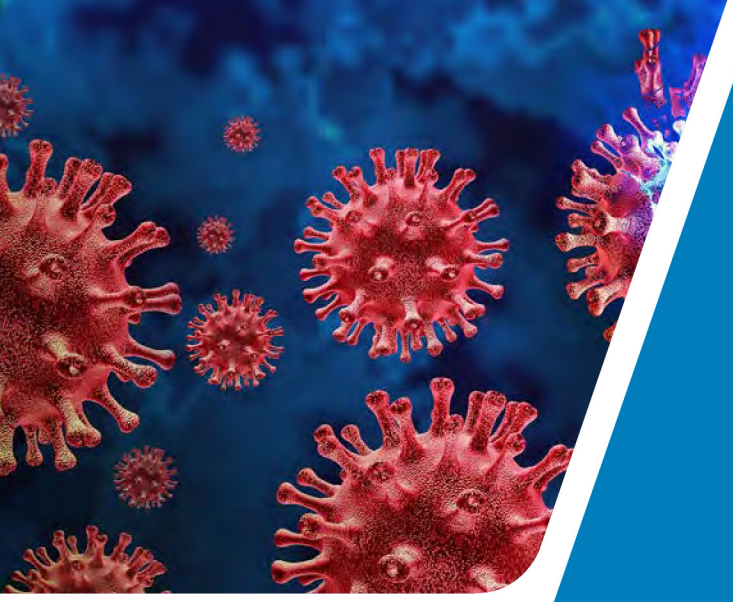

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Drug Safety Priorities 2022

February 2023

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Introduction

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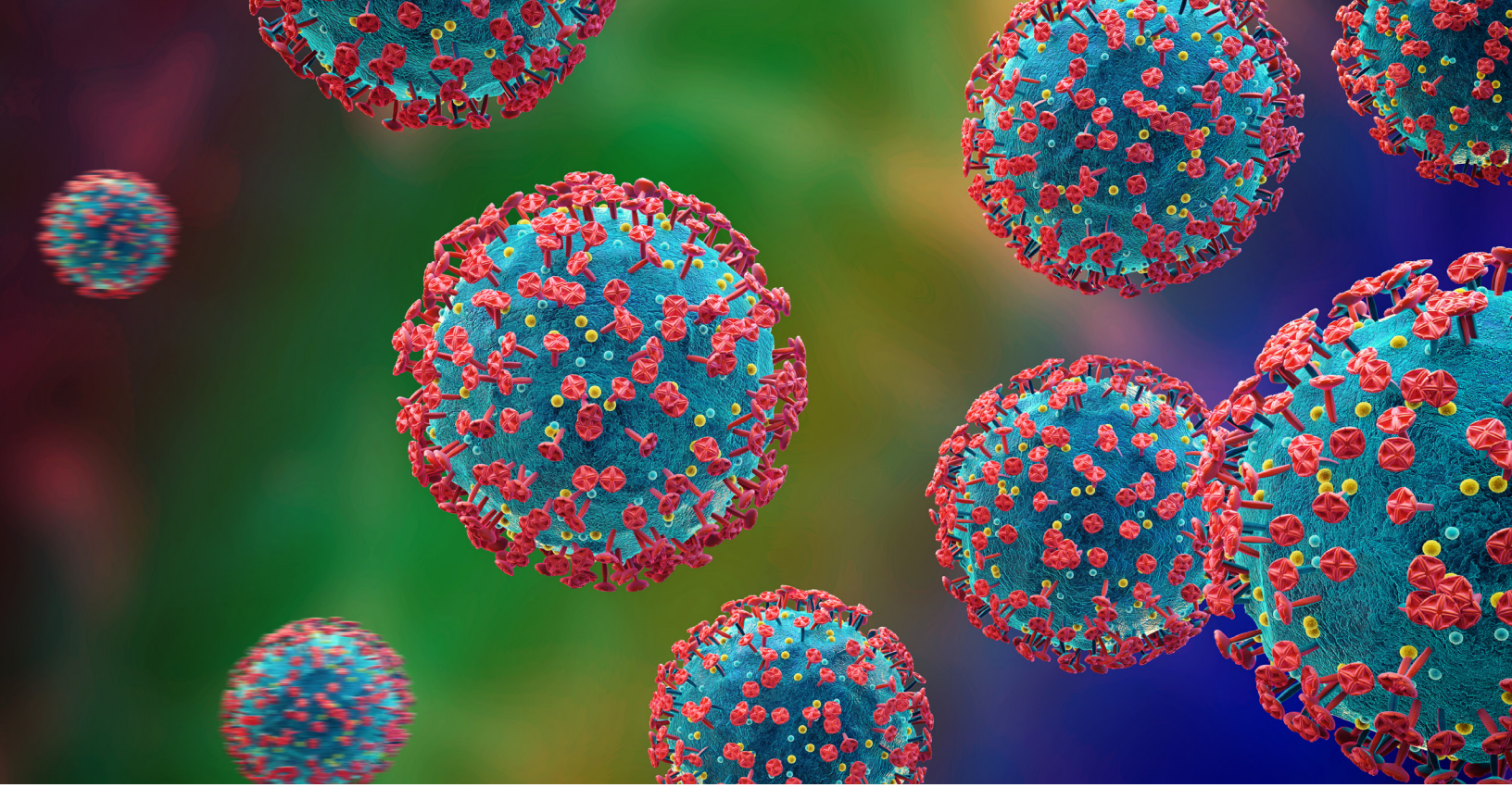
Over the past year, with the Coronavirus Disease 2019 (COVID-19) pandemic still ongoing, the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) continued to be engaged in numerous activities to protect and promote public health. A key area we focused on was ensuring the safety of the nation's prescription and over-the-counter medications, both when reviewing them for possible approval and through continued monitoring after they are on the market. Maintaining the safety of medications that Americans rely on is a complex undertaking as new side effects and risks can arise at any time, regardless of how long a medication has been in use or its past safety record. The CDER Drug Safety Priorities 2022—our eighth annual report—illustrates the broad range of safety efforts conducted involving multidisciplinary collaborations and highlights key achievements and milestones of this critical work.

We continued to prioritize activities addressing the public health crisis arising from the recreational use of opioids and other controlled substances, which have taken a devastating toll on our country, with overdose deaths reaching a record high of more than 108,000 in 2022. As part of this renewed commitment, this year we introduced FDA's Overdose Prevention Framework a vision for our future approach for addressing this evolving crisis that focuses on four priority areas: primary prevention; harm reduction; evidence-based treatment for substance use disorders; and protecting the public from unapproved, diverted, or counterfeit medications presenting overdose risks.

In addition, we maintained our robust postmarket surveillance and risk evaluation programs for safety issues with medications, continued to protect the public from contaminated medications, informed the public about safety issues and recalls with the potential to harm people's health, and worked to improve the overall quality of compounded medications. We also continued our work on other medication safety initiatives and programs, including activities to address unexpected—and potentially cancer-causing—impurities in medications; the Sentinel System, our electronic safety surveillance system; the Safe Use Initiative that works to minimize preventable harm from medications; and the use of a broad range of communication tools and technologies to transparently communicate medication safety information to the public. Our many accomplishments over the past year reflect the best of CDER's commitment to public health and safety.



COVID-19

The emergence of COVID-19 variants continued to impact the public health worldwide in 2022. FDA worked to address the continuing demand for certain products during the public health emergency, and we remained committed to facilitating access to safe and effective medications to help address critical needs of the American public. The Agency's safety focus included evaluating medications for emergency use authorization (EUA), taking actions against fraudulent unapproved products for COVID-19, and keeping the public informed. The latest COVID-19 news from FDA can be found here. The following highlights key drug safety actions taken in 2022.

Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use to diagnose, prevent or treat a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent.

Throughout 2022, FDA continued to make weekly updates to the COVID-19 EUA FAERS Public Dashboard to assist the public in searching for information related to adverse events with medications and therapeutic biological products authorized under an Emergency Use Authorization (EUA) during COVID-19.

Medication Shortages

CDER worked to increase patient access to critically needed medications in shortage during the pandemic. This included issuing nine enforcement discretion decisions designed to increase supplies of these needed medications, including dinutuximab, heparin, albuterol, etomidate, midazolam, propofol, contrast agents, cefotaxime, and afamelanotide.

Assessing the Safety of Products Used for COVID-19

To protect the public during the pandemic, CDER monitored and assessed the safety of novel and repurposed medications to treat or prevent COVID-19. We used multiple data sources to conduct surveillance for safety concerns and medication errors related to various products, provided guidance on how to adapt risk evaluation and mitigation strategy (REMS) programs during a pandemic, offered recommendations for labeling to minimize medication errors, and collaborated with other agencies and organizations to study the effects of medications used to treat or prevent COVID-19. The Agency also improved transparency and communication to the public about our review of the scientific information supporting the issuance of EUAs for drug or biological products, and provided timely information for drug companies on developing COVID-19-related treatments.

Surveillance

- Reviewed safety data, including adverse event reports and observational studies, as part of the overall benefit-risk assessment for COVID-19 therapeutics authorized under EUA or approved
- Conducted surveillance on case reports in the FDA Adverse Event Reporting System (FAERS) database, medical literature, the National Poison Data System, prescription and nonretail sales, and other data sources; and evaluated newly identified safety concerns and medication errors related to products used to treat or prevent COVID-19
- Reviewed and provided feedback on the quality and feasibility of proposals for real world data (RWD) analyses to help support evaluation of COVID-19 therapies
- Reviewed proprietary names (commonly known as brand names given by the drug companies), container labels, carton labeling, packaging, Fact Sheets, and Dear Health Care Professional letters for COVID-19 therapies
- Created a data-driven, evidence-based approach to monitor and assess signals of medication shortages leveraging CDER's regulatory tools to ensure patients have continued access to critical COVID-19 medications

Safety Assessment in Population–Based Data Sources

- Examined the use of systemic corticosteroids for COVID-19 in outpatient settings using data from the Sentinel System and three other large U.S. databases, and published the results in the Journal of the American Medical Association (JAMA)[1]
- Continued collaboration with the federal Veterans Health Administration (VA) and Centers for Medicare & Medicaid Services (CMS) to develop infrastructure and conduct a near real-time surveillance of EUA products in the CMS Medicare and VA populations
- Utilized FDA's Sentinel System to perform numerous new and existing activities designed to:
  - » Describe racial and ethnic distribution of testing, hospitalization, and death from COVID-19; and evaluate associations between race, ethnicity, and COVID-19, and between severe disease and in-hospital death among patients younger than 65 years
  - » Inform safety surveillance activities by characterizing utilization patterns and baseline characteristics of patients receiving certain EUA products
  - » Build and enhance infrastructure to analyze health care claims and electronic health record data to support epidemiological studies of COVID-19
  - » Conduct near real-time monitoring of critical medications in the inpatient setting to assess changes in utilization over time and by geography to inform the potential for medication shortages
  - » Describe the course of illness among hospitalized COVID-19 patients, including their characteristics, health care utilization, disease progression, and outcomes
  - » Assess the natural history of arterial and venous thrombotic events, including estimating the incidence of thrombotic events and risk of death following the event, evaluating risk factors for thrombotic events, and comparing risk of thrombotic events among patients with COVID-19 and patients with influenza. Results were published in JAMA.[2]
  - » Examine the natural history of COVID-19 disease in pregnant women, including medication utilization, disease severity, and clinical outcomes

1 Bradley MC, Perez-Vilar S, Chillarige Y, et al., 2022, Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings from April 2020 to August 2021, JAMA, 327(20):2015–2018.

