U.S. FOOD & DRUG ADMINISTRATION

Assessment in Support of the Sentinel System

September 2022

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1 Executive Summary

This assessment report fulfills the Prescription Drug User Fee Act (PDUFA) commitment to analyze and report on the impact of Sentinel System expansion and use for regulatory purposes.[1] The fifth reauthorization of PDUFA (PDUFA VI) in 2017 called for an "expanded set of commitments related to scaling up and expanding the Sentinel System while continuing to embed its use" in Food and Drug Administration (FDA) post-market surveillance operations for regulatory decisions.[2] In subsequent years, the advances in the use of Real-World Data (RWD)[3] to generate Real-World Evidence (RWE)[4] required FDA to expand the use of RWE to inform the regulatory decision making process. Recent changes include the emergence of COVID-19, the expectations for improved RWE quality brought on by 21st Century Cures Act (Cures Act)[5] requirements, and advances in new types of approved drugs (such as an increase in rare disease treatments). Within this context, Sentinel established itself over the last six years as a vital component of FDA's regulatory toolset by focusing on the following areas covered in this assessment:

- Expanding Sentinel data infrastructure to answer increasingly complex questions in an evolving post-market surveillance landscape
- Improving Sentinel's data analysis capability by providing a platform for methodological innovation
- Facilitating transparent communication and engagement opportunities to increase use and awareness of Sentinel's value
- Being responsive to FDA efforts to develop RWE by encompassing sources of RWD, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities brought on by the Cures Act[6]
- Building a modern system that would rely on the electronic health records (EHRs) from about 10 million lives as put forward by the Medical Data Enterprise included in the President's fiscal year 2019 budget[7]
- Enhancing Sentinel as a national resource as evidenced by use of the Sentinel infrastructure by groups outside of FDA such as the Centers for Disease Control and Prevention (CDC)
- Supporting FDA's public health mission (such as responding to the COVID-19 pandemic)

[1] U.S. Food and Drug Administration. (2017). PDUFA reauthorization performance goals and procedures fiscal years 2018 through 2022. https://www.fda.gov/media/99140/download

[2] Refer to Appendix C for a full list of PDUFA VI commitments related to Sentinel implementation.

[3] RWD are data relating to patient health status or the delivery of health care routinely collected from a variety of sources.

[4] RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

[5] The 21st Century Cures Act (Cures Act) was enacted in 2016 to accelerate medical product development and bring new innovations faster to patients who need them. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

[6] Refer to table 3 in the Sentinel 5-year Strategy: https://www.fda.gov/media/120333/download

[7] Refer to https://www.fda.gov/news-events/fda-voices/fda-budget-matters-cross-cutting-data-enterprise-real-world-evidence

This assessment report provides an overview of FDA's activities and progress in each of these seven areas. The following highlights demonstrate the Agency's progress in these target areas and discussed in further detail in this report:

- **Sentinel has met and far exceeded its FDA Amendments Act (FDAAA) requirement**[8] to maintain a network with access to a minimum of 100 million patient lives. Sentinel has access to over 360 million unique patient identifiers, some of which represent different periods of time in the same patient's life.
- **Sentinel supports FDA's mission to protect the public's health by helping to ensure the safety of drugs.** Sentinel contributed to FDA's regulatory mission through 82 studies resulting in over 40 regulatory actions from fiscal years 2017-2021. Sentinel also contributed to the public health outside of investigating safety concern product-outcome pairs with 22 public health studies, most of which related to COVID-19.
- **In 2019, FDA launched a five-year strategy**[9] **for the Sentinel System to guide investments in emerging data science disciplines** (such as natural language processing (NLP), machine learning (ML), and active signal identification) and to expand Sentinel's utility through EHR use. This strategy also addresses Sentinel's use of EHR for regulatory decision making, as required by the 2019 Medical Data Enterprise.
- **The Sentinel Innovation Center (IC) brings together experts from FDA, academia, clinical medicine, and industry to inform the meaningful use of EHRs for regulatory decision making.** The IC's progress contributes new knowledge about—and uses for—RWE in drug safety and other regulatory questions and shows the great potential for integrating high-quality, structured data into Sentinel.
- **Sentinel has increased the richness and use of supplemental data sources including EHR. This increase has strengthened and enhanced Sentinel's impact and value through its capability to address complex drug safety questions** by increasing the richness of available data and the types of questions Sentinel can answer. Recent innovation projects focus on signal identification and building tools to better query EHRs for FDA's regulatory purposes.
- **Consistent with the Sentinel Five-Year Strategy, FDA envisions Sentinel as a national resource**, accessible to multiple Sentinel stakeholders to broaden the use of Sentinel's tools, methods, and data infrastructure. Toward that end, Sentinel has demonstrated its value as a national resource through its publicly available tools and use of its infrastructure in over 20 studies by external groups such as the National Institutes for Health (NIH) Collaboratory Distributed Research Network and CDC.
- **FDA continues to explore methods to expand the breadth of safety concerns that Sentinel can address.** For example, safety concerns involving product use during pregnancy increased beginning in 2018. This affected the percentage of

[8] The Food and Drug Administration Amendments Act of 2007 (FDAAA) required establishing a post-market surveillance system to analyze data from at least 100 million lives by July 1, 2012.

[9] U.S. Food and Drug Administration. (2019). Sentinel System Five-Year Strategy 2019-2023. https://www.fda.gov/media/120333/download

questions that Sentinel could answer as its tools needed to be further developed for concerns related to medication use while pregnant and to in utero exposure. To improve upon this area, FDA invested in analytic enhancement projects, such as developing tools to assess medication exposures during pregnancy and their impact on neonatal or infant adverse events. FDA continues to integrate these analytic capabilities into regulatory work. Beyond its work on pregnancy safety, Sentinel is also exploring the use of negative controls in its analyses to assess the impact of and reduce unmeasured confounding.

- **Sentinel has been the focus of a substantial number of opportunities to improve and sustain sponsor and public outreach and engagement.** Each year, Sentinel offers an annual public workshop to present the latest advances and to seek feedback, several webinars on varying topics from approaches to evaluating drug safety in pregnancy to analyzing EHR data, and hundreds of publications and presentations to advance knowledge of analytic approaches to evaluate drug safety and of using RWD to generate RWE. The Sentinel website was also updated to find information more easily about Sentinel's work.

Sentinel has made substantial progress in developing methods and data linkages, testing, and incorporating novel technologies for more efficient performance, enhancing the use of RWD for evaluating medical product safety, and disseminating knowledge to advance regulatory science. Sentinel continues to deliver value both within and beyond its mandated mission.

2 Introduction

The Sentinel Initiative was created as the result of a 2007 congressional mandate to strengthen post-market surveillance of medical products.[10] The Center for Drug Evaluation and Research (CDER), Office of Surveillance and Epidemiology (OSE) serves as the Sentinel Initiative's executive sponsor. The Sentinel Infrastructure, managed by CDER/OSE, focuses surveillance activities on drug products. In tandem, the Center for Biologics Evaluation and Research (CBER) has developed and manages the Biologics Effectiveness and Safety (BEST) Initiative which focuses on surveillance activities of biological products. CBER BEST, which does not currently use the common Sentinel System infrastructure, is not a focus of this assessment. The Blood Surveillance Continuous Active Network (BloodSCAN) and the Post-market Rapid Immunization Safety Monitoring (PRISM) systems are no longer active elements of the Sentinel System. The types of information obtained via PRISM and BloodSCAN are now generated under the BEST Initiative. CBER conducts active surveillance of biological products using the BEST Initiative to fulfill the 2007 congressional mandate.

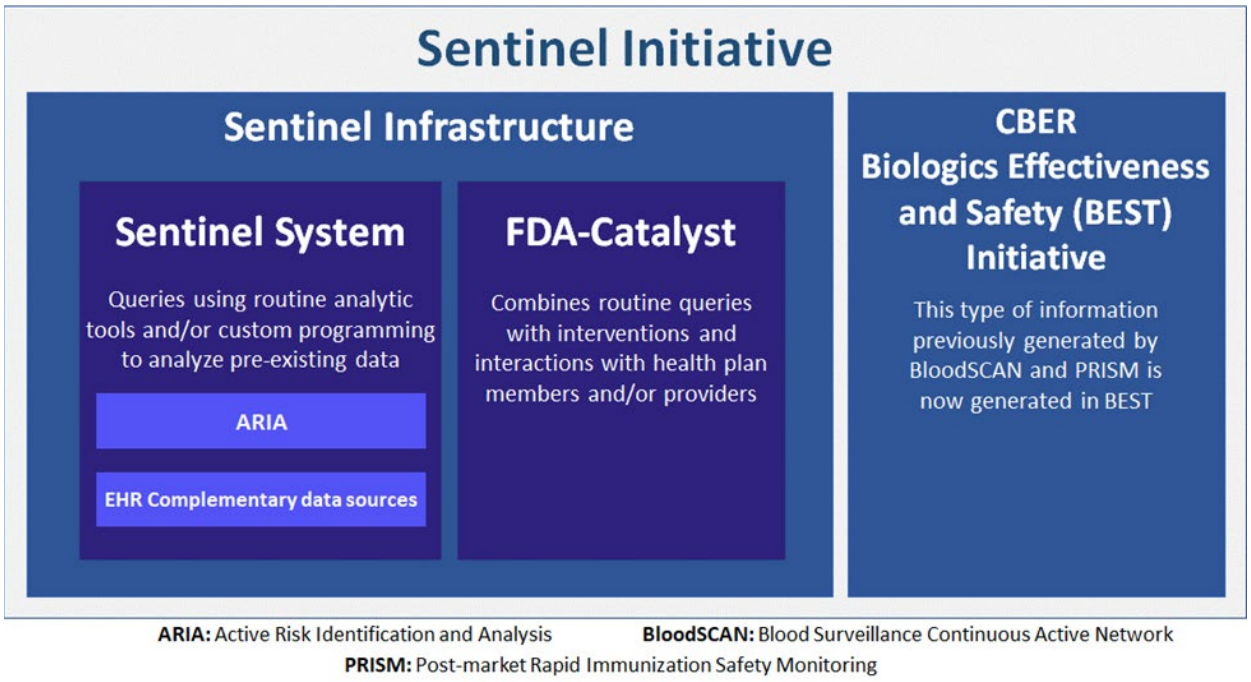


Figure 1. Components of the Sentinel Initiative

Major components of the Sentinel Infrastructure include the Sentinel System and FDA-Catalyst. The Sentinel System was initially developed to answer questions related to the safety of approved medical products by analyzing pre-existing electronic healthcare data. These questions are answered by using statistical methods that examine relationships between product use and adverse events in medical billing information and electronic health records.[11] The Active Risk

[10] More information about the FDA Amendments Act: https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf

[11] This description was retrieved from the Sentinel Initiative website. More information about the description of the Sentinel System can be found at: https://www.sentinelinitiative.org/about

Identification and Analysis (ARIA) system is the primary component of the Sentinel System which has two operational components. The first ARIA component consists of healthcare data from a network of data partners (distributed data) transformed into the Sentinel Common Data Model (SCDM). The second ARIA component consists of pre-defined, parameterized, reusable routine querying tools that can be used with Sentinel's distributed data to conduct post-market product analyses. Using routine querying tools shortens the turnaround time for Sentinel analyses compared to full, protocol-based observational studies that require de novo analytic programming. ARIA is the most widely used portion of the Sentinel System. Beyond ARIA, the Sentinel System includes additional EHR-based data sources that allow FDA to conduct a broader range of drug safety surveillance and public health studies. These data sources represent EHR data aggregators, EHR data warehouses that contain data from across a healthcare system, and multi-site EHR networks. Queries conducted in EHR-based data sources use different methods to analyze the data depending on the source, including web-based query interfaces, pre-defined analytic tools, and custom programming. In this report, "Sentinel" will be used in reference to the Sentinel System.

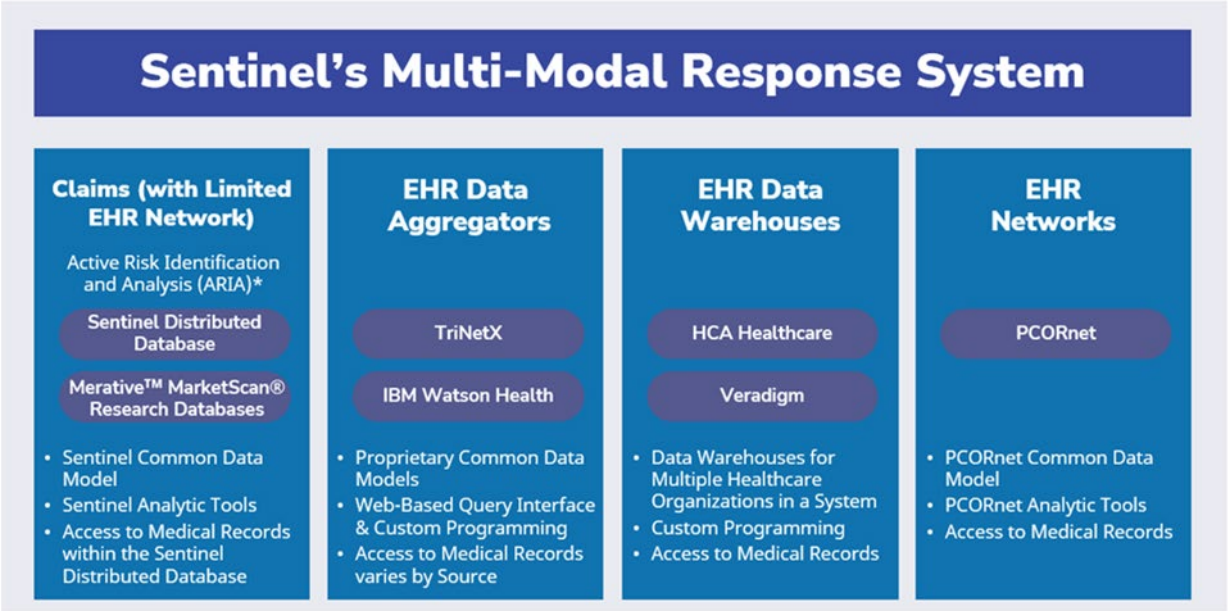


Figure 2. Sentinel System Data Sources

FDA-Catalyst, managed by CDER's Office of Medical Policy (OMP), is another component of the Sentinel Infrastructure. FDA-Catalyst employs routine queries coupled with interventions or interactions with patients and providers.[12] Although the number of FDA-Catalyst projects is limited, the introduction of FDA-Catalyst provided additional capabilities beyond the Sentinel System.

In July 2012, the fourth reauthorization of PDUFA (PDUFA V)[13] included goals and procedures committing the FDA to assess the Sentinel System for evaluating post-market drug safety

[12] More information about FDA-Catalyst can be found at: https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects

[13] U.S. Food and Drug Administration. (2012). PDUFA reauthorization performance goals and procedures fiscal years 2013 through 2017. https://www.fda.gov/media/99140/download

concerns. At that time, the potential contributions of Sentinel towards regulatory decision-making were acknowledged through obligating this user fee support for continued development and implementation of the Sentinel System. FDA conducted its first two assessments of Sentinel in 2015 and 2017[14] to examine Sentinel's operational maturity. These assessments focused on FDA's progress in transitioning from a pilot system (Mini-Sentinel) to a fully operational system that delivers the necessary data, methods, and capabilities to substantially enhance the Agency's regulatory decision-making process.

After the fifth PDUFA reauthorization in August 2017, the PDUFA VI[15] goals and procedures expanded the expectations of Sentinel's performance beyond operational maturity. Three primary areas were now of focus: (1) expanding Sentinel's breadth of available data; (2) advancing Sentinel's data analysis and methods capability; and (3) facilitating communication and engagement opportunities to increase use and awareness of Sentinel's value. PDUFA VI also mandated FDA to assess Sentinel integration into regulatory decision-making by the end of fiscal year (FY) 2022. This third assessment satisfies that mandate.

Unlike the previous two assessments, this assessment benefits from six years of Sentinel engagement and output within FDA's drug safety review process. This report draws on more data to support the analysis and documentation of Sentinel's continued operational maturity and its impact, accomplishment of outcomes, and overall value.

The following subsections present a brief history of Sentinel, an overview of FDA's planned priorities for Sentinel, and the purpose and scope of this third assessment. Appendix B describes the inputs and data sources used while conducting this assessment.

2.1 Background of the Sentinel System

Prior to 2007, the FDA Adverse Event Report System (FAERS)[16] was the principal tool CDER used for post-market drug safety surveillance. FAERS contains adverse event reports from manufacturers as required by regulation along with reports from consumers and healthcare professionals. At that time, FAERS data were supplemented occasionally with observational studies based on administrative claims data to examine certain drug safety issues. The FDA Amendments Act of 2007 (FDAAA) Section 905 required that FDA strengthen its existing post-market safety surveillance for drugs and biological products by directing FDA to create an active post-market risk identification and analysis (ARIA) system, which FDA operationalized as one component of the Sentinel System. FDAAA Section 901 required that FDA determine whether ARIA is sufficient to identify or assess a serious risk prior to requiring post-market studies or clinical trials.[17]

[14] The interim and final assessments of Sentinel for PDUFA V Commitment are available at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-v-commitment-assessment-sentinel-systems-strengths-limitations-and-appropriate-use

[15] U.S. Food and Drug Administration. (2017). PDUFA reauthorization performance goals and procedures fiscal years 2018 through 2022. https://www.fda.gov/media/99140/download

[16] More information regarding the FDA Adverse Event Reporting System (FAERS) can be found at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers

[17] These studies and clinical trials refer to Post-market Requirements (PMR) and Post-market Commitments (PMC). More information can be found here: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments

In response, in 2008 FDA announced its creation of Sentinel as a national system to assess the safety of FDA-regulated medical products across large sets of electronic health care data.[18] FDA launched the Mini-Sentinel pilot program in 2009 to test the feasibility of accessing and analyzing healthcare data and using it to improve FDA decision making. Following Mini-Sentinel's success, CDER transitioned to the full-scale Sentinel System in 2016 to meet the FDAAA requirement for regulated drug and biological products and provide evidence for FDA's regulatory decisions. In October 2017, CBER launched the BEST Initiative to provide evidence for CBER's regulatory decisions on specific biological products. CDER continues to use the Sentinel System for drug and biological products it regulates, while CBER has transitioned to using BEST for most of its post-market safety questions. BEST operates outside of the Sentinel Infrastructure supported by CDER OSE.[19]

The ARIA system,[20] the primary component of the Sentinel System implemented in 2016, combines the data in the SCDM and a set of analytic tools, including a web-based query builder application, in a distributed data environment designed to protect patient privacy.[21] Data contributors, who are primarily health insurers, provide aggregated data to address ARIA queries. Data consist primarily of administrative claims enhanced with select clinical data elements that include laboratory results and vital signs data. If FDA determines ARIA's data coverage and analytic tools are insufficient to evaluate a safety signal arising during the review of a product application, FDA may issue a post-market requirement (PMR), requiring, for example, an observational study or, if an observational post-marketing study will be insufficient, a clinical trial.[22]

In 2019, as part of the President's 2019 budget, FDA created the Medical Data Enterprise to build a modern system that would rely on EHR data from at least 10 million lives.[23] Creating the Medical Data Enterprise coincided with the creation of the 2019 Sentinel Five-Year Strategy, which sought additional expansion of Sentinel's utility to FDA and as a national resource. To support this expansion, FDA established three centers, via two separate contracts, to address the goals outlined in the 2019 Sentinel Five-Year Strategy:[24]

- The Sentinel Operations Center (SOC) oversees ARIA, FDA Catalyst, and core infrastructure development.
- The Innovation Center (IC) focuses on meeting the Real-World Evidence (RWE) Medical Data Enterprise requirement by establishing a query-ready distributed data network containing EHRs of at least 10 million lives.
- The Community Building and Outreach Center (CBOC) engages with non-FDA stakeholders, from the clinical research enterprise to health advocacy groups, to

[18] The 2008 announcement regarding the Sentinel Initiative can be found here: https://www.fda.gov/media/75240/download

[19] U.S. Food and Drug Administration. (November 2021). Biologics Effectiveness and Safety (BEST) Initiative [Government]. https://www.bestinitiative.org/.

[20] An explanation of the ARIA system and how it is used within the Sentinel System can be found on the Sentinel Initiative website. https://www.sentinelinitiative.org/studies/drugs

[21] In addition, the Sentinel toolset includes FDA Catalyst, which combines data from patient and provider interactions with the SCDM to demonstrate Sentinel's real-world evidence (RWE) capabilities.

[22] Refer to FDAAA sections 505(o)(3): https://www.govinfo.gov/content/pkg/PLAW-110publ85/html/PLAW-110publ85.htm

[23] Gottlieb, S. FDA budget matters: a cross-cutting data enterprise for real world evidence. Food and Drug Administration. https://www.fda.gov/news-events/fda-voices/fda-budget-matters-cross-cutting-data-enterprise-real-world-evidence (2018).

> broaden and activate a strong community to advance Sentinel's objectives (please refer to https://www.SentinelInitiative.org).

Sentinel Strategic Plan 2019-2023 and Priorities

In 2019, FDA released a five-year plan[24] for Sentinel to focus the Agency's investment on innovations emerging from new data science disciplines and to expand Sentinel's access to and use of EHRs. The plan targeted the years 2019–2023 for implementation and called for:

- Accelerating use of Sentinel within FDA and scaling capabilities to meet needs
- Exploring the utility of RWD as a tool to support drug development and assess medical product performance
- Facilitating response to legislative mandates regarding medical product safety and effectiveness evaluation
- Expanding Sentinel by facilitating its use by other stakeholders, and fostering innovation and development

The plan established five strategic aims:

1. Enhance the foundation of the Sentinel System
2. Further enhance safety analysis capabilities
3. Accelerate access to and broader use of RWD to generate RWE to evaluate medical product performance
4. Create a national resource by broadening the Sentinel System user base
5. Disseminate knowledge and advance regulatory science to encourage innovation

In carrying out this strategic expansion of Sentinel, FDA has worked to enhance Sentinel's capabilities as a national resource for regulatory decision making in medical product safety. Today, Sentinel complements and augments FDA's other post-market safety surveillance activities with a capability to query recent data, over 90% of which is refreshed at least three times per year.

2.2 Purpose and Scope of This Assessment

This assessment report fulfills a PDUFA VI commitment that must be completed by the end of federal FY 2022. PDUFA VI stipulates, in relevant part, that:[25]

> By the end of FY 2022, FDA will analyze and report on the impact of the Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes (e.g., in the contexts of labeling changes, PMRs, or PMCs[26]).

