U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Drug Safety Priorities Fiscal Year 2024

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Introduction

Jacqueline Corrigan-Curay, M.D., J.D.

Acting Director,
Center for Drug Evaluation and Research

In the past year, the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) continued its robust efforts to ensure that safe and effective prescription and nonprescription medications are available to improve the health of people in the United States. The Center's efforts to safeguard the medications Americans rely on is multifaceted and lengthy, continuing long after they are FDA-approved and available commercially, as new side effects and risks can emerge at any time. Thus, we continued to effectively monitor medications through our postmarket surveillance and risk evaluation programs. This CDER Drug Safety Priorities Fiscal Year 2024, our 10th yearly report covering the fiscal year ending September 30, shows the extensive safety activities conducted by multidisciplinary teams across CDER and features updates on the year's safety-related achievements and milestones.

As part of FDA's mission to protect and promote public health, we maintained rigorous premarket review of new drugs when evaluating them for possible approval and actively engaged in initiatives to modernize and improve the Center's New Drugs Regulatory Program (NDRP) to enhance our safety assessments. In fiscal year 2024 (FY24), we released an Impact Narrative Update on NDRP's modernization progress and ongoing efforts. We also published Artificial Intelligence and Medical Products: How CBER, CDER, CDRH, and OCP are Working Together, which describes areas of focus regarding the development and use of artificial intelligence (AI) across the medical product lifecycle. This document outlines our commitment toward upholding quality, safety, and effectiveness, as well as aligning efforts across FDA's centers to advance responsible use and build consistent regulatory approaches.

In addition, the CDER Quantitative Medicine Center of Excellence (QM CoE) was established in March 2024 to enable and organize the continuous advancement

and consistent use of quantitative medicine (QM) for drug development and regulatory decision-making across CDER. The QM CoE fosters integration of QM approaches to further therapeutic product development; identify, quantify, and address uncertainty earlier in a product's lifecycle; and contribute to the totality of understanding for a drug's benefits and risks. The CDER Center for Clinical Trial Innovation (C3TI) was established in April 2024 to strengthen and expand innovative approaches to clinical trials designed to generate the needed evidence of safety and improve the efficiency and effectiveness of drug development.

We continued to prioritize strategies to address the nation's overdose crisis that has resulted from nonmedical use of prescription opioids alone and together with other controlled and illicit substances, including prescription benzodiazepines, stimulants, and synthetic fentanyl. Despite an overall decrease in drug overdose deaths between 2023 and 2024, the related public health threats of polysubstance use and addiction continue to plague individuals, families, communities, and health systems with overdose deaths reaching more than 86,000 in 2024. As part of our ongoing commitment, in FY24 we launched the Prescribe with Confidence campaign, which provides free training, mentoring, and other resources to health care professionals who prescribe or plan to prescribe medications for opioid use disorder.

In addition, we worked to protect the public from impurities and contaminants in medications, releasing two guidance documents for industry related to drug products that may contain benzene and nitrosamines. These were: Reformulating Drug Products That Contain Carbomers Manufactured With Benzene, which provides recommendations for drug companies on tests that should be performed and the documentation that should be submitted to FDA to support the reformulation of drug products that use carbomers, which are polymers used as inactive ingredients, manufactured with benzene; and Control of Nitrosamine Impurities in Human Drugs, which describes the Agency's updated thinking about how drug companies can detect and prevent unacceptable levels of nitrosamine impurities in their products. We also worked with manufacturers to prevent and reduce the impact of medication shortages, including those that may be caused by safety-related quality issues, as part of our broader shortage-related efforts. Other safety-related activities included informing the public about product recalls and using a variety of communication tools to transparently communicate medication safety information; monitoring Sentinel, our electronic safety surveillance system; and working to improve the overall quality of compounded medications, including for glucagon-like peptide-1 receptor agonists (GLP-1 RAs), a class of medications used to treat people with type 2 diabetes or to help those with obesity or overweight to lose weight; and facilitating public-private health care collaborations to reduce preventable medication harm through the Safe Use Initiative. Our accomplishments over the past year reflect the best of CDER's commitment to public health and safety.

Postmarket Safety Surveillance of Marketed Medications and Premarket Evaluation

Pharmacovigilance

CDER continued efforts in postmarket surveillance in FY24, including the development of Pharmacovigilance Strategies (PVS) for medications. For example, we developed a PVS for nirsevimab because medication errors for this product were being reported in which the wrong dose was given to treat respiratory syncytial virus. As part of the PVS for medication errors with nirsevimab, we conduct monthly evaluations of reports submitted through FDA Adverse Event Reporting System (FAERS) and weekly evaluations of reports submitted through Vaccine Adverse Event Reporting System (VAERS), as well as review of the drug company's periodic safety reports. The Center uses a broad range of postmarketing surveillance and risk evaluation programs to evaluate and characterize new adverse events and medication errors that first appear postmarket when they become available commercially. This surveillance is especially important for products that are not required to undergo clinical testing for safety and efficacy or an approval process.

When we identify new safety information that may change the benefit-risk profile of a product, we investigate the issue and consider appropriate action. These may include requesting or requiring changes to the prescribing information about a medication, issuing a Drug Safety Communication or other public communications, requiring postmarketing studies after the medication has been approved, requiring or modifying a Risk Evaluation and Mitigation Strategy (REMS), or requesting a market withdrawal of the product, which is rare. We continue to maintain publicly available, searchable databases that contain safety-related information, including information on the following: FAERS, REMS (REMS@FDA), Drug Safety-related

Labeling Changes (SrLC), Medication Guides (MedGuides), and Postmarket Requirements and Commitments. This past year, we also led development of draft guidance documents under the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) process for postapproval safety information management of planning, designing, and analyzing pharmacoepidemiological drug safety studies. In addition, we implemented the latest ICH E2B standard for electronic reporting.

FDA posts quarterly reports of potential signals of serious risks and new safety information identified using the FAERS database, which contains reports of adverse events, medication errors, and product quality complaints submitted to FDA by patients, family members, and health care professionals through the MedWatch program. FAERS also contains reports from drug companies, which are required to submit them per FDA regulations. In addition, we finalized the document: Best Practices for FDA Staff in the Postmarketing Safety Surveillance of Human Drug and Biological Products, which outlines risk-based principles for the Center's conduct of ongoing postmarket safety surveillance.

A REMS is a drug safety program we can require for medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS can be designed to reinforce medication use behaviors and require actions that support safe use. Each REMS is routinely assessed to ensure that it continues meeting the goals of the program.

Medication Error Prevention and Analysis

Our work includes efforts to minimize the risk of medication errors related to naming, labeling, design, and packaging. As a part of that effort, we review medication proprietary or brand names to prevent confusion; evaluate human factors data and information to ensure the safe and effective use of medications; review proposed medication labeling, design, and packaging as a part of the premarket review for all original New Drug Applications and Biologics License Applications (NDAs and BLAs); and provide medication error prevention expertise for certain supplemental applications.

Highlighted Premarket Medication Error Prevention Reviews

MARCH 21 | Assessed proprietary name, labels and labeling, and human factors data to minimize the risk of medication error in premarket review of Duvyzat (givinostat), approved to treat Duchenne Muscular Dystrophy (DMD) in patients 6 years and older, the first nonsteroidal medication approved to treat patients with all genetic variants of DMD.

APRIL 12 | Clarified recommended pediatric dose titration and dosing during premarket review of Entresto Sprinkle (sacubitril and valsartan) oral pellets, approved to treat symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients 1 year and older.

APRIL 30 | Determined in premarket review that pre-filled syringes were not designed for administration of partial doses of Mircera (methoxy polyethylene glycol-epoetin beta) injection, approved to extend the indication to treat anemia associated with chronic kidney disease (CKD) down to 3 months old.

AUGUST 7 | Assessed proprietary name, labels and labeling, and human factors data to minimize risks of medication errors in premarket review of Zurnai (nalmefene hydrochloride) injection, approved as the first nalmefene hydrochloride auto-injector for the emergency treatment of known or suspected opioid overdose in adults and pediatric patients 12 years and older.

AUGUST 9 | Reviewed applicant's human factors validation study results in premarket review of Neffy (epinephrine) nasal spray to ensure user interface design supported safe and effective use by intended users, approved as the first epinephrine product not administered by injection to treat anaphylaxis.

AUGUST 12 | Clarified prescribing information to ensure dosing information clearly communicated users should only use one injection to achieve once daily recommended dosage in premarket review of Yorvipath (palopegteriparatide) injection, approved for use in adults with hypoparathyroidism.

Medication Error Surveillance

In addition to the premarket efforts to prevent medication errors, CDER has a robust postmarketing medication error surveillance program. We receive more than 100,000 of these reports each year. These reports are analyzed to identify cases where the contributing factors of the medication error were related to the proprietary names, labels, labeling, design, or packaging of medications. We work with applicants and manufacturers to reduce the risks of these medication errors, for example, by revising the carton labeling for a medication.

PDUFA VII User Fee Safety-Related Performance Goals

MARCH 25 | Published two Manuals of Policies and Procedures (MAPPs), MAPP 6702.1 Review of Risk Evaluation and Mitigation Strategy (REMS) Assessment Reports and MAPP 6702.3 Review of Proposed Methodological Approaches to Assess a Risk Evaluation and Mitigation Strategy (REMS), to fulfill a performance goal under Prescription Drug User Fee Act (PDUFA) VII.