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

Collaboration and Communication

- Continued collaboration with the American College of Medical Toxicology (ACMT) to create a Toxicology Investigators Consortium (ToxIC) COVID-19 Sub-Registry, an enhanced data collection tool within the ToxIC network, focusing on identifying potential adverse events related to COVID-19 drug products; and expanded Sub-Registry to include cases reporting new opioid and/or stimulant use, misuse/abuse, overdose, and/or withdrawal possibly related to COVID-19
- Responded to Congressional and media inquiries related to the safety of products used to treat or prevent COVID-19

Emergency Use Authorizations (EUAs) and Approvals

FDA continued working to expedite the availability of medications to combat COVID-19 through Emergency Use Authorizations (EUAs). In issuing an EUA, the FDA must determine, among other things, that, based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. We also approved or expanded the approved indication for the following COVID-19 therapeutics: Actemra (tocilizumab), Veklury (remdesivir), and Olumiant (baricitinib).

Hand Sanitizer Warnings

FDA has remained vigilant throughout the COVID-19 pandemic and continued to take action when safety and quality issues arose with hand sanitizers. We are especially concerned with:

- Products contaminated with harmful or poisonous ingredients such as methanol or 1-propanol. Methanol, also known as wood alcohol, is used to make rocket fuel and antifreeze, and 1-propanol is used to make industrial solvents. Methanol is very toxic, and 1-propanol can also be toxic when swallowed.
- Products contaminated with unacceptable levels of benzene, acetaldehyde, and acetal impurities. Benzene may cause certain types of cancer in humans. Animal studies show acetaldehyde may cause cancer in humans and serious illness or death. Acetal can irritate the upper respiratory tract, eyes, and skin.
- Products contaminated with micro-organisms. Use of contaminated hand sanitizer could lead to serious infections, including of the skin, soft tissues, lungs, and bloodstream. Individuals with compromised immune systems are at increased risk.
- Dangers from drinking any hand sanitizer under any condition. While hand sanitizers with methanol contamination are more life-threatening, FDA urges consumers not to drink any of these products, which are sometimes packaged to appear as drinks, candy, or in liquor bottles and could result in accidental ingestion or encourage ingestion. Children are particularly at risk with these products since ingesting only a small amount of hand sanitizer may be lethal to them.
- Certain hand sanitizers that may not contain sufficient concentrations of ethyl alcohol or isopropyl alcohol. Studies have found that sanitizers with lower concentrations or non-alcohol-based hand sanitizers are not as effective at killing germs as those with 60 percent to 95 percent alcohol.
- Hand sanitizers sold or offered for sale with false, misleading, or unproven claims they can prevent the spread of viruses such as COVID-19, including claims they can provide prolonged protection (e.g., for up to 24 hours)
- Products fraudulently marketed as “FDA-approved” since no hand sanitizers are approved by FDA

We are working to protect the public from poor quality, unsafe, and unapproved hand sanitizer products, in particular those contaminated with methanol. In 2022, the Agency continued to protect consumers by:

- Seeking the voluntary recall of more than 35 hand sanitizer products
- Adding 30 firms to the do-not-use list
- Issuing 31 hand sanitizer warning letters
- Adding 16 firms to Import Alert #66-78 (detention without physical examination of drugs, based on analytic test results)

Taking Actions Against Fraudulent Unapproved Products for COVID-19

FDA has continued to actively monitor for any companies marketing products with fraudulent COVID-19 prevention and treatment claims. We exercised our authority to protect consumers from companies selling unapproved products and making false or misleading claims, including by pursuing warning letters or injunctions against products and companies or individuals that violate the law. Through late October, FDA:

- Issued 20 warning letters to companies marketing products that fraudulently claim to treat COVID-19
- Issued another five warning letters to internet pharmacies unlawfully selling medications claiming to treat COVID-19

Issued Specific Compounded Medication Guidances Related to COVID-19

FDA issued temporary policies via guidances addressing the compounding of certain medications for hospitalized patients during the COVID-19 public health emergency. Human medication compounding is generally a practice in which a licensed pharmacist, a licensed physician, or a person under the supervision of a licensed pharmacist in the case of an outsourcing facility combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Compounded medications are not FDA-approved, meaning they have not undergone premarket review for safety, effectiveness, or manufacturing quality. We recommend FDA-approved medications be used to treat patients whenever possible, reserving compounded medications only for when a patient's medical needs cannot be met by an FDA-approved medication.

Postmarketing Surveillance of Generic Drugs

Once a medication is available for prescription or over-the-counter use, FDA continues to monitor its safety, efficacy, and quality so the Agency can take action if needed.

After FDA approval, drug manufacturers must report any problems or serious adverse health effects to FDA for evaluation.

FDA periodically inspects drug manufacturing plants and continues to monitor drug quality.

FDA monitors the FDA Adverse Event Reporting System (FAERS) and reviews MedWatch reports submitted by health care professionals, patients, and drug manufacturers to investigate concerns related to drug product quality and safety.

To help FDA track safety issues with medicines, FDA urges patients, consumers, and health care profession als to report side effects involving medicines to the FDA MedWatch program by completing and submitting the Report Online or calling 1-800-332-1088 to request a reporting form that can be mailed or faxed.

Visit www.fda.gov/drugs to learn more.

Safety Surveillance and Oversight of Marketed Medications

Pharmacovigilance

FDA maintains a wide-ranging array of postmarketing surveillance and risk evaluation programs to identify and evaluate new adverse events that did not appear during the medication development and approval process and to learn more about known adverse events. These reviews and evaluations are based on a detailed assessment of a variety of data. For example, FAERS is a database that contains adverse event and medication error reports submitted to FDA by patients, family members, and health care professionals through the MedWatch program. It also includes adverse event and medication error reports the drug companies are required to submit under the Code of Federal Regulations and the Federal Food, Drug, and Cosmetic Act (FD&C Act). These reports allow us to identify safety concerns and develop recommendations to improve product safety and protect the public.

FDA's risk evaluation program includes:

- Surveillance of various databases, including FAERS, and assessment of reports in those databases
- Conduct of epidemiologic studies data using various data sources, including the Sentinel System
- Review of study protocols and study results submitted by drug companies
- Surveillance and review of the published scientific literature

When we identify new safety-related information or information that may change the benefit-risk profile of a product, we investigate the issue and consider appropriate action, which may include requesting or requiring labeling changes, issuing Drug Safety Communications and other safety information, requiring postmarketing studies, requiring or modifying a risk evaluation and mitigation strategy (REMS), or rarely, requesting a market withdrawal of the product. Even if we have determined none of these actions are necessary at a specific point in time, we continuously monitor the safety of all drug products while they are being marketed.

FDA maintains searchable databases that contain safety-related information available to the public, including FDA Adverse Event Reporting System (FAERS), REMS (REMS@FDA), Drug Safety-related Labeling Changes (SrLC), Medication Guides (MedGuides), and Postmarket Requirements and Commitments. FDA also posts quarterly reports that list potential signals of serious risks/new safety information that were identified using the FAERS database.

FAERS Public Dashboard

FAERS, the FDA Adverse Event Reporting System, is a database containing adverse event reports, medication error reports, and product quality reports resulting in adverse events submitted to FDA and supports the Agency's postmarketing safety surveillance program. The FAERS Public Dashboard is a highly interactive web-based tool that allows the public to query FAERS data in a user-friendly fashion. The intent of the FAERS public dashboard is to expand access to FAERS data so that the general public can search for information related to human adverse events reported to FDA by the pharmaceutical industry, healthcare providers, and consumers.

Medication Error Prevention and Analysis

FDA works to increase the safe use of drug products by minimizing errors related to product naming, labeling, design, and packaging. The Office of Surveillance and Epidemiology (OSE) focuses on how proprietary names, commonly known as brand names, can contribute to confusion in the marketplace. As a member of the Agency's New Drug Application/Biologics License Application (NDA/BLA) review team that evaluates labels and labeling, we apply learning from postmarketing surveillance activities to minimize the risk of medication errors. Furthermore, OSE serves as CDER's lead in evaluating human factors data and information to ensure the safe and effective use of medical products that fall under the Center's jurisdiction.

Some 2022 medication error highlights completed by OSE include:

- Collaborated with the Center for Veterinary Medicine (CVM) to analyze and mitigate medication errors associated with pet exposure to human fluorouracil drug products that result in animal fatalities
- Updated the Phonetic and Orthographic Computer Analysis (POCA) software from POCA 4.4 to POCA 5.0 in September 2022 to include new features (i.e., new appearances for tabs in the tool bar, new data sources, filter function for results, upgraded advance export to Excel, etc.) for FDA staff and public online stakeholder users
- Finalized the Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022) for FDA staff and industry stakeholders

Human Factors and Use Related Risk Analysis Performance Goals

Under the reauthorization of the Biosimilar User Fee Act (BsUFA III), FDA established review performance goals for Human Factor Validation Study Protocols beginning in FY2023. Under the reauthorization of the Prescription Drug User Fee Act (PDUFA VII) and BsUFA III, FDA established review performance goals for Use Related Risk Analyses (URRA). We committed to publishing new draft guidance for review by staff and industry, describing considerations related to drug-device and biologic-device combination products on how a URRA along with other information can be used to inform the need for a human factors validation study to be submitted to a marketing application. The guidance will provide a comprehensive, systematic, and stepwise approach with examples, when applicable, to illustrate how to make this determination.

