U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

An Assessment of the Sentinel System (2022 to 2024)

September 2025

The Sentinel System is sponsored by the **U.S. Food and Drug Administration (FDA)** to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel Operations Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number 75F40119D10037. This report was prepared by the Sentinel Operations Center in collaboration with FDA.

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Executive Summary

The Food and Drug Administration Amendments Act of 2007 (FDAAA) mandated the Food and Drug Administration (FDA) to establish an active postmarket risk identification and analysis system. In response, the FDA established the Sentinel Initiative. A core program of the Sentinel Initiative is the Sentinel System, a national medical product safety surveillance system that includes one of the largest healthcare insurance claims data-based multisite distributed databases dedicated to medical product safety. This report covers activities and accomplishments of the Sentinel System from January 1, 2022, through December 31, 2024. This assessment report fulfills the Prescription Drug User Fee Act (PDUFA) VII commitment to "analyze, and report on the use of Sentinel for regulatory purposes." This commitment is one of seven aimed at maintaining the Sentinel Initiative capabilities and continuing integration into FDA's drug safety activities.

The cornerstone of the Sentinel System is the Active Risk Identification and Analysis (ARIA) system. Data for the ARIA system is provided through the Sentinel Distributed Database (SDD), which consists of a collection of harmonized electronic healthcare datasets from several sources formatted in the Sentinel Common Data Model (SCDM). Data within the SDD are analyzed by standardized SAS-based analytic tools, which equip the FDA to conduct multiple types of studies to best meet the FDA's needs.

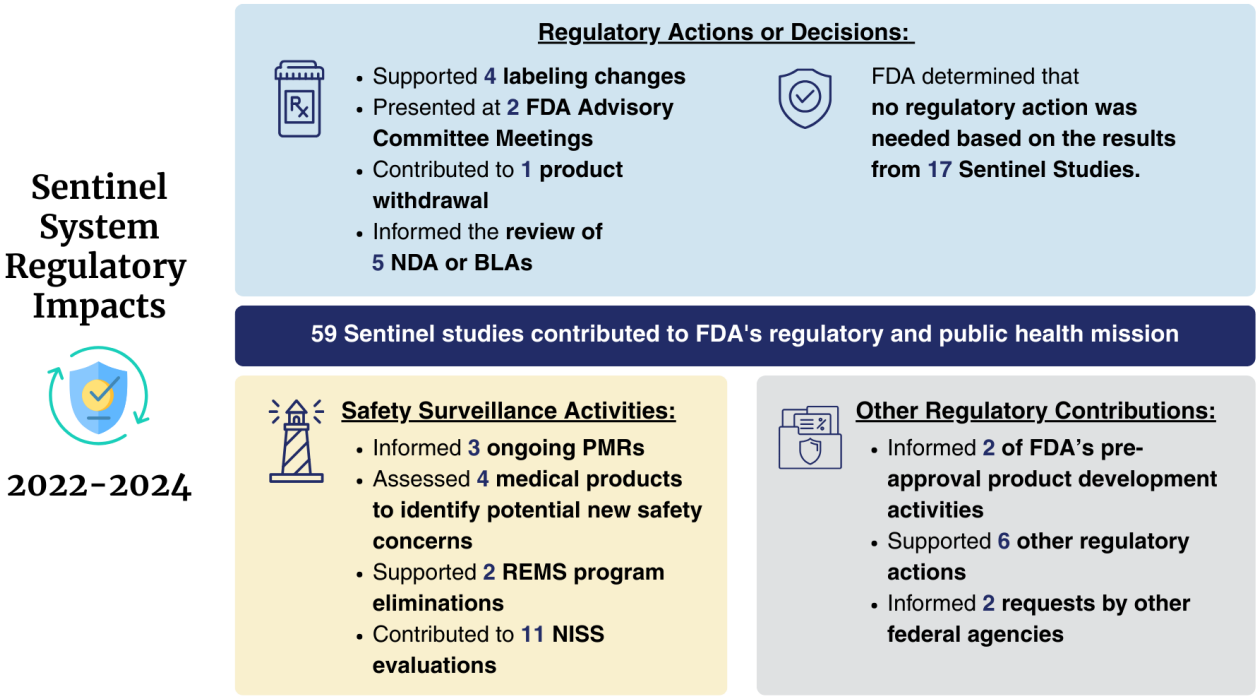
As of April 2024, the SDD contained over 1.3 billion person-years of data covering over 371 million unique patient identifiers, including 128.7 million members actively enrolled and accruing new data. Since 2022, the Sentinel System has expanded its capture of key populations and data elements. Specifically, the number of mother-infant linked deliveries has more than doubled to 11.8 million due to the addition of Centers for Medicare and Medicaid Services (CMS) Medicaid data.

Despite the large number of claims records, the lack of granular clinical details in claims data limits the ARIA system's ability to perform certain studies. In response, the Sentinel Innovation Center (IC) developed the Sentinel Real-World Evidence Data Enterprise (RWE-DE) to provide electronic health record (EHR) data that are linked with claims to fill this gap. In addition, the Sentinel System has utilized other EHR-based data (TriNetX, HCA Healthcare) as needed.

How the Sentinel System Informs Regulatory Decision Making

Key highlights of how the FDA used the Sentinel System between 2022 and 2024 to inform regulatory decision making are described below and summarized in Figure 1.

Figure 1. Sentinel System Regulatory Impacts, 2022 to 2024



BLA: Biologics License Application; NDA: New Drug Application; NISS: Newly Identified Safety Signal; PMR: Post Marketing Requirements; REMS: Risk Evaluation and Mitigation Strategy

Postmarket ARIA Studies Planned at Drug Approval

Between 2022 and 2024, the ARIA system was used to conduct postmarket safety monitoring, planned at the time of approval, for 12 drugs. Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(3))[*,1] authorizes the FDA to require certain postmarketing studies and clinical trials for prescription drugs approved under section 505(c) of the FD&C Act and biological products approved under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). Before requiring a postmarketing study under section 505(o)(3), the FDA must determine that reports under section 505(k)(1) of the FD&C Act and the active postmarketing risk identification and analysis system as available under section 505(k)(3) of the FD&C Act will not be sufficient to meet certain purposes.[†] Before requiring a postmarketing clinical trial, FDA must determine that a postmarketing study or studies will not be sufficient to achieve these same purposes.[††] Those FDA led studies for which the active postmarketing risk identification and analysis system, that the FDA has implemented as ARIA, was determined to be sufficient to assess the adverse events in various stages of analysis: drug uptake monitoring to assess feasibility (seven), final study in progress (one), and completed or

[*] See Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(3)

[†] Before requiring a 505(o)(3) PMR, FDA must find that required adverse event reporting (generally, FDA Adverse Event Reporting System [FAERS] reports), and Sentinel's ARIA system will not be sufficient to meet the above purposes

[††] See Section 505(o)(3)(D) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(3)

closed (four). In 2023, an ARIA system study that was conducted to meet one of the purposes described in section 505(o)(3) was completed by assessing the risk of serious infection among ustekinumab users with Crohn's disease. After reviewing the ARIA system findings, the FDA determined that no further regulatory action was needed.

Evaluating Postmarket Safety Signals

Between 2022 and 2024, the FDA utilized the Sentinel System to evaluate 11 newly identified safety signals (NISS) that were identified following product approval. In one example, the FDA identified a case report in the literature describing severe hypoglycemia in an infant associated with nadolol therapy for infantile hemangioma. The FDA then used the Sentinel System to characterize utilization of and indications for beta-blocker use in the pediatric population, and to assess the incidence of hypoglycemia associated with beta-blockers in this population. Based on the totality of data from the Sentinel System and other sources, the FDA approved safety-related labeling changes for beta-blocker products to describe the risk of hypoglycemia for pediatric patients and individuals unable to communicate symptoms of hypoglycemia.

Advancing the FDA's Postmarket Pharmacovigilance Activities: Signal Identification

Following successful pilots in 2022, the FDA integrated the ARIA system's signal identification capabilities into its routine pharmacovigilance activities. These analyses have focused on widely used new molecular entities. The results from these signal identification studies have largely reflected the safety profiles observed in clinical trials. To date, two analyses have generated statistically significant alerts that prompted the FDA to investigate the findings under the NISS process. Both NISS were closed during the pre-evaluation phase, in which the FDA determined, based on currently available information, that these safety signals did not warrant further evaluation, and the FDA continued its routine pharmacovigilance activities.

Contributing to Premarket Drug Evaluations

The FDA has used the Sentinel System to support review of New Drug Applications (NDAs). For example, analyses conducted in the ARIA system were presented at an FDA Endocrinologic and Metabolic Drugs Advisory Committee that discussed an NDA for sotagliflozin. Sotagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor, and the sponsor was seeking a new indication to improve glycemic control in adults with type 1 diabetes mellitus and chronic kidney disease. Information from this Sentinel study on rates of diabetic ketoacidosis informed the FDA's evaluation of the safety of sotaglifozin. The FDA has not approved the NDA.[2]

Informing Evaluations of Risk Evaluation and Mitigation Strategies (REMS)

The FDA has utilized the Sentinel System to support assessments of risk evaluation and mitigation strategies (REMS), which are required risk management plans to ensure that the benefits of certain medications outweigh their risks. A key example is the use of the Sentinel System to support the assessment of the REMS for clozapine. Clozapine is an atypical antipsychotic approved for treatment-resistant schizophrenia. The Clozapine REMS was a program developed and implemented jointly by multiple clozapine applicants in 2015 that required routine monitoring of absolute neutrophil counts (ANC) and documentation of the results of that monitoring to reduce the risk of neutropenia and agranulocytosis. As part of the FDA's regular review of all REMS, and in light of the FDA's continued

exercise of enforcement discretion with respect to certain aspects of the Clozapine REMS, the FDA undertook a reevaluation of the Clozapine REMS in September 2023. Analyses within the SDD provided data on clozapine utilization patterns and adherence to the REMS ANC screening requirements. A rapid chart review of patients' medical records in EHR data using a natural language processing (NLP) tool to expedite review also described clozapine patients who had experienced neutropenia. Results from these Sentinel System analyses were presented at the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee in November 2024. The FDA announced the elimination of the Clozapine REMS in February 2025, and the REMS was eliminated effective June 13, 2025. The ARIA system also supported the evaluation of the Lotronex REMS and Alosetron REMS programs. Findings from an ARIA system analysis that estimated the incidence of ischemic colitis among women initiating alosetron between 2016 and 2020 showed incidence rates consistent with those listed in the existing Prescribing Information. These Sentinel System results, along with findings from other data sources, supported the FDA's decision to eliminate both the Lotronex and Alosetron REMS programs, concluding they were no longer necessary to ensure the benefits outweigh the risks of the medications.

Providing Information on Drug Utilization Trends

The FDA has leveraged the Sentinel System to characterize changes in drug utilization, monitor national drug shortages, and track the uptake of newly approved drugs. For example, in March 2023, shortages of injectable methotrexate, indicated for acute lymphoblastic leukemia, non-Hodgkin lymphoma, and osteosarcoma, were identified due to a halt in production and distribution by a key manufacturer. There was concern about how the shortage might impact patients, particularly pediatric patients with cancer who rely on methotrexate for treatment. A federal partner requested assistance from the FDA to quantify the impact. In response, the FDA used the Sentinel System to look at utilization patterns of injectable methotrexate stratified by age, calendar month, and indication in a subset of the SDD with more frequent refreshes and fresher data and in TriNetX Live™. Results showed minimal changes in utilization among pediatric patients with cancer, though a decline in use was observed among adults. These results provided the FDA and other stakeholders valuable insights into the impact of methotrexate injection shortages on certain patient populations.

Responding to the COVID-19 Pandemic

The FDA leveraged the Sentinel System to study COVID-19. A key example was an international collaboration to study medication use patterns and potential adverse outcomes following COVID-19 infection during pregnancy. The study identified nearly 23,000 pregnancies with COVID-19 infection in the SDD and found no increased risk of adverse infant outcomes compared to pregnancies without COVID-19 infection. The Sentinel System was also utilized in a separate multi-national collaboration across seven countries spanning North America (United States and Canada) and Europe (England, Spain, Germany, Netherlands, Italy) to assess the risk of thromboembolism among patients with COVID-19 diagnosed in the ambulatory setting. This study found heterogeneity by country in the 90-day absolute risk of arterial and venous thromboembolism after COVID-19 diagnosis, both before and during COVID-19 vaccine availability.[3]

Partnering with Federal Agencies to Address Public Health Topics

The FDA has used the data and resources available within the Sentinel System to partner with other federal agencies. For example, findings from the Sentinel System were incorporated into the FDA's scientific and medical evaluation of marijuana report, conducted on behalf of the Department of Health and Human Services (HHS) and submitted to the Drug Enforcement Administration (DEA) of the

Department of Justice. Since 1970, marijuana has been federally classified as a Schedule I substance, though many states have legalized it for medical or recreational use. HHS, supported by the FDA investigations through the Sentinel System, reviewed marijuana's scheduling status to inform potential reclassification. The FDA used the Sentinel System to conduct descriptive analyses to describe healthcare encounters for cannabis-related disorders and poisonings.[4] The HHS evaluation was considered in proposing the DEA's recent proposed rule, published in the Federal Register (89 FR 44597, May 21, 2024), to reschedule marijuana from Schedule I to Schedule III under the Controlled Substances Act.

Expansion of Real-World Evidence Data Sources and Methodologies in the Sentinel System

The Sentinel System supported a range of initiatives to explore and build data infrastructure and develop methodologies to generate real-world evidence (RWE), which are crucial for conducting high-quality, robust studies that can guide better health decisions and policies.

A core focus of methods development in the Sentinel System is how to expand the use of EHRs for medical product safety surveillance. The Sentinel IC established the RWE-DE, which integrates EHR-claims linked data from two commercial sources and four academic institutions. These data sources include structured and some free-text EHR data, with Data Partners selected for their data linkage capabilities and capacity to share raw data with IC under data use agreements.

To explore further expanding the Sentinel System's data infrastructure, the IC evaluated opportunities offered by Health Information Exchanges (HIEs), which facilitate the secure exchange of health information among various entities.

In addition, from 2022 to 2024, several IC projects aimed to enhance pharmacoepidemiologic studies by using NLP to extract information from unstructured clinical notes for illustrative assessments of medical product safety surveillance.[5]

The IC has also focused on advancements in scientific methods for causal inference, including improvements in confounding control, and addressing challenges associated with partially observed data to support the ability to use RWE for regulatory decision making. For example, work conducted between 2023 and 2024 demonstrated that tuning the Least Absolute Shrinkage and Selection Operator (LASSO) model for propensity score estimation achieved superior confounding control in settings involving ultra-high-dimensional data structures. Another IC project implemented an enhanced plasmode simulation methodology to conduct a quantitative bias analysis to evaluate the threat of unmeasured confounding in non-randomized studies. This approach, which uses real individual patient-level data to inform parameters selection that preserves the natural correlation patterns between confounders and outcome, rather than deriving parameters from the literature, demonstrates a practical method that can be incorporated during either a study's design or analysis phase to quantify bias, and can allow for implementation of mitigation strategies before a study is conducted.

Other work focused on approaches to evaluating missing data patterns and identifying the best approaches to handle missing data in causal inference studies, which can greatly enhance confidence in analyses where important confounders are partially recorded in EHR databases.[6,7]

Public Accessibility and Dissemination to the Larger Scientific Community

The FDA is committed to transparency and accessibility in the Sentinel System. Results of all the ARIA system analyses and programming code for inferential analyses are made available to the public. From 2022 to 2024, results from 221 analyses across 93 studies have been posted to the Sentinel System website, and 39 analytic packages have been posted to the Sentinel public Git repository. This transparency enables other investigators to replicate the Sentinel System analyses using their own data or better understand the analytic methods of completed studies. Additionally, 51 papers have been published in peer-reviewed journals, and 120 presentations and posters were presented at scientific conferences from 2022 to 2024.

Conclusion

From 2022 to 2024, the Sentinel System has provided monitoring and assessment of postmarket medical product safety, contributing to key regulatory actions, safety assessments, and regulatory discussions, including informing product labeling and contributing data to the FDA Advisory Committee Meetings. The Sentinel System has also supported studies that do not primarily inform regulatory decision making, but actively contribute to the FDA's public health mission, and projects that expanded methods for the integration of clinical data into the Sentinel System landscape to meet identified gaps.

1 Introduction: Sentinel System Overview

The Food and Drug Administration Amendments Act of 2007 (FDAAA) mandated the FDA to establish a postmarket active risk identification and analysis system. This system, designed to enhance the FDA's existing postmarket capabilities, monitors risks associated with drug and biological products using data containing 100-million patient lives from disparate sources. In response, the FDA established the Sentinel Initiative. This assessment report fulfills the Prescription Drug User Fee Act (PDUFA) VII commitment to "analyze, and report on the use of Sentinel for regulatory purposes." This commitment is one of seven aimed at maintaining the Sentinel Initiative capabilities and continuing integration into FDA's drug safety activities.

A core program of the Sentinel Initiative is the Sentinel System, a national medical product safety surveillance system that includes one of the largest multisite distributed databases dedicated to monitoring the safety of medical products. The Sentinel System plays a vital role in supporting the FDA's mission to protect public health by enabling the continuous monitoring of FDA-regulated medical products.

The Sentinel System is managed by the FDA Center for Drug Evaluation and Research's (CDER) Office of Surveillance and Epidemiology. It serves as a critical resource for addressing emerging regulatory public health questions, informing decision making, and advancing new methodologies for medical product safety surveillance.

At the heart of the Sentinel System is the ARIA system, which provides the FDA with access to a wide range of data sources and analytic tools. The ARIA system relies upon primarily claims-based data with some claims-linked electronic health record (EHR) data formatted into the Sentinel Common Data Model (SCDM). The system also maintains a suite of SAS-based analytic tools, also known as Query Request Package (QRP), that are optimized to perform a variety of pharmacoepidemiology study designs on data formatted within the SCDM. Private and public insurers work with the Sentinel Operations Center (SOC) to transform their data into the SCDM. The formatted datasets remain distributed over the Data Partners' sites where each retains control of its own patient-level data. To perform analyses, a SAS-based code pack using QRP is distributed to Data Partners, who then execute the analyses on their dataset and return summary results to the SOC. The SOC aggregates these results from multiple Data Partners to create a final report for the FDA. Cumulatively, this distributed data network, known as the Sentinel Distributed Database (SDD), contains datasets covering over 1.3 billion person-years of data, representing over 371 million unique patient identifiers with over 24 billion unique medical encounters spanning from 2000 to 2024. Notably, the SDD includes around 11.8 million infant deliveries linked to their mothers. More information about the infrastructure that comprises the ARIA analytic system is available in Appendix B.

While the ARIA system primarily relies on claims-based data, the Sentinel System has evolved over the past five years to incorporate additional resources – most notably, EHRs. The Sentinel Innovation Center (IC) Real-World Evidence Data Enterprise (RWE-DE) utilizes EHRs to address the lack of granular clinical data from the claims-based ARIA system. The EHR resources used by the Sentinel System, which are further described in Appendix C, and the application of innovative methods to claims and EHR data resources can enhance Sentinel System capabilities to meet FDA's evolving needs.

2 The FDA's Utilization of Sentinel System

The FDA utilizes the Sentinel System to support a wide range of public health initiatives, with a primary focus on the FDA's regulation of medical products. The Sentinel System directly informs regulatory decision making, predominantly by providing information about the safety of specific medical products. In some cases, the FDA also uses the Sentinel System to address broader public health concerns that may not be tied directly to a regulated medical product, such as conducting studies to understand the impact of COVID-19 in specific populations and collaborating with other federal public health agencies. In addition, the FDA uses the Sentinel System to conduct studies that provide data insights or explore new methodologies. These efforts aim to enhance the system's capabilities and enable the FDA scientists to conduct high-quality studies with greater precision and efficiency.