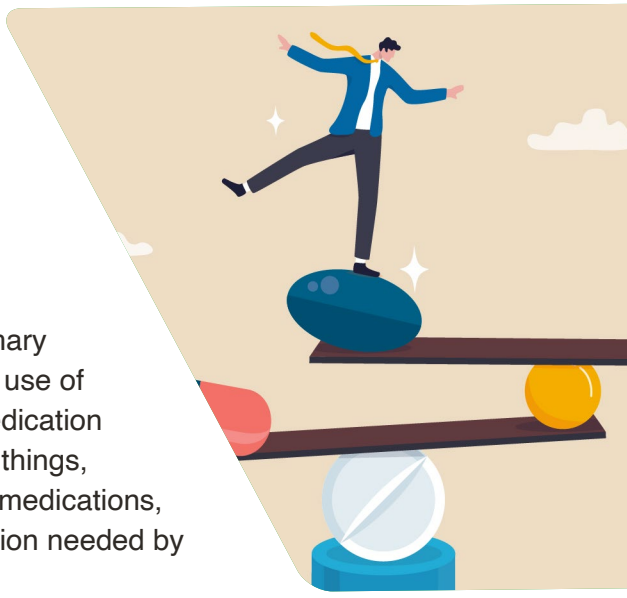
MAY 7 | Published the draft guidance for industry REMS Logic Model: A Framework to Link Program Design With Assessment to fulfill a performance goal and provide industry with a framework for a systematic, structured approach to the design, implementation, and evaluation of a REMS.

JULY 8 | Published the draft guidance Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products to meet both PDUFA VII and the Biosimilar User Fee Act III commitment to publish a guidance for review staff and industry, describing considerations related to drug-device and biologic-device combination products and how use-related risk analyses and other information is used to inform FDA when the results from a human factor validation study may need to be submitted to a marketing application.

Risk Management

CDER applies a benefit and risk framework to assess whether the benefit of a medication outweighs its risks for indicated uses.[1] We may do this by:

- Developing strategies to minimize risks while preserving benefits in the pre-approval phase
- Evaluating the effectiveness of such strategies and reassessing benefit-risk balance after a drug product is marketed
- Adjusting risk minimization strategies to further improve the benefit-risk balance



Our 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 safe and effective use of the medication. Medication Guides are also part of prescription medication labeling, and they contain approved information that, among other things, could help prevent serious adverse reactions. For nonprescription medications, the Drug Facts Label includes a summary of the essential information needed by consumers for safe and effective use.

1 FDA, 2013, Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation Plan - February 2013, Fiscal Years 2013-2017, https://www.fda.gov/media/84831/download.

For most prescription medications, labeling is sufficient to ensure the benefits of taking a medication outweigh the risks. In a limited number of cases, we may determine that a REMS will also be needed to ensure the benefits of the medication outweigh the risks; only a small number of the numerous medications FDA approves annually are subject to a REMS.

REMS Approvals

OCTOBER 17 | Approved Zilbrysq (zilucoplan) injection to treat generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive. The REMS outlines steps necessary to mitigate the risk of serious meningococcal infections and stresses that prescribers and patients should be alert to early infection signs and symptoms.

DECEMBER 5 | Approved Fabhalta (iptacopan) capsules to treat adults with paroxysmal nocturnal hemoglobinuria. It is also approved to reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression. The REMS mitigates the risk of serious infections caused by encapsulated bacteria and advises patients and prescribers to be aware of the early infection signs and symptoms.

MARCH 5 | Approved Jubbonti (denosumab-bbdz) injection, the first biosimilar denosumab product, to treat postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in men with osteoporosis at high risk for fracture; to treat glucocorticoid-induced osteoporosis in men and women at high risk of fracture; to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer; and to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. The REMS was necessary to mitigate the risk of severe hypocalcemia with advanced CKD and inform health care professionals of the need to assess patients for the presence of CKD-mineral bone disorder before initiating Jubbonti in patients with advanced CKD.

MARCH 19 | Approved Tryvio (aprocitentan) tablets to treat hypertension in adults that is not adequately controlled by other medications. The REMS was necessary to ensure prescribers are aware of the risk of embryo-fetal toxicity and the need to counsel patients on the actions necessary to minimize fetal exposure to the medication.

MARCH 29 | Approved Voydeya (danicopan) tablets as add-on therapy to ravulizumab or eculizumab to treat extravascular hemolysis in adults with paroxysmal nocturnal hemoglobinuria. The REMS mitigates the risk of serious infections caused by encapsulated bacteria and advises patients and prescribers to be aware of the early infection signs and symptoms.

MAY 28 | Approved BKEMV (eculizumab-aeeb) injection, the first biosimilar eculizamab product, to treat patients with paroxysmal nocturnal hemoglobinuria to

reduce hemolysis and atypical hemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy. The REMS mitigates the risk of serious meningococcal infections and advises patients and prescribers to be aware of the early infection signs and symptoms.

JUNE 20 | Approved Piasky (crovalimab-akkz) injection to treat patients 13 years and older with paroxysmal nocturnal hemoglobinuria and body weight of at least 40 kilograms. The REMS mitigates the risk of serious meningococcal infections and advises patients and prescribers to be aware of early infection signs and symptoms.

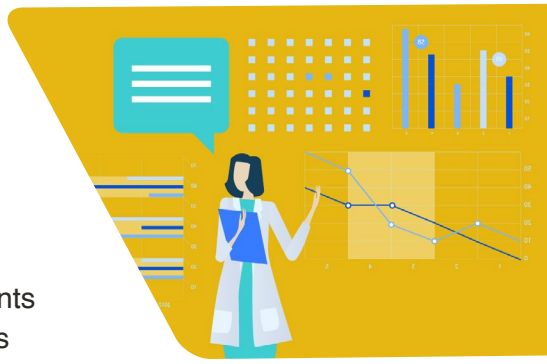
JUNE 25 | Approved phentermine and topiramate extended-release capsules, the first generic for Qsymia, for chronic weight management together with a reduced-calorie diet and increased physical activity in adults with obesity or overweight in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia. The REMS addresses the increased risk of embryo-fetal toxicity with major congenital malformations by requiring patients of reproductive potential be advised of the importance of preventing pregnancy and the need to discontinue the drug immediately if pregnancy occurs.

JULY 19 | Approved Epysqli (eculizumab-aagh) injection, the second biosimilar eculizumab product, to treat patients with paroxysmal nocturnal hemoglobinuria to reduce hemolysis and atypical hemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy. The REMS mitigates the risk of serious meningococcal infections and advises patients and prescribers to be aware of early infection signs and symptoms.

REMS Public Dashboard

The REMS Public Dashboard is a user-friendly web-based tool allowing patients, health care professionals, researchers, industry, and others to easily access information about REMS. In FY24, the REMS Public Dashboard was accessed by nearly 3,000 times each quarter, both domestically and by those outside the United States. We also provided a continuing education webinar on the REMS Public Dashboard targeting health care professionals.

Drug Utilization



Understanding patterns of medication utilization is a vital part of safety surveillance because changes in these patterns may signal emerging areas of concern. Drug utilization analyses are often performed as a part of the mosaic of assessments conducted in support of CDER's mission to ensure that safe and effective medications are available to improve the health of people in the United States. Drug utilization analyses provide valuable insights into emerging safety concerns, and context for the evaluation of adverse events associated with the use of medications. In FY24, drug utilization analyses were performed to understand the increasing use of medications commonly used to treat attention-deficit/hyperactivity disorder (ADHD). New initiations of stimulant prescriptions classified as controlled (Schedule II) substances, including amphetamine and dextroamphetamine, as well as non-stimulant medications used to treat ADHD (e.g., atomoxetine) were found to have significantly increased, particularly among adults, before and after March 2020 (i.e., before and during the COVID-19 pandemic). These findings were subsequently published in JAMA Psychiatry.[2]

Analyses have also been performed to assess emerging concerns of outpatient use of ketamine, including reports of use for mental health conditions such as depression or other conditions for which ketamine has not been determined to be safe and effective. Drug utilization analyses have also been conducted to monitor increasing reports of increased availability of compounded ketamine, a controlled substance with abuse concerns.

Medication Shortages

Drug utilization analyses have provided insights into medication shortage concerns and quantitative assessments to further support CDER's evidence-based regulatory decision making to prevent and mitigate medication shortages. Analyses have been performed to support ongoing regulatory activities exploring the increasing use of prescription stimulants, including to support discussions across FDA to address shortages of these medications. In addition, utilization of GLP-1 RAs was assessed to understand the extent of use and how these products are used in current clinical practice. These analyses showed a substantial uptake in the utilization of these medications and suggested off-label use, providing insight into possible reasons behind medication shortages.

2 Chai G, Xu J, Goyal S, et al, 2024, Trends in Incident Prescriptions for Behavioral Health Medications in the US, 2018-2022, JAMA Psychiatry, 81(4): 396–405, doi:10.1001/jamapsychiatry.2023.5045.

