoate)	Cataracts
	Diminished visual acuity
	Glaucoma
	Nasal septal perforation
Skyrizi (risankizumab)	Lymphoma
Stelara (ustekinumab)	Serious infections, assessed for patients with Crohn's disease
	Serious infections, assessed for patients with ulcerative colitis
Tremfya (guselkumab)	Lymphoma

Regulatory Impacts of Assessed Safety Concerns

Data from completed assessments have impacted regulatory decision-making for multiple medical products. The most common regulatory impact of a Sentinel study was the decision by the FDA to take no action. In some cases, these assessments provided FDA with reassuring information indicating that the safety concern required no response. Sentinel studies have informed Drug Safety-related Labeling Changes (SrLC) for 12 safety concerns, supported FDA Advisory Committee meetings for 11 safety concerns, and informed FDA Drug Safety Communications for five safety concerns (Figure 11). It is important to note that these regulatory impacts are limited to those related to Sentinel and that Sentinel is only one of multiple resources FDA considers when making a regulatory decision.

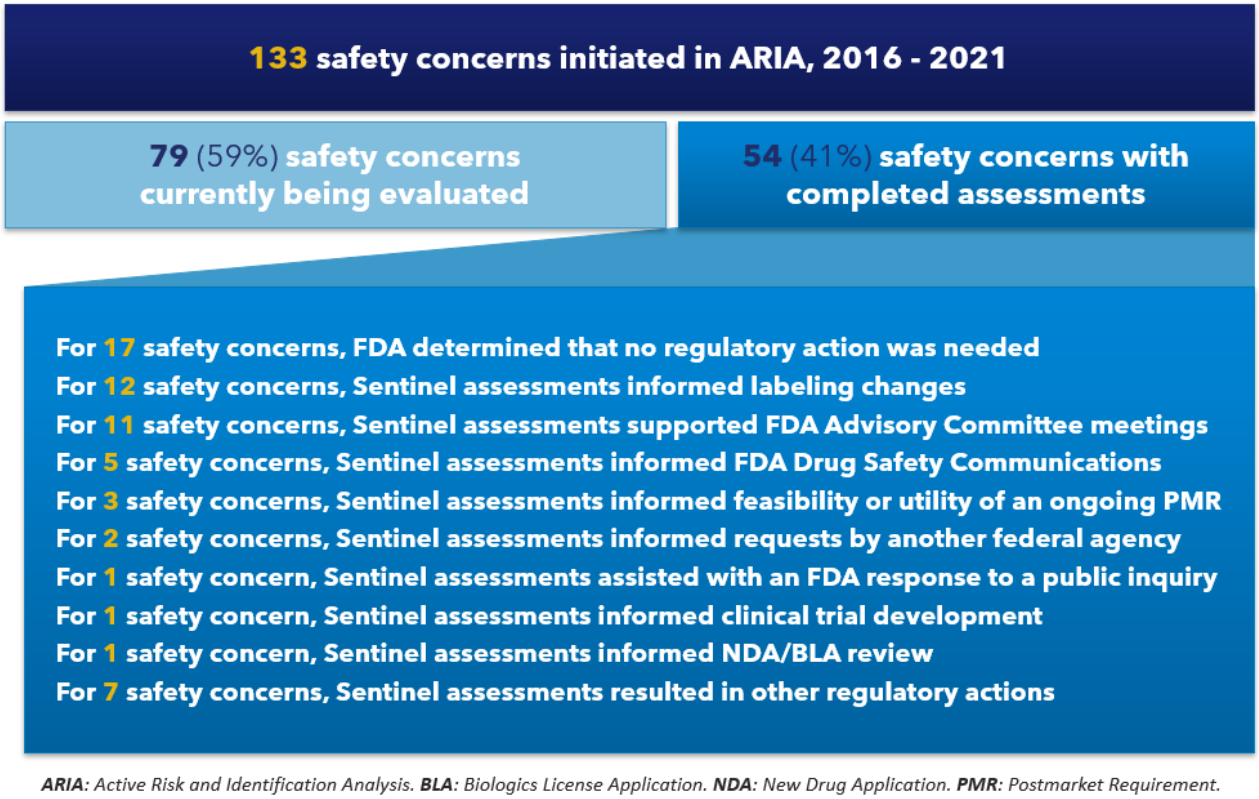


Figure 11: Regulatory Impacts of ARIA Assessments as of December 31, 2021. *This graphic depicts the outcomes of Sentinel ARIA assessments. A single safety concern may result in one or more regulatory impact.*

Examples of how the FDA has used the ARIA system to inform labeling changes and drug safety communications are below:

- Hydrochlorothiazide (HCTZ) and Non-Melanoma Skin Cancer: FDA assessed the risk of non-melanoma skin cancer for patients treated with HCTZ-containing products compared to non-HCTZ angiotensin-converting-enzyme inhibitor-containing products. FDA found an increased risk of non-melanoma skin cancer associated with HCTZ use, predominantly for squamous cell carcinoma and in white patients taking large cumulative doses. These findings informed additions to the label's *Adverse Reactions and Information for Patients* section.
- Parenteral Iron Products and Risk of Severe Adverse Reactions to Pregnant Women and their Fetuses: FDA characterized the frequency of intravenous iron utilization by gestational week relative to live birth and stillbirth deliveries. Information from this analysis contributed to a class-wide labeling update for parenteral iron products to add new safety information to the *Use in Specific Populations, Pregnancy* section of the label. This update describes the risk of severe adverse reactions to pregnant women and their fetuses.
- Oral Anticoagulants and Clinically Significant Uterine Bleeding: FDA conducted a study to examine severe uterine bleeding events in women treated with oral anticoagulants. These findings contributed to the following class-wide labeling change in section 8.3 for oral anticoagulants: "The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including [PRODUCT

name] should be assessed in females of reproductive potential and those with abnormal uterine bleeding."

- Etanercept (Enbrel) and Use in Pregnancy: As part of FDA's routine review of postmarket studies, FDA conducted a drug utilization analysis of tumor necrosis factor (TNF) alpha inhibitors in pregnant women in Sentinel. The study found that among pregnant women with a chronic inflammatory condition (ankylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, rheumatoid arthritis), there was a preference to use etanercept compared to other TNF alpha inhibitors. For most TNF alpha inhibitors, use during pregnancy decreased after the first trimester. This assessment was one source of evidence considered for the Pregnancy and Lactation Labeling Rule (PLLR) Conversion Safety Labeling Change for Enbrel (etanercept).
- Gadolinium-Based Contrast Agents (GBCAs) are Retained in the Body: FDA assessed the use of GBCAs in pregnancy. This study was presented at a Medical Imaging Drugs Advisory Committee meeting and supported the FDA's decision to require a new class warning and other safety measures for all gadolinium-based contrast agents for magnetic resonance imaging concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs.
- Serious Mental Health Side Effects for Asthma and Allergy Drug Montelukast (Singulair): FDA assessed the risk of neuropsychiatric events associated with montelukast use, a prescription medicine used for asthma and allergy. The Sentinel study was presented at a joint meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee, and contributed to the FDA discussions that resulted in strengthening existing warnings about serious behavior and mood-related changes with montelukast

Refer to Appendix D: Detailed List of Sentinel ARIA Studies and Their Analyses, Safety Concerns, and Regulatory Impacts for a complete list of Sentinel safety concerns, analyses, and regulatory impacts, and Appendix F: Definitions of Sentinel Regulatory Impacts for supporting definitions of regulatory impacts.

Analysis of ARIA Insufficiency

As previously mentioned, FDA must assess whether the ARIA system is sufficient to study a safety concern prior to issuing a PMR. Of 187 safety concerns considered for a PMR between 2016 and 2021, 22 concerns, or 12%, were converted into an ARIA system assessment. When the ARIA system is found insufficient to assess a safety concern, FDA develops a memo documenting the reason for insufficiency, which element of the required epidemiologic study the ARIA system is unable to address, the scientific background and justification for the determination. These memos are viewable on the Sentinel website's Assessing ARIA's Ability to Evaluate a Safety Concern webpage.

ARIA system sufficiency is evaluated based on the capabilities of the core ARIA system infrastructure of the Sentinel Distributed Database and analytic tools. Supplemental data streams, including those providing inpatient and ambulatory EHR data, and direct review of medical charts, are outside of the ARIA system's current scope and not considered in determining ARIA system sufficiency. For safety concerns identified prior to drug approval, a finding that the ARIA system is insufficient to assess the concern often leads to a PMR. For safety concerns identified after the drug is approved, FDA may use other data sources to gather information when the ARIA system is insufficient or issue a PMR.

The ARIA system may be found insufficient to address safety concerns for un-addressable reasons (e.g., limitations of health care data) or addressable reasons (e.g., further development of the system). Table 5 presents the underlying reasons for insufficiency for the 197 safety concerns that the ARIA system was found insufficient to address between 2016 and 2021. A single insufficient safety concern

may be associated with multiple underlying reasons for insufficiency and so may be counted in multiple categories. Included in the table are notes on the potential for development of the ARIA system to be expanded in the future to address these causes for insufficiency.

Trends in the causes of ARIA system insufficiency inform programmatic development. Resolving actionable instances of prior insufficiency through tool or data enhancements may allow a safety concern deemed insufficient to be assessed in the ARIA system in the future. From 2016 through 2021, multiple causes of ARIA system insufficiency have been addressed through enhancements to the capabilities of the ARIA system:

- In 2018, Sentinel integrated a Mother-Infant Linkage table within the Sentinel Common Data Model that captures linkages between live-birth deliveries in pregnant patients and infants. A subset of Sentinel Data Partners populates the Mother-Infant Linkage table largely using deterministic matching methods, though probabilistic matching methods were used by some. More information on linkage methods is available in Sentinel's Mother-Infant Linkage FAQ. The ARIA system was deemed insufficient for 24 safety concerns requiring assessment of infant outcomes following drug exposure in pregnant people prior to this enhancement (Table 5).
- Also in 2018, Sentinel introduced functionality to identify concomitant medical product use, defined as the overlapping exposure to two medical products. This was in direct response to ARIA system insufficiency determinations resulting at least in part from the inability of the analytic tools to capture concomitant product use episodes.
- Sentinel has also completed work to validate new outcome algorithms to enable ARIA system sufficiency for key safety concerns. As mentioned, Sentinel completed algorithm validation projects for serious infections and lymphoma to enable FDA utilization of the ARIA system to assess a safety concern rather than issuing a PMR.
- In 2019, Sentinel developed the analytic tool capability to perform signal identification for non-specific adverse fetal outcomes leveraging TreeScan statistical analyses. Lack of broad-based signal identification capabilities was identified as a driving factor of insufficiency for around 35% for the safety concerns that the ARIA system was not sufficient to address. A further discussion on implications of this development is included below.