From January 1, 2022, through December 31, 2024, the FDA advanced 86 studies through the Sentinel System. A comprehensive list of these studies, along with their associated study impacts, can be found in Appendix D. Where available, links to the Sentinel Initiative website are embedded for further reference. These 86 studies are further explored in:

- **Section 2: The FDA's Utilization of Sentinel System**, which highlights key regulatory use cases, and
- **Section 3: Improving the Sentinel System: Integrating EHR Data Within a Causal Analysis Framework**, which focuses on methodological advancements around the integration of EHR data

At its core, the Sentinel System is designed to generate evidence that informs the FDA's regulation of medical products, thus helping to protect patients. It is an important mechanism used to monitor the safety of newly approved products. In order to require a postmarketing requirement (PMR) under section 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)) to assess a known serious risk or a signal of a serious risk, or to identify a potential unexpected serious risk of a drug, the FDA must make a determination that the ARIA system within the Sentinel System will not be sufficient for these purposes. If the FDA determines that the ARIA system is sufficient, the Agency plans to use the ARIA system to conduct the study. The Sentinel System also supports a wide range of regulatory activities, including:

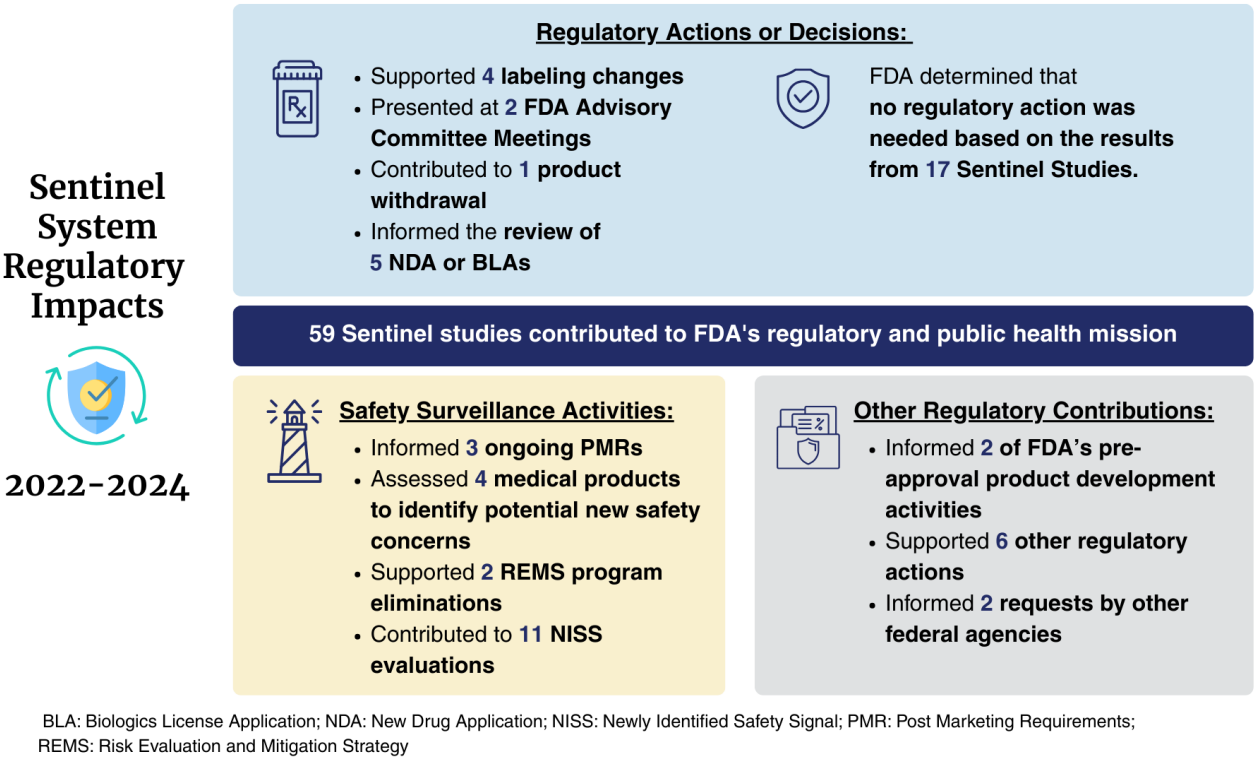
- Evaluating postmarket safety signals
- Advancing pharmacovigilance efforts through signal identification
- Contributing to premarket drug evaluations
- Informing evaluations of Risk Evaluation and Mitigation Strategy (REMS) programs
- Providing information on drug utilization trends
- Responding to emerging public health concerns, such as the COVID-19 pandemic
- Partnering with other federal agencies to address national health topics

Each of these regulatory activities is illustrated through recent vignettes that showcase the Sentinel System's work in action in Section 2.

Figure 1 highlights the broad regulatory impact of these activities from 2022 to 2024, which includes: information presented at two FDA Advisory Committee meetings, one product withdrawal, four labeling changes, and five NDA or Biologics License Application (BLA) reviews. In addition, the FDA concluded in 17 studies that no regulatory action was needed at the time to address safety concerns, based in part on the real-world evidence generated through Sentinel analyses. Beyond these specific outcomes, the

Sentinel System continues to play a critical role in ongoing safety surveillance and other regulatory initiatives. Select examples of these impacts are detailed throughout Section 2 vignettes. To learn more about how these impacts are defined, please refer to Appendix E.

Figure 1. Sentinel System Regulatory Impacts, 2022 to 2024



BLA: Biologics License Application; NDA: New Drug Application; NISS: Newly Identified Safety Signal; PMR: Post Marketing Requirements; REMS: Risk Evaluation and Mitigation Strategy

2.1 Postmarket ARIA Studies Planned at Drug Approval

A key role of the Sentinel System within the FDA's regulatory landscape is to conduct assessments or identification of serious risks when the FDA is considering a postmarket requirement under section 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)). This often occurs during the review of an NDA or BLA. Before requiring that an NDA or BLA holder conduct a postmarket study for these purposes, the FDA must first determine whether the safety concern can be studied using the FDA Adverse Event Reporting System (FAERS) and/or the ARIA system would be sufficient. If the FDA deems that the ARIA system is sufficient, the FDA uses it for the postmarket evaluation instead of requiring the sponsor to conduct the study. As of December 31, 2024, the ARIA system has been determined to be sufficient to assess 26 serious risks identified during the review of applications for 11 drugs, to meet one of the purposes described in section 505(o)(3) of the FD&C Act. The FDA has completed postmarket assessments for 16 of these serious risks, including those related to Ablysinol (dehydrated alcohol), Sinuva (mometasone furoate sinus implant), Stelara (ustekinumab), and Annovera (segesterone acetate and ethinyl estradiol vaginal system) products. Table 1 details the serious risks with completed postmarket assessments in the ARIA system. Table 2 details the remaining 10 serious risks for which studies remain in progress in the ARIA system as of December 31, 2024.

Table 1. Serious Risks with Completed Postmarket Assessments in Sentinel where ARIA was Deemed to be Sufficient in the Determination Required by Section 505(o)(3) of the FD&C Act Prior to Issuing a PMR at Approval

Medical Product	Outcome of Concern
Ablysinol (Dehydrated Alcohol)	All-cause mortality
	Atrioventricular block
	Heart failure
	Myocardial infarction*
	Percutaneous transluminal septal myocardial ablation (PTSMA) procedure frequency
	Permanent pacemaker placement
	Septal myectomy
	Ventricular arrhythmia
Annovera (Segesterone Acetate and Ethinyl Estradiol Vaginal System)	Arterial thromboembolism
	Venous thromboembolism
Sinuva (Mometasone Furoate Sinus Implant)	Cataracts
	Diminished visual acuity*
	Glaucoma
	Nasal septal perforation
	Ocular hypertension*
Stelara (Ustekinumab)	Serious infection, assessed for patients with Crohn's disease

**These risks were identified during the ARIA system study, rather than at the time of the product's initial approval.*

Table 2. Serious Risks with Active Postmarket Assessments In-Progress in Sentinel where ARIA was Deemed to be Sufficient in the Determination Required by Section 505(o)(3) of the FD&C Act Prior to Issuing a PMR at Approval

Medical Product	Outcome of Concern
Gimoti (Metoclopramide Nasal Spray)	Tardive dyskinesia and adverse central nervous system reactions
Ibsrela (Tenapanor)	Inflammatory bowel disease
Ilumya (Tildrakizumab)	Lymphoma
Invokana (Canagliflozin)	Renal cell carcinoma
Siliq (Brodalumab)	Hospitalized neutropenia
	Myocardial infarction and stroke
	Serious infection
Skyrizi (Risankizumab)	Lymphoma
Stelara (Ustekinumab)	Serious infection, assessed for patients with ulcerative colitis
Tremfya (Guselkumab)	Lymphoma

A highlight in 2024 was the completion of the assessment of the risk of serious infection with ustekinumab in Crohn's disease patients. Ustekinumab, sold under the brand name Stelara, is a human anti-IL-12/23p40 antibody approved for the treatment of psoriasis (September 2009), psoriatic arthritis (September 2013), Crohn's disease (September 2016), and ulcerative colitis (October 2019). As an

immunosuppressant, ustekinumab carries a risk of serious infections. For the Crohn's disease indication, the FDA determined that ARIA was sufficient to conduct postmarketing surveillance instead of requiring the sponsor to conduct a study under a PMR. Based on the results from the ARIA study, the FDA concluded that the safety information in ustekinumab labeling related to the risk of serious infections in patients with Crohn's disease was adequate and determined that no regulatory action for ustekinumab was needed.

In addition, over time, the FDA has planned to conduct other postmarket studies to evaluate potential safety concerns that arose during the review of an NDA or BLA where a PMR was not under consideration. In these cases, the planned monitoring of safety concerns using the ARIA system was described in the product's approval letter, the product approval package's Multi-Discipline Review, or the FDA's Pharmacovigilance Strategy. In total, the FDA has planned to monitor 22 such safety concerns across 6 products in the ARIA system; all studies remain in progress. Table 3 details these safety concerns.

Table 3. Additional Safety Concerns Identified During NDA or BLA Review with Planned ARIA Studies where a PMR was not Under Consideration

Medical Product	Outcome of Concern
Brexafemme (Ibrexafungerp)	Use in pregnancy
Mounjaro (Tirzepatide)	Arrhythmia
Olumiant (Baricitinib)	Acute myocardial infarction
	Deep vein thrombosis
	Pulmonary embolism
	Stroke
Litfulo (Ritlecitinib)	Acute myocardial infarction
	Deep vein thrombosis
	Pulmonary embolism
	Stroke
Leqselvi (Deuruxolitinib)	Acute myocardial infarction
	Deep vein thrombosis
	Pulmonary embolism
	Stroke
Rinvoq (Upadacitinib)	Acute myocardial infarction, assessed for patients with Crohn's disease
	Acute myocardial infarction, assessed for patients with ulcerative colitis
	Deep vein thrombosis, assessed for patients with Crohn's disease
	Deep vein thrombosis, assessed for patients with ulcerative colitis
	Pulmonary embolism, assessed for patients with Crohn's disease
	Pulmonary embolism, assessed for patients with ulcerative colitis
	Stroke, assessed for patients with Crohn's disease
	Stroke, assessed for patients with ulcerative colitis

2.2 Evaluating Postmarket Safety Signals

The Sentinel System is uniquely suited to assess postmarket safety signals due to its large database of real-world clinical data and accompanying standardized tools that streamline the implementation of a variety of study designs. The assessment of safety signals that arise in the postmarket setting has been a core use of the Sentinel System for over a decade.

Many of the potential postmarket safety concerns that the Sentinel System is used to evaluate are done so under CDER's Newly Identified Safety Signal (NISS) process. If a new potential safety signal is identified, currently available information is considered during a pre-evaluation phase by CDER staff to determine whether it warrants a full evaluation. If a NISS advances to the evaluation phase, an ARIA study may be one of the activities undertaken to evaluate the safety concern.[8]

Between 2022 and 2024, the FDA used the Sentinel System to evaluate 11 NISS identified post-approval, representing 18 safety concerns, depicted in Table 4. The FDA is also supporting the evaluation of an additional NISS, identified pre-approval, assessing renal cell carcinoma following canagliflozin use, represented in Table 2.

Table 4. Newly Identified Safety Signals (NISS)* Identified Post-Approval Evaluated by the FDA Using the Sentinel System, 2022 to 2024

Year	Medical Product(s) and Outcome(s) of Concern
2018	**Medical Product(s)**: Eliquis (apixaban), Pradaxa (dabigatran), Savaysa (edoxaban), Xarelto (rivaroxaban) **Safety Outcome(s)**: cutaneous small-vessel vasculitis
2018	**Medical Product(s)**: valsartan, angiotensin receptor blockers (ARBs) **Safety Outcome(s)**: nitrosamine impurity, switching patterns
2019	**Medical Product(s)**: dipeptidyl peptidase 4 (DPP-4) inhibitors **Safety Outcome(s)**: inflammatory bowel disease
2020	**Medical Product(s)**: Gilenya (fingolimod) **Safety Outcome(s)**: congenital urinary malformations, congenital cardiac malformations
2021	**Medical Product(s)**: beta-blockers **Safety Outcome(s)**: hypoglycemia
2021	**Medical Product(s)**: proton pump inhibitors **Safety Outcome(s)**: COVID-19 hospitalization, severe COVID-19
2022	**Medical Product(s)**: COVID-19 hospitalization **Safety Outcome(s)**: dexamethasone utilization characterization
2022	**Medical Product(s)**: Nuvigil (armodafinil), Provigil (modafinil) **Safety Outcome(s)**: congenital non-cardiac malformations
2023	**Medical Product(s)**: combined hormonal contraceptives

Year	Medical Product(s) and Outcome(s) of Concern
	Safety Outcome(s): [Safety Outcome Redacted]
2023	**Medical Product(s)**: Entyvio (vedolizumab), Tysabri (natalizumab) **Safety Outcome(s)**: interstitial lung disease
2023	**Medical Product(s)**: glucagon-like peptide-1 receptor agonists (GLP-1 RAs) **Safety Outcome(s)**: intentional self-harm

**In early 2020, the FDA transitioned from a Tracked Safety Issue (TSI) framework to the current Newly Identified Safety Signal (NISS) framework. Because some studies span multiple years, please note that certain safety signals listed in this table were initially opened under the TSI framework.*

An example of a potential safety concern evaluated as a NISS was the assessment of adverse fetal outcomes following use of Nuvigil (armodafinil) or Provigil (modafinil) among pregnant women. These products are indicated for patients with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. In preliminary animal studies, an increased risk of miscarriage and birth defects was observed. Review of an interim registry status report in 2019 identified a potential signal for cardiac malformations. The prevalence of cardiac malformations was higher among infants exposed to armodafinil or modafinil when compared to the rates in the Metropolitan Atlanta Congenital Defects Program. However, due to low sample size and potential confounding, further evaluation was necessary. The FDA determined that the ARIA system would be sufficient to study this safety concern.

From 2019 to 2020, the FDA used the ARIA system to conduct two analyses assessing the risk of cardiac malformations following pregnancies exposed to armodafinil or modafinil. In these analyses, there was no observed association between armodafinil or modafinil exposure during pregnancy and cardiac malformations. During the review of the results of these analyses and data from other sources, the FDA determined that further analyses were warranted to evaluate non-cardiac malformations. Therefore in 2022, further analyses were conducted in the ARIA system assessing the risk of non-cardiac malformations after exposure to armodafinil or modafinil during to pregnancy. Results from this analysis did not find an association between in utero exposure to armodafinil or modafinil and non-cardiac malformations. The FDA is currently reviewing the results of this study.

In a final example, the ARIA system was used to inform a decision on labeling for beta-blocker products related to the risk of hypoglycemia in pediatric patients. During routine postmarket surveillance, the FDA identified a case report in the literature describing severe hypoglycemia in an infant associated with nadolol therapy for infantile hemangioma. While select beta-blockers are approved by the FDA for specific pediatric indications including hypertension (metoprolol succinate), hemangioma (Hemangeol, an oral propranolol solution), and lowering of intraocular pressure (timolol ophthalmic solution), various beta-blockers have been used for a range of unapproved uses in the pediatric population. The hypoglycemia safety signal and the limited understanding of the magnitude and patterns of beta-blocker use in the pediatric population prompted a Sentinel study to comprehensively characterize beta-blocker use and assess the incidence of hypoglycemia associated with beta-blockers in this population. Based on the totality of data from the Sentinel System, FAERS, published case reports, and the National Poison Data System, the FDA approved class-wide safety-related labeling changes for beta-blocker products to describe the risk of hypoglycemia in pediatrics and in individuals unable to communicate signs of hypoglycemia. These changes are captured in the “Warnings and Precautions” and “Patient Counseling Information” sections of the Prescribing Information.

2.3 Advancing the FDA's Postmarket Pharmacovigilance Activities: Signal Identification

The establishment of a signal identification program within the Sentinel System fulfills a FDAAA congressional mandate to identify potential safety signals related to medical products. This initiative expands the utility of the Sentinel System by complementing the FDA's traditional reliance on passive surveillance tools, such as FAERS, with an active, hypothesis-free approach to signal identification. The Sentinel System utilizes TreeScan™, a free, publicly available data-mining software that supports various tree-based scan statistical methods for analyzing large datasets.

To advance this effort, the FDA's Division of Pharmacovigilance conducted three pilot TreeScan™ analyses in 2022. These pilots assessed products for all non-pregnancy-related and non-cancer outcomes. Utilization data for new molecular entities (NMEs) approved between 2017 and 2019 and select biosimilar products informed product selection. Semaglutide, erenumab, and filgrastim-sndz were chosen based on criteria including a minimum of 25,000 new users, product safety profiles, history of NISS, available surveillance summaries, route of administration, and feasibility of study design (e.g., availability of active comparators and self-controlled designs). Findings from these pilots included:

- **Semaglutide**: TreeScan™ identified various alerts including nausea/vomiting, diarrhea, constipation, gastrointestinal distress/pain, obesity, abnormal weight loss, metabolic issues, and sleep apnea. These alerts were consistent with known adverse events or comorbidities in patients likely using semaglutide for glucose control or weight loss. No further action has been taken.
- **Erenumab**: TreeScan™ identified statistically significant alerts for constipation, and abnormal findings on diagnostic imaging of central nervous systems, headache, other specific cerebrovascular disease, sepsis, pneumonia, cough, and COVID-19. A follow-up Patient Episode Profile Retrieval analysis of the "other specified cerebrovascular disease" alert indicated low suspicion of a causal relationship with Erenumab. No further action has been taken for the remaining alerts.
- **Filgrastim-sndz**: TreeScan™ identified a few alerts which were primarily related to musculoskeletal symptoms. No further action has been taken for these alerts.

Following the success of these pilots, the FDA formally integrated the Sentinel System's signal identification program into its routine pharmacovigilance activities. Subsequent signal identification analyses have focused on NMEs with high utilization: dupilumab, risankizumab-rzaa, guselkumab, baloxavir, bictegravir/emtricitabine/tenofovir alafenamide. Results in Sentinel signal identification studies have generally aligned with the known safety profiles from clinical trials.

When alerts warrant further investigation, the FDA leverages the Sentinel System's Patient Episode Retrieval Program to examine patient-level medical histories, which include information from medical encounters and prescription dispensings. To date, two signal identification analyses have produced statistically significant alerts that were further investigated as a NISS evaluation. Both alerts were closed during the pre-evaluation phase, with routine pharmacovigilance ongoing through FAERS and medical literature.

2.4 Contributing to Premarket Drug Evaluations

The FDA regularly uses contextual information to inform the review of NDAs and BLAs. Information on the prevalence and incidence of medical conditions, the size of indicated patient populations, and the utilization patterns of drugs within the same therapeutic class can offer valuable insights informing medical product approval or postmarket requirements. When the FDA utilizes the Sentinel System for these purposes, the findings may inform Advisory Committee discussions or be incorporated directly into the review of NDAs and BLAs.

In one example, Sentinel System findings informed FDA's review of a NDA for sotagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, with a proposed indication as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus and chronic kidney disease. SGLT2 inhibitors are a class of drugs commonly used to manage blood sugar in individuals with type 2 diabetes mellitus. To support discussions of the FDA Endocrinologic and Metabolic Drugs Advisory Committee on October 31, 2024, and the review of the NDA for sotagliflozin, the FDA used the Sentinel System to estimate real-world incidence rates of diabetic ketoacidosis (DKA) in patients with type 1 diabetes mellitus who initiated SGLT2 inhibitors off-label and in patients with type 1 diabetes mellitus by chronic kidney disease stage. The findings, presented at the Advisory Committee meeting, suggested crude incidence rates of DKA in patients with type 1 diabetes mellitus who initiated SGLT2 inhibitors off-label did not decline from 2013 to 2024. There was also indication of an increasing rate of DKA with advancing chronic kidney disease stage in patients with type 1 diabetes mellitus, regardless of SGLT2 inhibitor use. However, the contributing role of chronic kidney disease in the association between sotagliflozin and DKA remains unclear. It is unknown whether and how chronic kidney disease modifies the effect of sotagliflozin on the risk of DKA. After considering all evidence presented, the Advisory Committee voted 11-3 that the available data did not demonstrate the benefits of sotagliflozin outweighed the risks for the indication of improved glycemic control in patients with type 1 diabetes mellitus and chronic kidney disease. Information from this Sentinel study also informed FDA's review for sotagliflozin. The FDA has not approved the NDA.[2]

2.5 Informing Evaluations of Risk Evaluation and Mitigation Strategies (REMS)

Risk Evaluation and Mitigation Strategies (REMS) are required risk management plans to ensure that the benefits of certain medications outweigh their risks. Recently, the FDA utilized the ARIA system to support evaluations of two REMS programs.

One such evaluation focused on clozapine, an atypical antipsychotic initially approved in 1989 for treatment-resistant schizophrenia. In 2015, the FDA established the Clozapine REMS program to reduce the risk of clozapine-induced severe neutropenia through regular absolute neutrophil count (ANC) testing. As part of FDA's regular review of all REMS, and in light of the FDA's continued exercise of enforcement discretion with respect to certain aspects of the Clozapine REMS, the FDA initiated a reevaluation of the program in September 2023.

