U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology 2021 Annual Report

Detecting, Assessing, Preventing, and Managing Risks

April 2022

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Director's Message

It is my pleasure to share with you the 2021 Annual Report for the Office of Surveillance and Epidemiology (OSE).

OSE has four core functions – pharmacovigilance, pharmacoepidemiology, medication error prevention and analysis, and risk management – and operates across multiple disciplines to review and assess the safety of medicines. Everything in OSE is tied to these four core functions. These core functions are supported by staff specializing in medicine, pharmacy, regulatory science, regulatory affairs, epidemiology, human factors engineering, social science, safety surveillance, information technology, clinical informatics, project management, administration, contracting, training, and communication.

2021 was an extremely busy and productive year for OSE. As COVID-19 continued to shape our personal and professional lives, OSE staff continued our work to monitor, assess, and ensure the safety of medications available to the American public. As more therapies for COVID-19 became available under Emergency Use Authorizations (EUAs), we expanded our safety monitoring capabilities. Through these efforts, were able to understand the uptake of these products and update, as needed, the Fact Sheets that accompany them with new safety-related information. We also launched the COVID-19 EUA FDA Adverse Event Reporting System (FAERS) Public Dashboard in March 2021 to keep the public informed about adverse events reported for these products. As part of the nation's response to the COVID-19 public health emergency, our Commissioned Officers in the US Public Health Service continued to deploy around the United States to assist with various federal and state efforts.

Though our work on COVID-19 kept us quite busy, we also moved forward with several other initiatives, such as the launch of dedicated Drug Safety Teams with the Office of New Drugs, the initiation of multiple projects within the Sentinel Initiative to better use data from electronic health records, and the reorganization of our Office of Medication Error Prevention and Risk Management (OMEPRM) to improve premarket review efficiency and increase focus on the safe use of marketed medicines – just to name a few.

The keys to our success in 2021 were our staff's ongoing dedication to FDA's mission, its professionalism, and its commitment to robust science.

Best regards,

Gerald Dal Pan, MD, MHS

OSE Senior Leadership Team

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OSE Director

Robert Ball, MD, MPH, ScM
OSE Deputy Director

Donal Parks, MBA, MPM
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Judith Zander, MD
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Deputy Director, OPE

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Director, OMEPRM

OSE Organizational Structure

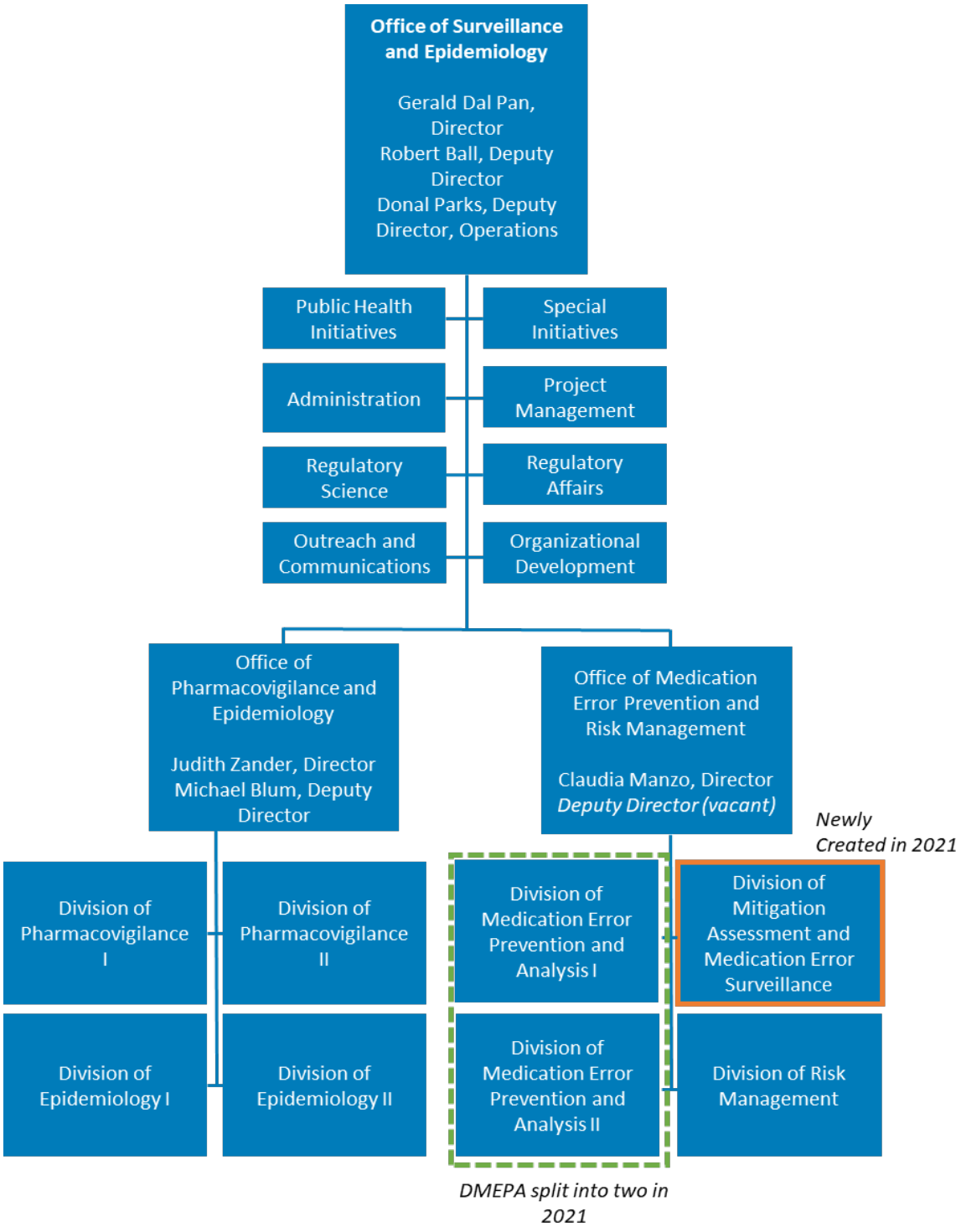


Figure 1: OSE organizational chart as of December 2021

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 risk assessment tools to identify and assess adverse events and medication errors that did not appear during the drug development process as well as to understand better those risks observed in clinical trials.

