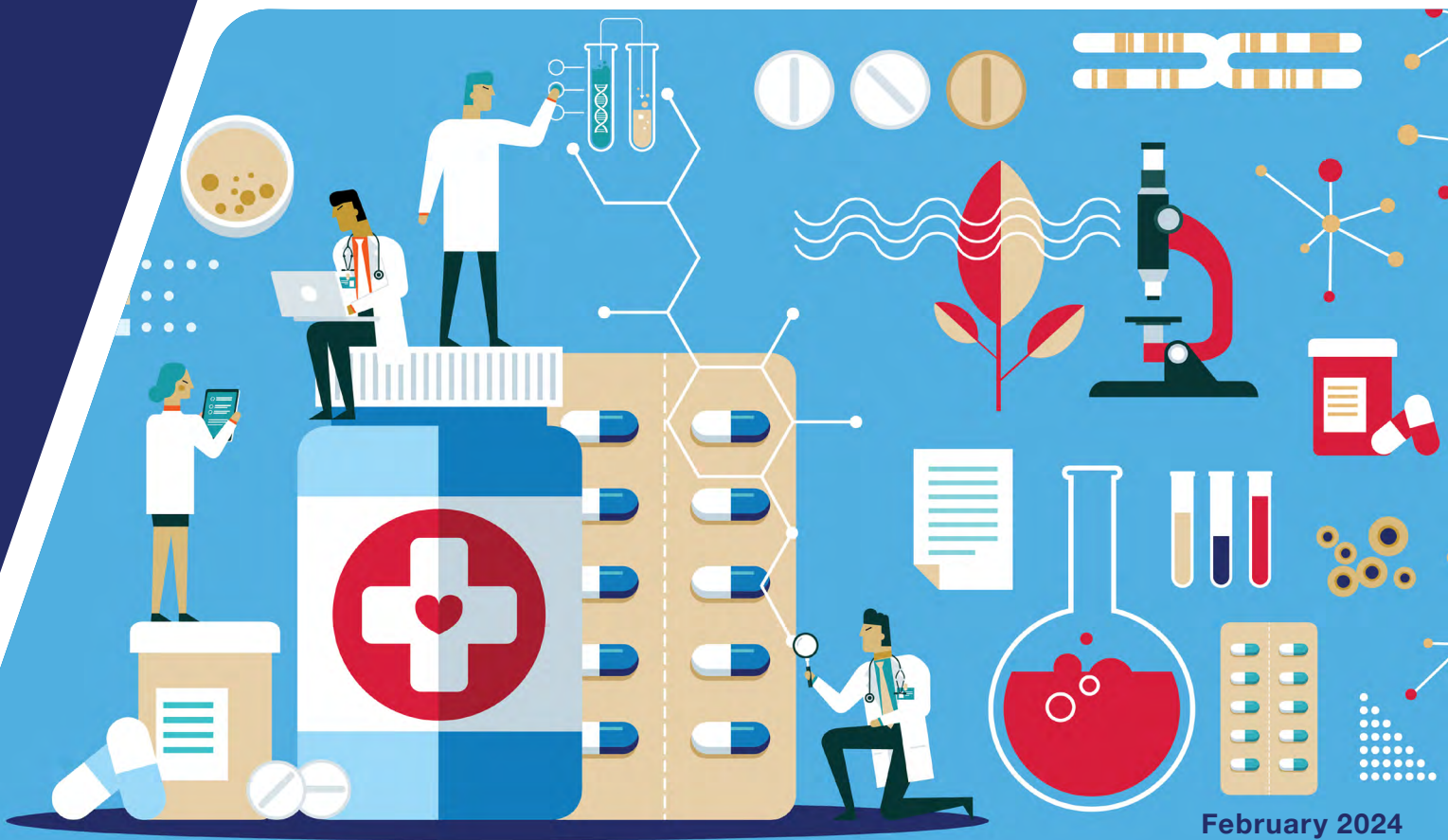
U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Drug Safety Priorities Fiscal Year 2023



February 2024

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Introduction

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Over the past year, the Center for Drug Evaluation and Research (CDER) continued to advance the Food and Drug Administration's (FDA) mission to protect and promote public health with a focus on safeguarding the nation's prescription and over-the-counter (OTC) medications through rigorous premarket review, postmarket surveillance, and risk evaluation programs. CDER Drug Safety Priorities Fiscal Year 2023, our ninth annual report covering the fiscal year ending September 30, 2023, illustrates the wide-ranging safety efforts carried out through multidisciplinary collaborations and highlights safety-related achievements and milestones.