Safety Surveillance of Unapproved Products

For products that are not FDA-approved, CDER enhanced surveillance efforts by evaluating all cases related to unapproved new drugs such as products marketed as supplements with a medical health claim and homeopathy products. Because adverse event data on unapproved products are limited in FAERS and available medical literature, we incorporated surveillance of nontraditional sources such as online marketplaces and social media video platforms. Surveillance was also expanded by partnering with colleagues across CDER offices and the Center for Food Safety and Applied Nutrition (CFSAN) to track safety issues associated with unapproved products, evaluate adverse events, collect and/or test product samples, issue public communications, and identify companies in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

CDER continued to track adverse event cases associated with tianeptine, an unapproved atypical antidepressant with opioid effects. Several cases of seizures, loss of consciousness, and death with Neptune's Fix products containing tianeptine were reported to FDA. Neptune Resources, LLC agreed to voluntarily recall all lots of Neptune's Fix Elixir, Neptune's Fix Extra Strength Elixir, and Neptune's Fix Tablets.

In FY24, we warned consumers not to use OPMS Black Liquid Kratom, which is marketed to include both mitragynine and 7-hydroxymitragynine (known to be tenfold more potent than mitragynine). Kratom is an unapproved herbal substance from Southeast Asia that can produce opioid- and stimulant-like effects. CDER worked with partners in CFSAN to track death cases tied to kratom and communicated regularly with the National Consumer Complaint Coordinator to collect follow-up data such as autopsy and toxicology reports obtained by consumer safety officers stationed at FDA district offices. The Center also heightened surveillance efforts for kratom beyond FAERS and reports published in available literature by adding further surveillance sources such as poison data, CFSAN Adverse Event Reporting System data, and consumer complaints.

Activities Related to Drug-Induced Liver Injury

CDER made contributions to ongoing public-private partnerships and other academic initiatives to improve prediction of drug-induced liver injury (DILI) risk in both premarket and postmarket settings and developed consensus among experts in best practices for liver safety. These initiatives included:

- A series of meetings and webinars convened by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ-DILI) and the Collaborative Research Liver Forum on best practices to assess and manage DILI
- Three co-authored manuscripts from IQ-DILI and the Liver Forum were published related to DILI in the elderly;[3] the prevention, detection, and management of Hepatitis B virus reactivation in immunosuppressive treatment trials;[4] and the use of liver biopsy to assess suspected DILI in Metabolic Dysfunction-Associated Steatohepatitis trials have been published in peer-reviewed scientific journals[5]
- The external review committee of LiverTox, an internationally recognized information source for individual drugs and biological products as well as dietary supplements associated with DILI, was curated by the National Library of Medicine and National Institute of Diabetes and Digestive and Kidney Diseases
- The National Institutes of Health-sponsored Drug-Induced Liver Injury Network, which maintains a registry of patients referred for assessment of suspected DILI
- An FDA initiative to evaluate new methodologies designed to characterize DILI liability of new drug products in development

3 Cohen EB, Patwardhan M, Raheja R, et al, 2024, Drug-induced Liver Injury (DILI) in the Elderly: Consensus statements and recommendations from the IQ-DILI Consortium, Drug Saf, 47(4): 301–319, doi:10.1007/s40264-023-01390-5.

4 Cohen EB, Regev A, Garg A, et al, 2024, Consensus Guidelines: Best Practices for the Prevention, Detection and Management of Hepatitis B Virus Reactivation in Clinical Trials with Immunosuppressive/Immunomodulatory Therapy, Drug Saf, 47(4): 321–332, doi:10.1007/s40264-024-01399-4.

5 Palmer M, Kleiner DE, Goodman Z, et al, 2024, Liver Biopsy for Assessment of Suspected Drug Induced Liver Injury in Metabolic Dysfunction-Associated Steatohepatitis Clinical Trials: Expert Consensus from the Liver Forum, Aliment Pharmacol Ther, 59(2): 201–216, doi:10.1111/apt.17762.

The Sentinel System

CDER proactively evaluates the safety of regulated medical products using a surveillance program called the Sentinel System, which informs regulatory decision-making. We successfully completed several signal identification analyses using tree-based scan statistics in Sentinel, providing valuable insights for further integrating these tools into FDA's routine pharmacovigilance program. The analytic packages and results from these projects are available on the Sentinel website.

The Center continued to work in FY24 on fuller utilization of Medicaid data in the Sentinel Common Data Model. Sentinel has proven to be a vital source of safety information that informs regulatory decision-making and expands the Agency's knowledge of how medical products perform once they are widely used in clinical practice. Each year in November, FDA holds an Annual Sentinel Initiative Public Workshop. In addition, nine peer-reviewed Sentinel publications were released in FY24.[6-14]

6 Weberpals J, Raman SR, Shaw PA, et al, 2024, smdi: an R package to perform structural missing data investigations on partially observed confounders in real-world evidence studies, JAMIA Open, 7(1): ooae008, doi:10.1093/jamiaopen/ooae008.

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

8 Desai RJ, Wang SV, Sreedhara SK, et al, 2024, Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center, BMJ, 384: e076460, doi:10.1136/bmj-2023-076460.

9 Wyss R, van der Laan M, Gruber S, et al, 2024, Targeted Learning with an Undersmoothed Lasso Propensity Score Model for Large-Scale Covariate Adjustment in Healthcare Database Studies, Am J Epidemiol, doi:10.1093/aje/kwae023.

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

11 Carrell DS, Floyd JS, Gruber S, et al, 2024, A general framework for developing computable clinical phenotype algorithms, J Am Med Inform Assoc, 31(8): 1785-1796, doi:10.1093/jamia/ocae121.

12 Hazlehurst B, Carrell DS, Bann MA, et al, 2024, Finding uncoded anaphylaxis in electronic health records to estimate the sensitivity of International Classification of Diseases, Tenth Revision, Clinical Modification codes, Am J Epidemiol, 193(10): 1494-1496, doi:10.1093/aje/kwae063.

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

14 Rai A, Maro JC, Dutcher S, Bright P, Toh S, 2024, Transparency, reproducibility, and replicability of pharmacoepidemiology studies in a distributed network environment, Pharmacoepidemiol Drug Saf, 33(6): e5820, doi:10.1002/pds.5820.

Highlighted Sentinel Completed and Ongoing Projects

APRIL | Onboarded EHR data partners with structured data fields and linked claims data from two commercial data partners. The data were converted into the Sentinel Common Data Model, which will allow FDA greater access to a variety of data resources through Sentinel to support regulatory work.

JULY | Created a linked EHR-claims Development Network to provide Sentinel with a standardized process for investigators to access free text notes at each of the development network sites. This supports Sentinel tasks and advance capabilities towards addressing ARIA insufficiencies.

SEPTEMBER | Addressed partially observed confounder data from EHRs in the context of non-randomized studies of medication outcomes, which aimed to systematically investigate approaches to detect underlying 'missingness' mechanisms; compare imputation approaches; and showcase sensitivity analyses to build confidence in pharmacoepidemiology analyses with partially observed confounder variables. The overall goal was to develop standardized 'toolkits' that can be readily implemented in EHRs to describe and address missingness in confounding variables when assumptions permit.

The Sentinel Initiative is comprised of multiple components, including the Sentinel System, which encompasses the Active Risk Identification and Analysis (ARIA) System; FDA-Catalyst, which supplements the Sentinel System; and the Center for Biologics Evaluation and Research (CBER) Biologics Effectiveness and Safety System (BEST), which supports the Sentinel Initiative but operates outside of the Sentinel Infrastructure. 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). We routinely use 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 Electronic Health Records (EHRs) to address regulatory questions. By making it possible to analyze emerging risks associated with FDA-regulated medical products, Sentinel enables the Agency to assess medical product safety, describe medical product utilization, and characterize medical events under real-world conditions.

Drug Safety Modernization

Under the direction of CDER's Drug Risk Management Board, a drug safety governance group, progress towards postmarket safety modernization continued in FY24. Many accomplishments are summarized in other sections of this report, however, the below are highlights of notable FY24 activities about guidance, policy, and organizational and process changes.

Guidance and Policy Activities

We published several guidance documents relating to safety surveillance and oversight of marketed medications, including:

- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
- E2D(R1) Post-Approval Safety Data: Definitions and Standards for Management and Reporting of Individual Case Safety Reports
- Reformulating Drug Products That Contain Carbomers Manufactured with Benzene

Organizational and Process Activities

JUNE 11 | Announced the Emerging Drug Safety Technology Program (EDSTP) in a Federal Register Notice. The program is designed to advance CDER's knowledge on the use of emerging technologies, such as AI, for pharmacovigilance by facilitating conversations with industry through Emerging Drug Safety Technology Meetings (EDSTMs). These meetings provide applicants and other relevant parties (e.g., academia, contract research organizations, pharmacovigilance vendors, software developers) that meet the eligibility and selection criteria for participation with an opportunity to meet with CDER staff to discuss their research, development, and use of AI and other emerging technologies in pharmacovigilance. Information about the program and selection criteria is available on the EDSTM Program website.

JULY 11 | Published the Workshop Report for the Optimizing the Use of Postapproval Pregnancy Safety Studies workshop held in September 2023, in collaboration with Duke-Margolis. The workshop examined post-approval pregnancy safety studies associated with FDA-approved products; analyzed sources and characteristics of quantitative human pregnancy data in Pregnancy and Lactation Labeling Rule product labeling; evaluated drug utilization data to form key considerations to construct a pregnancy safety study framework; designed a preliminary framework for determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for postapproval safety data; and planned demonstration projects to address knowledge gaps in the design and performance of different pregnancy safety study types to better inform the framework development.