OSE has four core functions – pharmacovigilance, pharmacoepidemiology, medication error prevention and analysis, and risk management – 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 COVID-19

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

The Secretary of Health and Human Services (HHS) declared a public health emergency on January 31, 2020 after cases of Coronavirus Disease 2019 (COVID-19) were confirmed in the United States. FDA has played a critical role in the pandemic response. In 2021, OSE continued its role in this response by expanding our four core functions and developing an office-wide COVID-19 core team. This build-up of infrastructure improved our ability to deliver rapid responses through surveillance and epidemiology. The OSE Immediate Office provided research, regulatory, project management, communication, and outreach that supported the various divisions with their many COVID-19 activities.

OSE COVID-19 Pandemic Activities

Pharmacovigilance	Pharmacoepidemiology	Medication Errors	Risk Management
• Adverse event monitoring for products used in relation to COVID-19 • Fact sheet safety labeling change updates • Adverse Event Summary & Hand Sanitizer surveillance data • Safety Assessments	• EUA active surveillance framework • Drug Utilization • Sentinel ARIA, Collaboration with Internal and Federal Partners • Safety Assessments	• Medication error monitoring for products used in relation to COVID-19 • Proprietary name, labeling, and packaging reviews • Dear Health Care Provider letters • Updates to consumer/ provider Fact Sheets • Safety Assessments	• Responded to inquiries on individual approved REMS requirements • Review of REMS modifications with proposed alternative methods to carry out safe use conditions to decrease risk for viral transmission

OSE IO: Coordinated scientific information across OSE and served as the OSE Scientific Lead for COVID-19 activities.

Figure 3: OSE's COVID-19 Pandemic Activities

Responding to COVID-19

We continued to make significant strides in 2021 by examining and analyzing data across at least 15 data sources, including new data tools to obtain and review near real-time drug sales and prescription data, and for surveillance using a variety of data sources, including population-based data sources.

FDA utilized its authority during the public health emergency to issue EUAs for products to prevent or treat COVID-19. FDA staff performed daily searches in FAERS to detect and assess adverse events and medication errors related to products used to treat COVID-19. These surveillance efforts led to the identification of safety issues resulting in updates to the Fact Sheets shortly after authorization for several products authorized for emergency use. In addition to conducting daily searches in FAERS, OSE monitored adverse event reports from a variety of data sources, as well as the medical literature.

In 2021, the OSE screened over 80,000 FAERS reports and 66,000 abstracts in the published medical literature related to COVID-19.

We reviewed proposed proprietary names, container labels, labeling, and packaging to prevent medication errors and help ensure the safe use of drug products authorized for emergency use and drug products that were imported during the pandemic to alleviate drug shortages. The pandemic impacted all aspects of healthcare delivery, including the medication use system. We identified vulnerabilities that could contribute to medication errors, including limitations of electronic health order entry systems and the lack of barcodes on container labels and carton labeling for product verification. We closely monitored medication error reports and fostered our partnerships with patient safety organizations such as the Institute of Safe Medication Practices (ISMP) to exchange safety information. We updated Fact Sheets, revised container labels and carton labeling, and collaborated on Dear Health Care Provider letters and other safety communications to help mitigate potential and identified medication errors.

For drug utilization analyses, OSE conducted regular assessments of drug sales and prescription data using HCA Healthcare data available to the Agency under contract to inform near real-time drug utilization patterns. In addition, we conducted 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. Descriptive data for monoclonal antibody utilization was assessed in Sentinel, CMS Medicare, and the Veterans Health Administration (VHA). OSE examined 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 Health Verity. OSE continued to monitor near real-time monitoring of critical drugs during COVID-19 using HCA Healthcare data in Sentinel.

Responding to COVID-19

Through surveillance using population-based data sources, OSE collaborated with federal partners to establish an active surveillance framework in CMS Medicare, VHA, and FDA's Sentinel System data sources. This active surveillance framework enhanced the understanding of COVID-19 natural history and created capacity for near-real time assessment of safety and effectiveness of therapeutics administered under an EUA using real-world data. A multi-data approach was developed within Sentinel to support COVID-19 related projects using multiple data partners. FDA used Sentinel's Data Partner network to build a database with the most current available data from national claims insurers and integrated delivery systems. This "rapid" database is routinely updated to support observational studies for COVID-19 related research and post-market surveillance of treatments administered during the pandemic. Further, rapid data in FDA Sentinel could be used to strengthen signals generated from FAERS and other resources. Additional information can be found on the FDA Sentinel page and the Sentinel Initiative website.

During the COVID-19 pandemic, the Sentinel Team published a master protocol designed to use electronic healthcare data to describe COVID-19 clinical characteristics and identify patient factors related to disease progression/prognosis. This is supporting a study addressing questions about the natural history of COVID-19 in pregnancy.

Our pharmacoepidemiologists were not only involved in these surveillance activities, but also in reviewing the COVID-19 observational literature. The pandemic led to an abundance of published medical literature, particularly on effectiveness of repurposed drugs in the treatment of COVID-19 early in the pandemic. Because this literature was often not peer reviewed, it often warranted rapid critique of study design and outcomes by our epidemiologists to inform staff on potential regulatory actions. These review activities also include reviewing sponsor-submitted proposals and protocols for safety and effectiveness studies for COVID-19 therapeutics under EUA and approved products used for COVID-19.

