U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology 2022 Annual Report

Detecting, Assessing, Preventing, and Managing Risks

May 2023

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OSE Director's Message

Director's Message

Greetings,

I am pleased to share with you the 2022 Office of Surveillance and Epidemiology (OSE) Annual Report.

2022 was a busy, productive,and exciting year for OSE. We continued to respond to public health emergencies – both COVID-19 and the opioid crisis – by analyzing and acting upon data from a wide variety of sources. Beyond these two areas, we detected and assessed risk across all of the drugs that CDER regulates using the FDA Adverse Event Reporting System (FAERS) database, the Sentinel System, and other sources of drug safety information. Our lifecycle approach to preventing risks relies on our well-established medication error prevention program, which includes premarket reviews of proposed proprietary names, human factors analyses for drug-device combination products, review of carton and container labeling and instructions for use, along with postmarket surveillance to detect medication errors. Our risk management program, which centers around the review of proposed risk evaluation and mitigation strategies (REMS) and modifications to those programs, took a big step forward in improving the efficiency of REMS review by requiring REMS documents for new REMS and REMS modifications to be submitted electronically in Structured Product labeling format. Drug safety modernization and innovation was also a big theme in 2022. OSE continued its work to integrate REMS into clinicians' and pharmacists' workflows through the REMS integration initiative, which seeks to use contemporary health data standards to efficiently transfer REMS-related information. We also developed and launched an operational pilot of the Information Visualization Platform (InfoViP), a decision support tool for post market safety surveillance that uses artificial intelligence to support OSE's safety reviewers' work. We also stood up all nine planned Drug Safety Teams and participated in a pilot program to develop and implement pharmacovigilance strategies to connect premarket potential risk with proactive pharmacovigilance monitoring strategies for selected products. We co-led development and implementation of an integrated safety assessment template, to foster collaborative assessment of safety information across CDER, and initiated a Pharmacovigilance Curriculum to strengthen foundation understanding across FDA. Each of these accomplishments is described in more detail below.

On behalf of my colleagues in OSE, I hope you find the 2022 OSE Annual Report useful and informative.

Best regards,

Gerald Dal Pan, MD, MHS

OSE Leadership Team

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OSE Director

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OSE Deputy Director

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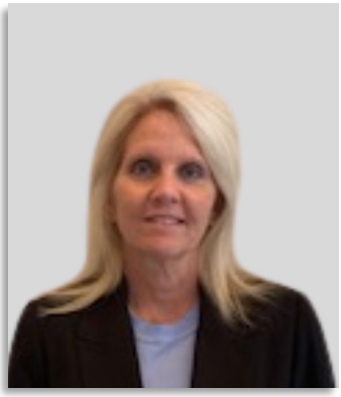

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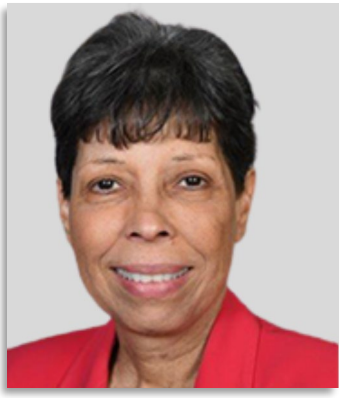

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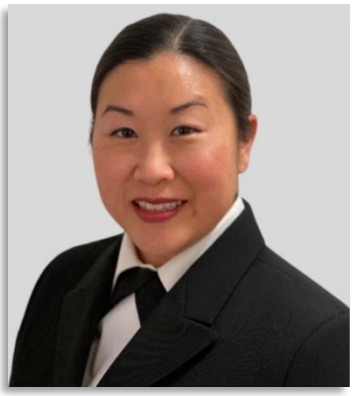

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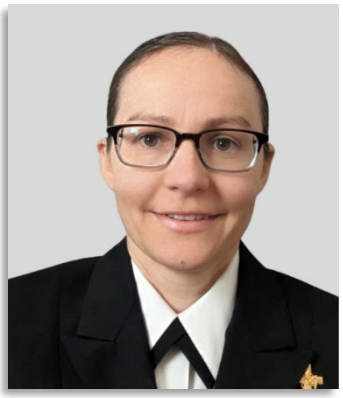

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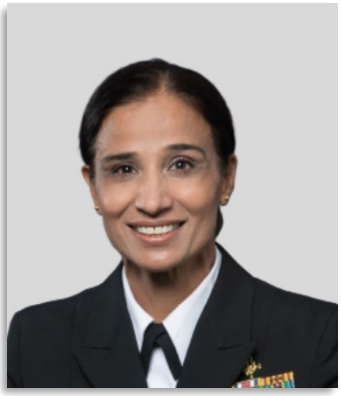

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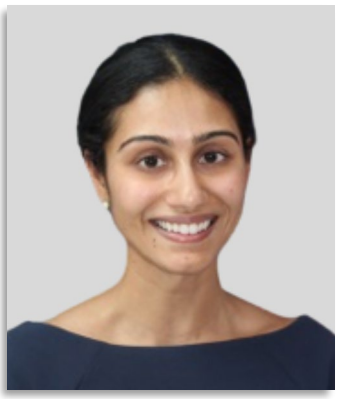

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OSE Leadership Team

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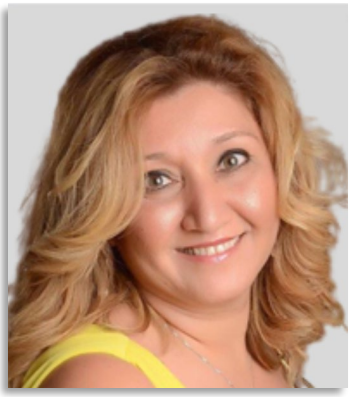

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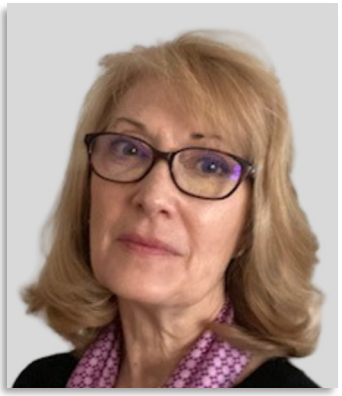
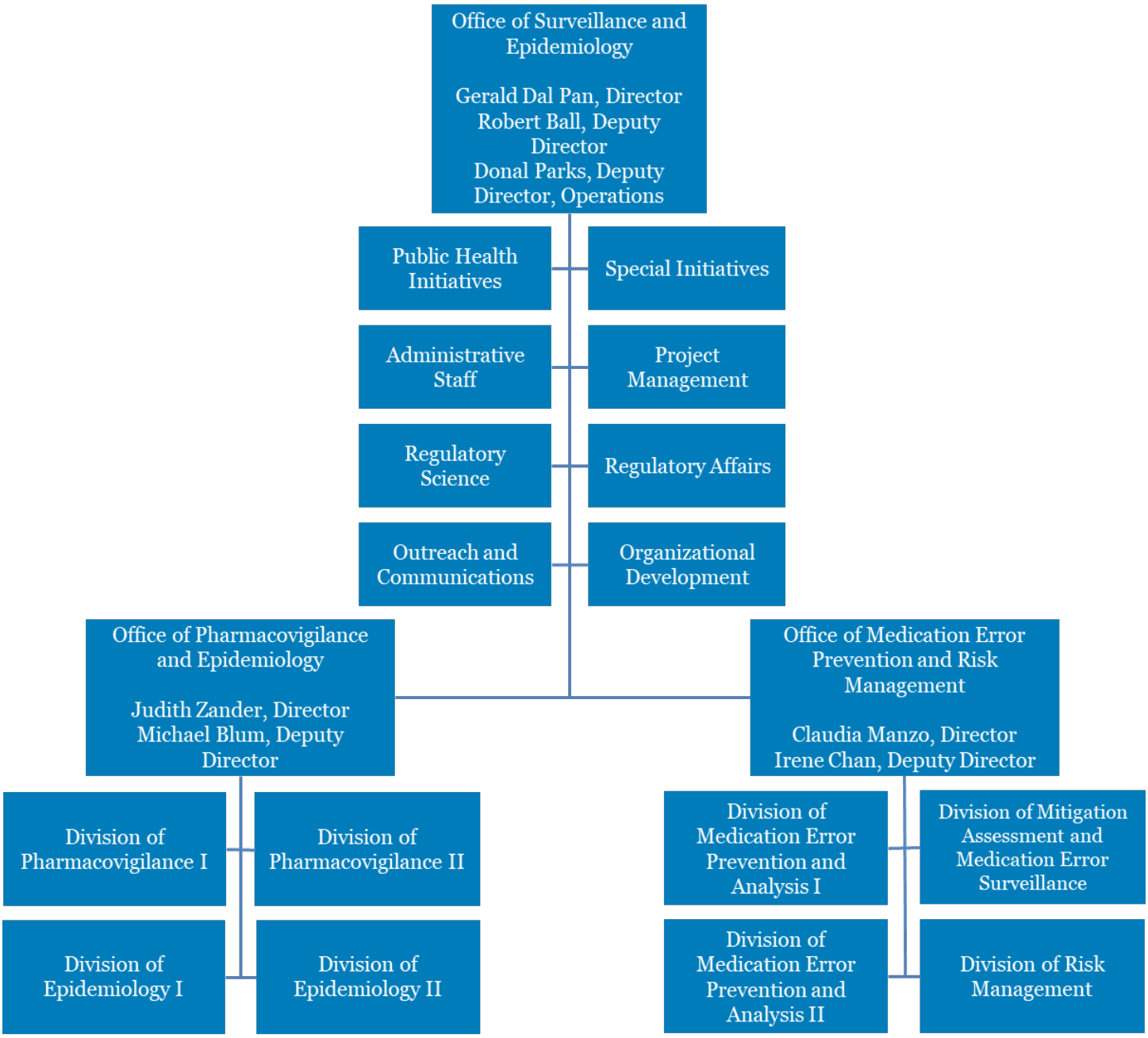
Director, Division of Mitigation and Medication Error Surveillance