Risk Management

Risk management is a critical consideration in assessing the benefit-risk balance of a medication, including:

- Development of strategies to minimize risks while preserving benefits
- Evaluation of the effectiveness of such strategies and reassessing benefit-risk balance
- Adjustments to risk minimization strategies when appropriate to further improve the benefit-risk balance

FDA's primary risk management tool for prescription medications is FDA-approved product labeling, often referred to as the "package insert" or the "prescribing information," which must contain a summary of the essential scientific information needed for the safe and effective use of the medication. For nonprescription, or over-the-counter (OTC), medications the "Drug Facts" labeling includes a summary of the essential information needed by consumers or health care professionals for

the safe and effective use of the medication. Medication Guides are also part of medication labeling and they contain approved information that can help patients avoid serious adverse events. For most medications, labeling is sufficient to ensure that the benefits outweigh the risks. In a limited number of cases, we may determine that a REMS will also be needed. A REMS is a drug safety program we can require for a relatively small number of medications with serious safety concerns to help ensure the benefits of the drug outweigh its risks. They are designed to reinforce medication-use behaviors and actions that support that medication's safe use.

Enhancements to the REMS Public Dashboard in 2022 allowed users access to REMS materials for each active REMS program. The REMS Public Dashboard is a user-friendly functional tool that improves access to data for certain medications with serious risks that need additional requirements to ensure safe use. Additional enhancements such as a searchable field for specific REMS requirements and additional data elements are currently under development.

Integrating REMS into the Healthcare System

OCTOBER 21 I We developed a proof-of-concept prototype that leverages existing data standards through a contract with the MITRE Corporation and in collaboration with stakeholders through an open community under the health data standards development organization Health Level Seven (HL7). The REMS Integration Use Case ultimately aims to advance and improve the quality of REMS data for feedback and evaluation, and optimize safe medication use and outcomes of these risk mitigation strategies. The next steps include planning for and implementing a pilot with a REMS administrator, using synthetic data in at least one health or prescriber system and one pharmacy system.

FDA-Duke Margolis Public Workshop: Challenges and Opportunities for REMS Integration, Innovation, and Modernization. FDA and the Duke-Margolis Center for Health Policy hosted a virtual public workshop to solicit feedback from key stakeholders on the REMS integration prototype. Speakers from FDA and MITRE provided an overview of the prototype's aims, core functions, and role in our ongoing efforts to integrate REMS. Patients, prescribers, pharmacists, health system representatives, informaticists, and other key stakeholders participated in a series of moderated panel discussions that focused on how the prototype can address challenges associated with integrating these requirements into clinical workflows to facilitate safe medication use.

REMS Training for CDER Staff

The REMS Logic Model training program was established in November 2022 and

presented to relevant CDER staff involved in the design and assessment of REMS programs. The training consists of an overview and seven modules. Each module's page includes a video presentation, a knowledge check quiz, and links to related internal and external resources. Future plans include broadening this training to staff in other CDER offices involved in the review of REMS to ensure they have a shared foundational understanding of how the REMS design corresponds to the development of the REMS Assessment, as well as CBER.

Modernizing and Improving REMS Assessments

FDA continues its efforts to modernize and improve REMS assessments. Through the reauthorization of the Prescription Drug User Fee Act (PDUFA) VII, we committed to add REMS review performance goals for review of methodological approaches and study protocols for assessments; update relevant guidances to incorporate assessment planning into the design, and existing policies and procedures for reviewing methodological approaches and study protocols used to assess a program; and develop draft guidance regarding the format and content of an assessment report, including the type of data that can support its elimination, and issue new or update existing policies and procedures to determine if modifications or revisions to the assessment plan are needed.

New REMS Approvals

APRIL 28 I FDA approved a REMS for Camzyos (mavacamten) to mitigate the risk of heart failure due to systolic dysfunction. Camzyos is a prescription medication used to treat adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms

The Sentinel System

In 2022, FDA's Sentinel System supported numerous activities to protect and promote public health during the COVID-19 pandemic as well as more generally, including those involving conducting public training, disseminating Sentinel research at public conferences, and holding a public workshop and a seminar series about the system.

The Sentinel Initiative, launched in 2008, began as the result of a Congressional mandate for FDA to establish a public-private partnership to develop an electronic medical product safety surveillance system using existing data. The principal operational component of the Sentinel Initiative is the Sentinel System, a network of databases (technically known as a distributed database) that included 13 partner institutions with 14 data marts as of October 2022.

Sentinel collaborators include data and academic partners that provide access to health care data and scientific, technical, and organizational expertise. Distributed data networks allow secure access to multiple data sources, achieving far larger sample sizes than could be achieved through a single source, while assuring that data are collected securely with full patient privacy safeguards in place.

When safety concerns arise, FDA staff can use Sentinel to assess potential risks that may be associated with FDA-regulated medical products, enabling product safety assessment under real-world conditions. Sentinel provides unparalleled capabilities for investigation of new safety signals that arise from spontaneous reporting systems like FAERS and other sources of safety information. In addition to investigating safety signals, we are also piloting Sentinel's analytic tools to identify unsuspected potential safety concerns using new approaches that scan thousands of health outcomes, looking for unexpected safety signals after product exposure. Such analyses mine large amounts of health care data without prespecifying a specific target medical product. Sentinel also supports inquiries on many different regulatory questions, including those related to medication errors,

The Sentinel System has transformed the way Agency scientists monitor FDA-regulated medical products. Now one of FDA's leading evidence-generation platforms that can explore and address regulatory questions posed by review teams, Sentinel serves to advance the science of real world data (RWD) and real world evidence (RWE). FDA routinely uses RWD made available through the Sentinel System to generate evidence about medication safety, drawing on data from insurance claims, hospital stays, outpatient doctor visits, and pharmaceutical dispensing data. Sentinel also queries data from partners with data from electronic health records (EHRs) to address regulatory questions and address questions arising from the COVID-19 pandemic. By making it possible to analyze emerging risks associated with FDA-regulated medical products and to study medical care more broadly, Sentinel enables the Agency to assess medical product safety, describe medical product utilization, and characterize medical events under real-world conditions.

risk mitigation strategies, generic medications, biosimilars, and medication safety in specific patient groups such as children and pregnant patients.

Now in its fourth year, the Sentinel System Five-Year Strategy 2019-2023 charts the development of the System through five strategic aims intended to expand its operational foundation, augment its safety analysis and signal detection capabilities, and leverage the System to accelerate access to and broader use of real world data (RWD) for real world evidence (RWE) generation. To advance these aims, FDA established three centers as part of the System: the Sentinel Operations Center (SOC), the Sentinel Innovation Center (IC), and the Community Building and Outreach Center (CBOC). SOC continues to focus on conducting medical product assessments and enhancing the infrastructure of the System to support our regulatory needs. The IC carries out work to advance analytic tools and accelerate novel data source acquisition and evaluation, with a goal of establishing a query-ready system of electronic health records (EHR). The CBOC focuses on building the System user community and engaging stakeholders.

2022 Highlights

In 2022, FDA's Sentinel System supported numerous activities to protect and promote public health during the COVID-19 pandemic (see the COVID-19 section of this report). To support these activities, Sentinel enhanced its data infrastructure by building and maintaining a database with near real-time data from six Data Partners and incorporating use of several additional data sources derived from EHRs. Sentinel also collaborated with the Reagan-Udall Foundation and Friends of Cancer Research on the COVID-19 Evidence Accelerator, a forum for stakeholders across the health care spectrum that shared RWD and generated ideas on COVID-19. Additional Sentinel highlights include:

APRIL 29 I Sentinel held a public training on Inverse Probability of Treatment Weighting (IPTW), an analytic tool in Sentinel that can reduce confounding bias in observational studies of medical treatments. Simultaneously, the Sentinel Views dashboard was released, which allows FDA investigators and the public to easily visualize results from inferential analyses conducted in Sentinel. These initiatives engaged Sentinel stakeholders and support Sentinel's vision of serving as a national resource for medical product safety surveillance and real-world evidence generation.

AUGUST 24-28 I Investigators disseminated Sentinel work at the 38th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), leading three symposia and providing 15 oral presentations and scientific posters

OCTOBER 3 I FDA completed an assessment of the Sentinel System covering the period 2017-2021, the period since the prior assessment, and found Sentinel

has established itself as a vital component of FDA's regulatory tools. The assessment report fulfilled a commitment of PDUFA VI to analyze and report on the impact of Sentinel System expansion and use for regulatory purposes. Sentinel contributed to FDA's regulatory mission through 82 studies, resulting in more than 40 regulatory actions, and contributed more broadly the nation's public health via 22 additional studies not directly related to medication safety, many of which supported FDA's COVID-19 response.

NOVEMBER 15-16 I The 14th Annual Sentinel Initiative Public Workshop was held virtually, bringing together Sentinel stakeholders to discuss strategic aims for the continued development of the Initiative. Sessions featured key leads from each CDER Sentinel coordinating center to discuss past and current activities, as well as data and methodological advancements supporting the robust development of RWE for active medical product surveillance. Participants also discussed how the Initiative is working to expand partnerships and build the stakeholder community.

Throughout 2022, the Sentinel Innovation and Methods Seminar Series brought leading experts to present on various topics, including feature engineering, natural language processing, advanced analytics, and data interoperability. This 10-part seminar series engaged Sentinel's scientific community by sharing information on emerging technologies and advances in methods relevant to Sentinel's work.

Optimization of the Sentinel Initiative

FDA committed under PDUFA VII to maintain the Sentinel Initiative's capabilities and continued integration into FDA medication safety activities. Additionally, FDA plans to get external input and conduct demonstration projects to see if the system's capabilities can address questions of product safety during pregnancy and how real-world evidence (RWE) can be used for studying effectiveness.

Drug Safety Modernization

Under the direction of CDER's Drug Risk Management Board (DRMB), significant progress towards postmarket safety modernization was seen in 2022. The DRMB is a cross-CDER governance board responsible for three key objectives: (1) facilitating and coordinating decisions around major product safety issues, (2) providing clear and consistent guidance enabling an appropriate response to major safety issues, and (3) systematically communicating decisions and resulting actions across the Center and to other stakeholders as appropriate. In addition, the DRMB facilitates and coordinates all new and existing marketed product-safety initiatives across CDER, including the modernization of the Center's framework capabilities for safety surveillance of marketed products. Many accomplishments are summarized in other sections of this report, but below are highlights of notable activities about guidance and policy, and organizational and process changes.

Guidance and Policy Activities

FDA published several documents in preparation for the electronic transmission of premarketing and postmarketing safety reports in the International Council for Harmonisation (ICH) E2B (R3) format, the international standard for transmitting medication adverse event reports. These documents are located at the FDA Adverse Event Reporting System (FAERS) Electronic Submission webpage.