Ongoing Efforts to Address Controlled Substances and the Overdose Crisis

CDER and FDA took important steps in its continuing activities and actions to address the drug overdose crisis, which is multifaceted and has evolved beyond prescription opioids, resulting in the need for an expanded approach. The current crisis, driven by illicit opioids such as fentanyl and its analogues, also involves other controlled substances being used in combination with opioids, including benzodiazepines and stimulants (particularly methamphetamine), and other substances of concern, such as xylazine. CDER's FY24 actions and activities supporting each of the FDA Overdose Prevention Framework's priorities included:

- **OCTOBER 4 |** Published the new draft guidance Stimulant Use Disorders: Developing Drugs for Treatment to assist sponsors in developing treatments for stimulant use disorders.
- **OCTOBER 4 |** Hosted the public meeting Mitigating Risks from Human Xylazine Exposure through a cooperative agreement with the Reagan-Udall Foundation for the FDA to explore real-world experiences and scientific evidence on emerging data trends for human xylazine exposure and examine concrete strategies for drug development and clinical research.
- **OCTOBER 10 |** Warned patients and health care professionals about potential risks associated with compounded ketamine products, including oral formulations, to treat psychiatric disorders.
- **NOVEMBER 13 |** Joined other HHS federal partners to hold a Tribal Listening Session on the use of high-dose buprenorphine to treat opioid use disorder (OUD), which will help inform federal guidance and activities on buprenorphine dosing in the context of fentanyl.

- **NOVEMBER 16 |** Issued a warning letter in collaboration with FDA's CFSAN and Center for Veterinary Medicine (CVM) to Discover Health, LLC, doing business as Discover CBD and Strain Snobs, for selling and introducing into interstate commerce products unproven claims to treat or cure opioid addiction.
- **NOVEMBER 21 |** Warned consumers not to purchase or use any Neptune's Fix products or any other product containing tianeptine, a potentially dangerous substance that is not FDA-approved for any medical use.
- **DECEMBER 12-13 |** Funded the public workshop Adult Attention-Deficit/Hyperactivity Disorder (ADHD): Diagnosis, Treatment, and Implications for Drug Development hosted by the National Academies' Forum on Drug Discovery, Development, and Translation and the Forum on Neuroscience and Nervous System Disorders.
- **DECEMBER 14 |** Issued a warning letter citing the unlawful sale of controlled substances by the online pharmacy www.trinexpharmacy.com.
- **DECEMBER 15 |** Announced final approval and implementation of required labeling updates for immediate-release and extended-release/long-acting opioid analgesics to continue efforts to address the evolving crisis, and to urge health care professionals to take a more patient-centered approach when prescribing opioid analgesic products.
- **DECEMBER 17 |** Published the research article A Social Media Analysis of Kratom Use to Discontinue Stimulants.[15]
- **JANUARY 10 |** Published the research article Trends in Incident Prescriptions for Behavioral Health Medications in the US, 2018-2022.2
- **JANUARY 16 |** Announced an open period for applications to support the development, implementation, and evaluation of a human abuse potential study on the use of botanical kratom.
- **JANUARY 17 |** Announced an extension on the shelf-life of Narcan 4 milligram naloxone hydrochloride nasal spray products, used to treat opioid overdoses, from 3 to 4 years.
- **JANUARY 31 and FEBRUARY 1 |** Hosted the virtual public meeting Advancing Psychedelic Clinical Study Design through a cooperative agreement with the Reagan-Udall Foundation to bring together researchers, regulated industry, and other key stakeholders to discuss scientific issues that arise while working with psychedelics in clinical trials and drug development.

15 Settle JR, Smith A, Rausch P, Rw R, 2024, A social media analysis of kratom use to discontinue stimulants, J Addict Dis, 42(4): 508-514, doi:10.1080/10550887.2023.2292304.

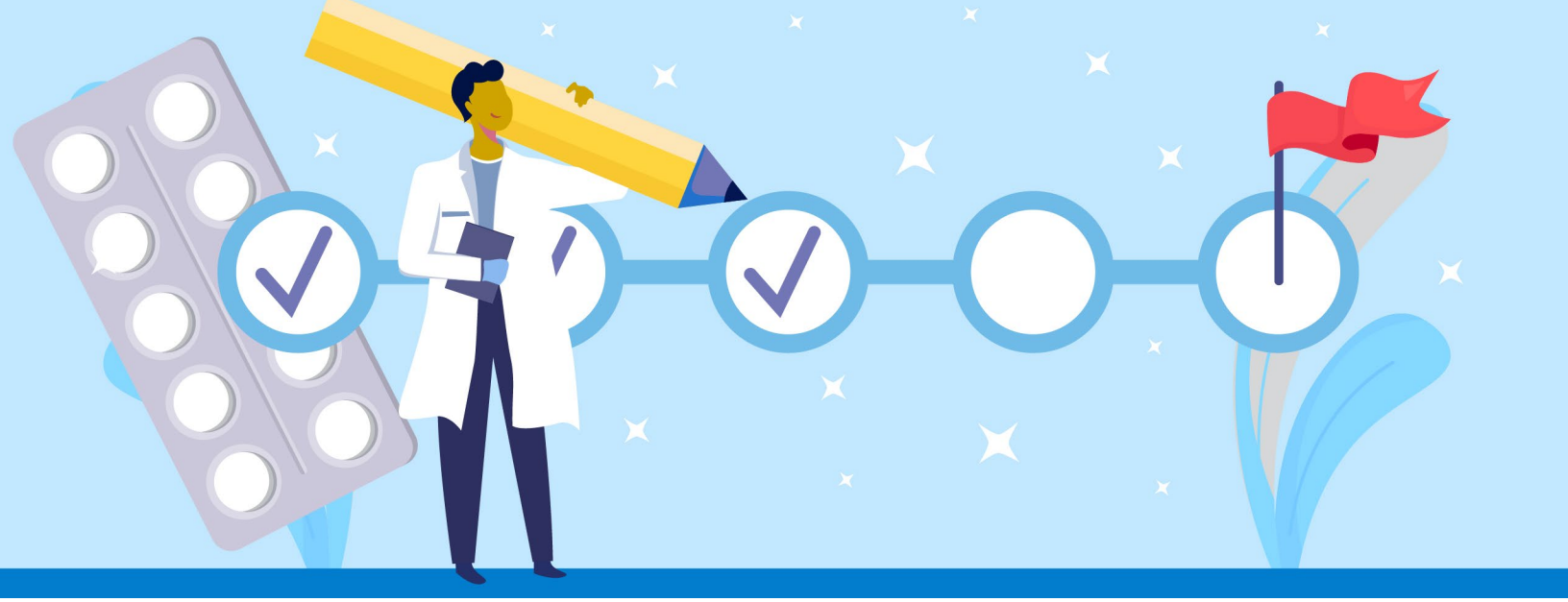
- **FEBRUARY 5 |** Provided grant funding for a new clinical practice guideline detailing dental pain management strategies for adolescents and adults issued by the American Dental Association, the University of Pittsburgh, and the University of Pennsylvania.
- **APRIL 10 |** Published the research article Higher First 30-Day Dose of Buprenorphine for Opioid Use Disorder Treatment is Associated with Decreased Mortality.[16]
- **APRIL 19 |** Approved a higher dose naloxone intranasal spray to treat opioid overdoses.
- **APRIL 23 |** Approved a generic over-the-counter naloxone nasal spray to treat opioid overdose.
- **MAY 23 |** Published the research article The Impact of More Restrictive Hydrocodone Rescheduling on Unintentional Pediatric Opioid Exposures.[17]
- **MAY 23 |** Launched the Prescribe with Confidence campaign to help primary care professionals recognize and treat OUD. Research shows OUD treatment is most effective when medications are used, and primary care professionals treating other chronic health conditions are in a key position to also prescribe these medications. The campaign provides free training and resources from government agencies and trusted organizations on a single web page for busy prescribers to get started, which can be particularly helpful in rural communities where there is often a higher incidence of OUD and a current lack of providers who prescribe these medications.
- **JUNE 4 |** Convened a meeting of the Psychopharmacologic Drugs Advisory Committee to discuss the overall benefit-risk profile, including potential public health impact, of a new drug application for midomafetamine (MDMA) capsules to treat post-traumatic stress disorder.
- **JUNE 17 |** Provided a grant funding the draft Clinical Practice Guideline on Benzodiazepine Tapering issued by the American Society of Addiction Medicine in partnership with numerous other professional societies.
- **JUNE 18 |** Published a summary of the patient listening sessions held in March 2024 on ADHD to help FDA staff better understand patient perspectives about their diagnosis and the risks and benefits associated with stimulant and non-stimulant treatment for ADHD.

16 Lei F, Lofwall MR, McAninch J, et al, 2024, Higher First 30-Day Dose of Buprenorphine for Opioid Use Disorder Treatment Is Associated with Decreased Mortality, J Addict Med, 18(3): 319-326, doi:10.1097/ADM.0000000000001300.