Cynthia LaCivita, PharmD
Director, Division of Risk Management

OSE Organizational Structure

Figure 1: OSE organizational chart



OSE Organizational Structure

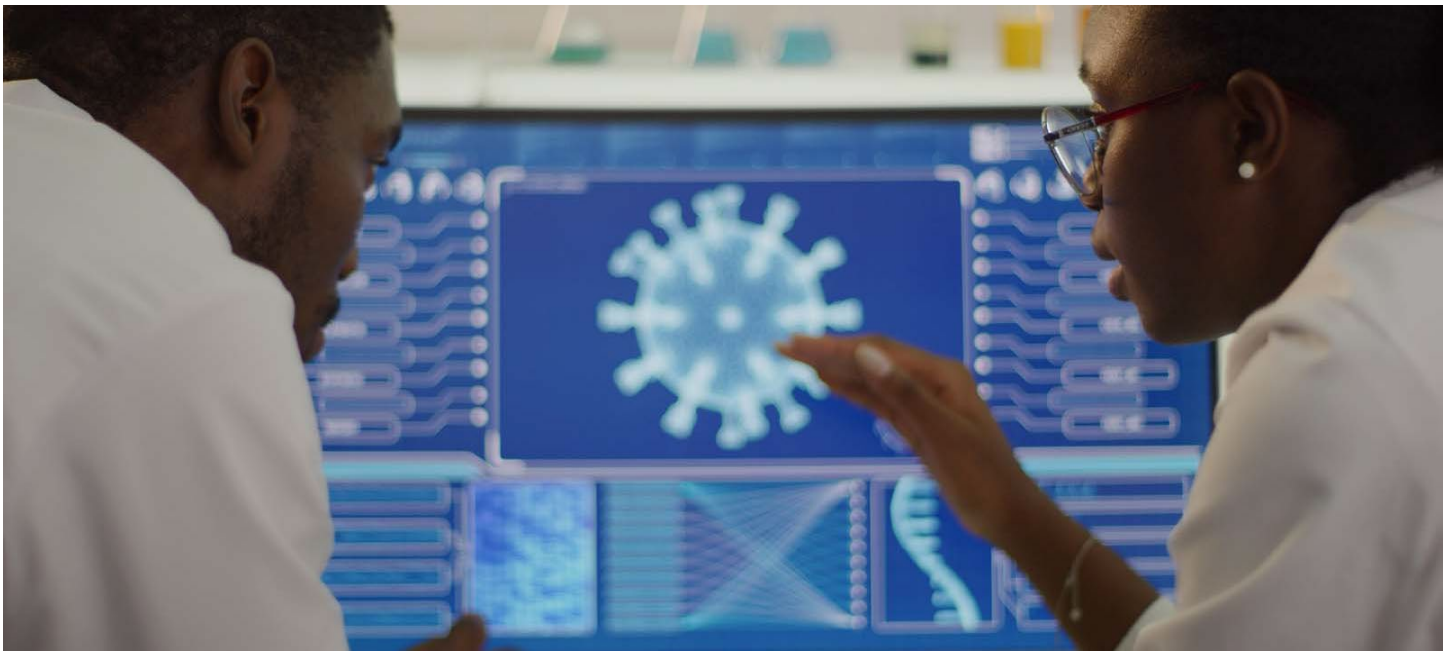
Who We Are and What We Do

OSE, within the Center for Drug Evaluation and Research (CDER), works to detect, assess, prevent, and manage the risks of medications so that they can be relied upon to treat disease and improve health. OSE participates in the safety analysis of drugs before they are marketed to patients and consumers. After the drugs are marketed, we utilize a variety of approaches to identify and assess adverse events and medication errors that did not appear during the drug development process as well as to better understand and manage the known risks of medications.

OSE has four core functions – pharmacovigilance, pharmacoepidemiology, medication error prevention and analysis, and risk management (see Figure 2) – and operates across multiple disciplines to review and assess the safety of medicines. Everything in OSE is tied to these four core functions.

Figure 2: OSE's four core functions

Responding to Public Health Emergencies



OSE in Action: Continued Response to the COVID-19 Pandemic in 2022

During the COVID-19 Public Health Emergency, FDA used its authority to issue Emergency Use Authorizations (EUAs) for products to prevent or treat COVID-19. Consequently, many drugs were being used to treat or prevent COVID-19, resulting in OSE's need to initiate heightened surveillance of these drugs and other activities through use of its four core functions, as shown in Figure 3. OSE moved beyond routine pharmacovigilance practices to monitor drugs to treat or prevent COVID-19 by accessing near real-time data for drug utilization, medication error and adverse event surveillance from various data sources.

OSE's Adverse Event Surveillance during COVID-19 Pandemic

- OSE staff performed daily searches in the FDA Adverse Event Reporting System (FAERS) to detect and assess adverse events related to products used to treat COVID-19.
- We monitored adverse event reports from a variety of data sources as well as the medical literature.
- These surveillance efforts led to the identification of safety issues resulting in updates to the Fact Sheets for two antiviral products authorized for emergency use.

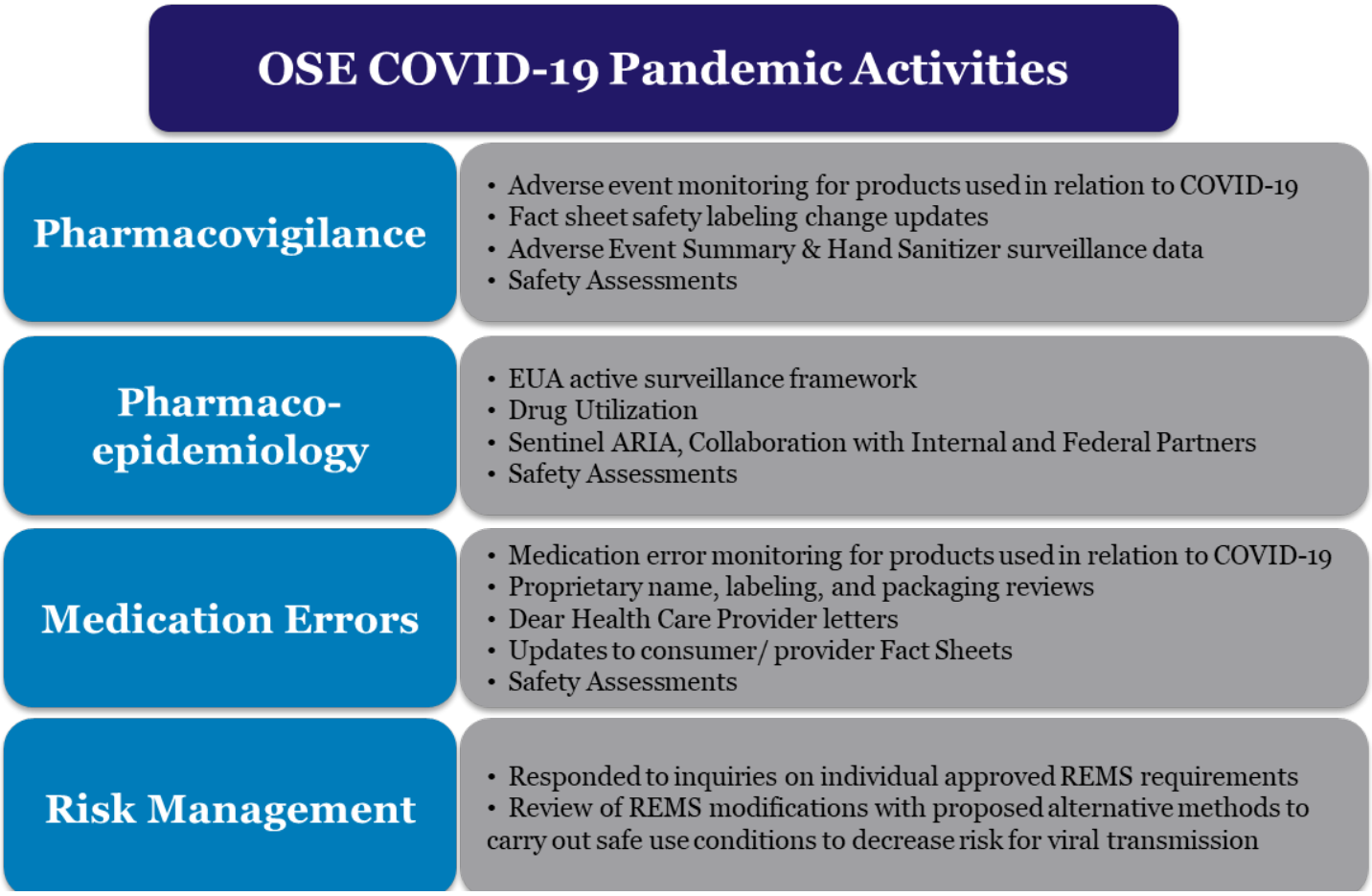
In 2022, OSE screened over 40,000 FAERS reports and 62,000 abstracts in the published medical literature related to COVID-19.