The Sentinel System analyses provided insights into clozapine use, adherence to ANC monitoring, and the incidence of neutropenia and agranulocytosis. These analyses drew from a variety of data sources, including the Sentinel System's large national commercial insurers, integrated delivery systems, CMS' Medicaid and Fee-for-Service Medicare data, and MarketScan® Research Databases. Additionally, the Sentinel Innovation Center's (IC) Real-World Evidence Data Enterprise (RWE-DE) was used to conduct

a chart review of patients with EHR data linked to Medicare and Medicaid claims to describe patients who experienced neutropenia while on clozapine.

Findings from the Sentinel analyses were presented along with other data at the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee on November 19, 2024. The committee voted 14-1 that the REMS requirements for ANC documentation and verification were not necessary for the safe use of clozapine, nor were the provider education requirements.[9] On February 24, 2025, the FDA announced the elimination of the Clozapine REMS program, reasoning that it was no longer needed to ensure the drug's benefits outweigh its risks, and the REMS was eliminated effective June 13, 2025. This decision is expected to improve patient access to clozapine and reduce burden on the healthcare delivery system.

The ARIA system also supported the evaluation of the Lotronex REMS and Alosetron REMS programs. Alosetron, sold under the brand name Lotronex, was initially approved in 2000 for severe diarrhea-predominant irritable bowel syndrome in women, but was voluntarily withdrawn shortly after amid reports of ischemic colitis and complications of constipation. The FDA reapproved alosetron in 2002 with a risk management program, including a boxed warning for serious gastrointestinal adverse reactions, such as ischemic colitis. In 2010, the Lotronex REMS program was approved, requiring prescriber training, patient acknowledgement forms, and the affixation of a REMS program sticker on a hard copy prescription. A separate, comparable, REMS was approved in 2015 upon approval of the first generic version of alosetron hydrochloride.

Following REMS program modifications in 2016 that made prescriber training optional and removed the prescription sticker requirement, the FDA did not identify any new data suggesting a change in the frequency or severity of ischemic colitis and serious complications of constipation. As one contributing source of information, the ARIA system was used to estimate the incidence of ischemic colitis among women initiating alosetron or eluxadoline (a comparator not associated with ischemic colitis) between 2016 and 2020. The findings showed that incidence rates of ischemic colitis between 2016 and 2020 following the REMS program modifications were consistent with those listed in the existing Prescribing Information.

These Sentinel System results, along with findings from other data sources, supported the FDA's decision to eliminate both the Lotronex and Alosetron REMS programs, concluding they were no longer necessary to ensure the safe use of the medications.

2.6 Providing Information on Drug Utilization Trends

The FDA has effectively leveraged the Sentinel System to monitor utilization patterns of the FDA-approved medical products. One notable example involved tracking the impact of a national drug shortage. In March 2023, a shortage of injectable methotrexate – a folate analog metabolic inhibitor indicated for acute lymphoblastic leukemia, non-Hodgkin lymphoma, and osteosarcoma – was identified following a distribution halt by a key manufacturer. This shortage was particularly concerning for pediatric cancer patients who depend on methotrexate for treatment.

In response to a request from a federal partner to assess the impact, the FDA used the Sentinel System to analyze utilization patterns of injectable methotrexate. The analysis was stratified by age group, calendar month, and clinical indication, using two key data sources: the Rapid SDD – a specialized subset of the SDD with more frequent data refreshes – and TriNetX Live™, an EHR data source refreshed every two to four weeks (see Appendix C for more information).

Findings from the Rapid SDD indicated minimal changes in methotrexate use among pediatric patients, though a decline in use was observed among adults. These results provided the FDA and other stakeholders valuable insights into the impact of methotrexate injection shortages on certain patient populations.

In another example, the FDA utilized the SDD to examine evolving utilization patterns of stimulant medications, such as amphetamine/dextroamphetamine or methylphenidate, indicated for attention-deficit/hyperactivity disorder (ADHD). Over recent decades, the prescribing of these medications has risen. Labeling for this drug class includes a boxed warning for abuse, misuse, and addiction, and the FDA wanted to better understand risk in the current context of increased use. Patients' characteristics – such as comorbid conditions, history of substance use, and demographic factors – can influence both prescribing decisions and the patient's risk for misuse.

To better understand these prescribing trends and inform potential future inferential studies of stimulant medication safety, CDER's Office of Surveillance and Epidemiology conducted a series of analyses using the Sentinel System. These analyses focused on utilization patterns and baseline characteristics of patients who initiated Schedule II stimulant medications between January 2017 and March 2023. The study population included U.S. children and adults (aged 18 years and older) with commercial insurance or Medicare coverage.

The FDA assessed utilization trends across three key time periods, defined as pre-pandemic, during the COVID-19 pandemic, and the post-pandemic period for the purposes of this study. Results showed the average daily dose of commonly prescribed Schedule II stimulants remained consistent with routine clinical practice. Additionally, patterns of use and baseline diagnoses did not differ meaningfully between the pre-pandemic and pandemic periods.

These descriptive findings informed ongoing scientific discussions with external researchers funded by the FDA to study prescription stimulant use and misuse.[10]

The FDA also routinely uses the Sentinel System to monitor the uptake of NMEs. Each year, these descriptive analyses are conducted to provide information on the utilization of products approved within the past five to seven years. These data play a critical role in pharmacovigilance planning, helping the FDA's Division of Pharmacovigilance determine when a product has sufficient use to support data mining analyses aimed at identifying unknown adverse health outcomes (i.e., signal identification). See Section 2.3 Advancing the FDA's Pharmacovigilance Activities: Signal Identification for more information.

2.7 Responding to the COVID-19 Pandemic

FDA utilized the Sentinel System to aid in its response to the COVID-19 pandemic. As treatment guidelines were issued and various therapeutics were developed and deployed, the data provided by the Sentinel System continued to provide valuable insights into medical product safety and aided regulatory decisions.

In June 2020, preliminary results for the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial conducted in the United Kingdom reported both benefit from dexamethasone in severely ill hospitalized patients with COVID-19, and potential harm in those not requiring oxygen.[11] In October 2020, the National Institutes of Health (NIH) issued COVID-19 treatment guidelines advising against systemic corticosteroid use in patients with mild to moderate COVID-19. In 2021, the FDA assessed clinical characteristics and new systemic corticosteroid use among non-hospitalized COVID-19 patients

in four SDD commercial claims insurers as part of a larger project that also included data from Medicare, HealthVerity, and the Veterans Health Administration. The findings showed that despite recommendations to the contrary, "9.4% of non-hospitalized patients with COVID-19 in the Sentinel System and 16.4% in Medicare received systemic corticosteroids in an outpatient setting within 14 days of COVID-19 diagnosis, often on the day of diagnosis."[12] These findings were published in the Journal of the American Medical Association (JAMA) and contributed to an official CDC Health Advisory against inappropriate use of corticosteroids in outpatients with mild-to-moderate COVID-19.[13] The study was also cited in updated NIH COVID-19 treatment guidelines.

In addition, following safety concerns identified in the UK RECOVERY trial about the use of high dose dexamethasone in hospitalized COVID-19 patients requiring no oxygen supplementation or simple oxygen only, the FDA examined the use of the dexamethasone dose used in hospitalized COVID-19 patients in a large U.S. hospital network, HCA Healthcare (HCA). The HCA dataset used for the FDA's COVID-19 work spanned from January 2020 through June 2024, covering 142 HCA hospitals across 18 states, with significant representation from Texas, Florida, Virginia, and Colorado. More information about HCA data can be viewed in Appendix C. The findings of the study on use of dexamethasone in hospitalized COVID-19 patients showed that almost 80% of hospitalized patients received standard daily doses of dexamethasone (≤6 mg daily). However, over 20% of COVID-19 hospitalizations requiring no oxygen or simple oxygen received higher doses of dexamethasone.[14] The findings were published in Pharmacoepidemiology and Drug Safety.[14]

Also, within HCA, the FDA explored how respiratory support was captured, since invasive mechanical ventilation and supplemental oxygen use are markers of COVID-19 illness severity in hospitalized patients. While administrative data captured mechanical ventilation during hospitalization adequately, evidence of respiratory support via supplemental oxygen extracted from semi-structured nursing notes improved ascertainment of hospitalizations requiring supplemental oxygen.[15] This study showed the value of detailed clinical information in inpatient EHR data for studies that require respiratory support to appropriately capture the severity of illness in hospitalized patients with respiratory illness such as COVID-19.

Once COVID-19 therapeutics were developed, the FDA leveraged the Sentinel System to conduct monitoring of therapeutics issued Emergency Use Authorization (EUA). A series of analyses assessed whether the use of several of these therapeutics followed the authorized use of these products, and described patient outcomes, such as anaphylaxis and hospitalization rates, in patients receiving these medical products. Periodic EUA monitoring suggested that the COVID-19 EUA treatment use followed the Fact Sheet directives and did not identify any new safety signals.

The Sentinel System's role in monitoring EUA products lent itself to contributing to the FDA's review of a NDA for Paxlovid (nirmatrelvir and ritonavir). Pre-approval product utilization data were available as a function of Paxlovid's EUA, so the FDA used the Sentinel System to estimate the size of the indicated 'at-risk' population who were being treated with therapeutics that interact with Paxlovid to inform product labeling. The assessment indicated that more than 50% of Paxlovid-eligible patients may have been on therapies that could adversely interact with Paxlovid. However, most of the commonly used medical products that could induce drug-drug interactions when taken with Paxlovid may not prevent patients from taking Paxlovid, as they were therapies that could be temporarily withheld or adjusted to a lower dose with minimal impacts. Findings from the drug interaction assessment were included in the FDA's New Drug Application review of Paxlovid, in which adverse reactions due to drug-drug interactions were reviewed. After reviewing the totality of the information available, the FDA approved

Paxlovid with a boxed warning included in the product labeling to underscore and ensure that prescribers were aware of the drug interaction risk.

The Sentinel System was also utilized in a multi-national collaboration across seven countries in North America (United States and Canada) and Europe (England, Spain, Germany, Netherlands, Italy) to assess the risk of thromboembolism among persons with COVID-19 diagnosed in the ambulatory setting. The study found heterogeneity by country in the 90-day absolute risk of arterial and venous thromboembolism after COVID-19 diagnosis, both before and during COVID-19 vaccine availability.[3]

In a second international collaboration, a large project aimed at understanding the impacts of COVID-19 on pregnancy was undertaken, involving eight European countries, the United Kingdom, Canada, Saudi Arabia, and the U.S. The Sentinel System team adapted the "COVID-19 infectiOn aNd medicineS In preGNancy" (CONSIGN) study protocol as part of an international collaboration to examine medication use patterns among pregnant women in the United States. The two aims of the CONSIGN project were to: 1) describe severity and clinical outcomes of COVID-19 disease in pregnant women and compare these data with those of non-pregnant women of reproductive age with COVID-19; and 2) describe and estimate the rates of adverse infant and maternal outcomes in pregnant women with and without COVID-19 during pregnancy. The study found that selected medication utilization was higher post-COVID-19 among pregnant women with COVID-19, compared to pregnant women without COVID-19 and to non-pregnant women with COVID-19. In the investigation of adverse infant outcomes, nearly 23,000 pregnancies with COVID-19 were identified and no increased risk of adverse infant outcomes was found compared to pregnancies without COVID-19. Among less than 5% of pregnancies with severe COVID-19 in the third trimester, a higher proportion of low birth weight was noted. The interpretation of findings may be challenging due to the evolution of the COVID-19 pandemic with changes in treatment and prevention recommendations that may have impacted COVID-19 severity.

During the COVID-19 pandemic, studies and reports emerged that showed a disproportionate burden of COVID-19 infections, hospitalizations, and deaths among some racial and ethnic groups. With support from the FDA Office of Minority Health, the FDA led an assessment of the association between race and COVID-19 outcomes adjusted for baseline demographic, clinical, and socioeconomic characteristics using claims data from the SDD. An observational cohort study was performed that evaluated the occurrence of hospitalization, critical COVID-19, and inpatient mortality in the 30 days following a COVID-19 diagnosis or during a hospitalization for COVID-19. An association between race and COVID-19 outcomes was determined with white race as the reference category using multivariable logistic regression models that controlled for demographic, clinical, and socioeconomic differences at baseline. When comparing across race categories, some race groups had increased odds relative to the white race group for hospitalization and mortality following COVID-19 in the United States in the first year of the pandemic, which aligned with findings reported in early literature.

The Sentinel System learned and adapted following the COVID-19 pandemic. Looking towards the future, one known challenge introduced by the pandemic was the impact of changes in healthcare utilization due to the COVID-19 pandemic on the validity of medical product safety studies using secondary claims data. In the United States, stay-at-home orders, infection control guidelines, and unemployment-related changes to insurance coverage led to decreases in healthcare utilization, while concurrently there was an increase in telemedicine to safely see patients.[16,17] These changes in healthcare utilization can threaten the validity of pharmacoepidemiology studies that rely on secondary data. Participants observed in the data may be sicker (threatening generalizability), however, exposure and outcome misclassification may occur, and inaccurate identification of confounders and effect

measure modifiers may lead to residual confounding.[17] A project conducted within the Sentinel System in 2023 summarized changes in healthcare utilization among the insured in the United States between 2020 and 2022. It also replicated a known positive product-outcome association using pandemic-era data to observe the potential impact that the known changes in utilization might have on results; by using a known positive association as a use case, variations in the results of the replicated study would indicate variances in the underlying data. The greatest impact of the changes to healthcare utilization was found to be between March and July 2020, the first quarter of the pandemic. Results from the project suggested that future studies using data from this quarter should consider the contribution of this period to the overall study period. To minimize the potential impact of this three-month time frame, studies may restrict the calendar periods or include sensitivity analyses to understand the impact of parameter choices potentially affected by shifts in healthcare utilization, such as modifying the length of assessment windows. Recommendations from this project are routinely considered in safety studies performed within the Sentinel System that include data from the COVID-19 pandemic era.

Additionally, the Sentinel System conducted a project to showcase its capability for prospective surveillance during events such as the COVID-19 pandemic. Sequential surveillance of therapeutics using electronic health data enables routine monitoring to detect statistically significant increased risks of specific adverse events. This involves designing and repeatedly conducting inferential studies as data accumulates to quickly identify any increased risk for outcomes of interest. Monitoring continues until findings either 1) suggest a potential safety concern that warrants further follow-up or regulatory action or 2) suggest that no further action is needed regarding the potential safety concern. The Sentinel System integrated sequential surveillance into its routine analytic tools, enabling multiple executions of cohort or self-controlled risk interval analyses as new data become available. The FDA conducted a project to demonstrate these capabilities for monitoring the safety of new medications, with COVID-19 therapeutics as a use case. Within this activity, investigators developed a master protocol to guide critical design and analysis decisions in future sequential surveillance studies. The project demonstrated that the data within the SDD and the Sentinel System's analytic tools are well-suited for conducting continuous sequential surveillance of medical products.

From 2022 to 2024, the Sentinel System continued to contribute valuable information to support the FDA's response to COVID-19. Across these projects, the FDA supported monitoring of therapeutics used under EUA, monitoring of pandemic-related drug shortages, informed approval of Paxlovid, assessment of the differential impact of the pandemic on specific populations, such as pregnant women, and performance of methods projects to strengthen our abilities to monitor medicines during a public health emergency.

2.8 Partnering with Federal Agencies to Address Public Health Topics

The FDA has used the data and analytic capabilities of the Sentinel System to partner with other federal agencies on a range of public health initiatives. One notable example is the FDA's contribution to the HHS' recommendation to reschedule marijuana. FDA's scientific and medical evaluation, conducted on behalf of HHS and submitted to the Drug Enforcement Administration (DEA) of the Department of Justice, informed a reassessment of marijuana's federal scheduling status. Although marijuana (cannabis and cannabis-derived plant materials that contain more than 0.3% delta-9 tetrahydrocannabinol on a dry weight basis) has been classified as a Schedule I drug under the United States Controlled Substances Act since 1970 – rendering its use illegal at the federal level – a growing

number of states, localities, and territories have enacted laws permitting its use for medical purposes, or both medical and adult (i.e., recreational) use.

As a part of HHS' review, the FDA used the Sentinel System to conduct descriptive analyses to describe healthcare encounters for cannabis-related disorders and poisonings related to the use of cannabis and other select substances among commercially insured individuals aged 18 to 64 years, spanning the years 2016 to 2022. Results were incorporated into the HHS evaluation, which provides a basis for the DEA's recent proposed rule published in the Federal Register (89 FR 44597, May 21, 2024), to reschedule marijuana from Schedule I to Schedule III under the Controlled Substances Act.

The FDA has separately partnered with the CDC on several disease surveillance projects utilizing the Sentinel System's data infrastructure and analytic tools. In 2022, the CDC conducted a descriptive study of the incidence and prevalence of type 1 and type 2 diabetes mellitus by age, over time, in the SDD. In 2024, this analysis was conducted again to provide results with more recent data and to add information on type 1 and type 2 diabetes mellitus trends in the Medicaid population.

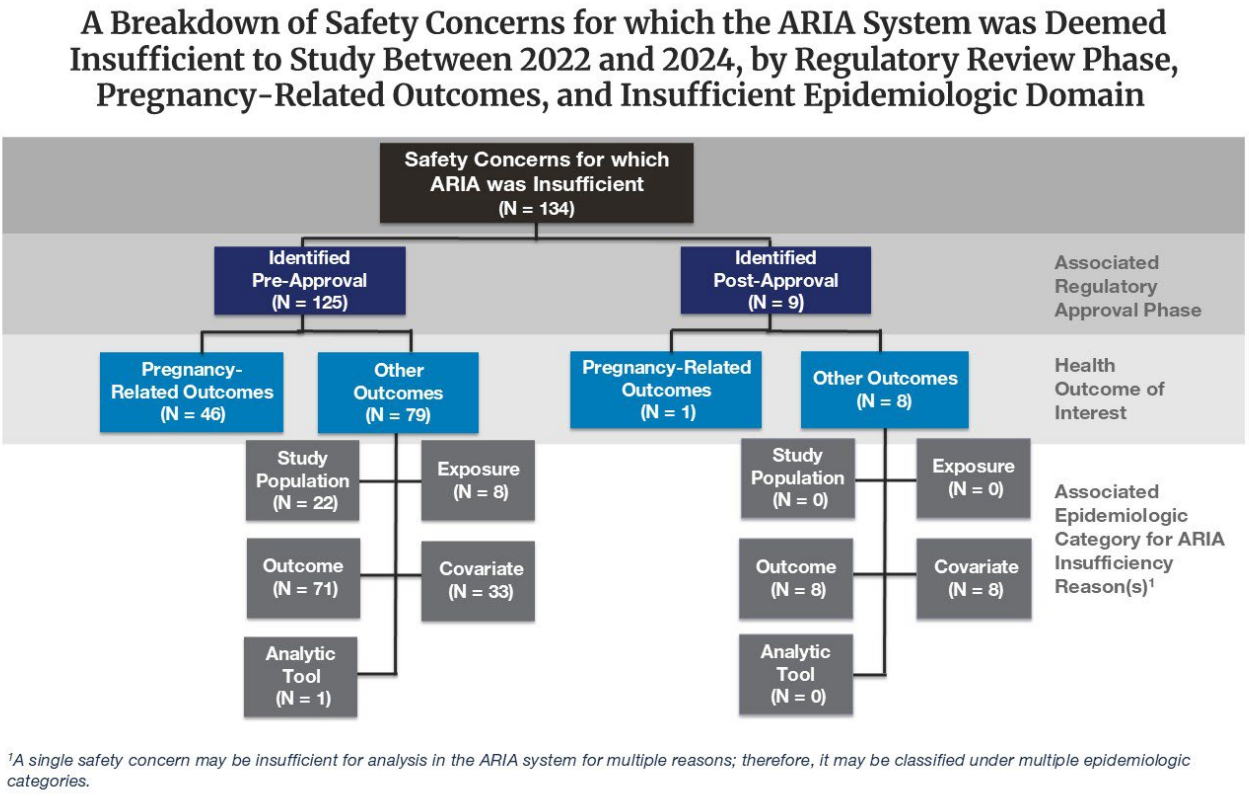
The CDC also utilized the wide geographic distribution of the Sentinel System's data to add geographic data to a study of doxycycline as post-exposure prophylaxis (PEP) treatment for Lyme disease given that the infection is emerging in many states with historically low incidence. The analysis described single-dose doxycycline dispensing in an outpatient cohort in the United States. From 2010 to 2020, a total of 427,105 patients received at least one dispensing; most patients were 65 years of age or older. The study suggests that Lyme disease PEP may be under prescribed for certain groups, including children. In 2024, this Sentinel analysis was being updated to incorporate the Medicaid population, allowing for a more detailed examination of Lyme disease PEP uptake among children.