17 Mallama C, Karami S, Zhang D, et al, 2024, The impact of more restrictive hydrocodone rescheduling on unintentional pediatric opioid exposures, Pharmacoepidemiol Drug Saf, 33(6): e5793, doi:10.1002/pds.5793.

- **JUNE 18 |** Published the research article State Cannabis Legalization and Trends in Cannabis-Related Disorders in US Older Adults, 2017 to 2022.[18]
- **JUNE 27 |** Hosted the hybrid public workshop on Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest through a cooperative agreement with the Reagan-Udall Foundation to explore topics such as the scope of ketamine use in approved products and compounded products, potential safety concerns, and online promotion of and access to ketamine.
- **JULY 25-26 |** Hosted regulatory organizations, academia, social media, internet, technology, controlled substances experts, and other interested parties at the fifth Online Controlled Substances Summit in partnership with the Reagan-Udall Foundation to discuss innovative solutions to reduce the illegal availability of controlled substances online.
- **AUGUST 7 |** Approved the first nalmefene hydrochloride auto-injector to treat opioid overdose in adults and pediatric patients 12 years and older.
- **AUGUST 30 |** Issued a warning letter to Root Bioscience Brands, LLC, doing business as Naternal, for selling and introducing into interstate commerce products with unproven claims to treat or cure of opioid addiction.
- **SEPTEMBER 6 |** Hosted the hybrid public workshop Advancing Treatments for Post-Traumatic Stress Disorder (PTSD) through a cooperative agreement with the Reagan-Udall Foundation to bring together researchers and scientists, drug developers, federal partners, and interested communities with lived PTSD experience to explore efforts to accelerate treatment development, including for psychedelic drugs.
- **SEPTEMBER 16 |** Announced that manufacturers would discontinue production of all transmucosal immediate-release fentanyl (TIRF) medications by the end of the month, and as a result, TIRF REMS will no longer accept new enrollments for patients, prescribers, or pharmacies.
- **SEPTEMBER 17 |** Awarded a cooperative agreement to Baylor College of Medicine to support the development, implementation, and evaluation of a human abuse potential study on the use of botanical kratom.

18 Perez-Vilar S, Duenas PF, Radin R, et al, 2024, State cannabis legalization and trends in cannabis-related disorders in US older adult, 2017 to 2022, JAMA Network Open, 7(6): e2417634, doi: 10.1001/jamanetworkopen.2024.17634.



Ensuring the Quality, Safety, and Effectiveness of Generic Medications

CDER approved 59 first-time generics in FY24. These are first approvals by the Agency permitting manufacturers to market a generic medication in the United States. The generic drug program continued to play a crucial role in ensuring safe, effective, and high-quality generic medications are available to patients by evaluating their safety before approval and monitoring them postmarket. We followed 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, etc.), route of administration (e.g., oral, topical, nasal, or intramuscular, etc.), conditions of use, and labeling (with certain exceptions). More than 30,000 generic medications are currently approved by FDA, and 90 percent of prescriptions filled in the United States are generic medications. Generics result in significant savings for patients and the health care system. The savings accrued across the health system during the first year after approval for new generic medications approved from 2018 to 2022 are estimated at more than $88 billion.

Safety Surveillance of Generic Medications

Through our numerous safety and surveillance activities, CDER continued working to ensure the safety and therapeutic equivalence of generic medications. The Center reviewed Bio-Investigational New Drug Applications (Bio-INDs) and pre-approval serious adverse event reports from Bio-INDs and non-IND bioequivalence studies that were intended to support Abbreviated New Drug Applications (ANDAs). We assessed health hazard evaluations for potential generic medication product recalls; analyzed adverse event reports regarding potential quality and therapeutic equivalence issues; followed medication distribution patterns;

and identified emerging safety issues. Through Covered Product Authorization requests, we assisted generic drug applicants in accessing samples of drugs that are subject to a REMS to support safe generic medication development. CDER developed, implemented, and maintained REMS for all generics that required them. Additionally, we initiated Generic Drug User Fee Amendments (GDUFA)-related postmarket safety research and performed generic medication safety and surveillance outreach through presentations and publications to patients, health care professionals, pharmacists, and medication safety-focused organizations.

Drug Safety Alerts

DECEMBER 27 | Provided input for the CDER Alert on the updates to labeling for promethazine hydrochloride injection products to further reduce the risk of severe chemical irritation and damage to tissues from intravenous administration.

MAY 16 | Provided input supporting an update to a CDER Alert for patients, caregivers, and health care professionals regarding cross-compatibility issues with autoinjector devices that are optional for use with glatiramer acetate injection products highlighting a new warning added to labeling, which explains that using an autoinjector that is not compatible with a specific glatiramer acetate injection product may increase the risk of medication errors.

Guidance and Policy Activities

APRIL 1 | Contributed to documents describing electronic submission of bioavailability/bioequivalence (BA/BE) premarket safety reports Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies Guidance for Industry; Technical Specification Document–FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products; and FDA E2B(R3) Core and Regional Data Elements and Business Rules.

SEPTEMBER 4 | Contributed to updating the CDER Nitrosamine Impurity Acceptable Intake Limits guidance web page.

SEPTEMBER 5 | Contributed to the guidance for industry Control of Nitrosamine Impurities in Human Drugs.

Outreach

MARCH 14-15 | Served as panel member for Q&A discussions in the Center for Research on Complex Generics Workshop, Drug-Device Combination Products: Updates and Challenges in Demonstrating Generic Substitutability.

APRIL 11 | Presented "Successful Practices for Pharmacology/Toxicology (Pharm/Tox) Justification in ANDAs" and "Bio-IND Best Practices: an Analysis of Common Clinical Safety Hold and Non-hold Issues and Comparative Analysis Update" at the FDA Generic Drugs Forum (GDF) 2024: Regulatory Considerations to Enhance Generic Drug Access.

APRIL 25 | Presented "Consideration factors on study population selection for bioequivalence studies with pharmacokinetic endpoints" at the FDA webinar Facilitating Generic Drug Product Development through Product-Specific Guidances.

SEPTEMBER 24-25 | Presented "Monitoring Tracked Potential Signals for Generic Mixed Amphetamine Salt Product Postmarket Adverse Event Reports" at FDA's Fall 2024 Small Business and Industry Assistance Workshop on Advancing Generic Drug Development: Translating Science to Approval.

Generic Drug REMS Highlights

The generics program provided expertise on the statutory and regulatory requirements and recommendations in FDA guidance documents related to ANDAs subject to a REMS. We also assisted in developing, implementing, managing, and evaluating related activities submitted to ANDAs. This fiscal year, the program participated in CDER's cross-office efforts to:

- Evaluate established REMS materials aiding in the approval of 16 new ANDAs subject to REMS
- Evaluate and approve six shared system REMS modifications, resulting in 122 approved ANDA supplements
- Manage two reviews of shared system REMS revisions impacting 48 ANDAs

We aided the review and approval of an ANDA-only shared system REMS for the first generic phentermine and topiramate extended-release capsules to treat obesity. The REMS addresses the increased risk of embryo-fetal toxicity with major congenital malformations by requiring patients of reproductive potential be advised of the importance of preventing pregnancy and the need to discontinue the drug immediately if pregnancy occurs.

Efforts to Protect and Ensure the Safety of Subjects in Bioequivalence Studies for Generic Drug Development

As part of CDER's efforts to provide appropriate recommendations to ensure the safety of subjects for BE studies, we engaged in the following activities throughout FY24:

- Clinical risk assessment for selection of study population and design of BE studies for product-specific guidances (PSGs), including 54 oral and two non-oral generic products
- Communications with generic drug companies related to the safety of study populations in their development programs
- Internal research to develop a standardized framework on clinical risk assessment for generic drug development, including:
  - Utilization of pharmacogenomic information in BE studies
  - Safety considerations and data analysis for the selection of subject populations in BE studies with pharmacokinetic endpoints
  - Data collection and analysis to develop a decision-making procedure related to reproductive toxicity for the selection of BE study populations
  - Comparison of subject population, dose, and study type in BE guidance recommendations for global harmonization and regulatory innovation
  - Reassessment of REMS recommendations in PSGs

Research Related to *N*-Nitrosamines

CDER advanced research in FY24 to address knowledge gaps regarding suitable antioxidants to mitigate the formation of *N*-nitrosamine impurities in drug products, effective concentration levels for these antioxidants, and whether those concentrations might alter the BA/BE of a generic medication. For example, we studied different antioxidants and pH modifiers to assess their potential to mitigate the formation of *N*-nitroso-bumetanide and *N*-nitroso-dimethylamine (NDMA) and evaluated assays to assess the potential of *N*-nitrosamine impurities to cause genetic damage. The Center regularly conducts research on strategies to reduce or prevent the occurrence of *N*-nitrosamine impurities in drug products. These impurities include small molecule nitrosamines, and nitrosamine drug substance related impurities (NDSRIs) in drug products that may increase the risk of cancer if patients are exposed to them above recommended acceptable intake limits.