OSE's Medication Error Monitoring during COVID-19 Pandemic

- OSE staff continued heightened medication error surveillance by performing weekly searches in FAERS and collaborating with patient safety organizations such as the Institute of Safe Medication Practices to identify medication errors.
- We recommended revisions to container labels, carton labeling, packaging, and Fact Sheets; and reviewed Dear Health Care Provider letters and other safety communications to minimize and prevent medication errors.

Responding to Public Health Emergencies

Figure 3: OSE used its four core functions to combat the pandemic in 2022



Responding to Public Health Emergencies

Monitoring Drug Usage During COVID-19 Pandemic

The COVID-19 pandemic exacerbated drug shortages and created new challenges for FDA to identify and mitigate drug shortages. Even before the COVID-19 pandemic, drug shortages were a persistent challenge. COVID-19 highlighted vulnerabilities and gaps in information on drug supply. OSE staff took the following measures to obtain data on both demand and supply of prescription medicines:

- Conducted regular assessments of drug sales and prescription data using Symphony Health and HCA Healthcare data available to the Agency under contract to inform near real-time drug utilization patterns.
- Performed internal analyses of anti-SARS-CoV-2 monoclonal antibody utilization using available data in HHS Protect, a secure US government platform for COVID-19 healthcare information.
- Assessed descriptive data for monoclonal antibody utilization and antivirals in Sentinel, CMS Medicare, and the Veterans Health Administration (VHA).
- Examined inpatient and outpatient use of systemic corticosteroids for COVID-19, clinical and demographic characteristics of users, concomitant therapies, COVID-19 severity, and outcomes (hospitalization and death) using data from Sentinel, CMS Medicare, VHA, and HealthVerity - Largest Healthcare Data Ecosystem. OSE confirmed that despite NIH recommendations against use, increasing numbers of non-hospitalized COVID-19 patients were prescribed systemic corticosteroids.
- Continued near real-time monitoring of critical drug usage during COVID-19 using HCA Healthcare data in Sentinel.

OSE's Active Surveillance Coronavirus Activities

- Using Sentinel's Data Partner Network*, we developed a multi-data approach to support COVID-19 related projects to build a database with the most currently available data from national claims insurers and integrated delivery systems.
- OSE routinely updated this "rapid" database to support observational studies for COVID-19 related research and post-market surveillance of treatments administered during the pandemic. The Rapid Distributed Database is comprised of a subset of existing Sentinel Data Partners that provide more frequent data refreshes. Participating Data Partners refresh their datasets every 1-to-2-months rather than the 3-to-12-month schedule decreasing the standard data lag. This "rapid data" approach supports time-sensitive analyses.
- We updated study methods to reflect the changing EUAs, availability of prevention and treatment options, viral variants, and other factors.
- We used rapid data in FDA Sentinel to further study signals generated from FAERS and other resources.
- In 2022, OSE's active surveillance using CMS Medicare, VHA, and FDA's Sentinel System continued to provide capacity for near-real time assessment of safety and effectiveness of therapeutics administered under an EUA using real-world data.

*Additional information on Sentinel's Network can be found on the FDA Sentinel page and the Sentinel Initiative website.

Responding to Public Health Emergencies

OSE's Public Health Initiatives Program's Continued Response to the Opioid Public Health Crisis

In response to the opioid public health crisis, OSE recruited experts, educated healthcare providers, and worked with other government agencies to decrease the use of prescription opioids and prevent new addiction. OSE's Public Health Initiatives program has allowed for improved coordination of the resources of the pharmacovigilance, pharmacoepidemiology, medication error prevention, and risk management functions to address the full scope of the opioid crisis.

- OSE characterized the risks of human exposure to xylazine, a drug used as a sedative and analgesic in veterinary medicine that is increasingly detected in the illegal drug supply and in drug overdoses. OSE led a cross-office, cross-center collaboration to develop an effective public communication strategy to warn healthcare providers about the identified risks associated with xylazine. As a result, the Xylazine CDER Alert was published on November 8, 2022. We also communicated via a Dear Stakeholder Letter distributed to various health care groups, including primary care services, emergency medical services, and addiction services.
- OSE, the Center for Food Safety and Applied Nutrition, and other centers across FDA collaborated to issue an FDA Consumer Update to warn consumers and healthcare providers about the risks of tianeptine, an unapproved drug that has been linked to serious harm, overdose, and death. Information characterizing the risks and adverse effects associated with tianeptine nonmedical use came from a pharmacovigilance review by DPV and an integrated OPE review. The update also discussed steps taken by FDA to protect the public from tianeptine products, including sending warning letters to companies illegally marketing tianeptine products as dietary supplements, and issuing import alerts to help stop tianeptine shipments at our borders.

Collaborating with Other Government Agencies

Morphine Milligram Equivalents (MMEs) have been used to inform switching patients between opioid analgesics and to indicate misuse, abuse, and overdose potential, as well as set thresholds for prescribing and dispensing of opioid analgesics.

- In 2022, OSE led the development of an Interagency MME Workgroup to further enhance the science behind the determination and application of MMEs and to continue to progress on the lessons learned from the FDA Internal MME Workshop held in June 2021.
- The interagency workgroup currently consists of representatives from many FDA offices and subject matter experts from the Centers for Disease Control and Prevention, National Institutes of Health, Indian Health Service, and VHA.
- OSE subject matter experts participated on HHS's Behavioral Health Coordinating Council (BHCC) Overdose Prevention Subcommittee, Buprenorphine Availability in Pharmacies workgroup, and the Buprenorphine Guidelines Evaluation workgroup.

Responding to Public Health Emergencies

- Under the Buprenorphine Guidelines Evaluation workgroup, OSE authors helped draft the Early Changes in Waivered Clinicians and Utilization of Buprenorphine for Opioid Use Disorder After Implementation of the 2021 HHS Buprenorphine Practice Guidelines report.
- Additionally, as part of FDA's mission to ensure that safe and effective drugs are available, OSE, in collaboration with the Office of Biostatistics, is working on understanding geographical distribution of prescription buprenorphine products used to treat opioid use disorder to inform possible geographic disparities and explore potential equity concerns for access to buprenorphine for the treatment of OUD.
- OSE collaborated with other agencies to provide guidance on an ongoing government-funded study to describe patient-reported use of opioid analgesics after acute pain in diverse populations and across multiple settings of care. The outcomes are as follows:
  - To provide support for acute pain guideline development;
  - To provide subject matter expertise on a clinical practice guideline for the management of dental pain that was completed in 2022; and
  - To announce, review, and award a grant to develop evidence-based opioid prescribing guidelines for obstetric pain.

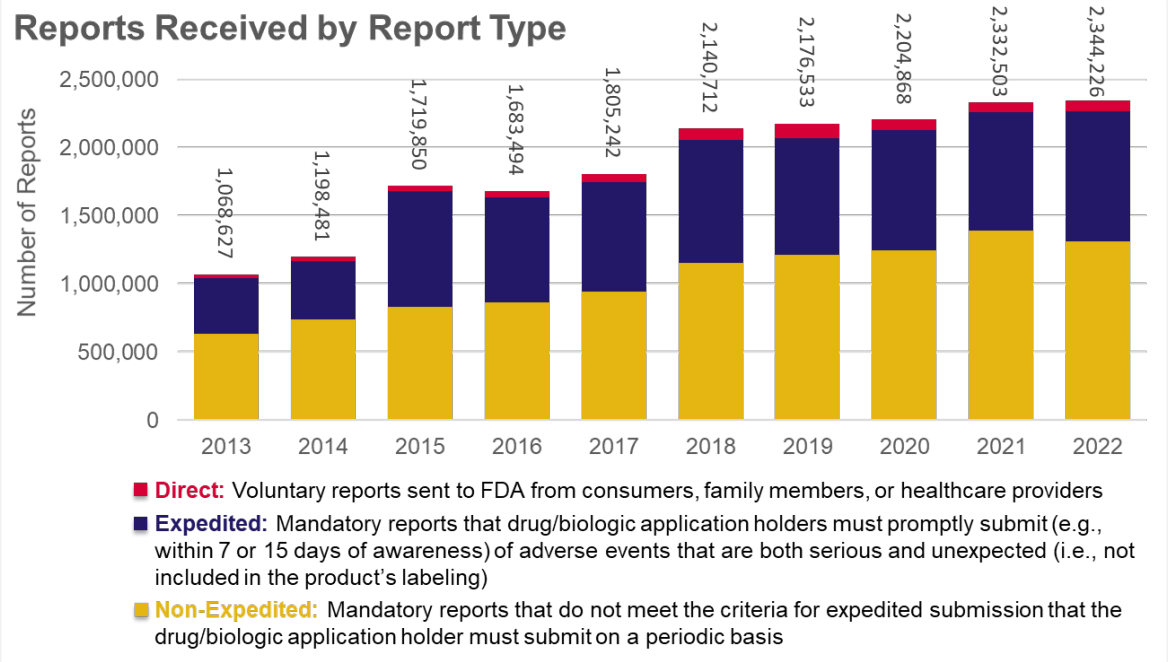
Detecting and Assessing Risks

Beyond COVID-19, OSE uses several approaches for post-marketing surveillance and risk assessment to identify adverse events and medication errors that may not have appeared during the drug development process. OSE maintains two primary systems for postmarketing drug safety surveillance, a "passive" system known as FAERS, and an "active" system known as the Sentinel System.