PDUFA VI called for an "expanded set of commitments related to scaling up and expanding Sentinel while continuing to embed its use" in FDA's post-market surveillance operations for

[24] U.S. Food and Drug Administration. (2019). Sentinel System Five-Year Strategy 2019-2023. https://www.fda.gov/media/120333/download

[25] U.S. Food and Drug Administration. (2017). PDUFA reauthorization performance goals and procedures fiscal years 2018 through 2022. https://www.fda.gov/media/99140/download

[26] Definitions and further information about PMRs and PMCs can be found at: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments

regulatory decisions.[27] To meet this challenge, Sentinel established itself over the last six years as a vital component in FDA's regulatory toolset in three core initiatives covered in this report:

- Expanding Sentinel data infrastructure to answer increasingly complex questions in an evolving post-market surveillance landscape
- Improving ARIA's data analysis capability by providing a platform for methodological innovation
- Facilitating transparent communication and engagement opportunities to increase use and awareness of Sentinel's value

The RWD/RWE ecosystem has continued to evolve, resulting in subsequent, substantial changes to Sentinel to address developing needs. Changes included the recent emergence of COVID-19, the expectations around improved RWE quality brought on by Cures Act[28] requirements, and changes in types of approved drugs (such as an increase in rare disease treatments). As a result, this assessment evaluates Sentinel's impact in the following additional areas:

- Methodological advances to help FDA understand how RWD can be used to generate RWE (as outlined in the FDA's RWE Framework[29] and required by the 2019 President's Budget for the Medical Data Enterprise)
- Sentinel as a national resource such as use of the Sentinel infrastructure by non-FDA stakeholders
- Support FDA's public health mission (such as responding to the COVID-19 pandemic)

Finally, this report concludes with a summary of Sentinel's ongoing and planned activities during its current contract period to further embed its use in FDA regulatory decisions.

[27] Refer to Appendix C for a full list of PDUFA VI commitments related to Sentinel implementation.

[28] The 21st Century Cures Act (Cures Act) was enacted in 2016 to accelerate medical product development and bring new innovations faster to patients who need them. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

[29] https://www.fda.gov/media/120060/download

3 Sentinel System Impact Assessment

Sentinel has addressed its commitment to expand and integrate Sentinel into FDA regulatory processes by implementing activities in six areas:

- Data infrastructure expansion
- ARIA data analysis and tool enhancements
- Communication and engagement
- Advances in RWE for the Medical Data Enterprise
- Signal Identification
- Other uses for public health

This section describes Sentinel's assessed impact in these areas following the last assessment completed in 2017. Through this third assessment, FDA leadership, staff, Congress, industry, and the public can better understand Sentinel's value and usefulness in regulatory decision making to ensure product safety.

3.1 Data Infrastructure Expansion

Sentinel System data infrastructure refers to various components used in the Sentinel Distributed Database (SDD) and supplemental data sources. The primary components of the SDD infrastructure include the SCDM and data partners that maintain an SDD. Although the FDA exceeds its mandated requirements for patient lives, the everchanging post-market surveillance landscape requires Sentinel to continue exploring ways to expand available data to address new types of drugs and evolving safety signals of concern. The following subsections explore the progress Sentinel has made in maintaining the core data infrastructure components to meet the ongoing demands of the post-market surveillance landscape.

Sentinel Distributed Database

The SDD is a federated database physically separated across multiple data partner environments. The SOC independently establishes relationships with data partners who create and maintain copies of their organization's patient data in the SCDM format. The SDD includes data partners that are either national health insurers that principally provide claims data or integrated delivery systems (IDS) that offer clinical data along with administrative claims data. Sentinel's data partner network meets the FDAAA requirement to maintain a network with access to a minimum of 100 million lives. The total number of patient identifiers available in the Sentinel data partner network varies, mostly due to the increase or decrease in participating data partners over time. As of 2021, however, Sentinel has access to data from claims-based data partners covering 341 million unique patient identifiers, far exceeding the FDAAA requirement for 100 million patient lives. The SDD also has access to data from integrated delivery systems covering 22.8 million patient identifiers. Although only representing 6% of the SDD, these integrated delivery systems provide claims data enhanced with select clinical data typically obtained from EHRs. In total for 2021, the SDD contained 363.8 million unique patient identifiers across United States from partnering national and regional health insurers and IDS. Figure 3 indicates the number of unique patient identifiers available in the SDD over time.

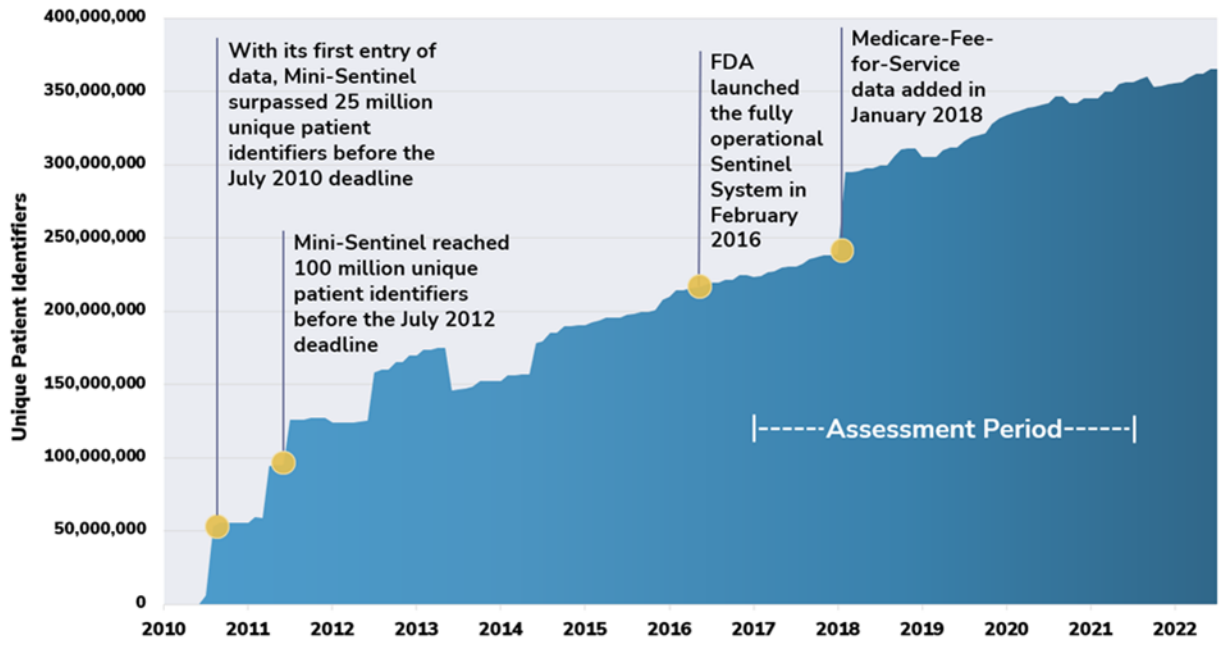


Figure 3. Number of Patient Lives in the Sentinel Distributed Database

Starting in 2021, data partners were further categorized as *core* partners that participate in all distributed queries by default and *specialty* partners participating in distributed queries when their specific populations or available data are useful to achieving study objectives. The six core data partners represent about 95 percent of Sentinel's data. Data partners typically refresh their portion of the SDD quarterly to annually; however, refreshes can occur more often if needed for a specific project. Data partners participating in the Rapid COVID-19 SDD, which was designed to answer questions related to emergent areas of interest (e.g., COVID-19 treatment or patterns of care), have committed to more frequent refreshes of every one to two months. The Reagan-Udall Foundation for the FDA organized the COVID Evidence Accelerator with Friends of Cancer Research to rapidly collect and analyze RWD to answer key COVID-19 questions. Sentinel's infrastructure and partner relationships were instrumental in this initiative.

Through the SDD, FDA can conduct studies that analyze data through programming packages (query packages) distributed to the data partner network. The data partners run the queries against their local data behind their firewall, protecting the privacy of patient data. The data partners return summary level data through a secure portal to the SOC, where results are aggregated, and reports are compiled for FDA. Through this process, relevant FDA regulatory decisions can be informed by RWE generated from RWD on a large scale. The SDD contains data for over 360 million patient lives, including more than 60 million patients with laboratory records and nearly 6 million mother-infant pairs, which are live birth deliveries linked to a mother such that prescription drug use during pregnancy and the impact of in-utero exposure can be studied. Sentinel also has the capacity to request access to de-identified patient-level medical chart data for more than 180 million enrollment records contained within the SDD. This capacity for de-identified medical chart data to be shared with the SOC can be leveraged when FDA requires information only available in medical charts, for example to confirm health outcomes of interest identified in claims data, to support FDA decisions. The Agency's access to this large dataset within its post-market surveillance system means FDA exceeds its FDAAA-mandated requirement for 100 million patients. The size of the SDD, richness of its data, and diverse set of

data contributors consistently generate positive sentiment toward Sentinel by the FDA user community.[30]

FDA evaluates new safety concerns to determine whether ARIA[31] can adequately address each concern using the SDD and parameterizable querying tools rather than issuing a PMR to industry. In these evaluations, known as ARIA sufficiency assessments, FDA assesses whether the SDD has the necessary data and whether the querying tools have the analytic capabilities to support an ARIA study. ARIA sufficiency is assessed across multiple dimensions, including study population, exposures, covariates of interest, health outcomes of interest, and analytic tool capabilities. ARIA sufficiency is bolstered by the type of data linkages available across data partners over time. The creation of the mother-infant linkage (MIL) table in the SCDM enabled FDA to assess potential safety concerns in infants related to medical product use in pregnancy, which previously could not be evaluated in ARIA. The number of linked mother-infant pairs in the SDD has increased by 16.3 percent, beginning with 4.9 million deliveries in 2019 and continuing with 5.7 million in 2021. The number of patient identifiers included in the SCDM Laboratory Results table has increased by 44.6 percent from 2017–2021. The number of patient identifiers included in the SCDM Vital Signs table has increased by 14.8 percent from 2017–2021. The number of patient identifiers included in the SCDM Cause of Death (COD) table has decreased by 16.7 percent over the same period. The decrease in available COD data is due to increased restrictions in specific state laws that resulted in data partners removing that data from the SDD. However, mortality is a key concern when assessing drug safety and needs to be an available outcome. FDA continues to work with the CDC's National Center for Health Statistics to pursue linkage to their National Death Index, which would provide data on date and causes of death, thus enabling robust drug safety studies where mortality is a key concern.

Access to patient data with laboratory information and vital signs allows inclusion of these variables in queries as covariates or to better characterize a health outcome of interest or population cohort. Ultimately, improved linkage can increase the range of concerns ARIA can address through increased capture of health outcomes, exposures, covariates, and population characteristics. When interviewed, Sentinel users continue to request increased laboratory and vital signs information as a significant future improvement. These users also suggest that ARIA sufficiency will improve if the FDA expands access to the following information:

- EHR linkage with claims data
- Health risk factors (e.g., smoking and obesity)
- Clinical health outcomes data
- Expanded linked mother-infant pairs
- Socio-demographic information (e.g., race, education, and income)

As there is not a national patient identifier to link across sources, the number of unique patients across all of Sentinel's data partners is unknown. The count of patient lives spans the years 2000-2021 from U.S. data, during which time a patient may have switched from one health insurance plan to another. Patients who move from one health insurance plan to another in the SDD will

[30] Based on feedback received through focus groups, interviews, and surveys conducted for this assessment. Refer to Appendix B for details regarding input sources for this assessment.

[31] The Active Risk Identification and Analysis (ARIA) combines the data in the Sentinel Common Data Model format and a set of analytic tools, including a web-based query builder, in a distributed data environment designed to protect patient privacy.

appear in the SDD as separate patient lives because they contribute to different databases during different periods of care.

Sentinel Common Data Model

The SCDM is core to the overall Sentinel technical solution: it allows partners within the distributed data network to extract, transform, and load (ETL) their data into a common structure, allowing common queries (i.e., SAS programs) to be distributed and executed.[32] The SCDM is organized into several logical sections where administrative, clinical, and linked data for patients can be captured and stored within each data partner's secure data environment.

The SCDM allows the distributed data network to function as an integrated and interoperable system. The SOC has automated aspects of SCDM maintenance to ease the burden on data partners. It has developed programs that update the SCDM structure and confirm that the refreshes of Sentinel data partners' ETL of data into the SCDM are quality-checked and validated.

The SCDM has proven scalable and extensible. While scalability largely depends on the individual data environments of the data partners, the sheer volume of patient records across the SDD (over 360 million patient identifiers) demonstrates that the structure of the SCDM can accommodate a large scale. The series of changes to the SCDM that have occurred over the years confirm the SCDM's extensibility to improve the utility of data within the data partner network. These changes include such important enhancements as:

- Addition of Prescribing, Facility, and Provider Tables in 2020. The prescribing table includes prescriptions written by a provider.[33] The facility table includes the location of the care facility.[34] The provider table shows the medical specialty of the provider.
- Expanded capture of Laboratory Results and COVID-19 Diagnostic Test Results in 2020
- Additional of a Mother-Infant Linkage Table in 2018

Given that the SOC must coordinate with multiple data partners on updates to the structure of the SCDM as well as to perform regular refreshes of the data (at least three times per year or annually depending on data partner agreements), there are some inherent challenges to Sentinel's flexibility. This inflexibility includes a lengthy process for changing the SCDM and performing the quality assurance to validate that data partners have successfully updated their versions of the SCDM and are ready to execute new query packages.

The intent of ARIA tools was to create modular programs to reduce the time for routine queries. FDA stakeholders comment that timeliness is related to complexity; descriptive studies are quick while inferential analyses take longer. There is a tradeoff of losing customization with ARIA tools; some internal stakeholders' comment that their questions need to be adapted to fit with the

[32] https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

[33] Prior discovery phase findings indicated that provider and facility fields were not populated in a standardized manner across data partners, and that the SCDM could be optimized to improve the identification of facilities and individual providers associated with clinical exposures and outcomes of interest. The addition of prescribing table grants the ability to link medical specialty to diagnoses and procedures, as well as dispensing and prescribing, enhancing FDA's ability to understand medical product utilization.

[34] The facility table is populated at the granularity of a 5-digit ZIP code.

output from the ARIA tools. Sentinel attempts to include high priority variables in the SCDM and statistical analyses to meet anticipated needs.

Supplemental Data Sources

The FDA Sentinel Five-Year Strategy proposes expansion of data sources outside the SDD to assist in various analyses using RWD. The IC is building a query-capable EHR system, but in the meantime, EHR sources such as National Patient-Centered Clinical Research Network (PCORnet) and TriNetX are used for some queries. Increasing the richness of available data and the types of questions Sentinel can answer will enhance Sentinel's value. These data sources include additional information not in claims, such as non-prescription and inpatient medications as well as lifestyle factors such as smoking status, and the possibility of using unstructured data, such as medical record chart notes.

Since 2020, the percentage of studies using data outside of the SDD has increased as indicated by Figure 4.[35] This includes electronic health record-based sources such as HCA Healthcare, PCORnet and TriNetX, as well as the claims-based Merative (previously IBM) MarketScan database. HCA Healthcare, the nation's largest hospital network, provides inpatient EHR data while PCORnet and TriNetX provide both inpatient and outpatient EHR data. A study is a grouping of one or more safety concerns that contains one or more analyses, or queries, which are run in the SDD or a supplemental data source. Some studies have multiple, queries each of which may use a different source (e.g., one study can be composed of one query run in SDD and another query run in MarketScan). Sentinel leverages MarketScan to test queries before distribution to the SDD or other sources. As of the start of 2022, FDA introduced changes to use MarketScan more fully to make ARIA query design more iterative. MarketScan is an interim step before using other data sources; thus, Figure 4 only depicts MarketScan's use when the results were based on its data, not when it was used as a test database for ARIA queries. A study may be represented more than once if its queries cover multiple sources.

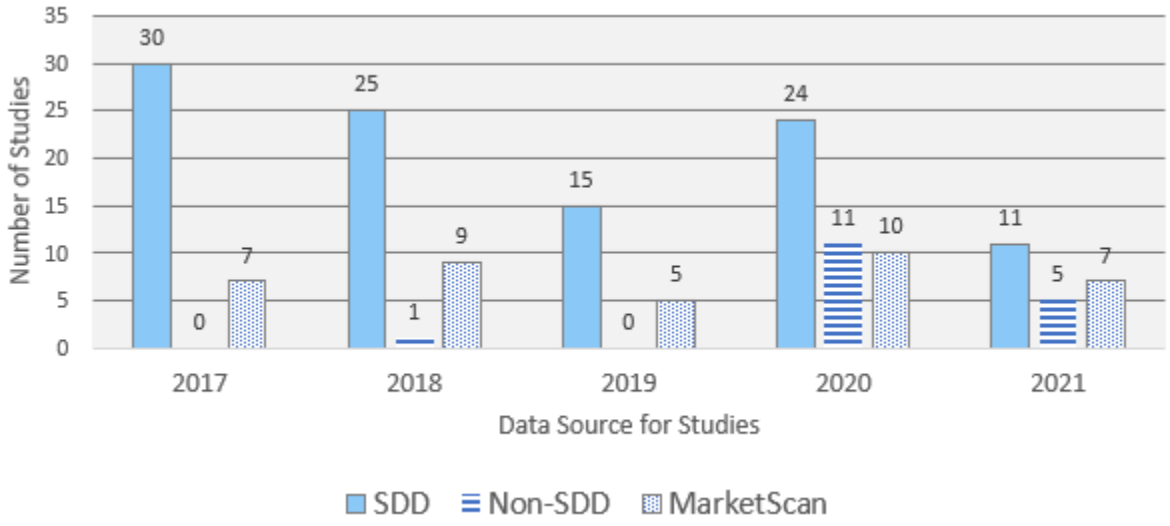


Figure 4. Number of Studies Using SDD and Other Data Sources

[35] Years of studies are based on the fiscal year of the query distribution date for the earliest query associated with a study.

Figure 5 summarizes the number of queries using PCORnet, TriNetX, and HCA Healthcare as sources. The first PCORnet query was distributed in fiscal year 2020 followed by a second in 2021. TriNetX has been used 18 times since fiscal year 2020. Seventeen queries of HCA Healthcare data have been run between FY2018-2021.[36]

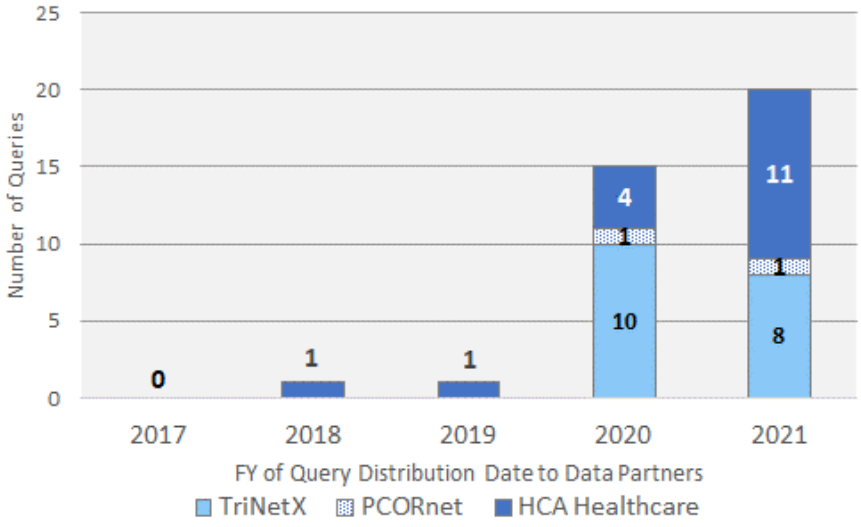


Figure 5. Number of Queries Using PCORnet, TriNetX, and HCA Healthcare

In most recent years, public health studies related to COVID-19 account for much of these non-SDD data sources. For queries of HCA Healthcare, 14 of 17 queries related to monitoring of critical drugs and natural history of disease for COVID-19, but also supported regulatory studies for use of antipsychotics among infants and incidence of neonatal enteroviral sepsis.

EHR sources such as PCORnet, TriNetX, and HCA Healthcare support many methodological studies as well as some regulatory studies. Some examples of non-ARIA regulatory analyses which used TriNetX and PCORnet were for the analysis of:

- Corticosteroid utilization patterns in hospitalized patients with and without a COVID-19 diagnosis in TriNetX
- Emergency Use Authorization (EUA) of baricitinib

3.2 Active Post-market Risk Identification and Analysis System (ARIA) Data Analysis and Tool Enhancements

The ARIA system contained within the Sentinel System consists of a set of reusable analytic tools in a distributed data environment designed to protect patient privacy. As required by FDAAA, through ARIA, FDA scientists can investigate safety concerns without issuing a PMR to drug sponsors. FDA also uses ARIA to provide information to support regulatory decision making (e.g., labeling changes, safety communications, and REMS[37]). The following subsections

[36] Fiscal year refers to date the query distribution package was sent to Sentinel data partners.

[37] Risk Evaluation and Mitigation Strategies available at: https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems.

evaluate ARIA's capabilities in the areas of study design and query development; sufficiency determinations for using ARIA; and analytic tools and methods.

Study Design and Query Development

Sentinel studies can support a spectrum of needs. They help fulfill FDA's regulatory mission for post-market surveillance where the principal focus is on safety concerns with specific drugs. Through Sentinel, FDA can also conduct analyses outside of the realm of drug safety to meet broader public health needs or support analytic tools and methods development. This may involve the development of methods or evaluation of analytic methods or characterizations of Sentinel's RWD to provide insight to FDA on feasibility for future analyses. In this report, studies are grouped into three categories:

- **Regulatory:** ARIA studies or other studies (e.g., studies using a data source other than the SDD, such as TriNetX) conducted for regulatory purposes. This category includes COVID-19 work that relates to a single product.
- **Methods:** Studies in support of expanding Sentinel's data and populations or expanding ARIA's analytic capabilities and reach, with the goal of enhancing FDA's ability to conduct regulatory studies.
- **Public Health:** Studies performed that are not included in other categories but support public health. Examples studies include *Racial and ethnic differences in COVID-19 testing, hospitalization, and mortality*[38] and *Risk of Arterial and Venous Thrombotic Events in Patients with COVID-19 Compared to Influenza*.[39]

Sentinel studies are powered by the capability to query data within the SDD or through non-SDD sources. The SOC provides an arsenal of different query types and makes these available to FDA staff for their studies. Figure 6 shows the distribution of queries for different study types between 2017 and 2021.

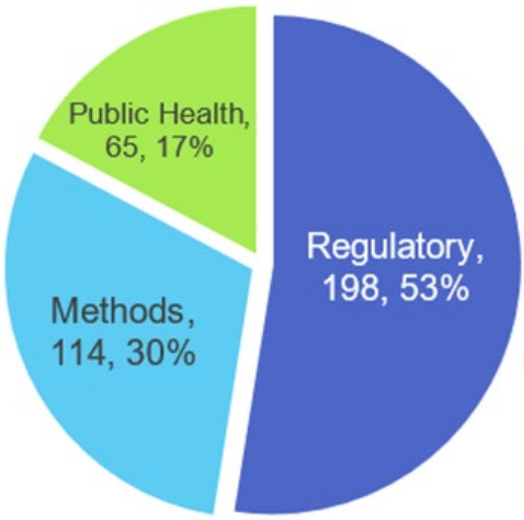


Figure 6. Query Distribution by Study Type between 2017-2021[36]

[38] https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/comparison-race-and-ethnicity-covid-19-testing

[39] https://www.sentinelinitiative.org/news-events/publications-presentations/association-covid-19-vs-influenza-risk-arterial-and-venous

Most of the queries between 2017–2021 were conducted to address regulatory questions or for a methodological purpose. ARIA queries use the SDD and/or MarketScan data and routine (i.e., reusable) querying tools, which may incorporate some custom programming. Non-ARIA queries may employ the SDD, data partners' data not in the SCDM, MarketScan, or other supplemental data sources (e.g., PCORnet, HCA Healthcare, and TriNetX) and fully customized analytical programming. Routine querying tools, primarily developed in SAS, are grouped into four categories depending on the analytic purpose complexity:

- **Level 1 Analysis (L1)** for performing descriptive analyses of cohorts of interest, exposure rates, and episodes of care
- **Level 2 Analyses (L2)** for performing retrospective inferential analyses, including adjustment for confounding with effect estimates and confidence intervals
- **Level 3 Analyses (L3)** for performing complex adjustment for confounding repeatedly as part of prospective sequential analysis
- **Signal Identification Analyses** to detect new and unsuspected safety concerns

These routine querying tools can be customized to address specific study needs. Routine queries with additional customization are designated with a plus (+) indicator to show that some modifications from the standard query types occurred, which may suggest a greater level of effort to produce those queries. Other queries are simply designated as "fully custom" because they involve completely new programming to meet the requirements of the analysis.