Organizational and Process Activities

SEPTEMBER 30 I Throughout 2022, CDER continued to support implementation of the Newly Identified Safety Signal (NISS) process, a major modernization initiative achieved in April 2020, which allowed for a standardized, interdisciplinary approach to systematically identify, evaluate, and resolve safety signals. The Lifecycle Signal Tracker (LiST) workflow tool supports the NISS process, providing the ability to capture and manage all safety signals for marketed medications. An assessment was completed of the NISS process and LiST tool by a contractor as ongoing process improvement and to meet a PDUFA VI commitment. We made the Executive Summary of the report publicly available.

ONGOING I The following activities were undertaken to support the development and implementation of the organizational changes needed to support efficient and effective postmarket safety:

- Implemented Drug Safety Teams (DSTs) for all therapeutic areas. DSTs bring together multidisciplinary, cross-functional staff from across CDER to address important, complex, and urgent safety issues. Each DST is responsible for a designated portfolio of medications, typically aligned by therapeutic areas.
- Launched the Integrated Safety Assessment (ISA) review template. The ISA serves as a single review document for newly identified safety signals, incorporating data analyses and opinions across multiple disciplines within CDER.
- Undertook development of a process for Pharmacovigilance Strategies (PVS), which is in progress. Using a risk-based approach, PVS will be developed and implemented for select products to further characterize their safety profiles over the products' life cycles.
- Began to develop a Pharmacovigilance Curriculum to be utilized across CDER safety staff to ensure they have a shared foundational understanding of the regulatory processes and science involved in postmarket safety work.

Nitrosamine Impurities and Benzene Contaminants in Medications: FDA's Continuing Multidisciplinary Response

After learning in June 2018 that certain generic versions of valsartan, a high blood pressure and heart failure drug, contained unexpected impurities that posed a potential safety concern, FDA investigated and took regulatory action with respect to some drug products, and we continue to monitor drug products for these impurities. These impurities, known as nitrosamines–including, for example, N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-nitroso-varenicline, Nitroso-STG-19 (NTTP)), and nitrosoamine drug-substance-related impurities (NDSRIs)–are potentially cancer-causing substances that can be generated during the drug manufacturing process when certain other chemicals, and reaction and processing conditions are present, and NDSRIs can also form during storage of the drug product.

Several more drug products have since been found to contain unacceptable levels of nitrosamines, including, for example, the heartburn drugs ranitidine and nizatidine, the type 2 diabetes drugs metformin and sitagliptin, the tuberculosis drugs rifampin and rifapentine, the smoking cessation drug varenicline, and the high blood pressure drug quinapril/hydrochlorothiazide. Key 2022 actions addressing N-nitroso-varenicline impurities in varenicline and NTTP impurities in sitagliptin products include:

Nitrosamines are common contaminants found in water and foods, including cured and grilled meats, dairy products, and vegetables. Everyone is exposed to some level of nitrosamines. FDA does not expect nitrosamines to cause harm when ingested at low levels. Although nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, a person taking a drug that contains nitrosamines at or below the acceptable intake limit every day for 70 years is not expected to have an increased risk of cancer.

MAY 5 I We announced any newly manufactured varenicline for the U.S. market should have levels of the N-nitroso-varenicline impurity at or below the Agency's acceptable intake limit of 37 ng per day

AUGUST 9 I We announced FDA recently became aware of a nitrosamine impurity, NTTP, in certain samples of sitagliptin. To avoid a shortage and help ensure patients have access to an adequate supply of the medication, FDA said it would not object to the temporary distribution of sitagliptin containing NTTP above the acceptable intake limit of 37 ng per day, and up to 246.7 ng per day.

FDA provided consumers in June 2022 with a web page providing information on benzene contamination in drug products. The agency also alerted drug manufacturers to the risk of benzene contamination from drug components and other potential risk factors in December 2021 and announced that we were evaluating the root cause of benzene contamination in certain medications. Certain hand sanitizers and aerosol drug products have been recalled due to benzene contamination. This contamination may be related to inactive ingredients such as thickening agents, a spray propellant, or other drug components made of hydrocarbons.

Benzene is a chemical used in the production of a wide range of industrial products, including chemicals, dyes, detergents, and some plastics. Benzene is released into the air in cigarette smoke, emissions from automobiles, and burning coal and oil. In small amounts over long periods of time, benzene can decrease the formation of blood cells. Long-term exposure to benzene through inhalation, oral intake, and skin absorption may result in cancers such as leukemia and other blood disorders.

Continued Efforts to Address the Drug Overdose Crisis

As part of FDA's continuing efforts to combat the non-medical use of opioids and other controlled substances, which resulted in a record high of more than 108,000 Americans dying from drug overdoses in 2022, we announced the establishment of the FDA Overdose Prevention Framework in August 2022. The drug overdose crisis is multifaceted and has evolved beyond the non-medical use of the illicit and prescription opioids FDA has focused on addressing, resulting in the need for an expanded approach. Other controlled substances, including benzodiazepines and stimulants, particularly methamphetamine, are often being used in combination with opioids. The COVID-19 pandemic has also exacerbated the overdose crisis. The U.S. Department of Health and Human Services (HHS) announced in October 2021 an Overdose Prevention Strategy with support from FDA and other HHS agencies.

Deriving from the HHS strategy, FDA identified priorities to provide a framework and focus for our actions to address the crisis and sustain long-term recovery outcomes, announcing the establishment of the FDA Overdose Prevention Framework on August 30, 2022. The framework details FDA's vision to undertake impactful, creative actions to prevent drug overdoses and reduce deaths through initiatives and activities nested within four priorities:

- Supporting primary prevention by eliminating unnecessary initial prescription medication exposure and inappropriate prolonged prescribing
- Encouraging harm reduction through innovation and education
- Advancing development of evidence-based treatments for substance use disorders
- Protecting the public from unapproved, diverted, or counterfeit drugs presenting overdose risks

FDA also undertook additional overdose-related actions and activities in 2022 aimed at supporting primary prevention and encouraging harm reduction, including:

FEBRUARY 9 I We published the draft guidance for industry Development of Non-Opioid Analgesics for Acute Pain, which intends to provide recommendations to companies developing nonopioid analgesics for acute pain lasting up to 30 days, typically in response to some form of tissue injury, such as trauma or surgery. This guidance supports the HHS Overdose Prevention Strategy.

FEBRUARY 28 I We approved a military-only usage and chemical incident response indication for a naloxone hydrochloride auto-injector product to treat opioid overdose

MARCH 29 I Through a cooperative agreement with the Agency, the Reagan-Udall Foundation hosted a virtual public meeting Naloxone Access: Answering Questions to explore the most frequently asked questions about access to the opioid reversal agent naloxone. Harm reduction specialists, physicians, pharmacists, and regulators shared their experiences in addressing the availability of this life-saving medication for heroin, fentanyl, and prescription opioid overdose.

APRIL 20 I We published a Federal Register notice seeking public comment on a potential change that would require opioid analgesics used in outpatient settings to be dispensed with prepaid mail-back envelopes and that pharmacists provide patient education on safe disposal of opioids

JUNE 21 I We approved the second generic naloxone intranasal spray to treat opioid overdose

SEPTEMBER 22 I We issued the immediately-in-effect guidance Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act (DSCSA) for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency. The guidance is intended to clarify the scope of the public health emergency exclusion and exemption under the DSCSA concerning the distribution of FDA-approved naloxone products to harm-reduction programs during the opioid emergency. Harm-reduction programs help save lives by making naloxone available in underserved communities. We will continue to support harm reduction programs' ability to acquire FDA-approved naloxone products. This guidance supports the FDA Overdose Prevention Framework.

SEPTEMBER 30 I We published an update on actions the Agency has taken to align with the National Academies for Sciences, Engineering, and Medicine's (NASEM) recommendations regarding *Opioid Approval and Monitoring by FDA*

NOVEMBER 16 I We issued a Federal Register Notice about the safety and effectiveness of certain naloxone medication products for nonprescription use that may help facilitate the development and approval of these products, including through the switch of certain products from prescription status to nonprescription status

Naloxone is a medication to help reduce opioid overdose deaths that can be administered by individuals with or without medical training. If naloxone is administered quickly, it can counter the opioid overdose effects, usually within minutes. Currently, most states allow pharmacists to dispense naloxone to consumers who request it through a standing order from the state's health department. This allows a pharmacist to dispense naloxone without a prescription for an individual patient, a family member or friend, or anyone who may be around those who use opioids.

Protecting the Public from Unapproved, Diverted, or Counterfeit Drugs Presenting Overdose Risks

FEBRUARY 10 I We issued a Consumer Update warning consumers to avoid all products containing tianeptine, which is not approved by the Agency for any medical use but has been found to be used for recreational purposes, which has resulted in serious harmful effects. Despite that, some companies are illegally marketing and selling products containing tianeptine to consumers. The companies are also making dangerous and unproven claims that tianeptine can improve brain function and treat anxiety, depression, pain, opioid use disorder, and other conditions. Cases described in medical journals, in calls to U.S. poison control centers, and in reports to FDA suggest that tianeptine is being used for non-medical purposes. We have also identified cases in which people experienced serious harmful effects from using tianeptine by itself or with other medications. These effects included agitation, drowsiness, confusion, sweating, rapid heartbeat, high blood pressure, nausea, vomiting, slowed or stopped breathing, coma, and death.

APRIL 12 I FDA and the Drug Enforcement Administration (DEA) issued joint warning letters to operators of two websites illegally selling Schedule II stimulants, including amphetamine products marketed as Adderall. These websites were selling these products online without a prescription, which places consumers at risk. The illegal sale of prescription medication stimulants online puts Americans at

risk because they may be getting other drugs or substances, and it contributes to recreational use of and overdose from these products. FDA's BeSafeRx campaign helps consumers learn about how to safely buy prescription medications online.

JUNE 30 I FDA, in collaboration with the Federal Trade Commission, issued warning letters to four companies selling unapproved kratom products and one company selling essential oils to treat or cure opioid use disorder (OUD) and withdrawal symptoms

Other Drug Overdose Crisis Activities

JANUARY 12 I We issued a Drug Safety Communication warning of reported dental problems associated with medications containing buprenorphine that are dissolved in the mouth. Despite these risks, buprenorphine is an important treatment option for OUD and pain, and the benefits of these medications clearly outweigh the risks.