We supported the development and evaluation of non-opioid treatments to manage pain and doubled down on solutions to rein in the nonmedical use of prescription and illicit opioids. The public health crisis of addiction and overdose continues to persist in our country, with drug overdose deaths reaching more than 106,000 in 2023. As part of our ongoing commitment to address the nation's overdose crisis, we made changes to the prescribing information of two highly misused drug classes, opioids and stimulants, to increase safe use and address concerns of nonmedical use, addiction, and overdose. We also released the following related Drug Safety Communications to alert health care professionals and the public: FDA updates prescribing information for all opioid pain medicines to provide additional guidance for safe use, and FDA updating warnings to improve safe use of prescription stimulants used to treat ADHD and other conditions. Additionally, we approved the first OTC naloxone nasal sprays, lifesaving emergency treatments that reverse opioid overdose. In fiscal year 2023 (FY23), we also updated the FDA and Kratom web page to better inform the public about safety issues with this herbal substance that is not FDA-approved for any use, and we continue to track deaths associated with kratom to help us better understand the risks associated with this substance imported from Asia.

In response to the Administration's directive to explore whether marijuana should remain listed as Schedule I under the Controlled Substances Act, we conducted an expansive review of numerous data sources to inform a scientific and medical assessment called an Eight Factor analysis (8FA). This review informed FDA's recommendation to the Drug Enforcement Administration (DEA) to down-schedule marijuana to Schedule III. We also completed an assessment of the capabilities and usefulness of a variety of epidemiologic, pharmacovigilance, and drug utilization data sources for monitoring the safety of unapproved cannabis-derived products.

We continued to protect the public from impurities and contaminants in medications, including activities to address unexpected impurities; informed the public about product recalls; and worked to improve the overall quality of compounded medications. We also continued our work on other medication safety initiatives and programs, including 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 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 Update: CDER continues to monitor and assess the safety of medications used to treat Coronavirus Disease 2019 (COVID-19) and protect consumers from unsafe, unapproved, and fraudulent COVID-19 treatments. We maintained heightened surveillance of serious adverse events and medication errors, including by reviewing published scientific literature for information about COVID-19 therapeutics.[1] We will continue to maintain our robust postmarket surveillance and risk evaluation programs for additional medications to treat COVID-19 as they enter the market.

1 Diak IL, Swank K, McCartan K, et al, 2023, The Food and Drug Administration's (FDA's) Drug Safety Surveillance During the COVID-19 Pandemic, Drug Saf, 46(2):145-155, doi:10.1007/s40264-022-01256-2.

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 drug development and approval process, as well as to learn more about known adverse events. 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 changes to the prescribing information about a drug, issuing Drug Safety Communications, requiring postmarketing studies after the drug has been approved, requiring or modifying a Risk Evaluation and Mitigation Strategy (REMS), or rarely, requesting a market withdrawal of the product. We continue to maintain publicly available searchable databases that contain safety-related information, including information on FDA Adverse Event Reporting System (FAERS), REMS (REMS@FDA), Drug Safety-related Labeling Changes (SrLC), Medication Guides (MedGuides), and Postmarket Requirements and Commitments.

We also post 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 that are required to submit them per FDA regulations. In FY23, FDA completed reviews of 98 newly identified safety signals (NISS), including one related to a naloxone hydrochloride product administration error where a person attempted to administer a syringe that did not contain a needle. In response, FDA required labeling

changes to carton labeling for naloxone syringes to include the warning statement "Needle not included."

As part of CDER's cross-center evaluation of marijuana, the CDER Office of Surveillance and Epidemiology (OSE) completed a review of epidemiologic and pharmacovigilance data sources to inform the 8FA provided to DEA. We also co-authored published articles in peer-reviewed scientific journals about safety issues with various drugs, including those involving products that include or are related to cannabidiol, amphetamines, and angiotensin-receptor-blockers used to treat high blood pressure.[2-4]

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 are designed to reinforce medication use behaviors and require actions that support safe use.