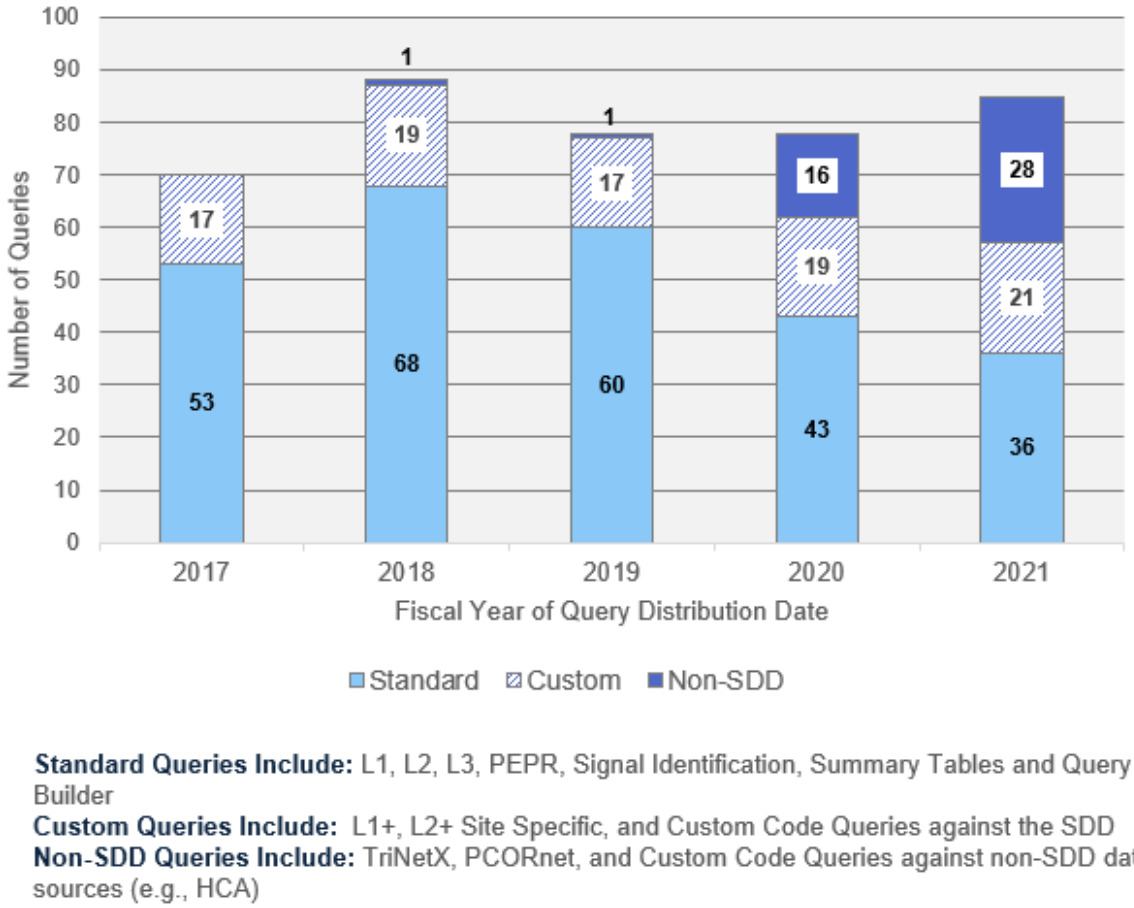
Table 1 shows the distribution of query types between 2017 and 2021.[36] In addition to L1 and L2 queries, standard queries consist of Summary Tables, which create descriptive tables from the SCDM datasets, and Query Builder, which converts queries designed in a user-friendly interface to a SAS package. Query Builder replaced Summary Tables, which ended in 2019. Queries involving some level of customization consist of L1+, L2+, L3, Patient Episode Profile Retrieval (PEPR), and other fully custom queries performed using the SDD. PEPR generates patient profiles of deidentified claims data over a specific timeframe to provide relevant clinical context for a finding. Non-SDD queries are developed against the PCORNet, TriNetX, HCA, and other data sources.

Table 1. All Sentinel System Queries by Fiscal Year

Query Type	2017	2018	2019	2020	2021
L1	30	55	42	26	24
L1+	8	11	5	7	13
L2	2	3	3	4	1
L2+	6	1	8	8	6
L3	2	0	0	0	0
Signal Identification	0	3	0	0	1
PEPR	1	3	4	3	4
Summary Table	18	4	11	1	0
Query Builder	0	0	0	9	6

Query Type	2017	2018	2019	2020	2021
Custom SDD[40]	3	7	4	2	0
Custom Non-SDD (e.g., MarketScan, HCA)	0	1	1	5	19
PCORnet	0	0	0	1	1
TriNetX	0	0	0	10	8
Site Specific	0	0	0	2	2
Total	**70**	**88**	**78**	**78**	**85**

Figure 7 shows that, over time, the number of standard queries decreased and non-SDD queries increased. This is generally indicative of the importance of EHR data to FDA's work as well as the need to do more in-depth and complex analyses to provide meaningful results. COVID-19 accelerated the need for EHR-based data sources, as seen with the increase in fiscal years 2020 and 2021.



Standard Queries Include: L1, L2, L3, PEPR, Signal Identification, Summary Tables and Query Builder
Custom Queries Include: L1+, L2+ Site Specific, and Custom Code Queries against the SDD
Non-SDD Queries Include: TriNetX, PCORnet, and Custom Code Queries against non-SDD data sources (e.g., HCA)

Figure 7. Query Customization and Source by Distribution Date[36]

[40] Since 2017, these custom queries include FDA Catalyst queries, TreeScan, and other methods such as death data exploration.

Sufficiency Determinations for Using ARIA

When a PMR is under consideration, the ARIA determination (sufficient or insufficient) is documented in an ARIA Sufficiency Memorandum (i.e., "ARIA Memo"). If FDA determines that ARIA is not sufficient, the ARIA Memo documents the reasons driving the insufficiency determination.

Section 505(o)(3)[41] of the Federal Food, Drug, and Cosmetic (FD&C) Act authorizes FDA to require certain post-marketing studies and clinical trials to assess a known serious risk related to the use of the drug involved, to assess signals of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicates the potential for a serious risk. This law requires FDA to determine if both FAERS and ARIA are not sufficient to assess the potential risk before requiring a post-market observational study or clinical trial.

FDA may require different types of post-market data to inform regulatory decisions. This requirement might include data from: clinical trials, observational (epidemiologic) studies, animal studies, laboratory experiments, or other data. FDA assesses whether ARIA is sufficient to address observational studies prior to requiring a post-market observational study from industry. The ARIA assessment considers both the tools available through ARIA and the data in the SCDM.

From 2017–2021, the number of Section 505(o)(3) PMR requests ranged between 155 to 196 per year, inclusive of clinical trials, observational studies, animal studies, and laboratory experiments. The number of these PMR requests during this period that were potentially suitable for evaluation by ARIA, and for which an ARIA sufficiency assessment was performed, was between 14 to 43 per year; this subset excludes clinical trials, animal studies, and laboratory experiments that lie outside of ARIA's scope. The number of requests where ARIA was an appropriate system and then deemed sufficient is indicated in Figure 8 as the "sufficiency rate."

The sufficiency rate is the number of requests where ARIA was sufficient over the total requests evaluated for ARIA sufficiency. This rate fluctuated with a peak of 21 percent in 2017 and a low of 0 percent in 2021. Through 2021, 7.6 percent (n=11) of the 145 observational PMRs were determined to be sufficient to be addressed by ARIA. FDA has not yet found ARIA sufficient for questions pertaining to use of a medication during pregnancy. These pregnancy-related study requests increased in 2018 and are a main reason for ARIA insufficiency determinations. To increase the sufficiency rate for ARIA studies, FDA tasked the IC with exploring and addressing common insufficiency categories. The SOC also supports methods development to enhance ARIA's tools.

[41] Guidance for the implementation of section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act is available at: https://www.fda.gov/media/131980/download.

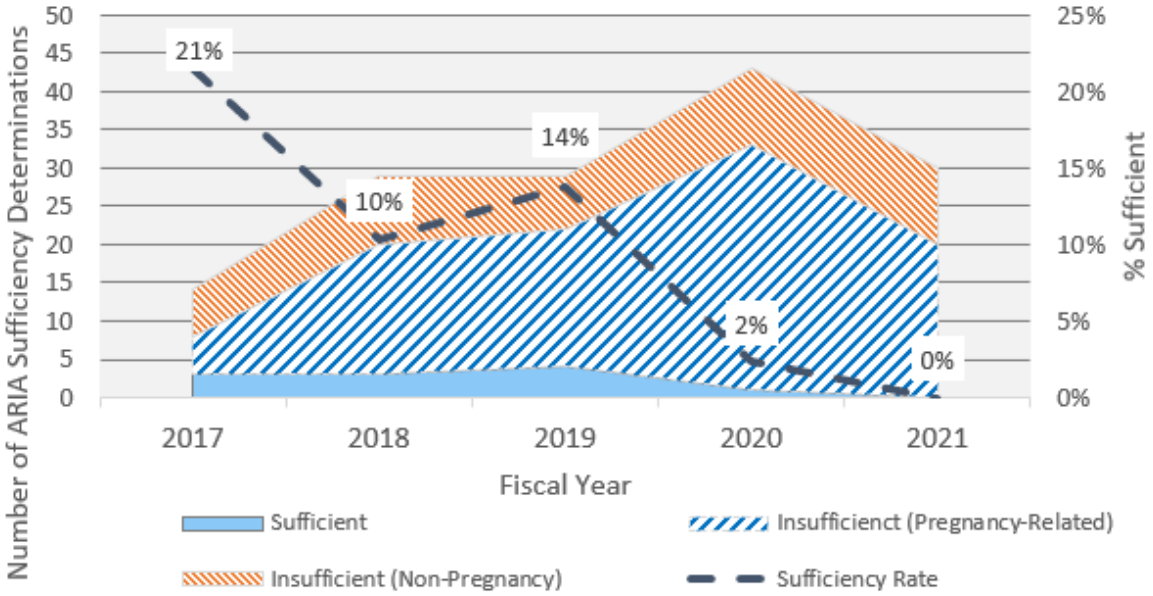


Figure 8. Number of ARIA Sufficiency Determinations and Sufficiency Rate

Studies where ARIA is deemed *insufficient* may result in requiring a PMR. ARIA can be deemed insufficient for one or more of the following categories:

- **Surveillance or study population—**the patient population to be studied cannot be identified or is too small
- **Exposure of interest—**the drug product(s) cannot be captured in claims data or there are limitations to the completeness or granularity of exposure data, such as over-the-counter use of medications.
- **Outcome of interest—**the adverse event(s) being investigated cannot be captured in claims data which may include unacceptable specificity and sensitivity
- **Covariates of interest—**insufficient capture of variables that should be considered and/or controlled for to understand the relationship between the exposure and outcome, such as smoking, alcohol use, or Body Mass Index (BMI).
- **Surveillance design/analytic tools—**if the required study design or analytic tool is not part of the ARIA options.

The average number of insufficiency categories per safety concern pair, which is a drug-adverse event combination, declined from 2.85 categories in 2017 to a low of 1.52 in 2019, and then began rising again to 2.61 categories in 2021. The only insufficiency category that has steadily decreased has been surveillance/study population, which may have some correlation with the trend in greater number of patient lives and incorporation of Medicare data to the SDD in 2018. As reflected in Figure 9 and Figure 10, surveillance design/analytic tools and health outcome of interest are the most common two categories for insufficiency when either totaled at the safety concern pair or when summarized in the ARIA memo. Each safety concern or ARIA memo may be represented more than once as there are typically multiple insufficiency reasons, as mentioned above. However, insufficiency rates in most recent years are driven by pregnancy-related study requests and the lack of sufficient pregnancy-related outcomes represented in claims data in the absence of chart validation. The individual categories in figure 10 correspond with the proportion

of insufficiency determinations reported for each category. For example, 92 percent (n=12) of 13 insufficiency determinations for safety concern pairs included surveillance or study population as at least one reason.

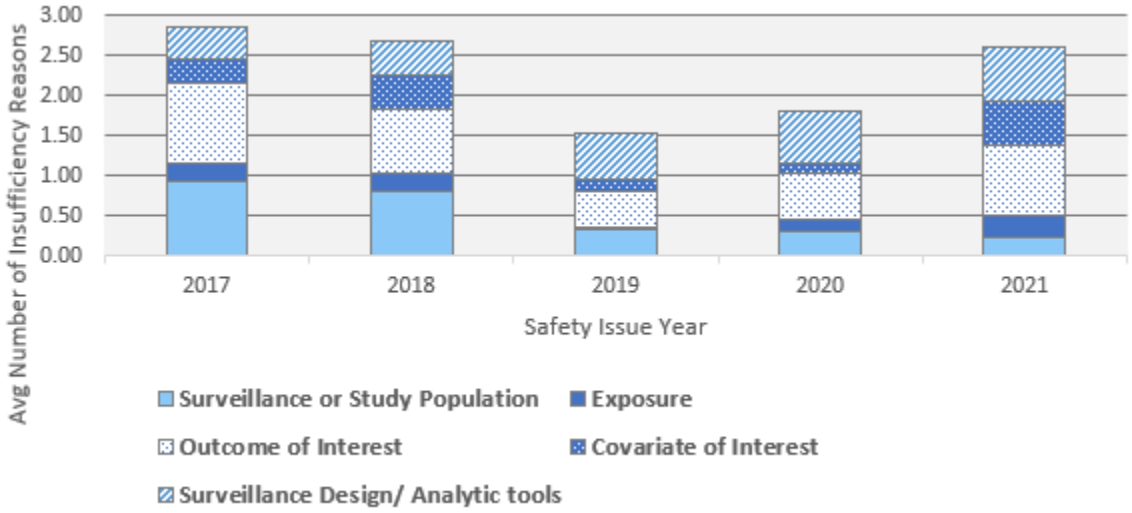


Figure 9. Insufficiency Categories per Safety Concern Pair

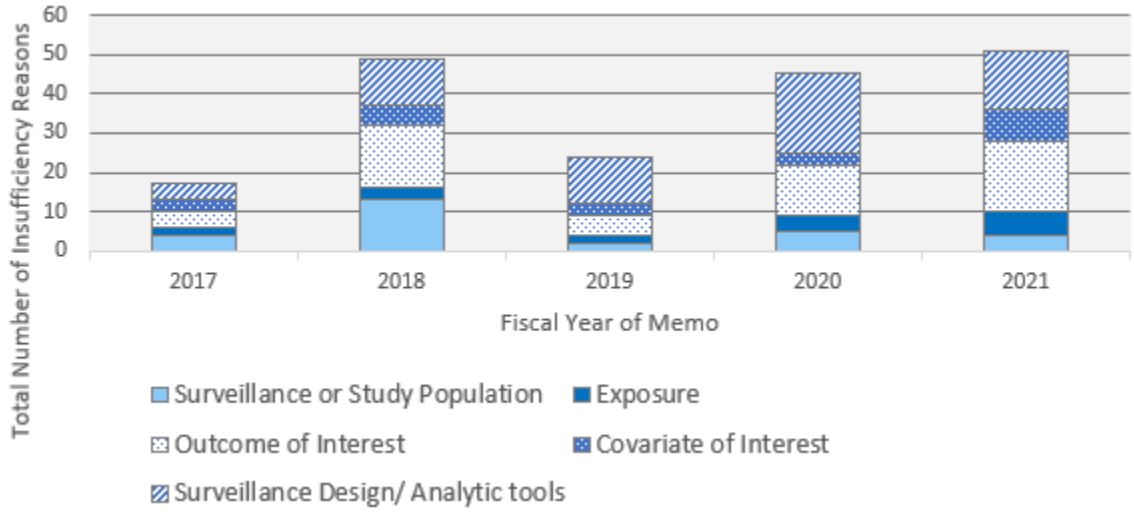


Figure 10. Insufficiency Categories by ARIA Memo

Because pregnant women are traditionally excluded from clinical trials, RWD can offer insight on drug use among pregnant women and potential risk of the drug to the woman or infant. In recent years, FDA has increasingly sought post-market studies to assess maternal, fetal, and infant outcomes associated with drug use in pregnancy. There is often limited information on risks associated with drug use in pregnancy from premarket clinical trials, and FDA is generally interested in assessing a broad range of maternal, fetal, and infant outcomes in post-market studies. While the routine querying tools include the ability to assess signal identification in pregnancy, there is not yet a routine process within FDA to conduct these queries and thus ARIA

is usually insufficient for these studies. This is one reason this topic has been prioritized for the PDUFA VII reauthorization.[42]

When removing ARIA sufficiency determinations for post-market studies to assess potential risks from drug exposure during pregnancy, the number of other post-market studies for which ARIA sufficiency was assessed plateau around 11 each year, with 53 total (42 insufficient) from 2017 to 2021 as indicated in Figure 11. Pregnancy-related study requests totaled 92 in this period. When removing pregnancy-related study requests, ARIA was found to be sufficient to conduct a post-market study in 20.8 percent of ARIA sufficiency assessments from 2017 to 2021 to meet the requirements of section 505(o)(3) of the FD&C Act prior to requiring a PMR.

Because further understanding on how to consider the performance of ARIA tools in the context of claims-based representation of specific pregnancy outcomes is required, the most common insufficiency category for pregnancy-related questions is surveillance design/analytic tools. When FDA requires a post-market study to assess a broad range of pregnancy-related outcomes, FDA staff identify surveillance design/analytic tools as a reason driving insufficiency because signal identification capabilities to identify potential unspecified fetal anomalies have not been fully implemented yet as part of routine regulatory procedures; the roll-out of such tools is still in the pilot phase. Figure 12 indicates totals from safety issue pairs. While there can be multiple categories recorded for one pair, the category of surveillance design/ analytic tools was recorded in 71 of 73 pairs.

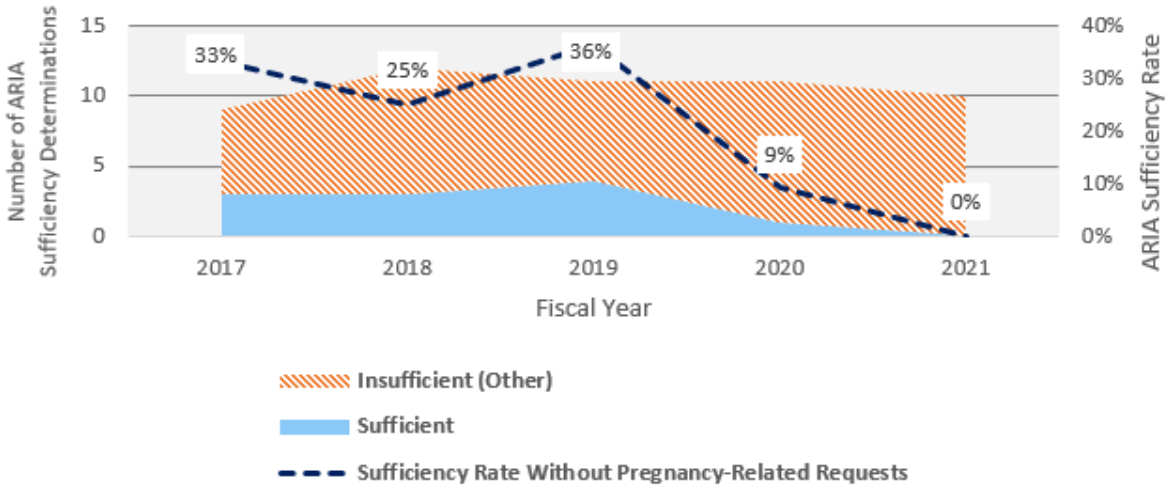


Figure 11. ARIA Sufficiency Determinations Excluding Pregnancy-Related Requests

[42] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027. https://www.fda.gov/media/151712/download

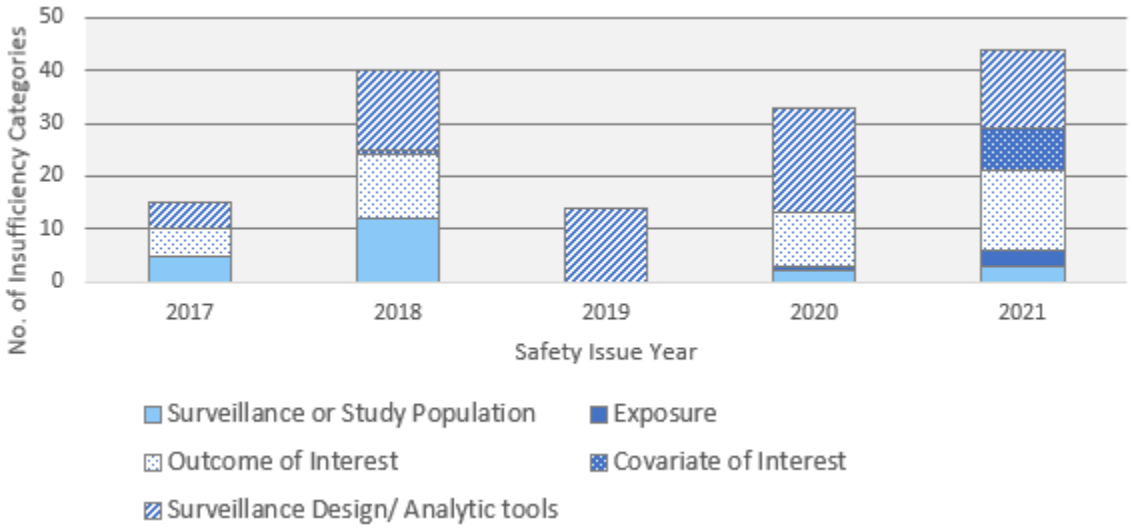


Figure 12. ARIA Insufficiency Categories for Pregnancy-Related Safety Concern Pairs

Analytic Tools and Methods

A strategic aim of Sentinel is to continue acquiring more impactful data and to innovate tools and methods for more valuable types of analyses.[43] Innovative tools and data development has been a core focus of Sentinel's work since its inception, but with the introduction of the IC and integration of ARIA, the scope of methods work has expanded. Figure 13 depicts methods studies that occur within ARIA. Presented in Figure 14 are development projects of the SOC and IC that occur outside of the ARIA system.