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains adverse event reports, medication error reports and product quality complaints related to drugs and therapeutic biological products. Drug product manufacturers and other entities are required to submit reports of adverse events associated with their products that they receive or otherwise obtain. Additionally, the public (e.g., healthcare professionals and consumers) can voluntarily submit adverse event reports directly to FDA via the MedWatch Program.

Figure 4: FAERS reports received by report type

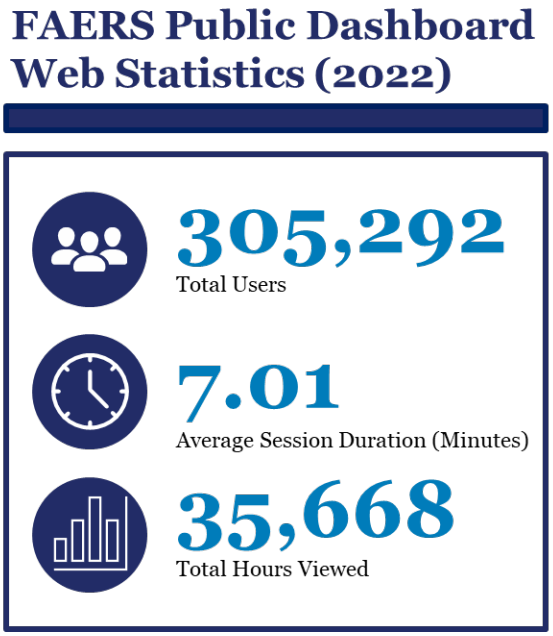


As shown in Figure 4, the total number of FAERS reports in 2022 was slightly higher than the total number in 2021. Of the over 2.3 million reports received in 2022, over 1.3 million were described as serious adverse events not listed in the product labeling. OSE monitors these reports and generates safety signals, which it further investigates, and then takes action when necessary.

Detecting and Assessing Risks

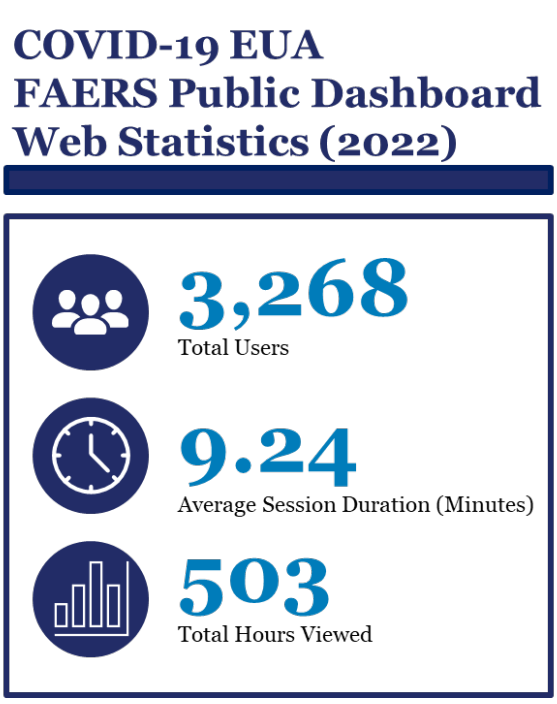
Upgrades to FAERS in 2022

FDA upgraded FAERS to FAERS II in 2021, which modernized the collection, management, and analysis of postmarket adverse event (AE) reports. FAERS II allows companies to submit postmarket AE reports and product quality defect reports. In April 2022, FDA published technical specification and formatting guides on International Council for Harmonisation (ICH) E2B(R3) format, which will be implemented in 2023 and will allow for transmission of premarketing as well as postmarking safety reports. The goal of the FAERS II program is to create a single system that encompasses the entire Product Safety Lifecycle and provides stakeholders with a one-stop shop solution that improves FDA's case data intake, case processing, data quality, and data analytics capabilities.



FAERS Public Dashboard and FAERS COVID-19 Public Dashboard

In September 2017, OSE launched the FAERS Public Dashboard, which expanded access to FAERS data to the public by providing a means to search for information on adverse events related to human drugs. Prior to the development of the dashboard, raw FAERS data (going back to 1968) were made available to the public only in complex data files. The dashboard is designed for public use anywhere in the world and allows users to query FAERS data in a highly interactive, user-friendly way. The data in the FAERS Public Dashboard is updated quarterly.



There was a rapid uptake of the products authorized under an EUA to combat the ongoing COVID-19 pandemic. In order to keep the public adequately informed of adverse events reported for these products, more frequent updates to the FAERS Public Dashboard were needed during COVID-19 for these products. The COVID-19 EUA FAERS Public Dashboard was therefore launched in March 2021. In 2022, it continued to be updated on a weekly basis to provide more efficient access to safety information for drugs and therapeutic biologic products used under an EUA for COVID-19.

Detecting and Assessing Risks

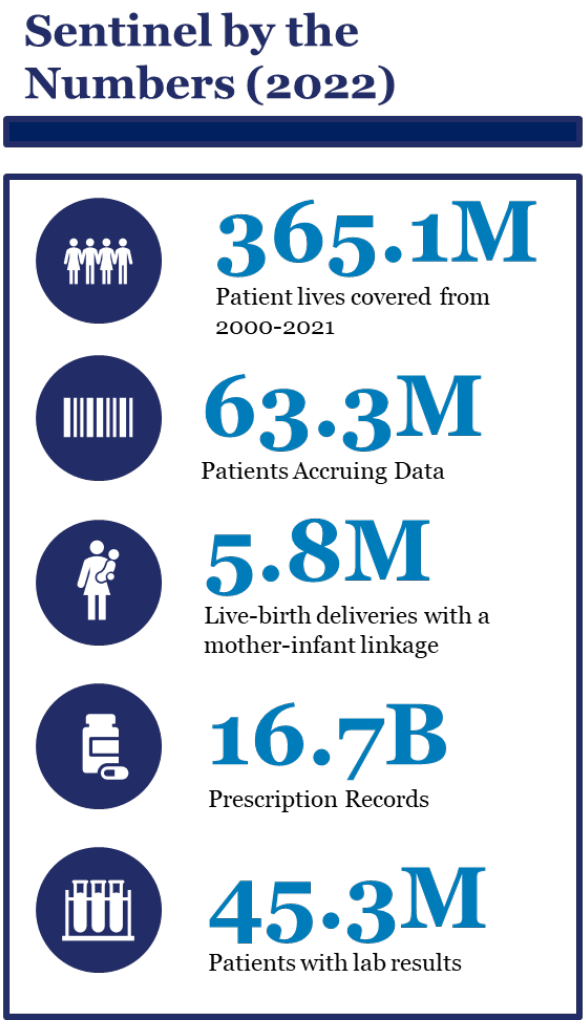
Sentinel

The Sentinel System was developed to analyze large quantities of electronic healthcare data efficiently to monitor the safety of marketed drugs and to help inform regulatory decision making. FDA also uses Sentinel to advance our understanding of how real-world evidence can be used for studying effectiveness.

The "active surveillance" capabilities of Sentinel are an important complement to FAERS data. Instead of waiting to receive safety data, Sentinel enables FDA to conduct specific analyses using large healthcare administrative claims databases. When a safety signal arises from FAERS or elsewhere, Sentinel can be used to systematically study the issue in a larger patient population.

Sentinel continues to build upon the core innovations that were responsible for many of the achievements in its first decade: participation of partners who bring their knowledge and expertise to the Sentinel network, and reusable analytic tools in the Sentinel Common Data Model with the ability to trace important clinical information back to the medical record. Sentinel remains one of the world's largest multi-site, privacy-preserving, medical product safety surveillance systems with highly curated data capturing approximately 800 million person-years of longitudinal data and more than 63.3 million patients actively accruing new data. During 2022, OSE utilized the Sentinel System in 70 medical product assessments. Additional information on Sentinel can be found on the FDA Sentinel page and the Sentinel Initiative website.

Figure 5: Sentinel's impact



Real World Evidence and Integration of Electronic Health Records

Real-world data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Real-world evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

In 2022, the Sentinel Initiative's Innovation Center refined their Master Plan and continued to work towards integrating Electronic Health Record (EHR) data into the Sentinel System to enable in-depth investigations of medication outcomes. Incorporating EHR data allows Sentinel to increase its generalizability and clinical rigor, without compromising the timing for data access and analysis. Until recently, we couldn't analyze disparate impacts for patients who were pregnant, or for patients by race in observational studies. Today, we are able to access a broader selection of data sources much more quickly, which increases the generalizability of study findings. Due to lack of standardization across EHRs, integrating EHR data remains an ongoing challenge, but in 2022 the Sentinel Initiative made notable strides to establish data quality metrics to ensure better integration moving forward. This will allow the agency to interpret ever-larger sets of complex safety information and take necessary action to protect patients.