Table 5: Distribution of Root Causes of ARIA Insufficiency and Opportunities for Future Development of ARIA.

Reasons for Insufficiency	# of Determinations	Direction of Future Development
Insufficient supplemental structured clinical data	89	This is an inherent limitation of claims-based data, which comprises the bulk of current ARIA dataset. Addressable with the addition of EHR data elements into ARIA. The Sentinel Innovation Center is currently working to build a new data resource containing EHRs from 10 million lives.
Inability of ARIA tools to perform required analysis	82	A main driver of this category of insufficiency is the repeated need to assess the safety of a medical product without a defined outcome of interest. Sentinel has integrated signal identification abilities leveraging TreeScan methods into Sentinel's analytic tools and is performing ongoing methods work to demonstrate use, with the aim of integrating use of signal identification in routine regulatory use.
Study requires data elements captured in unstructured clinical data, such as clinical notes	73	This is an inherent limitation of current claims-based data, which comprises the bulk of current ARIA data. Upon integration of EHR data into the ARIA system, ongoing research and development will be needed to fully utilize unstructured data. The Sentinel Innovation Center is currently developing feature engineering capabilities to enable extraction and analysis of this information.
Absence of validated code algorithm	72	This is actionable with further research and development. It requires resources to validate code list algorithms.
Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate	60	Coding terminologies introduce inherent limitations for identification of certain clinical concepts in all electronic healthcare data sources (i.e., both claims and EHR). In many cases, no program enhancement will address limitation.
Inadequate sample size	57	This is non-actionable as low uptake or background rates are the driving factor.
Requires linkage to additional data source that is unavailable	52	This is an inherent limitation of current datasets that comprise ARIA data. Additional linkages are possible with significant financial resources. Data governance issues must be addressed.
Insufficient observation time available	44	This is actionable with further research and development.
Insufficient mother-infant linkage	24	This was addressed with 2018 integration of Mother-Infant Linkage table.
Insufficient inpatient data	18	This is an inherent limitation of claims-based data, which comprises the bulk of the current ARIA dataset. Addition of EHR data through the work of the Sentinel Innovation Center will address this limitation.
Inability to identify over-the-counter medication use	8	This is an inherent limitation of both claims and EHR data. It is unlikely that this could be addressed within the current ARIA infrastructure.
Insufficient race capture of information on race	3	This is in inherent limitation of U.S. healthcare data. FDA is working with Sentinel Data Partners to understand approaches to better capture this data.
Insufficient representation of the population of interest	1	FDA added Medicare data to the Sentinel Distributed Database in 2018 and is working to integrate Medicaid data in 2022, which will partially address these limitations. Certain population whose health record data is captured in specialty systems or are uninsured may still be unrepresented.

A key to interpreting insufficiency determinations is the changing trends in FDA's issuance of PMRs for safety concerns related to pregnancy and infant outcomes. In 2014, FDA held a public meeting entitled "Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting" which led to a 2019 draft guidance on Post-approval Pregnancy Safety Studies. This guidance acknowledged that while pregnancy registries were important for their prospective and detailed patient level data collection, they often failed to meet enrollment targets. Therefore, "complementary studies," typically observational database studies, were introduced as an additional requirement. Thus began the practice of "twin" postmarket requirements: a registry and an observational database study for drugs where in utero exposure was a potential risk.[23] Since 2016, the proportion of safety concerns found insufficient that relate to assessment of adverse pregnancy and fetal outcomes has increased over time, which may reflect an overall increase in the issuance of PMRs due to this policy. Figure 12 shows the total counts of safety concerns for which ARIA was found insufficient from 2016 through 2021 with safety concerns pertaining to adverse pregnancy health outcomes explicitly parsed.

In 2019, Sentinel integrated the analytic capability to perform signal identification for non-specific outcomes leveraging TreeScan statistical analyses. There is ongoing work to show use of this capability for pregnancy specifically, which is further described in the prior Sentinel's Analytic Tools section of this report. Following this work, FDA plans to integrate this analytic capability into their regulatory process and enable further use to address safety concerns.

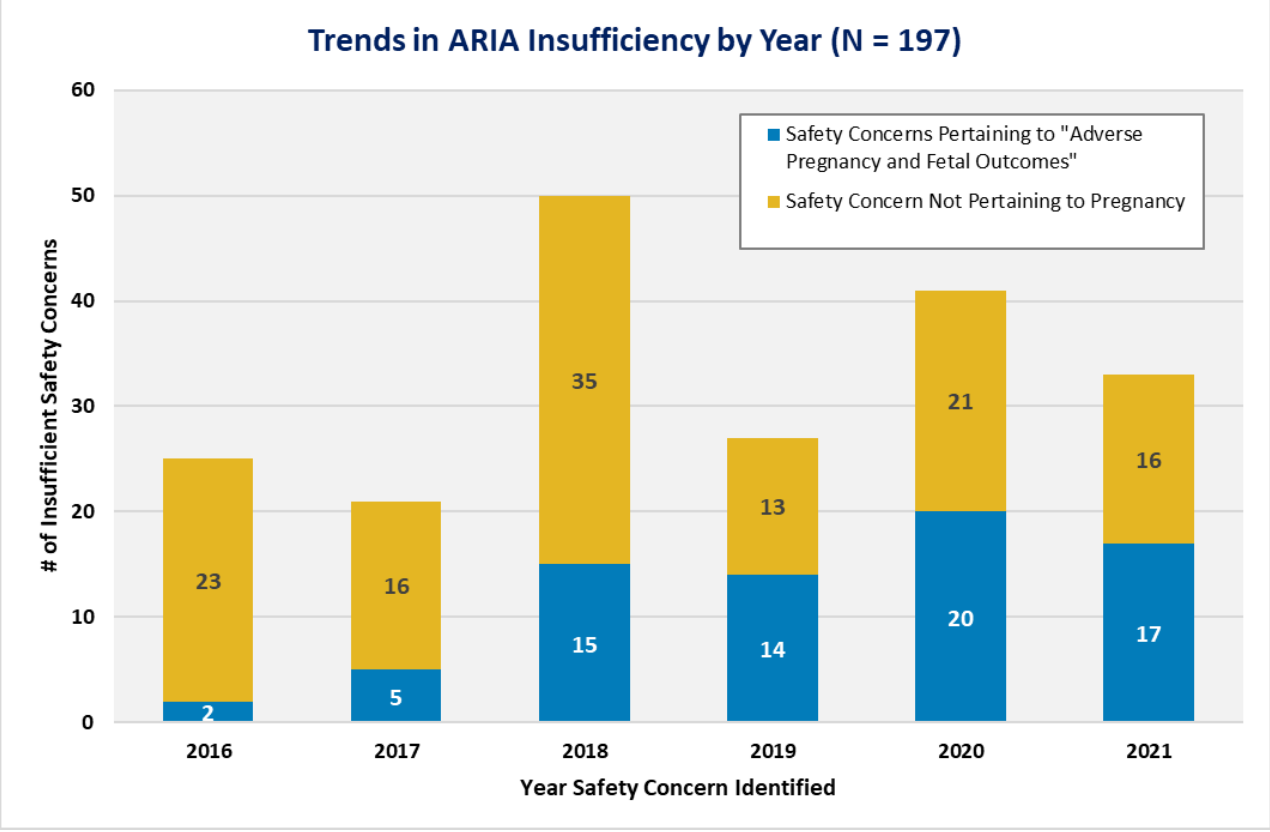


Figure 12: Trends in ARIA Insufficiency by Year. *This graphic depicts counts of insufficiency since the launch of Sentinel in 2016, further indicating which safety concerns were insufficient due to health outcomes related to adverse pregnancy and fetal outcomes versus all other health outcomes. Note that when a PMR is issued for a pregnancy registry and a complementary study, the safety concern is only counted once.*

Many of the other reasons for insufficiency may be attributed to the boundaries of the ARIA system. The Sentinel Innovation Center is pursuing an opportunity to stand up an analysis-ready database with claims-linked, structured EHR data and investigating advanced methods for integrating unstructured data. More information is provided in the Sentinel Innovation Center section of this report. Incorporating structured and unstructured EHR data into the ARIA system may help address core causes of insufficiency and increase the ARIA system's ability to assess drug safety concerns.

In addition to the root causes of insufficiency presented above, FDA tracks which elements of an epidemiological design require capabilities beyond the ARIA system. When the ARIA system is found insufficient to address a safety concern, one or more of five epidemiologic study categories are identified as having requirements that the ARIA system could not address:

- Surveillance or Study Population
- Exposure(s) of Interest
- Outcome(s) of Interest
- Covariate(s) of Interest
- Surveillance Design or Analytic Tools

The "domains" of insufficiency, when analyzed in conjunction with the medical products and health outcomes that FDA has wanted to study, help inform which kinds of medical products or outcomes the ARIA system is currently well-suited to address, and which are harder to assess. Of the 48 safety concerns found insufficient due to inability to ascertain the exposure of interest, antithrombotic agents, immunosuppressants, and drugs used in diabetes were top three medical products that were unable to be assessed in the ARIA system. Results are presented in Table 6.

Insufficient sample size is a leading reason for insufficiency amongst safety concerns found insufficient due to exposure. Given the large sample size in the Sentinel Distributed Database, it is likely that this is due to low uptake of the medical product, treatment guidelines, or because it is a therapeutic for a rare disease or indication.