Methods studies within ARIA have centered around validation studies, such as validating health outcomes of interest in ICD-10-CM codes[44], and descriptive studies of the SDD to characterize population cohorts, duration of drug use or follow-up windows, linkage to mother-infant pairs, and coding practices. These types of studies, referenced in Figure 13, offer insight into the information in the SDD and inform study design, such as how to define a health outcome of interest using ICD-10-CM codes. A total of 36 studies have begun since FY 2017 through FY 2021.[35]

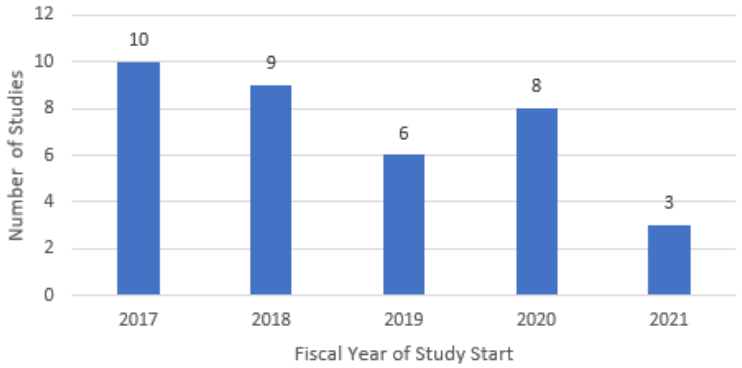


Figure 13. Number of ARIA Methods Studies Initiated per Fiscal Year

[43] https://www.sentinelinitiative.org/methods-data-tools/methods

[44] https://www.cms.gov/medicare/coding/icd10

Outside the ARIA system, IC development projects focus on further improving methods for causal inference and advanced analytics such as NLP, ML, and signal identification in EHRs. These projects recently emphasized approaches to better query EHRs for FDA's regulatory purposes such as EHR-based signal identification and using methods to processing unstructured EHR elements. SOC methods development projects intend to improve the ability to identify potential risks associated with drug use in pregnancy, access to more complete race/ethnicity data and extending TreeScan (a data mining method developed for disease surveillance) capabilities. More details regarding querying EHRs and TreeScan active signal identification is available in Section 3.4 and 3.5. Most development projects from 2020 to date are still in progress; of those projects started before 2020, FDA has completed a total of 47 between 2017 and 2019 (2017, 15; 2018, 21; and 2019, 11). Six in-progress studies were posted in FY 2022. Overall, from 2017-present, 59 projects are completed, and 28 projects are in progress as indicated in Figure 14. The fiscal year listed for a project in Figure 14 is determined by the date the project was posted to the Sentinel website.

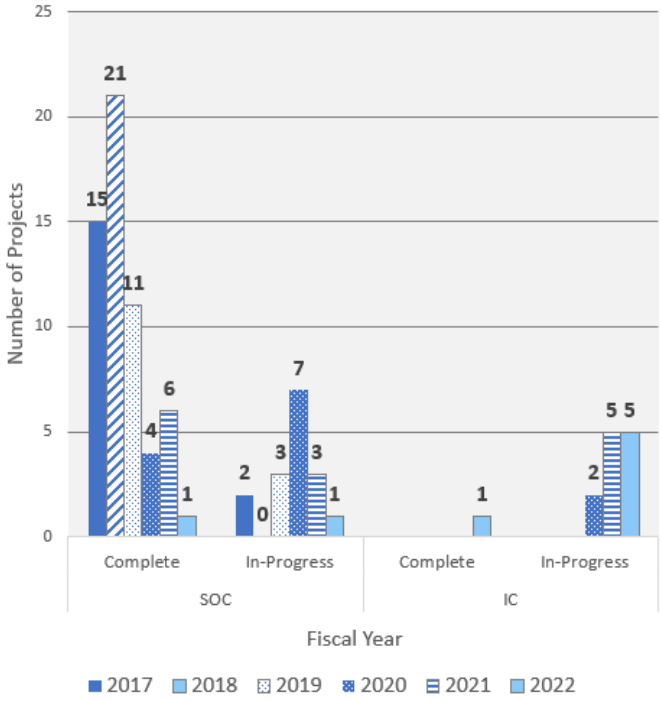


Figure 14. Number of SOC and IC Development Projects by Fiscal Year

3.3 Communication and Engagement

The FDA remains committed to increasing the use and awareness of Sentinel's value by deepening and broadening stakeholder engagement with Sentinel tools and data infrastructure as well as the results from Sentinel analyses. Sentinel can also benefit through expanded, transparent communication and engagement because these valuable interactions can accelerate the development of new methods and novel uses of the Sentinel System. As a result, the FDA anticipates that a wider, more engaged user base can ensure a more sustainable system to support a broad range of public health contributions. This subsection examines the extent of Sentinel's communication and engagement efforts in four areas: (1) sponsor and public outreach and

engagement; (2) sponsor and public access to Sentinel; (3) solicitation of public feedback; and (4) communication to industry regarding Sentinel use.

Sponsor and Public Outreach and Engagement

In immediate response to the PDUFA VI commitment to engage the public to solicit stakeholder feedback on Sentinel, the Sentinel team, in collaboration with the Margolis Center for Health Policy at Duke University, convened a public workshop on December 3, 2018, to explore challenges and opportunities regarding implementation of signal identification in Sentinel.[45] The three-session workshop explored topics related to signal identification in Sentinel, including statistical approaches and considerations about communication of results, and solicited feedback from workshop attendees. Apart from this workshop, FDA convenes annual workshops, which began after Mini-Sentinel's inception, to present the latest Sentinel advances and to seek feedback from industry, patients, consumers, and other stakeholders on future directions for Sentinel.

One of FDA's 2019 contracts for the Sentinel System funded a Community Building and Outreach Center (CBOC) to engage external stakeholders, broadening Sentinel's community and advancing Sentinel's outreach in alignment with the Sentinel Five-Year Strategy. In addition to this targeted effort, Sentinel's engagement with the public is integrated into project deliverables across all three coordinating center activities (SOC, IC, CBOC) with a focus on four areas: (1) public workshops, (2) public training, (3) journal publications and conferences, and (4) webinars. In response to many requests for information about Sentinel, FDA hosted the International Regulators' Forum in April 2019 to help international regulators understand more about how FDA operationalizes Sentinel.

Annual public training sessions are technical and instructional. These training sessions focus on how to leverage Sentinel's analytic capabilities to conduct pharmacoepidemiologic studies. These sessions often include hands-on demonstrations of query executions in the SCDM. Annual public training sessions for Sentinel began in 2017. After the renewed engagement activities beginning in 2019, participant registrations have steadily increased, averaging 253 registrants over the five-year period. Notably, the 460 registrations for the most recent public training session in April 2022 more than doubled the number of previous years. Annual public training sessions are recorded and available on the Sentinel website for download after the sessions.[46]

In addition to the annual training sessions, sponsors or the public can draw on webinars for a broad selection of exploratory topics related to Sentinel analyses, methods projects, and capabilities. Recent examples include a webinar series on Sentinel innovation and methods that the IC and SOC have conducted since 2020.[47] Webinars are available as live and recorded sessions. Including the annual public training and additional webinar sessions, FDA produced 24 webinars since the 2017 assessment through calendar year 2021.

Journal publications offer an opportunity for Sentinel to publicly share peer-reviewed findings with the scientific community. As of calendar year 2021, federal and contracted members of the

[45] More information regarding the workshop is available at: https://healthpolicy.duke.edu/events/implementation-signal-detection-capabilities-sentinel-system.

[46] Training, workshop, and webinar recordings are available at: https://www.sentinelinitiative.org/news-events/meetings-workshops-trainings.

[47] The latest 2022 Sentinel Innovation and Methods Seminar Series, including upcoming webinars, can be found at: https://sentinelinitiative.org/news-events/meetings-workshops-trainings/2022-sentinel-innovation-and-methods-seminar-series

Sentinel team have published 104 articles in peer-reviewed journals since Sentinel's last assessment in 2017. Similarly, Sentinel presentations at academic conferences and industry events showcase Sentinel's contributions to the global scientific community. From calendar year 2017 through 2021, Sentinel team members have developed 155 presentations for events and conferences. Notably, to date 3 manuscripts were published, and 16 presentations delivered related to Sentinel COVID-19 data. The Sentinel website provides a full list of journal articles and presentations.[48] Table 2 provides a summary of sponsor and public engagement in public workshops, public training, journal publications, and webinars as of December 2021.

Table 2. Summary of Sentinel Sponsor and Public Engagement Since the Last Assessment

Engagement	2017	2018	2019	2020	2021	Totals
Workshops	1	3	2	1	1	**8**
Training	1	1	2	1	None*	**5**
Publications	14	27	24	18	21	**104**
Conferences	1	1	1	1	1	**5**
Presentations	30	37	26	42	20	**155**
Webinars	None	3	1	8	12	**24**

*Held in early 2022 due to COVID-19

Industry and Public Access to Sentinel

The Sentinel public website, www.sentinelinitiative.org, is the central mechanism for FDA's communication with industry and the public regarding Sentinel information and engagement. There are two ways to inquire about potentially conducing a safety surveillance study that uses the Sentinel Infrastructure. By navigating to "Engage with Sentinel," a user may: (1) fill out a contact form for government agencies or contracted partners or (2) private sector entities, academic institutions, or individuals may contact the Reagan-Udall Foundation for the Food and Drug Administration.[49]

The Reagan-Udall Foundation provides education about how to use the Innovation in Medical Evidence and Development Surveillance (IMEDS) database to answer important post-market research questions. Besides surveillance activities, the IMEDS distributed database can be used for population characterization and effectiveness studies.

In 2018, Sentinel also launched a publicly accessible Git found at dev.sentinelsystem.org and accessible through the Sentinel public website. The Git features a continuously updated collection of code and documentation related to Sentinel SAS® querying processes and tools, analytic tools, data quality, and the Sentinel Common Data Model. The website maintains a list of routine querying tools that are current, in progress, or retired and linked to detailed documentation on the Git.[50] The website also identifies numerous routine querying methodologies grouped into three analysis levels (Level 1, Level 2, and Level 3) and further sub-

[48] Journal articles and presentations are available at: https://www.sentinelinitiative.org/news-events/publications-presentations.

[49] The Reagan-Udall foundation provides a means for FDA to interact directly with its stakeholders on topics of product development, innovation, and product safety. http://www.reganudall.org

[50] Routine querying tools and methodologies are available at: https://www.sentinelinitiative.org/methods-data-tools/routine-querying-tools.

divided into analysis types (for example, exposures and follow-up time, self-controlled risk interval design, etc.). Each analysis type is linked to detailed documentation available on the Git.

Communications to Sponsors Regarding Sentinel Use

CDER's Manual of Policies and Procedures (MAPPs) and Standard Operating Procedures and Policies (SOPPs) provides the following policy and procedure document that informs sponsors about the planned use of Sentinel, which fulfills a PDUFA VI commitment:[51]

- MAPP 6701.4: Notifying Applicants of Sentinel Analyses and Results (effective August 17, 2020)[52]

FDA has also published industry guidance that describes Sentinel's role in the regulatory process. A notable example includes:[53]

- Post-marketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry (October 2019)[54]

3.4 Advances Using RWE for the Medical Data Enterprise

With the acceleration of changes in the post-market surveillance ecosystem, the FDA acknowledged it needed to expand its approach to the development of the Sentinel System. These changes include expectations for improved RWE quality brought on by Cures Act[55] requirements, changes in the types of approved drugs (such as an increase in rare disease treatments), and evolving safety signals of concern. FDA also recognizes that routinely collected EHR data have the potential to improve safety studies and transform traditional clinical trials, potentially reducing costs and leading to enhanced patient outcomes. As a result, in 2019 the FDA embarked on activities to build a "Medical Data Enterprise" bolstered by EHR data from more than 10 million patients in addition to claims data.[56]

Use of EHR for Regulatory Decisions

The 2019 RWE Medical Data Enterprise required that FDA establish a query-capable EHR database with at least 10 million patient lives. A key goal of the 2019 Sentinel Five-Year Strategy is incorporating EHRs to enhance Sentinel's capability to make causal inferences and to increase FDA's understanding of RWE. As a result of the strategy and subsequent formation of the Sentinel 3-Center model, FDA tasked the Innovation Center with building this capability.

[51] A full listing of publicly available MAPP and SOPPs is available at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

[52] The MAPP 6701.4 document is available at: https://www.fda.gov/media/141216/download.

[53] Although, not in response to PDUFA VI commitments, the Guidance for Industry: Postmarking Studies and Clinical Trials-Implementation of Section 505(o)(3) of the FD&C Act (April 2011) is a foundational document of Sentinel's use. Available at https://www.fda.gov/media/131980/download

[54] The draft guidance document is available at: https://www.fda.gov/media/148646/download.

[55] The 21st Century Cures Act was enacted in 2016 to accelerate medical product development and bring new innovations faster to patients who need them. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

[56] Gottlieb, S. FDA budget matters: a cross-cutting data enterprise for real world evidence. Food and Drug Administration. https://www.fda.gov/news-events/fda-voices/fda-budget-matters-cross-cutting-data-enterprise-real-world-evidence (2018).

At the 2022 Sentinel Innovation Day hosted on April 28, speakers noted recent achievements and challenges of working with EHRs.[57] The topics included adding EHR-based data to common data models, computable phenotyping, and enhancing causal inference. Examples of the types of projects that the IC is undertaking include:

- How data partners employ NLP capabilities
- Priority unstructured data elements to obtain from EHRs and recommendations on how to integrate them into the SCDM
- Test results of prediction performance of automated phenotyping models, such as PheNorm[58]
- Demonstration of a feasible, scalable, and replicable NLP system to extract under-reported phenotypes from EHRs
- A proposed framework to guide decisions on conducting studies with non-randomized data that are secondary

The IC's work to date aligns closely with the project timeline outlined in its Master Plan.[59] Its team brings together experts from FDA, academia, and clinicians to inform the meaningful use of EHRs for regulatory decision making. The IC's progress contributes new knowledge to using RWE for regulatory decision-making and shows the great potential in integrating high-quality EHR data into Sentinel.

3.5 Signal Identification

Another important aspect of post-market surveillance is safety signal identification. Rather than further evaluating a known or previously identified potential safety concern, this type of analysis uses RWD to proactively identify new potential safety concerns.

The FDA is developing capabilities in active safety signal identification within Sentinel, which remains one of the outstanding objectives of the Sentinel Five-Year Strategy. As the Agency further develops and integrates this capability, the identification of unexpected safety signals could complement sources such as FAERS, literature reviews, and other forms of reporting from the public, providers, and industry. Advantages of conducting safety signal identification functions within Sentinel in comparison to other methods include the possibility of earlier identification of potential issues as well as having a much larger dataset against which to look for adverse outcomes. Additionally, FDA, by using Sentinel, will have transparency over the methods used to detect safety signals as well as the ability to refine approaches to provide greater confidence in future signal identification-driven findings, something that's not possible or in FDA's control when signals are sourced from outside the FDA.

[57] Presentation and recording of the 2022 Innovation Day are available at: https://www.sentinelinitiative.org/news-events/meetings-workshops-trainings/2022-innovation-day-sentinel-public-training-april-28-29#:~:text=Friday%2C%20April%2029%2C%202022,observational%20studies%20of%20medical%20treatments.

[58] The related publication can be found at: https://doi.org/10.1093/jamia/ocx111

[59] Sentinel Innovation Center Master Plan is available at: https://www.sentinelinitiative.org/news-events/publications-presentations/innovation-center-ic-master-plan

The SOC has worked on several methodological studies using TreeScan technology to detect previously unseen patterns in adverse events related to product usage.[60] A few completed projects address the integration of TreeScan's capabilities in ARIA tools and one ongoing pregnancy study involves TreeScan. This type of operationalized signal identification activity holds great promise in fulfilling FDA's drug safety mission, and the FDA is conducting additional pilot studies with a goal toward routine implementation in 2023. FDA will need to develop policies and procedures for using such signal identification methods within its normal post-market safety workflows.

3.6 Other Uses for Public Health Purposes

Sentinel has matured as a national safety surveillance system that links diverse data resources for shared analytic purposes. Consistent with its five-year strategy, FDA envisions access to Sentinel by multiple Sentinel stakeholders within and outside the Agency to broaden use of Sentinel's tools, methods, and data infrastructure. This vision delivers value in several ways beyond Sentinel's primary purpose. First, by broadening the number and types of questions asked, Sentinel data can grow and expand in scope. By creating a broader base of uses and users, Sentinel further establishes itself as a robust resource in the drug surveillance ecosystem. Lastly, the broader reach will expand Sentinel's insights into other public health questions for direct translation into actions that benefit patients.[61]

To date, Sentinel has demonstrated its value in three ways. Perhaps the most prominent role was the 17 public health studies conducted in Sentinel related to COVID-19 (refer to Table 3). Sentinel also contributed to FDA's regulatory mission through 82 studies resulting in over 40 regulatory actions. More than 20 Sentinel studies contributed to public health in other agencies and other FDA offices. The following subsections provide further detail of Sentinel's use in these three areas.

Sentinel's Use for COVID-19 Studies

FDA worked with SOC to develop a database in response to emergent needs brought on by COVID-19 that required more timely access to data than was typically available in Sentinel. As of May 2022, 114 million unique IDs are represented in the Rapid COVID-19 SDD. Currently, 6 data partners participate in the Rapid COVID-19 SDD. (Note: one small data partner stopped contributing at the end of FY 2021, but a large national insurer was added in May 2022, bringing the total back to 6 data partners). Data refreshes vary by data partner, ranging from monthly (3 data partners) to every 6 weeks (1 data partner) to every 8 weeks (2 data partners).

In fiscal years 2020 and 2021, there were 17 studies comprising 48 queries related to COVID-19, with some of these studies still ongoing. The information generated from these Sentinel analyses informed and continues to support FDA's regulatory work or its broader public health mission in several ways, including:

[60] A list of all completed and in-progress signal identification projects are listed on the Sentinel website: https://sentinelinitiative.org/methods-data-tools/signal-identification-sentinel-system

[61] Further insight into FDA's vision of Sentinel as a national resource can be found in the Sentinel Five-Year Strategy. U.S. Food and Drug Administration. (2019). Sentinel System Five-Year Strategy 2019-2023. https://www.fda.gov/media/120333/download

- Provided information on use of products authorized under an EUA, describing product use under EUA, describing populations specified under EUA and not authorized under EUA, describing patient outcomes following EUA product use, and designing cohorts of EUA product users and non-users to inform future potential studies of safety and effectiveness of EUA products such as monoclonal antibodies.[62]
- Provided descriptive epidemiologic information on real-world use of COVID-19 therapeutics[63] and informed public health advisements of federal partners (CDC Health Advisory: Updated Information on Availability and Use of Treatments for Outpatients with Mild to Moderate COVID-19 who are at increased risk for Severe Outcomes of COVID-19[64]).
- Generated data across multiple, complementary healthcare claims and EHR sources to inform understanding of racial and ethnic disparities in United States COVID-19 testing, hospitalization, and mortality.[65]
- Examined incidence of thromboembolic events in COVID-19 patients as compared to influenza patients and risk factors for these events in COVID-19 patients. The findings of these analyses may inform future care of patients at high risks of these events.[66]
- Provided highly granular, near real-time information on trends in the administration of key drugs used for treatment of hospitalized U.S. patients. This trend data informed FDA's understanding of drug shortage and drug supply concerns during the COVID-19 pandemic.[67]
- Described the natural history of hospitalized COVID-19 patients. Use of oxygen is a key component of COVID-19 severity that this project confirmed is not sufficiently captured using medical codes. This effort produced detailed information on levels of oxygen supplementation during hospitalization via extraction of data from semi-structured EHR fields.[68]

[62] More information regarding Sentinel's contribution to EUA surveillance can be found on the Sentinel website: https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/use-monoclonal-antibodies-mabs-under-emergency-use https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/hospitalization-and-anaphylaxis-following-monoclonal https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/bamlanivimab-bamlanivimab-and-etesevimab-and-casirivimab

[63] The related publication can be found at: https://jamanetwork.com/journals/jama/fullarticle/2791078

[64] More information regarding the official CDC Health Advisory can be found at: https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_463.pdf

[65] More information regarding the race and ethnicity study can be found at: https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/comparison-race-and-ethnicity-covid-19-testing

[66] More information can be found on the Sentinel project page and related publication: https://sentinelinitiative.org/methods-data-tools/methods/assessment-natural-history-coagulopathy-covid-19 https://jamanetwork.com/journals/jama/fullarticle/2795268

[67] More information can be found at: https://www.sentinelinitiative.org/methods-data-tools/methods/near-real-time-monitoring-critical-drugs-care-patients-covid-19

[68] More information can be found at: https://www.sentinelinitiative.org/sites/default/files/communications/publications-presentations/Sentinel_Presentation_Assessing_Natural_History_Drug_Use_Treatment_Impact_for_COVID-19.pdf

- Described the natural history of COVID-19 in pregnant women, including understanding of the prevalence of medicines used by trimester of pregnancy and describing severity and clinical outcomes in pregnant women with COVID-19, according to treatments received during pregnancy. This information may inform future treatment and care for pregnant women with COVID-19.[69]
- Generated descriptive information on real-world COVID-19 patient treatments and outcomes to inform design decisions for ongoing National Institutes of Health (NIH) Accelerating COVID-19 Therapeutic Interventions and Vaccine (ACTIV) trials, including leveraging laboratory and vital signs data available from EHR data partners.[70]

Table 3 lists the 19 presentations and publications delivered or published about COVID-19 using Sentinel data through July 2022.

Table 3. Sentinel Presentations and Publications Related to COVID-19

Title	Date	Type
Assessing Natural History, Drug Use and Treatment Impact for COVID-19 in the Sentinel System	05/13/2020	Presentation
Risk of Thromboembolic Events With COVID-19: A Sentinel System Investigation – Potential Aims/Methods	06/23/2020	Presentation
Coagulopathy Assessment in Patients with COVID-19: A TriNetX Analysis	06/23/2020	Presentation
Risk of Thromboembolic Events With COVID-19: A Sentinel System Investigation – Update on Methods	07/14/2020	Presentation
Risk of Thromboembolic Events With COVID-19: A Sentinel System Investigation – Focus on Endpoints	08/04/2020	Presentation
Defining COVID-19 Cohorts in Real-World Data	08/18/2020	Presentation
Leveraging the Sentinel System for COVID-19	10/14/2020	Presentation
Studying the Natural History of COVID-19: Risk of Arterial and Venous Thrombotic Events in the Sentinel System	10/14/2020	Presentation
Natural History of Coagulopathy in COVID-19	10/26/2020	Presentation
Descriptive Assessment of Coagulopathy Among COVID-19 Patients: Feasibility Data Review	10/27/2020	Presentation
Natural History of Coagulopathy in Patients with COVID-19 in a Real-World Electronic Health Data Network	11/05/2020	Presentation
Validation of Claims-based Algorithms to Identify Hospitalized COVID-19 Events within the FDA Sentinel System	12/02/2020	Presentation
A COVID-19-Ready Public Health Surveillance System: The FDA's Sentinel System (https://doi.org/10.1002/pds.5240)	04/02/2021	Publication
Outpatient-Identified COVID-19 and Subsequent Hospitalized Thrombotic Events	08/23/2021	Presentation

[69] More information can be found at: https://www.sentinelinitiative.org/methods-data-tools/methods/covid-19-pregnancy-study-implementation

[70] More information can be found at: https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Thrombotic_events_death_inpatient_identified_COVID19.pdf

Title	Date	Type
Comparing Outcomes in Trial-Eligible vs Real-World COVID-19 Patients: The Case of Invasive Mechanical Ventilation	08/23/2021	Presentation
Strategies for the Use of Real-World Data to Conduct COVID-19-Related Pharmacoepidemiology	08/25/2021	Presentation
Monitoring Medication Use During the COVID-19 Pandemic in the Sentinel System: The Case of Anticoagulation for Thrombosis	09/15/2021	Presentation
Validation of Diagnosis Codes to Identify Hospitalized COVID-19 Patients in Health Care Claims Data (https://pubmed.ncbi.nlm.nih.gov/34913208)	12/16/2021	Publication
Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021 (https://jamanetwork.com/journals/jama/fullarticle/2791078)	04/08/2022	Publication

The Sentinel website provides updates to all Sentinel publications and presentations.[71] Appendix E presents a full list of Sentinel publications and presentations since 2017 (to coincide with the end of the PDUFA V Sentinel Assessment) through July 2022.