COVID-19 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 and the need for data on both demand and supply. OSE collaborated with other offices to develop innovative quantitative, data-driven approaches to inform near real-time drug utilization patterns to enhance and support identification, refinement, and validation of signals of drug shortages and other supply disruptions. OSE rapidly created capabilities for near real-time monitoring of critical drugs used in the inpatient setting during COVID-19 using HCA Healthcare data in Sentinel. We also performed weekly assessments of drug sales and prescription data using proprietary drug sales distribution and utilization databases available to the Agency under contract to inform near real-time drug utilization patterns to inform safety.

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.

As shown in Figure 4, there has been a steady increase of report volume over the last 10 years. In 2021, there was more than a 6% increase in adverse event reports that are both serious and not listed in the product's labeling compared to 2020. Of the over 2.3 million reports received in 2021, almost 1.4 million were described as serious adverse events not listed in the product labeling.

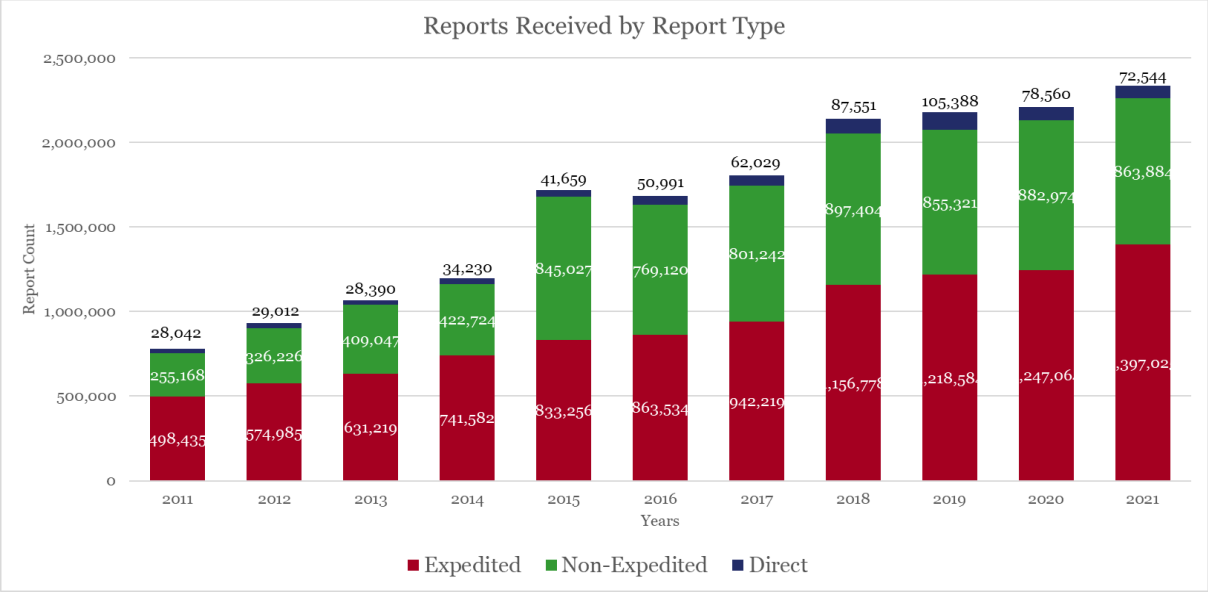


Figure 4: FAERS Reports Over the Past Decade

Detecting and Assessing Risks

FAERS Public Dashboard and FAERS COVID-19 Public Dashboard

In September 2017, OSE launched the FAERS Public Dashboard. The FAERS Public Dashboard expanded access to FAERS data to the public by providing a means to search for information on human adverse events related to human drugs. Prior to the development of the dashboard, only raw FAERS data (going back to 1968) were made available to the public in complex data files on a quarterly basis. 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 has been updated quarterly since its inception.

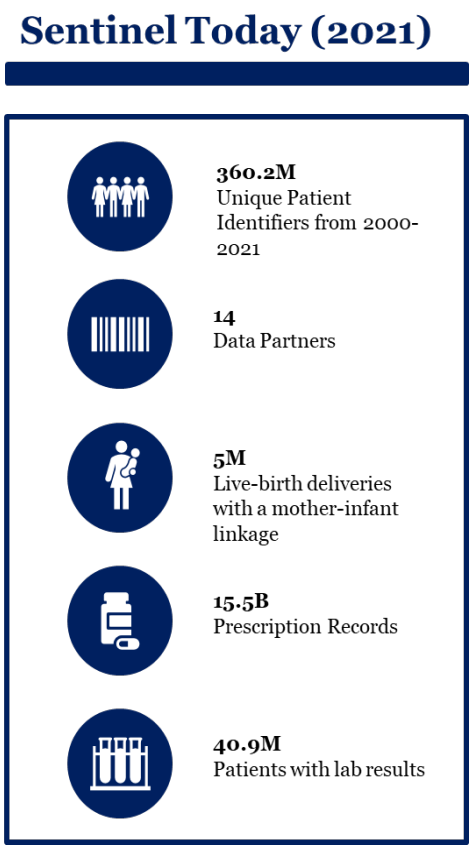
There was a rapid uptake of the products authorized under an EUA to combat the ongoing COVID-19 pandemic. In order to keep the public adequately informed of adverse events reported for these products, more frequent updates to the FAERS Public Dashboard were needed during COVID-19. The COVID-19 EUA FAERS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

FAERS is only one piece of the many safety surveillance data sources used by OSE. When a potential safety concern is identified, further evaluation may be performed, which can include literature reviews and conducting studies using tools such as the Sentinel System.

Sentinel

The Sentinel System was developed to analyze large quantities of electronic healthcare data efficiently to monitor the safety of marketed drugs 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 search for it when needed to conduct specific analyses. 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



Detecting and Assessing Risks

approximately 800 million person-years of longitudinal data and more than 64 million patients actively accruing new data. OSE utilized the Sentinel System in 81 medical product assessments in 2021.