Table 6: Distribution of Safety Concerns Insufficient for Assessment in ARIA Attributed to Capture of Product Exposure, by Regulatory Approval Stage *(N = 48 Safety Concerns).*

Medical Product (ATC 2nd Level Therapeutic Subgroup)	Safety Concerns Identified Pre-Approval	Safety Concerns Identified Post-Approval	Total
Antithrombotic agents	2	5	7
Immunosuppressants	7	0	7
Drugs used in diabetes	2	4	6
Blood substitutes and perfusion solutions	4	1	5
Antiprotozoals	4	0	4
Analgesics	0	3	3
Antineoplastic agents	0	3	3
Other alimentary tract / metabolism products	3	0	3
Antivirals for systemic use	1	1	2
Anesthetics	0	1	1
Bile and liver therapy	1	0	1
Calcium homeostasis	1	0	1
Contrast media	0	1	1
Drugs for acid related disorders	0	1	1
Immunostimulants	0	1	1
Lipid modifying agents	1	0	1
Vitamins	1	0	1
Total	27	21	48

Table 7 shows the distribution of health outcomes of interest for 132 safety concerns that were deemed insufficient due to inability to identify the outcome(s). Pregnancy related outcomes ranked the highest, likely due to the 2019 guidance for pregnancy PMRs previously discussed and the common need to identify non-specific fetal outcomes requiring signal identification capabilities. For cancer-related outcomes, insufficient observation time drove insufficiency determinations since considerable follow-up time is needed to identify long-latency outcomes. Other driving factors of insufficiency for outcomes were the inability to identify the outcomes through code-based algorithms (i.e., absence of validated code list algorithm or inability to identify clinical concepts with available terminologies/existing algorithms). Supplemental clinical data and requirements for linkages to external data sources were other driving factors.

Table 7: Distribution of Safety Concerns Insufficient for Assessment in ARIA Attributed to Capture of Health Outcome, by Regulatory Approval Stage *(N = 132 Safety Concerns)*.

Health Outcome (MedDRA System Organ Class)	Safety Concerns Identified Pre-Approval	Safety Concerns Identified Post-Approval	Total
Pregnancy, puerperium, and perinatal conditions	42	3	45
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	9	1	10
General disorders and administration site conditions	9	0	9
Cardiac disorders	6	0	6
Infections and infestations	4	2	6
Injury, poisoning and procedural complications	1	4	5
Nervous system disorders	4	1	5
Psychiatric disorders	4	1	5
Immune system disorders	4	0	4
Respiratory, thoracic, and mediastinal disorders	2	2	4
Hepatobiliary disorders	2	1	3
Surgical and medical procedures	3	0	3
Blood and lymphatic system disorders	2	0	2
Musculoskeletal and connective tissue disorders	2	0	2
Renal and urinary disorders	2	0	2
Skin and subcutaneous tissue disorders	2	0	2
Vascular disorders	2	0	2
Gastrointestinal disorders	0	1	1
Metabolism and nutrition disorders	0	1	1
Product Issues	0	1	1
Other[1]	12	2	14
Total	112	20	132

[1] *A recording of "Other" indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.*

Figure 13 displays the breakdown of safety concerns the ARIA system was found insufficient to address by regulatory approval stage and categorizes the epidemiology category the ARIA system was insufficient to address in each intended study. Of the 133 safety concerns studied in the ARIA system, 70% were identified post-approval.

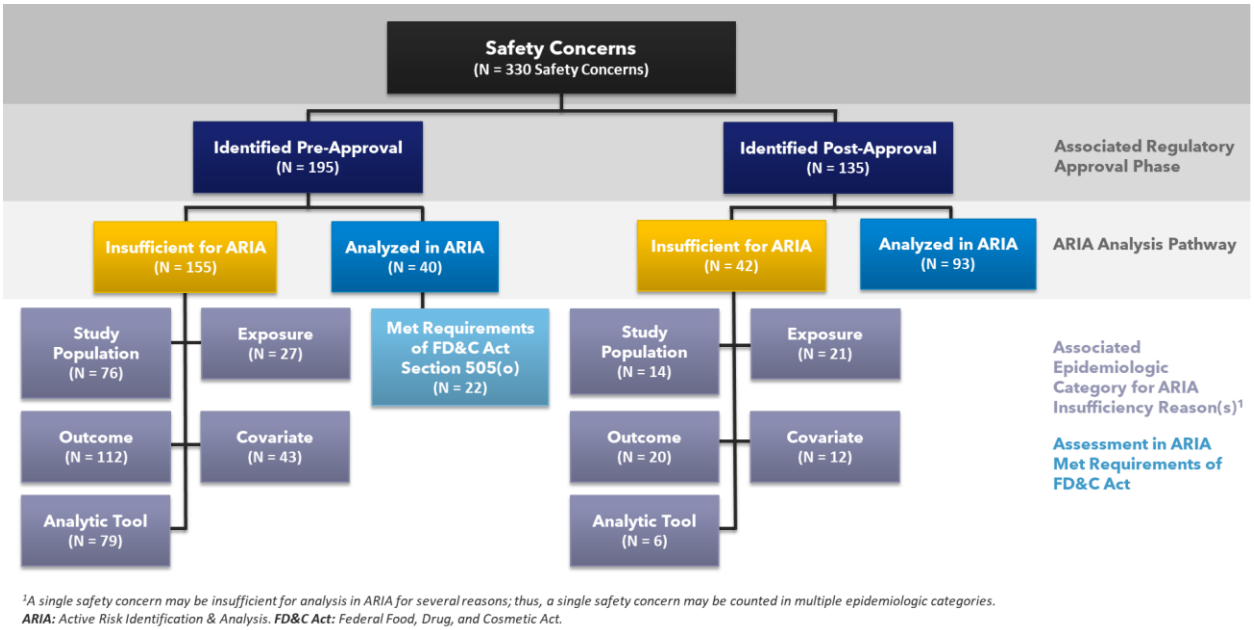


Figure 13: Breakdown of Safety Concerns by Regulatory Approval Phase. *In accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 505(o), FDA assesses whether ARIA is sufficient to study safety concerns prior to issuing a postmarket requirement (PMR). This figure breaks down which safety concerns were insufficient for evaluation in ARIA, by regulatory approval phase and epidemiologic categories for ARIA insufficiency reason(s). A single safety concern for which ARIA was determined to be insufficient may be associated with one or more epidemiologic categories of insufficiency.*

3.1.2. Expanded Medical Product Safety Work within the Center for Drug Evaluation and Research

While investigation of safety concerns in the ARIA system is the Center for Drug Evaluation and Research's core use of Sentinel, the Center also uses Sentinel to support work of its various offices.

Support of Risk Identification and Mitigation Strategy (REMS) Drug Safety Program

Sentinel has developed capabilities to support the Risk Evaluation and Mitigation Strategies (REMS) drug safety program. FDA requires a REMS for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh the risks. Sentinel has analyzed several medical products associated with the REMS program, including vericiguat, dronedarone, and mycophenolate. Sentinel also developed an Interrupted Time Series analytic tool to assist in assessing impact of regulatory actions, such as implementation of a REMS. This tool was beta-tested in an analysis assessing a 2010 FDA Drug Safety Communication for long-acting beta-antagonists (LABAs). Sentinel has supported monitoring of uptake of drugs that fall under approved REMS that employ "Elements to Assure Safe Use" (ETASU) and require medical interventions or other actions by healthcare professionals prior to prescribing or dispensing the product. In another example, Sentinel estimated the number of pregnancies among women with heart failure to understand patterns in heart failure therapy and health outcomes to inform FDA's decision on whether to issue a REMS. The Sentinel analysis provided information that contributed to the review team's determination that existing labeling would provide sufficient information to ensure the benefits of vericiguat outweigh its risks.

Generic Drugs

The Office of Generic Drugs has used Sentinel in a variety of ways. In 2016, a prototype analytic tool was developed that could assess switching patterns between brand and generic drugs. In 2018, this tool was integrated into the core Sentinel analytic toolset and has been used in multiple analyses since. For example, this was recently used to examine switching rates among users of different generic immediate release mixed amphetamine salts after FDA received reports of a lack of effectiveness with specific generic products.

Medication Errors

Sentinel analyses have also produced insights into medication error analysis and prevention. In one example, Sentinel characterized the incidence, cause, outcomes, and stage, (e.g., dispensing or prescribing), of low-dose oral methotrexate to identify potential errors in its administration. Supported by a chart review, Sentinel found the incidence of methotrexate wrong frequency dosing errors to be 0.4%. FDA used these findings to revise the methotrexate labeling in 2019. The revised labeling added a new Warnings and Precautions section on the risk of improper dosing, removing an option for doses given every 12 hours for three days each week, and further recommending that patients and caregivers be instructed to take methotrexate as directed as dosing errors have led to fatal toxicity. In July 2020, the Institute for Safe Medication Practices highlighted the labeling revision in their Medication Safety Alert! newsletter.

FDA-Catalyst

FDA-Catalyst is a program within the Sentinel Initiative that combines data collected from interactions with patients and/or providers (i.e., primary data) with the Sentinel System data infrastructure (i.e., secondary data). It is overseen by the Office of Medical Policy within the Center for Drug Evaluation and Research.

A key project was the Implementation of a Randomized Controlled Trial to Improve Treatment with Oral Anticoagulants in Patients with Atrial Fibrillation (IMPACT-AFib). The FDA used the Sentinel Distributed Database to identify patients with atrial fibrillation who were provided with an educational intervention to determine whether additional educational efforts in stroke prevention would result in increased use of oral anticoagulants in accordance with guideline-based best practices.[1,24,25]

FDA-Catalyst has also sponsored the development of the FDA MyStudies System. Analysis of health outcomes can be limited in administrative claims and EHRs due to missing information around over-the-counter drug use, patient reports on pain and discomfort, social behaviors, and environmental factors. In an effort to address these limitations, Sentinel developed the FDA MyStudies mobile application, a customizable mobile device application developed to collect data on patient's experience in real time.[26] Sentinel then worked with Kaiser Permanente Washington to execute a pilot of the application with a cohort of pregnant women. Participants used the application to provide information not readily available in electronic health data, including short-term illness history during pregnancy, smoking and vaping history, and vitamin use history, among others. This information was linked to their EHR data at Kaiser Permanente Washington to provide a more complete picture of maternal health factors.[27] Following the completion of this pilot project, the FDA MyStudies system was leveraged to support the Limit JIA clinical trial and SPARC IBD studies as real-world evidence demonstration projects.