2.9 ARIA's Inability to Evaluate Certain Safety Concerns

Within the ARIA program, cases where the ARIA system was deemed insufficient, pursuant to section 505(o)(3) of the FD&C Act, to assess a safety concern and the reasons for that insufficiency are recorded.[18] Reasons for insufficiency are tracked at the safety concern level, by a unique exposure/outcome/year combination. Memoranda that outline why the ARIA system was found insufficient are included in the action package for NDA and BLA approvals and are linked on Sentinel's website. The FDA tracks and analyzes reasons for insufficiency to inform future program development and to ensure that the ARIA system is as robust as possible. For a comprehensive list of safety concerns considered for assessment in the ARIA system from 2022 to 2024, please refer to Appendix F.

The ARIA system insufficiency is measured in two stages. The epidemiologic domain of the study that the ARIA system cannot address is identified (capture of study population, outcomes, exposures/comparators, covariates, or a lack of methodological capability of the analytic tool (e.g., statistical model insufficiency). Within each domain, the root cause of the insufficiency is subsequently selected from a predefined list, and an explanation is provided as to why the ARIA system could not meet study needs. A summary of the insufficiency by domain broken out by approval stage is provided in Figure 2.

Figure 2. A Breakdown of Safety Concerns for which the ARIA System was Deemed Insufficient to Study Between 2022 and 2024, by Regulatory Review Phase, Pregnancy-Related Outcomes, and Insufficient Epidemiologic Domain

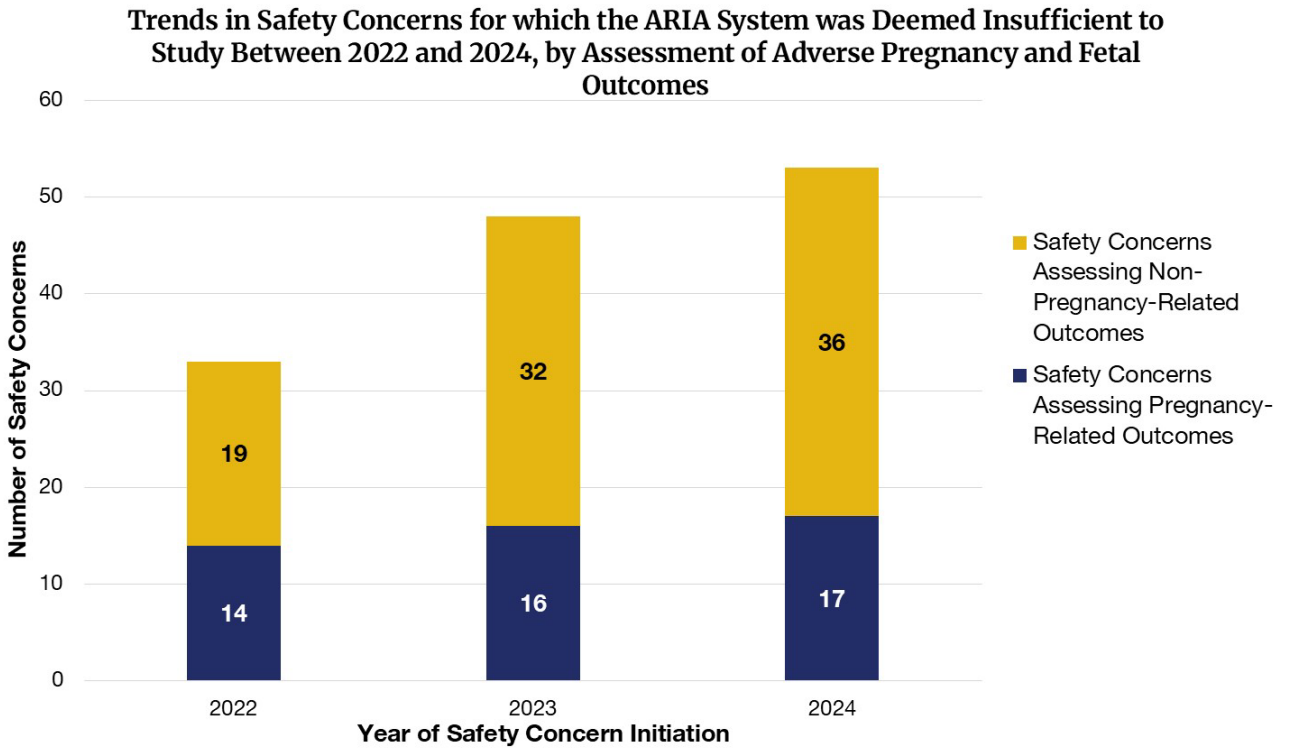


[1]A single safety concern may be insufficient for analysis in the ARIA system for multiple reasons; therefore, it may be classified under multiple epidemiologic categories.

Since the root causes of insufficiency are generally only documented when issuing a PMR when an ARIA system-based assessment is not sufficient, and most PMRs are issued during product application approval, the majority of the ARIA system insufficiency determinations reflect safety concerns identified pre-approval (n=125 in pre-approval and n=9 in post-approval as seen in Figure 2.

Evaluation of the ARIA system sufficiency in the context of pregnancies has unique challenges,[18] therefore, safety concerns for which the ARIA system was deemed insufficient due to the inability to identify unexpected adverse fetal or maternal outcomes not specified in the analysis have been excluded from the remaining tables. As part of the PDUFA VII commitments, the FDA has committed to undertaking a series of demonstration projects to inform a new FDA framework for monitoring the safety of medical products in pregnancy that optimizes the use of registries and electronic healthcare data sources. More information on these projects and their framework development was presented at a 2022 public meeting on Optimizing the Use of Post-Approval Pregnancy Studies. The demonstration projects are underway and will inform an update to the proposed framework and development of guidance or other appropriate documentation of internal policies and procedures to implement a standardized process for determining whether and what type of pregnancy postmarketing studies are appropriate by September 30, 2027.

Figure 3. Trends in Safety Concerns for which the ARIA System was Deemed Insufficient to Study Between 2022 and 2024, by Assessment of Adverse Pregnancy and Fetal Outcomes



Understanding the root causes of the ARIA system insufficiency is critical to understanding which enhancements or changes may expand the reach and capability of ARIA. Some limitations are inherent in claims data or EHR data and are unlikely to be easily addressed within observational data. Table 5 below presents the number of safety concerns for which the ARIA system was deemed insufficient per root cause from January 1, 2022, through December 31, 2024, excluding those related to the inability to identify unexpected adverse fetal or maternal outcomes not specified in the analysis. In many cases, the ARIA system is determined to be insufficient to assess a safety issue based on more than one root cause.

The top drivers of insufficiency fall into two main categories. First, insufficiency due to inherent limitations of all electronic healthcare data (i.e., poor identification of clinical concepts with coding algorithms and absence of validated code algorithms). Second, insufficiency due to limitations of claims data, which lack the comprehensive information available in clinical data (both structured and unstructured). The establishment of the Sentinel RWE-DE described in Appendix C, which links claims data with EHR data, is a part of a strategic, long-term effort to address the limitations of relying solely on claims data. One tradeoff with using the RWE-DE is a smaller sample size as compared to claims only data, which can limit studies that can be performed solely using these datasets. Other potential uses of these datasets include making use of an internal subsample of patients with clinical data in the EHR linked to claims data to measure potential issues with confounding control in a larger, claims-only study (Section 3.3). Additionally, multiple methods projects have been undertaken to address known

limitations of using EHR data (e.g., missingness), as well as identify how to best integrate these data into medical product safety monitoring.

Table 5. Root Causes of Insufficiency Determinations, 2022 to 2024

Root Causes of ARIA Insufficiency	# of Safety Concerns*	Direction of Future Development
Insufficient supplemental structured clinical data	60	This is an inherent limitation of claims-based data, which comprises the bulk of the current ARIA system dataset. Integration of large EHR-claims linked datasets into ARIA would address this insufficiency.
Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate	43	Coding terminologies introduce inherent limitations for identification of certain clinical concepts in all electronic healthcare data sources (i.e., both claims and EHR). In many cases, no program enhancement will address these limitations of using codes to describe clinical concepts.
Absence of validated code algorithm	25	This is often actionable through targeted research and development. Validating new code list algorithms requires dedicated resources including clinical expertise, data access, and methodological rigor. As medical terminology and coding practices continually evolve, this challenge requires ongoing investment to keep algorithms current and reliable.
Study requires data elements captured in unstructured clinical data, such as clinical notes	25	This is an inherent limitation of current claims-based data, which comprises the bulk of current ARIA system data. Work outlined in Section 3.2 Developing Novel Feature Engineering Methods aimed at addressing this root cause of insufficiency.
Insufficient observation time available	25	This is actionable with further research and resources. Linkages between disparate data sources require adoption of uniform privacy-preserving linkage methods. Developing data governance amongst multiple partners requires substantial collaboration and investment of time and resources.
Requires linkage to additional data source that is unavailable	21	This is an inherent limitation of current datasets that comprise the ARIA system data. Additional linkages are possible with significant financial resources. Data governance issues must be addressed.
Inability to identify over-the-counter medication use	9	This is an inherent limitation of both claims and EHR data. It is unlikely that this could be addressed within the current ARIA system infrastructure.
Inadequate sample size	3	This is non-actionable as low uptake or background rates are the driving factor.
Insufficient inpatient data	2	This is an inherent limitation of claims-based data, which comprises the bulk of the current ARIA system dataset.

Inability of ARIA system tools to perform required analysis	1	This indicates that the ARIA toolset did not include the analytic capabilities required for a desired study. Historically, a main driver of this category of insufficiency is the need to screen for potential safety signals associated with a medical product's use in pregnancy. Sentinel has now integrated signal identification abilities leveraging TreeScan™ methods into Sentinel's analytic tools for routine regulatory use.

** The ARIA system may be considered insufficient to assess a safety concern based on one or more root causes. Safety concerns are deduplicated if ARIA was identified as insufficient to assess the same root cause in multiple epidemiologic domains. For example, if ARIA was deemed insufficient to assess a safety concern due to the absence of a validated code algorithm for both outcome and covariate epidemiologic domains, it is only reflected once in this table for that specific root cause. Safety concerns are excluded for which the primary focus was adverse pregnancy or fetal outcomes, stillbirths, or neonatal deaths.*

As seen in Figure 2 inability to capture the outcome or covariate remains the leading causes of insufficiency of the ARIA system, followed by inability to identify the study population. Understanding the underlying drivers of insufficiency in these two domains can help target program enhancements.

The most common root causes for insufficient outcome ascertainment are reported in Table 6. Two of the top three causes for insufficient outcome capture are due to limitations in code terminologies: Inability to adequately capture clinical concepts with available code algorithms was the leading cause (n=29 safety concerns), and lack of a validated code algorithm was the third most cited cause (n=21 safety concerns). However, around half of these safety concerns were also associated with an additional root cause driving insufficient outcome capture, suggesting that while outcome validation studies may allow the ARIA system to address more safety concerns, the allocation of resources to these validations must also consider other underlying root causes of insufficient outcome capture.

Following code-based limitations, lack of access to structured clinical data was the leading driving root cause of insufficiency (Table 6). The lack of structured clinical data accounted for more than twice as many insufficiency determinations than the lack of unstructured clinical data. This was driven entirely by the need for laboratory and/or vital sign data.

The addition of the RWE-DE (described in Section 3.1) in developing algorithms that utilize EHR data may expand utility of the Sentinel System. Since many outcomes cannot be ascertained in ARIA because of multiple reasons for insufficiency, the FDA developed a fitness for purpose assessment tool that can be utilized to evaluate the effort required for development of a "computable phenotype" – an algorithm that uses data elements of a health record, such as lab values or text in the clinical notes of the record – to identify patients with a specific health condition or clinical outcome. The tool evaluates the effort required for computable phenotyping development for health outcomes of interest based upon the scientific objective, and the clinical and data complexities. The intended use of this tool is to aid in the FDA's future decision making on whether the development of a computable phenotype for any given outcome would be worth the investment. More information is provided in Section 3.4.

Other frequent reasons for insufficient outcome capture include insufficient observation time and the need for additional linkages. Insufficient observation time was largely associated with cancer outcomes, which generally have a long latency period between exposure and outcome. For the lack of linkage to additional data sources, cause-of-death data, patient-reported outcomes, physician-administered

assessments, niche study needs (e.g., dental records, travel medication, etc.), and cancer-related clinical and laboratory data were the cited data sources that were not available within the ARIA system and/or not linkable and required to meet study needs. Of the four safety concerns that could not be assessed in the ARIA system due to the need for cause-of-death data, three were specifically focused on evaluating major adverse cardiovascular events. This particular outcome requires access to outpatient death data. All of these safety concerns were identified in 2022 and 2023; in 2024, the Sentinel System's Medicare and Medicaid datasets added linkages with the National Death Index (NDI), which may address this cause of insufficiency in the future.

Table 6: Root Causes of ARIA Insufficiency for Capture of Outcomes of Interest, 2022 to 2024

Root Causes of ARIA Insufficiency	Number of Safety Concerns*
Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate	29
Insufficient supplemental structured clinical data	23
Absence of validated code algorithm	21
Insufficient observation time available	20
Requires linkage to additional data source that is unavailable	19
Study requires data elements captured in unstructured clinical data, such as clinical notes	9
Other	5

**Safety concerns are excluded for which the primary focus was adverse pregnancy or fetal outcomes, stillbirths, or neonatal deaths. The ARIA system may be considered insufficient to study a safety concern due to one or more root causes.*

The ten most frequent health outcomes by MedDRA Class for safety concerns for which the ARIA system was deemed insufficient are displayed in Table 7. Outcomes are recorded using MedDRA terminology and reported at the System Organ Class level (highest level in the MedDRA hierarchy). The higher count of infections and infestations includes eight safety concerns aiming to identify Progressive Multifocal Leukoencephalopathy. There is a validated claims-based algorithm for Progressive Multifocal Leukoencephalopathy with a positive predictive value of 90.0% (95% CI: 81.7–98.3%). However, the FDA determined that signal evaluation of the safety concern required a more precise outcome definition through either a medical chart review or a claims-based algorithm developed in the indicated population (patients with multiple sclerosis).

Table 7: Most Common Outcomes by MedDRA Class for Which ARIA is Insufficient, 2022 to 2024

Outcome[1,2]	Number of Safety Concerns
Infections and infestations	18
Nervous system disorders	10
Immune system disorders	8
Cardiac disorders	8
Other[3]	7
Vascular disorders	7

Hepatobiliary disorders	7
Injury, poisoning and procedural complications	5
Gastrointestinal disorders	4
Neoplasms benign, malignant, and unspecified (Including cysts and polyps)	4

[1]Outcomes were classified at the MedDRA System Organ Class (SOC) level
[2]Outcomes related to pregnancy were excluded from this table
[3]An outcome categorized as 'Other' lacks sufficient representation in MedDRA terminology

Following insufficient outcome ascertainment, inability to sufficiently capture covariates to appropriately control for confounding was the second most frequently cited domain of ARIA insufficiency (Figure 2). The root causes for ARIA insufficiency to assess covariates are reported in Table 8. The top root causes were similar for covariates as for outcomes, with the exception that the absence of unstructured clinical data, such as clinical notes, was a higher driver of ARIA insufficiency to assess covariates. The third domain in which the ARIA system was found most frequently insufficient was the capture of study population, which also shared the same top root causes (data not shown).

Table 8: Root Causes of ARIA Insufficiency for Capture of Covariates, 2022 to 2024

Root Causes of ARIA Insufficiency	Number of Safety Concerns*
Insufficient supplemental structured clinical data	30
Study requires data elements captured in unstructured clinical data, such as clinical notes	22
Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate	12
Inability to identify over-the-counter medication use	9
Insufficient observation time available	7
Requires linkage to additional data source that is unavailable	3
Insufficient inpatient data	0
Insufficient capture of race and ethnicity	0
Other	0

**Safety concerns are excluded for which the primary focus was adverse pregnancy or fetal outcomes, stillbirths, or neonatal deaths. The ARIA system may be considered insufficient to study a safety concern due to one or more root causes*.

Considering this information, the Sentinel System strategically addresses the areas that can enhance the utility of the ARIA system for medical product safety monitoring. The PDUFA VII Pregnancy Demonstration projects are exploring the potential to expand the use of electronic healthcare databases to supplement safety monitoring of medical product usage among pregnant women, including validating the Sentinel System's methods for signal detection of undefined adverse pregnancy or fetal outcomes. Work on integrating more clinical data, both structured and unstructured, is occurring within the newly developed RWE-DE. See Section 3 for more information.

While work is ongoing to build out the data infrastructure to integrate clinical data into the ARIA system, it optimally functions for addressing study questions that can be best addressed using claims-based data.

3 Improving the Sentinel System: Integrating EHR Data Within a Causal Analysis Framework

The Sentinel Innovation Center (IC) was established in 2019 in response to the FDA's Sentinel System Five-Year Strategy 2019 to 2024, which aimed to enhance the Sentinel System's capabilities by expanding access to EHR data and integrating methodological and data science innovations.[19] Its mission is to maximize the utility of EHR data for medical product safety surveillance. As of October 2024, the Sentinel IC portfolio formally merged with the Sentinel Operations Center (SOC).

The IC has focused its efforts on several strategic priority areas:

1. **Data Infrastructure**: broadening access to both structured and unstructured linked claims-EHR data through the launch of the RWE-DE
2. **Feature Engineering**: developing methods to extract meaningful variables (i.e., features) from unstructured data sources using advanced techniques such as natural language processing (NLP) and machine learning, and transforming them into structured formats suitable for analysis
3. **Causal Inference**: addressing the unique methodological challenges of using EHR data for measuring health outcomes of interest and confounders, such as nonrandom data missingness and residual confounding
4. **Use Case Demonstrations**: launching a series of analyses to demonstrate the practical application of the RWE-DE and novel methodologies developed through the separate strategic priority areas

Through these initiatives, described further below, the IC is advancing the science of real-world evidence generation and strengthening the FDA's ability to monitor the safety of medical products in a rapidly evolving data landscape.

3.1 Data Infrastructure: Launching the Real-World Evidence Data Enterprise (RWE-DE)

To support the FDA in addressing key regulatory needs for clinical data, the IC has built an analysis-ready, large-scale data infrastructure of linked EHR and claims data: the RWE-DE. This data source aims to enhance the ARIA system by integrating EHR data linked with healthcare insurance claims. This integration addresses key limitations of the ARIA system, particularly its lack of detailed clinical information, which has historically constrained the system's ability to accurately identify certain exposures, outcomes, sub-populations of interests, health conditions, or covariates in pharmacoepidemiologic studies.[20,21]

The RWE-DE comprises two components:

- **The Commercial Network**, which includes two commercial EHR-claims linked data assets (TriNetX, HealthVerity) and offers broad population coverage, with over 21 million lives represented.

- **The Development Network**, which includes four academic institutions (Mass General Brigham, Duke University Health System, Vanderbilt University Medical Center, and Kaiser Permanente Washington), and offers the opportunity to directly access granular clinical data, including free-text notes with minimal restrictions through institutional affiliation of academic investigators. Over 4.5 million lives are represented.

In addition to partnerships with commercial EHR aggregators, as described in Appendix C, other population-based data sources could significantly contribute to the RWE-DE in the future. The IC investigated Health Information Exchanges (HIEs), which facilitate the electronic movement of healthcare information among different healthcare information systems, and Health Information Organizations (HIOs), created at the state or regional level, which are designed to allow healthcare professionals and patients to securely share a patient's medical information electronically, regardless of the care setting. HIEs and HIOs may provide an opportunity to assemble a large-scale, patient-centric data asset for the Sentinel System.

The IC conducted a scoping review to assess the size and capabilities of key state and regional HIOs with mature data infrastructures suitable for Sentinel's use.[22] Through a collaboration with Civitas Networks for Health, a nonprofit organization representing HIOs as a multi-stakeholder collaboration, and by reviewing the annual HIO survey sponsored by the Office of the National Coordinator for Health Information Technology (currently known as "The Assistant Secretary for Technology Policy/Office of the National Coordinator for Health Information Technology"), the IC engaged select HIOs that demonstrated advanced data capabilities for application to the RWE-DE.

From this review, the IC partnered with MyHealth Access Network, Oklahoma's state-designated non-profit HIO, which serves nearly six million patients within the Master Patient Index (a centralized database that uniquely identifies each patient in the network) and links over 4,000 providers. The partnership aimed to explore the utility of their claims data by implementing an analysis comparable to routine Sentinel analyses.

Working with MyHealth Access Network, the IC demonstrated how an analysis could be implemented in a patient-centric EHR and claims data environment; they identified a cohort of patients with type 2 diabetes mellitus who started either a dipeptidyl peptidase-4 (DDP-4) inhibitor or SGLT2 inhibitor. The scoping review exercise helped assess the current landscape of the HIOs in the United States with respect to their size, geographic coverage, services offered, connectivity, participation in national networks, and key challenges to their ongoing development.

3.2 Developing Novel Feature Engineering Methods

3.2.1 Natural Language Processing (NLP) Methods

While structured data from EHRs and claims are commonly used for research, there is also valuable information contained in unstructured clinical notes. To extract this information for application to medical product safety surveillance, scalable methods like natural language processing (NLP) are needed. Since 2021, several IC projects have aimed to test, validate, and improve the use of NLP in pharmacoepidemiologic studies. These were methods oriented projects designed to evaluate approaches that could be used in future regulatory activities.