We also conducted research to assess the effect of certain inactive ingredients, called excipients, in metformin products approved to treat type 2 diabetes on the formation of NDMA during manufacturing; studied the effect of secondary amine drug substances with chemical structures that might support the formation of NDSRIs in a drug product; and developed analytical methods to detect NDSRIs in multiple drug products, resulting in the construction of an analytical platform that can be broadly utilized for analysis of these impurities across a range of drug products. Our research has supported the development of powerful tools to study *N*-nitrosamines, identified underlying risk factors contributing to the formation of these impurities, elucidated how NDSRIs occur in drug products, and provided insights about prevention.

CDER continued to work on cellular and animal testing systems to inform the compound-specific risk of small molecule nitrosamines and NDSRIs and led a research project with National Center for Toxicological Research collaborators to investigate NDSRI metabolism and activation. We facilitated and participated in a nitrosamines session at the Generic Drug Science and Research Initiatives Public Workshop in May 2024. Our nitrosamine experts also supported research conducted as part of the FDA/Health and Environmental Sciences Institute Research Roadmap Planning on Hazard and Risk Assessment of Nitrosamine Impurities in Drugs.

Two CDER-funded research studies were completed in FY24 establishing evidence indicating that generics could potentially be reformulated to incorporate antioxidants that mitigate the risk of occurrence of *N*-nitrosamine impurities without altering the BA/BE of a generic product. One was a contract research study by Absorption Systems to evaluate the impact of several antioxidants on cellular permeability of several drugs using a Caco-2 monolayer system. The other study

focused on assessing the potential effect of antioxidants on the functionality of three intestinal transport proteins and was performed under an FDA grant to the Centers of Excellence in Regulatory Science and Innovation, a joint undertaking with the University of California San Francisco and Stanford University. This research directly supported advice in the most recent nitrosamine guidance on the BE data needed to support reformulations that reduce nitrosamines.

We also initiated a project investigating a potential approach for suppressing NDSRIs by using amorphous solid dispersion in the formulation design. This approach may potentially be generalized to other vulnerable active pharmaceutical ingredients in products as an additional mitigation strategy to the ones currently available.

Safe Use Initiative: Collaborating to Reduce Preventable Harm from Medications

CDER's Safe Use Initiative (SUI) continued to foster public and private collaborations within the health care community, including through funding and participating in research studies seeking to reduce preventable medication-related harm. Ongoing projects in FY24 include examination of whether instruction to pharmacists incorporated into the EHR as part of the electronic prescription will reduce errors in administering pediatric liquid medications; intervention designed to reduce the frequency of programming and response to unnecessary alarms and assess their potential impact on clinical staff workflow; and assessment of hospital needs specific to direct-acting anticoagulant prescribing. The program focuses on identifying and mitigating medication-related risks that can occur during prescribing, dispensing, and patient use. We do this by developing, implementing, and evaluating interventions with our current and potential partners in SUI programs and projects, including federal agencies, health care professionals, pharmacies, hospitals, patients, and the organizations representing them.

The SUI-supported study, entitled Assessment of a Pharmacist-Led Interprofessional Transitions of Care Program Targeting Patients with Multiple Recent Hospital Admissions: The ICARE Program, was completed in FY24. The overall goals of this project were to: 1) reduce the risk for medication-related harm in patients with a history of multiple recent hospital admissions at East Alabama Medical Center (EAMC), and 2) move these patients from an inpatient to outpatient setting through initiation of an innovative, interdisciplinary, pharmacist-led transitions of care (TOC) program at Auburn University Harrison College of Pharmacy. As part of TOC, a pharmacist completes follow-up telehealth visits with patients four times within 30 days of discharge for reminders and assessment of medication- and self-care-related behaviors to decrease the risk for readmission. A social worker also contacts each patient to evaluate social risks and need for

connection to community resources such as transportation, nutrition and food services, and patient assistance programs.

Analyses were conducted by comparing 48 patients in the outpatient intervention that completed at least one pharmacist visit with the 18 that did not complete any outpatient visits. Results showed that the 30-day all-cause readmission rate for individuals not completing any outpatient visits was more than double (55.6%) versus the percentage for those completing at least one outpatient visit with the pharmacist (22.9%, p=0.01). There were no significant differences between participant demographics between these two groups.

Continuing Oversight and Outreach of Compounded Medications and Fraudulent Products

As part of CDER's responsibilities to oversee compounded medications and monitor products being illegally marketed with unproven, false, or misleading claims, our FY24 regulatory activities included issuing six warning letters and one untitled letter to compounding facilities, as well as 10 state referral letters. The Center held seven regulatory meetings with companies and oversaw more than 30 recall events. We also issued 29 immediate public notifications to alert consumers and retailers about CDER's testing results indicating the presence of hidden drug ingredient in products promoted for sleep aid, pain relief, weight loss, and sexual enhancement/energy. The compounding program oversees the quality and safety of compounded medications and vigilantly monitors online marketplaces and retail stores for products illegally marketed with unproven, false, or misleading claims about their ability to diagnose, cure, treat, or prevent diseases or conditions. Use of medications marketed with unproven claims or formulated with hidden drug ingredients can cause serious health problems. Our program works to protect patients from poor-quality compounded medications, while preserving access to lawfully marketed compounded medications for patients who have a medical need for them.

Human drug compounding is generally a practice in which a licensed pharmacist or 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. However, they may present a greater risk of harm to patients than approved medications because they do not undergo FDA premarket review for safety, effectiveness, and quality.

Guidance and Policy Activities

DECEMBER 7 | Issued two draft guidance documents that describe our interim policies regarding the use of bulk drug substances in compounding by outsourcing facilities while CDER develops the list of bulk drug substances these facilities can use in compounding: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act and Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act.

MARCH 19 | Issued the proposed rule Drug Products or Categories of Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act and sought public comments through the Federal Notice process; comments were accepted until June 18. The rule would establish criteria for the lists of drug products or categories of drug products that present demonstrable difficulties for compounding. The rule would also codify three categories of drugs that present demonstrable difficulties for compounding: 1) oral solid modified-release drug products that employ coated systems, (2) liposome drug products, and (3) drug products produced using hot melt extrusion.

Outreach

OCTOBER 10 | Warned patients and health care professionals about potential risks associated with compounded ketamine products to treat psychiatric disorders, including oral formulations.

OCTOBER 10 | Issued letters to the National Association of Boards of Pharmacy (NABP) and Federation of State Medical Boards expressing concerns with use of the salt forms in compounded medications and explaining the conditions under which compounded semaglutide products may be legally permissible.

NOVEMBER 7-8 | Hosted the 12th Inter-governmental Working Meeting on Drug Compounding with state regulators and NABP at which state and federal regulators discussed compounding oversight, efforts to support the implementation of the Compounding Quality Act, and opportunities to protect the public health through federal-state collaboration and regulatory discussions.

JUNE 5 | Alerted health care professionals, compounders and patients of potential safety risks associated with sulfite-containing compounded drugs.

JULY 26 | Alerted health care professionals, compounders and patients of dosing errors associated with compounded injectable semaglutide products.

AUGUST 21 | Convened stakeholders from across the compounding industry at the FDA 2024 Compounding Quality Center of Excellence Annual Conference to discuss emerging trends and best practices, good manufacturing practice

requirement topics, progress made in the outsourcing facility industry, and ways to address remaining challenges.

Actions Against Fraudulent Products

NOVEMBER 3 | Warned consumers of hidden drug ingredients in Dr. Ergin's SugarMD Advanced Glucose Support.

NOVEMBER 15 | Entered a consent decree against Arizona-based company for distribution of unapproved contraceptive drugs by federal court, U.S. District Court for the District of Arizona.

DECEMBER 20 | Warned consumers that using fat-dissolving injections that are not FDA approved can be harmful.

DECEMBER 21 | Warned consumers not to use counterfeit Ozempic (semaglutide) found in U.S. drug supply chain and updated the FDA web page on Concerns with Unapproved GLP-1 Drugs Used for Weight Loss to include information about counterfeit products.

JANUARY 11 | Issued letters urging convenience stores, gas stations, and other retailers to stop selling Neptune's Fix and any other tianeptine-containing products.

FEBRUARY 29 | Released the Medication Health Fraud and Avoiding Medication Scams with Cynthia Ng podcast to help consumers and health care professionals avoid unlawfully promoted products.

Communicating Drug Safety: Global Outreach Tools and Technologies

Throughout FY24, CDER continued to develop and expand its mission to ensure timely communication of accurate and relevant information regarding medication safety and public health using a broad range of communication tools and technologies. The Center's multidisciplinary staff of health care professionals, scientists and researchers, senior strategists and advisors, medical communications specialists, web and graphic designers enabled us 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 platforms; respond to inquiries from the public about a range of topics related to human medications; and conduct social science and risk communications research to help FDA understand the use and misuse of medications and other substances and ensure complex scientific information is understandable and relevant to the public.

Drug Safety Communications

We released four Drug Safety Communications (DSCs) in FY24, providing information on new or emerging clinically important postmarket safety issues with medications used to treat the common medical conditions of seizures, osteoporosis, menopause symptoms, and Type 2 diabetes and overweight and obesity. The DSCs ensure timely release of safety information about prescription and nonprescription (over-the-counter) medications to patients, caregivers, health care professionals, and the public to support informed health decision-making. DSCs communicate safety issues that, for example, may describe serious or life-threatening adverse events or certain other warnings or precautions related to use of a medication or

class of medications or affect a special population of patients, and they contain actionable recommendations for patients and health care professionals.