The Sentinel System has been able to address public health crises, such as COVID-19. Notable achievements in 2021 include:

- Drug safety analyses conducted in Sentinel informed updates to the labeling of oral anticoagulant products for the risk of clinically significant uterine bleeding and the labeling of parenteral iron products for the risk of severe adverse reactions in pregnant women.
- The Sentinel Innovation Center and the Community Building and Outreach Center separately published their Master Plans, which outline core projects to advance the Sentinel System's strategic aims.
- FDA initiated multiple projects through the Sentinel Innovation Center with capabilities to utilize Electronic Health Record (EHR) data in areas including natural language processing and machine learning.
- FDA completed an end-to-end redesign of the Sentinel Initiative website through the Community Building and Outreach Center to improve the usability of information.
- Sentinel has continued supporting FDA's response to the COVID-19 pandemic by expanding and enhancing data infrastructure, launching new scientific studies, and coordinating with other national and international partners.

During the COVID-19 pandemic, the Sentinel Team participated in the Reagan-Udall Foundation COVID-19 Evidence Accelerator activities to share insights, compare results, answer key questions about COVID-19, and lead a workstream to evaluate coagulopathy in COVID-19 patients.

Preventing Risks

OMEPRM Reorganization to Support Medication Safety

OSE's OMEPRM is the lead for CDER's medication error prevention and analysis program and risk evaluation and mitigation strategy (REMS) program. As the number and complexity of approved medicines in the U.S. continues to increase, the number of serious adverse events and medication errors in the U.S. population also continues to increase. This situation requires strategies to help ensure the safe use of medicines and mitigate risks associated with their use.

In 2021, OMEPRM implemented a reorganization to:

- Manage resources more effectively and support the high-volume workload
- Prioritize post-marketing aspects of our medication error and REMS programs
- Increase research initiatives and special projects to strengthen the science of our medication error and REMS programs
- Promote career opportunities and professional development and increase the program's ability to retain highly skilled professionals.

The reorganization split the Division of Medication Error Prevention and Analysis into two divisions that focus on premarket work (DMEPA I and DMEPA II); established a new division, the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES), to focus on postmarket REMS assessment and medication error surveillance activities; and restructured DRM to focus on premarket REMS and REMS modification review activities (See Figure 5).

Preventing Risks

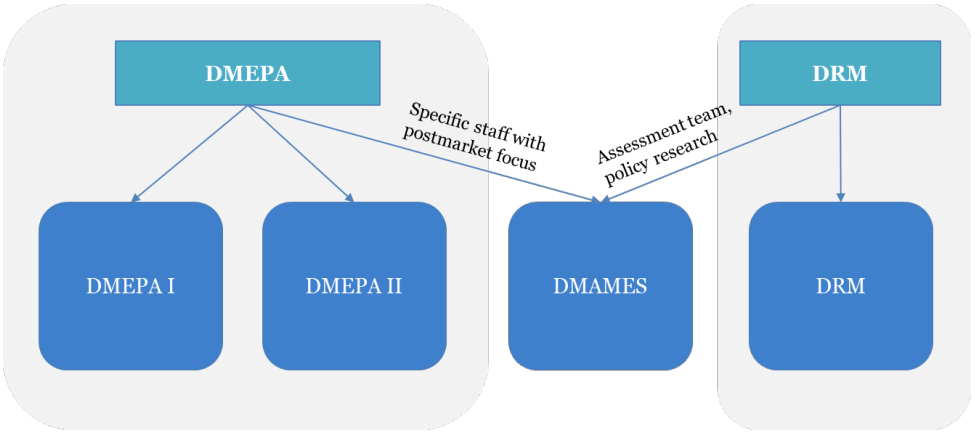


Figure 5: Details on the 2021 Reorganization of OMEPRM

These changes in OMEPRM established divisions with clearer and more focused areas of expertise to increase efficiency across programs and help us enhance our scientific leadership in these areas. Once fully staffed, the additional efficiency we achieve will be channeled toward the development of more guidance for regulated industry and expansion of our scientific expertise to enable better regulatory decisions.

Prevention of Medication Errors Throughout a Product's Lifecycle

As part of the FDA preapproval process for new drug products, DMEPA I and II review and determine the acceptability of proposed proprietary names for drugs and for biological products, distinguishing suffixes included in nonproprietary names to minimize medication errors associated with product name confusion. Both divisions also review proposed container labels, carton labeling, prescribing information (including the Instructions for Use and Medication Guides), packaging, and human factors submissions to minimize or eliminate hazards that can contribute to medication errors. Fiscal Year 2021 user fee goals for the review of proprietary names are listed in Table 1.

In FY 2021, DMEPA I and II exceeded user fee goals by completing their reviews of proprietary names within the required timeframe greater than 93% of the time.

Preventing Risks

Application Type	Receipts	Performance Goal Met (%)	Performance Goal Exceeded
IND	190	96	Yes
NDA/BLA	213	96	Yes
BsUFA IND	8	100	Yes
BsUFA BLA	15	93	Yes
ANDA*	29	96	N/A
Total	455		

Table 1: Proprietary Name Reviews from October 1, 2020 – September 30, 2021

**Note: Proprietary Name Reviews (PNRs) are not subject to GDUFA II but the performance is being tracked based on a 180-day review timeframe*

FDA's nonproprietary naming convention for biological products approved in a 351(a) BLA and for biosimilars or interchangeable biosimilar biological products approved in a 351(k) BLA consists of a distinguishing suffix added to the core name. This unique four-letter suffix should be attached to the core name by a hyphen. DMEPA reviewed 41 nonproprietary suffixes in FY 2021 (See Table 2).

Human factors engineering (HF) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system. HF applies theory, principles, data and methods to optimize patient safety in the healthcare environment. In FY2021, OMEPRM received 85 HF protocols and 356 other HF submissions or consults including HF validation study results reports, formal industry meeting requests, and use-related risk analyses.