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. As a part of that effort, OSE focuses on how proprietary or brand names can contribute to confusion when drugs are on the market. As part of the review team that evaluates labels and labeling (called the New Drug Application/Biologics License Application team), 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.

FY23 medication error highlights the work and progress of the Prevention of Overdoses and Treatment Errors in Children Taskforce (PROTECT) Initiative, a collaborative effort bringing together public health agencies, professional and private sector organizations, health care advocates, and academic experts to develop strategies to keep children safe from unintentional medication overdoses.

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

2 Perez-Vilar S, Karami S, Long K, et al, 2023, Cannabidiol exposures in the United States, National Poison Data System, July 2014-June 2021, Clin Toxicol (Phila), 61(2):123-130, doi:10.1080/15563650.2022.2156881.

3 Perez-Vilar S, Kempner ME, Dutcher SK, et al, 2023, Switching patterns of immediate-release forms of generic mixed amphetamine salts products among privately and publicly insured individuals aged 15-64 years in the United States, 2013-2019, Pharmacoepidemiol Drug Saf, 32(10):1178-1183, doi:10.1002/pds.5661.

4 Eworuke E, Shinde M, Hou L, et al, 2023, Valsartan, Losartan and Irbesartan use in the USA, UK, Canada and Denmark after the nitrosamine recalls: a descriptive cohort study, BMJ Open, 13(4):e070985, doi:10.1136/bmjopen-2022-070985.

Protocols beginning in FY23. 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. In September, FDA issued a guidance document: Application of Human Factors Engineering Principles for Combination Products: Questions and Answers, which finalized the 2016 draft version. The updated guidance contains questions and answers for industry and FDA staff on the application of human factors engineering principles to the development of combination products comprised of a medical device and drug or biological product. We also supported activities to fulfill a performance goal under PDUFA VII commitments to develop a consistent and transparent approach for determination of post-approval pregnancy safety studies that can be used to obtain timely safety evidence for regulatory decision making.

Risk Management

FDA applies a benefit and risk framework to assess whether the benefit of a medication outweighs its risks for patients for whom it is indicated.[5] FDA considers risk management in its assessment of a medication's benefit-risk balance during the premarket review process and, if approved, through monitoring after a drug is on the market, including by:

- Developing strategies to minimize risks while preserving benefits
- Evaluating the effectiveness of such strategies and reassessing benefit-risk balance
- Adjusting 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 safe and effective use of the medication. For OTC medications, the Drug Facts Label includes a summary of the essential information needed by consumers for safe and effective use. Medication Guides are also part of prescription drug labeling, and they contain approved information that can help patients avoid adverse events. For most 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.

5 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.

Highlighted New REMS Approvals

MAY 23 | Brixadi (buprenorphine) for subcutaneous (under the skin) injection was approved to treat moderate to severe opioid use disorder. The REMS was necessary to mitigate the risk of serious harm or death that could result from faulty self-administration (i.e., failure to administer Brixandi subcutaneously).

AUGUST 14 | Hepzato Kit (melphalan for Injection/Hepatic Delivery System) was approved as a liver-directed treatment for adult patients with uveal melanoma (in the tissues of the eye) with certain metastases of the cancer to their liver. The REMS mitigates the risk of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events.

REMS Public Dashboard

The REMS Public Dashboard is an interactive web-based tool that aims to improve data access and transparency by allowing health care providers, research organizations, academia, industry, and others to analyze REMS data in a user-friendly way. In FY23, the REMS public dashboard data refresh process was automated, and the refresh frequency was increased to a weekly basis to improve the timeliness of REMS data availability for public use. In FY23, we also published an article on the REMS public dashboard, which provides the public with details on how to use this interactive platform.[6]

Unapproved Products with Abuse Concerns

For products that are not FDA-approved, CDER enhanced its surveillance efforts by evaluating all cases related to dietary supplements with a health claim and homeopathy products, in addition to other unapproved products currently captured in our surveillance. Because data on unapproved products is limited in FAERS and the available medical literature, we incorporated surveillance of nontraditional sources such as online marketplaces and video platforms. Surveillance was also expanded by partnering with colleagues across FDA to communicate on, collect samples of, and track safety issues associated with unapproved products, including in CDER's Office of Unapproved Drugs and Labeling Compliance's Health Fraud Branch, Office of Regulatory Affairs' Health Fraud Team, and Center for Food Safety and Applied Nutrition's (CFSAN) Signals Management Branch.