Drug Safety Communications (DSCs) support more informed decision making by patients and health care professionals and help prevent or mitigate medication-related harm. Across the four DSCs issued during FY24, visitors spent an average of 36 seconds viewing the DSC information.

The four DSCs released in FY24, which are posted on the DSC home page where all DSCs are published in English, Chinese, and Spanish, generated more than 210,000 views by unique people through September 30. The key safety information provided in the DSCs are also circulated through numerous other channels, including the DSC-specific listserv 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 dissemination channels include MedWatch E-list and Drug Info listservs; FDA's Facebook page, X (formerly Twitter) feed, and LinkedIn page; and targeted outreach to media, patient advocacy groups, health care professionals and organizations, and other interested communities. CDER also issues Drug Safety Podcasts for each DSC, which are available on FDA's website, Apple Podcasts, YouTube Podcasts, Spotify, and ReachMD, and the four FY24 DSC podcasts generated more than 57,000 engagements through the end of September. As is often the case, media outlets widely reported the safety information provided in the FY24 DSCs, including AP News, NBC News, Reuters, Wall Street Journal, Washington Post, MedPage Today, Medscape, Healio, and other multiple trade press publications. The following four DSCs were issued in FY24:

NOVEMBER 28 | FDA warns of rare but serious drug reaction to the antiseizure medicines levetiracetam (Keppra, Keppra XR, Elepsia XR, Spritam) and clobazam (Onfi, Sympazan). This reaction, called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), can be life-threatening if not diagnosed and treated quickly. It may start as a rash but can quickly progress, resulting in injury to internal organs, the need for hospitalization, and possibly death. As a result, we added a new warning about this risk to the prescribing information for these medications.

JANUARY 11 | Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity. Our preliminary evaluation did not find evidence that the class of medications used to treat type 2 diabetes, obesity, or overweight called GLP-1 RAs, cause suicidal thoughts or actions. However, because of the small number of suicidal thoughts or actions observed both in people using GLP-1 RAs and the control groups who were not taking these medications, we could not definitively rule out that a small risk may exist. As a result, we are continuing to look into this issue and will communicate our final conclusions and recommendations after we complete our review or have more information to share.

JANUARY 19 | FDA adds Boxed Warning for increased risk of severe hypocalcemia in patients with advanced chronic kidney disease taking osteoporosis medicine Prolia (denosumab). In patients with advanced chronic kidney disease taking Prolia, severe hypocalcemia resulted in serious harm, including hospitalization, life-threatening events, and death. As a result, we revised the Prolia prescribing information to include a new *Boxed Warning*, FDA's most prominent warning, communicating this increased risk.

SEPTEMBER 12 | FDA adds warning about rare occurrence of serious liver injury with use of Veozah (fezolinetant) for hot flashes due to menopause. At the time of publication, FDA confirmed one case of medication-induced serious liver injury where the patient experienced symptoms of fatigue, nausea, itching, yellow eyes and skin, light-colored stools, and dark urine within 40 days of starting Veozah. As a result, we added a warning about this risk to the existing warning on elevated liver test values in the prescribing information, as well as information to advise patients to discontinue Veozah immediately and seek medical attention including hepatic laboratory tests if they experience signs or symptoms that may suggest liver injury. Stopping the medication could prevent worsening liver injury and potentially restore normal liver function.

DSC Outreach

4 FY24 DSCS WERE VIEWED MORE THAN

210,000

times by unique people

REACHED MORE THAN:

95,000 DSC listserv subscribers

137,000 Drug Information listserv subscribers

507,000 MedWatch listserv subscribers

PUSHED TO MORE THAN:

LinkedIn	Facebook	X
768,000 followers	**832,000** followers	**341,000** followers

LinkedIn	Facebook	X
72,862 impressions	**19,106** impressions	**24,219** impressions
629 reactions	**331** engagements	**542** engagements
1,261 clicks to the DSC		
106 reposts		

Responding to Public Inquiries

CDER continued its efforts to respond to public inquiries about medications, responding to more than 41,000 inquires in FY24 received by phone, email, mailed letters, and on FDA social media platforms such as Facebook and LinkedIn. Expert responses were developed by a team of pharmacists, nurses, and other health care professionals who field questions from consumers, journalists, research organizations, nonprofit organizations, drug companies, other government agencies, academia, and partners from international government and research institutions.

Top Public Inquiries	
Recalls	2,291
Personal Import/Export	2,151
GLP-1 RAs	1,729
Opioids	1,487
Shortages	1,359
Expanded Access	1,004
Drug Approvals	580
Compounding	573
Registration & Listing	518

Public Inquiry Responses	
Phone	23,589
Email	17,356
Letters	279
Social Media	434*
TOTAL	**41,658**

**Facebook and LinkedIn*

Social Media Engagement

CDER significantly expanded communication outreach in FY24 by 'meeting' people where they are already engaging on social media platforms, including X, Facebook, LinkedIn, Instagram, Threads, and YouTube. Medication safety information is now actively shared through several FDA platforms, including to more than 831,000 Facebook followers, 765,000 LinkedIn followers, and 341,000 X followers, facilitating exponential growth in the distribution of the Agency's public health messages, safety communications, and medication safety warnings. The @FDACDERDirector account on X – launched to provide the director's perspective on CDER actions and initiatives, including those regarding medication safety – had more than 3,500 followers in FY24, including those from media outlets, current and former FDA officials, consumers, health care professionals, industry, health organizations, and other health and government leaders. In addition to posting content and engaging in two-way communication, CDER also monitors the comments and questions users post on FDA's Facebook and LinkedIn platforms to obtain immediate feedback on its actions and decisions.

In FY24, CDER actively disseminated information through more than: 990 posts on X, 555 posts on LinkedIn, 325 posts on Facebook, 90 posts on Threads, and 60 posts on Instagram. We also:

- Provided information to more than 137,000 subscribers through our Drug Information email bulletins
- Expanded social media outreach for Drug Safety Communications and three safety campaigns – Remove the Risk about opioid drug disposal, BESAFE Rx about safely buying medications online, and a sunscreen campaign – as well as for rare diseases, oncology events, generics, and biosimilars
- Leveraged social media to increase awareness and understanding of biosimilars through YouTube using our "Twins" ads in English and Spanish and "What Patients Need to Know" animated video in Spanish, and to promote related multimedia education materials in eight additional languages
- Added stories and reels to Instagram and Facebook to highlight sunscreen safety, health fraud, MedWatch reporting, fentanyl disposal, drug recalls, advisory committee meetings, clinical trial participation, medication shortages, children's cough and cold medications, and safe storage of medications

Drug Safety-Related Labeling Changes

Not every safety concern can be identified at the time a medication is approved for marketing. If new safety concerns emerge after a medication is marketed, FDA may request or require a drug safety-related labeling change. CDER approved more than 6,000 of these labeling changes in FY24. The drug safety-related labeling changes (SrLCs) database includes labeling changes requested or required by FDA, as well as those voluntarily submitted by drug companies. The database makes safety information available in near real-time, and patients, health care professionals, and health information vendors or others can search a user-friendly portal. Those accessing the database also can provide feedback to assist FDA in continually upgrading how safety labeling information is organized and presented. The FY24 drug SrLCs included the following types:

Safety-Related Labeling Changes*	
Adverse Reactions	1,148
Boxed Warnings	366
Contraindications	478
Drug Interactions	634
Patient Counseling Information and/or Medication Guides	1,140
Use in Specific Populations	1,020
Warnings and Precautions	1,228
TOTAL	**6,014**

CDER Small Business and Industry Assistance (SBIA)

In FY24, CDER continued to help small pharmaceutical business and industry navigate the wealth of FDA information and assist their understanding of relevant regulations, including by hosting the following training conferences, workshops, and webinars that had a drug safety focus or component:

NOVEMBER 3 | Hosted a webinar on Implementing Drug Supply Chain Security Act (DSCSA): Stabilization Period and Expectations.

OCTOBER 31-NOVEMBER 1 | Hosted the Pharmaceutical Quality Symposium 2023: Quality, Supply Chain & Advanced Manufacturing.

NOVEMBER 16 | Hosted a webinar on Common Issues with Standard Exchange for Nonclinical Data (SEND) Data Submitted for Safety Pharmacology Studies.

DECEMBER 6-7 | Hosted the FDA Clinical Investigator Training Course (CITC) 2023.

FEBRUARY 13-15 | Co-hosted a joint workshop on global clinical trials in good clinical practice, bioequivalence, and pharmacovigilance in the post pandemic world at the US-FDA, Medicines and Healthcare products Regulatory Agency-United Kingdom, and Health Canada Good Clinical Practice & Pharmacovigilance Compliance Symposium.

FEBRUARY 22 | Co-hosted a joint webinar to provide information on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and updates to interested communities and solicit input at the Joint US FDA – Health Canada ICH Public Meeting.

MARCH 7 | Hosted a webinar on Integrated Safety Analyses in Drug Marketing Applications: Avoiding Common Mistakes.

MAY 16 | Hosted a webinar on Statistical Considerations for Premarketing Risk Assessment.

MAY 29-30 | Hosted the Regulatory Education for Industry (REdI) Annual Conference 2024: Innovation in Medical Product Development.