Work Type	# Completed
Suffix review for 351(a) BLA	22
Suffix review for 351(k) BLA	13
IND	6

Table 2: Nonproprietary suffix review for biological products from October 1, 2020 – September 30, 2021

In the postmarketing setting, 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 collaboratively investigates medication error safety signals for marketed drug products, including non-prescription, prescription, generics, and biosimilars and other therapeutic biological products, to determine if regulatory action is needed to mitigate the errors.

Managing Risks

Risk Evaluation and Mitigation Strategies (REMS)

REMS are designed to reinforce medication use behaviors and actions that support the safe use of a particular medication. 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.

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. FDA has approved nearly 300 REMS programs and over 700 REMS modifications since 2008.

Managing Risks

Creation of REMS Public Dashboard

Information about the characteristics of REMS programs is manually processed by OSE staff. It has become increasingly challenging to interpret the volume of REMS data gathered over time in a meaningful way that allows an understanding of how these programs, at a high level, have evolved over the years. In response to this need, OSE developed a user-friendly REMS Public Dashboard in 2021 for efficient report-generating capabilities, data retrieval, and analysis of REMS information available on the REMS@FDA website. This allows health care providers, research organizations, academia, industry, and other federal agencies to access data and generate reports.

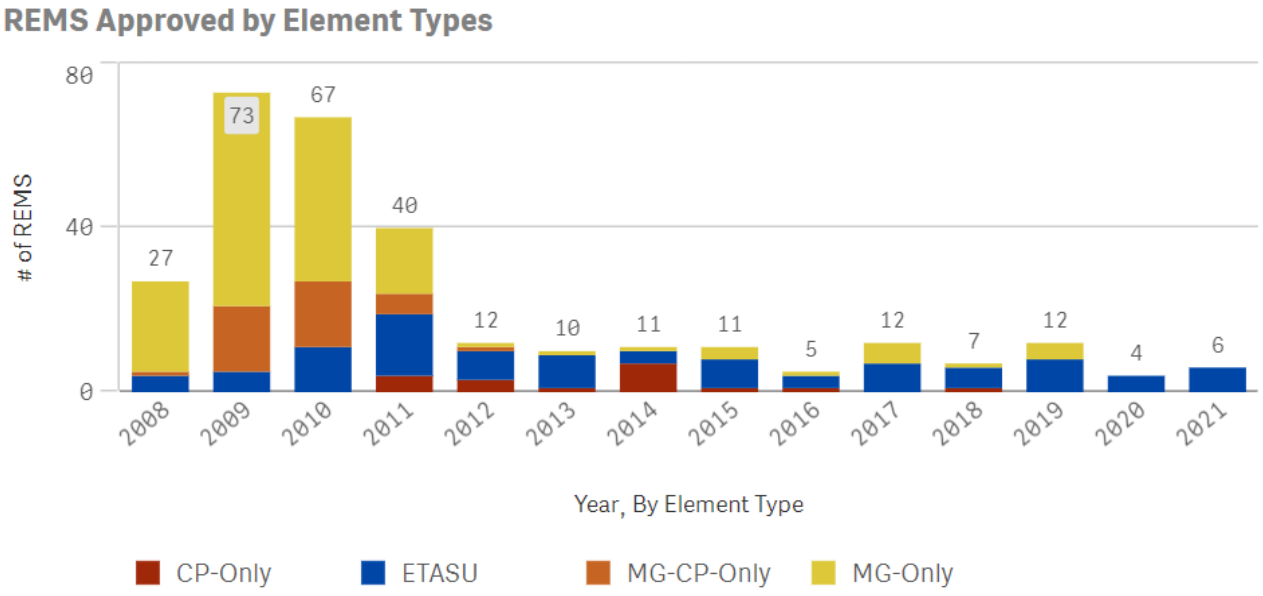


Figure 6: REMS Approved by Element Types

Managing Risks

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, ETASU, REMS modifications, revisions, and released REMS programs that are no longer in effect because the REMS met its goals and was no longer necessary to ensure that the benefits of the drug outweigh its risks.