We required a new warning about these risks, which include tooth decay, cavities, oral infections, and loss of teeth even in patients with no history of dental issues, to be added to the prescribing information and the patient Medication Guide for all buprenorphine-containing medications dissolved in the mouth. Regular adherence to buprenorphine to treat OUD reduces withdrawal symptoms and the desire to use opioids, without causing the cycle of highs and lows associated with opioid misuse. The comprehensive approach of buprenorphine combined with counseling and other behavioral therapies is often one of the most effective ways to treat OUD.

MARCH 17 I We published the research article Evaluating opioid analgesic prescribing limits: A narrative review,[3] which examines evidence from studies evaluating the patient or public health impact of federal and state opioid analgesic prescribing guidelines and laws, describes gaps and challenges in current research, and highlights opportunities for improving future research

3 Seitz AE, Janiszewski KA, Guy GP, Tapscott RT, Einstein EB, Meyer TE, Tierney J, Staffa J, Jones CM, Compton WM, 2022, Evaluating Opioid Analgesic Prescribing Limits: A Narrative Review, Pharmacoepidemiol Drug Saf, 31(6):605-613, doi: 10.1002/pds.5425.

APRIL 4-5 I Through a cooperative agreement with FDA, the Duke-Margolis Center hosted the Identifying Key Competencies for Opioid Prescriber Education virtual public workshop, which focused on identifying gaps in the content of existing opioid prescriber education offerings and core competencies that should be included in educational content for opioid prescribers and other health care professionals, including prescriber education under a Risk Evaluation and Mitigation Strategy (REMS)

May 17 I At the RADARS (Researched Abuse, Diversion and Addition Related Surveillance) System 16th Annual Virtual Meeting, we presented results of the research project Evaluation of Stimulant Abuse in the United States: A Mosaic Epidemiology Study, which used several databases in the RADARS system to characterize stimulant use examining demographics, drugs of interest, motivations, and behaviors, as well as trajectories of use to learn more about this emerging public health issue. Manuscripts are in development.

MAY 31 I FDA, in collaboration with Harvard University and Massachusetts General Hospital, published the research article Modeling the evolution of the US opioid crisis for national policy development,[4] which discusses FDA's initiative to develop a data-driven, national-level simulation model of the opioids system named SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects). It includes baseline projections of the opioid crisis, including opioid misuse rates and prevalence of opioid use disorder and overdose deaths over the next 10 years across different scenarios.

JUNE 27 I FDA, in collaboration with Harvard University and Massachusetts General Hospital, published the research article Reducing opioid use disorder and overdose deaths in the United States: A dynamic modeling analysis,[5] which discusses the Agency's initiative to develop SOURCE and describes an initial analysis of 11 high-level interventions and the effects that SOURCE projects those interventions may have on the opioid crisis

ONGOING I Throughout 2022, FDA was involved in ongoing education and outreach campaigns to help support the safe use of opioids. Remove the Risk aims to raise awareness among patients and consumers about the serious dangers of keeping unused prescription opioids and to provide information about safe disposal of these medications. In addition, through a long-term CDER collaboration with Partnership to End Addiction, the Search and Rescue campaign provides health care professionals with tools and resources to help patients avoid prescription medication misuse and addiction.

4 Lim, TY, Stringfellow EJ, Stafford CA, et al., 2022, Modeling the Evolution of the U.S. Opioid Crisis for National Policy Development, PNAS, 119(23)e2115714119, https://doi.org/10.1073/pnas.2115714119.

5 Stringfellow EJ, Lim TY, Humphreys K, et al., 2022, Reducing Opioid Use Disorder and Overdose Deaths in the United States: A Dynamic Modeling Analysis, Science Advances, 8(25), doi:10.1126/sciadv.abm8147.

Ensuring the Quality, Safety, and Effectiveness of Generic Medications

In 2022, FDA's generic medication program continued to evaluate the safety of generic medications before they are approved, and monitor their safety after approval and throughout the time these medications are available for sale in the United States. Effective post-market surveillance is essential to ensuring FDA-approved generic medications provide the same therapeutic effect and safety as brand-name medications.

The Office of Generic Drugs (OGD) follows a rigorous review process to ensure that, compared to the brand-name medication, a generic medication has the same:

- active ingredients (the ingredients that treat a condition or symptoms)
- strength
- dosage form (e.g., tablet, capsule, suspension, injection, cream, patch, or liquid, etc.)
- route of administration (e.g., oral, topical, nasal, or intramuscular, etc.)
- conditions of use
- labeling (with certain exceptions)

FDA's generic medication program substantially increased the availability of affordable, high-quality, safe, and effective medications in the United States by promoting medication competition. More than 10,000 generic medications are currently approved by FDA, and 90 percent of prescriptions filled in the United States are for these medications. Increasing the availability of generic medications helps to create competition in the marketplace, which can reduce the cost of treatment and increase access for more patients. Generics result in significant savings for patients and the health care system. For example, the savings accrued across the health system during the first year after approval for new generic medications approved in 2018, 2019, and 2020 are estimated at more than $53 billion.

OGD's Safety Surveillance of Generic Medications

OGD continued working to ensure the safety and therapeutic equivalence of generic medications through our numerous safety and surveillance activities. We reviewed Bio-Investigational New Drug Applications (Bio-INDs) and pre-approval serious adverse event reports from Bio-INDs and non-IND bioequivalence (BE)/bioavailability (BA) studies that were intended to support Abbreviated New Drug Applications (ANDAs). In addition, we were responsible for assessing health hazard evaluations for potential generic medication product recalls. We analyzed generic medication quality and therapeutic equivalence adverse event reports and trends, followed generic medication distribution patterns, and identified emerging safety issues. We assisted generic drug applicants in developing, implementing, and maintaining Risk Evaluation and Mitigation Strategies (REMS) for all generic medications.

Together, we supported CDER's postmarket safety efforts, including identifying, evaluating, and resolving newly identified safety signals consistent with CDER's MAPP 4121.3 Collaborative Identification, Evaluation and Resolution of a Newly Identified Safety Signal. We also initiated Generic Drug User Fee Amendments (GDUFA)-related postmarket safety research and performed generic medication safety and surveillance outreach through presentations and publications to generic medication stakeholders including patients, healthcare providers, pharmacists, and medication safety focused organizations.

With support from CDER's Office of Global Policy and Strategy, we initiated an ORISE Fellowship project looking at global approaches to generic medication postmarketing safety surveillance. This provided a unique and invaluable opportunity to reach out to some of our global partners enabling us to add global perspectives to our important work to ensure the quality, safety, and effectiveness of generic medications.

OGD Safety and Surveillance Highlights in 2022

Highlights of OGD's safety and surveillance work in 2022 include the following:

Drug Safety Alerts

APRIL 21 | Updated its Drug Safety Alert related to vinca alkaloid labeling for preparation in intravenous infusion bags only

AUGUST 18 | Provided instrumental support in developing and publishing a Drug Safety Alert for patients, caregivers, and health care providers regarding cross-compatibility issues with autoinjector devices that are optional for use with glatiramer acetate injection

NOVEMBER 22 | Provided instrumental support in developing a Drug Safety Alert for health care professionals about compatibility issues with prefilled glass syringes and certain Luer-activated valve (LAV) connectors was led and further developed through collaboration with CDER and CDRH and published

Guidance and Policy Activities

APRIL 14 | Updated MAPP 5210.5 (Rev. 3) Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs, which reflects current policies and procedures and includes a checklist for completeness of these important submissions

AUGUST 3 | Published Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies Guidance for Industry

Premarketing Safety Reporting

We supported the pre-market IND safety reports managed by the Office of Strategic Programs and the International Council for Harmonisation (ICH) E2B(R3) Working Group in revising and publishing the following documents to help the industry prepare for the electronic submission of premarket safety reports in ICH E2B(R3) format to FDA.

ONGOING | OGD staff continued work with CDER's Drug Nitrosamine Impurities Task Force addressing ongoing issues related to the presence of nitrosamine impurities in many prescription and over-the-counter drug products. CDER established acceptable intakes for several nitrosamine impurities and chaired a workshop session to identify research priorities for nitrosamine toxicity and safety assessment. We also collaborated with FDA's National Center for Toxicologic Research and the Nitrosamine International Technical Working Group to optimize and harmonize principles of the safety assessment for nitrosamine impurities.

Generic Drug REMS Highlights in 2022

The OGD REMS team continued to serve as experts on the statutory and regulatory requirements and recommendations in FDA guidance documents related to abbreviated new drug applications (ANDAs) containing a REMS or subject to one. The team assisted in developing, implementing, managing, and evaluating related activities submitted to ANDAs. Generic medications are required to follow the same REMS requirements as the brand-name medications. Throughout 2022, the team actively participated in CDER's cross-office efforts to:

- Evaluate and approve separate system REMS
- Evaluate established REMS materials to aid in the approval of 27 new ANDAs subject to REMS
- Evaluate and approve various Shared System REMS modifications, ultimately affecting 126 approved ANDAs
- Collaborated on the new REMS Public Dashboard launched by FDA on December 17, 2021, which is an interactive web-based tool that allows for analysis and visualization of the REMS data files
- Collaborated on a Federal Register Notice regarding REMS

Information on approved REMS for NDAs and ANDAs is available at REMS@FDA.

Generic Substitution and Safety of Generic vs Brand-Name Drugs

As part of GDUFA-funded research projects, FDA is conducting ongoing research to evaluate generic substitution in various ways, including clinical studies of substitution in patients, analyzing medical informatics data to evaluate generic utilization and substitution, and patient and provider perceptions impacting generic substitution. FDA completed its analysis of a study in 2022 investigating the bioequivalence of a generic tacrolimus product and its reference product. The results of the study will help us understand the impact of product attributes on the pharmacokinetic performances between generic and reference products and improve the review standards for equivalence.

FEBRUARY 7 I FDA reported research[6] to evaluate the application of pharmacogenomic (PGx) information that can be applied in product-specific guidance development for bioequivalence studies for generic medication development to further enhance subject safety and bioequivalence study data quality. Currently, recommendations on subject recruitment based on PGx information in BE studies are limited. This ongoing research will be useful in

6 Clin Pharmacol Ther 2022;111:suppl S1:P-094; https://doi.org/10.1002/cpt.2521

determining when PGx information can be used to identify those who may be vulnerable to serious adverse events, minimize carryover effects in a crossover study, and ensure balanced groups in a parallel study.