FDA-Catalyst is also supporting an effort to link a subset of patients in the RELIANCE trial, led by the PCORnet Chronic Obstructive Pulmonary Disease (COPD) Patient-Powered Research Network, to Medicare fee-for-service data. The RELIANCE trial seeks to evaluate the efficacy of roflumilast versus azithromycin therapy in preventing COPD exacerbations. In parallel, Sentinel, in collaboration with the Department of Population Health Sciences at the Duke University School of Medicine, will link Medicare-eligible patients from the RELIANCE trial to traditional fee-for-service Medicare data.

The goal of this linkage activity is to better understand primary and secondary outcomes while also providing an opportunity for Sentinel to test distributed regression analysis methods. The results of this project will ultimately help inform the FDA's use of real-world evidence and support the development of infrastructure and methods to conduct pragmatic clinical trials.

COPD, Asthma, and Respiratory Disease Effectiveness

As part of the COPD, Asthma, and Respiratory Disease Effectiveness (CARE) for 21st Century Cures project of the Office of Medical Policy, Sentinel has assessed feasibility for comparative effectiveness studies of medications used for the management of COPD and asthma. The Sentinel Distributed Database and Sentinel's analytic tools are being used to identify distinct cohorts of COPD and asthma patients within the Database; to collect data on those patients' exposure to therapeutics; detect rates of exacerbations, hospitalizations and medication use among the COPD and asthma cohorts defined in the initial analyses; and conduct comparative effectiveness analyses of patients treated with azithromycin and roflumilast for preventing COPD and asthma exacerbations. These analyses were supplemented by a sub-study focused on acute respiratory failure, in which Sentinel developed definitions for diagnoses of acute respiratory failure among patients with COPD and asthma. The CARE analyses will culminate in an additional study designed to prospectively replicate the ongoing RELIANCE trial mentioned above. This work will add to knowledge about how real-world data can be used for comparative effectiveness evaluations and contribute towards the use of "real-world evidence" towards regulatory decision-making.

3.2. COVID-19 Response

FDA used Sentinel to support their response to the COVID-19 pandemic. A key contribution of Sentinel was the quick expansion of data sources to meet FDA's needs for response, including the development of the Rapid Distributed Database, increased work with PCORnet and HCA Healthcare, and onboarding of new Sentinel Data Partners such as TriNetX. The ability to quickly adapt to the changing needs introduced by the COVID-19 pandemic was possible due to the existing infrastructure, processes, and personnel already in place. This enabled Sentinel to implement a multi-pronged approach to the COVID-19 response. While initially driven by the COVID-19 pandemic response, these data sources have diversified the real-world data available to FDA for regulatory decision-making.

FDA also used Sentinel to perform a variety of COVID-19 related analyses, including:

- A project that validated claims-based algorithms for identifying hospitalized COVID-19 patients;
- A project that developed a master protocol for assessing the natural history of COVID-19;
- An assessment of the natural history of disease among hospitalized COVID-19 patients in collaboration with HCA Healthcare that described patient characteristics, healthcare utilization, disease progression, and outcomes in adult and pediatric patients hospitalized with COVID-19;
- A project to describe the national history of coagulopathy among COVID-19 patients in the Rapid Distributed Database, which included active engagement with the Reagan-Udall Foundation for the Food and Drug Administration's Evidence Accelerator Parallel Analysis Workgroup;[28]
- A project to assess the association between race and ethnicity and critical COVID-19 and in-hospital death that use data from the Rapid Distributed Database, TriNetX, and PCORnet;
- A project in collaboration with the European Medicines Agency to understand the natural history of COVID-19 disease in pregnant women, including disease severity and clinical outcomes of COVID-19, medication utilization, and impact of COVID-19 treatment on neonatal outcomes that was performed in the Rapid Distributed Database;
- A project to perform near real-time monitoring of utilization of critical drug supplies that utilized inpatient data from HCA Healthcare, TriNetX, and IBM® Explorys;

- A project monitoring a set of Emergency Use Authorization (EUA) monoclonal antibodies and antivirals to understand utilization patterns and medical and drug coverage requirements in the Rapid Distributed Database; and
- A project evaluating use of systemic corticosteroids for COVID-19 patients in the outpatient setting after the issuance of treatment guidelines by the National Institutes of Health in the Rapid Distributed Database.[29]

Analyses in HCA Healthcare during the pandemic also provided invaluable insight into the capture of oxygen related therapies in the hospital setting, revealing that identification of such care via diagnosis and procedure codes alone greatly underestimates use – a lesson of import to the wider field of epidemiology. The size and depth of the inpatient data available from HCA Healthcare can help strengthen Sentinel's ability to assess drug safety concerns after the COVID-19 pandemic phase ends.

An important aspect of Sentinel's COVID-19 work was engaging with the Reagan-Udall Foundation for the Food and Drug Administration's COVID-19 Evidence Accelerator. The Evidence Accelerator provided a unique venue for major data organizations, government and academic researchers, and health systems to gather and design studies and share their results. Sentinel led the Parallel Analysis workstream describing the natural history of coagulopathy in COVID-19 and presented methods and study findings at more than 10 Evidence Accelerator meetings.

Collaboration with international partners played a major role in COVID-19 activities. Following the completion of an Assessment of the Natural History of Coagulopathy in COVID-19, the study was replicated by European Medicines Agency (EMA) and Health Canada. The Canadian Network for Observational Drug Effect Studies, supported by Health Canada, executed their analysis on their data formatted into the Sentinel Common Data Model and using the same analytic programming code used by the Sentinel System. These international teams have coordinated to perform an international meta-analysis of these studies and develop an associated manuscript. Sentinel is also working with EMA to replicate an EMA protocol, called CONSIGN, that assesses medication use among pregnant women with COVID-19 and investigates disease severity and clinical outcomes for these women compared to non-pregnant women with COVID-19. Sentinel will also partner in the future with EMA to conduct a meta-analysis to combine the results from the European and U.S. studies.

3.3. Use of Sentinel Outside of the Center for Drug Evaluation and Research

FDA has supported projects across FDA centers through Sentinel. Below, key engagements outside of the Center for Drug Evaluation and Research are described.

Medical Countermeasures Initiative

The Office of Counterterrorism and Emerging Threats engaged with Sentinel as part of the Medical Countermeasures Initiative. The goal of their work was to understand the potential contribution of Sentinel to study medical countermeasure safety and effectiveness as well as provide baseline information for comparison during a public health emergency. Influenza served as the use case in three activities. The first analysis in the Sentinel Distributed Database described individuals with influenza-like illness in three influenza seasons and estimated the incidence of ordinal endpoints in the inpatient setting including hospitalization, intensive care unit stay, mechanical ventilation, and in-hospital death overall and with respect to treatment timing.[3] This was followed by an activity to examine whether residual confounding was evident in evaluating the association between influenza antivirals and influenza complications in observational studies.[4] Finally, HCA Healthcare was leveraged to assess baseline characteristics, treatment, and endpoints among patients hospitalized with influenza-like illness solely in inpatient EHR data.[5] As previously mentioned, in March of 2020, Sentinel was able to leverage this work with HCA Healthcare to quickly add COVID-19 cohorts at the FDA's request. This was possible due to the previous foundational work that had been completed.

Biological Products

The Center for Biologics Evaluation and Research (CBER) performed a variety of projects with Sentinel to support postmarket surveillance of biological products. In 2017, CBER completed a project in Sentinel with HCA Healthcare to explore capture of transfusion-related acute lung injury in inpatient electronic medical record data, a project that included a chart review for case definition. Key findings were limitations of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes as mechanisms to identify transfusion related acute lung injury as an outcome.[30] CBER engaged with Sentinel to enable a mechanism to query the Sentinel Distributed Database as needed through 2021, completing over 45 analyses. Key highlights included a series of queries related to the FluMist vaccine in children in response to a temporary withdrawal from the market due to effectiveness concerns and analyses to provide information on adherence to FDA-approved rotavirus vaccine administration schedules in infants.

Medical Devices

The Center for Devices and Radiological Health has engaged with Sentinel to perform several regulatory analyses. Of note is a series of analyses aimed at investigating the safety of Essure, a permanently implanted birth control device for women. In response to reports that women were having additional surgeries to remove the Essure implants due to adverse symptoms, Sentinel supported the Center for Devices and Radiological Health with performing a comparative analysis of adjusted rates of hysterectomy and salpingectomy surgeries among women with the Essure hysteroscopic sterilization compared to those that underwent laparoscopic tubal ligation.

4. Sentinel as a National Resource

Sentinel is a valuable repository of longitudinal data for a large, geographically diverse population. With full capture of medical interactions including exposures and outcomes, Sentinel's data are the largest resource of its kind, allowing for sample sizes large enough to support many complex studies with sufficient statistical power. It has been shown to detect rare events like intussusception following rotavirus vaccination and generate valuable information on medications with low exposure prevalence in select populations. Due to the distributed nature of the network and strict policies protecting patient privacy, none of Sentinel's Data Partners practice data obfuscation including date shifting, thereby enabling accurate analyses of trends of medical product utilization or health outcomes over time.

Sentinel is committed to sharing resources, including analytic code and assessment results, with outside investigators. The Public Accessibility of Tools, Methods, and Results section of this report describes the mechanisms in place that accomplish such. Further, the Publications and Contributions to the Scientific Community and Public Events sections detail how Sentinel broadens its user base. All told, the use of these resources beyond FDA's walls demonstrates the far reach of the Sentinel infrastructure.