In FY23, we characterized the risks of human exposure to xylazine, a drug approved for use in animals as a sedative and analgesic but is unsafe for

6 Toyserkani GA, Lee JH, Zhou EH, 2023, The Risk Evaluation and Mitigation Strategy (REMS) Public Dashboard: Improving Transparency of Regulatory Activities, Pharmaceut Med, 37(5):349-353, doi:10.1007/s40290-023-00489-5.

humans. It can have serious and life-threatening side effects that appear similar to those associated with the use of opioids. Xylazine is increasingly detected in the illegal drug supply and in drug overdoses. OSE led a cross-office, cross-center collaboration to develop a comprehensive communication strategy to warn health care providers about the risks associated with xylazine, which included FDA issuing an alert on the risks of xylazine exposure in humans and a letter to stakeholders distributed to various health care groups, including primary care services, emergency medical services, and addiction services.

We released the FDA and Kratom web page to better inform the public about safety issues with products containing kratom, an unapproved herbal substance from Southeast Asia that can produce opioid- and stimulant-like effects. FDA has warned against the use of unapproved kratom products for medical treatment and determined that kratom is an unsafe food additive. For our work on Kratom, we worked with partners in CFSAN to identify death cases and communicate regularly with the National Complaints Coordinator to collect follow-up data such as autopsy and toxicology reports obtained by consumer safety officers stationed at district offices. We heightened surveillance efforts for kratom beyond FAERS and reports published in scientific 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 Disease

CDER made contributions in FY23 to ongoing public-private partnerships and other academic initiatives to improve prediction of Drug-Induced Liver Disease (DILI) risk in both pre- and postmarket settings and develop a consensus among experts in best practices for liver safety. These initiatives include:

- The external review committee of LiverTox, an internationally recognized information source for individual drugs, biological agents, and herbals associated with DILI, curated by the National Library of Medicine and National Institute of Diabetes and Digestive and Kidney Diseases
- A series of meetings and webinars convened by 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; a co-authored manuscript from IQ-DILI has been published in Alimentary Pharmacology and Therapeutics[7]
- A workshop coordinated by the Critical Path Institute and the Office of New Drug's Division of Applied Regulatory Science to support the development of reliable complex in vitro models for DILI, as well as a workshop on DILI at the 2023 Annual Meeting of the Society of Toxicology

7 Palmer M, Kleiner DE, Goodman Z, et al, 2023, 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, epub ahead of print October 25, 2023, doi:10.1111/apt.17762.

- The National Institutes of Health-sponsored Drug-induced Liver Injury Network, which maintains a registry of patients referred for assessment of suspected DILI
- A recent consensus conference on Drug-induced Autoimmune Hepatitis (DI-AIH) co-sponsored by the International Autoimmune Hepatitis Group to enhance the classification of subtypes of DILI-AIH as reflected by a co-authored, peer-reviewed publication[8]
- Provided expertise in DILI risk analysis to support an FDA initiative to evaluate new methodologies designed to characterize the toxicological profiles of new drug products in development