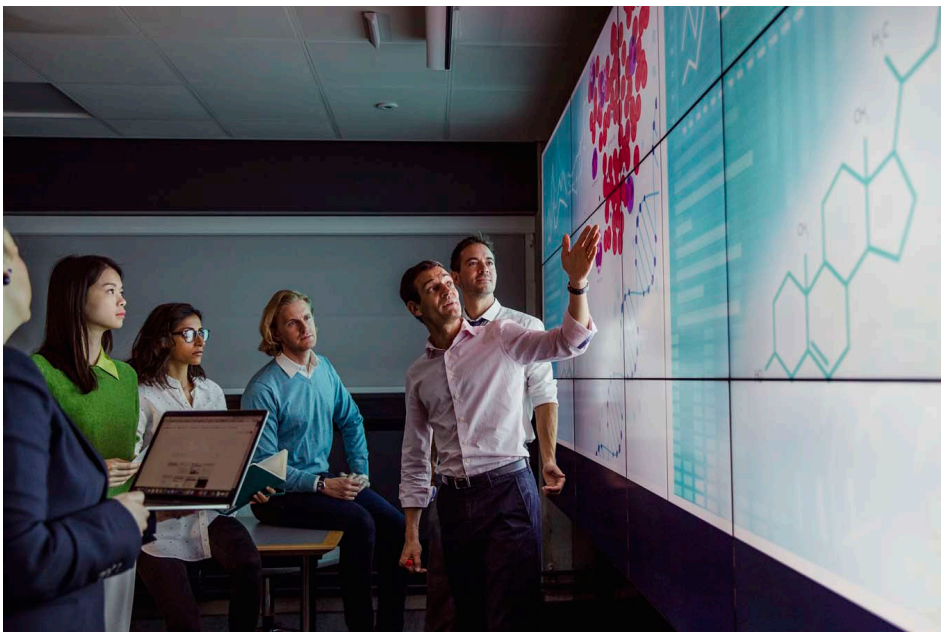
Detecting and Assessing Risks

Use of Sentinel for Pregnancy Studies

Linkages established between mothers' and infants' health records help us study the relationship between drug exposure during pregnancy and infant outcomes. Also, data with a shorter lag time allow us to characterize the use of recently approved drugs more quickly during pregnancy. A recent example from the Sentinel website is an analysis of Ibrexafungerp use in pregnancy. Ibrexafungerp is an antifungal agent used to either treat vulvovaginal candidiasis (VVC) or to reduce the incidence of recurrent VVC in post-menarchal women and is contraindicated for use in pregnancy due to findings of severe embryo-fetal toxicity from animal studies. This query aims to identify early signaling of ibrexafungerp use in pregnant patients. Other examples that can be found on the Sentinel website are below:

- Ixekizumab & Use in Pregnancy – 2021
- Women with Heart Failure & Pregnancy – 2020
- HER2 Antagonists & Use in Pregnancy and Oligohydramnios – 2020
- Multiple Sclerosis Drugs & Use in Pregnancy - 2017

Preventing Risks



Prevention of Medication Errors Throughout a Product's Lifecycle

As part of the FDA preapproval process for new drug products, the two Divisions of Medication Error and Prevention Analysis (DMEPA I and II) review and determine the acceptability of proposed proprietary names for drugs and for biological products as well as distinguishing suffixes included in nonproprietary names of biological products to minimize medication errors associated with product name confusion. Both divisions also review proposed container labels, carton labeling, prescribing information, patient labeling (including the Instructions for Use and Medication Guides), packaging, and human factors submissions to minimize or eliminate hazards that can contribute to medication or use errors. Fiscal Year (FY) 2022 user fee goals for the review of proprietary names are listed in Table 1. The proprietary naming (PN) goals for IND and BsUFA IND were not met for FY 2022 because of increased PN submissions and staffing shortages. OSE re-evaluated resource allocation and advanced hiring to ensure adequate resources are allotted to support the Proprietary Name program. As a result of these efforts, OSE met 100% of PN performance goals for the first quarter of FY 2023 (Oct 1, 2022 to Dec 31, 2022).

Premarket Measures to Reduce Medication Errors

Human factors (HF) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system. OSE's human factors program exists to enhance patient safety in the healthcare environment by focusing on the design of medical products. By collecting data from representative participants in realistic situations, HF studies help determine whether the design of the user interface supports the safe and effective use of the medical product. For example, in one HF study, several potential drug overdose errors occurred due to application of more than one skin patch or transdermal system (TDS), too frequent replacement of the TDS, and failure to remove the TDS as directed.

Application Type	Receipts	Performance Goal Met (%)	Performance Goal Exceeded (%)
IND	167	49	No
NDA/BLA	195	97	Yes
BsUFA IND	13	17	No
BsUFA BLA	24	100	Yes
ANDA*	24	100	N/A

Table 1: Proprietary Name Reviews from October 1, 2021 – September 30, 2022
**Note: Proprietary Name Reviews (PNRs) are not subject to GDUFA II but the performance is being tracked based on a 180-day review timeframe*

423 *Total Proprietary Name Reviews conducted from October 1, 2021 – September 30, 2022*

Preventing Risks

DMEPA reviewed the root causes for the errors, evaluated the feedback from the study participants, and recommended additional risk mitigations to address the use errors. The Applicant implemented the additional risk mitigations and conducted another HF study that demonstrated the mitigations were effective and the revised user interface supports safe and effective use.

Total Non-proprietary Suffix Reviews conducted from October 1, 2021 – September 30, 2022 **54**

A use-related risk analysis (URRA) serves as the backbone of a human factors engineering process. Sponsors utilize URRAs to identify and characterize use-related risk associated with the medical product's user interface design, and the URRA helps to identify hazards that may require further risk mitigation strategies.

In FY2022, OSE received 77 HF validation study protocols and 374 other HF submissions or consults, including HF validation study results reports, formal industry meeting requests, and use-related risk analyses.

Work Type	No. Completed
Suffix Review for 351(a) BLA	32
Suffix Review for 351(k) BLA	15
IND	7

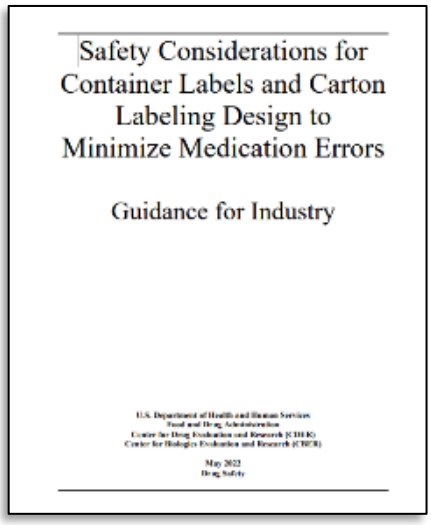
Table 2: Nonproprietary suffix review for biological products from October 1, 2021 – September 30, 2022

Monitoring and Analyzing Medication Error Reports After Drug Approval

DMAMES is the CDER scientific lead for medication error pharmacovigilance, which includes surveillance planning, safety signal detection, assessment, understanding, and prevention of medication errors. DMAMES works collaboratively with DMEPA I and II and others within CDER to investigate medication error safety signals for marketed drug products, including non-prescription, prescription, generics, biosimilars and other therapeutic biological products, to determine if regulatory action is needed to mitigate the errors. Additionally, postmarket monitoring of medication errors helps to assess the effectiveness of the HF and Proprietary Name program as well as other premarket measures to reduce medication errors.

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

OSE published a final guidance to help human prescription drug and biological product sponsors, application holders, and applicants minimize medication errors associated with their products. This guidance focuses on safety aspects of the application holder's container label and carton labeling design. It provides a set of principles and recommendations for ensuring that critical elements of a product's container label and carton labeling are designed to promote safe dispensing, administration, and use of the product. The guidance also provides examples of container label and carton labeling designs that resulted in postmarketing medication errors.


Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Guidance for Industry

Managing Risks

Risk Evaluation and Mitigation Strategies (REMS)

A REMS is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of a particular medication. While all medications have labeling that informs health care professionals and patients about medication risks, only a few medications require a REMS. REMS are not designed to mitigate all the adverse events of a medication; rather, REMS focus on preventing, monitoring, and/or managing a specific serious risk by informing, educating, and reinforcing actions to reduce the frequency and/or severity of the event.

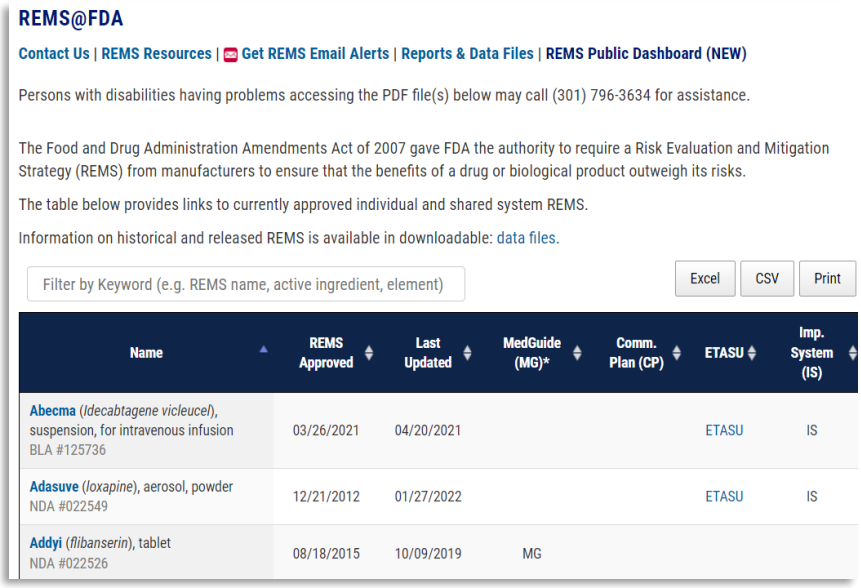
REMS may include a Medication Guide (MG), Communication Plan (CP), certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, and/or Elements to Assure Safe Use (ETASU). REMS with ETASU have additional requirements to mitigate risks, such as pregnancy tests to avoid prenatal exposure to a teratogenic drug. Manufacturers are required to assess the effectiveness of the REMS in meeting its risk mitigation goal.