From 2021 to 2023, the IC partnered with investigators at Kaiser Permanente Washington to develop a general framework for identifying patients with specific clinical conditions (phenotypes) through a

variety of approaches, including natural language processing methods incorporating EHR data. Algorithm development was organized into five stages: (1) assessing fitness-for-purpose, (2) creating gold standard data, (3) feature engineering, (4) model development, and (5) model evaluation. The framework provides an integrated set of principles, strategies, and practical guidelines intended to enhance the overall efficiency and transparency of the effort as well as the performance, transportability, and reusability of the algorithms developed.[23]

In 2021, the IC partnered with Vanderbilt University Medical Center on a project that improved probabilistic phenotyping through enhanced ascertainment with NLP. This project aimed to advance computable phenotyping for identifying incident outcomes that rely on unstructured data and lack a clear reference standard.

This IC study developed and validated a novel incident phenotyping approach using unstructured clinical textual data, independent of EHR, and note type. Based on a published, validated approach (PheRe) for ascertaining social determinants of health and suicidality, this method was validated on two phenotypes that share common challenges with respect to accurate ascertainment: suicide attempt and sleep-related behaviors. With samples of 89,428 records and 35,863 records, respectively, validation was conducted using both silver standard (diagnostic coding) and gold standard (manual chart review) methods.[24]

The study showed an area under the precision-recall curve (AUPRC) of ~0.77 (95% confidence interval (CI) 0.75–0.78) for suicide attempt and AUPRC ~0.31 (95% CI 0.28–0.34) for sleep-related behaviors.[24] Lessons learned include that scalable phenotyping models, like most healthcare artificial intelligence (AI), require algorithm vigilance and debiasing prior to implementation.

From 2021 to 2024, the FDA and IC partnered with Oracle Health, John Snow Labs, National Jewish Health, and Children's Hospital of Orange County, on the "MOSAIC-NLP (Multi-source Observational Safety study for Advanced Information Classification using NLP)" project. The project aimed to demonstrate how unstructured EHR data, extracted using NLP tools, could help improve the validity of population-based pharmacoepidemiologic studies within linked healthcare claims and EHR data environments. As a use case, this study examined the association between montelukast treatment and the labeled risk of serious neuropsychiatric events for patients with asthma.

MOSAIC used deidentified linked EHR and claims data from the Oracle Health dataset.[25] Unstructured clinical notes underwent an NLP process using annotation guidelines and machine learning models to extract additional data elements to augment the structured data. Approximately 109,000 patients across 112 health systems met the inclusion criteria for the pharmacoepidemiology study; those patients had a total of more than 17 million clinical notes. A sample of 4,200 clinical notes were annotated and used to train named entity recognition NLP models. The models were applied to the final data set of more than 17 million notes to extract information for input into the pharmacoepidemiology study.

The NLP models utilized in the MOSAIC project efficiently abstracted the information with high precision for most entities across more than 17 million clinical notes. Overall, the proportion of patients with documented neuropsychiatric events increased moderately with the addition of structured EHR to claims data and increased considerably with the further addition of unstructured EHR, illustrating the value of linked data sources compared to claims data alone.

In an additional project aimed at evaluating automated phenotyping algorithms that can reduce development time and operator dependence compared to manually developed algorithms, IC investigators at Kaiser Permanente Washington and Vanderbilt University Medical Center evaluated

PheNorm applied to symptomatic COVID-19 disease to investigate its potential feasibility for rapid phenotyping of acute health conditions. Models at each institution achieved AUC, sensitivity, and positive predictive value of 0.853, 0.879, 0.851 and 0.804, 0.976, and 0.885, respectively, at quantiles of model-predicted risk that maximize F1 score (the harmonic mean of PPV and sensitivity).[26] This work established that the PheNorm approach could be applied at multiple study sites with substantially reduced overhead cost compared to traditional approaches, given that preliminary results for this work indicate that models trained at one site may be transportable to other sites with little decrease in performance.

3.2.2 Feature Engineering Table

Building on prior IC projects, an additional feature engineering project populated the newly developed feature engineering table with the concepts defined using free-text data from the commercial EHR-claims linked network and from the Development Network, with the aim of addressing certain ARIA system insufficiency scenarios. The Feature Engineering Table project was completed in Spring 2025. Key variables of interest may be absent from structured fields but recorded in free-text notes in EHRs because the information is not needed for billing or it is time consuming to enter in structured fields.

Natural language processing enables computational systems to transform free text into structured data fields using algorithms. Clinical text, in this case from EHR (e.g., progress notes), is processed, and the resulting features are made available for use as discrete or continuous variables that may be used in statistical models or in subsequent feature engineering to create more complex NLP features. The general procedure of transforming unstructured text documents to records within a common data model is one in which text is processed through one or more NLP pipelines, generating a set of “engineered features” from the NLP output (e.g., an assertion of the presence or absence of specific concepts), which can then be stored in the common data model alongside other information.

Therefore, this project aimed to populate the feature engineering table with the following concepts, which are not well captured in structured data: smoking status, suicide ideation/self-harm, anaphylaxis, substance use disorder, and obesity. Partner sites populating the table include TriNetX and the Sentinel Development Network (Duke University Health System, Vanderbilt University Medical Center, Kaiser Permanente Washington, and Mass General Brigham). The result of this activity is a feature engineering table comprised of individual features, identified through the Unified Medical Language System (UMLS), Systematized Nomenclature of Medicine (SNOMED), and/or International Classification of Diseases (ICD)-10 codes, linked to structured Sentinel data through the patient ID, and optionally an encounter ID.

3.3 Advancing Causal Inference

In a series of studies aimed at developing methods for evaluating data missingness patterns and identifying the best approaches to handle data missingness, IC investigators developed a systematic approach with three groups of diagnostics.[6,7,27,28] These methods have been publicly released as a readily reusable R package and are currently being used within the Sentinel IC projects. The same workgroup also proposed a cutting-edge approach to multiple imputations – termed the high dimensional multiple imputation (HDMI) – that is based on automatically identifying auxiliary variables from claims and EHRs to improve performance of multiple imputations.

3.3.1 Improving Confounding Adjustments Using EHR Data

Advancements in causal inference scientific methods could improve the FDA's regulatory decision making capacity. As regulatory decisions are often predicated on inferring causal relationships between medical product exposure and outcomes of interest, improving causal inference from real-world data for purposes of evaluating safety and effectiveness of medical products is an important goal of the Sentinel IC. Recent projects have aimed to improve causal inference through successfully addressing confounding adjustment and missing confounder data. The IC has evaluated the feasibility of improved confounding adjustment from ultra-high-dimensional data structures that include EHR-based variables through a combination of automated feature generation algorithms and advanced statistical and machine learning approaches for causal inference. Specifically, there has been recent interest in the use of regularized machine learning tools (e.g., Least Absolute Shrinkage and Selection Operator (LASSO)-based models) combined with targeted learning methods for improved large-scale covariate adjustment.[29] An IC workgroup used simulations to thoroughly evaluate the performance of the LASSO-based tools using linked EHR-claims data. The workgroup demonstrated that tuning the LASSO model for propensity score estimation using the principles of collaborative-controlled targeted learning achieved superior confounding control in settings involving ultra-high-dimensional data structures.[29] Complementary activities included development of a toolkit for routine assessment of missing confounder data from EHRs. Based on simulations and application in two empirical case examples, the project demonstrated that such assessments are feasible to conduct in a timely manner and can enhance confidence in analyses where important confounders are partially recorded in EHR databases.[6,7,27]

3.3.2 Subset Calibration Methods

The IC has also led the development of methods designed to address incomplete confounder information when assessing the safety of interventions. These methods leverage additional confounder data available on a subset of the study population where such information is missing from the larger population. The three approaches evaluated were multiple imputation, subset calibration through raking weights, and targeted maximum likelihood estimation.[30]

3.3.3 Negative Control Methods

Negative control variables can be incorporated into analyses to detect scenarios where observed covariate adjustment may not fully control confounding bias. One type of negative control variables is disconnected negative controls, which are variables associated with unmeasured confounders but not causally related to treatment or outcome.[31,32] Identifying disconnected negative control variables is time consuming, difficult to scale, and error-prone. Therefore, as part of the PDUFA VII commitment on "Use of Real-World Evidence,"[33] the FDA and the IC are conducting a methods development project to apply the data-driven automated negative control estimation (DANCE) algorithm, which automatically identifies disconnected negative controls, in settings typically used in Sentinel studies.[34] [33]

Two complementary studies are underway to test and implement the DANCE algorithm: 1) simulation study - evaluating and tailoring DANCE for large-scale healthcare database studies using plasmode simulation (Aim 1), and 2) empirical study - applying DANCE algorithm to a drug safety use case in multisite implementation (Aim 2). In the simulation study (Aim 1), plasmode simulation is used to maintain the complex covariate correlations from real-world data while creating simulated variables (unmeasured confounders, treatment, outcome, and negative controls). In the empirical study (Aim 2), the DANCE algorithm is being applied using data from Mass General Brigham and HealthVerity to a use case with a known positive association:

comparing risk of genital infections among SGLT-2 inhibitors versus DPP-4 inhibitors. These methods development studies were initially proposed at a public workshop in March 2023 and are anticipated to be completed by September 2027.

3.4 Culminating Use Case Demonstrations

The IC initiated a series of use case projects to demonstrate the practical utility of the RWE-DE and novel methodologies to supplement the ARIA system through the integration and use of granular clinical data.

One ongoing use case project aims to implement and refine a fitness-for-purpose assessment process that can be used to approximate the effort required for development of a health outcome of interest computable phenotype, as a function of scientific objective, clinical complexity, and data complexity. This fitness-for-purpose framework was developed through the application of the tool criteria to several health outcomes of interest, varying in complexity, for which claims-based algorithms alone are insufficient. This tool enables the RWE-DE to be used in a scalable way for medical product safety surveillance.

In a second use case project conducted from 2023 to 2024, the IC utilized the RWE-DE Commercial Network to conduct a protocol-based pharmacoepidemiologic analysis. This project addressed a safety concern that the ARIA system was previously deemed insufficient to assess due to inadequate capture of the health outcome of interest: acute pancreatitis. This use case was particularly relevant to the IC's recent methodological development, as there was an opportunity to apply a computable phenotyping algorithm for acute pancreatitis that was developed and validated in the RWE-DE Development Network's Kaiser Permanente Washington site. This algorithm was applied to assess the risk of acute pancreatitis following SGLT2 inhibitor use among patients with type 2 diabetes mellitus. In addition to enhancing the capture of the health outcome of interest, the study also identified previously unavailable covariates such as alcohol misuse and smoking from EHR data, potentially improving confounding adjustment. The project was able to address data missingness using previously honed IC methods such as multiple imputation, finding that an increase in risk of acute pancreatitis following SGLT2 inhibitor use was unlikely. Overall, this study demonstrates that the use of rich clinical information from EHR data sources, such as the RWE-DE for the identification of indications, outcomes, and confounders, can improve medical product safety surveillance assessments.

In addition to considering how the RWE-DE can address prior instances of the ARIA system insufficiency, additional use case projects aim to demonstrate how previous assessments conducted in the ARIA system can also be enhanced through the application of innovative methods using EHR data. These projects are ongoing and are scheduled to be completed in Spring 2025. The five specific aims of these projects include: 1) rapid evaluation of the balance of confounding factors unmeasured in claims data but measurable in EHR data; 2) correcting claims analyses for unmeasured confounding using subset calibration tools; 3) real-time outcome validation of code-based algorithms utilizing NLP-assisted chart validation techniques; 4) identifying use of cannabis-derived products from unstructured free-text notes using NLP; and 5) expanding on a principled quantitative bias analysis at the design stage to better assess potential unmeasured confounding.[35]

Regarding the fifth aim, an enhanced plasmode simulation methodology was applied in a quantitative bias analysis to assess the threats to validity of unmeasured confounding while addressing the limitations of simplistic simulations that rely on unrealistic assumptions.[36,37] This approach preserves the natural correlation patterns among multiple confounders and outcomes from real-world data, and is

particularly useful when investigators have access to some confounding variable measurements in a subset of the population. This approach was implemented using a case example of varenicline versus bupropion, both used for smoking cessation, on risks of neuropsychiatric hospitalizations (with suicidal ideation as an unmeasured confounder) and major adverse cardiovascular events (with body mass index, blood pressure, and smoking pack-years as unmeasured confounders). Results showed that claims-based variable adjustment provided relative bias close to zero for both outcomes, indicating that EHR-measured confounders were unlikely to cause strong residual confounding. This approach provides a practical method for quantifying bias in non-randomized studies by leveraging information on important potential confounding variables only available in a subset of the population. Of note, this simulation approach can be used at the design phase so the potential impact of unmeasured confounders can be assessed, and mitigation can be implemented before the study is initiated.

In summary, the Sentinel IC projects and resulting use cases enhance data infrastructure, explore novel approaches to create features from data, improve methods to control confounding, and enhance causal inference for pharmacoepidemiologic studies. These efforts showcase the success of innovative tools and methods that improve the FDA's ability to assess the safety and effectiveness of medical products, ultimately enhancing regulatory decision making.

4 Public Accessibility and Communications

4.1 Public Accessibility of Tools, Methods, and Results

The Sentinel System provides public access to the analytic tools used to both check quality and run analyses on data formatted in the SCDM. The public Git website is the primary platform for accessing the Sentinel System's analytic tools. A catalogue of available code and documentation resources is available in Sentinel's Analytic Tools.

The FDA is dedicated to transparency in its regulatory analyses. From 2022 to 2024, 221 results have been posted to the Sentinel System website, and 39 analytic packages (including all inferential analysis) have been posted to the Sentinel public Git. This offers the opportunity for investigators to replicate Sentinel analyses on local data sets. The Sentinel System's analytic tools enable users to identify potential medical product safety concerns, characterize populations of interest, analyze the use of medical products, and assess their impact on health outcomes.

4.2 Publications and Contributions to the Scientific Community

The FDA is dedicated to publishing results from the Sentinel System through academic journals and sharing information at relevant conferences. From 2022 to 2024, 51 papers presenting findings from Sentinel studies have been published in peer-reviewed journals such as *Pharmacoepidemiology Drug Safety, BMC Medical Research Methodology, American Journal of Epidemiology*, and more. See Appendix G for a complete list of Sentinel publications from 2022 to 2024.

Additionally, the FDA's Sentinel System enables substantial contributions to the scientific community through presentations at national and international conferences. From 2022 to 2024, 120 presentations

and posters have been presented at scientific conferences, sharing findings and lessons learned in medical product safety surveillance.

The FDA is also committed to promoting stakeholder engagement and increasing awareness of the Sentinel System tools and infrastructure. Sentinel's Community Building and Outreach Center (CBOC) was established in 2019 to support these efforts. The CBOC aimed to increase stakeholder engagement and awareness through various outreach and communication strategies, including a quarterly Sentinel newsletter, educational webinars, and a redesign of the Sentinel Initiative website to improve both user experience and access to publicly available resources. The CBOC operated through 2024, and since that time its core functions have been carried forward by the SOC.

4.3 Public Events

The Sentinel System uses various communication channels to connect with stakeholders, including trainings, webinars, and workshops. These channels enable the Sentinel System to engage with stakeholders in multiple ways.

The Sentinel IC hosts an IC Webinar series that features presentations by leading experts and innovators on topics relevant to the SOC and IC. From 2022 to 2024, the IC Webinar series hosted 37 webinars with topics ranging from Regional Health Information Exchanges as Critical National Infrastructure: Supporting Federal Agency Missions, Overview of CDER's Real-World Evidence Demonstration Projects, Data-driven Phenotyping Algorithms for Acute Health Conditions: Applying PheNorm to COVID-19, and more. All materials can be found on the Sentinel website:

- 2022 Sentinel Innovation Center and Webinar Series
- 2023 Sentinel Innovation Center and Webinar Series
- 2024 Sentinel Innovation Center and Webinar Series

From 2022 to 2024, the Sentinel System conducted four Annual Public Training events, which have been attended by federal regulators, industry experts, and scholars. The subjects covered have ranged from research on maternal health and pregnancy to Inverse Probability of Treatment Weighting (IPTW). The materials can be found on the Sentinel website:

- 2023 Sentinel Public Training: Signal Identification Among Infants Following Maternal Medication Use During Pregnancy & Innovation Day
- 2022 Sentinel Public Training Day: Inverse Probability of Treatment Weighting & Innovation Day

Annual Public Workshops have been hosted by the Duke-Margolis Institute for Health Policy under a cooperative agreement with the FDA. These events aim to promote engagement and collaboration with patients, industry, academia, and consumers, reinforcing existing partnerships and cultivating new relationships. The SOC has partnered with the Duke-Margolis Institute for Health Policy on six public workshops since 2019. Sentinel's online Training Center offers open and long-term access to training content.

5 Conclusion

The FDA's Sentinel System continues to play a crucial role in advancing the agency's mission to protect public health. From 2022 to 2024, the Sentinel's ARIA system has provided comprehensive monitoring and assessment of medical product safety and contributed to key regulatory actions and discussions, including informing product labeling and contributing data discussed at FDA Advisory Committee meetings.

The FDA remains committed to expanding the Sentinel System's capabilities, as demonstrated by recent enhancements in analytic and data infrastructure, exploration of new data sources, and development of novel methodological approaches for causal inference. Looking ahead, the Sentinel System is well-positioned to respond to new and emerging public health trends while maintaining its foundational scientific rigor.

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Appendices

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

Abbreviation	Definition
ADHD	Attention-deficit/hyperactivity disorder
ANC	Absolute neutrophil count
AUPRC	Area under the precision-recall curve
ARIA	Active Risk Identification and Analysis
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
CMS	Center for Medicare and Medicaid Services
DEA	Drug Enforcement Administration
DKA	Diabetic ketoacidosis
EHR	Electronic health record
EUA	Emergency Use Authorization
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FD&C Act	Federal Food, Drug, and Cosmetic Act
HCA	HCA Healthcare
HHS	Department of Health and Human Services
HIE	Health Information Exchange
HIO	Health Information Organization
IC	Innovation Center
IPTW	Inverse Probability of Treatment Weighting
LASSO-based models	Least Absolute Shrinkage and Selection Operator-based models
MOSAIC	Multi-source Observational Safety study for Advanced Information Classification
NDA	New Drug Application
NDI	National Death Index
NISS	Newly Identified Safety Signal
NMEs	New molecular entities
NIH	National Institutes of Health
NLP	Natural language processing
NMEs	New molecular entities
PDUFA	Prescription Drug User Fee Act
PEP	Post-exposure prophylaxis
PMR	Postmarketing Requirements
REMS	Risk Evaluation and Mitigation Strategy

RWD	Real-world data
RWE	Real-world evidence
RWE-DE	Real-World Evidence Data Enterprise
SCDM	Sentinel Common Data Model
SDD	Sentinel Distributed Database
SGLT2	Sodium-glucose cotransporter-2
SOC	Sentinel Operations Center
TSI	Tracked Safety Issue
UMLS	Unified Medical Language System

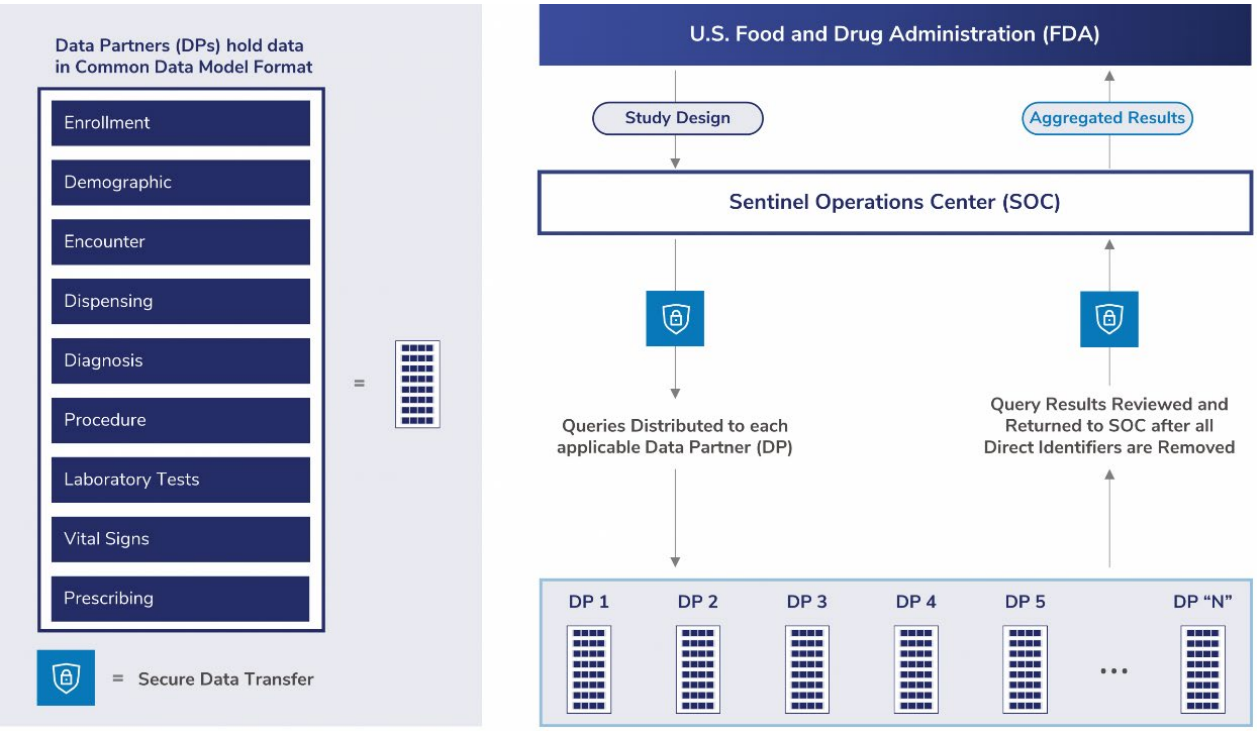
Appendix B. The Active Risk Identification and Analysis (ARIA) System's Data Resources and Tools

At the heart of the Sentinel System is the ARIA system, which provides the FDA with access to a wide range of data sources and analytic tools. The ARIA system is comprised of two main components – the SDD, which consists of electronic healthcare data formatted in the SCDM, and SAS-based computer programs that equip the FDA with tools to analyze these data. These components are described in further detail below.