Contributions to the FDA Regulatory Mission

Beyond supporting safety concerns that meet the requirements of FD&C Act Section 505(o) prior to requiring a PMR, Sentinel has contributed to FDA's regulatory actions and decision-making through a variety of post-market surveillance activities. Between 2017 and 2021, the 82 studies completed in ARIA resulted in 43 regulatory actions[72]:

- Contributed to 6 labeling changes[73]
- Contributed to 2 drug safety communications[73]
- Provided information to support 6 advisory committee meetings[74]
- Provided information regarding the feasibility / utility of industry to complete 3 ongoing PMRs, supported 10 ARIA sufficiency determinations, enabled responses to 2 other Agency requests, and supported the review of 1 New Drug Application (NDA) or Biologics License Application (BLA)[75]

Sentinel can provide reassuring data when assessing a safety concern; in these instances, a regulatory action, such as a labeling change, is generally not needed. Many safety studies that Sentinel conducts find no increased risk associated with a drug, which provides reassuring safety information and does not lead to a specific regulatory action like a labeling change. No action indicated was reported for 7 studies since 2017.

There are also 6 other uncategorized regulatory actions. This category encompasses regulatory actions that did not fit into an existing category. The lower number of regulatory actions in

[71] Journal articles and presentations are available at: https://www.sentinelinitiative.org/news-events/publications-presentations.

[72] A list of all Sentinel drug studies and regulatory outcomes can be found at: https://sentinelinitiative.org/studies/drugs#how-drug-safety-studies-inform-fdas-regulatory-process

[73] A comprehensive list of labeling changes and safety communications can be found at: https://sentinelinitiative.org/news-events/fda-safety-communications-labeling-changes

[74] A detailed list of related advisory committee topics can be found at: https://sentinelinitiative.org/news-events/fda-advisory-committee-meetings

[75] Details regarding this NDA/BLA review can be found at: https://sentinelinitiative.org/studies/drugs/gimoti-metoclopramide

recent years is likely due to studies that are ongoing or where a health outcome has not yet occurred or been documented. Table 4 summarizes Sentinel regulatory actions by fiscal year of the first query distributed in a study.[35]

Table 4. Sentinel Regulatory Actions by Study Fiscal Year

Regulatory Action	2017	2018	2019	2020	2021	Totals
Advisory Committee	1	2	3	0	0	**6**
Drug Safety Communication	1	1	0	0	0	**2**
Informed ARIA Sufficiency	2	3	1	3	1	**10**
Informed continued feasibility / utility of an ongoing PMR	2	0	0	1	0	**3**
Informed NDA/BLA Review	0	1	0	0	0	**1**
Informed Other Agency Request	0	0	1	0	1	**2**
Labeling Change	3	2	0	1	0	**6**
No action indicated	2	2	3	0	0	**7**
Other Regulatory Action	2	1	1	2	0	**6**
Total	**13**	**12**	**9**	**7**	**2**	**43**

The FDA does not have a standard process to quantify the value of a regulatory action. The regulatory decisions provide a value in protecting public health. Sentinel delivers value to industry by informing ARIA sufficiency determinations and by supporting FDA decisions related to ongoing PMR studies and by monitoring market product uptakes for planned studies to address safety signals.

Outside of CDER, the FDA Office of Counterterrorism and Emerging Threats (OCET) and the Center for Devices and Radiological Health (CDRH) have leveraged Sentinel. OCET's Medical Countermeasures Initiative evaluated Sentinel's potential contribution to access the safety and effectiveness of FDA-regulated medical products that may be used in the event of a potential public health emergency. Influenza was the case study for three studies and learnings were quickly applied to respond to COVID-19 in March 2020. CDRH studies[76] centered on the use and adverse events of birth control devices, including stents, robotic-assisted devices, and those used for fibroid surgery and permanent birth control.

Sentinel as a National Resource

Sentinel has demonstrated its value as a national resource beyond its mandated purpose by contributing to studies outside the FDA post-market surveillance ecosystem, in some cases conducted by—or in collaboration with—organizations outside of FDA. These organizations include other Federal agencies, academia, and industry. A notable example of Sentinel studies that contributed to broader public health goals include a study conducted in collaboration with the CDC that described the epidemiology of latent tuberculosis infection.[77] One FDA Catalyst study, *Implementation of a randomized controlled trial to imProve treatment with oral*

[76] The CDRH studies can be found on the Sentinel website: https://sentinelinitiative.org/studies/devices-radiological-health

[77] https://www.sentinelinitiative.org/methods-data-tools/sentinel-national-resource/incidence-latent-tuberculosis-infection-descriptive

AntiCoagulanTs in patients with Atrial Fibrillation (IMPACT-AFib)[78], leveraged the Sentinel System to advance FDA's understanding of RWE, and specifically, pragmatic clinical trials. Using the data of five Sentinel data partners, 80,000 patients were randomized to receive education information in two phases and to compare health outcomes between them.[79]

Sentinel has also served as an international resource, highlighted through its collaboration with the Canadian Network for Observational Drug Effect Studies (CNODES)[80] on drug safety questions. Through this collaboration, Sentinel has shared pre-programmed, parameterizable analytic tools with CNODES, who are able to conduct parallel analyses on their data in the SCDM. Sentinel has also collaborated with the international regulators through the International Coalition of Medicines Regulatory Authorities (ICMRA). Through ICMRA, Sentinel is working with the European Medicines Agency (EMA), Health Canada, and their collaborators on a multinational meta-analysis to assess the incidence of arterial and venous thrombotic events among COVID-19 patients. Sentinel is also conducting a meta-analysis with the EMA on the natural history of COVID-19 among pregnant women -- CONSIGN (Covid-19 infectiON and medicineS In pregnancy).

Since 2015, IMEDS[81] used Sentinel for 7 studies.[82] NIH Collaboratory Distributed Research Network[83] employed Sentinel's infrastructure for 3 studies and the Biologics & Biosimilars Collective Intelligence Consortium (BBCIC)[84] drew on Sentinel for 10 studies.

Table 5 provides a comprehensive list of publications and analyses to which Sentinel contributed as a national resource. More information about these studies and Sentinel's contributions as a national resource can be found on the Sentinel website.[85]

Table 5. Sentinel Contributions as a National Resource

Publication or Analysis	Date	Organization
A Comparative Assessment of Observational Medical Outcomes Partnership and Mini-Sentinel Common Data Models and Analytics: Implications for Active Drug Safety Surveillance (https://pubmed.ncbi.nlm.nih.gov/26055920/)	06/09/2015	Other Organization
Replication of Mini-Sentinel Study Assessing Mirabegron and Cardiovascular Risk in Non-Mini-Sentinel Databases (https://pubmed.ncbi.nlm.nih.gov/29134621/)	03/05/2018	Other Organization
Do FDA Label Changes Work? Assessment of the 2010 Class Label Change for Proton Pump Inhibitors Using the Sentinel System's Analytic Tools (https://pubmed.ncbi.nlm.nih.gov/29392851/)	03/27/2018	Reagan-Udall Foundation

[78] More information regarding the IMPACT-AFib project can be found at:
https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects/implementation-randomized-controlled-trial-improve
https://clinicaltrials.gov/ct2/show/NCT03259373

[79] https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects/implementation-randomized-controlled-trial-improve

[80] https://www.cnodes.ca/cdm-overview/

[81] https://reaganudall.org/programs/research/about-imeds

[82] Visit the Reagan Udall website for a complete list of IMEDS studies that have used Sentinel: https://reaganudall.org/programs/research/post-market-research

[83] https://rethinkingclinicaltrials.org/nih-collaboratory-drn/

[84] https://www.bbcic.org/

[85] More information about Sentinel as a national resource can be found at: https://www.sentinelinitiative.org/methods-data-tools/sentinel-national-resource

Publication or Analysis	Date	Organization
Risk of Venous Thromboembolism in Rheumatoid Arthritis Patients Treated with Biologic and Non-Biologic DMARDs (https://ard.bmj.com/content/77/Suppl_2/932.1)	06/16/2018	Reagan-Udall Foundation
Cancer Screening Results and Follow-up Using Routinely Collected Electronic Health Data: Estimates for Breast, Colon, and Cervical Cancer Screenings (https://pubmed.ncbi.nlm.nih.gov/30350029/)	10/22/2018	NIH
Harnessing the Biologics and Biosimilars Collective Intelligence Consortium to Evaluate Patterns of Care (https://pubmed.ncbi.nlm.nih.gov/31397619/)	08/09/2019	BBCIC
Barriers and Facilitators to Conduct High-Quality, Large-Scale Safety and Comparative Effectiveness Research: The Biologics and Biosimilars Collective Intelligence Consortium Experience (https://pubmed.ncbi.nlm.nih.gov/31402533/)	08/11/2019	BBCIC
Descriptive Analysis of Long- And Intermediate-Acting Insulin and Key Safety Outcomes in Adults With Type 2 Diabetes Mellitus (https://pubmed.ncbi.nlm.nih.gov/31405345/)	08/12/2019	BBCIC
Antibiotic Dispensing Following Pediatric Visits in the US Emergency Departments and Outpatient Settings from 2006 to 2016 (https://pubmed.ncbi.nlm.nih.gov/31467679/)	08/27/2019	NIH
Chemotherapy-Induced Peripheral Neuropathy (CIPN) and its Treatment: An NIH Collaboratory Study of Claims Data (https://pubmed.ncbi.nlm.nih.gov/31494735/)	09/07/2019	NIH
Capture of Biologic and Biosimilar Dispensings in a Consortium of U.S.-Based Claims Databases: Utilization of National Drug Codes and Healthcare Common Procedure Coding System Modifiers in Medical Claims (https://doi.org/10.1002/pds.4934)	12/04/2019	BBCIC
Incidence of Statin Use in Older Adults With and Without Cardiovascular Disease and Diabetes Mellitus, January 2008 - March 2018Publication (https://pubmed.ncbi.nlm.nih.gov/31805056/)	12/05/2019	NIH
Safety Surveillance and the Estimation of Risk in Select Populations: Flexible Methods to Control for Confounding while Targeting Marginal Comparisons via Standardization (https://doi.org/10.1002/sim.8410)	12/10/2019	Other Organization
Mapping from the International Classification of Diseases (ICD) 9th to 10th Revision for Research in Biologics and Biosimilars Using Administrative Healthcare Data (https://doi.org/10.1002/pds.4933)	12/18/2019	BBCIC
Considerations for Using Distributed Research Networks to Conduct Aspects of Randomized Trials (https://pubmed.ncbi.nlm.nih.gov/31956724/)	01/02/2020	NIH
Incidence of Serious Infections and Design of Utilization and Safety Studies for Biologic and Biosimilar Surveillance (https://doi.org/10.18553/jmcp.2020.26.4.417)	04/26/2020	BBCIC
Diagnosed Prevalence of Alzheimer's Disease and Related Dementias in Medicare Advantage Plans (https://pubmed.ncbi.nlm.nih.gov/32647744)	07/05/2020	NIH
Impact of the Transition from ICD–9–CM to ICD–10–CM on the Identification of Pregnancy Episodes in US Health Insurance Claims Data (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7571578/)	10/15/2020	Other Organization
Building an Active Medical Product Safety Surveillance System in Taiwan: Adaptation of the U.S. Sentinel System Common Data Model Structure to the National Health Insurance Research Database in Taiwan (https://doi.org/10.1002/pds.5168)	11/04/2020	Other Organization

Publication or Analysis	Date	Organization
Utilization Patterns and Characteristics of Users of Biologic Anti-Inflammatory Agents in a Large, US Commercially Insured Population (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7771154/)	12/29/2020	BBCIC
Patient Characteristics and Utilization Patterns of Short-Acting Recombinant Granulocyte Colony-Stimulating Factor (G-CSF) Biosimilars Compared to Their Reference Product (https://pubmed.ncbi.nlm.nih.gov/33517548/)	01/30/2021	BBCIC
Incidence of Latent Tuberculosis Infection: A Descriptive Analysis (https://www.sentinelinitiative.org/methods-data-tools/sentinel-national-resource/incidence-latent-tuberculosis-infection-descriptive)	02/12/2021	CDC
Health Outcomes Coding Trends in the US Food and Drug Administration's Sentinel System During Transition to International Classification of Diseases-10 Coding System: A Brief Review (https://pubmed.ncbi.nlm.nih.gov/33638243/)	02/27/2021	Other Organization
Identifying Prescribing Cascades in Alzheimer's Disease and Related Dementias: The Calcium Channel Blocker-Diuretic Prescribing Cascade (https://pubmed.ncbi.nlm.nih.gov/33715299/)	03/14/2021	NIH
BBCIC Research Network Analysis of First-Cycle Prophylactic G-CSF Use in Patients Treated with High Neutropenia Risk Chemotherapy (https://doi.org/10.6004/jnccn.2021.7027)	08/16/2021	BBCIC

4 Ongoing and Future Activities

Since its 2007 mandate, Sentinel has matured into a robust evidence-generating platform for drug safety surveillance. In 2019, the FDA launched a five-year strategy for the Sentinel System that promotes use of emerging data science disciplines (such as NLP, ML, and active signal identification) and focuses expansion activities on access to EHR data to enhance Sentinel's capabilities.[86] Although a year remains in the five-year strategy, the program has progressively developed methods and data linkages, tested novel technologies for incorporation into Sentinel, adopted RWD for effectiveness, and disseminated knowledge to advance regulatory science.

4.1 Ongoing ARIA Methods Development

In addition to supporting the end-to-end process of query specification, testing, and implementation, the SOC has numerous methods development projects underway that enhance ARIA's tools. The SOC expects to complete the following projects by the end of FY22:

- Expanding the capabilities of Sentinel tools to query laboratory results data.
- Adding two ARIA tool enhancements: (1) One tool related to the Cox Proportional Hazard Assumption Test to enable verification that the Cox proportional hazards assumption was not violated using statistical tests, and (2) Adding Kaplan Meier (KM) curve estimation for Inverse Probability of Treatment Weighting (IPTW).

The SOC expects to complete the following projects by the end of FY23:

[86] U.S. Food and Drug Administration. (2019). Sentinel System Five-Year Strategy 2019-2023. https://www.fda.gov/media/120333/download

- A project exploring improvements to capturing race and ethnicity data in the Sentinel system
- Continuing support related to the COVID-19 pandemic through the expansion of the Rapid COVID-19 SDD and numerous related studies, such as assessing the natural history of COVID-19 in hospitalized patients and understanding racial and ethnic differences in COVID-19 testing, hospitalization, and mortality
- Linking participants in the Patient-Centered Outcomes Research Institute (PCORI) Roflumilast or azithromycin to prevent chronic obstructive pulmonary disease (COPD) exacerbations (RELIANCE) trial to Medicare data to demonstrate use of RWE in pragmatic clinical trials[87]

4.2 Ongoing RWE Medical Data Enterprise Development

The IC has a variety of completed and ongoing projects to carry out its Master Plan[88] and fulfill the 2019 RWE Medical Data Enterprise requirement. These projects are aimed at helping FDA to establish a query-capable EHR database for at least 10 million patient lives (refer to subsection 3.4 for recent accomplishments). Ongoing projects include:

- Developing a framework to use NLP and ML to improve health outcome of interest (HOI) identification algorithms to be incorporated into the SDD
- Developing a framework for conducting medication safety and effectiveness analyses using linked claims-EHR data
- Identifying best approaches for incorporating information derived from unstructured EHR elements for incorporation into a common data model framework
- Recommending approaches for EHR-based signal identification
- Developing NLP algorithms for population cohort identification, covariates, and health outcomes—which are three areas that contribute to ARIA insufficiency—from unstructured EHR data
- Designing a computable phenotyping strategy for EHR data to identify incident conditions that applies rapid NLP to leverage unstructured EHR data

In addition, the FDA is working on developing a set of algorithms to augment assessment of mortality through probabilistic linkage of EHRs with alternative data sources, such as publicly available obituaries and social media. This project could provide an alternative to the administrative complexities of using sources such as the National Death Index. Together, these projects seek to demonstrate the feasibility of using EHR data for safety surveillance and causal inference as well as for expanding the SCDM and SDD to new data sources, data elements, and ultimately, new methods to identify population cohorts, covariates, and HOIs.

[87] https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects/fda-catalyst-alignment-cms-linkage-pcori-reliance-trial

[88] Sentinel Innovation Center Master Plan is available at: https://www.sentinelinitiative.org/news-events/publications-presentations/innovation-center-ic-master-plan

4.3 Sentinel Process Improvement

FDA scientists work with the Sentinel Program staff to develop study objectives to evaluate whether the data and analytic tools within Sentinel support the implementation of the study that they are planning. FDA epidemiologists determine the sufficiency of ARIA to answer a question of interest to FDA and document determinations of insufficiency via memos. Although Sentinel's place in FDA's human drug review program is well established, Sentinel Program staff are continuing to develop and update written procedures to assist FDA scientific community interactions and to complement the current written procedures on Sentinel operations and process. Collectively, these written procedures, along with currently available industry guidance, establish a baseline of processes designed to communicate a prescription for interaction with Sentinel staff.

5 Summary

As evidenced in its previous assessment delivered in 2017, Sentinel is a mature system that is widely accepted within FDA as a useful regulatory decision-making tool for safety concerns.[89] This assessment demonstrates Sentinel's capability beyond its mandated scope as a valuable contributor supporting other regulatory decisions, public health, and as a national resource. As an established resource for RWE with a large foundation of over 360 million patient lives represented by claims and EHR data, Sentinel has proven its value beyond conducting PMR assessments. Between FY 2017 and FY 2021, the 82 regulatory studies completed in ARIA:[90]

- Contributed to 6 labeling changes
- Contributed to 2 drug safety communications
- Provided information to support 6 advisory committee meetings
- Provided information regarding the feasibility / utility of 3 ongoing PMRs
- Supported 10 ARIA sufficiency determinations
- Enabled responses to 2 other Agency requests
- Supported the review of 1 NDA/BLA
- Supported 7 studies confirming drug safety where no regulatory action was required
- Supported 17 studies related to COVID-19 regulatory or other public health issues

Additionally, recent Sentinel innovation projects emphasize signal identification and building tools to better query EHRs. Other innovation projects work to improve the availability of pregnancy and race/ethnicity data. As Sentinel continues to enhance its analytic tool and capabilities through ongoing methods development activities, Sentinel further establishes itself as a trusted, reliable RWE resource in the safety ecosystem and for other public health needs.

[89] *Sentinel Initiative Final Assessment Report*, September 2017: https://www.fda.gov/media/107850/download

[90] Sentinel often confirms the safety of a drug; thus, no regulatory outcome is necessary.

Appendix A Glossary

Term/Acronym	Definition
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccine
AI	Artificial Intelligence
ARIA	The Active Risk Identification and Analysis system is the primary component of the Sentinel System that acquires and transforms healthcare data into the SCDM for post-market analysis. ARIA also provides FDA the routine queries and other tools to analyze these data.
BBCIC	Biologics & Biosimilars Collective Intelligence Consortium
BEST	Biologics Effectiveness and Safety; To fulfill the FDAAA requirement for a post-market surveillance system for biological products, the Center for Biologics Evaluation and Research (CBER) released its Biologics Effectiveness and Safety (BEST) Initiative in 2017
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CBOC	Community Building and Outreach Center. The CBOC engages with non-FDA stakeholders, from the clinical research enterprise to health advocacy groups, to broaden and activate a strong community to advance Sentinel's objectives.
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
COD	Cause of Death
COVID-19	COVID-19 is an infectious disease caused by the SARS-CoV-2 virus.
Cures Act	Also, 21st Century Cures Act, was enacted in 2016 to accelerate medical product development and bring new innovations faster to patients who need them. More about the Cures Act can be found at: https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act
EHR	Electronic Health Records
ETL	Extract, Transform, and Load
EUA	Emergency Use Authorization. The EUA facilitates the availability and use of medical countermeasures needed during a public health emergency. More about EUAs can be found at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	The Food and Drug Administration Amendments Act of 2007 (FDAAA) required establishing a post-market surveillance system for drugs and biological products to analyze data from at least 100 million lives by July 1, 2012.
FDA-Catalyst	A supplemental component of the Sentinel System that employs routine queries coupled with interventions/interactions with patients and providers.
FY	Fiscal Year. This term specifically refers to the federal fiscal year which begins in October and ends the following September.
HCA Healthcare	HCA Healthcare is a data source used by Sentinel for health data. More about HCA Healthcare can be found at: https://hcahealthcare.com/
HOI	Health Outcome of Interest

Term/Acronym	Definition
IC	Innovation Center. The IC focuses on meeting the RWE Medical Data Enterprise requirement by establishing a query-ready distributed data network containing EHRs of at least 10 million lives.
IDS	Integrated Delivery Systems. IDSs offer clinical data along with administrative claims data.
IMEDS	Innovation in Medical Evidence Development and Surveillance
L1	Level 1 Analysis (L1) for descriptive analyses of cohorts of interest, exposure rates, and episodes of care.
L2	Level 2 Analyses (L2) for retrospective inferential analyses, including adjustment for confounding with effect estimates and confidence intervals.
L3	Level 3 Analyses (L3) for complex adjustment for confounding repeatedly as part of prospective sequential analysis.
MAPP	Manual of Policies and Procedures
MarketScan	MarketScan, or Merative MarketScan, is a data source used by Sentinel for health data. More about MarketScan can be found at: https://www.merative.com/
Medical Data Enterprise	Established through the President's 2019 budget, the Medical Data Enterprise refers to a modern system that would rely on EHR data from a minimum of 10 million lives.
Methods Studies	Studies performed that are not included in other categories but support public health. Examples studies include Racial and ethnic differences in COVID-19 testing, hospitalization, and mortality and Risk of Arterial and Venous Thrombotic Events in Patients with COVID-19 Compared to Influenza.
MIL	Mother-Infant Linkage
ML	Machine Learning
NDA	New Drug Application
NIH	National Institutes of Health
NLP	Natural Language Processing
OMP	The Office of Medical Policy in FDA's Center for Drug Evaluation and Research.
OSE	The Office of Surveillance and Epidemiology in FDA's Center for Drug Evaluation and Research.
PCORI	Patient-Centered Outcomes Research Institute
PCORnet	National Patient-Center Clinical Research Network. PCORnet is a data source used by Sentinel for health data. More about PCORnet can be found at: https://pcornet.org/
PDUFA	Prescription Drug User Fee Act
PEPR	Patient Episode Profile Retrieval
PMC	Post-market Commitment. PMCs are studies or clinical trials that a sponsor has agreed to conduct, but that are not required by a statute or regulation.
PMR	Post-market Requirement. This requirement can include a requirement for observational study or, if an observational post-marketing study will be insufficient, a clinical trial. PMRs include studies and clinical trials that sponsors are required to conduct under one or more statutes or regulations.
Public Health Studies	Studies performed that are not categorized in other categories (regulatory or methods) but support public health.