APRIL 1 I FDA-sponsored research[7] in collaboration with the Yale University-Mayo Clinic Center of Excellence in Regulatory Science and Innovation published in JAMA Internal Medicine compared serum thyrotropin levels between patients who continued taking the same sourced generic levothyroxine product and those who switched. The focus on levothyroxine allowed the researchers to execute a real-world clinical review of FDA-approved therapeutic equivalents available from several different generic manufacturers, within the limitations dictated by available claims data. The study found that among a population of patients (N > 15,000) undergoing properly monitored levothyroxine treatment over time, those who switched among generic drug products maintained the same level of thyroid function as those who consistently used a single generic levothyroxine product based on average serum thyrotropin level. These results establish evidence to mitigate concerns over levothyroxine product switching.

MAY 21 I FDA published the results of a study[8] in Clinical and Translational Science comparing the pharmacodynamic effects of the brand name formulation Toprol XL versus two generic formulations of metoprolol extended release (ER) tablets with different time to maximum concentration (Tmax) in adults with hypertension with one generic medication releasing metoprolol faster than the brand product and one slower. These data will help FDA better understand the possible clinical implications of differences in the shape of pharmacokinetic profiles between brand and generic products.

7 Brito JP, Deng Y, Ross JS, Choi NH, Graham DJ, Qiang Y, Rantou E, Wang Z, Zhao L, Shah ND, Lipska KJ, 2022, Association Between Generic-to-Generic Levothyroxine Switching and Thyrotropin Levels Among US Adults, JAMA Intern Med, 182(4):418-425, doi: 10.1001/jamainternmed.2022.0045.

8 Mosley S, Kim S, El Rouby N, et al., 2022, A Randomized, Cross-over Trial of Metoprolol Succinate Formulations to Evaluate PK and PD End Points for Therapeutic Equivalence, Clin Transl Sci, 15(7):1764-1775, doi: 10.1111/cts.13294.

Safe Use Initiative: Collaborating to Reduce Preventable Harm from Medications

FDA's Safe Use Initiative (SUI) continued working to create and facilitate public and private collaborations within the health care community to help reduce preventable harm from medication errors, which can include the wrong medications dispensed to patients, medications taken for too long, or not long enough. We did this by developing, implementing, and evaluating interventions with our current and potential partners in SUI programs and projects, including federal agencies; health care professionals; professional societies, pharmacies, and hospitals; and patients, caregivers, consumers, and the organizations representing them. Safe Use supports many of its collaborations through funding as well as participating in research studies that seek to reduce preventable medication-related harm, and by maintaining an open and continuous announcement to solicit proposals for this research.

2022 Studies

Several SUI-supported studies were completed, published, and/or presented in 2022, including:

January 30 | Manganese Contamination in Neonatal Parenteral Nutrition. This study[9] on manganese contamination in neonatal parenteral nutrition was completed in 2021 and now published.

AUGUST 10 | Perioperative Medication Safety Self-Assessment for Hospitals and Ambulatory Surgical Centers (ASCs) and Targeted Risk-Reduction Tool Development. We completed a project involving the development, testing, and implementation of a perioperative medication safety self-assessment of systems and practices in hospitals and ambulatory surgical centers in the U.S. using a self-assessment instrument. Between May 2021 and February 2022, the Institute for Safe Medication Practices (ISMP) collected assessment responses from 326 hospitals and 60 ambulatory surgery centers in the U.S. In April 2022, preliminary comparative data from the self-assessment were distributed to participants to allow comparison of their results to demographically similar facilities, identify gaps that could result in medication errors, ascertain areas where they were ahead of the national curve, and develop and prioritize an organization-specific action plan for improvement. Based on findings from a national summit held in late 2021, analysis of the assessment data and a literature review, ISMP created and distributed a consensus-based risk-reduction tool entitled ISMP Guidelines for Safe Medication Use in Perioperative and Procedural Settings. The Guidelines prioritize 71 best practice statements that lend themselves to the biggest opportunities for safety improvement in this setting, which can be downloaded without cost.

OCTOBER 11 | Mentored Implementation and Dissemination of Anticoagulation Stewardship (MIDAS) Program. We completed a project examining the ability of an anticoagulation stewardship program to reduce preventable harm using a Mentored Implementation Program in five diverse hospitals. A Stewardship Guide and Self-assessment were developed in a previous FDA-funded project. In this effort, paired physician-pharmacist teams served as mentors for five different hospitals. The hospitals conducted self-assessments at the beginning of the program, created an interdisciplinary team, and worked with the mentors to create an individualized implementation plan. Mentoring took place monthly over a 12-month period. The hospitals shared lessons learned with each other and provided updates quarterly. A content-development committee then used the implementation plans and lessons learned to create a "playbook" that other institutions can use to create and carry out their own programs. The Advancing Anticoagulation Stewardship: A Playbook is available for download from the National Quality Forum without cost.

9 Sauberan J, Mercier M, Katheria A, 2022, Sources of Unintentional Manganese Delivery in Neonatal Parenteral Nutrition, J Parenter Enteral Nutr, 46(6):1283-1289, doi: 10.1002/jpen.2315.

ONGOING | A Scalable, Patient-centered Approach to "Right-sizing" Opioid Prescriptions. This study is collecting data from patients undergoing elective surgical procedures and those seen in the Emergency Department (ED) for acute pain. Information is being collected on the number of doses of opioid pain medication used, the number of days of medication used, and the way patients feel about their ability to treat their pain. Understanding how much medication most patients actually used will inform revision of standard orders for surgeries to reflect actual patient need, which can help ensure patients are provided enough medication while minimizing the number of pills remaining that could be diverted or misused. To date, several thousand patients have been enrolled and data collection is ongoing. A number of articles have been published, including on the text messaging methods[10] and on opioid consumption[11] after elective spine surgery.

In a second phase of this study, prescriber "report cards" are being tested to further assist with prescribing the appropriate number of pills. Using a stepped-wedge cluster randomized trial, this will test the effect of providing prescribers monthly comparative feedback on their patients' quantity of unused pills. Report cards will contain information on pills prescribed and actually used by patients for each surgical provider for each common procedure. The hypothesis is that compared with usual care, regular feedback will prompt prescribers to reduce the number of pills prescribed, thereby reducing the number left over without impacting patients' ability to manage their pain. Multiple surgical specialties are participating.

ONGOING | Leveraging the Electronic Health Record (EHR) to Promote Pharmacy Adoption of Dosing Best Practices and Reduce Parent Errors in Administering Pediatric Liquid Medications. Enrollment is ongoing in this study examining whether an instruction to pharmacists incorporated into the EHR as part of the electronic prescription will reduce errors in administering pediatric liquid medications. The instructions specify the prescription should be in "mL only" units and that an appropriate-sized dispensing device should be given to the patient. Follow-up with patients assesses the effectiveness of the instructions to the pharmacist and if the intervention reduces dosing errors made by parents.

ONGOING | Preventable Harm from Pediatric Outpatient Medication Errors: Measure Development. This study seeks to develop an understanding of current measures in outpatient pediatric medication safety and assess the gap between current measures and needs. Development of measures is necessary in defining and establishing quality-improvement programs. Development of quality measures in pediatrics has lagged those in other areas. The project includes a systematic literature review, which has been completed, and input from stakeholders, including health care providers, parents, and patients. The interviews with organizational leaders are ongoing.

10 Agarwal AK, Ali ZS, Shofer F, et al., 2022, Testing Digital Methods of Patient-Reported Outcomes Data Collection: Prospective Cluster Randomized Trial to Test SMS Text Messaging and Mobile Surveys, JMIR Form Res, 6(3):e31894, doi: 10.2196/31894.

11 Punchak MA, Agarwal AK, Joshi D, et al., 2022, Understanding the Natural History of Postoperative Pain and Patient-Reported Opioid Consumption After Elective Spine and Nerve Surgeries with an Automated Text Messaging System, Neurosurgery, 90(3):329-339, doi: 10.1227/NEU.0000000000001822.

ONGOING | Assessment of a Pharmacist-led Interprofessional Transitions of Care Program Targeting Patients with Multiple Recent Hospital Admissions: The ICARE Program. In order to decrease the rate of 30-day readmissions and improve patient care during care transitions, the investigators of this study are implementing the ICARE program: **I**dentify at admission, **C**ounsel before discharge, secure **A**ccess to medications, **R**each out for follow-up, **E**ngage community providers to develop a pharmacist-led, hospital-community collaborative TOC program to decrease medication-related harm in patients at high risk for hospital readmission due to multiple recent admissions. Previous studies have examined the impact of TOC services on outcomes related to specific diseases. One gap in the current literature is an examination of the impact of a TOC program on patients at high risk for readmission due to a history of multiple admissions.

ONGOING | Reducing Preventable Medication Errors through Minimizing Work Distractions: Evaluating Data from Smart Pump Usage in Health Systems across the Midwest. The purpose of this study is to use a national-level dataset to analyze detailed infusion events data from smart-pump infusion programming alerts and operational alarms and quantify their impact on clinical workflow. The overall goal is to use these data as the foundation for a framework for reducing preventable harm during intravenous (IV) medication administration using IV smart pumps. Smart infusion pumps with dose-error reduction systems (DERS) have resulted in documented improvement in infusion practice and medication safety, including better control of rate, hard and soft dose limitations, and consistency of delivery. It is estimated that more than 88 percent of U.S. hospitals utilize these medical devices, up from about 30 percent in 2005. However, infusion devices continue to be associated with more adverse event reports to FDA than other medical technologies. Although alert settings and alarm thresholds can be adjusted, most efforts to review the settings and data are not systematically optimized and are highly variable across health systems.

ONGOING | Oral Anticoagulation Surveillance and Improvement through Stewardship (OASIS). This is the third anticoagulation safety study Safe Use has funded through the Anticoagulation Forum (ACF). (See Projects Completed in 2022 above). The study involves assessing hospital needs specific to direct-acting anticoagulant (DOAC) prescribing, to be followed by the development and implementation of an electronic health record-based DOAC dashboard to support anticoagulation stewardship and reduce prescribing errors. Resulting resources will be disseminated to promote widespread use of the dashboard in the acute-care setting.

Compounded Medications: Continuing Oversight and Stakeholder Outreach

In 2022, FDA's compounding program continued to protect patients from unsafe, ineffective, and poor-quality compounded medication, while preserving access to lawfully marketed compounded medications for patients who have a medical need for them. Human medication compounding is generally a practice in which a licensed pharmacist, a licensed physician, or a person under the supervision of a licensed pharmacist in the case of an outsourcing facility combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. Compounded medications can serve an important medical need for certain patients, but because they do not undergo FDA premarket review for safety, effectiveness, and quality, they may present a greater risk of harm to patients than FDA-approved medications. To help mitigate these risks, FDA developed a novel approach to engage facilities that compound sterile medications and help them produce the highest quality medications.