Managing Risks

Structured Product Labeling (SPL) improves integrating REMS into the healthcare system

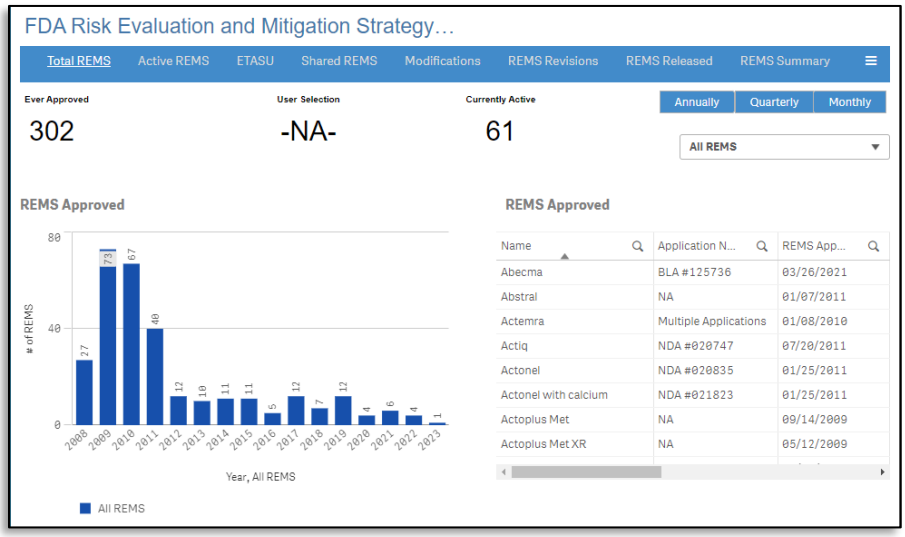
On December 28, 2022, FDA began requiring documents for new REMS and REMS modifications to be submitted electronically in Structured Product Labeling (SPL) format. SPL is a markup language that allows computers to more easily identify and process text and data in a document. SPL promotes the design and structuring of the standardized REMS document and allows for a clearly defined format and development of consistent REMS Documents. Consistently designed REMS documents allow for faster review and tracking.

Figure 6: REMS @ FDA website



SPL also makes REMS data more accessible and available for analysis compared to other formats of the REMS document. Structuring and encoding the REMS Document in SPL format allows for computers to "read", identify, and potentially populate specific information in databases such as the REMS@FDA website and the REMS dashboard. See Figures 6 and 7, respectfully. REMS SPL files are made publicly available for download via the National Libraries of Medicine's DailyMed website and contain information linking the REMS Document to the corresponding SPLs containing the prescribing information and identifiers such as the National Drug Code (NDC) that can be linked into pharmacy information management systems at the point of dispensing and to assist in clinical decision support. Moving forward, REMS SPL will help clarify the REMS requirements, identify the responsible stakeholders, and allow integration of the actionable REMS requirements within a clinician's workflow.

Figure 7: REMS Public Dashboard



Managing Risks

REMS Structured Product Labeling improves the compatibility of the REMS document with the REMS Public Dashboard. The REMS Public Dashboard serves to improve data access and transparency, and also allows users to quickly visualize trends and locate details of the REMS programs to inform emerging research and regulatory issues in the context of current drug safety. Data used in this dashboard are pulled from existing data files available on the REMS@FDA website. Users can create visualizations and charts for total and active REMS programs, REMS with ETASU,

REMS modifications, revisions, and released REMS programs. In 2022, four REMS with ETASU were created, 37 REMS were modified, and two REMS were released. As shown in Figure 8, only REMS with ETASU have been approved for the past three years.

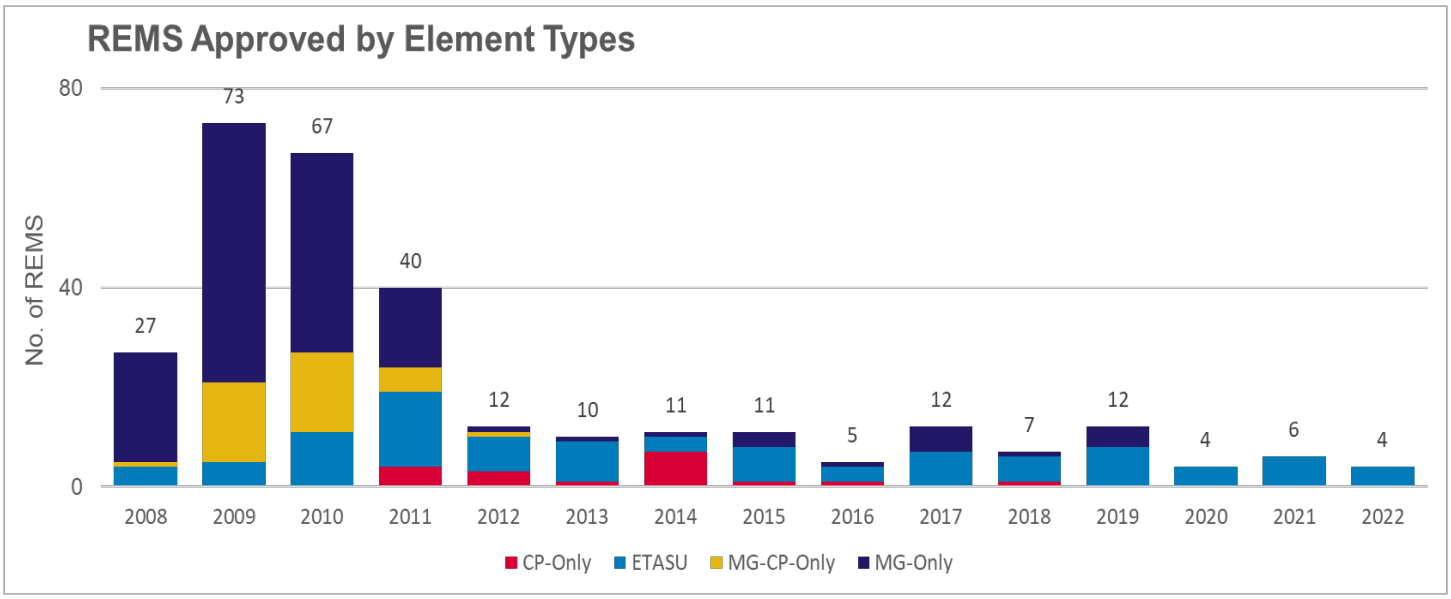
REMS Public Dashboard Web Statistics (2022)

23,200
Total Users

10.26
Average Session Duration (Minutes)

3,967
Total Hours Viewed

Figure 8: REMS Approved by Element Types



Drug Safety Modernization and Innovation

Advances in informatics and data science are transforming the identification, analysis, and management of drug risks. OSE is harnessing the potential of these advances to improve the efficiency of drug safety activities not only within FDA but also for stakeholders at the point of care.

REMS Integration and Innovation

REMS requirements can be burdensome for prescribers, pharmacists, and patients because:

- Completion of REMS requirements is often done outside of stakeholders' clinical workflows.
- In some cases, manual processes are used, which can be costly and time-consuming for prescribers and pharmacists and can create delays or barriers to medication access for patients.
- Each REMS program is slightly different, which can make it difficult to exchange information across REMS systems, electronic health records, and pharmacy information management systems.