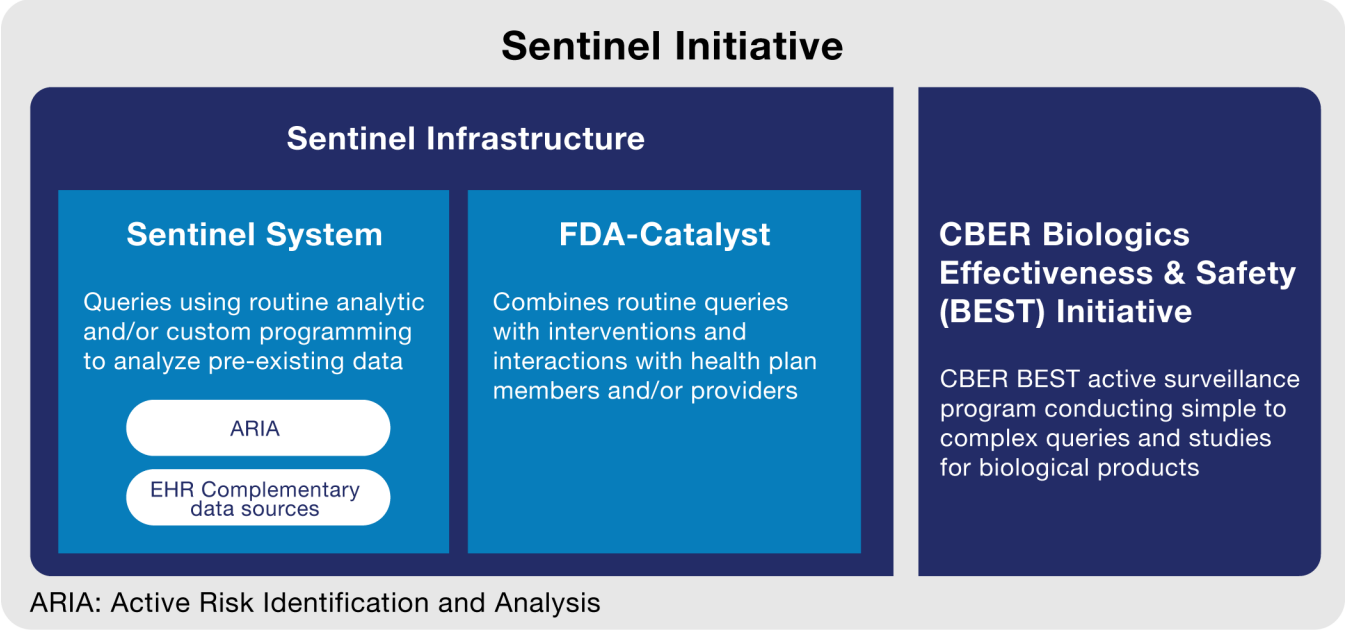
The Sentinel System

The Sentinel Initiative is FDA's active surveillance program that enables FDA to evaluate the safety of regulated medical products and informs regulatory decision making. Through a series of methodological and infrastructure development projects, FDA has developed capabilities to conduct hypothesis-free signal identification analyses in the Sentinel System to complement existing passive surveillance systems (e.g., FAERS). We successfully completed pilot projects in the Sentinel System to inform the integration of these signal identification tools into FDA's routine pharmacovigilance program. The analytic packages and results from these projects are available on the Sentinel website.

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.

8 Andrade RJ, Aithal GP, de Boer YS, et al, 2023, Nomenclature, Diagnosis and Management of Drug-Induced Autoimmune-Like Hepatitis (DI-ALH): An Expert Opinion Meeting Report, J Hepatol, 79(3):853-866, doi:10.1016/j.jhep.2023.04.033.

To date, the Sentinel Initiative has provided vital information to patients and providers about the safety of drugs and vaccines by contributing to multiple labeling changes and Drug Safety Communications, supporting FDA Advisory Committee meetings, and highlighting potential ways to intervene in the opioid crisis. 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. In FY23, we conducted analyses in the Sentinel System contributing to the FDA approval of Paxlovid, the first oral antiviral pill for treatment of COVID-19 in adults. FDA conducted a number of assessments of amyloid-related imaging abnormalities (ARIA) to determine the need for postmarketing requirements. The Sentinel System has proven to be a vital source of safety information that informs regulatory decision-making and expands our knowledge of how medical products perform once they are widely used in medical practice. Each year we hold an Annual Sentinel Initiative Public Workshop.