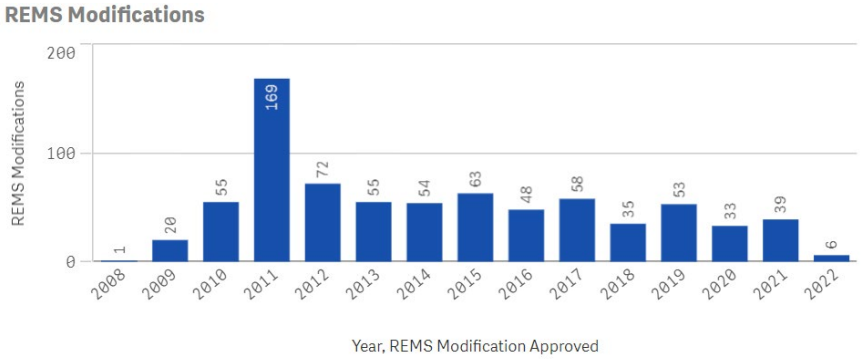


Figure 7: REMS Modifications

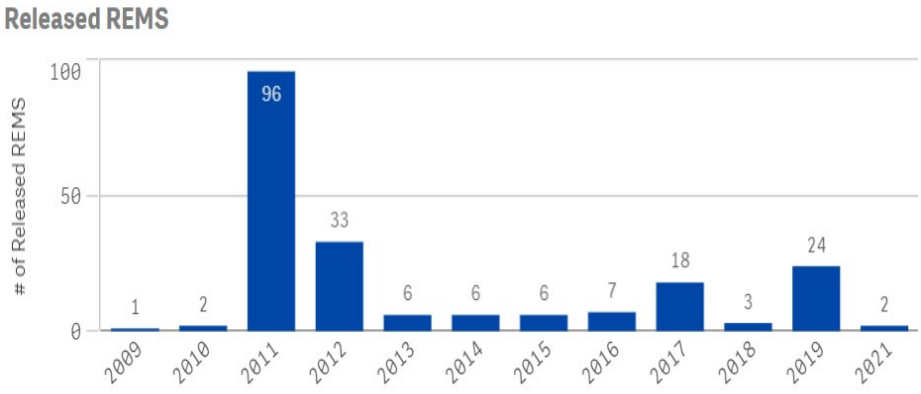


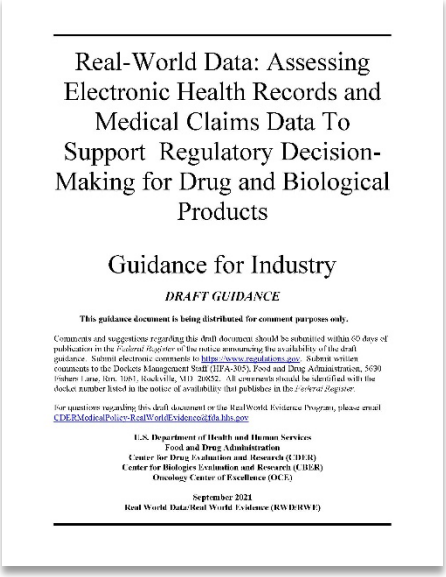
Figure 8: Released REMS

Drug Safety Modernization and Innovation

The world of postmarketing safety continues to evolve. There are many more sources of safety data and richer data sets available to our epidemiologists and clinicians than ever before, and new methods and technology have enabled us to support the analyses of the data much more quickly. For example, a few years ago, we couldn't analyze disparate impacts for patients who were pregnant, or for patients by race in observational studies. Today, we often can. A few years ago, we could only access safety information that was several months old. Today, we can access a broader selection of validated data sources much more quickly, which means our staff must interpret ever-larger sets of complex safety information, to see the big picture, and take necessary action to protect patients.

Real World Evidence (RWE) Claims Guidance for Industry

The 21st Century Cures Act, passed in 2016, is meant to accelerate medical product development and bring innovations faster and more efficiently to patients. The Act requires FDA to develop a framework and guidance on the potential use of RWE to help support approvals of new indications for drugs or biological products already approved by the FDA, or to help support or satisfy post-approval study requirements for these products.



Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the Real World Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)

In September 2021, FDA issued a draft guidance that provides recommendations for evaluating the relevance and reliability of EHRs and medical claims data used in a clinical study. Specifically, this guidance is intended to provide sponsors, researchers, and other interested stakeholders with considerations when aiming to use EHRs or medical claims data in clinical studies to support a regulatory decision on effectiveness or safety.

Drug Safety Teams

In 2021, we launched three new Drug Safety Teams, each of which oversees the safety of a portfolio of marketed drugs. These expert multi-disciplinary teams monitor and prioritize the range of safety issues arising within therapeutic areas such as neurology, oncology, and infectious disease. Drug Safety Teams facilitate sharing of information about safety issues from all CDER Offices with scientific safety responsibilities and increase efficient safety evaluations.

Use of Artificial Intelligence

Artificial intelligence (AI) is being explored as part of a decision support tool to efficiently extract and organize information in such a way as to allow expert's time to focus more on complex tasks associated with public health impact. AI is being applied to data contained in individual case safety reports within FAERS to derive a visualization of the temporal relationship between the drug and adverse event, to support the identification of duplicate reports, and assist in the triaging of reports with high information quality.

Drug Safety Modernization and Innovation

Supply Chain Surveillance Using Advanced Analytics

OSE continues to provide scientific leadership and expertise on data-driven, evidence-based approaches to identify, refine, and validate signals of drug shortages and other supply issues. To aid in assessing the risk of shortages of certain critical medicines, OSE's expertise in drug utilization data and analysis is integral to the launch of CDER's new drug supply chain surveillance system, with the goal of earlier detection of and response to supply chain disruptions. CDER staff uses the increased visibility into the surveilled pharmaceuticals' availability and supply and demand in their various roles in addressing drug shortages.

Computerized Labeling Assessment Tool (CLAT)

OSE reviews proposed container labels and other labeling for drug products to ensure the product conforms with applicable statutes, regulations, standards, FDA guidance for industry, and best practices for patient safety. However, much of the labeling review process is manual, and thus labor- and time-intensive, and may be subjective based on individual reviewer perspective or prone to possible discrepancies related to human factors. In 2021, FDA awarded a contract to develop a prototype for the CLAT, which will use modern artificial intelligence methods, including machine learning, natural language processing, and image processing, to automate manual labeling review efforts. Automating the labeling reviews will create operational efficiencies and help streamline and standardize the review process to ensure consistency across different products and review teams.

Engaging the Public

OSE's Continued Response to the Opioid Public Health Crisis

Workshop on Morphine Milligram Equivalents (MMEs) to Identify Knowledge Gaps, Research Opportunities, and Future Directions

In June 2021, FDA held a two-day virtual public scientific workshop attended by more than 300 participants from government, academia, industry, patient advocacy groups, healthcare providers, and researchers to discuss the scientific basis of MMEs. 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. The workshop: 1) provided an understanding of the science and data underlying existing MME calculations for opioid analgesics; 2) discussed the gaps in these data; and 3) considered future directions to refine and improve the scientific basis of MME applications.

FDA/Duke Margolis Meetings on Mandatory Prescriber Education on Opioids

Through a cooperative agreement with FDA, the Duke-Margolis Center for Health Policy convened a public workshop with over 300 attendees in October 2021 to consider ways in which we can use our authorities to enhance prescriber education around prescribing opioid analgesics, including through the exploration of mandatory prescriber education as part of the Opioid Analgesic REMS. The purpose was to give stakeholders an opportunity to provide input on aspects of the current opioid crisis that could be mitigated in a measurable way by requiring mandatory prescriber education as part of the REMS.

Engaging the Public

Public Health Outreach Activities

Sentinel Outreach: 13th Annual Sentinel Public Workshop (November 2021)

In collaboration with the Duke-Margolis Center for Health Policy, OSE held the 13th Sentinel Annual Public Workshop in November 2021. This year's meeting featured a keynote by CDER Director Dr. Patrizia Cavazzoni. The virtual public workshop highlighted milestones and strategic initiatives underway to enhance and build a more robust Sentinel Initiative, and stakeholders discussed opportunities to advance Sentinel's existing data, infrastructure, and technology.