4.1. Use of Sentinel Outside of FDA

Centers for Disease Control and Prevention (CDC)

Sentinel partnered with the CDC on three distinct study questions for the purposes of disease surveillance. Many of CDC's current programs, such as the SEARCH for Diabetes in Youth study, rely on clinical registry sites, which can present challenges in efficiency, cost, and generalizability. As a complement to registry data, CDC worked with FDA to conduct a descriptive study estimating incidence and prevalence of type 1 and type 2 diabetes by age and over time in the Sentinel Distributed Database. Another project characterized patients diagnosed with latent tuberculosis to supplement the current use of national surveys that face the challenge of small sample size. Finally, the wide geographic distribution of Sentinel allowed CDC to add geographic data to a study of doxycycline as post-exposure prophylaxis treatment for Lyme disease given that the infection is emerging in many states with historically low incidence.

Reagan-Udall Foundation for the Food and Drug Administration, including Innovation in Medical Evidence Development and Surveillance (IMEDS) Program

In an effort to extend the capabilities of Sentinel to industry, the Reagan-Udall Foundation for the Food and Drug Administration launched the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program, a public-private partnership that facilitates access to FDA's Sentinel System. The IMEDS System Distributed Database is a subset of the Sentinel Distributed Database and includes healthcare claims data on 111 million patient-lives across nine health plan partners. Study activities within the IMEDS program are a collaborative effort between industry sponsors, the IMEDS Operations Center, the IMEDS Analytic Center, and participating IMEDS Network Partners. IMEDS has completed or initiated nine projects from five different industry sponsors on a range of topics, including collaborations with the European Medicines Agency[6].

National Institutes of Health (NIH) Pragmatic Trials Collaboratory

The NIH Pragmatic Trials Collaboratory enables investigators funded by the National Institutes of Health (NIH) and other not-for-profit sponsors to collaborate with investigators based on Sentinel Data Partners that participate in the FDA's Sentinel System. The network is especially useful for supporting multi-site research programs. It fully leverages Sentinel's data, methods, tools, and querying infrastructure. It can also support direct contact with providers and payors to collect new information or support randomized clinical trials. Studies that have participated in the NIH Collaboratory have assessed Alzheimer's disease and related dementias[7], statin use in older adults with and without cardiovascular disease and diabetes[8], chemotherapy-induced peripheral neuropathy, antibiotic dispensings[9], and cancer screening results.[10]

Biologics and Biosimilars Collective Intelligence Consortium

The Biologics & Biosimilars Collective Intelligence Consortium is a non-profit research consortium dedicated to evaluating the real-world safety and effectiveness of biologics, including biosimilars. The Consortium has used Sentinel's publicly available analytic tools in projects assessing biologic anti-inflammatory agents[11], biologic and biosimilar surveillance[12], biologics and biosimilars ICD-9 to ICD-10 code mapping[13], and long and intermediate acting insulin[14], among others.

4.2. Public Accessibility of Tools, Methods, and Results

Sentinel is committed to transparency of its regulatory analyses and public accessibility of the analytic tools used by FDA for Sentinel analyses. Many of the above organizations can leverage Sentinel's infrastructure due to this commitment to transparency and accessibility.

Sentinel's public Git website is the core mechanism for providing access to Sentinel's analytic tools. The Git website provides further transparency and supports replicability of Sentinel assessments. Sentinel's Git website provides a user-friendly, industry standard platform for the public to access the code and supporting materials for Sentinel's analytic tools. Sentinel's technical resources include:

1. Code and documentation for Sentinel's analytic tools
   - Sentinel Routine Querying System
   - Sentinel Routine Querying System Documentation
   - Sentinel Query Request Package Reporting Tool
   - Sentinel Routine Querying Reporting Tool Documentation
   - Sentinel's Analytic Lookup Files Program Repository
2. Code and documentation for Sentinel's data quality review and characterization programs
   - Quality Assurance Package
   - Quality Assurance Mother-Infant Linkage (MIL) Package
   - Quality Assurance Package Documentation
3. Sentinel Common Data Model documentation
   - Sentinel Common Data Model
4. FDA MyStudies application
   - MyStudies Mobile Application System

While the Git website is aimed at potential users of Sentinel's tools, the Sentinel Initiative website serves as a key mechanism for the broader public audience to engage with the Sentinel program. Sentinel is committed to posting results for all completed analyses. The Sentinel website together with the Git site also support the FDA's applicant notification[15] process by providing platforms to share analytic code and results with sponsors. As of December 31, 2021, reports from 245 analyses are available for viewing on the Sentinel website and 30 analytic packages from completed analyses are available for download from the Git website.

Between 2020 and 2021, the website underwent three major enhancements to improve user engagement, searchability of relevant content, and website organization. Examples of this work included the consolidation of Sentinel Drug Studies to create a central repository of projects by status, an expanded FDA Safety Communication & Labeling Changes webpage to highlight some of the ARIA system's regulatory impacts, and the Sentinel Training Center to help a variety of different stakeholders learn more about Sentinel and its analytic capabilities. The Sentinel as a National Resource webpage provides an overview of how Sentinel's data and tool infrastructure has been used by other entities.

4.3. Publications and Contributions to the Scientific Community

Sentinel has made important contributions to public health by sharing results and insights in peer-reviewed journals and at scientific conferences. Sentinel has published 200 papers in more than 50 distinct peer-reviewed journals, including New England Journal of Medicine, Journal of the American Medical Association, Annals of Internal Medicine, Journal of the American Medical Association Internal Medicine, and Diabetes Care.

Sentinel also makes significant contributions to the scientific community through presentations at national and international conferences. Since 2016, Sentinel has delivered 162 presentations and posters at scientific conferences. These presentations enable sharing of findings and lessons learned in medical product safety surveillance.

4.4. Public Events

The Sentinel System employs various communication mechanisms to connect with stakeholders: online platforms, peer-reviewed publications, and public sessions. Public workshops and training sessions, which take place online and in person, present unique opportunities for existing partners and interested stakeholders to gain a better understanding of all aspects of the Sentinel program. Recordings of all sessions, as well as slide presentations, are posted to Sentinel's online Training Center to ensure open, long-term access.

Public webinars, meetings, and workshops give a broad view of Sentinel's capabilities and current work. Recent themes from didactic webinars include the Sentinel Common Data Model and Sentinel Distributed Database for pandemic preparedness and medical product safety assessments, emerging applications of natural language processing and machine learning, new analytical capacities, and expanded data sources. Public workshops also present an opportunity to reinforce existing partnerships and cultivate new relationships. An International Regulators' Forum, held in 2019, was also dedicated to sharing information about Sentinel with international regulatory agencies and supporting Sentinel's international partnerships.

Annual Public Meetings are two-day events, hosted by the Duke-Margolis Center for Health Policy under a cooperative agreement with the FDA. The Sentinel Operations Center also partners with the FDA to host two public workshops as needed. These events aim to promote engagement and collaboration with patients, industry, academia, and consumers.

Annual public trainings are hosted by the Sentinel Operations Center with a focus on technical applications of pharmacoepidemiologic methods in a distributed data setting. To date, trainings have been attended by federal regulators, industry, and academia, with topics ranging from comparative analytic capabilities, studies in maternal health and pregnancy, to hands-on demonstrations of executing an analysis against data in the Sentinel Common Data Model. As shown in Table 8, attendance has climbed steadily since 2018.

Table 8: Annual Sentinel Public Training Attendees, 2018 through 2021.

Year	Public Training Topic	Attendees
2018	• Comparative Analytic Capabilities • Methods of Identifying Unexpected Safety Concerns • TreeScan Analysis	142
2019	• Applications in Medical Product Safety • Creating a Cohort Identification and Descriptive Analysis Analytic Package: SAS® Software-Based Lab	167
2020	• Maternal Health and Pregnancy	211
2022 (Postponed from 2021)	• Comparative Analysis Method: Inverse Probability and Treatment Weighting	Postponed to 2022

5. Conclusion

FDA has directly supported their mission to protect public health by investing and using Sentinel to help safeguard medical product safety. The ARIA system has been a critical tool for FDA for monitoring and assessing medical product safety, supporting the agency's regulatory decision-making in multiple ways. Further, FDA has been able to increase the return on investment of Sentinel by using the system to support other mission-critical work within FDA, such rapid response to the COVID-19 pandemic, provision of information for the Risk Evaluation and Mitigation Strategies (REMS) program and using FDA-Catalyst to develop and test novel sources of real-world evidence.

FDA's continued commitment to accessibility of Sentinel has fostered use of the infrastructure by industry, other research institutions, and collaboration with other government agencies. Publicly available tools, documentation, and trainings help further the use of the Sentinel architecture.

Ongoing work within the Sentinel Innovation Center holds promise for further integration of real-world data, specifically linked claims-electronic health record (EHR) data. Sentinel continues to grow and adapt to evolving needs while maintaining the scientific rigor required for regulatory-grade analyses.

6. Appendices

Appendix A: Common Abbreviations Used in this Report and Their Definitions

Abbreviation	Definition
ARIA	Active Risk Identification and Analysis
ATC	Anatomical Therapeutic Chemical
CDC	Centers for Disease Control and Prevention
EHR/s	Electronic Health Record/s
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
IMEDS	Innovation in Medical Evidence Development and Surveillance
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health
PDUFA	Prescription Drug and User Fee Act
PMR	Postmarket Requirement
REMS	Risk Evaluation and Mitigation Strategy

Appendix B: Implementation of the Sentinel Distributed Database

Structure

The Sentinel Distributed Database consists of claims and claims-linked-to- electronic health record (EHR) data that Sentinel Data Partners format into the Sentinel Common Data Model. Data Partners maintain and store data at their site. All datasets undergo a rigorous quality assurance process. In aggregate, these datasets make up the Sentinel Distributed Database, representing 788 million person-years of data in the 2000-2021 period.