ARIA: Active Risk Identification and Analysis

Drug Safety Modernization

Under the direction of CDER's Drug Risk Management Board (DRMB), a cross-CDER drug safety governance group, progress towards postmarket safety modernization continued in FY23. 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

In FY23, FDA published several guidance documents relating to safety surveillance and oversight of marketed medications, including:

- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
- Format and Content of a REMS Document Guidance for Industry
- REMS Document Technical Conformance Guide
- Application of Human Factors Engineering Principles for Combination Products: Questions and Answers

Organizational and Process Activities

CDER participated in activities to support the development and implementation of the organizational changes needed to support efficient and effective postmarket safety surveillance and review, including the evaluation of the Drug Safety Team (DST) program to assess its impact and value. The program is comprised of teams that bring together multidisciplinary, cross-functional staff from across CDER to collaboratively manage complex and urgent safety issues. Each DST is responsible for a portfolio of medications, typically aligned by therapeutic areas. CDER continued to support implementation of the Newly Identified Safety Signal (NISS) process, a major modernization initiative achieved in 2020, which allowed for a standardized, interdisciplinary approach to systematically identify, evaluate, and resolve safety signals. We launched and promoted use of the Integrated Safety Assessment template as a single review document for NISS, incorporating data analyses and opinions across multiple disciplines. The Essentials of Postmarket Drug Safety Curriculum for CDER safety staff was updated to ensure a shared foundational understanding of the regulatory processes and science involved in postmarket safety work. In addition, we undertook development of a process for Pharmacovigilance Strategies (PVS). Using a risk-based approach, PVS will be developed and implemented for select products to further characterize safety profiles throughout their life cycle.

MARCH 8 | CDER organized and presented at the FDA/Duke-Margolis public workshop Understanding the Use of Negative Controls to Assess the Validity of Non-Interventional Studies of Treatment Using Real-World Evidence. Negative controls are potentially useful methodological tools to identify and address biases and confounding in observational studies and support the validity of results. This workshop provided a level-setting discussion on how negative controls can support more robust analyses to support causal inferences in medical product safety and effectiveness studies.

SEPTEMBER 18-19 | CDER organized and presented Optimizing the Use of Postapproval Pregnancy Safety Studies at the FDA/Duke-Margolis public workshop. We 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 for the construction of a pregnancy safety study framework; designed a preliminary framework for determining the viable and optimal non-interventional pregnancy studies to meet regulatory needs for post-approval 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 development of the framework. The findings were presented at the public workshop and CDER staff served as panelists to discuss external stakeholder feedback on FDA's proposed framework, including potential opportunities to optimize the use of post-approval pregnancy safety studies.

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

The issue of nitrosamine impurities and benzene contaminants in medications continued to be a high priority for CDER in FY23. We formed a new cross-Center program overseen by the Emerging Impurities and Contaminants Committee (EICC). The EICC drove projects and initiatives to improve how we responded to novel or complex impurities and contaminants that required a sustained coordinated Center-level response. The program contributed to the advancement of drug safety by bringing together experts from across the Center on a consistent basis to develop timely solutions for these issues, including developing new guidance.

The program supports CDER's mission to help ensure the availability of safe and effective medications to improve the health of people in the United States, by driving consistency, efficiency, and innovation in our management of emerging impurity and contaminant issues using our operations, policy, and applied regulatory research. In doing so, the program elevates our ability to manage and coordinate emerging impurity and contaminant issues as they arise and drives the proactive development and implementation of initiatives focused on these issues. Early accomplishments of the EICC include:

JANUARY 23 I Establishing the EICC Charter. The Committee began meeting on a regular basis to develop a coordinated program to address emerging impurity and contaminant issues. The Committee quickly established a roster of experts from across CDER, identified strategic priorities, and initiated activities to further advance program maturity to manage emerging impurities and contaminants, such as nitrosamines and benzene.

MAY 4 | Federal Register: Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities in Human Drug Products; Establishment of a Public Docket; Request for Comments

AUGUST 4 | Directing the program's focus on developing the published guidance document, Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs). NDSRIs are a class of nitrosamine impurities that have been identified in many drug products and could also be present in active pharmaceutical ingredients. This guidance provides a framework for applicants and manufacturers of drug products, including prescription and OTC drug products, for predicting the mutagenic and carcinogenic potential of NDSRIs that could be present in drug products and recommends acceptable intake (AI) limits for NDSRIs.

Since publishing the guidance, the program has continued to engage in its core responsibilities of operations, policy, and applied regulatory research. By applying cross-disciplinary expertise, the program will continue to address emerging impurities and contaminants in drug products.

Nitrosamines and Benzene

Nitrosamines: Nitrosamines are commonly 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 AI limit every day for 70 years is not expected to have an increased risk of cancer.