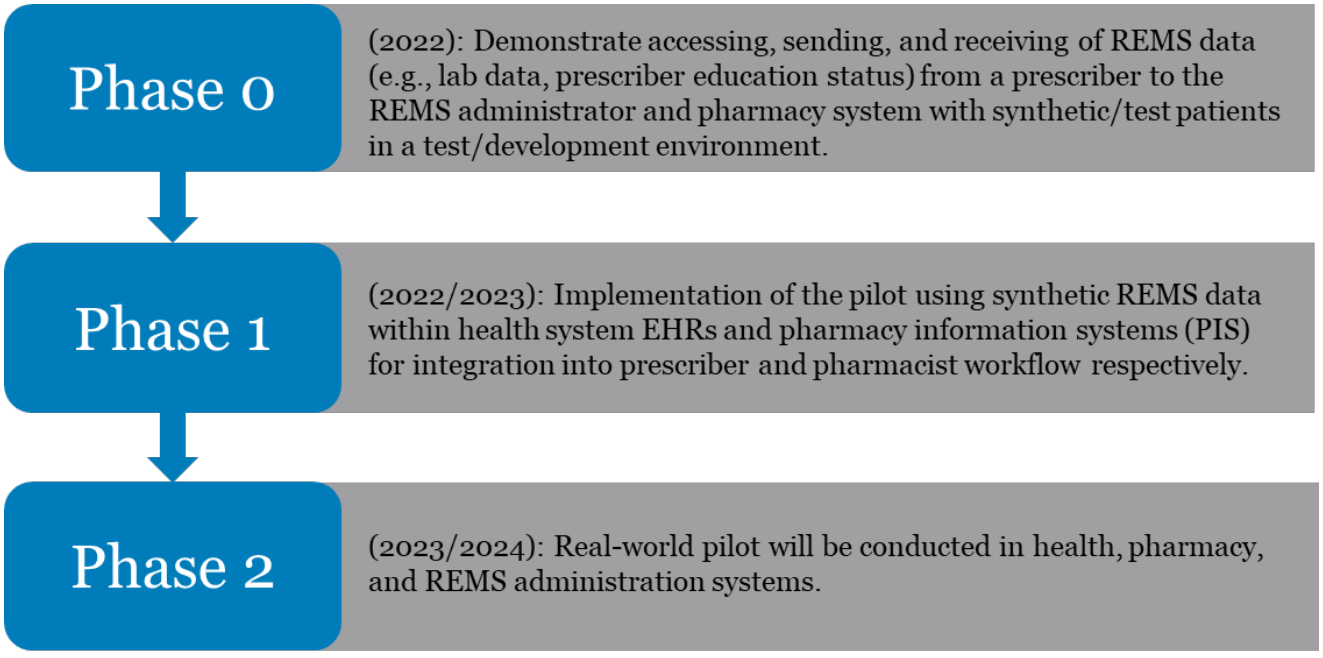
Drug Safety Modernization and Innovation

The FDA, under a contract with the MITRE Corporation and with stakeholders through an open community under the health data standards development organization Health Level Seven (HL7), is working to reduce the burden of REMS implementation and optimize patient outcomes by integrating REMS into prescribers' and pharmacists' clinical workflows:

- HL7 is a set of international standards used to support exchange of health data across the health care system.
- By using contemporary health data standards, such as Fast Healthcare Interoperability Resources (FHIR; an EHR and medical data standard) and National Council for Prescription Drug Programs (NCPDP) SCRIPT (an e-prescribing standard), prescribers and pharmacists could complete REMS requirements without having to go outside of their workflows, and many steps could be automated, increasing efficiency of implementation and reducing burden of these REMS programs.
- OSE has supported the development of an open-source proof-of-concept REMS Integration prototype that will allow certain REMS activities to be integrated into standard health information technologies.
- Such REMS integration could not only reduce burden but also promote timely and safe medication access for patients and improve data quality to optimize timely feedback on patient outcomes, enabling more robust REMS program evaluations.
- The aim of this prototype is to demonstrate the art of the possible with technical REMS integration and to help drive conversations with the community around opportunities to enhance REMS.

In October 2022, FDA and the Duke Margolis Center for Health Policy held a public workshop on REMS integration and innovation during which panelists and stakeholders generally expressed broad support for this standards-based approach. The CodeX® REMS Integration Use Case is open to the public, and there are regular public calls for those interested in contributing. By the end of 2022, as shown in Figure 9, the use case transitioned to phase 1 using synthetic data, which will test the REMS integration prototype in 2023 with select REMS drug(s), drug sponsors who are interested in participating, and in real-world health and pharmacy systems. Later in 2023 and 2024, the plan is to conduct a real-world pilot using the infrastructure of at least one health system.

Figure 9: Planned CodeX® REMS Integration Use Case Phases



Drug Safety Modernization and Innovation

Information Visualization Platform (InfoViP): OSE's New Artificial Intelligence Safety Surveillance Tool

The volume of Individual Case Safety Reports (ICSRs) in FAERS continues to increase annually. To address this increasing workload, OSE developed the Information Visualization Platform (InfoViP), a decision support tool for post market safety surveillance, to improve the efficiency and scientific validity of ICSRs review and evaluation process. InfoViP incorporates artificial intelligence (AI) and advanced visualizations to support OSE safety reviewers' work. InfoViP has three main functionalities:

- A temporal data visualization feature, which applies natural language processing (NLP) capabilities to ICSR structured fields and narratives to identify and extract clinical concepts relevant to post-market safety surveillance to create a visualization of the timeline of events, including when the drug was taken in relation to the adverse event.
- The duplicate detection algorithm also uses NLP to efficiently compare numerous data points among a large group of ICSRs to detect potential duplicates and present them to the safety reviewer for confirmation.
- A classification algorithm to identify assessable ICSRs uses both NLP and machine learning to identify and triage high-quality ICSRs for review because it can simultaneously look at multiple data points contained in each ICSR and classify them based on their level of information quality.

Collectively, these functionalities can facilitate the development of more consistent and timely safety surveillance decisions by leveraging advanced techniques.

Modernized Standards for Postapproval Safety Data Management

It is important to establish an internationally standardized procedure in order to improve the quality of post-approval safety information and to harmonize the way to gather and report information. The existing ICH E2D guideline entitled "Post Approval Safety Data Management: Definition and Standards for Expedited Reporting" was last updated in 2003, and the definitions used to describe the various sources of post approval safety reports are no longer optimal to capture current practices. Increasingly diverse sources, such as social media (i.e., technologies and platforms such as patient forums and social networks), market research programs, and patient support programs have become a primary source of postapproval adverse event reports for many products. An FDA multicenter team, led by OSE, has participated in an ICH Expert Working Group (EWG) for the past three years to update the guideline. The EWG met in person in November 2022 for the first time since the opening meeting and strengthened the progress being made towards addressing the challenges of adverse event reporting from new and diverse data sources.

Drug Safety Teams

In 2022, we stood up all nine planned Drug Safety Teams (DSTs), each with a portfolio of drugs within therapeutic areas such as neurology, oncology, infectious disease, as well as for unapproved (e.g., homeopathic, monographs) and compounded drugs. Each DST consists of expert multidisciplinary staff from OSE and other CDER Offices who provide oversight and advice for the management of a broad range of important, emergent, and complex safety issues. Through multidisciplinary discussions and collaboration, the purpose of the DSTs is to facilitate prioritization and resolution of postmarket safety issues in a timely and consistent manner.

Pharmacovigilance Strategies

OSE participated in the Pharmacovigilance Strategy pilot program in 2022. A Pharmacovigilance Strategy is an internal FDA plan for coordinated monitoring and assessment of safety information across multiple disciplines and data sources to further characterize the safety profile or to assess current risk mitigation measures for a drug product or drug class. A Pharmacovigilance Strategy can encompass routine and additional pharmacovigilance activities, such as monitoring spontaneous postmarket case reports, the medical literature, or through the assessment of a postmarket safety study.

Engaging Stakeholders

OSE engages multiple stakeholders by holding scientific meetings and public workshops, convening interagency workgroups, collaborating with international partners, and giving presentations at conferences. In 2022 the return of in-person events began to increase as the pandemic receded, giving OSE presenters the opportunity to interact directly with stakeholders. Additionally, collaboration with other federal agencies has allowed OSE to share expertise and expand understanding in many fields, particularly the opioid crisis.

Engaging the Public—Sentinel Workshop and Innovation Day

Sentinel enhances the FDA's ability to proactively monitor the postmarket safety of medical products and complements FAERS. By using a distributed data approach, Sentinel can monitor the safety of regulated drugs and biologics, while securing and safeguarding patient privacy. In 2022, the Sentinel team held two major outreach events—a public workshop and a public training—to improve the public's understanding of the Sentinel system.

Engaging Stakeholders

- 2022 Sentinel Public Workshop — November 15-16, 2022
    - On November 15th and 16th, FDA, under a cooperative agreement with the Duke Margolis Center for Health Policy, hosted the 14th Annual Sentinel Initiative Public Workshop. The workshop was a webinar and provided an opportunity for attendees to discuss recent achievements and developments as well as engage with the broader community of patients, consumers, and scientific stakeholders.

    - Participants heard from Sentinel Initiative leadership on a range of key issues including recent studies and applications of Sentinel to protect and promote public health during the ongoing COVID-19 pandemic.

- 2022 Sentinel Innovation Day — April 28, 2022, and Public Training on April 29, 2022
    - The 13th Annual Sentinel Public Training was a two-day event held in April 2022. The Innovation Center highlighted challenges and opportunities for integrating electronic health record-based data in common data models, computable phenotyping to aid medical product safety investigations, advanced analytic approaches to improve confounding adjustments in Sentinel investigations, and a causal inference framework for Sentinel.

    - Investigators from the Sentinel Operations Center discussed the opportunities presented by the new Inverse Probability of Treatment Weighting (IPTW) tool within the Sentinel Routine Querying System, and how researchers can conduct analyses of routinely collected electronic health data in the Sentinel Common Data Model format. IPTW is a statistical method that can be used in observational studies to improve our ability to draw valid conclusions about the safety of medical treatments.

Engaging other Federal Organizations to Analyze the Drug Supply Chain

OSE took steps to increase the understanding of the drug supply chain to allow for more data driven assessment of risks to supply. Also, steps were taken to increase resilience and maintain the security and integrity of the supply of human pharmaceuticals.