Over time, the Sentinel Common Data Model has expanded to broaden Sentinel's study capabilities. Each enhancement to the Sentinel Common Data Model explicitly addresses an FDA need or otherwise benefits the ARIA system through increasing the likelihood of ARIA system sufficiency for newly identified safety concerns. A summary of benefits from major enhancements is provided below in Table 9.

Table 9: Enhancements to the Sentinel Common Data Model by Year.

Year	Major Enhancement	Program Benefits
2016	Addition: Inpatient Pharmacy and Inpatient Transfusion tables	• Increases ability to identify exposures of medical products administered in the inpatient setting
2018	Addition: Mother-Infant Linkage table	• Enables assessment of association between prenatal medical product exposures and adverse infant outcomes
2020	Expansion: Addition of COVID-19 results to Laboratory table	• Enables analyses of COVID-19 related safety issues to support FDA's COVID-19 pandemic response
	Addition: Prescribing table	• Allows FDA to better understand prescribing patterns which may affect medical product safety and use, particularly the relationship between physicians' prescribing and patient utilization and adherence • Enables international Data Partners to provide pharmaceutical information from datasets that only capture prescribing
	Addition: Provider table	• Provides information on specialties for any provider who provided a health care service to a patient with records in the pharmacy dispensing, diagnoses, procedures, and prescription tables
	Addition: Facility table	• Captures location data, indicating where care took place, enabling more precise and efficient targeting of specific medical records for chart review, still considered to be the gold-standard validation for claims-based condition, exposure, and outcome identification algorithms
2022, projected	Projected Addition: Patient-reported measures tables	• Supports data from routine screening instruments such as the Patient Health Questionnaire 9 (PHQ-9)

Sentinel has created SAS-based analytic tools that can be parameterized to run a variety of descriptive and comparative analyses on data formatted to the Sentinel Common Data Model. To execute an analysis, Sentinel distributes a parameterized analytic program to Sentinel Data Partners for execution against their own datasets. Data Partners return aggregated results with direct identifiers or other potentially

identifiable information removed, as depicted in Figure 14. Results from Data Partners are aggregated at Sentinel and delivered to FDA.

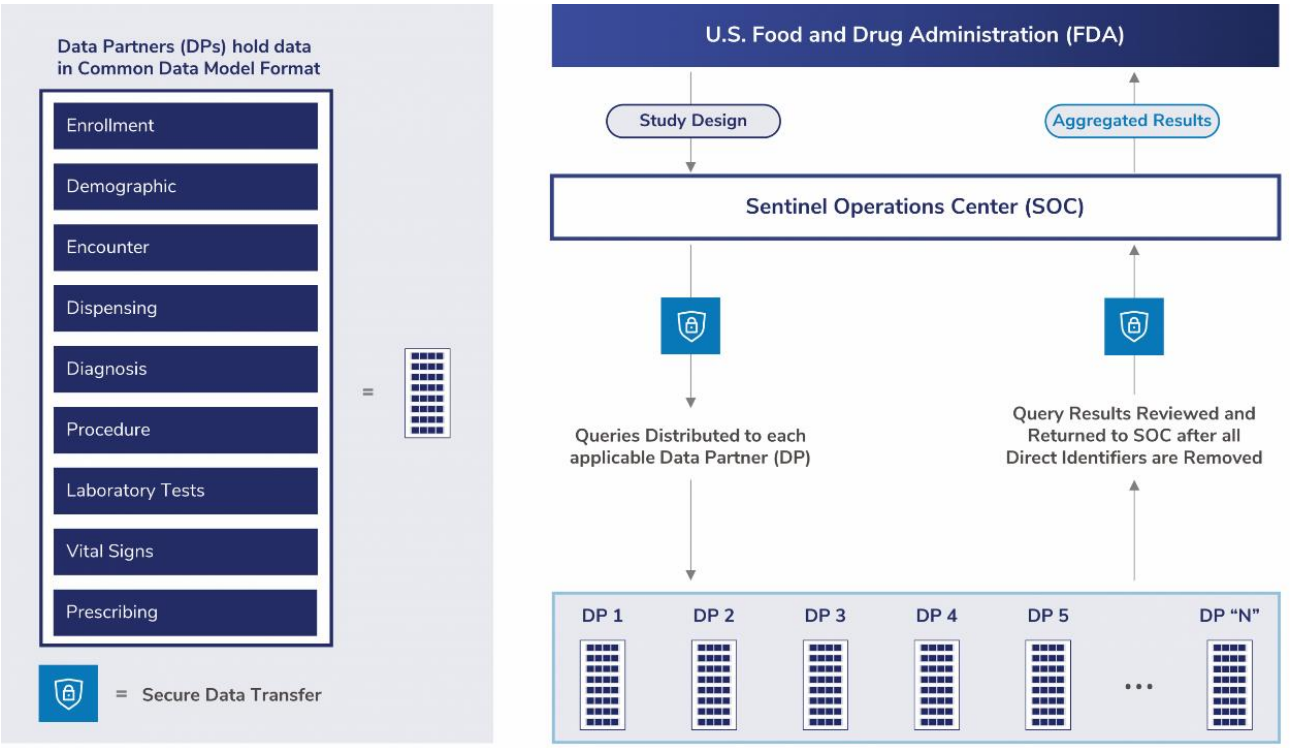


Figure 14: A Combined Collection of Datasets: The Sentinel Distributed Database. *This figure illustrates Sentinel's distributed data approach.*

Data Quality and Review

The Sentinel data quality review and characterization process is a joint effort between Sentinel and Data Partners. Given the distributed structure of the Sentinel System, it is essential that each Data Partner confirm that its data are transformed according to the specifications of the Sentinel Common Data Model so that distributed software packages run without error and results can be aggregated across Data Partners.

Sentinel develops and maintains a quality review and characterization software package that Data Partners execute against refreshed databases prior to making them available for analyses. The software package checks more than 900 different parameters and produces a list of errors and anomalies for the Data Partner to review and resolve. These errors are categorized into Level 1, 2, and 3 checks, as depicted in Figure 15.

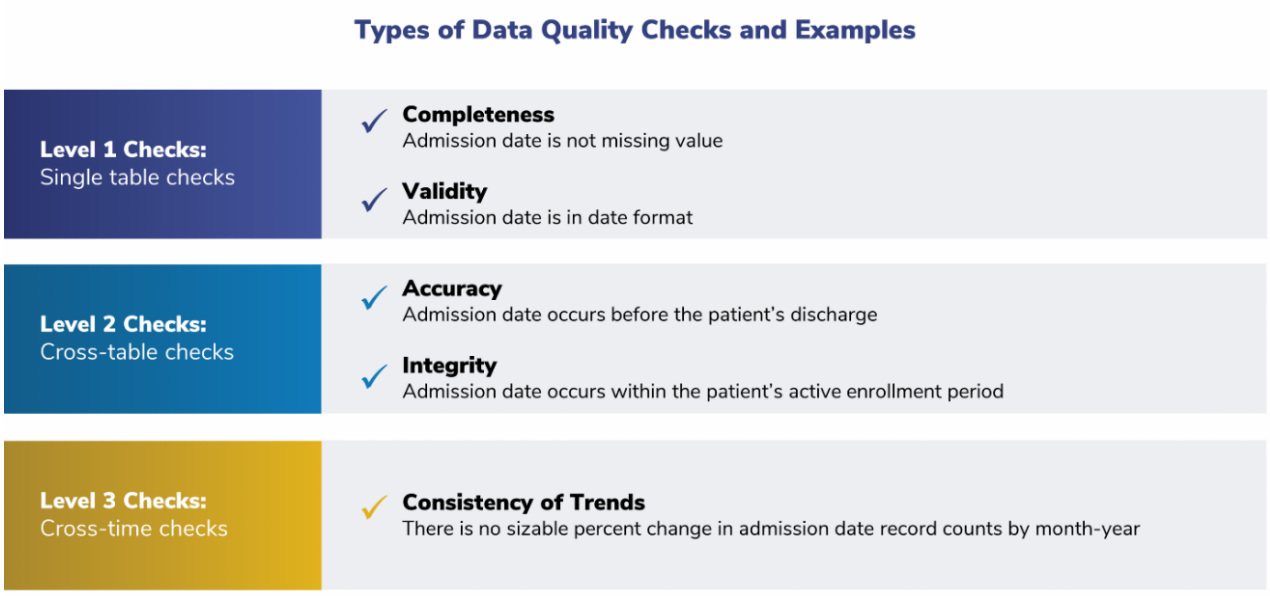


Figure 15: Type of Data Quality Checks and Examples*. Sentinel distributes a quality assurance computer program. This program checks the data according to the standards specified in the Sentinel Common Data Model. There are three levels of data checks, as depicted here. Fine print provides examples of each category of check.*

Once the quality review software package has run all initial checks without failing, output of the program is provided to Sentinel to perform additional quality checks. Sentinel ultimately approves the data for use in analyses and repeats this process for all refreshes of data by a Data Partner. Figure 16 visualizes this quality review process.