Safety-Related Drug Topic Webinars

Often centered on medication safety or safety-related topics, FDA Drug Topics webinars offer live online continuing education for free on a variety of topics for physicians, physician assistants, nurse practitioners, nurses, pharmacists, and pharmacy technicians. These webinars remain online and are available on demand to interested professionals. We also released several new Medscape Courses to educate health care professionals about the safety and effectiveness of biosimilars. Four safety-related webinars conducted in FY24 include:

OCTOBER 24 | Naltrexone Injection for Opioid Use Disorder - FDA's Efforts to Reduce Medication Errors.

NOVEMBER 28 | Advancing Transparency and Regulatory Science Activities on the Risk Evaluation and Mitigation Strategy (REMS).

APRIL 30 | Electronic Submission of Safety Reports – Ready for Primetime?

MAY 21 | Fraudulent Drugs: You're Using What?

Online Communications

Medication safety news, announcements, and information continued to be distributed to multiple audiences in FY24, using a variety of electronic media supported by a broad portfolio of services, with traffic on CDER web pages amounting to 41.5 million individual sessions. The services making this possible include video production and photography, and development of web graphics, publications, custom-designed flow-charts, posters, infographics, illustrations, and other materials. We also maintain web content, including medication safety information and safety-related regulatory documents; manage databases of information open to the public; and develop web and mobile applications, including optimizing applications for viewing formats such as smart phones and tablets. The extent of some of this online engagement in FY24 on both FDA.gov and FDA.gov/drugs web pages are depicted in the following tables:

FDA.gov Web Traffic

Traffic Volume	Users	Engaged–Sessions*
Mobile	16,837,964	12,960,337
Desktop	12,432,084	13,781,545
Tablet	438,387	359,463
Smart TV	2,950	2,828

** Number of sessions that lasted longer than 10 seconds, or had a conversion event, or had two or more screen or page views.*

Traffic Sources	% of Sessions
Search Engines	69.7
Direct (URLs & Bookmarks)	19.0
Referrals	7.0
Email	3.5
Social Media	1.1

Top 10 Google Searches Leading to FDA Safety Content*	
1	Royal Honey (Same Rank)
2	Orange Book (3)
3	Drugs@FDA (4)
4	Eye Drop Recall (New)
5	Honey Pack (New)
6	Semaglutide (New)
7	Royal Honey VIP (6)
8	FDA Drug Shortage List (New)
9	National Drug Code (NDC) Lookup (Same Rank)
10	FDA Drug Safety (7)

** FY24 search rankings compared to FY23 in parentheses.*

Top 10 Most Viewed CDER Web Pages*	
CDER Web Pages	**Views†**
1. FDA warns consumers not to purchase or use certain eye drops from several major brands due to risk of eye infection (New)	2,597,600
2. Drugs (1)	1,955,169
3. Drug Approvals and Databases (2)	1,006,629
4. Novel Drug Approvals for 2024 (New)	762,922
5. National Drug Code Directory (9)	669,959
6. Oncology (Cancer) / Hematologic Malignancies Approval Notifications (New)	620,557
7. High Blood Pressure – Understanding the Silent Killer (4)	607,060
8. Drug Shortages (3)	454,192
9. Public Notification: Royal Honey VIP contains hidden drug ingredient (10)	439,428
10. Approved Drug Products with Therapeutic Equivalence Evaluations I Orange Book (5)	434,632

** FY24 search rankings compared to FY23 in parentheses.*

† The number of app screens or web pages users were shown. Repeated views of a single screen or page are counted.

Social and Behavioral Science Research

Throughout FY24, CDER social and behavioral science (SBS) researchers conducted a range of studies gathering evidence from health care professionals, patients, caregivers, and consumers about drug and drug safety-related issues to help inform the Center's policy, regulatory, and communication decisions. This research includes studies to enhance our understanding of knowledge, perceptions, needs, desires, and behaviors related to opioids and a variety of other drugs and substances involved in the overdose crisis. The SBS research also helps identify the best ways to address infodemics about drugs and their safety, especially during public health emergencies, to improve trust in the FDA and provide the public accurate and reliable information needed to make the best health decisions for themselves and their families. Highlights of the FY24 SBS research programs and projects include the following:

Studies Related to Opioids and Other Addictive Medications

Exploring Health Care Providers' Practices, Perspectives, and Experiences Co-Prescribing Benzodiazepines and Opioid Analgesics. This study, completed in FY24, was a two-phase qualitative study to enhance CDER's understanding of the context surrounding the prescribing of benzodiazepines alone and in conjunction with opioid analgesics and how the use of these medications relates to current prescription use, nonmedical use, and addiction in the United States. The study, consisting of drug subject matter experts from across CDER and led by social scientists, obtained data on prescribers' motivations, behaviors, and experiences, including related to prescribing guidelines and tapering benzodiazepines in patients taking them alone and with opioids, which were gaps in knowledge and practice widely noted in a 2021 public meeting by patient advocates, researchers, clinicians, and those working in other federal public health agencies.

Exploring Perceptions and Experiences Related to Kratom Among Users and Healthcare Providers. As part of a series of multidisciplinary public health policy research studies being undertaken CDER-wide on the addictive substance kratom, social scientists are conducting a set of iterative, qualitative research projects designed to provide in-depth understanding of its use, effects, and impacts of varying kratom state policies on the nation's overdose crisis. FDA has raised significant concerns over the past several years about potential safety risks with the use of kratom, a botanical substance imported from Southeast Asia, and has not approved any products containing kratom or its active ingredients. The first phase of this study will consist of focus groups with kratom users to be followed by a series of individual in-depth interviews, including with health care professionals to examine their knowledge, attitudes, and beliefs about kratom and how they discuss and address its use with patients. The findings from this study will be used in conjunction with other CDER research to develop comprehensive information on the effects of kratom use and state-level kratom policy.

Exploring Barriers to Buprenorphine Access for Opioid Use Disorder (OUD). Despite its effectiveness for treating OUD and recently relaxed prescribing requirements (e.g., expanding the number of health care professionals eligible to prescribe), prescriptions for buprenorphine products have not increased as expected. To better understand remaining barriers to buprenorphine access, CDER will conduct a survey to gather data on this critically important topic. Participants will consist of DEA-licensed physicians, physician assistants, and nurse practitioners. The study's findings will complement other CDER research and inform FDA's efforts to address barriers and misperceptions, including through communication and educational efforts related to prescribing buprenorphine for OUD.

Proactive Pharmacovigilance Through Online and Social Media Monitoring and Analysis. Throughout FY24, CDER researchers continued to conduct proactive pharmacovigilance by monitoring and analyzing public conversations about opioids and other addictive substances in online forums and on social media. The objective of this novel approach, which provides real-time access to these discussions, is to obtain an understanding of the kinds of substances being used, especially those that are new or emerging; the adverse events being experienced; and the social contexts and trends surrounding their use for nonmedical or recreational purposes. In addition to conducting routine monitoring and developing monthly social media research reports concerning the nonmedical use of prescription opioids and associated substances, in FY24 we conducted six-month trend reports in January and July. These reports covered 56 substances from 17 drug classes, including FDA-approved prescription medications and unregulated substances such as tianeptine, phenibut, xylazine, and medetomidine. We also conducted more in-depth reporting on two other specific drug classes related to broader CDER work: dual orexin receptor antagonists and "stronger and longer" opioid reversal agents. Finally, to help increase the efficiency of the extensive time and effort involved in manually analyzing the vast amount of unstructured online and social media data, we completed the first phase of a pilot project investigating the use of a natural language processing model and continued to enhance the qualitative data analysis coding capabilities available in CDER's Opioid Data Warehouse.

SBS Studies on Other CDER Safety Topics

Addressing Medication Infodemics. In line with the priority initiatives identified by the White House, U.S. Surgeon General, and FDA Commissioner to address the significant negative health impacts associated with medical infodemics, CDER social scientists are conducting studies to identify the most effective ways to provide accurate information about FDA-regulated medications to the public. These studies are intended to help CDER understand the information needs and desires of consumers and health care professionals, especially during public health emergencies when anxiety is often high, and information can change rapidly; and identify the resources and tools that would best support their needs. The findings from these studies will inform evidence-based guidance for FDA to communicate accurate and reliable information about a variety of topics, including the safety

and efficacy of regulated drug products, to help consumers and health care professionals make the best health decisions possible.

Message and Materials Testing. Researchers completed two studies as part of CDER's communications testing program in FY24. The main objectives of the studies conducted under this testing program are to gain practical and actionable evidence and develop recommendations for enhancing the messages and materials being tested. Specifically, these studies investigate with small groups of target consumer or health care professional audiences whether a variety of communication materials are clear and understandable, are meeting their objectives, and to detect potential unintended effects and identify suggestions for improvement. The studies completed in FY24 assessed information about FDA's accelerated drug approval program included in the patient package insert information for medications approved through this regulatory pathway and draft taglines related to CDER's communication goals to strengthen trust, improve visibility, and increase awareness of the Center's mission. Other studies underway this year included testing information on the "Ways for Consumers to Contact FDA about Human Drugs" web page, an article and infographic about FDA's Bad Ad Program, and FDA's Purple Book Database.

Among the research outcomes, CDER social scientists shared the findings from these studies internally and externally.

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993