The Compounding Quality Center of Excellence, launched in 2019, is designed to enhance collaboration with outsourcing facilities, compounders, and other stakeholders to improve the overall quality of compounded medications. FDA advanced the implementation of this Center in 2022, including by:

- Developing and holding multiple live, instructor-led training and self-guided online courses
- Holding in September 2022 the annual conference convening outsourcing facilities and other stakeholders to enhance collective learning about how to protect patients from unsafe, ineffective, and poor-quality compounded medications while preserving access to them for patients who need them. The conference program included:
  - » In-depth sessions on current good manufacturing practice (cGMP) topics, including visual inspection during stability and release testing, and qualification of container closure systems
  - » A pre-conference session on outsourcing facility basics concerning product and adverse event reporting, registration, and other requirements
  - » Updates on FDA policies and topics
- Engaging in research to better understand the outsourcing facility sector and its needs to inform current and future program areas for the Center

In June 2022, a federal court permanently enjoined a Colchester, Vermont, compounder from distributing medications unless they are manufactured in compliance with the Federal Food, Drug and Cosmetic Act (FDCA). FDA inspections revealed record-keeping violations, labeling inadequacies, improper airflow, structural disrepair, and the presence of mold in cleanroom suites that can cause diseases in humans that may be deadly to immunocompromised patients.

Communicating Drug Safety: Global Outreach Through Diverse Tools and Technologies

Throughout 2022, CDER's Office of Communications (OCOMM) continued to develop and expand its mission to protect and promote public health through a broad range of communication tools and technologies and the expertise and efforts of a multidisciplinary staff of health care professionals, science and medical communications specialists, researchers, web and graphic designers, and senior strategists and advisors. These professionals enable OCOMM to:

- Provide strategic communication advice to CDER and FDA leadership
- Develop and coordinate overarching public communication initiatives and educational activities
- Devise and deploy comprehensive communication strategies that ensure consistent branding, messaging, and direction of communication initiatives and tools
- Offer expertise on communication products across a variety of media
- Respond to inquiries from the public about a range of topics related to human medications
- Conduct social science and risk communications research

Communicating Drug Safety Across Multiple Audiences and Platforms

Drug Safety Communications (DSCs) provide important new or emerging safety information about marketed prescription and over-the-counter (OTC) medications to patients, caregivers, health care professionals, and the public. Six DSCs were issued in 2022, generating more than 94,000 views by unique people. These DSCs communicate safety issues that, for example, may describe serious or life-threatening adverse events or certain other warnings or cautions related to use of a medication or class of medications or affect a large number of patients, and they contain actionable recommendations for patients and health care professionals. The purpose of the DSCs is to support more informed decision-making by patients and health care professionals and help prevent or mitigate medication-related harm.

The DSC home page is consistently a highly visited page on FDA's web site. The key safety information contained in the DSCs is also broadly circulated through many other channels, including large email listservs, one of which is a DSC-specific list that allows patients and health care professionals to request email alerts about medications or medical specialties of specific interest to them from the 78 different topics offered. Other channels through which the information is disseminated include FDA's Facebook page, Twitter feeds, and LinkedIn page; podcasts; and targeted outreach to media, health care professionals, patient advocacy groups, and other stakeholders. Throughout 2022, DSC information was widely reported, including by Reuters, Healio, MedPage Today, Medscape, and multiple other trade press publications.

Among the six DSCs issued in 2022, two involved high-profile issues or drug products because they involved treatment for opioid use disorder (OUD) or babies and young children, including:

JANUARY 12 I FDA warns about dental problems with buprenorphine medicines dissolved in the mouth to treat opioid use disorder and pain. Dental problems have been reported with medicines containing buprenorphine that are dissolved in the mouth. The dental problems, including tooth decay, cavities, oral infections, and loss of teeth, can be serious and have been reported even in patients with no history of dental issues. Despite these risks, buprenorphine is an important treatment option for OUD and pain, and the benefits of these medications clearly outweigh the risks.

MARCH 30 I FDA recommends thyroid monitoring in babies and young children who receive injections of iodine-containing contrast media for medical imaging. Our review showed that underactive thyroid or a temporary decrease in thyroid hormone levels were uncommon. However, the conditions should be identified and treated early when needed to prevent potential future complications, especially in babies born premature and young children with underlying conditions such as

heart issues. As a result, we recommended thyroid monitoring within 3 weeks after receiving injections of contrast media containing iodine, also called “contrast dye,” for X-rays and other medical imaging procedures.

Drug Safety Communications (DSCs) support more informed decision making by patients and health care professionals and help prevent or mitigate medication-related harm.

Across all DSCs issued during 2022, visitors spent an average of almost two and a half minutes on DSC content. In comparison, most users generally stay on websites for less than 15 seconds.

In conjunction with each DSC, Drug Safety Podcasts were issued, providing an additional platform where patients and consumers can find emerging safety information about medications. The six podcasts issued in 2022 generated more than 7,300 engagements and are available on FDA’s website and on Apple Podcasts, Google Podcasts, Spotify, and ReachMD.

Often centered on medication safety or safety-related topics, FDA’s Drug Information Webinars offer free live online continuing education for physicians, physician assistants, nurse practitioners, nurses, pharmacists, and pharmacy technicians. These webinars remain online and are available on demand to interested professionals. Two safety-related webinars were conducted in 2022:

MAY 24 I Reporting and Public Viewing of Individual Case Safety Reports (ICSRs) webinar

NOVEMBER 29 I The Safety Evaluation and Surveillance of Generic Drugs webinar

DSC Outreach

6 DSCS VIEWED OVER
101,000
times

REACHED MORE THAN:

49,000 DSC listserv subscribers

120,000 Drug Information listserv subscribers

404,000 MedWatch listserv subscribers

PUSHED TO MORE THAN:

561,000
LinkedIn followers

793,000
Facebook followers

338,000
Twitter followers

LinkedIn

69,293
impressions

343
reactions

1,117
clicks to the DSC

Facebook

464
likes

87
shares

Twitter

67
likes

66
retweets

Responding to Public Inquiries

OCOMM responds to public inquiries about all human medications, receiving and managing more than 43,000 public inquiries between October 1, 2021, and September 30, 2022. These inquiries are received via phone, email, letters, and through social media platforms such as Facebook and LinkedIn. Expert responses are developed and facilitated by a team of pharmacists, nurses, and other health professionals who field questions from consumers, health care professionals, journalists, research organizations, nonprofit organizations, drug companies, other government agencies, and academia, as well as from international stakeholders in government and research institutions.

Top 10 Public Inquiries	
Coronavirus	5,758
Isotretinoin REMS	3,334
Clinical Trials/INDs (non-EA)	2,022
Personal Import/Export	1,792
Opioids	1,206
Expanded Access	977
Registration & Listing	541
OTC Monographs	525
Nitrosamines	383
Recalls	314

Public Inquiries Managed Between October 1, 2021–September 30, 2022	
Phone	27,210
Email	17,826
Letters	227
Social Media	550*
TOTAL	**45,813**

**Facebook and LinkedIn*

Social Media Engagement

The CDER Social Media team has significantly expanded the Center's communications outreach by 'meeting' people where they are already engaging on social media platforms, including Twitter, Facebook, LinkedIn, and YouTube. Medication safety information is now actively pushed through several FDA platforms, including to more than 793,000 Facebook followers, 338,000 Twitter followers, and 561,000 LinkedIn followers, facilitating exponential growth in the distribution of the Agency's public health messages, safety communications, and medication safety warnings. In addition to posting content and engaging in two-way communication, the Social Media Team also performs social listening, monitoring the comments and questions users post on FDA's social media channels to obtain immediate feedback on FDA actions and decisions.

As of September 30, the @FDACDERDirector Twitter account had 3,229 followers from media, current and former FDA officials, consumers, health care providers, industry, stakeholder groups, health organizations, and other health and government leaders. The account was launched in 2020 to provide a head of Center perspective on CDER actions and initiatives, including those regarding medication safety. Between October 1, 2021, and September 30, 2022, the CDER Social Media Team:

- Actively disseminated FDA information to followers on Twitter through 956 tweets and Facebook through more than 320 posts
- Provided information to more than 120,000 subscribers on our Drug Information Listserv through 248 messages sent, generating more than 353,000 unique URL "click-throughs" to FDA website content
- Expanded social media outreach for COVID-19 communications, Facebook Events, DSCs, the Remove the Risk opioid disposal campaign, BESAFE Rx online pharmacy campaign relaunch, and a sunscreen campaign

Social Media Outreach on FDA Platforms	
Facebook	
Facebook followers	793,000
Replied to comments	319
Public Likes/Shares	40,991
LinkedIn	
FDA page followers	561,000
Small Business and Industry Assistance (SBIA) Showcase page followers	23,223
Global Alliance of Drug Information Specialists (GADIS) Group members	1,307
Twitter	
Total followers	338,000
Tweets	687
Retweets	5,850
Likes	9,885

Drug Safety-related Labeling Changes

Not every safety concern can be identified at the time a drug product is approved for marketing. As a result, if new safety concerns emerge after a medication is marketed, FDA may require a drug safety-related labeling change, with more than 8,000 of these changes made between October 1, 2021 and September 30, 2022. The drug safety-related labeling changes (SrLCs) database includes safety labeling changes required or ordered by FDA, as well as labeling changes that are voluntarily submitted by product sponsors. The database makes safety information available in near real-time and can be easily searched through a user-friendly portal by stakeholders such as health care professionals, patients, and health information technology and information vendors. Stakeholders accessing the database provide valuable feedback that assists FDA in continually upgrading how safety labeling information is organized and presented.

Safety-Related Labeling Changes*	
Adverse Reactions	1,612
Boxed Warnings	252
Contraindications	704
Drug Interactions	1,020
Patient Counseling Information and/or Medication Guides	1,468
Use in Specific Populations	1,328
Warnings and Precautions	1,732
TOTAL	8,116

**Between October 1, 2021-September 30, 2022.*

CDER Small Business and Industry Assistance (SBIA)

CDER SBIA is often the first stop for a small pharmaceutical business trying to contact the Agency. Our goal is to help small pharmaceutical business and industry navigate the wealth of information that FDA offers, and to assist in understanding human drug product regulation.