The Sentinel Distributed Database (SDD)

The SDD provides the FDA with access to a network of Data Partners that supply administrative healthcare claims, claims linked to electronic healthcare data (EHR), Medicare fee-for-service claims, and Medicaid claims. All data are formatted into the SCDM. Figure 4 illustrates how the SDD is organized.

Figure 4. A Combined Collection of Datasets: The Sentinel Distributed Database. *This figure illustrates Sentinel's distributed data approach.*



As of April 2024, the SDD encompassed over 1.3 billion person-years of data, representing over 371 million unique patient identifiers with over 24 billion unique medical encounters spanning from 2000 to 2024. Notably, the SDD includes around 11.8 million infant deliveries linked to their mothers. Additional metrics characterizing the SDD are regularly updated in the Key Database Statistics.

Since 2022, the number of mother-infant linked deliveries in the SDD has more than doubled, largely due to the integration of Medicaid data from the Centers for Medicare & Medicaid Services (CMS). Medicaid currently finances care for about 42% of all births in the United States, and nearly two-thirds of adult women enrolled in Medicaid are of reproductive age (aged 19 – 44 years). This makes Medicaid data an essential resource for analyzing maternity care and birth outcomes.[38] Notably, the Medicaid population differs significantly from those covered by commercial insurance in terms of demographic and socioeconomic characteristics, offering unique insights into maternal health.

Another significant milestone was the successful linkage of National Death Index (NDI) data with CMS Medicare and Medicaid records, as well as with a specific cohort from two national insurers. This enhancement expanded the number of individuals with fact-of-death data from 36.9 million to 41.3 million across the entire SDD. Additionally, the number of records with cause-of-death information increased from 4.2 million to nearly 82.4 million.

The SDD comprises claims and claims-linked-to-EHR data, which Sentinel Data Partners standardized into the SCDM. Each Data Partner maintains and stores their data locally, ensuring data control and patient confidentiality. All datasets undergo a rigorous quality assurance process, described next.

Data Quality in the Sentinel System

The Sentinel System's data quality review and characterization process is a collaborative effort between the SOC and Sentinel Data Partners. Due to the distributed structure of the Sentinel System, it is critical that each Data Partner ensures their data is accurately transformed according to the specifications of the SCDM. This consistency enables distributed analytic tools to run seamlessly and ensures that results can be reliably aggregated across Data Partners.

To support this process, the SOC develops and maintains a comprehensive quality review and characterization software package. Data Partners run this software on their refreshed databases before making them available for studies. The tool checks more than 900 parameters, generating a detailed list of errors and anomalies for the Data Partner to review and address. These are categorized into three levels of check – Level 1, Level 2, and Level 3 – as depicted in Figure 5.

Figure 5. Type of Data Quality Checks and Examples

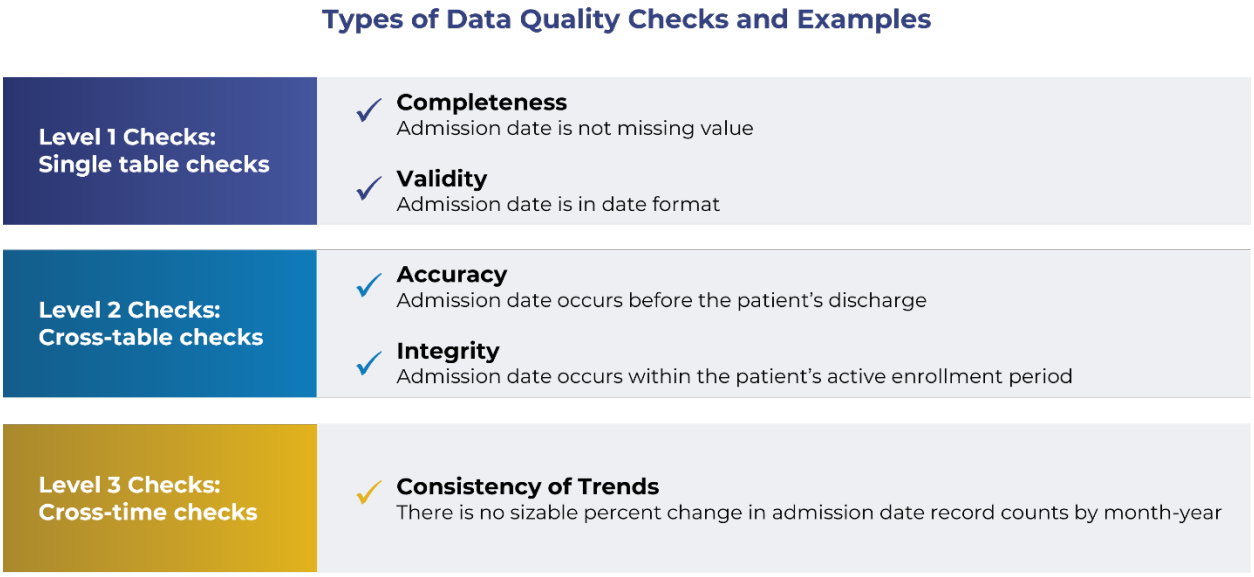
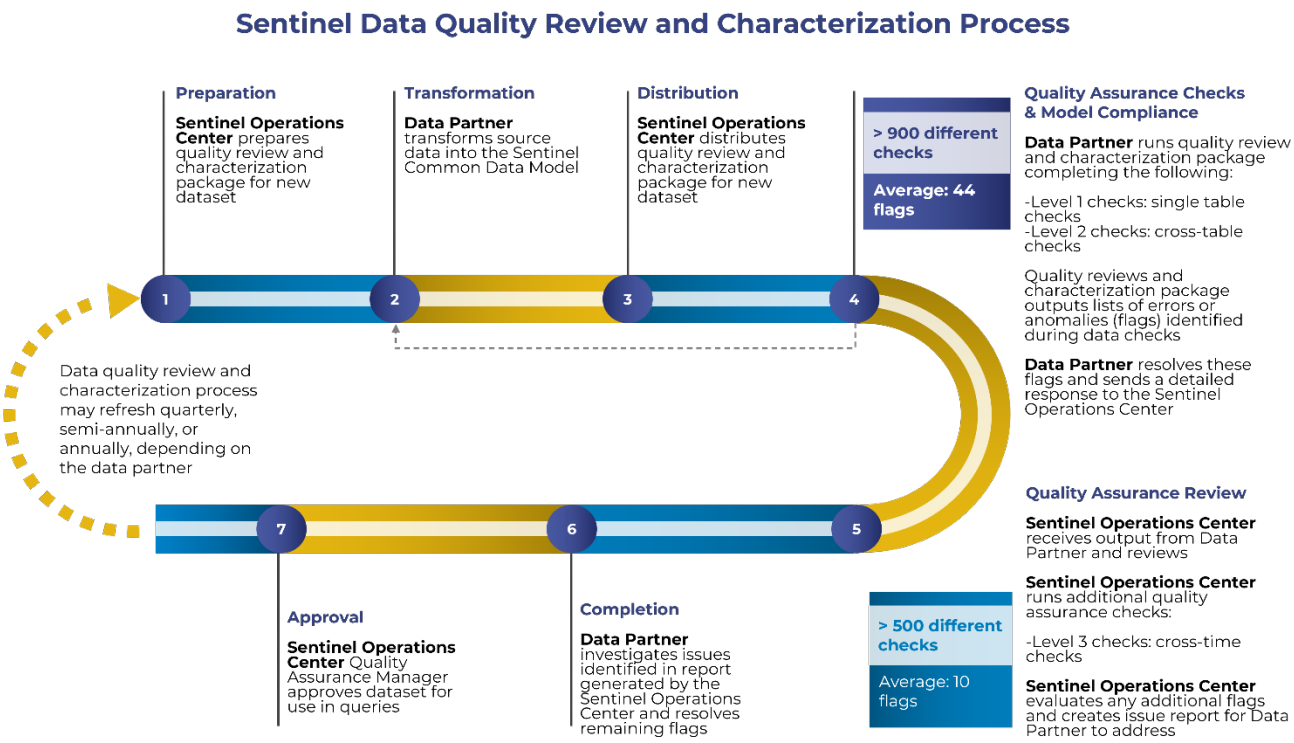


Figure 6 (below) illustrates the complete data quality review and characterization process.

Figure 6. Sentinel Data Quality Review and Characterization Process. *The data quality review process is a joint effort between Sentinel and its Data Partners, ensuring that Sentinel data are of the highest quality.*



The Sentinel Common Data Model (SCDM)

The SCDM is a standardized structure and format for electronic healthcare data, enabling consistent analysis across multiple sites using the same analytic code. Its design prioritizes data quality, data integrity, comprehensive documentation, and usability for a broad range of stakeholders, including the FDA, industry, and academic researchers. Specifications for the SCDM are available to the public.

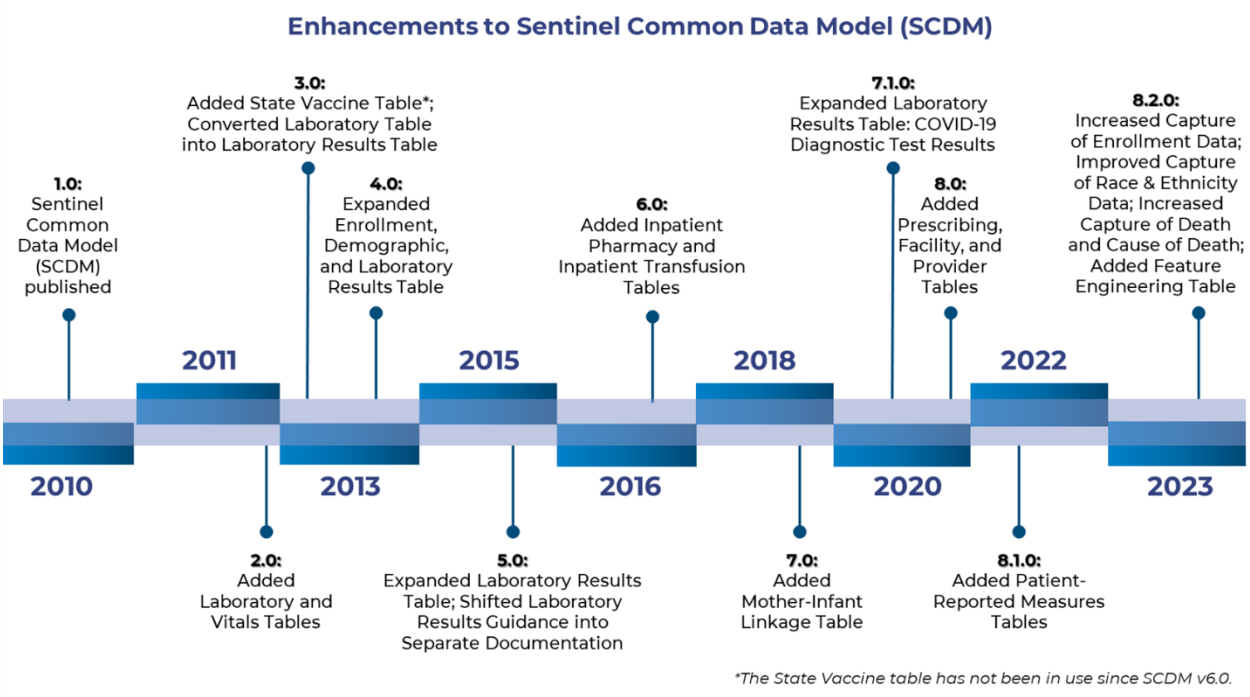
A key feature of the SCDM is its commitment to data integrity, achieved by preserving data elements from the original source data. This approach prevents the loss of detail often associated with data mapping and serves as the closest analogue to primary data collection, such as that used in clinical trials. As a result, the FDA gains greater flexibility in study design and a clearer understanding of the data supporting regulatory decision making.

The SCDM supports a wide range of coding terminologies, including those used by international collaborators, allowing native data streams to retain their original formats. It is also grounded in the concept of health system enrollment, which facilitates longitudinal studies by ensuring comprehensive capture of patient information over time.

This model aligns with the FDA's rigorous standards for observational data, particularly the need for complete capture of exposures and adverse outcomes in studies intended to support causal inference in pharmacoepidemiologic research.

Over time, the SCDM has evolved and expanded to enhance the FDA's ability to investigate a broader array of exposures and outcomes of interest. Figure 7 illustrates key enhancements that have strengthened the model's capacity to support real-world evidence (RWE) generation.

Figure 7. Enhancements to Sentinel Common Data Model (SCDM)



Notably, from 2022 to 2024, the FDA has prioritized RWE initiatives aimed at improving the SCDM's ability to capture and classify clinical data – whether structured, semi-structured, or unstructured. Key enhancements included:

- **Integration of patient-reported measures** from clinically validated instruments, such as the Patient Health Questionnaire-9 screening tool for depression screening and the Physical Activity Vital Sign tool for assessing adult physical activity.
- **Expanded support for Logical Observation Identifiers Names and Codes (LOINC)-coded laboratory tests or procedures.**
- **Inclusion of CDC vaccine codes** to enable the tracking of vaccinations, including COVID-19 vaccines, influenza, and others.
- **Capability to incorporate outputs from natural language processing (NLP)** applied to unstructured clinical data.

In addition, the SCDM has been refined to improve the capture of data elements that were previously underrepresented in the SDD. These refinements include:

- **Expanded race and ethnicity categories**, enabling imputation using methodologies such as the imputation algorithm developed by Research Triangle Institute (RTI) to improve the accuracy of race and ethnic coding.[39]
- **New mechanisms to capture death and cause-of-death** from non-traditional sources, such as obituaries and social media, using machine learning probabilistic algorithms.[40]

These enhancements have significantly broadened Sentinel's study capabilities. Each update to the SCDM is designed to meet specific FDA needs or to strengthen the ARIA system.

A summary of the benefits from major enhancements is provided in Table 9.

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

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

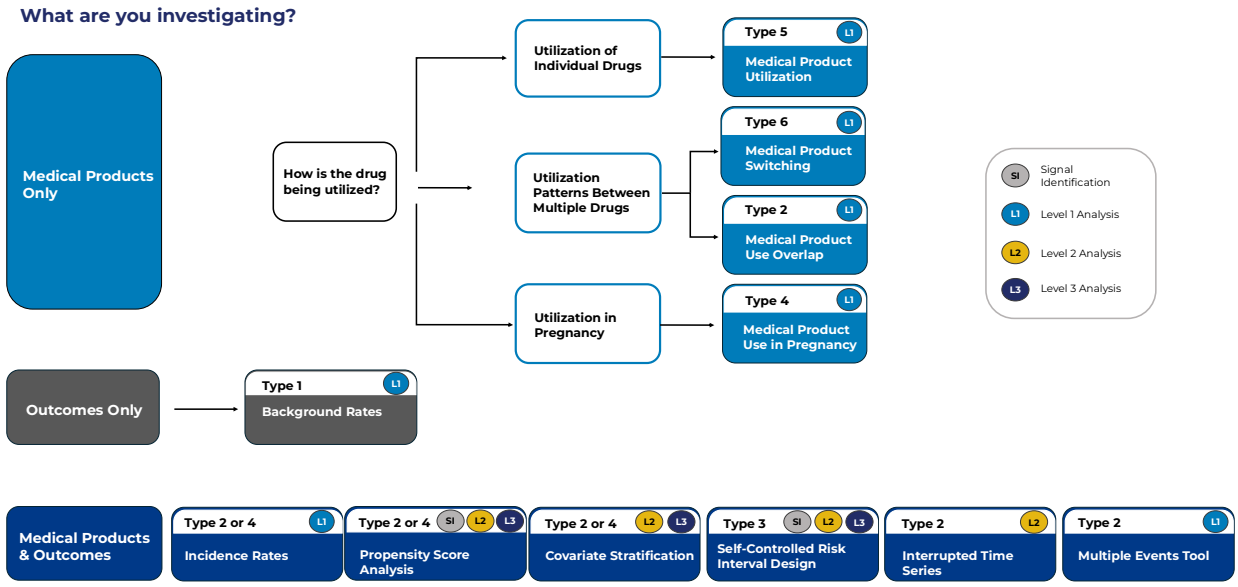
Year	Major Enhancement	Program Benefits
		and the Physical Activity Vital Sign tool to assess physical activities in adults.
2023	Addition: Feature Engineering Table	• Enables utilization of data derived from EHR unstructured data sources via Natural Language Processes methods (NLP) developed in the IC.
	Expansion: Imputed race and ethnicity	• Allows for more accurate capture of the source of race and ethnicity when included from an imputation algorithm compared to self-reported data.[39]
	Expansion: Plan and payer types	• Allows characterization of enrollment types (e.g., Fee-for-service, managed care) to identify disparities in exposure and outcomes by insurance plans and payers.

Sentinel's Analytic Tools

The Sentinel System offers a comprehensive suite of analytic tools that enable the FDA investigators and other users to efficiently design and implement medical product safety analyses. Analytical approaches are classified into distinct types based on the nature of the investigation – specifically if the focus is solely on outcomes or involves both medical products and outcomes. For instance, analyses examining drug utilization patterns fall under Medical Product Utilization (Type 5), while studies assessing medication use during pregnancy are categorized as Medical Product Use in Pregnancy (Type 4). Figure 8 provides an overview of all the types of the Sentinel System's analyses. These tools are reusable, highly adaptable, and can parameterize a wide range of pharmacoepidemiologic study designs. Sentinel analyses are structured across three levels: Level 1 provides descriptive analyses; Level 2 supports comparative analyses; and Level 3 facilitates prospective sequential surveillance. The underlying SAS code for Sentinel's analytic tools is publicly accessible and is accompanied by detailed documentation to assist both internal and external users of the Sentinel System:

- Sentinel Routine Querying System
- Sentinel Routine Querying System Documentation
- Sentinel Query Request Package Reporting Tool
- Sentinel Routine Querying Reporting Tool Documentation
- Sentinel's Analytic Lookup Files Program Repository
- Quality Assurance Package
- Quality Assurance Mother-Infant Linkage (MIL) Package
- Quality Assurance Package Documentation
- Sentinel Common Data Model

Figure 8. What Routine Querying Tool Should You Use?



The FDA may utilize any of the Sentinel System's analytic modules to investigate medical product safety concerns. Table 10 provides a summary of how specific modules have been employed in FDA analyses.