Term/Acronym	Definition
Regulatory Studies	ARIA studies or other studies (e.g., using another data source such as TriNetX) conducted for regulatory purposes. This category includes COVID-19 work that relates to a single product.
RELIANCE	RELIANCE is a pragmatic clinical trial funded by PCORI to compare long-term use of Roflumilast or Azithromycin to prevent COPD exacerbations.
REMS	Risk Evaluation and Mitigation Strategy. REMS is a drug safety program through which FDA can ensure the benefits of a medication outweigh its risks. More about REMS can be found at: https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems
RWD	Real World Data
RWE	Real World Evidence
Safety Concern Pair	A safety concern pair refers to a drug-adverse event combination.
SCDM	Sentinel Common Data Model
SDD	Sentinel Distributed Database. The SDD is a federated database physically separated across multiple data partner environments and includes national health insurers and integrated delivery systems.
Signal Identification	Signal identification is the detection of new and unsuspected potential safety concerns.
SOC	Sentinel Operation Center. The SOC oversees ARIA, FDA Catalyst, and core infrastructure development.
SOPP	Standard Operating Procedures and Policies
TreeScan	TreeScan is a data mining method developed for disease surveillance and searches for excess risk.
TriNetX	TriNetX is a data source used by Sentinel for health data. More about TriNetX can be found at: https://trinetx.com/about-trinetx/

Appendix B Inputs and Data Sources for This Assessment

This assessment employed inputs from qualitative and quantitative sources. Qualitative inputs consisted of one-on-one interviews, focus groups, surveys, presentations, journal articles, and government-furnished information. Quantitative inputs were the Sentinel operational metrics and data outputs produced by the Sentinel Operations Center (SOC), Innovation Center (IC), and Community Building and Outreach Center (CBOC) over the last five years. This assessment relied on the inputs and data sources presented in Table 6.

Table 6. Inputs and Data Sources Used

Inputs / Sources	Description
One-on-One Interviews	This assessment relies on input from 11 one-on-one interviews with Sentinel leadership and users within and outside FDA: • Eight interviews drew on input from Center for Drug Evaluation and Research (CDER) staff, including executive leadership, users, and those who manage Sentinel System users. • Three interviews solicited input from Sentinel users outside FDA, such as individuals representing the Centers for Disease Control and Prevention, the Assistant Secretary for Planning and Evaluation, and the National Institutes of Health.
Sentinel User Focus Groups	FDA assembled nine user focus groups representative of the Sentinel user community from the Office of the Commissioner and many offices within CDER. Of the 79 invitees, 58 participated in one of the nine user focus groups. The following CDER organizations were represented: • Office of Surveillance and Epidemiology (OSE)/Office of Medication Error Prevention and Risk Management (OMEPRM) • OSE/Office of Pharmacovigilance and Epidemiology (OPE) • Sentinel Executive Committee • OSE, Immediate Office • Office of Translational Science (OTS)/Office of Biostatistics (OB)/Division of Biometrics VII • OSE Immediate Office, Regulatory Science Staff (RSS), Regulatory Science and Applied Research • OSE Immediate Office, RSS, Sentinel Program management team
Sentinel Contractor Focus Groups	Two focus groups represented the contractor organizations supporting the Sentinel program via the SOC, IC, or CBOC.

Inputs / Sources	Description
Sentinel User Surveys	80 individuals received a Sentinel User Survey and 21 recipients responded, representing: • CDER, OSE, OPE, Divisions of Epidemiology • CDER, OSE, OMEPRM • CDER, OSE, OPE • CDER, OTS, OB, Division of Biometrics • CDER Office of Generic Drugs • CDER Office of New Drugs • Center for Devices and Radiological Health • Office of Counterterrorism • Office of Medical Policy
Environmental Scan Sources	A preliminary environmental scan gathered data from sources internal and external to FDA. These sources included: • Background or contextual information (10 sources) • Publicly available FDA media regarding the Sentinel initiative and PDUFA requirements (6 sources) • Academic journal articles (19 sources) • Previous Sentinel final and interim assessments (2 sources) • Current strategies and plans (4 sources) • Trade publications (41 sources). A list of these sources is available in the deliverable document, Maturity Assessment in Support of the Sentinel Program: Environmental Scan Sources.
Government-Furnished Information	The FDA Sentinel government team provided a wide range of Sentinel-related documents as supplemental information. These documents consisted of presentations, contracts, best practices, and training materials produced within the last five years.
Sentinel Annual Workshop 2021	The annual Sentinel workshop topics covered Sentinel master plan implementations, methods, international collaborations, and COVID-19 response.
Sentinel Operational Data	The SOC provided operational data to assess data robustness; ARIA sufficiency and Post-market Requirement (PMR) replacements; query type, complexity, and duration; and study outcomes. Data were stratified by date to show trends over time. When necessary, data points were obtained from statistical information reported on the Sentinel Initiative website. When comparative sources were discrepant (for example, between statistical data on the website versus data provided by the SOC), the FDA deferred to the data provided by SOC because as these data were the most recent. Additionally, the SOC provided an assessment of the SOC's operational output, which will be made public and will align to the related information found in this assessment.
Ad Hoc Meetings	The FDA conducted ad hoc meetings throughout the assessment to address gaps in retrieved information.

Appendix C PDUFA VI Commitments Regarding Sentinel

In 1992, Congress enacted the Prescription Drug User Fee Act (PDUFA), which has been reauthorized every five years. PDUFA allows the Food and Drug Administration (FDA) to collect fees from companies that produce certain drug and biological products. User fees provide support for enhancing and modernizing the U.S. drug safety system through initiatives such as Sentinel.

PDUFA VI included an expanded set of commitments related to scaling up and expanding Sentinel while continuing to embed its use in FDA's operations. The following PDUFA VI Goals and Procedures for Fiscal Years (FY) 2018–2022 are relevant to Sentinel:[91]

a) FDA will work toward expanding the Sentinel System's sources of data and enhancing the system's core capabilities.
b) FDA will enhance its communication with sponsors and the public regarding general methodologies for Sentinel queries, including what the Agency has learned regarding the most appropriate ways to query and use Sentinel data. This can be done through enhancement of existing mechanisms and/or greater frequency of such mechanisms.
c) FDA will evaluate additional ways to facilitate public and sponsor access to Sentinel's distributed data network to conduct safety surveillance.
d) By the end of FY 2019, FDA will hold or support a public meeting engaging stakeholders to discuss current and emerging Sentinel projects and seek stakeholder feedback and input regarding gaps in the current system to facilitate the further development of Sentinel and its system of Active Risk Identification and Analysis (ARIA).
e) By the end of FY 2020, FDA will establish policies and procedures (Manual of Policies and Procedures [MAPP] and Standard Operating Procedures and Policies [SOPP]) to facilitate informing sponsors about the planned use of Sentinel to evaluate a safety signal involving their respective products. These MAPPs and SOPPs will address what types of evaluations and what information about the evaluations will be shared with sponsors, and the timing of such communications.
f) By the end of FY 2020, FDA will facilitate integration of Sentinel into the human drug review program in a systematic, efficient, and consistent way through staff development and by updating existing SOPPs and MAPPs, as needed.
g) By the end of FY 2020, FDA will develop a comprehensive training program for review staff (e.g., epidemiologists, statisticians, medical officers, clinical analysts, project managers, and other review team members) to ensure that staff have a working knowledge of Sentinel, can identify when Sentinel can inform important regulatory questions, and are able to consistently participate in use of Sentinel to evaluate safety concerns.
h) By the end of FY 2022, FDA will analyze, and report on the impact of the Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, Post-market Requirements, or Post-market Commitments.

[91] U.S. Food and Drug Administration. (2017). PDUFA reauthorization performance goals and procedures fiscal years 2018 through 2022. https://www.fda.gov/media/99140/download

Appendix D Sentinel Common Data Model

Figure 15 was extracted from SentinelInitiative.org, available at: https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

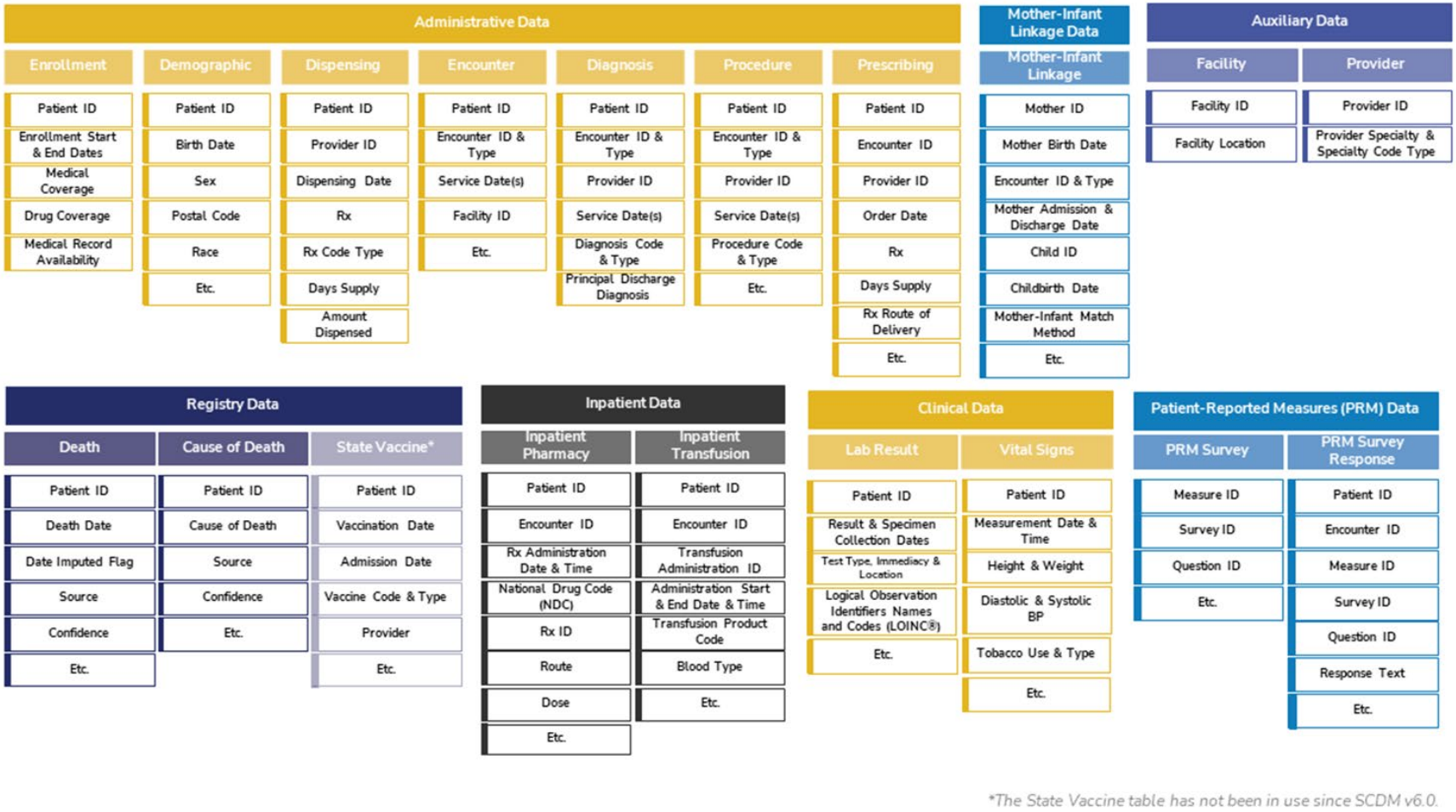


Figure 15. Sentinel Common Data Model

Appendix E Sentinel Publications and Presentations

The following tables list Sentinel publications and presentations since the last Sentinel assessment in 2017 through July 2022, respectively. Publications and presentations related to COVID-19 are denoted with an asterisk preceding the title.

Table 7. Sentinel Publications

Title	Date Posted
Missing Laboratory Results Data in Electronic Health Databases: Implications for Monitoring Diabetes Risk (https://doi.org/10.2217/cer-2016-0033)	01/06/2017
Antiemetic Use Among Pregnant Women in the United States: The Escalating Use of Ondansetron (https://doi.org/10.1002/pds.4185)	02/20/2017
Statistical Power for Postlicensure Medical Product Safety Data-Mining (https://doi.org/10.5334%2Fegems.225)	06/12/2017
Sentinel Modular Program for Propensity-Score Matched Cohort Analyses: Application to Glyburide, Glipizide, and Serious Hypoglycemia (http://dx.doi.org/10.1097/EDE.0000000000000709)	07/04/2017
Retrieving Medical Records Within FDA's Sentinel Distributed Network: Lessons Learned During a Protocol-Based Assessment Involving 13 Data Partners (https://institutionalrepository.aah.org/jpcrr/vol4/iss3/59/)	08/10/2017
Enrollment and Retention in 34 United States Pregnancy Registries Contrasted with the Manufacturer's Capture of Spontaneous Reports for Exposed Pregnancies (https://doi.org/10.1007/s40264-017-0591-5)	08/29/2017
The Impact of FDA Regulatory Activities on Incident Dispensing of LABA-Containing Medication: 2005-2011 (https://doi.org/10.1080/02770903.2017.1378355)	09/14/2017
A Review of the Performance of Different Methods for Propensity Score Matched Subgroup Analyses and a Summary of their Application in Peer-Reviewed Research Studies (https://doi.org/10.1002/pds.4328)	10/06/2017
Development and Application of Two Semi-Automated Tools for Targeted Medical Product Surveillance in a Distributed Data Network (https://doi.org/10.1007/s40471-017-0121-0)	10/06/2017
Prospective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study (https://doi.org/10.2337/dc17-0476)	11/01/2017
Safety Assessment of Niacin in the U.S. Food and Drug Administration's Mini-Sentinel System (https://doi.org/10.1002/pds.4343)	11/06/2017
Outcomes of Dabigatran and Warfarin for Atrial Fibrillation in Contemporary Practice: A Retrospective Cohort Study (https://doi.org/10.7326/M16-1157)	11/14/2017
Opioid Tolerance and Urine Drug Testing among Initiates of Extended-Release or Long-Acting Opioids in Food and Drug Administration's Sentinel System (https://www.wmpllc.org/ojs/index.php/jom/article/view/736)	11/20/2017
Chart Validation of Inpatient ICD-9-CM Administrative Diagnosis Codes for Ischemic Stroke Among IGIV Users in the Sentinel Distributed Database (https://doi.org/10.1002/pds.4398)	12/01/2017
Prospective Surveillance Pilot of Rivaroxaban Safety within the US Food and Drug Administration Sentinel System (https://doi.org/10.1002/pds.4375)	01/10/2018
Chart Validation of Inpatient ICD-9-CM Administrative Diagnosis Codes for Acute Myocardial Infarction (AMI) Among Intravenous Immune Globulin (IGIV) Users in the Sentinel Distributed Database (https://doi.org/10.1002/pds.4398)	02/15/2018

Title	Date Posted
Chart Validation of Inpatient ICD-9-CM Administrative Diagnosis Codes for Venous Thromboembolism among Intravenous Immune Globulin Users in the Sentinel Distributed Database (https://doi.org/10.1097/MD.0000000000009440)	02/23/2018
Assessment of Quadrivalent Human Papillomavirus Vaccine Safety Using the Self-Controlled Tree-Temporal Scan Statistic Signal-Detection Method in the Sentinel System (https://doi.org/10.1093/aje/kwy023)	02/23/2018
Sequential Surveillance for Drug Safety in a Regulatory Environment (https://doi.org/10.1002/pds.4407)	03/05/2018
Utilization of Drugs with Pregnancy Exposure Registries During Pregnancy (https://doi.org/10.1002/pds.4409)	03/08/2018
Evaluation of the US Food and Drug Administration Sentinel Analysis Tools in Confirming Previously Observed Drug-Outcome Associations: The Case of Clindamycin and Clostridium difficile Infection (https://doi.org/10.1002/pds.4420)	03/13/2018
Relative Performance of Propensity Score Matching Strategies for Subgroup Analyses (https://doi.org/10.1093/aje/kwy04)	03/15/2018
A Query Workflow Design to Perform Automatable Distributed Regression Analysis in Large Distributed Data Networks (http://doi.org/10.5334/egems.209)	05/25/2018
Diagnosis-Based Cohort Augmentation using Laboratory Results Data: The Case of Chronic Kidney Disease (https://doi.org/10.1002/pds.4583)	06/22/2018
Assessing the Impact of the New ICD-10-CM Coding System on Pharmacoepidemiologic Studies — An Application to the Known Association Between Angiotensin-Converting Enzyme Inhibitors and Angioedema (https://doi.org/10.1002/pds.4550)	06/26/2018
Early Impact of the ICD-10-CM Transition on Selected Health Outcomes in 13 Electronic Health Care Databases in the United States (https://doi.org/10.1002/pds.4563)	06/26/2018
Extension of Disease Risk Score-Based Confounding Adjustments for Multiple Outcomes of Interest- An Empirical Evaluation (https://doi.org/10.1093/aje/kwy130)	06/26/2018
Outpatient Influenza Antivirals in a Distributed Data Network for Influenza Surveillance (https://doi.org/10.1111/irv.12598)	07/27/2018
Data Mining for Adverse Drug Events with a Propensity Score Matched Tree-Based Scan Statistic (https://doi.org/10.1097/ede.0000000000000907)	08/01/2018
Data Enclaves for Sharing Information Derived From Clinical and Administrative Data (https://doi.org/10.1001/jama.2018.9342)	08/06/2018
Incidence of Heart Failure and Cardiomyopathy Following Initiation of Medications for Attention-Deficit/Hyperactivity Disorder: A Descriptive Study (https://doi.org/10.1097/jcp.0000000000000939)	08/10/2018
Evaluation of Switching Patterns in FDA's Sentinel System: A New Tool to Assess Generic Drugs (https://doi.org/10.1007/s40264-018-0709-4)	08/17/2018
Evaluating Automated Approaches to Anaphylaxis Case Classification Using Unstructured Data from the FDA Sentinel System (https://doi.org/10.1002/pds.4645)	08/28/2018
Association of Risk for Venous Thromboembolism With Use of Low-Dose Extended- and Continuous-Cycle Combined Oral Contraceptives: A Safety Study Using the Sentinel Distributed Database (https://doi.org/10.1001/jamainternmed.2018.4251)	10/01/2018
Misclassification in Assessment of First Trimester In-Utero Exposure to Drugs used Proximally to Conception - The Example of Letrozole Utilization for Infertility Treatment (https://doi.org/10.1093/aje/kwy237)	10/15/2018

Title	Date Posted
Assessment of Prior Opioid Tolerance Among New Users of Fentanyl Transdermal System in FDA's Sentinel System (https://doi.org/10.1002/pds.4677)	10/31/2018
Overall and Cause-Specific Mortality in the Sentinel System: A Power Analysis (https://doi.org/10.1002/pds.4692)	11/13/2018
Use of Tumor Necrosis Factor-alpha Inhibitors During Pregnancy Among Women Who Delivered Liveborn Infants (https://doi.org/10.1002/pds.4695)	11/14/2018
FDA-Catalyst - Using FDA's Sentinel Initiative for Large-Scale Pragmatic Randomized Trials: Approach and Lessons Learned During the Planning Phase of the First Trial (https://doi.org/10.1177/1740774518812776)	11/19/2018
Diagnostic Algorithms for Cardiovascular Death in Administrative Claims Databases: A Systematic Review (https://doi.org/10.1007/s40264-018-0754-z)	11/23/2018
The FDA Sentinel Initiative — An Evolving National Resource (https://doi.org/10.1056/NEJMp1809643)	11/29/2018
How Pharmacoepidemiology Networks Can Manage Distributed Analyses to Improve Replicability and Transparency and Minimize Bias (https://doi.org/10.1002/pds.4722)	01/15/2019
Evaluation of the US Food and Drug Administration Sentinel Analysis Tools Using a Comparator with a Different Indication: Comparing the Rates of Gastrointestinal Bleeding in Warfarin and Statin Users (https://doi.org/10.1007/s40290-018-00265-w)	01/19/2019
Use of FDA's Sentinel System to Quantify Seizure Risk Immediately Following New Ranolazine Exposure (https://doi.org/10.1007/s40264-019-00798-2)	02/08/2019
A New Analytic Tool Developed in the Sentinel System to Assess Safe Use Recommendations (https://doi.org/10.1002/pds.4724)	02/12/2019
Cross-Network Directory Service: Infrastructure to Enable Collaborations Across Distributed Research Networks (https://doi.org/10.1002/lrh2.10187)	02/14/2019
The Devil's in the Details: Reports on Reproducibility in Pharmacoepidemiologic Studies (https://doi.org/10.1002/pds.4730)	03/06/2019
Evaluating the Use of Bootstrapping in Cohort Studies Conducted with 1:1 Propensity Score Matching — A Plasmode Simulation Study (https://doi.org/10.1002/pds.4784)	04/24/2019
Applying Sequential Surveillance Methods That Use Regression Adjustment or Weighting to Control Confounding in a Multi-Site, Rare Event, Distributed Setting: Part 2 In-Depth Example of a Re-Analysis of the MMRV Combination Vaccine and Seizure Risk (https://doi.org/10.1016/j.jclinepi.2019.04.019)	05/02/2019
Leveraging the Entire Cohort in Drug Safety Monitoring: Part 1 Methods for Sequential Surveillance that Use Regression Adjustment or Weighting to Control Confounding in a Multi-Site, Rare Event, Distributed Data Setting (https://doi.org/10.1016/j.jclinepi.2019.04.012)	05/17/2019
Evaluation of Use of Technologies to Facilitate Medical Chart Review (https://doi.org/10.1007/s40264-019-00838-x)	05/20/2019
Antipsychotic Use and Stroke: A Retrospective Comparative Study in a Non-Elderly Population (https://doi.org/10.4088/jcp.18m12636)	06/04/2019
Validation of Febrile Seizures Identified in the Sentinel Post-Licensure Rapid Immunization Safety Monitoring Program (https://doi.org/10.1016/j.vaccine.2019.05.042)	06/08/2019
Kawasaki Disease and 13-Valent Pneumococcal Conjugate Vaccination Among Young Children: A Self-Controlled Risk Interval and Cohort Study with Null Results (https://doi.org/10.1371/journal.pmed.1002844)	07/02/2019
Development of an Algorithm to Detect Methotrexate Wrong Frequency Error Using Computerized Health Care Data (https://doi.org/10.1002/pds.4858)	08/13/2019