Benzene: Benzene is a known human carcinogen used in the production of a wide range of industrial products, including chemicals, dyes, detergents, and some plastics, and should not be used in the manufacture of medications. 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

FDA took significant steps to expand availability and access to opioid overdose reversal products as part of our comprehensive approach to addressing the drug overdose crisis. We approved the first nonprescription naloxone nasal spray product in March 2023 and the first generic version in July 2023. We are also expanding opioid disposal options by requiring mail-back envelopes be made available in outpatient settings for patients to dispose of their unused opioid medications safely and securely. This will reduce opportunities for nonmedical use, accidental exposure, overdose, and potential new cases of opioid use disorder. To advance the conversation on ways to remove unused opioids from patients' homes, FDA participated in a workshop, Defining and Evaluating In-Home Drug Disposal Systems for Opioid Analgesics, convened by the National Academies of Sciences, Engineering, and Medicine. We also issued a Federal Register notice to seek information and public comments to help our assessment of in-home disposal methods. Using the available science and data, we continued to seek new ways to address the complex challenges and devastation caused by the evolving drug overdose crisis.

Through the FDA Overdose Prevention Framework established in August 2022, FDA detailed four key priorities to focus our actions to address the crisis and sustain long-term recovery outcomes:

- 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 continued to undertake overdose-related actions and activities in FY23 aimed at supporting each of the Framework's priorities, including:

OCTOBER 11, 2022 | Through a cooperative agreement with FDA, the Duke-Margolis Center hosted the public workshop Challenges and Opportunities for REMS Integration, Innovation, and Modernization to solicit feedback from key stakeholders on a REMS integration prototype

NOVEMBER 8 | Issued an alert to health care professionals warning of increasing reports of serious side effects from individuals exposed to fentanyl, heroin, and other illicit drugs contaminated with xylazine that naloxone may not be able to reverse

NOVEMBER 15 | Issued a Federal Register notice to alert application holders of certain prescription naloxone drug products of the Agency's preliminary assessment that these products are safe and effective for use without a prescription and the possibility that we may make a conclusive determination of this through approval of a nonprescription naloxone drug product

NOVEMBER 28 | Held a stakeholder call to discuss naloxone access and affirm the Agency's commitment to support the efforts of harm-reduction groups to acquire FDA-approved naloxone products

JANUARY 30, 2023 | Co-authored and published the research article Concordance between controlled substance receipt and post-mortem toxicology in opioid-detected overdose deaths: A statewide analysis[9]

FEBUARY 13 | Published the research article The impact of hydrocodone rescheduling on utilization, abuse, misuse, and overdose deaths[10]

FEBUARY 14 | Convened a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss a supplemental new drug application for brand name Narcan (naloxone hydrochloride) nasal spray, indicated for nonprescription treatment of known or suspected opioid overdose

FEBUARY 16 | Published the results of Ohio State University's External Review of FDA Regulation of Opioid Analgesics analyzing FDA's implementation of the 2017 National Academies for Sciences, Engineering, and Medicine's recommendations along with key regulatory policies and decisions, including those related to labeling

9 Howell BA, Black AC, Grau LE, et al, 2023, Concordance Between Controlled Substance Receipt and Post-mortem Toxicology in Opioid-detected Overdose Deaths: A Statewide Analysis, Drug Alcohol Depend, 244:e109788, doi:10.1016/j.drugalcdep.2023.109788.

10 Karami S, Ajao A, Wong J, et al, 2023, The Impact of Hydrocodone Rescheduling on Utilization, Abuse, Misuse, and Overdose Deaths, Pharmacoepidemiol Drug Saf, 32:735-751.