OSE participated in reviewing drug supply chain work and documents, both internally and with federal partners, such as the Administration for Strategic Preparedness and Response (ASPR) Public Health Supply Chain and Industrial Base one-year report. We also supported Department of Health and Human Services (DHHS) and ASPR requests to inform ASPR's supply chain activities. For example, we helped with analyses of the distribution of high-risk critical drugs whose supply may have been impacted by the COVID-19 pandemic.

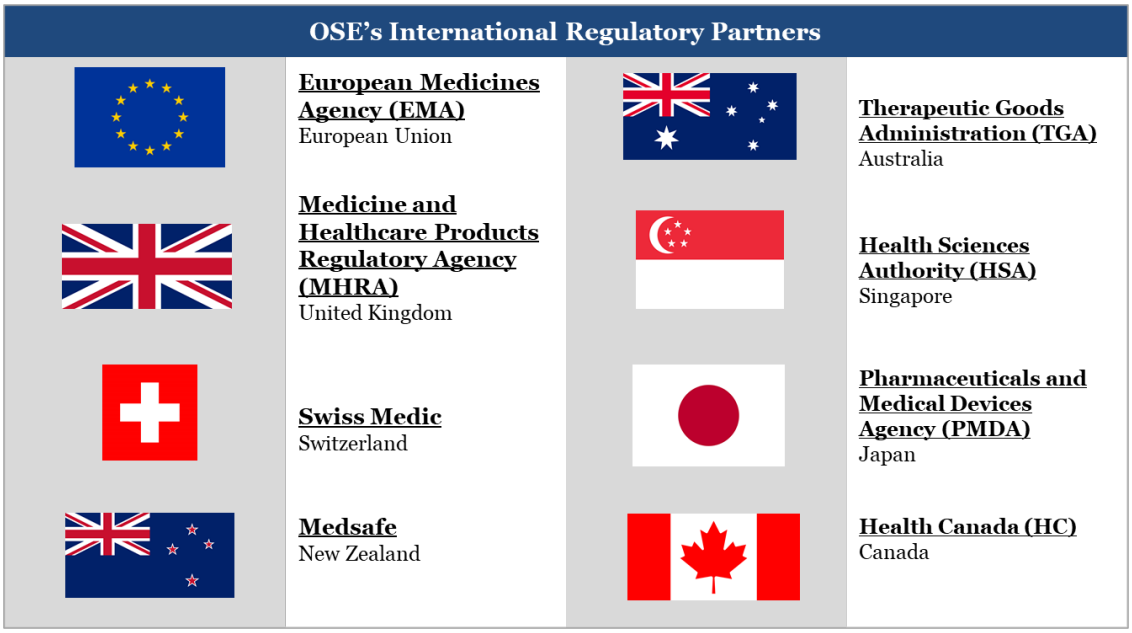
OSE enhanced surveillance of antibiotics, antivirals, and analgesics used in the pediatric population due to the winter surge in COVID-19, respiratory syncytial virus (RSV), and influenza among children. We supported other US government entities by collecting, analyzing, and sharing new data on over-the-counter children's analgesic products.

Engaging Stakeholders

Engaging the International Community

OSE regularly exchanges information with international regulators (see Figure 10) on safety surveillance topics, adverse event reporting, and other issues of common interest. The goal of these interactions is to collaborate on drug safety activities and support global harmonization on similar regulatory programs. In 2022, OSE exchanged information on more than 200 topics, including several pertaining to the COVID-19 pandemic.

Figure 10: OSE's regulatory collaborators around the globe

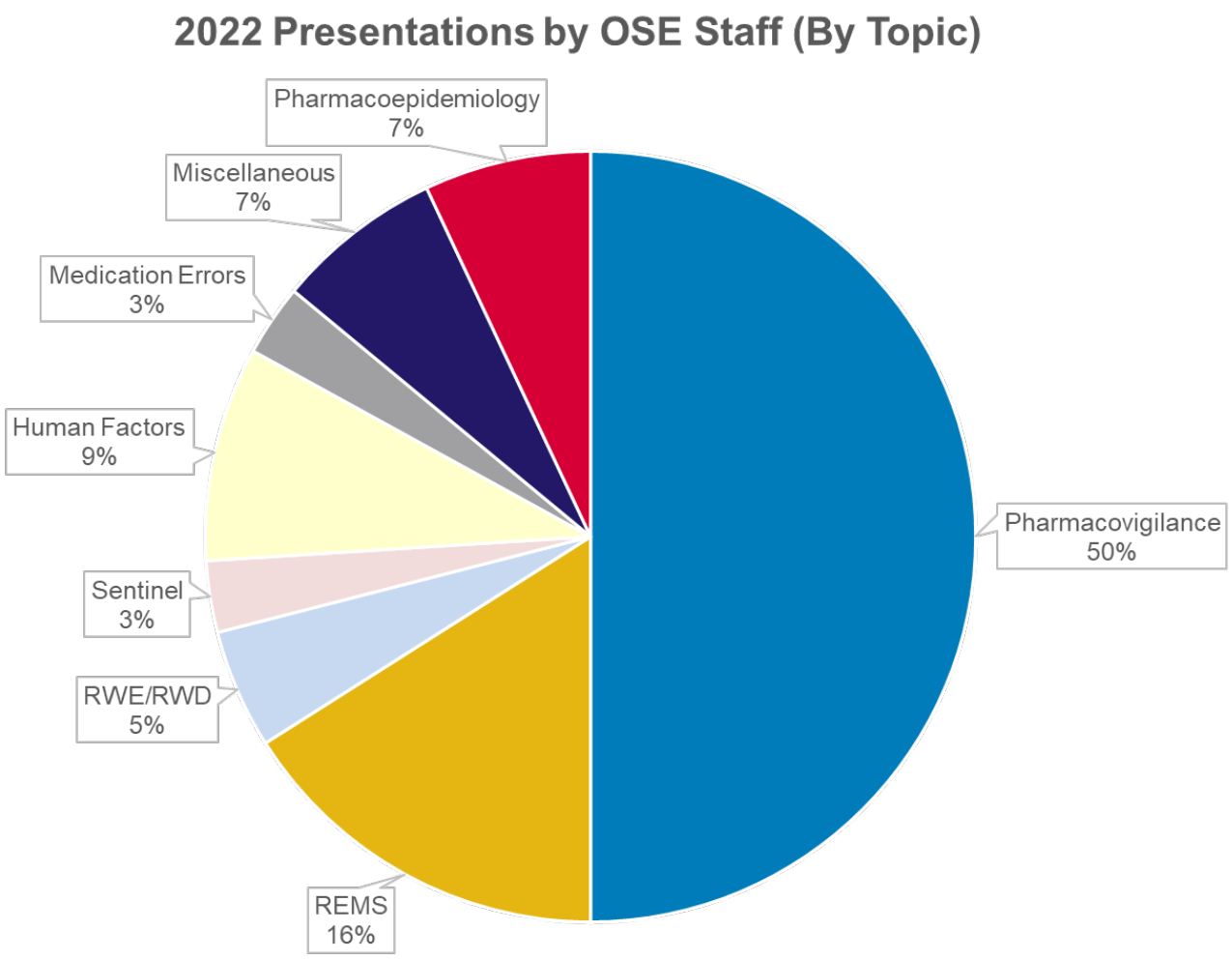


Engaging Stakeholders

OSE Presentations

In 2022 OSE staff gave nearly 100 presentations as seen in Figure 11, on a wide variety of topics, reaching thousands of students, researchers, as well as industry professionals in the U.S. and overseas. Presentations on topics such as Sentinel, FAERS, and the REMS Public Dashboard serve to improve stakeholder engagement and help users better understand and utilize tools developed by OSE.

Figure 11: Presentations by OSE staff during 2022 broken down by topic



Looking to the Future

Priorities for 2023 and Beyond

In 2023, OSE will start to implement responsibilities under the Prescription Drug User Fee Act VII, the Generic Drug User Fee Act III, and the Biosimilar User Fee Act III, which will broaden our capabilities in pharmacovigilance, risk management, pharmacoepidemiology, and medication error prevention. In accordance with the SUPPORT Act, OSE will continue to explore additional innovative strategies to confront the nonmedical use of opioids, including enhanced education for prescribers on managing pain and appropriate prescribing of opioid analgesics, and disposal options for patients.

OSE looks forward to growing the nine Drug Safety Teams' ability to provide cross-functional, interdisciplinary, and scientific expertise to facilitate discussion and guidance of safety issues.

Sentinel, in the final year of its five-year strategic plan, will continue evaluating new approaches to expand its use of data in electronic health records. The Sentinel Newsletter will continue to disseminate knowledge and advance regulatory science.

Regarding our efforts to modernize postmarket drug safety, OSE will continue to explore novel methods, including artificial intelligence, to increase efficiency in processing the growing number of ICSRs submitted to the FDA Adverse Event Reporting System. We will transform the REMS review process by applying a Logic Model, which is a systematic, structured approach that incorporates REMS assessment planning into the design of the REMS. We will continue to support the HL7® CodeX® REMS Integration Use Case which aims to reduce the burden associated with REMS implementation by integrating REMS activities into the health care system.

One additional priority is to continue interactions with international regulatory partners to promote the exchange of information.

Appendix: OSE 2022 Publications

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