Title	Date Posted
First-Trimester Exposure to Gadolinium-based Contrast Agents: A Utilization Study of 4.6 Million U.S. Pregnancies (https://doi.org/10.1148/radiol.2019190563)	08/20/2019
Bystander Ethics and Good Samaritanism: A Paradox for Learning Health Organizations (https://doi.org/10.1002/hast.1031)	08/20/2019
Identification of Potential Drug Name Confusion Errors in the Sentinel System (https://doi.org/10.1002/pds.4891)	09/04/2019
Use of Time-Dependent Propensity Scores to Adjust Hazard Ratio Estimates in Cohort Studies with Differential Depletion of Susceptibles (https://doi.org/10.1097/ede.0000000000001107)	09/26/2019
Use of Sodium–Glucose Cotransporter 2 Inhibitors in Patients With Type 1 Diabetes and Rates of Diabetic Ketoacidosis (https://doi.org/10.2337/dc19-1481)	10/10/2019
Reproducing Protocol-based Studies Using Parameterizable Tools – Comparison of Analytic Approaches Used by Two Medical Product Surveillance Networks (https://doi.org/10.1002/cpt.1698)	10/19/2019
Healthcare Database Networks for Drug Regulatory Policies: International Workshop on the Canadian, US and Spanish Experience and Future Steps for Italy (https://doi.org/10.1007/s40264-019-00871-w)	10/22/2019
Quantifying How Small Variations in Design Elements Affect Risk in an Incident Cohort Study in Claims (https://doi.org/10.1002/pds.4892)	11/17/2019
Use of Antidiabetic Drugs During Pregnancy among U.S. Women with Livebirth Deliveries in the Mini-Sentinel System (https://doi.org/10.1186/s12884-019-2609-8)	11/27/2019
Understanding Utilization Patterns of Biologics and Biosimilars in the United States to Support Postmarketing Studies of Safety and Effectiveness (https://doi.org/10.1002/pds.4908)	12/11/2019
The Risk of Febrile Seizures following Influenza and 13-Valent Pneumococcal Conjugate Vaccines (https://doi.org/10.1016/j.vaccine.2020.01.046)	01/31/2020
Translating Claims-Based CHA2DS2-VaSc and HAS-BLED to ICD-10-CM: Impacts of Mapping Strategies (https://doi.org/10.1002/pds.4973)	02/17/2020
Distributed Regression Analysis Application in Large Distributed Data Networks: Analysis of Precision and Operational Performance (https://doi.org/10.2196/15073)	04/06/2020
Using and Improving Distributed Data Networks to Generate Actionable Evidence: the Case of Real-World Outcomes in the Food and Drug Administration's Sentinel System (https://doi.org/10.1093/jamia/ocaa028)	04/11/2020
Conducting Prospective Sequential Surveillance in Real-World Dynamic Distributed Databases (https://doi.org/10.1002/pds.5002)	05/25/2020
Concomitant Filled Prescriptions of Oxymorphone or Oxycodone with CYP3A Inhibitors and Inducers (https://doi.org/10.18553/jmcp.2020.26.5.668)	05/26/2020
Practical Challenges in the Conduct of Pragmatic Trials Embedded in Health Plans: Lessons of IMPACT-AFib, an FDA-Catalyst Trial (https://doi.org/10.1177/1740774520928426)	06/26/2020
Underuse of Oral anticoagulants in privately insured patients with atrial fibrillation: A population targeted by IMplementation of a randomized controlled trial to ImProve treatment with Oral AntiCoagulanTs in atrial fibrillation patients (IMPACT-AFib) (https://doi.org/10.1016/j.ahj.2020.07.012)	07/24/2020
Consequences of Depletion of Susceptibles for Hazard Ratio Estimators Based on Propensity Scores (https://doi.org/10.1097/ede.0000000000001246)	08/06/2020
Risk of Psychiatric Adverse Events among Montelukast Users (https://doi.org/10.1016/j.jaip.2020.07.052)	08/11/2020

Title	Date Posted
Utilization of Sacubitril/Valsartan in Real-World Settings (https://doi.org/10.1007/s40256-020-00433-x)	08/24/2020
Risk of Stroke and Bleeding in Atrial Fibrillation Treated with Apixaban Compared with Warfarin (https://doi.org/10.1007/s11606-020-06180-8)	09/28/2020
Phosphodiesterase Type 5 Inhibitor Use Among Pregnant and Reproductive-Age Women in the United States (https://doi.org/10.1002/pds.5112)	10/05/2020
Complementary Use of U.S. FDA's Adverse Event Reporting System and Sentinel System to Characterize Direct Oral Anticoagulants-Associated Cutaneous Small Vessel Vasculitis (https://doi.org/10.1002/phar.2468)	10/08/2020
Leveraging the Capabilities of the FDA's Sentinel System To Improve Kidney Care (https://doi.org/10.1681/ASN.2020040526)	10/19/2020
Functional Clustering Methods for Longitudinal Data with Application to Electronic Health Records (https://doi.org/10.1177%2F0962280220965630)	11/11/2020
Incidence of Uterine Bleeding following Oral Anticoagulant Use in Food and Drug Administration's Sentinel System (https://doi.org/10.1016/j.ajog.2020.11.034)	11/26/2020
The FDA MyStudies App: A Reusable Platform for Distributed Clinical Trials and Real-World Evidence Studies (https://doi.org/10.1093/jamiaopen/ooaa061)	12/11/2020
Medical Chart Validation of Inpatient Diagnosis Codes for Transfusion-Related Acute Lung Injury 2013-2015 (https://doi.org/10.1111/trf.16251)	01/27/2021
Identification and Validation of Anaphylaxis Using Electronic Health Data in a Population-Based Setting (https://doi.org/10.1097/EDE.0000000000001330)	02/02/2021
Risk of Non-Melanoma Skin Cancer in Association with Use of Hydrochlorothiazide-Containing Products in the United States (https://doi.org/10.1093/jncics/pkab009)	02/04/2021
A General Propensity Score for Signal Identification using Tree-Based Scan Statistics (https://doi.org/10.1093/aje/kwab034)	02/22/2021
Electronic Phenotyping of Health Outcomes of Interest Using a Linked Claims-Electronic Health Record Database: Findings from a Machine Learning Pilot Project (https://doi.org/10.1093/jamia/ocab036)	03/12/2021
* A COVID-19-Ready Public Health Surveillance System: The FDA's Sentinel System (https://doi.org/10.1002/pds.5240)	04/02/2021
Validity of ICD-10-CM Diagnoses to Identify Hospitalizations for Serious Infections Among Patients Treated With Biologic Therapies (https://doi.org/10.1002/pds.5253)	04/22/2021
Validation of an Electronic Algorithm for Hodgkin and Non-Hodgkin Lymphoma in ICD-10-CM (https://doi.org/10.1002/pds.5256)	04/26/2021
Utilization of Hydroxyprogesterone Caproate among Pregnancies with Live Birth Deliveries in the Sentinel Distributed Database (https://doi.org/10.1080/14767058.2021.1910669)	04/29/2021
Risk of Severe Abnormal Uterine Bleeding Associated with Rivaroxaban Compared with Apixaban, Dabigatran and Warfarin (https://doi.org/10.1007/s40264-021-01072-0)	05/20/2021
Validation of an ICD-10-based Algorithm to Identify Stillbirth in the Sentinel System (https://doi.org/10.1002/pds.5300)	06/04/2021
Use of a Mobile App to Capture Supplemental Health Information During Pregnancy: Implications for Clinical Research (https://doi.org/10.1002/pds.5320)	07/03/2021
Who Gets Treated for Influenza: A Surveillance Study From the US Food and Drug Administration's Sentinel System (https://doi.org/10.1017/ice.2021.311)	08/05/2021
Incidence of Severe Uterine Bleeding Outcomes among Oral Anticoagulant Users and Nonusers (https://doi.org/10.1016/j.ajog.2021.08.051)	09/01/2021

Title	Date Posted
Risk of Hospitalized Depression and Intentional Self-Harm with Brand and Authorized Generic Sertraline (https://doi.org/10.1016/j.jad.2021.09.088)	10/05/2021
Prescription Medication Use and Baseline Health Status of Women with Live Birth Deliveries in a National Data Network (https://doi.org/10.1016/j.ajogmf.2021.100512)	10/14/2021
Using Inpatient Electronic Medical Records to Study Influenza for Pandemic Preparedness (https://doi.org/10.1111/irv.12921)	10/25/2021
Emerging Technologies and Their Impact on Regulatory Science (https://doi.org/10.1177/15353702211052280)	11/16/2021
Self-Controlled Assessment of Thromboembolic Event (TEE) Risk Following Intravenous Immune Globulin (IGIV) in the U.S. (2006–2012) (https://doi.org/10.1007/s11239-021-02610-4)	11/24/2021
* Validation of Diagnosis Codes to Identify Hospitalized COVID-19 Patients in Health Care Claims Data (https://doi.org/10.1002/pds.5401)	12/16/2021
Broadening the Reach of the FDA Sentinel System: A Roadmap for Integrating Electronic Health Record Data in a Causal Analysis Framework (https://doi.org/10.1038/s41746-021-00542-0)	12/20/2021
Evaluating Confounding Control in Estimations of Influenza Antiviral Effectiveness in Electronic Health Plan Data (https://doi.org/10.1093/aje/kwac020)	02/02/2022
Utility of Fertility Procedures and Prenatal Tests to Estimate Gestational Age for Live-births and Stillbirths in Electronic Health Plan Databases (https://doi.org/10.1002/pds.5414)	02/05/2022
* Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021 (https://doi.org/10.1001/jama.2022.4877)	04/08/2022
New-Onset Cancer Cases in FDA's Sentinel System: A Large Distributed System of US Electronic Healthcare Data (https://doi.org/10.1158/1055-9965.EPI-21-1451)	07/15/2022
Novel Methods for Pregnancy Drug Safety Surveillance in the FDA Sentinel System (https://doi.org/10.1002/pds.5512)	07/24/2022

Table 8. Sentinel Presentations

Title	Date Posted
Type 1 and Type 2 Diabetes Mellitus Identification Using ICD-9-CM Codes Within a Cohort of New Users of Drugs Labeled for Type 2 Diabetes Mellitus (https://www.sentinelinitiative.org/news-events/publications-presentations/type-1-and-type-2-diabetes-mellitus-identification-using-icd)	08/23/2017
Randomized Clinical Trial Using FDA's Sentinel Infrastructure: An Analysis Assessing Feasibility (https://www.sentinelinitiative.org/news-events/publications-presentations/type-1-and-type-2-diabetes-mellitus-identification-using-icd)	08/24/2017
Medical Product and Performance Evaluation Programs Using Distributed Data Sources (https://www.sentinelinitiative.org/news-events/publications-presentations/medical-product-and-performance-evaluation-programs-using)	08/24/2017
Developing a Mobile App for Studies of Medication Safety (https://www.sentinelinitiative.org/news-events/publications-presentations/developing-mobile-app-studies-medication-safety)	08/24/2017
Developing a Mother-Infant Cohort in Sentinel's PRISM Program as a Resource to Monitor the Safety of Vaccine Use During Pregnancy (https://www.sentinelinitiative.org/news-events/publications-presentations/developing-mother-infant-cohort-sentinels-prism-program)	08/25/2017

Title	Date Posted
Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year (https://www.sentinelinitiative.org/news-events/publications-presentations/integrating-sentinel-routine-regulatory-drug-review-snapshot)	08/25/2017
Practical Lessons Learned for Identification of Thromboembolic Events and Intravenous Immunoglobulin Exposure in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/practical-lessons-learned-identification-thromboembolic)	08/25/2017
Protocol-Based Assessment of Thromboembolic Events (TEEs) after Intravenous Immune Globulin (IVIg) in the Sentinel Distributed Database (2006-2012) (https://www.sentinelinitiative.org/news-events/publications-presentations/protocol-based-assessment-thromboembolic-events-tees-after)	08/25/2017
Expansion of the US FDA's Sentinel System to Inpatient Blood Transfusion Data from Hospital Corporation of America: New Surveillance Options (https://www.sentinelinitiative.org/news-events/publications-presentations/expansion-us-fdas-sentinel-system-inpatient-blood)	08/25/2017
Evaluation of Case-Finding Algorithm for Venous Thromboembolism Outcome (https://www.sentinelinitiative.org/news-events/publications-presentations/evaluation-case-finding-algorithm-venous-thromboembolism)	08/25/2017
Opportunities for Rapid Monitoring of New Cancer Treatments: Tyrosine Kinase Inhibitors in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/opportunities-rapid-monitoring-new-cancer-treatments)	08/25/2017
Using the Self-Controlled Risk Interval (SCRI) Method to Study Vaccine Safety (https://www.sentinelinitiative.org/news-events/publications-presentations/using-self-controlled-risk-interval-scri-method-study)	08/25/2017
Assessment of Transfusion-Related Acute Lung Injury After Red Blood Cell, Plasma and Platelet Administration: Initial Results in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/assessment-transfusion-related-acute-lung-injury-after-red)	08/25/2017
Tumor Necrosis Factor-alpha Inhibitor (TNFi) Utilization among Women with Live Birth (https://www.sentinelinitiative.org/news-events/publications-presentations/tumor-necrosis-factor-alpha-inhibitor-tnfi-utilization-among)	08/25/2017
Trends of Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccination During Pregnancy in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/trends-tetanus-diphtheria-and-acellular-pertussis-tdap)	08/25/2017
Impact of ICD-10-CM Transition on Selected Cardiovascular-Related Events in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/impact-icd-10-cm-transition-selected-cardiovascular-related)	08/25/2017
TreeScan™: A Novel Data-Mining Tool for Medical Product Safety Surveillance (https://www.sentinelinitiative.org/news-events/publications-presentations/treescan-novel-data-mining-tool-medical-product-safety)	08/25/2017
A Review of Methods for Propensity Score Matched Subgroup Analysis and Their Application in Peer Reviewed Research Studies (https://www.sentinelinitiative.org/news-events/publications-presentations/review-methods-propensity-score-matched-subgroup-analysis)	08/25/2017
Identification of Name Confusion Medication Errors in the US FDA's Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/identification-name-confusion-medication-errors-us-fdas)	08/25/2017
Early Post-Approval Surveillance of New Molecular Entity Uptake in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/early-post-approval-surveillance-new-molecular-entity-uptake)	08/25/2017

Title	Date Posted
Feasibility Analysis of Mortality Outcomes in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/feasibility-analysis-mortality-outcomes-sentinel-distributed)	08/25/2017
Evaluation of Test Data in Distributed Research Networks: A Sentinel System Example (https://www.sentinelinitiative.org/news-events/publications-presentations/evaluation-test-data-distributed-research-networks-sentinel)	08/25/2017
Assessment of Prior Opioid Tolerance Among New Users of Fentanyl Transdermal System in FDA's Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/assessment-prior-opioid-tolerance-among-new-users-fentanyl-0)	08/25/2017
Dispensings of Influenza Antiviral Medications in the Sentinel System as a Source of Data for Influenza Surveillance (https://www.sentinelinitiative.org/news-events/publications-presentations/dispensings-influenza-antiviral-medications-sentinel-system)	08/25/2017
Curating Inpatient Medication Use Data from a Hospital Network Electronic Medication Administration Record (eMAR) System: Lessons from the Sentinel System About Expanding Drug Safety Surveillance Potential (https://www.sentinelinitiative.org/news-events/publications-presentations/curating-inpatient-medication-use-data-hospital-network)	08/25/2017
Distributed Regression Analysis in a Distributed Health Data Network (https://www.sentinelinitiative.org/news-events/publications-presentations/distributed-regression-analysis-distributed-health-data)	08/25/2017
Listening to Patient Voices in Pharmacoepidemiological Research - Opportunities for Innovation and Inclusion (https://www.sentinelinitiative.org/news-events/publications-presentations/listening-patient-voices-pharmacoepidemiological-research)	08/25/2017
Prospective Surveillance Pilot of Rivaroxaban Safety within the US Food and Drug Administration Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/prospective-surveillance-pilot-rivaroxaban-safety-within-0)	08/25/2017
Promises and Challenges of Screening for Adverse Events in Sentinel (https://www.sentinelinitiative.org/news-events/publications-presentations/promises-and-challenges-screening-adverse-events-sentinel)	08/27/2017
Sentinel Modular Program for Propensity Score–Matched Cohort Analyses: Application to Glyburide, Glipizide, and Serious Hypoglycemia (Video Abstract) (https://www.sentinelinitiative.org/news-events/publications-presentations/sentinel-modular-program-propensity-score-matched-cohort-0)	10/06/2017
Methods for Examining Data Quality in Healthcare Integrated Data Repositories (https://www.sentinelinitiative.org/news-events/publications-presentations/methods-examining-data-quality-healthcare-integrated-data)	01/03/2018
Butterfly Effect in Studies Using Claims Data? Some Small Perturbations in Study Design Lead to Differences in Causal Inference (https://www.sentinelinitiative.org/news-events/publications-presentations/butterfly-effect-studies-using-claims-data-some-small)	01/12/2018
Small Changes, Big Differences? Cohort Variation by Parameter Specifications in Claims-Based Drug Use Evaluations (https://www.sentinelinitiative.org/news-events/publications-presentations/small-changes-big-differences-cohort-variation-parameter)	05/21/2018
Developing the Infrastructure to Assess Pregnancy Outcomes Following Vaccination: Influenza Vaccines and Spontaneous Abortion as a Use Case (https://www.sentinelinitiative.org/news-events/publications-presentations/developing-infrastructure-assess-pregnancy-outcomes)	08/20/2018
Diagnostic Algorithms for Identification of Cardiovascular Death in Administrative Claims Databases: A Systematic Review (https://www.sentinelinitiative.org/news-events/publications-presentations/diagnostic-algorithms-identification-cardiovascular-death)	08/20/2018

Title	Date Posted
Computational Algorithms for Distributed Regression Analysis Based on SAS Software (https://www.sentinelinitiative.org/news-events/publications-presentations/computational-algorithms-distributed-regression-analysis)	08/20/2018
A New Analytic Tool Developed in the Sentinel System to Assess Adherence To FDA's Safe Use Recommendations (https://www.sentinelinitiative.org/news-events/publications-presentations/new-analytic-tool-developed-sentinel-system-assess-adherence)	08/20/2018
Estimating "Optimal" Durations for Initial Opioid Analgesic Prescription Following Common Surgical Procedures (https://www.sentinelinitiative.org/news-events/publications-presentations/estimating-optimal-durations-initial-opioid-analgesic)	08/20/2018
Data-Mining for Adverse Events Using the Self-Controlled Tree-Temporal Scan Statistic (https://www.sentinelinitiative.org/news-events/publications-presentations/data-mining-adverse-events-using-self-controlled-tree)	08/20/2018
Validation of the Combined Comorbidity Score in the ICD-10 Era: Application to High-Risk Populations (https://www.sentinelinitiative.org/news-events/publications-presentations/validation-combined-comorbidity-score-icd-10-era-application)	08/20/2018
Performance of a Distributed Regression Analysis Software and Workflow (https://www.sentinelinitiative.org/news-events/publications-presentations/performance-distributed-regression-analysis-software-and)	08/20/2018
Sequential and SequentialDesign: Tools For Prospective Sequential Medical Product Safety Surveillance (https://www.sentinelinitiative.org/news-events/publications-presentations/sequential-and-sequentialdesign-tools-prospective-sequential)	08/20/2018
Extension of Disease Risk Score-Based Confounding Adjustments for Multiple Outcomes Of Interest – An Empirical Evaluation (https://www.sentinelinitiative.org/news-events/publications-presentations/extension-disease-risk-score-based-confounding-adjustments-0)	08/20/2018
Long Live the "Medical Data Janitors": International Data Quality Assurance Practices in Distributed Data Network (https://www.sentinelinitiative.org/news-events/publications-presentations/long-live-medical-data-janitors-international-data-quality)	08/20/2018
Advances in the Study of Medication Errors in Computerized Healthcare Databases and Spontaneous Reporting Systems in Europe and North America (https://www.sentinelinitiative.org/news-events/publications-presentations/advances-study-medication-errors-computerized-healthcare)	08/20/2018
Quantifying Prevalence and Mortality Associated with Neonatal Enteroviral Sepsis (NES) Using Inpatient Data in FDA's Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/quantifying-prevalence-and-mortality-associated-neonatal)	08/20/2018
Early Lessons on ICD-10-CM/PCS Transition in Claims-Based Drug Safety Assessments (https://www.sentinelinitiative.org/news-events/publications-presentations/assessing-impact-new-us-icd-10-cm-coding-system)	08/21/2018
Evaluation of Switching Patterns in FDA's Sentinel System – A New Tool to Assess the Substitutability of Generic Drugs (https://www.sentinelinitiative.org/news-events/publications-presentations/evaluation-switching-patterns-fda-s-sentinel-system-new-tool)	08/21/2018
A Comparison of Drug Utilization Metrics for Two Drug Classes with Nationally Projected Sales and Patient-level Data from the Sentinel Database (https://www.sentinelinitiative.org/news-events/publications-presentations/comparison-drug-utilization-metrics-two-drug-classes)	08/21/2018
Minor Differences, Major Consequences? Lessons Learned from Replication of a Claims-Based Drug Safety Assessment (https://www.sentinelinitiative.org/news-events/publications-presentations/minor-differences-major-consequences-lessons-learned)	08/21/2018

Title	Date Posted
Use of Multiple Sclerosis Drugs Among Live Birth Pregnancies in the United States (https://www.sentinelinitiative.org/news-events/publications-presentations/use-multiple-sclerosis-drugs-among-live-birth-pregnancies)	08/21/2018
Signal Detection using TreeScan with Drug Classes: Pilot Projects in Sentinel (https://www.sentinelinitiative.org/news-events/publications-presentations/signal-detection-using-treescan-drug-classes-pilot-projects)	08/21/2018
Assessing the Impact of the New U.S. ICD-10-CM Coding System on Pharmacoepidemiologic Studies: An Application Between Angiotensin-Converting Enzyme Inhibitors and Angioedema (https://www.sentinelinitiative.org/news-events/publications-presentations/assessing-impact-new-us-icd-10-cm-coding-system)	08/21/2018
Data Mining for Adverse Drug Events with a Propensity Score Matched Tree-Based Scan Statistic (https://www.sentinelinitiative.org/news-events/publications-presentations/data-mining-adverse-drug-events-propensity-score-matched-0)	08/22/2018
First Trimester Exposure to Gadolinium Contrast; A Utilization Study of 4.6 Million Live-Birth Pregnancies (https://www.sentinelinitiative.org/news-events/publications-presentations/first-trimester-exposure-gadolinium-contrast-utilization)	08/22/2018
Using Time-Dependent Propensity Scores to Correct for Differential Depletion of Susceptibles when Estimating Hazard Ratios in Time-to-Event Data (https://www.sentinelinitiative.org/news-events/publications-presentations/using-time-dependent-propensity-scores-correct-differential)	08/22/2018
Misclassification of Time-at-Risk Due to Free Drug Sample Use: A Simulation Study (https://www.sentinelinitiative.org/news-events/publications-presentations/misclassification-time-risk-due-free-drug-sample-use)	08/22/2018
Assessment of Transfusion-Related Acute Lung Injury (TRALI) after Blood Transfusion (https://www.sentinelinitiative.org/news-events/publications-presentations/assessment-transfusion-related-acute-lung-injury-trali-after)	08/24/2018
Validation of Transfusion Administrations Among Potential Transfusion-Related Acute Lung Injury (TRALI) Patients Included in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/validation-transfusion-administrations-among-potential)	08/25/2018
International Comparison of Approaches to Common Data Models for Comparative Effectiveness Research (https://www.sentinelinitiative.org/news-events/publications-presentations/international-comparison-approaches-common-data-models)	09/12/2018
Harnessing Big Data for Medical Product Safety Surveillance: The Experience of the Sentinel Initiative (https://www.sentinelinitiative.org/news-events/publications-presentations/harnessing-big-data-medical-product-safety-surveillance)	10/19/2018
Collection of Patient-Provided Information through a Mobile Device Application for Use in Medical Product Safety Surveillance (https://www.sentinelinitiative.org/news-events/publications-presentations/collection-patient-provided-information-through-mobile)	11/04/2018
A Generalizable Smartphone-Based Clinical Research Platform (https://www.sentinelinitiative.org/news-events/publications-presentations/generalizable-smartphone-based-clinical-research-platform)	11/05/2018
Drug Safety in Pregnancy in a Large, Multisite Database: FDA MyStudies App (https://www.sentinelinitiative.org/news-events/publications-presentations/drug-safety-pregnancy-large-multisite-database-fda-mystudies)	11/29/2018
Drug Safety in Pregnancy in a Large, Multisite Database: Mother-Infant Linkage in Sentinel (https://www.sentinelinitiative.org/news-events/publications-presentations/drug-safety-pregnancy-large-multisite-database-mother-infant)	11/30/2018