There were 1,247 attendees on both days of the 13th Annual Sentinel Workshop.

Potential Medication Error Risks with Investigational Drug Container Labels (Public Meeting, May 2021)

On May 18-19, 2021, FDA held a two-day public meeting attended by more than 700 participants to solicit input from stakeholders on the: 1) risk of medication errors potentially related to the content and format of information on investigational drug container labels; 2) prevalence and nature of such errors; and 3) to gather information on practices that minimize the potential for medication errors. Panelists included representatives from clinical trial sites, contract research organizations, sponsors, institutional review boards, Health Canada, the United Kingdom's Medicines and Healthcare Products Regulatory Agency, and FDA who provided their perspectives on the current state and opportunities for future collaboration to identify and mitigate potential medication error risks with investigational drug products.

Engaging the International Community

OSE exchanges information with international regulators 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 2021, OSE exchanged information on more than 200 topics, including several pertaining to the COVID-19 pandemic.

Figure 9: OSE's international regulatory partners

Engaging the Public

OSE Collaboration with International Coalition of Medicines Regulatory Authorities (ICMRA) to Combat COVID-19

ICMRA is an alliance of global regulators that was formed in 2012 to jointly address common areas of concern, including medication safety issues. In 2020 and 2021, the ICMRA coordinated the safety monitoring of COVID-19 treatments among international partners.

We completed a study in Sentinel to assess the risks of arterial and venous thromboembolic events (blood clots), and related death, among COVID-19 patients and to compare these risks to patients with influenza. Following a COVID-19 diagnosis, 2.8% of patients experienced an arterial thromboembolism and 1.8% experienced a venous thromboembolism. After an arterial or venous thromboembolic event, the risk of death was over 3-fold higher for patients with COVID-19 than for patients with influenza. The FDA Sentinel team is expanding this study globally via an ICMRA collaboration by combining data from Europe, Canada, and the United States. This study is ongoing.

OSE participated with ICMRA on collaborative studies on the impact of COVID-19 infection and medicines in pregnancy using real world data. The study is using the FDA's Sentinel System to evaluate the use of medications and clinical outcomes of COVID-19 disease in pregnant women. OSE plans to share the results with the ICMRA working group for an international meta-analysis.
The National Institutes of Health (NIH) COVID-19 treatment guidelines advise against corticosteroid use in patients with mild-to-moderate COVID-19 who do not require hospitalization or supplemental oxygen. OSE presented findings from our study at the ICMRA meeting in May 2021. The study was conducted in four large including Sentinel. Among 2.2 million eligible COVID-19 patients from April 2020 to December 2020, between 3.4-12.2% received

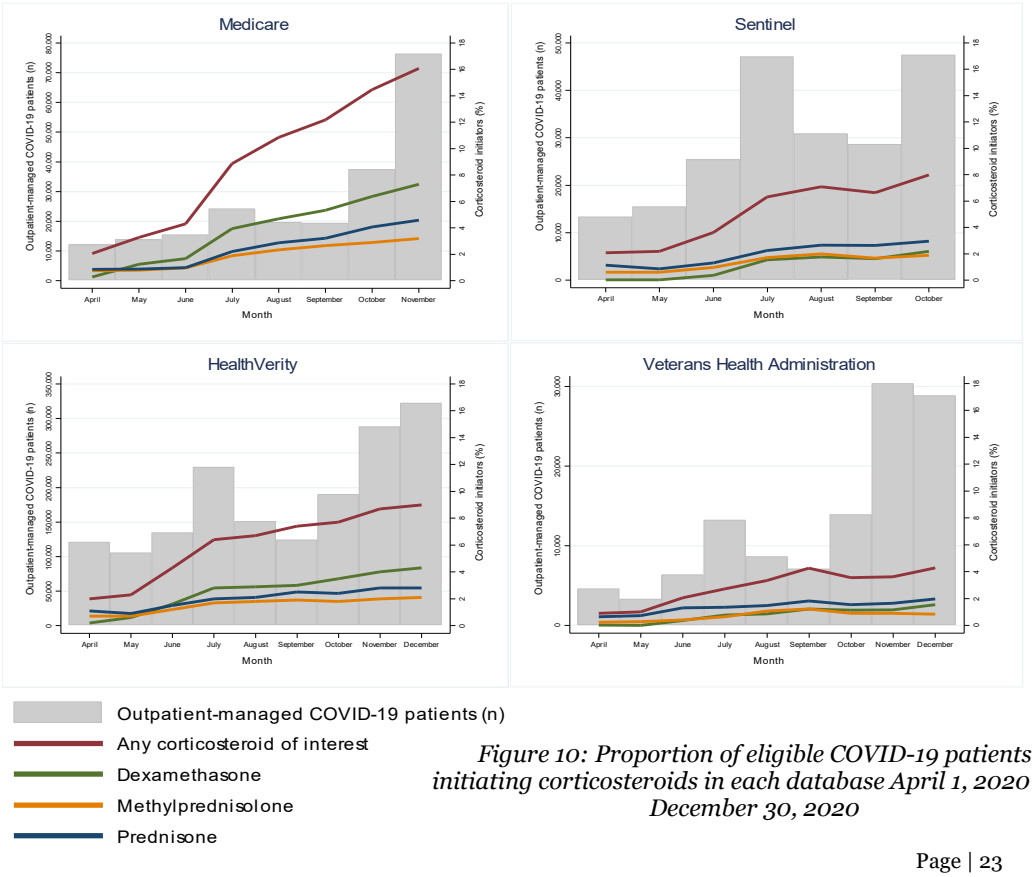


Figure 10: Proportion of eligible COVID-19 patients initiating corticosteroids in each database April 1, 2020 and December 30, 2020

corticosteroids in an outpatient setting within 10 days of COVID-19 diagnosis (Figure 10); over 50% on the same day of diagnosis largely through pharmacy dispensings (67.0-91.1%). Despite NIH recommendations against use, increasing numbers of non-hospitalized COVID-19 patients were prescribed systemic corticosteroids.