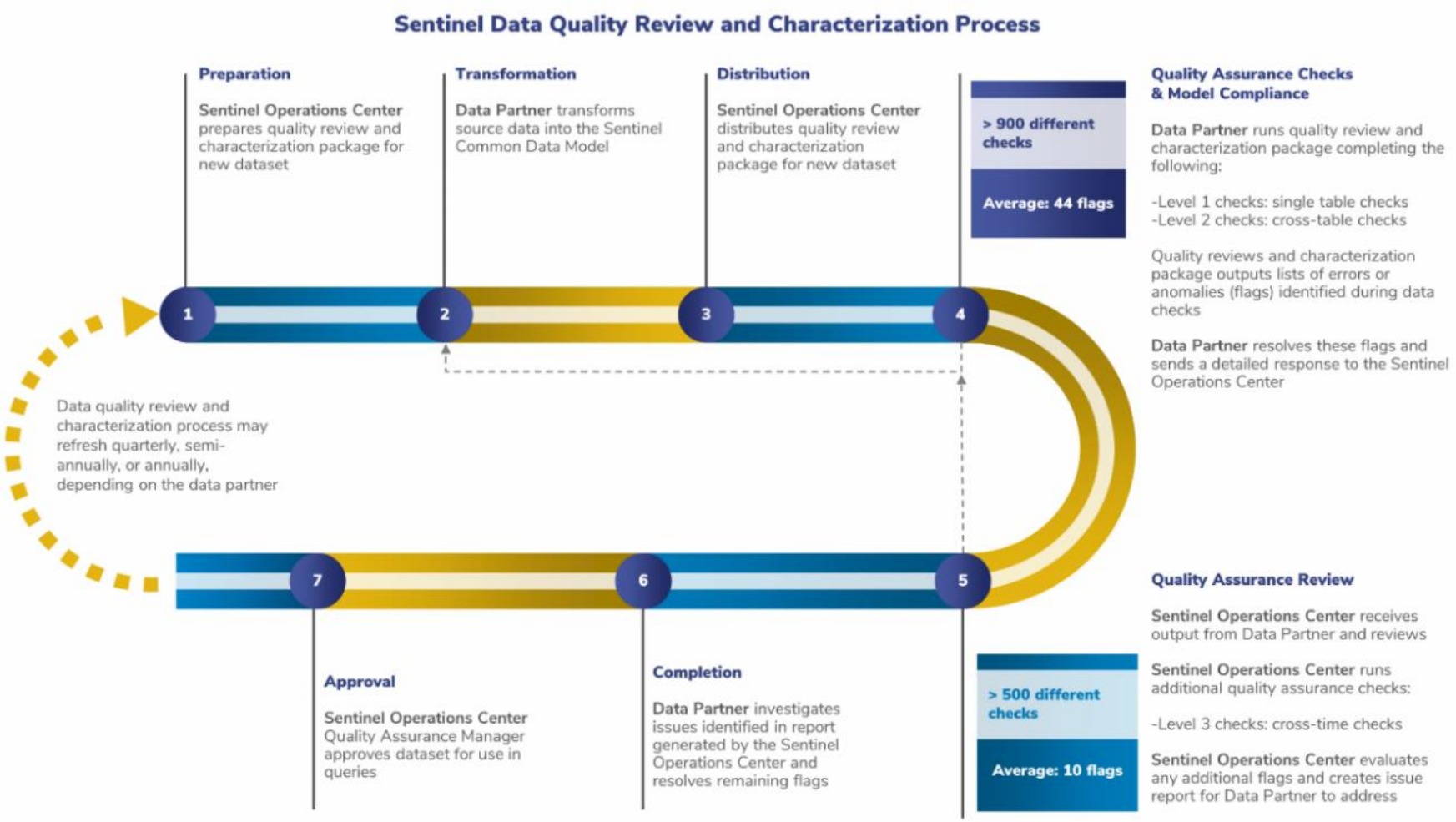


Figure 16: Sentinel Data Quality Review and Characterization Process. The data quality review process is a joint effort between Sentinel and its Data Partners, ensuring that Sentinel data are of the highest quality.

Appendix C: Sentinel's Analytic Tools

Sentinel's suite of analytic tools increases Sentinel's ability to sufficiently address safety concerns within the Active Risk Identification and Analysis (ARIA) system. These analytic tools are pre-defined, parameterized, and re-usable, enabling faster and reliable analyses. The primary distributed ARIA system tool is the Query Request Package, which consists of modules allowing users to select the cohort(s) of interest and perform a specific analysis. The Sentinel analytics tool is built in SAS®. The SAS code is publicly available, along with documentation, and is maintained to support users within and outside of the Sentinel System.

The Cohort Identification and Descriptive Analysis module within the Sentinel analytics tool is the foundation of the ARIA system. The Cohort Identification and Descriptive Analysis module is used to identify, extract, and characterize cohorts of interest based on the specification of user-defined options. For example, users may define medical product exposure(s), health outcome(s), continuous enrollment requirements, inclusion and/or exclusion criteria, pertinent age groupings, and key demographics, among other epidemiologic study design elements.

Over time, several cohort identification strategies have been added to the Cohort Identification and Descriptive Analysis module to increase ARIA system sufficiency. For example, in 2018, an enhancement to the Cohort Identification and Descriptive Analysis module allowed users to calculate simple background rates of health outcomes of interest or rates of medical product use. This module can also characterize patterns of medical product use, describe overlap between primary and secondary treatment episodes, and evaluate product switching patterns. It may also be used for more complex queries that identify the occurrence of health outcomes of interest during exposure to a medical product of interest, including assessment of multiple health outcomes of interest, and evaluating health outcomes of interest during periods of concomitant treatment with other products.

Later in 2018, the Cohort Identification and Descriptive Analysis module introduced the ability to characterize medical product use during pregnancies resulting in live births. This analytic tool enhancement followed the expansion of the Sentinel Common Data Model to include a table linking mothers to their infants and allows the identification of infant birth health outcomes, or of maternal health outcomes following a mother's medical product exposure during pregnancy.

The Cohort Identification and Descriptive Analysis module may be used alone for descriptive purposes or in conjunction with one of several analytic modules to perform a comparative analysis:

- The **propensity score analysis** module uses output from the Cohort Identification and Descriptive Analysis module to create propensity score-adjusted cohorts. It allows users to estimate a propensity score based on predefined covariates, a high-dimensional propensity score, or a hybrid approach. In a general population, the propensity score analysis module uses matching, stratification, or weighting for confounder adjustment, and follows the analytic cohort for outcome assignment in a survival analysis framework. It can be used for one-time, retrospective studies or prospective sequential surveillance with multiple hypothesis tests.

- The **covariate stratification** module uses output from the Cohort Identification and Descriptive Analysis module to stratify an exposure and comparator cohort based on a predefined combination of sex, age group, and/or year of index date. In the non-pregnant population, the covariate stratification module follows the analytic cohort for outcome assignment in a survival analysis framework and can be used for one-time, retrospective studies or prospective sequential surveillance with multiple hypothesis tests. In a population of pregnant women that have delivered infants, the covariate stratification module uses binary outcome assignment and can only be used for one-time, retrospective studies. A separate analytic tool is used to aggregate and summarize results across Sentinel Data Partner sites and perform effect estimation. In the non-pregnant

population, hazard ratios are estimated. In the population of pregnant women that have delivered infants, odds ratios are estimated.

- A **signal identification module** was developed to evaluate potential adverse events related to the use of medical products without prespecifying an outcome of interest. This tool uses output from the Cohort Identification and Descriptive Analysis module and propensity score analysis module to elevate counts of health outcomes of interest among new users of medical products and identify new and unsuspected potential safety concerns. The signal identification module can be paired with two types of study designs – a fixed ratio (1:1) propensity score matched design or a self-controlled risk interval design – to generate an analytic dataset that contains data on several thousand exposure-outcome pairs. The module can be used for prospective sequential surveillance for select study designs. A separate analytic tool is used to aggregate and summarize results across Data Partner sites, which is then analyzed for signal identification using tree-based scan statistical software.
- The **interrupted time series** module was introduced in 2019 to estimate the effects of an intervention over time. This tool uses output from the Cohort Identification and Descriptive Analysis module to compare continuously measured data before and after specified intervention dates. Typically, these data (i.e., study endpoints) are counts of patients that receive a certain medical product or procedure. A separate analytic tool is used to aggregate and summarize results across Data Partner sites and perform effect estimation. Segmented linear regression is used to estimate differences in the slope and level of the study endpoint over time by comparing the post-intervention interval to the pre-intervention interval and analyze pre- and post-intervention time periods. Plots are also generated to visually display the pre- and post-intervention time series.
- The ARIA system tools also include a separate **analytic reporting tool** that is designed to run against the output of Sentinel's analytic modules. The reporting tool allows users to aggregate across multiple Data Partner sites in the Sentinel Distributed Database and create formatted reports. For inferential analyses, users can adjust for confounders and generate effect estimates, utilizing various methods based upon the study design and balancing technique requested in Sentinel's analytic tools.

Appendix D: Detailed List of Sentinel ARIA Studies and Their Analyses, Safety Concerns, and Regulatory Impacts

See accompanying Excel file "*An-Assessment-of-the-Sentinel-System_Detailed-List-of-Sentinel-Studies.xlsx*" for a detailed list of the Sentinel Studies referenced in this assessment.

This data set parses Sentinel ARIA system studies by those actively being evaluated (or anticipated evaluation is known) and those associated with completed assessments. Supporting information per ARIA system study includes:

- All analyses associated with the ARIA system study, categorized by type of analysis and analytic module used, if applicable.
- All safety concerns associated with the ARIA system study.
- All regulatory impact(s) which have been realized as a function of a completed Sentinel study. Note for studies including safety concerns associated with the ARIA system analyses, but were ultimately insufficient for evaluation in the ARIA system, "ARIA Insufficient" is applied as the regulatory impact. Formal regulatory impact(s) are not applicable for these insufficient safety concerns.

Appendix E: Detailed List of ARIA Safety Concerns

See accompanying Excel file "*An-Assessment-of-the-Sentinel-System_Detailed-List-of-Safety-Concerns.xlsx*" for a detailed list of the safety concerns referenced in this assessment.

This data set includes:

- Safety Concern Year
  - Year in which the safety concern was identified
- Assessment Status of each safety concern's associated study
  - Ongoing: study underway and/or future analyses anticipated
  - Completed: a terminal Sentinel analyses is complete; the study may be assessed for regulatory impact
- ARIA Sufficiency
  - Sufficient: the safety concern was assessed in the ARIA system, or is otherwise actively being evaluated in the ARIA system
  - Insufficient: The ARIA system was unable to assess the safety concern
- FDA Center
  - Organizational FDA center associated with the safety concern
- Regulatory Approval Phase associated with identification of a safety concern
  - Pre-approval
  - Post-approval
- Medical Product(s) Under Evaluation
  - Brand and generic names of medical products, if applicable
  - Drug class, if applicable
  - Anatomic Therapeutic Chemical (ATC) classification
- Safety Outcome(s) Under Evaluation
  - Medical Dictionary for Regulatory Activities (MedDRA) classification, using Preferred Term (PT) or High Level Term (HLT)

Appendix F: Definitions of Sentinel Regulatory Impacts

The following table offers operating definitions for each of the regulatory impacts claimed in this report. Where "Other Regulatory Action" was noted, the definition further lists the specific regulatory impacts realized.