Title	Date Posted
Drug Safety in Pregnancy in a Large, Multisite Database: Sentinel Pregnancy Tool and Transition to ICD-10 (https://www.sentinelinitiative.org/news-events/publications-presentations/drug-safety-pregnancy-large-multisite-database-sentinel)	11/30/2018
Drug Safety in Pregnancy in a Large, Multisite Database: Validation of an ICD-10-based Algorithm to Identify Stillbirth in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/drug-safety-pregnancy-large-multisite-database-validation)	11/30/2018
Evidence from Real-World Data Sentinel Initiative of U.S. FDA (https://www.sentinelinitiative.org/news-events/publications-presentations/evidence-real-world-data-sentinel-initiative-us-fda)	02/20/2019
Medical Product Safety: Ten Years of the U.S. Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/medical-product-safety-ten-years-us-sentinel-system)	05/23/2019
Signal Identification Methods in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/signal-identification-methods-sentinel-system)	06/12/2019
A General Propensity Score for Signal Detection using Tree-Based Scan Statistics (https://www.sentinelinitiative.org/news-events/publications-presentations/general-propensity-score-signal-detection-using-tree-based)	08/25/2019
Thinking Globally While Acting Locally: Developing Time-on-Treatment Data In International Settings (https://www.sentinelinitiative.org/news-events/publications-presentations/thinking-globally-while-acting-locally-developing-time)	08/25/2019
Experience from US FDA Sentinel Initiative Studies (https://www.sentinelinitiative.org/news-events/publications-presentations/experience-us-fda-sentinel-initiative-studies)	08/25/2019
Phosphodiesterase Type 5 (PDE-5) Inhibitor Use Among Pregnant Women and Women of Reproductive Age in the United States (https://www.sentinelinitiative.org/news-events/publications-presentations/phosphodiesterase-type-5-pde-5-inhibitor-use-among-pregnant)	08/25/2019
Epidemiology of Pediatric Respiratory Syncytial Virus-Associated Illnesses in Young Children (https://www.sentinelinitiative.org/news-events/publications-presentations/epidemiology-pediatric-respiratory-syncytial-virus)	08/25/2019
Characteristics of NOAC Users Aged Less Than 65 Years in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/characteristics-noac-users-aged-less-65-years-sentinel)	08/25/2019
Evidence of Residual Confounding in Healthcare Database Studies of Oseltamivir and Influenza Complications (https://www.sentinelinitiative.org/news-events/publications-presentations/evidence-residual-confounding-healthcare-database-studies)	08/25/2019
Exposure to N-nitrosodimethylamine (NDMA)/N-nitrosodiethylamine (NDEA)-contaminated Angiotensin-II Receptor Blockers Products in the United States (https://www.sentinelinitiative.org/news-events/publications-presentations/exposure-n-nitrosodimethylamine-ndman-nitrosodiethylamine)	08/25/2019
Characteristics of Febuxostat and Allopurinol Initiators and Utilization Patterns in Real-World Settings (https://www.sentinelinitiative.org/news-events/publications-presentations/characteristics-febuxostat-and-allopurinol-initiators-and)	08/25/2019
Analysis of SGLT2 Inhibitor Use in Patients with Type-1 Diabetes Mellitus and Rates of Diabetic Ketoacidosis (https://www.sentinelinitiative.org/news-events/publications-presentations/analysis-sglt2-inhibitor-use-patients-type-1-diabetes)	08/25/2019
13-Valent Pneumococcal Conjugate Vaccine (PCV13) and Kawasaki Disease (https://www.sentinelinitiative.org/news-events/publications-presentations/13-valent-pneumococcal-conjugate-vaccine-pcv13-and-kawasaki)	08/26/2019

Title	Date Posted
Confounding Variable Capture in Large Healthcare Administrative Claims Database: A Trend Analysis in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/confounding-variable-capture-large-healthcare-administrative)	08/26/2019
Utility of Prenatal Tests and Fertility Coding to Estimate Pregnancy Start in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/utility-prenatal-tests-and-fertility-coding-estimate)	08/26/2019
Duration of Follow-up of Chronic Condition Cohorts in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/duration-follow-chronic-condition-cohorts-sentinel-system)	08/26/2019
Dolutegravir Use Among Women of Child-Bearing Potential and During Early Pregnancy (https://www.sentinelinitiative.org/news-events/publications-presentations/dolutegravir-use-among-women-child-bearing-potential-and)	08/27/2019
Characteristics and Treatment Status of Those with Influenza-Like Illness: Implications for Effectiveness Studies and Surveillance (https://www.sentinelinitiative.org/news-events/publications-presentations/characteristics-and-treatment-status-those-influenza-illness)	08/27/2019
Utilization of Prescription Anti-Obesity Drugs in the U.S. Food and Drug Administration's (FDA) Sentinel System, 2008-2017 (https://www.sentinelinitiative.org/news-events/publications-presentations/utilization-prescription-anti-obesity-drugs-us-food-and-drug)	08/27/2019
Identification of Ordinal Endpoints Indicating Influenza Complications: A Feasibility Analysis Relevant to the Study of Medical Countermeasures (https://www.sentinelinitiative.org/news-events/publications-presentations/identification-ordinal-endpoints-indicating-influenza)	08/27/2019
Complementary Use of US FDA's Adverse Event Reporting System and Sentinel Distributed Database to Characterize Direct Oral Anticoagulants Associated Cutaneous Small Vessel Vasculitis (https://www.sentinelinitiative.org/news-events/publications-presentations/complementary-use-us-fdas-adverse-event-reporting-system-and)	08/27/2019
Biosimilar Use in the United States: A Sentinel Analysis of Filgrastim and Infliximab (https://www.sentinelinitiative.org/news-events/publications-presentations/biosimilar-use-united-states-sentinel-analysis-filgrastim)	08/27/2019
Myopathy and Rhabdomyolysis with Concomitant Use of Ticagrelor and High-Intensity Statins in the Elderly (https://www.sentinelinitiative.org/news-events/publications-presentations/myopathy-and-rhabdomyolysis-concomitant-use-ticagrelor-and)	11/14/2019
Redesigning PopMedNet for Distributed Regression Analysis with Vertically Partitioned Data (https://www.sentinelinitiative.org/news-events/publications-presentations/redesigning-popmednet-distributed-regression-analysis)	11/19/2019
Medical Product Safety Surveillance: Data Quality in the Sentinel Initiative (https://www.sentinelinitiative.org/news-events/publications-presentations/medical-product-safety-surveillance-data-quality-sentinel-0)	12/02/2019
Sentinel Mother-Infant Linkage and Pregnancy Analyses (https://www.sentinelinitiative.org/news-events/publications-presentations/sentinel-mother-infant-linkage-and-pregnancy-analyses)	02/19/2020
Hydrochlorothiazide Use and Risk of Non-Melanoma Skin Cancer (https://www.sentinelinitiative.org/news-events/publications-presentations/hydrochlorothiazide-use-and-risk-non-melanoma-skin-cancer)	03/05/2020
* Assessing Natural History, Drug Use and Treatment Impact for COVID-19 in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/assessing-natural-history-drug-use-and-treatment-impact)	05/13/2020
Hydrochlorothiazide Use and Risk of Non-Melanoma Skin Cancer (https://www.sentinelinitiative.org/news-events/publications-presentations/hydrochlorothiazide-use-and-risk-non-melanoma-skin-cancer-0)	06/11/2020

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* Risk of Thromboembolic Events With COVID-19: A Sentinel System Investigation – Potential Aims/Methods (https://www.sentinelinitiative.org/news-events/publications-presentations/risk-thromboembolic-events-covid-19-sentinel-system-1)	06/23/2020
* Coagulopathy Assessment in Patients with COVID-19: A TriNetX Analysis (https://www.sentinelinitiative.org/news-events/publications-presentations/coagulopathy-assessment-patients-covid-19-trinetx-analysis)	06/23/2020
* Risk of Thromboembolic Events With COVID-19: A Sentinel System Investigation – Update on Methods (https://www.sentinelinitiative.org/news-events/publications-presentations/risk-thromboembolic-events-covid-19-sentinel-system-0)	07/14/2020
* Risk of Thromboembolic Events With COVID-19: A Sentinel System Investigation – Focus on Endpoints (https://www.sentinelinitiative.org/news-events/publications-presentations/risk-thromboembolic-events-covid-19-sentinel-system)	08/04/2020
* Defining COVID-19 Cohorts in Real-World Data (https://www.sentinelinitiative.org/news-events/publications-presentations/defining-covid-19-cohorts-real-world-data-0)	08/18/2020
Assessing Data Source Characteristics in Multi-site Analyses (https://www.sentinelinitiative.org/news-events/publications-presentations/assessing-data-source-characteristics-multi-site-analyses)	09/08/2020
Asthma Maintenance Medication Users in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/asthma-maintenance-medication-users-sentinel-system)	09/17/2020
Percutaneous Transluminal Septal Myocardial Ablation and Common Procedural Complications: A Descriptive Study (https://www.sentinelinitiative.org/news-events/publications-presentations/percutaneous-transluminal-septal-myocardial-ablation-and)	09/17/2020
Replication of Protocol-Based Analyses of Saxagliptin and Sitagliptin using Sentinel Modular Programs (https://www.sentinelinitiative.org/news-events/publications-presentations/replication-protocol-based-analyses-saxagliptin-and)	09/17/2020
Incidence of Ocular Adverse Events Associated with Mometasone Implants among Patients with Nasal Polyposis (https://www.sentinelinitiative.org/news-events/publications-presentations/incidence-ocular-adverse-events-associated-mometasone)	09/17/2020
Improving Identification of Anaphylaxis (https://www.sentinelinitiative.org/news-events/publications-presentations/improving-identification-anaphylaxis)	09/17/2020
Comparing Three Signal Identification Methods with Self-Controlled Designs (https://www.sentinelinitiative.org/news-events/publications-presentations/comparing-three-signal-identification-methods-self)	09/17/2020
Validation of an ICD-10-based Algorithm to Identify Stillbirth in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/validation-icd-10-based-algorithm-identify-stillbirth)	09/17/2020
Antipsychotic Medication Use among Hospitalized Infants Using Inpatient Data in FDA's Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/antipsychotic-medication-use-among-hospitalized-infants)	09/20/2020
Risk of Stroke and Bleeding in Nonvalvular Atrial Fibrillation Treated with Apixaban Compared to Warfarin in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/risk-stroke-and-bleeding-nonvalvular-atrial-fibrillation)	09/20/2020
Incidence of Cutaneous Small Vessel Vasculitis associated with Oral Anticoagulant Use (https://www.sentinelinitiative.org/news-events/publications-presentations/incidence-cutaneous-small-vessel-vasculitis-associated-oral)	09/20/2020

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Utilization of IV Iron among Pregnant Women with Live Births or Stillbirths; A Study in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/utilization-iv-iron-among-pregnant-women-live-births-or)	09/20/2020
Factors Related to Sodium Glucose Cotransporter 2 Inhibitor (SGLT2i) and Dipeptidyl Peptidase 4 Inhibitor (DPP4i) Dispensing among Naive, Incident, and Prevalent New Users (https://www.sentinelinitiative.org/news-events/publications-presentations/factors-related-sodium-glucose-cotransporter-2-inhibitor)	09/21/2020
Assessing the Feasibility of Evaluating Tacrolimus Use after Solid Organ Transplantation in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/assessing-feasibility-evaluating-tacrolimus-use-after-solid)	09/21/2020
Risk of Non-Melanoma Skin Cancer Associated with Hydrochlorothiazide-Containing Products in the United States (https://www.sentinelinitiative.org/news-events/publications-presentations/risk-non-melanoma-skin-cancer-associated-hydrochlorothiazide)	09/21/2020
Incidence of Severe Abnormal Uterine Bleeding Following Oral Anticoagulant Use (https://www.sentinelinitiative.org/news-events/publications-presentations/incidence-severe-abnormal-uterine-bleeding-following-oral)	09/21/2020
Utilization Characteristics for Inhaled Corticosteroid-based Asthma Medications in the Sentinel System, 2008-2019 (https://www.sentinelinitiative.org/news-events/publications-presentations/utilization-characteristics-inhaled-corticosteroid-based)	09/22/2020
Comparative Risk Assessment of Severe Abnormal Uterine Bleeding associated with Non-Vitamin K Oral Anticoagulants (https://www.sentinelinitiative.org/news-events/publications-presentations/comparative-risk-assessment-severe-abnormal-uterine-bleeding)	09/22/2020
Replicating the Findings of a Medicare Study on Stroke, and Bleeding Risk in Patients Using NOACs for Atrial Fibrillation in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/replicating-findings-medicare-study-stroke-and-bleeding-risk)	09/22/2020
Use of Hydroxyprogesterone Caproate and Progesterone During the 2nd and/or 3rd Trimester Among Pregnancies with Live Birth Deliveries in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/use-hydroxyprogesterone-caproate-and-progesterone-during-2nd)	09/22/2020
Utilization of Spironolactone in Patients with Reduced or Preserved Ejection Fraction Heart Failure (https://www.sentinelinitiative.org/news-events/publications-presentations/utilization-spironolactone-patients-reduced-or-preserved)	09/23/2020
Utilization of Sacubitril/Valsartan in Real-World Settings (https://www.sentinelinitiative.org/news-events/publications-presentations/utilization-sacubitrilvalsartan-real-world-settings-0)	09/23/2020
Risk of Neuropsychiatric Adverse Events among Montelukast Users (https://www.sentinelinitiative.org/news-events/publications-presentations/risk-neuropsychiatric-adverse-events-among-montelukast-users)	09/23/2020
When Decisions Can't Wait: Delivering Rapid Real-World Studies (https://www.sentinelinitiative.org/news-events/publications-presentations/when-decisions-cant-wait-delivering-rapid-real-world-studies)	10/13/2020
* Leveraging the Sentinel System for COVID-19 (https://www.sentinelinitiative.org/news-events/publications-presentations/leveraging-sentinel-system-covid-19)	10/14/2020
* Studying the Natural History of COVID-19: Risk of Arterial and Venous Thrombotic Events in the Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/studying-natural-history-covid-19-risk-arterial-and-venous)	10/14/2020
* Natural History of Coagulopathy in COVID-19 (https://www.sentinelinitiative.org/news-events/publications-presentations/natural-history-coagulopathy-covid-19)	10/26/2020

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* Descriptive Assessment of Coagulopathy Among COVID-19 Patients: Feasibility Data Review (https://www.sentinelinitiative.org/news-events/publications-presentations/descriptive-assessment-coagulopathy-among-covid-19-patients)	10/27/2020
* Natural History of Coagulopathy in Patients with COVID-19 in a Real-World Electronic Health Data Network (https://www.sentinelinitiative.org/news-events/publications-presentations/natural-history-coagulopathy-patients-covid-19-real-world)	11/05/2020
Antipsychotic Medication Use Among Hospitalized Infants Using Inpatient Data in FDA's Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/antipsychotic-medication-use-among-hospitalized-infants-0)	11/17/2020
* Validation of Claims-based Algorithms to Identify Hospitalized COVID-19 Events within the FDA Sentinel System (https://www.sentinelinitiative.org/news-events/publications-presentations/validation-claims-based-algorithms-identify-hospitalized)	12/02/2020
Validation of an Electronic Algorithm for Hodgkin and Non-Hodgkin Lymphoma in ICD-10-CM (https://www.sentinelinitiative.org/news-events/publications-presentations/validation-electronic-algorithm-hodgkin-and-non-hodgkin)	12/15/2020
Using Prenatal Tests to Estimate Pregnancy Start in Health Insurance Claims Data (https://www.sentinelinitiative.org/news-events/publications-presentations/using-prenatal-tests-estimate-pregnancy-start-health)	12/15/2020
Using Prenatal Tests to Estimate Pregnancy Start in Health Insurance Claims Data (https://www.sentinelinitiative.org/news-events/publications-presentations/using-prenatal-tests-estimate-pregnancy-start-health-0)	06/29/2021
The Sentinel Experience (https://www.sentinelinitiative.org/news-events/publications-presentations/sentinel-experience)	07/10/2021
Early Uptake of New Molecular Entities Approved in 2017 in a Multisite National US Healthcare Data Network (https://www.sentinelinitiative.org/news-events/publications-presentations/early-uptake-new-molecular-entities-approved-2017-multisite)	08/23/2021
* Outpatient-Identified COVID-19 and Subsequent Hospitalized Thrombotic Events (https://www.sentinelinitiative.org/news-events/publications-presentations/outpatient-identified-covid-19-and-subsequent-hospitalized)	08/23/2021
* Comparing Outcomes in Trial-Eligible vs Real-World COVID-19 Patients: The Case of Invasive Mechanical Ventilation (https://www.sentinelinitiative.org/news-events/publications-presentations/comparing-outcomes-trial-eligible-vs-real-world-covid-19)	08/23/2021
Prescription Medication Use and Baseline Health Status of Women with Live Birth Deliveries in a National Data Network: The Sentinel Distributed Database Mother-Infant Linkage Table (https://www.sentinelinitiative.org/news-events/publications-presentations/prescription-medication-use-and-baseline-health-status-women)	08/23/2021
Pregnancy in Women with Heart Failure: A Cross-Sectional Study in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/pregnancy-women-heart-failure-cross-sectional-study-sentinel)	08/23/2021
How Under-Coded is Pediatric Hypertension? Comparison of Claims and Electronic Health Record (EHR) Data (https://www.sentinelinitiative.org/news-events/publications-presentations/how-under-coded-pediatric-hypertension-comparison-claims-and)	08/23/2021
Post-Keratoplasty Fungal Keratitis in the Sentinel Distributed Database: Prevalence and Time Trends (https://www.sentinelinitiative.org/news-events/publications-presentations/post-keratoplasty-fungal-keratitis-sentinel-distributed)	08/23/2021
Use of Tree-Based Scan Statistics for Surveillance of Infant Outcomes Following Maternal Perinatal Medication Use: A Propensity Score Matched Case Study	08/23/2021

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(https://www.sentinelinitiative.org/news-events/publications-presentations/use-tree-based-scan-statistics-surveillance-infant-outcomes)	
Statistical Power for Use of Tree-Based Scan Statistics for Surveillance of Infant Outcomes Following Maternal Perinatal Medication Use (https://www.sentinelinitiative.org/news-events/publications-presentations/statistical-power-use-tree-based-scan-statistics)	08/23/2021
Use of a Mobile App to Capture Supplemental Health Information During Pregnancy: Implications for Clinical Research (https://www.sentinelinitiative.org/news-events/publications-presentations/use-tree-based-scan-statistics-surveillance-infant-outcomes)	08/23/2021
A New Analytic Tool for Interrupted Times Series Analysis to Assess the Impact of FDA Regulatory Actions (https://www.sentinelinitiative.org/news-events/publications-presentations/new-analytic-tool-interrupted-times-series-analysis-assess)	08/24/2021
No Differential Risk of Cutaneous Small Vessel Vasculitis with Oral Anticoagulant Use Among Patients with Atrial Fibrillation (https://www.sentinelinitiative.org/news-events/publications-presentations/no-differential-risk-cutaneous-small-vessel-vasculitis-oral)	08/24/2021
New Frontiers in Computable Phenotyping for Medical Product Safety Evaluation (https://www.sentinelinitiative.org/news-events/publications-presentations/new-frontiers-computable-phenotyping-medical-product-safety)	08/24/2021
Characteristics and Outcomes of Pregnancies in Women with Heart Failure: A Retrospective Cohort Study in the Sentinel Distributed Database (https://www.sentinelinitiative.org/news-events/publications-presentations/characteristics-and-outcomes-pregnancies-women-heart-failure)	08/25/2021
Improving Methods of Identifying Anaphylaxis for Medical Product Safety Surveillance Using Natural Language Processing and Machine Learning (https://www.sentinelinitiative.org/news-events/publications-presentations/improving-methods-identifying-anaphylaxis-medical-product)	08/25/2021
* Strategies for the Use of Real-World Data to Conduct COVID-19-Related Pharmacoepidemiology (https://www.sentinelinitiative.org/news-events/publications-presentations/strategies-use-real-world-data-conduct-covid-19-related)	08/25/2021
* Monitoring Medication Use During the COVID-19 Pandemic in the Sentinel System: The Case of Anticoagulation for Thrombosis (https://www.sentinelinitiative.org/news-events/publications-presentations/monitoring-medication-use-during-covid-19-pandemic-sentinel)	09/15/2021
Reliable Insights Regarding Medication Outcomes From Real World Data – Key Principles of an Evidence Generation Framework (https://www.sentinelinitiative.org/news-events/publications-presentations/reliable-insights-regarding-medication-outcomes-real-world)	11/01/2021
Real-World Data: Data Networks, Standardization, and Federated Analysis (https://www.sentinelinitiative.org/news-events/publications-presentations/real-world-data-data-networks-standardization-and-federated)	01/18/2022
CNODES Webinar: Surveillance of Adverse Infant Outcomes Following Maternal Medication Use During Pregnancy Using Tree-Based Scan Statistics (https://www.sentinelinitiative.org/news-events/publications-presentations/cnodes-webinar-surveillance-adverse-infant-outcomes)	03/09/2022
A Landscape Analysis of Valganciclovir Treatment for Congenital Cytomegalovirus Infection in the United States (US), 2008-2021 (https://www.sentinelinitiative.org/news-events/publications-presentations/landscape-analysis-valganciclovir-treatment-congenital)	03/28/2022
Use of Real-World Data for Surveillance of Medications in Pregnancy (https://www.sentinelinitiative.org/news-events/publications-presentations/use-real-world-data-surveillance-medications-pregnancy)	05/09/2022
Scalable Algorithm Development: An Alternative to Algorithm Reuse? (https://www.sentinelinitiative.org/news-events/publications-presentations/scalable-algorithm-development-alternative-algorithm-reuse)	05/17/2022