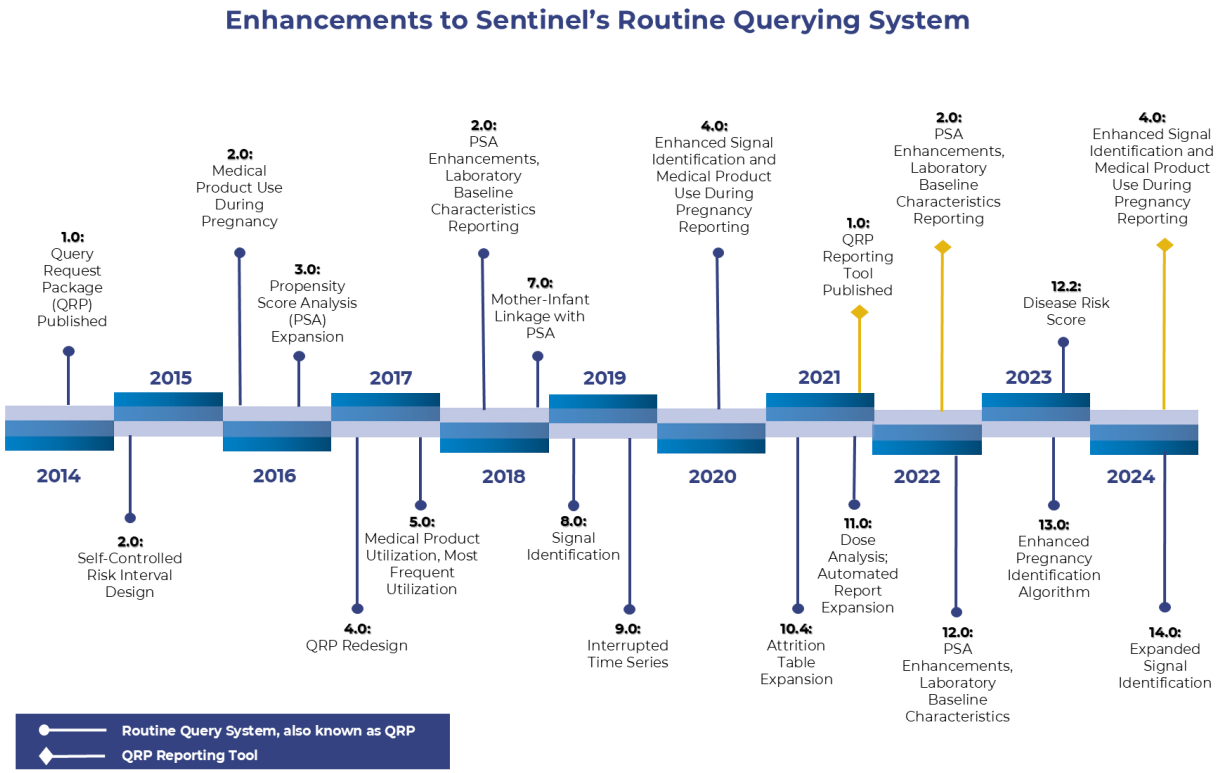
Table 10: Utilization of Sentinel's Analytic Modules, 2022 to 2024

Module Category	Analytic Module	Number of Analyses
Descriptive	Incidence Rates (including concomitant use and multiple events)*	38
	Medical Product Utilization*	29
	Background Rates	27
	Medical Product Use in Pregnancy	14
	Medical Product Switching	0
Comparative Analytic Modules	Propensity Score Analysis (PSA) Modules	32
	PSA with Inverse Probability of Treatment Weighting	13
Signal Identification	Propensity Score Analysis	8
	Self-Controlled Risk Interval Design	5
Patient-Level Line Lists	Patient Episode Profile Retrieval	11

**Two analyses were conducted using both Product Utilization and Incidence Rates modules and are counted in both rows.*

The Sentinel System's analytic tools have been progressively refined to more effectively support the FDA's evolving needs in safety surveillance (Figure 9).

Figure 9. Enhancements to Sentinel's Routine Querying System



Notably, from 2022 to 2024, the FDA prioritized several key enhancements to the Sentinel System's analytic tools:

- **Enhancements to Assess Medical Product Safety in Pregnancy**
  In 2023 and 2024, several enhancements were made to improve the evaluation of perinatal exposures and outcomes for both mothers and infants. The algorithm used to identify pregnancy episodes was updated to include pregnancies ending in non-live births (e.g., stillbirths). Additionally, the tool was expanded to assess medical product use during the postpartum period, offering insights into medication use by new mothers. New user options were introduced to define covariates and cohort entry criteria relative to either the start or end of pregnancy, allowing for more clinically relevant analyses. Finally, support for time-to-event analysis of maternal outcomes was added, complementing the existing binary outcome approach.

- **Enhancements for Signal Identification using TreeScan™**
  In 2019, the Sentinel System introduced the capability to conduct signal identification analysis using tree-based scan statistics, following a public training session in 2018. This method detects statistically elevated rates of adverse health outcomes following

exposure to a medical product – without the need to pre-specify outcomes – enabling early identification of potential safety concerns. As a hypothesis-generating approach, it is typically followed by further investigation, such as a clinical review or a targeted pharmacoepidemiologic study. The Sentinel System utilizes TreeScan™, a free publicly available data-mining software that supports various tree-based scan statistical methods for analyzing large datasets.

In 2024, enhancements were made to improve confounding control in these analyses. Specifically, the tools were updated to support propensity score stratification or Inverse Probability of Treatment Weighting (IPTW) for studies involving maternal/infant outcomes post-pregnancy and for studies involving all outcomes in non-pregnant women. These additions strengthen the Sentinel System's ability to detect signals involving rare exposures (e.g., newly marketed drugs) or small populations (e.g., pregnant women).

- **Enhancements to Enable Customized Patient Risk Computation**
  Sentinel's analytic tools have been enhanced to calculate a range of pre-defined risk scores and support the easier implementation of custom scores. These scores help characterize analytic cohorts by estimating patient health risks, such as major bleeding or diabetes complications, and can be incorporated into propensity score models to better control for disease severity.

  Newly supported pre-defined risk scores include:
  - HAS-BLED (major bleeding risk)[41]
  - CHA2DS2-VASc (stroke risk in atrial fibrillation)[42]
  - Obstetric Comorbidity Index[43]
  - Claims-Based Frailty Index[44]
  - Adapted Diabetes Complications Severity Index[45]
  - Pediatric Comorbidity Index[46]

  Users can also define additional custom risk scores as needed.

- **Enhancements to Improve Capacity for Laboratory Data Analysis**
  A subset of SDD Data Partners provides clinical laboratory results. Previously, Sentinel's analytic tools used laboratory data only to define exposures, outcomes, and cohort criteria. In 2022, enhancements to the tools expanded this functionality, allowing laboratory results to be used as covariates. This enables inclusion of laboratory values in cohort definitions and baseline tables. Newly supported laboratory concepts include SARS-CoV-2 test results, glucose levels, and international normalized ratio (INR), among others.

- **Enhancements to Conduct Propensity Score Analyses**
  Enhancements made in 2022 to the propensity score modules significantly improved the accuracy and reliability of treatment effect analyses. Key updates include the introduction of weighted Kaplan-Meier curves for more precise time-to-event analysis, robust tests for the proportional hazards assumption to validate model assumptions, enhanced subgroup analyses for more granular effect estimation, and the Firth

correction to reduce potential bias in small-sample models. Together, these improvements offer a more nuanced and dependable assessment of treatment effects.

Appendix C. Additional Electronic Healthcare Record (EHR) Data Resources in the Sentinel System

To enhance the capabilities of the ARIA system in conducting pharmacoepidemiologic studies, additional data resources and their associated analytic tools are employed. A detailed overview of these resources and tools is provided below.

Sentinel Real-World Evidence Data Enterprise (RWE-DE)

The Sentinel IC's RWE-DE aims to enhance the ARIA system by integrating EHR data linked with healthcare insurance claims. This integration addresses key limitations of the ARIA system, particularly its lack of detailed clinical information, which has historically constrained the system's ability to accurately identify certain exposures, outcomes, indications, or covariates in pharmacoepidemiologic studies.[20,21]

The RWE-DE comprises two components:

- **The Commercial Network**, which includes two commercial EHR-claims linked data assets (TriNetX, HealthVerity)
- **The Development Network**, which includes four academic institutions (Mass General Brigham, Duke University Health System, Vanderbilt University Medical Center, and Kaiser Permanente Washington)

These networks are illustrated in Figure 10, while Figure 11 details the types of data available in the RWE-DE and their mapping to the SCDM.

The Commercial Network offers broad population coverage, with over 21 million lives represented. The commercial partners, TriNetX and HealthVerity, were selected after a systematic review and completion of a descriptive analysis based on their ability to:

1) Link EHRs with closed insurance claims data for longitudinal tracking of over 10 million patients
2) Represent diverse care settings via HealthVerity, which primarily covers ambulatory care, and TriNetX, which emphasizes hospital-based care
3) Support flexible data governance, enabling Sentinel investigators to access source data within the SCDM

Specifically, HealthVerity includes ambulatory care EHRs from three sources linked to closed medical claims from over 150 payers and closed pharmacy claims from a major pharmacy benefit manager (2018 – 2019). TriNetX includes inpatient and ambulatory care EHRs from 20 unique healthcare organizations,[47,48] linked to closed claims from over 150 payers (2010 – 2023). Both partners also provide access to free-text clinical notes for select subsets.

The Development Network offers the opportunity to directly access granular clinical data including free-text notes with minimal restrictions through institutional affiliation of academic investigators. The data assets include:

- Mass General Brigham (EHRs linked to national Medicare and Medicaid claims)

- Duke University Health System (EHRs linked to Medicare claims)
- Vanderbilt University Medical Center (EHRs linked to Tennessee Medicaid claims)
- Kaiser Permanente Washington (EHRs linked to its own insurance claims)

Together, the Development Network contributes data on 4.5 million lives. All data from both networks are harmonized into the SCDM.

By incorporating EHR-linked claims data, the RWE-DE significantly expands the Sentinel System's ability to capture granular clinical details. This advancement improves the validity of medical product evaluations and broadens the scope of research questions that can be addressed using the Sentinel System's real-world data.

Figure 10. The Sentinel RWE-DE Based on EHR + Claims Data

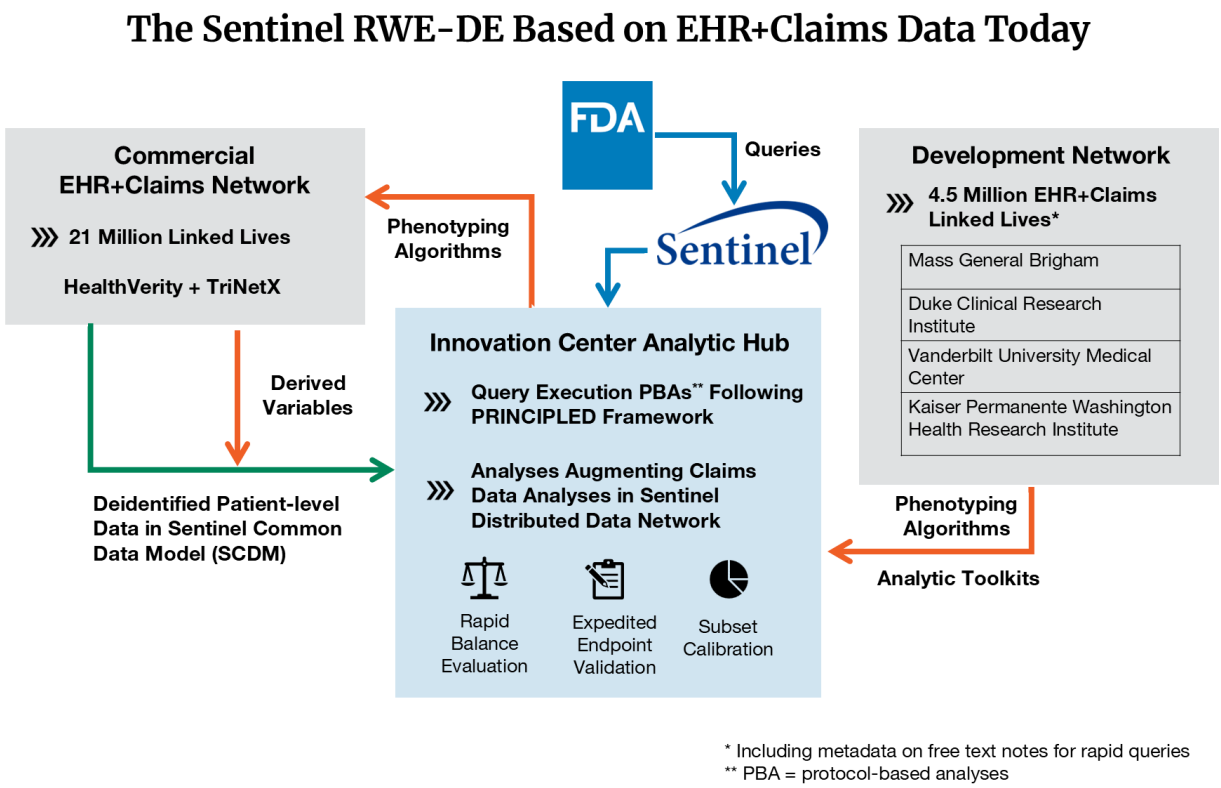
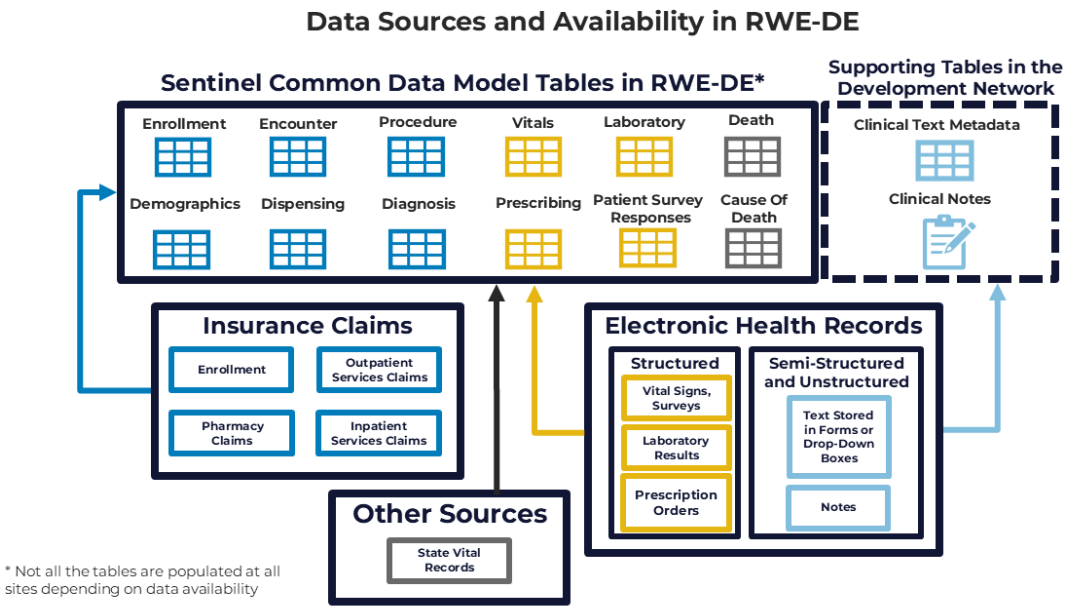


Figure 11. Data Sources in the RWE-DE



TriNetX LIVE™ Platform

The TriNetX LIVE™ Platform and TriNetX LIVE™ Regional Networks offer access to EHR data contributed by a broad network of healthcare organizations. These organizations, which are independently operated and not owned by TriNetX, collectively contribute approximately 150 million patient records. Most contributors update their data at regular intervals – typically every one, two, or four weeks – ensuring timely access to near real-time clinical information. The FDA began leveraging use of this resource during the COVID-19 pandemic to support initiatives requiring the most current EHR data available.

The TriNetX LIVE™ Platform features a user-friendly graphical interface that enables users to query the TriNetX LIVE™ Regional Networks to define study cohorts, review cohort characteristics, and conduct advanced analyses. Under the Sentinel System, the FDA maintained active licenses to routinely query the TriNetX LIVE™ Regional Networks during specific periods to meet regulatory needs.

HCA Healthcare

HCA Healthcare (HCA) serves a Sentinel Data Partner providing inpatient EHR data to the Sentinel System on an as-needed basis. Representing approximately 6% of all inpatient care in the United States, HCA operates 182 hospitals nationwide.

During the COVID-19 pandemic, HCA provided frequently refreshed inpatient data from a subset of its hospitals to support the FDA's efforts to understand the clinical progression of COVID-19 and to support evaluation of the safety and effectiveness of COVID-19 treatments in real-world patient populations.

The dataset used for this COVID-19 work spanned from January 2020 through June 2024, covering 142 HCA hospitals across 18 states, with significant representation from Texas, Florida, Virginia, and Colorado. To ensure database completeness, only records from discharged patients with complete billing information were included.

The database included information on:

- Diagnoses and procedures recorded during inpatient stays
- Patient demographics, including self-reported race (available for over 90% of patients)
- Medication use during inpatient stays, including frequency and timing of administration
- Self-reported medication use prior to admission and post-discharge
- Selected laboratory results, including SARS-CoV-2 test results and other relevant lab tests for targeted analyses

Appendix D: Comprehensive List of Sentinel System Studies (2022 to 2024), Including Analyses, Safety Concerns, and Impacts

See accompanying Excel file "*An-Assessment-of-the-Sentinel-System_2022-to-2024_Comprehensive-List-of-Sentinel-System-Studies.xlsx*" for a comprehensive list of the Sentinel Studies supported from 2022 to 2024.

This dataset categorizes Sentinel System studies into two groups – or tabs, in the Excel file:

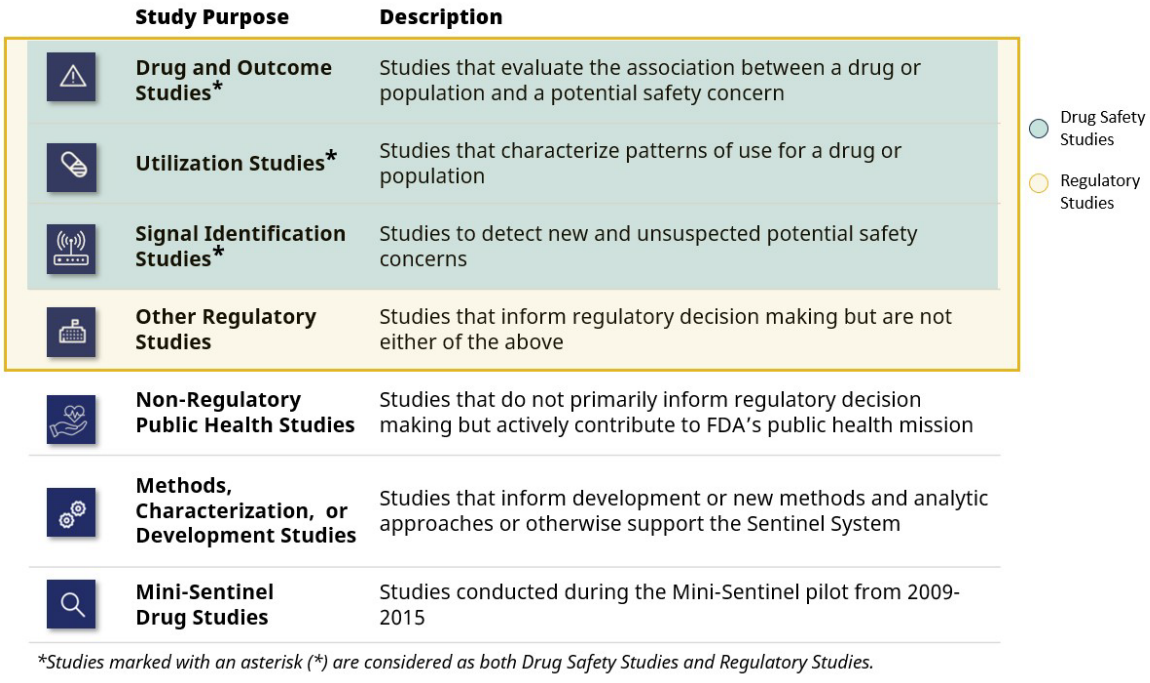
1) **Active**: studies actively under evaluation, or with future evaluations anticipated, as of December 31, 2024
2) **Completed**: studies completed between 2022 to 2024

For each study, the following supporting information is provided:

Data Element	Description
Study	The title of the Sentinel System study. When available, the title links to the corresponding Drug Study webpage on the Sentinel Initiative website. Studies in early stages of evaluation may be listed as "Non-Public Information." The syntax will carry over to additional data elements for the study.
Study Purpose	The FDA's intent for initiating the study categorized as: • *Regulatory – Drug and Outcome Studies* • *Regulatory – Utilization Studies* • *Regulatory – Signal Identification Studies* • *Regulatory – Other Regulatory Studies* • *Non-Regulatory Public Health* • *Methods, Characterization, or Development* Descriptions of these study types are available in Figure 12.
Analyses Supported (2022 to 2024)	All analyses conducted within the Sentinel System in support of the study between 2022 and 2024. Analyses conducted prior to 2022 are excluded. For a complete history, refer to the study's Drug Study webpage.
Associated Analytic Module	The analytic module used for analyses conducted with Sentinel's Query Request Package (QRP) tool. Modules include: • *Background Rates* • *Exposures and Follow-Up Time* • *Medical Product Use During Pregnancy* • *Medical Product Utilization* • *Self-Controlled Risk Interval Design*

Data Element	Description
	• *N/A:* the analysis did not use the standard Sentinel QRP tool (e.g., TriNetX Network)
Medical Product(s) Under Evaluation (ATC Terminology)	The medical product(s) evaluated in the Sentinel System study, classified using the World Health Organization (WHO)'s Anatomical Therapeutic Chemical (ATC) terminology. Note the following definitions of supporting values: • *Other*: a product is pertinent to the safety concern but is not well-represented by ATC terminology • *N/A*: no specific product is associated with the safety concern
Outcome(s) Under Evaluation (MedDRA Terminology)	The outcome(s) evaluated in the Sentinel System study. Outcomes are reported using the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)'s Medical Dictionary for Regulatory Activities (MedDRA) terminology. Note the following definitions of supporting values: • *Other*: an outcome is pertinent to the safety concern but is not well-represented by MedDRA terminology • *N/A*: no specific outcome is associated with the safety concern
Study Impact	For completed Sentinel System studies, the observed impacts resulting from the study. For more information on Sentinel System study impacts, please consult Appendix E.