Regulatory Impact	Definition
No Regulatory Action Required	*FDA determined that no new action was necessary based on the available information attained from Sentinel. For example, Sentinel data may have provided reassuring new safety information to help demonstrate the adequacy of current product labeling.*
Labeling Change	*Sentinel data contributed to a Drug Safety-Related Labeling Change (DSRLC).*
FDA Advisory Committee Meeting	*Sentinel data were presented at an FDA Advisory Committee (AC) meeting or included in the AC meeting background materials.*
FDA Drug Safety Communication	*Sentinel data contributed to an FDA Drug Safety Communication issued via FDA's MedWatch: The FDA Safety Information and Adverse Event Reporting Program.*
Informed ARIA Sufficiency	*Sentinel data contributed to an assessment of ARIA's ability to evaluate a current or future regulatory question of interest.*
Informed Feasibility or Utility of an Ongoing Postmarket Requirement (PMR)	*Sentinel data contributed insights into how FDA should approach an ongoing PMR.*
Assisted with an FDA Response to a Public Inquiry	*Sentinel data assisted with an FDA response to a public inquiry, such as a Citizen's Petition or Congressional Inquiry.*
Informed Clinical Trial Development	*Sentinel data contributed to the creation, modification, or discontinuation of a clinical trial.*
Informed a New Drug Application (NDA) / Biologics License Application (BLA) Review	*Sentinel data informed an ongoing NDA or BLA for a separate medical product of interest.*
Informed Requests by Another Federal Agency	*Sentinel data were utilized by an agency external to the FDA, including the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), or a Government Accountability Office (GAO) report, among others.*
Other Regulatory Actions	*Sentinel data contributed to a regulatory impact that is not best represented by other categories listed. For the seven (7) cases noted in this report, such impacts include:* • **Makena (Hydroxyprogesterone Caproate Injection) and Its Generics & Use in Pregnancy**: *FDA initiated this analysis to better understand utilization of hydroxyprogesterone caproate (HPC) injection, including Makena® and its generics, among pregnant women in the United States. Sentinel analysis results were presented at an FDA Advisory Committee Meeting for consideration in assessing the potential public health impact of withdrawing Makena's accelerated drug approval. Following the FDA Advisory Committee Meeting, the FDA's Center for Drug Evaluation and Research (CDER) recommended withdrawing Makena's accelerated approval.*

Regulatory Impact	Definition
	• **Aldactone (spironolactone) & Indications for Use**: *FDA pursued a study in the Sentinel System to describe utilization patterns for spironolactone in patients with heart failure (HF) with preserved ejection fraction (HFpEF). The study was initiated as the FDA Center for Drug Evaluation and Research (CDER) Division of Cardiology and Nephrology was considering data from a clinical trial sponsored by the National Institutes of Health (NIH) that found a significantly lower incidence of heart failure (HF) hospitalization among HFpEF patients treated with spironolactone compared to placebo. While there was lower initiation of spironolactone following HFpEF compared to HFrEF diagnosis, the dosing and duration of the first continuous spironolactone episode were similar. As a result of this study, no regulatory action was taken.* • **Zantac (Ranitidine) & Duration of Use**: *This analysis provided information on use patterns of prescription ranitidine in patients with Medicare and private health care insurance. These data, in addition to data from other sources, were used to provide context for CDER's Nitrosamine Impurities Task Force to better understand the use patterns among U.S. individuals. These data also informed the feasibility of a Sentinel analysis to evaluate clinical outcomes associated with prescription ranitidine use.* • **Dolutegravir (Tivicay and Combination Products Juluca, Triumeq) & Exposure in Pregnancy**: *FDA assessed the feasibility of conducting a postmarket study in Sentinel to further investigate preliminary results from an observational study suggesting a higher risk of neural tube defects among offspring of pregnant women using dolutegravir (see the related FDA Drug Safety Communication below). The Sentinel analysis identified insufficient product exposure in pregnant women to support a robust safety assessment.* • **Multiple Sclerosis (MS) Drugs & Exposure before, during, and after Pregnancy**: *Sentinel data contextualized enrollment and recruitment in multiple sclerosis pregnancy registries and described patterns of drug use before, during, and after pregnancy.* • **Qsymia (Phentermine and Topiramate Extended Release) & Patient Characteristics**: *Sentinel data contributed important information regarding potentially viable sources of information to evaluate cardiovascular risk.* • **Respiratory Syncytial Virus-Associated Illness**: *Sentinel data contributed to an assessment of respiratory syncytial virus-associated illness (RSV-AI) and patterns of health care utilization to help inform development of novel RSV therapeutics.*

Appendix G: Fulfillment of Sentinel's Strategic Plan

In January 2019, FDA published a Sentinel System Five-Year Strategy report covering years 2019 through 2023. The document outlines how the Sentinel System and FDA-Catalyst, as part of the broader agency-wide Sentinel Initiative, can continue to grow and achieve its ambitious vision. Specifically, FDA detailed five strategic aims, pictured in Figure 17.

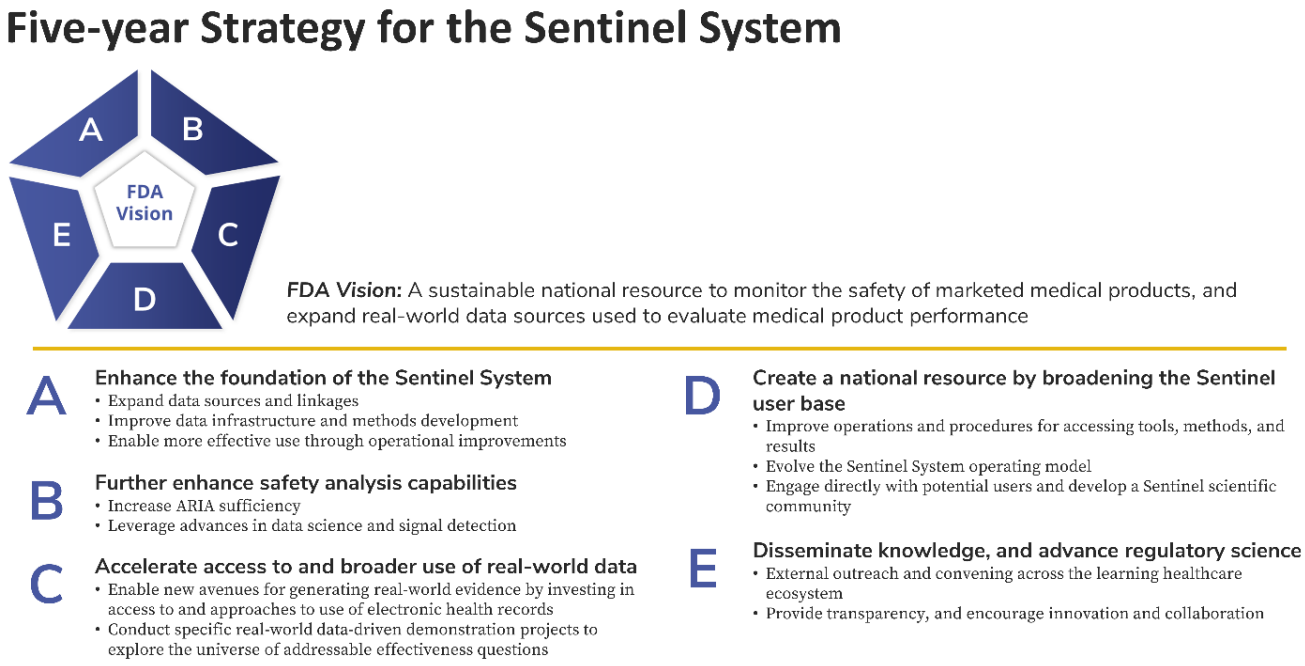


Figure 17: Five-Year Strategy for the Sentinel System. *This graphic depicts the key strategic aims and activities in support of FDA's Vision.*

Table 10 provides a crosswalk of Sentinel strategic aims and activities, and their realized fulfillment mechanisms.

Table 10: Crosswalk of Sentinel's Strategic Plan and Realized Fulfillment Mechanisms.

Sentinel Strategic Aim	Sentinel Strategic Activity	Fulfillment Mechanism(s)
Enhance the foundation of the Sentinel System	*Expand data sources and linkages*	a) Data Resources and Analytic Tools
	Improve data infrastructure and methods development	a) Data Resources and Analytic Tools
	Enable more effective use through operational improvements	a) Public Accessibility of Tools, Methods, and Results
Further enhance safety analysis capabilities	*Increase ARIA sufficiency*	a) Sentinel Innovation Center b) Data Resources and Analytic Tools c) Analysis of ARIA Insufficiency
	Leverage advances in data science and signal detection	a) Sentinel's Analytic Tools b) Sentinel Innovation Center
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*	a) Sentinel Innovation Center b) COVID-19 Response
	Conduct specific real-world data-driven demonstration projects to explore the universe of addressable effectiveness questions	a) FDA-Catalyst
Create a national resource by broadening the Sentinel user base	*Improve operations and procedures for accessing tools, methods, and results*	a) Public Access of Tools, Methods, and Results
	Evolve the Sentinel System operating model	In 2019, Sentinel adopted a three center composition of the Sentinel Initiative. These centers collaborate to advance regulatory science using the Sentinel System: • Community Building and Outreach Center • Innovation Center • Operations Center
	Engage directly with potential users and develop a Sentinel scientific community	a) Public Accessibility of Tools, Methods, and Results b) Public Events c) Sentinel as a National and International Resource
Disseminate knowledge, and advance regulatory science	*External outreach and convening across the learning healthcare ecosystem*	a) Publications and Contributions to the Scientific Community b) Public Events
	Provide transparency, and encourage innovation and collaboration	a) Public Access of Tools, Methods, and Results

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