SEPTEMBER 29 I FDA Compounding Incidents Program: Adverse Events Associated with Compounded Drugs from Outsourcing Facilities
SBIA Chronicles

JUNE 6 I Regulatory Education for Industry (REdI) Annual Conference 2022 - Day 2 - Part 3
Enhancement and Modernization of FDA Drug Safety System: Review of Postmarket Safety

APRIL 27 I Generic Drugs Forum 2022: The Current State of Generic Drugs, Day 2, Session 3
Project Management of Premarket and Postmarket Generic Drug Safety

Educational and Outreach Campaigns

During 2022, FDA continued its public outreach campaigns and education efforts to provide information to consumers and patients about the safe use and disposal of certain FDA-regulated products. This included launching the Don't Get Burned campaign in October, a component of the Agency's national campaign to raise awareness about sun safety and encourage proper sunscreen use and application. In addition, FDA and United States Pharmacopeia (USP) developed the infographic Biosimilars: Are they the same quality? based on feedback and understanding obtained from a series of research studies conducted with healthcare professionals. The infographic is intended to help healthcare practitioners explain to patients how biosimilar biological products are high-quality products, and safe and effective treatment options. It also highlights the steps the Agency follows to ensure the quality, safety, and effectiveness of biosimilars before they are available to patients and continued monitoring after approval. We also offer materials for health care professional degree programs to use when educating students on biosimilar and interchangeable biosimilar products and the drug approval pathway.

We relaunched the BeSafeRx campaign, which helps consumers learn about how to safely buy prescription medications online, and we were involved in ongoing education and outreach campaigns to help support the safe use of opioids. The campaign Remove the Risk aims to raise awareness among patients and consumers about the serious dangers of keeping unused prescription opioids and to provide information about safe disposal of these medications. In addition, through a long-term CDER collaboration with Partnership to End Addiction, the Search and Rescue campaign provides health care professionals with tools and resources to help patients avoid prescription medication misuse and addiction.

Online Communications

Medication safety news, announcements, and information continued to be distributed to multiple audiences using a variety of digital and electronic media supported by a broad portfolio of services, with traffic on CDER web pages (FDA.gov/drugs) between January 1 and September 30, 2022, amounting to nearly 20 million individual sessions. The portfolio of services making this possible includes video production and photography, web graphics, online publications, custom-designed flow-charts, posters, infographics, illustrations, and other materials. The online communications team also maintains FDA web content, including medication safety information and safety-related regulatory policy documents; manages public databases; and develops web and mobile applications, including optimizing applications for viewing formats such as smart phones and tablets.

The extent of this online engagement on both FDA.gov and FDA.gov/drugs web pages are depicted below, including 1) the platforms from which the traffic coming, 2) the 10 most-viewed CDER web pages—collectively accounting for more than four million online visits, and 3) the topics, questions, and documents generating the most online traffic through September 30. Also tracked are trending topics on social media, as well as the leading subjects of news stories and other informational outlets, and those carried via newsfeeds and social media.

FDA.gov Web Traffic Between January 1–September 30, 2022		
Traffic Volume	**Users**	**Sessions***
Mobile	58,624,428	73,144,668
Desktop	35,046,470	58,698,496
Tablet	1,986,350	2,581,402

** Number of individual online sessions initiated by all users with periods of inactivity less than 30 minutes.*

FDA.gov Web Traffic Between January 1–September 30, 2022	
Traffic Sources	**% Of Sessions**
Search Engines	62
Direct (URLs)	20
Referrals	11
Social Media	4
Email	2

Top 10 Google Searches Leading to FDA Safety Content	
1	Royal Honey
2	Metformina
4	NDC Lookup
4	Montelukast
5	Lishou Slimming Coffee
6	Royal Honey VIP
7	Orange Book
8	Hydroxychloroquine
9	Metformina Para Que Sirve
10	Hand Sanitizer

Top 10 Most Viewed CDER Web Pages in 2022 With 2021 Ranking	
	Unique Pageviews*
1. Drugs (1**)	1,366,542
2. Drug Approvals and Databases (2)	888,309
3. High Blood Pressure – Understanding the Silent Killer (5)	468,897
4. National Drug Code Directory (6)	388,601
5. La FDA actualiza las advertencies relativas al uso de la meformina, una medicina para la diabetes, en ciertos pacientes con una funcion renal deteriorada (New)	321,404
6. Disposal of Unused Medicines: What You Should Know (8)	306,524
7. Public Notification: Royal Honey VIP contains hidden drug ingredient (New)	240,112
8. Public Notification: Royal Honey contains hidden drug ingredient (New)	235,155
9. Drug Disposal: Drug Take Back Locations (10)	233,472
10. Public Notification: Kingdom Honey Royal Honey VIP contains hidden drug ingredient (New)	222,651

**Number of sessions during which the page was viewed one or more times in the same session.*

***2021 ranking of most-viewed CDER web pages for comparison purposes*

Social and Behavioral Science Research

OCOMM's research team continued to conduct a range of social and behavioral science research studies throughout the year to gather evidence directly from health care professionals, patients, caregivers, and consumers related to numerous drug and drug safety-related issues.

- The goal of this research is to enhance understanding of our stakeholders' knowledge, perceptions, needs, desires, and behaviors.
- Findings from these studies provide detailed and comprehensive evidence to inform policy, regulatory, and communication decisions aimed at enabling health care professionals, patients, and the public to make informed health decisions.
- These studies involve qualitative, quantitative, and mixed methods, including detailed, in-depth research, testing of materials and messages, and exploratory pharmacovigilance studies conducted through monitoring and analysis of open-source data available online and through social media.

Highlights of 2022 Research Programs and Projects

Studies related to opioids and other abused drugs

Abuse-deterrent Formulation Opioids. OCOMM social scientists and CDER opioid subject matter experts completed work on a three-phase study exploring and assessing the knowledge, attitudes, and understanding regarding abuse-deterrent formulation (ADF) opioids among prescribers and pharmacists, including related to the ADF terminology. Based on findings from focus groups with opioid prescribers and pharmacists in the first study phase and a follow-up nationwide survey completed in 2021 to obtain more representative data, the final third phase, an experimental study, was completed in 2022. The findings from this series of studies will be used to inform CDER's discussions about these products.

Substances Used as Adjuncts or Alternatives to Prescription Opioids. OCOMM social scientists and opioid subject matter experts from across CDER completed a study involving in-depth qualitative interviews with patients undergoing treatment for opioid and substance use disorders related to the use of four specific substances – benzodiazepines, gabapentinoids, kratom, and cannabidiol – and how these substances relate to the use, misuse, and addiction associated with prescription opioids and other substances. These qualitative findings will inform quantitative survey studies among both health care professionals and users of various substances to obtain more generalizable results.

An OCOMM-led multidisciplinary cross-CDER research team also completed the first of a two-phase qualitative study to enhance CDER's understanding of the context surrounding the prescribing of prescription benzodiazepines and how the use of these medications relates to current prescription use, misuse, and addiction in the United States. This includes prescribers' motivations and experiences when prescribing benzodiazepines alone and in conjunction with or as alternatives to prescription opioids, as well as related to the tapering of benzodiazepines in patients who have been taking them long term, and concerning guidelines used when prescribing them. The first focus group phase was completed in 2022, the findings from which are being used to inform the follow-up interview phase.

Proactive Pharmacovigilance Through Social Media Monitoring and Analysis. OCOMM researchers continued to employ this novel method for proactive pharmacovigilance to obtain an understanding of the social contexts and trends surrounding opioids and other prescription medications, particularly their use for nonmedical or recreational purposes, being discussed in publicly available online discussion forums and on social media. In addition to conducting routine monitoring and developing monthly social media research reports throughout 2022 concerning the non-medical use of prescription opioids and other substances used with them, we initiated a six-month trend report and included coverage of non-medical use of benzodiazepines in these monthly reports. OCOMM also completed an in-depth study and began another one. The completed study involved exploring the use of kratom for self-treatment of stimulant use disorder. Social scientists also undertook a project investigating how consumers are using benzodiazepines for medical or recreational purposes; how and why they are discussing tapering off these medications, including substances being used as alternatives to, replacements for, or in conjunction with benzodiazepine; and what negative effects/adverse events they are experiencing with these medications. In addition, after learning about reports of deaths associated with delta-8 THC products that may have been contaminated, OCOMM conducted an exploratory analysis to determine the topics being discussed online and through social media about experiences with potential contamination of these products. Based on concerns about the preponderance of xylazine in other drugs that surfaced as part of OCOMM's regular monthly opioids monitoring, social scientists also conducted online/social media research related to negative effects and treatment-related issues consumers reported about the substance, the findings from which were provided to CDER's Controlled Substances Program and contributed to an 8 Factor Analysis.

Other Studies

Biosimilar Products. OCOMM completed a study to assess a set of educational materials whose aim was to help patients better understand about biological products that are demonstrated to be biosimilar to an FDA-licensed biological product. The project involved obtaining feedback about an educational infographic, fact sheet, and video public service announcement to be posted on FDA's website or disseminated to patients through other methods. This study is a follow-up to related projects that collected information about knowledge, awareness, and understanding of biological products and biosimilars from patients and health care professionals. A manuscript is in development.

Combatting Misinformation During Public Health Emergencies. OCOMM has undertaken a multiphase research project to develop data aimed at identifying optimal message strategy(ies) for FDA to correct misinformation that surfaces about public health emergencies such as COVID-19. The research findings from two experimental studies will be used to inform an evidence-based guidance on corrective messaging that combats misinformation during public health crises, which FDA can employ when developing messages addressing misinformation on a broad array of issues that surface, including the availability, safety, and efficacy of medications and other treatments and preventions.

Message and Materials Testing. Two studies assessing COVID-19-related information and materials were undertaken in 2022. The first involved assessing three question-and-answer (Q&A) documents and two videos concerning FDA-authorized or approved COVID-19 vaccines and boosters for children ages 5-11, 12-15, and children 16+ and adults. Feedback on these communication materials was elicited through in-depth individual interviews with a small group of adults, including parents or caregivers of children in the various age groups. The videos and some of the Q&A content, which was already posted on the Agency's website prior to testing, were intended to inform parents/caregivers and consumers about the benefits and risks of the COVID-19 vaccines and answer common questions, including about eligibility and boosters. The second study aimed to assess two Q&A documents and one prescribing checklist about Paxlovid, a COVID-19 treatment that was authorized under Emergency Use Authorization to treat patients meeting strict requirements. These documents were developed to help educate healthcare providers about the requirements for prescribing Paxlovid. These two studies each resulted in a number of recommendations aimed at enhancing the materials, which were provided to FDA developers of the materials.

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