Figure 12. Sentinel Study Purpose



	Study Purpose	Description
	Drug and Outcome Studies*	Studies that evaluate the association between a drug or population and a potential safety concern
	Utilization Studies*	Studies that characterize patterns of use for a drug or population
	Signal Identification Studies*	Studies to detect new and unsuspected potential safety concerns
	Other Regulatory Studies	Studies that inform regulatory decision making but are not either of the above
	Non-Regulatory Public Health Studies	Studies that do not primarily inform regulatory decision making but actively contribute to FDA's public health mission
	Methods, Characterization, or Development Studies	Studies that inform development or new methods and analytic approaches or otherwise support the Sentinel System
	Mini-Sentinel Drug Studies	Studies conducted during the Mini-Sentinel pilot from 2009-2015

**Studies marked with an asterisk (*) are considered as both Drug Safety Studies and Regulatory Studies.*

Appendix E: Definitions of Sentinel Study Impacts

The FDA assesses the regulatory impacts of a Sentinel study upon its completion. This appendix includes the following regulatory impacts:

Study Impact	Definition
Labeling Change, including: Adverse Reactions Warnings and Precautions Boxed Warning Contraindications Use in Specific Populations (e.g., Pregnancy and Lactation) Drug Interactions Medication Guide Patient Package Insert Other Label Section	Sentinel data contributed to a Drug Safety-related Labeling Change (SrLC).
Product Withdrawal	Sentinel data contributed to withdrawal of approval of a marketing application of a medical product.
Supported FDA response to a public inquiry	Sentinel data supported a FDA response to a public inquiry including, but not limited to, a Citizen Petition or Congressional inquiry.
Drug Safety Communication	Sentinel data contributed to a FDA Drug Safety Communication issued via the FDA's MedWatch: The FDA Safety Information and Adverse Event Reporting Program.
FDA Advisory Committee Meeting	Sentinel data were presented at a FDA Advisory Committee (AC) meeting or included in the AC meeting background materials.
Contributed to a Tracked Safety Issue (TSI)/Newly Identified Safety Signal (NISS)	Sentinel data contributed to a TSI or NISS at the opening, pre-evaluation, or evaluation stage.
Informed Other Agency Request	Sentinel data were utilized by an agency external to the FDA, including the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), or a Government Accountability Office (GAO) report, among others.
Informed pre-approval product development	Sentinel data were utilized by the FDA to inform product development activities, such as to support recommendations on drug development or clinical trial development. These include analyses conducted outside the context of a drug application review, often to describe the epidemiology of disease, risk factors, or background rates.

Study Impact	Definition
Informed Feasibility or Utility of an Ongoing Postmarket Requirement (PMR)	Sentinel data contributed insights into ongoing PMRs.
Informed New Drug Application (NDA) or Biologics License Application (BLA) Review	Sentinel data informed an ongoing NDA or BLA review for a medical product.
Aided the Agency's Evaluation of a Postmarket Risk Evaluation and Mitigation Strategy (REMS)	Sentinel data contributed to the Agency's evaluation of a postmarket Risk Evaluation and Mitigation Strategy (REMS).
Supported Monitoring for New Safety Signals	Sentinel data supported the monitoring of new or unexpected safety signals as a function of routine pharmacovigilance activities.
FDA Determined No Regulatory Action Needed, Based on Available Evidence	The FDA determined that no new action was necessary at the time, based on the available information obtained from the Sentinel System.
Other Regulatory Action	Sentinel data contributed to a regulatory impact that is not best represented by the options above including, but not limited to: • Helped with the identification and selection of the PDUFA VII demonstration projects products • Contributed to regulatory discussions about the use of oxymorphone drugs, including the product Opana ER which was withdrawn from the market • Results shared with FDA's nitrosamine task force • Provided use information on an unapproved use of a medical product • Assisted the review of requests for orphan drug designations • Contributed to CDC HAN Alert, 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, issued April 25, 2022 • Provided data on patterns in inpatient utilization of dexamethasone and other corticosteroids during the COVID-19 pandemic to inform strategies for allocating existing corticosteroid drug supplies.

Study Impact	Definition
	• Data helped monitor the availability for critical drugs (including to understand the impact on supply chain and potential for shortages), gain insight into clinical practice patterns, and understand regional differences in standard of care. • Provided descriptive data of the dexamethasone doses used in hospitalized COVID-19 patients[14]
Included Safety Concern for Which ARIA was Ultimately Deemed Insufficient for Assessment	While at least one analysis was conducted in the ARIA system, the results suggested that the ARIA system is insufficient to evaluate the study question of interest.
Other non-regulatory impact to FDA's public health initiatives	The study purpose was neither regulatory nor methods, but Sentinel data supported FDA's mission to protect public health.

Appendix F: Comprehensive List of Sentinel System Safety Concerns (2022 to 2024)

See accompanying Excel file "*An-Assessment-of-the-Sentinel-System_2022-to-2024_Comprehensive-List-of-Safety-Concerns.xlsx*" for a detailed list of the Sentinel System safety concerns newly identified between 2022 and 2024.

For each safety concern, the following supporting information is provided:

Data Element	Description
Safety Concern Year	The year in which the Sentinel System safety concern was identified.
Medical Product Under Evaluation – Generic Name	The medical product(s) evaluated in the Sentinel System study. Products are reduced to nonproprietary (generic) names only, if applicable.
Medical Product Under Evaluation – Brand Name	The brand names of medical product(s) evaluated in the Sentinel System study, if applicable.
Outcome Under Evaluation	The outcome evaluated in the Sentinel System study, if applicable.
Study Purpose	The FDA's intent for initiating the study categorized as: • *Regulatory – Drug and Outcome Studies* • *Regulatory – Utilization Studies* • *Regulatory – Signal Identification Studies* • *Regulatory – Other Regulatory Studies* • *Non-Regulatory Public Health* • *Methods, Characterization, or Development*
ARIA Sufficiency	For safety concerns considered for evaluation in the ARIA system, this value represents the final determination of whether the safety concern could be studied: • *Sufficient* • *Insufficient* • *N/A: this value represents methods, characterization, or development work, as well as use of non-ARIA system data sources (i.e., EHR data sources)*
Study Status	The status of the Sentinel System study evaluating the safety concern: • *Active*: studies actively under evaluation, or with future evaluations anticipated, as of December 31, 2024 • *Completed*: studies completed between 2022 to 2024 • *Grey shading:* The ARIA system is insufficient for study of these safety concerns

Data Element	Description
FDA Center	FDA's sponsoring body of the Sentinel System study.
Regulatory Review Phase	The phase in which the FDA identified the safety concern: • *Pre-approval* • *Post-approval* • *N/A*
Drug Class(es) Under Evaluation	The drug class(es) associated with the medical product under evaluation.
ATC Code and Description	The medical product(s) evaluated in the Sentinel System study, classified using the World Health Organization (WHO)'s Anatomical Therapeutic Chemical (ATC) terminology. Note the following definitions of supporting values: • *Other*: a product is pertinent to the safety concern but is not well-represented by ATC terminology • *N/A*: no specific product is associated with the safety concern
MedDRA Code and Description	The outcome(s) evaluated in the Sentinel System study. Outcomes are reported using the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)'s Medical Dictionary for Regulatory Activities (MedDRA) terminology. Note the following definitions of supporting values: • *Other*: an outcome is pertinent to the safety concern but is not well-represented by MedDRA terminology • *N/A*: no specific outcome is associated with the safety concern

Appendix G: List of Sentinel Publications from 2022 to 2024

1. Htoo PT, Measer G, Orr R, et al. Evaluating Confounding Control in Estimations of Influenza Antiviral Effectiveness in Electronic Health Plan Data. *Am J Epidemiol.* 2022;191(5):908-920. doi:10.1093/aje/kwac020

2. Taylor LG, Bird ST, Stojanovic D, et al. Utility of Fertility Procedures and Prenatal Tests to Estimate Gestational Age for Live-Births and Stillbirths in Electronic Health Plan Databases. *Pharmacoepidemiol Drug Saf.* 2022;31(5):534-545. doi:10.1002/pds.5414

3. Bradley MC, Perez-Vilar S, Chillarige Y, et al. Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings from April 2020 to August 2021. *JAMA.* 2022;327(20):2015-2018. doi:10.1001/jama.2022.4877

4. Haug NR, Wagner AK, McGlynn KA, Leonard CE, Nguyen MD, Major JM. New-Onset Cancer Cases in FDA's Sentinel System: A Large Distributed System of US Electronic Healthcare Data. *Cancer Epidemiol Biomarkers Prev.* 2022;31(10):1890-1895. doi:10.1158/1055-9965.EPI-21-1451

5. Suarez EA, Nguyen M, Zhang D, et al. Novel Methods for Pregnancy Drug Safety Surveillance in the FDA Sentinel System. *Pharmacoepidemiol Drug Saf.* 2023;32(2):126-136. doi:10.1002/pds.5512

6. Ajao A, Cosgrove A, Eworuke E, et al. A Cohort Study to Assess Risk of Cutaneous Small Vessel Vasculitis Among Users of Different Oral Anticoagulants. *Pharmacoepidemiol Drug Saf.* 2022;31(11):1164-1173. doi:10.1002/pds.5514

7. Lo Re V 3rd, Dutcher SK, Connolly JG, et al. Association of COVID-19 vs Influenza with Risk of Arterial and Venous Thrombotic Events Among Hospitalized Patients. *JAMA.* 2022;328(7):637-651. doi:10.1001/jama.2022.13072

8. Floyd JS, Bann MA, Felcher AH, et al. Validation of Acute Pancreatitis Among Adults in an Integrated Healthcare System. *Epidemiology.* 2023;34(1):33-37. doi:10.1097/EDE.0000000000001541

9. Brown JS, Mendelsohn AB, Nam YH, et al. The US Food and Drug Administration Sentinel System: A National Resource for a Learning Health System. *J Am Med Inform Assoc.* 2022;29(12):2191-2200. doi:10.1093/jamia/ocac153

10. Eworuke E, Hampp C, Menzin TJ, Burk J, Kluberg SA. Should Insulin Billing Procedure Codes be Considered for Exposure Ascertainment in Pharmacoepidemiology Studies? *Am J Pharmacother Pharm Sci.* 2022;3. doi:

10.25259/AJPPS_7_2022

11. Suarez EA, Nguyen M, Zhang D, et al. Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs. *Epidemiology.* 2023;34(1):90-98. doi:10.1097/EDE.0000000000001561

12. Eworuke E, Cosgrove A, Her QL, Lyons JG, Martin D, Adimadhyam S. Spironolactone Utilization among Patients with Reduced and Preserved Ejection Fraction Heart Failure. *Pharmacoepidemiology.* 2022; 1(3):89-100. doi: 10.3390/pharma1030009

13. Carrell DS, Gruber S, Floyd JS, et al. Improving Methods of Identifying Anaphylaxis for Medical Product Safety Surveillance Using Natural Language Processing and Machine Learning. *Am J Epidemiol.* 2023;192(2):283-295. doi:10.1093/aje/kwac182

14. Lu CY, Hou L, Kolonoski J, et al. A New Analytic Tool for Assessing the Impact of the US Food and Drug Administration Regulatory Actions. *Pharmacoepidemiol Drug Saf.* 2023;32(3):298-311. doi:10.1002/pds.5552

15. Lyons JG, Suarez EA, Fazio-Eynullayeva E, et al. Assessing Medical Product Safety During Pregnancy Using Parameterizable Tools in the Sentinel Distributed Database. *Pharmacoepidemiol Drug Saf.* 2023;32(2):158-215. doi:10.1002/pds.5568

16. Walker WL, Schmit KM, Welch EC, et al. Using the Food and Drug Administration's Sentinel System for Surveillance of TB infection. *Int J Tuberc Lung Dis.* 2022;26(12):1170-1176. doi:10.5588/ijtld.22.0259

17. Eworuke E, Welch EC, Haug N, et al. Comparative Risk of Angioedema With Sacubitril-Valsartan vs Renin-Angiotensin-Aldosterone Inhibitors. *J Am Coll Cardiol.* 2023;81(4):321-331. doi:10.1016/j.jacc.2022.10.033

18. Eworuke E, Shinde M, Hou L, et al. Valsartan, Losartan and Irbesartan Use in the USA, UK, Canada and Denmark after the Nitrosamine Recalls: A Descriptive Cohort study. *BMJ Open.* 2023;13(4):e070985. Published 2023 Apr 17. doi:10.1136/bmjopen-2022-070985

19. Lo Re V 3rd, Dutcher SK, Connolly JG, et al. Risk of Admission to Hospital with Arterial or Venous Thromboembolism Among Patients Diagnosed in the Ambulatory Setting with COVID-19 Compared with Influenza: Retrospective Cohort Study. *BMJ Med.* 2023;2(1):e000421. Published 2023 Jun 6. doi:10.1136/bmjmed-2022-000421

20. Cocoros NM, Gurwitz JH, Cziraky MJ, et al. Pragmatic Guidance for Embedding Pragmatic Clinical Trials in Health Plans: Large Simple Trials Aren't So Simple. *Clin Trials.* 2023;20(4):416-424. doi:10.1177/17407745231160459

21. Davis SE, Zabotka L, Desai RJ, et al. Use of Electronic Health Record Data for Drug Safety Signal Identification: A Scoping Review. *Drug Saf.* 2023;46(8):725-742. doi:10.1007/s40264-023-01325-0

22. Perez-Vilar S, Kempner ME, Dutcher SK, et al. Switching Patterns of Immediate-Release Forms of Generic Mixed Amphetamine Salts Products Among Privately and Publicly Insured Individuals Aged 15-64 years in the United States, 2013-2019. *Pharmacoepidemiol Drug Saf.* 2023;32(10):1178-1183. doi:10.1002/pds.5661

23. Maro JC, Nguyen MD, Kolonoski J, et al. Six Years of the US Food and Drug Administration's Postmarket Active Risk Identification and Analysis System in the Sentinel Initiative: Implications for Real World Evidence Generation. *Clin Pharmacol Ther.* 2023;114(4):815-824. doi:10.1002/cpt.2979

24. Fuller CC, Cosgrove A, Shinde M, et al. Treatment and Care Received by Children Hospitalized with COVID-19 in a Large Hospital Network in the United States, February 2020 to September 2021. *PLoS One.* 2023;18(7):e0288284. Published 2023 Jul 11. doi:10.1371/journal.pone.0288284

25. Webster-Clark M, Toh S, Arnold J, McTigue KM, Carton T, Platt R. External Validity in Distributed Data Networks. *Pharmacoepidemiol Drug Saf.* 2023;32(12):1360-1367. doi:10.1002/pds.5666

26. Ter-Minassian M, DiNucci AJ, Barrie IS, Schoeplein R, Chakravarty A, Hernández-Muñoz JJ. Improving Data Capture of Race and Ethnicity for the Food and Drug Administration Sentinel Database: A Narrative Review. *Ann Epidemiol.* 2023;86:80-89.e2. doi:10.1016/j.annepidem.2023.07.006

27. Apata J, Lyons JG, Bradley MC, et al. Assessing the Risk of Intentional Self-Harm in Montelukast Users: An Updated Sentinel System Analysis using ICD-10 Coding. *J Asthma*. 2024;61(7):653-662. doi:10.1080/02770903.2023.2293064

28. Smith JC, Williamson BD, Cronkite DJ, et al. Data-Driven Automated Classification Algorithms for Acute Health Conditions: Applying PheNorm to COVID-19 Disease. *J Am Med Inform Assoc.* 2024;31(3):574-582. doi:10.1093/jamia/ocad241

29. Weberpals J, Raman SR, Shaw PA, et al. SMDI: An R package to Perform Structural Missing Data Investigations on Partially Observed Confounders in Real-World Evidence Studies. *JAMIA Open.* 2024;7(1):ooae008. Published 2024 Jan 31. doi:10.1093/jamiaopen/ooae008

30. Lo Re Iii V, Cocoros NM, Hubbard RA, et al. Risk of Arterial and Venous Thrombotic Events Among Patients with COVID-19: A Multi-National Collaboration of Regulatory Agencies from Canada, Europe, and United States. *Clin Epidemiol.* 2024;16:71-89. Published 2024 Feb 10. doi:10.2147/CLEP.S448980

31. Desai RJ, Wang SV, Sreedhara SK, et al. Process Guide for Inferential Studies Using Healthcare Data from Routine Clinical Practice to Evaluate Causal Effects of Drugs (PRINCIPLED): Considerations from the FDA Sentinel Innovation Center. *BMJ.* 2024;384:e076460. Published 2024 Feb 12. doi:10.1136/bmj-2023-076460

32. Wyss R, van der Laan M, Gruber S, et al. Targeted learning with an undersmoothed LASSO propensity score model for large-scale covariate adjustment in health-care database studies. *Am J Epidemiol.* 2024;193(11):1632-1640. doi:10.1093/aje/kwae023

33. Fuller CC, Rosen E, Rai A, et al. Validity of inpatient electronic health record-based measures of oxygen-related therapy in the United States: Lessons applicable for studying COVID-19 endpoints. *Pharmacoepidemiol Drug Saf.* 2024;33(4):e5785. doi:10.1002/pds.5785

34. Carrell DS, Floyd JS, Gruber S, et al. A General Framework for Developing Computable Clinical Phenotype Algorithms. *J Am Med Inform Assoc.* 2024;31(8):1785-1796. doi:10.1093/jamia/ocae121

35. Hazlehurst B, Carrell DS, Bann MA, et al. Finding Uncoded Anaphylaxis in Electronic Health Records to Estimate the Sensitivity of International Classification of Diseases, Tenth

Revision, Clinical Modification codes. *Am J Epidemiol.* 2024;193(10):1494-1496. doi:10.1093/aje/kwae063

36. Weberpals J, Raman SR, Shaw PA, et al. A Principled Approach to Characterize and Analyze Partially Observed Confounder Data from Electronic Health Records. *Clin Epidemiol.* 2024;16:329-343. Published 2024 May 21. doi:10.2147/CLEP.S436131

37. Rai A, Maro JC, Dutcher S, Bright P, Toh S. Transparency, Reproducibility, and Replicability of Pharmacoepidemiology Studies in a Distributed Network Environment. *Pharmacoepidemiol Drug Saf.* 2024;33(6):e5820. doi:10.1002/pds.5820

38. Thai TN, Winterstein AG, Suarez EA, et al. Triple Challenges-Small Sample Size in Both Exposure and Control Groups to Scan Rare Maternal Outcomes in a Signal Identification Approach: A Simulation Study. *Am J Epidemiol*. 2024;193(12):1805-1813. doi:10.1093/aje/kwae151

39. Lyons JG, Shinde MU, Maro JC, et al. Use of the Sentinel System to Examine Medical Product Use and Outcomes During Pregnancy. *Drug Saf.* 2024;47(10):931-940. doi:10.1007/s40264-024-01447-z

40. Shu D, Zou G, Hou L, et al. A Simple Cox Approach to Estimating Risk Ratios without Sharing Individual-Level Data in Multisite Studies. *Am J Epidemiol.* 2025;194(1):226-232. doi:10.1093/aje/kwae188

41. Her, QL, Li, D, Vilk, Y, et al. A Distributed Regression Analysis Application Package Using SAS. *Stat Biosci.* 2024. doi: 10.1007/s12561-024-09445-6

42. Schneeweiss S, Desai RJ, Ball R. A Future of Data-Rich Pharmacoepidemiology Studies: Transitioning to Large-Scale Linked Electronic Health Record + Claims Data. *Am J Epidemiol.* 2025;194(2):315-321. doi:10.1093/aje/kwae226

43. Horgan CE, Burk J, Eworuke E, et al. Identifying Pediatric Hypertension in Observational Data: Comparing Clinical and Claims Cohorts in Real-World Data. *Am J Epidemiol.* 2025;194(2):407-419. doi:10.1093/aje/kwae233

44. Eworuke E, Shinde MU, Hou L, et al. Exposure to Valsartan Products Containing Nitrosamine Impurities in the United States, Canada, and Denmark. *Pharmacoepidemiol Drug Saf.* 2024;33(9):e5849. doi:10.1002/pds.5849

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47. Chen C, Eworuke E, Rai A, et al. Use of Hydrochlorothiazide in the United States Following Label Update About Skin Cancer Risk. *Pharmacoepidemiol Drug Saf.* 2024;33(10):e70040. doi:10.1002/pds.70040

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49. Raman SR, Hammill BG, Shaw PA, et al. Analyzing Missingness Patterns in Real-World Data Using the SMDI Toolkit: Application to a Linked EHR-Claims Pharmacoepidemiology Study. *BMC Med Res Methodol.* 2024;24(1):246. Published 2024 Oct 19. doi:10.1186/s12874-024-02330-2

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