OSE Presentations

OSE staff continued to share expertise by giving 109 presentations and/or moderating at scientific meetings. Staff presented on a wide range of topics, including real-world evidence and drug safety in populations not well represented in clinical development programs, as well as those specific for COVID-19, such as adverse event monitoring of COVID therapies.

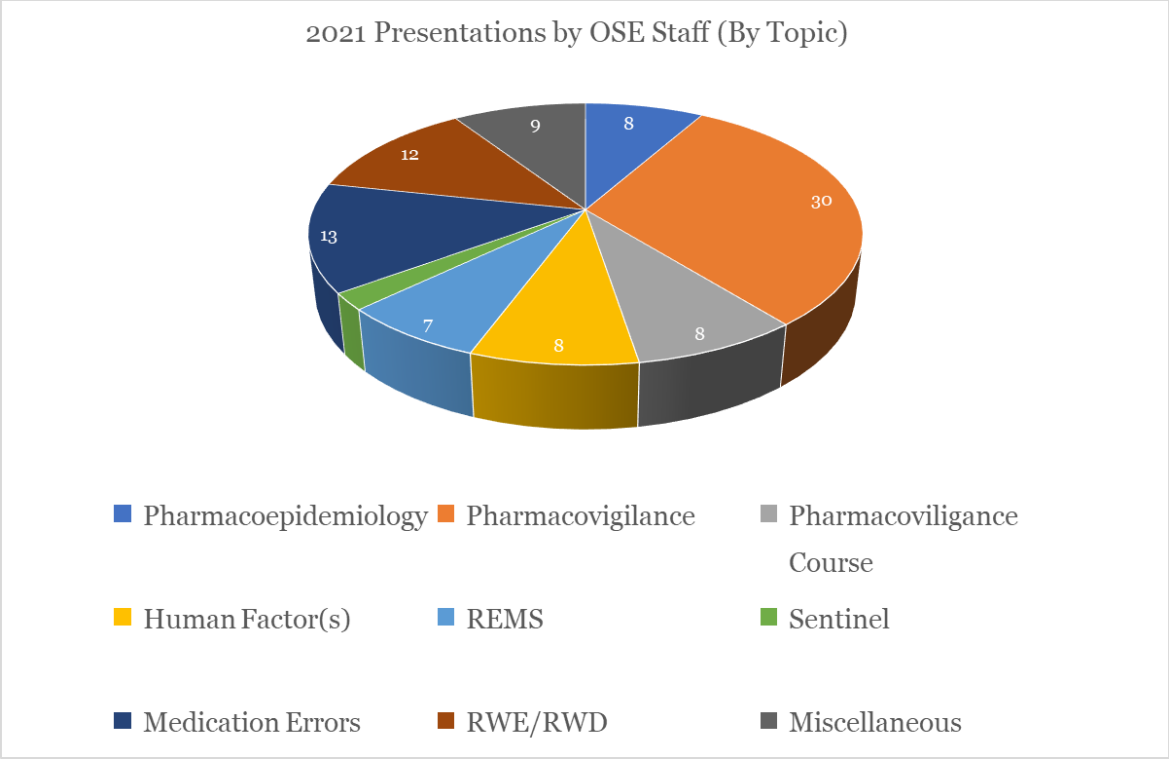


Figure 11: Presentations by OSE staff during 2021

Looking to the Future

Priorities for 2022 and Beyond

In 2022, OSE plans to broaden our risk management, pharmacoepidemiology, medication error prevention, and pharmacovigilance capabilities to support the reauthorization and implementation of the Prescription Drug User Fee Act (PDUFA) VII, Generic Drug User Fee Act (GDUFA) III, and Biosimilar User Fee Act (BsUFA) III.

We plan to finalize the draft "Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff" document as required under the 21st Century Cures Act.

OSE looks forward to the continued development and expansion of the Drug Safety Teams' scope and responsibilities, including the addition of two new Drug Safety Teams, a major modernization initiative. A total of nine Drug Safety Teams are expected to be fully implemented by the end of the first quarter of 2022.

In accordance with the SUPPORT Act, we will continue to explore additional innovative strategies to confront the nonmedical use of opioids, including enhanced education for prescribers and disposal options for patients.

Looking to the Future

Consistent with its five-year strategic plan, Sentinel will further explore methods to optimize surveillance work using electronic health records data and will focus on strengthening causal inference to broaden use of real-world data to evaluate effectiveness. The Sentinel Newsletter, launched in 2021, will continue to be published quarterly through 2022 to disseminate knowledge and promote Sentinel as a national resource. We will continue to explore novel methods to evaluate the growing number of FAERS reports. In 2022, FDA plans to upgrade FAERS with a new process for the electronic submission of Investigational New Drug (IND) safety reports designed to improve our ability to detect, track, and act upon safety signals.

OSE will improve the development of assessment measures and methods to assess the effectiveness of a REMS and improve the efficiency of FDA's reviews of assessment reports. In September 2021, FDA awarded two task orders to the MITRE Corporation to collaborate on a prescriber education landscape analysis and to develop a limited Proof-of-Concept Prototype that demonstrates how prescribers can complete REMS prescriber education and other REMS activities within their workflow and how verification that the education requirements have been met can be automated. In 2022, OSE proposes to continue this work to more fully integrate REMS activities into the health care system. In the long-term, this project will enable the FDA and the nation to tap into the full potential of the REMS program. Information regarding the REMS Prototype Use Case can be found here.

We look forward to strengthening our interactions with international regulatory partners to increase the exchange of information and support global harmonization on regulatory programs of mutual interest, including products to address COVID-19.

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