FEBUARY 28 | Announced an action to restrict the unlawful entry of xylazine active pharmaceutical ingredients and finished dosage form drug products into the United States

MARCH 7 | Approved a naloxone intranasal spray to treat opioid overdose

MARCH 8-9 | Through a cooperative agreement with FDA, the Reagan-Udall Foundation hosted the public meeting Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose to explore the evolving context surrounding fatal overdoses; and discuss epidemiological trends, drug supply changes, public health interventions to manage overdose, and drug development opportunities

MARCH 16 | Published the draft guidance for industry Development of Local Anesthetic Drug Products With Prolonged Duration of Effect intended to provide FDA's recommendations for assisting developers in generating the data necessary to support different indications and labeling claims for these drugs

MARCH 29 | Approved the first OTC naloxone nasal spray, expanding access and availability of this first-line treatment for opioid overdose

APRIL 3 | Announced we are requiring manufacturers of opioid analgesics dispensed in outpatient settings to make prepaid, mail-back envelopes available to outpatient pharmacies and other dispensers as an additional opioid analgesic disposal option

APRIL 13 | Issued a Drug Safety Communication and a statement announcing several updates to the prescribing information for immediate-release (IR) and extended-release/long-acting (ER/LA) opioid analgesics, including the addition of statements that the risk of overdose increases as the dosage increases for all opioid pain medications; IR opioids should not be used for an extended period of time unless a patient's pain remains severe enough to require them and alternative treatment options continue to be inadequate; ER/LA opioid pain medications should be reserved for severe and persistent pain that requires an extended treatment period with a daily opioid pain medication and for which alternative treatment options are inadequate; and a new warning about opioid-induced hyperalgesia, a condition in which opioids cause increased pain (hyperalgesia) or an increased sensitivity to pain (allodynia)

APRIL 19 | Convened a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss a postmarketing requirement issued to holders of new drug applications for ER/LA opioid analgesics to evaluate their long-term efficacy and the risk of opioid-induced hyperalgesia

MAY 9 | Partnered with the Substance Abuse and Mental Health Services Administration (SAMHSA) to issue a joint letter to health care professionals to clarify buprenorphine prescribing recommendations

MAY 10-11 | In partnership with FDA and SAMHSA, the Reagan-Udall Foundation hosted the public meeting Considerations for Buprenorphine Initiation and Maintenance Care to explore RWE and scientific evidence for buprenorphine initiation strategies, as well as medication dosing and management during continued treatment across different care settings

MAY 11 | Issued a Drug Safety Communication and a statement announcing updates to the prescribing information for a class of stimulant medications used to treat attention deficit/hyperactivity disorder (ADHD) and other disorders related to risks associated with these medications; and address concerns related to misuse, nonmedical use, addiction, and overdose

MAY 22 | Approved a nalmefene intranasal spray to treat opioid overdose

MAY 23 | Approved an extended-release buprenorphine injection to treat moderate to severe opioid use disorder

JUNE 8 | Hosted internet stakeholders, regulatory organizations, academia, and other stakeholders at the fourth Online Controlled Substances Summit (formerly the "Online Opioid Summit")

JUNE 20-21 | Announced the opening of Notice of Funding Opportunities (NOFOs) to encourage applications to support the development of two evidence-based clinical practice guidelines to manage 1) acute low back pain and 2) acute postoperative pain in patients who have undergone diagnostic and procedural laparoscopic abdominal surgeries. These NOFOs support the Agency's primary prevention priority under the Overdose Prevention Framework. On September 15, we awarded cooperative agreements to support the development of these evidence-based clinical practice guidelines.

JUNE 26-27 | Participated in the National Academies of Sciences, Engineering, and Medicine's public workshop Defining and Evaluating In-Home Drug Disposal Systems for Opioid Analgesics to provide an opportunity for stakeholders to examine in-home drug disposal options, with a focus on removing unused opioid analgesics from the home

JULY 6 | Approved the first generic application for naltrexone extended-release injectable suspension indicated to treat alcohol and opioid use disorder

JULY 18 | Approved the first generic over-the-counter naloxone nasal spray to treat opioid overdose

JULY 21 | Co-authored and published the research article Characteristics and Prescribing Patterns of Clinicians Waivered to Prescribe Buprenorphine for Opioid Use Disorder Before and After Release of New Practice Guidelines[11]

11 Jones CM, Olsen Y, Ali MM, et al, 2023, Characteristics and Prescribing Patterns of Clinicians Waivered to Prescribe Buprenorphine for Opioid Use Disorder Before and After Release of New Practice Guidelines, JAMA Health Forum, 4(7):e231982, doi:10.1001/jamahealthforum.2023.1982.

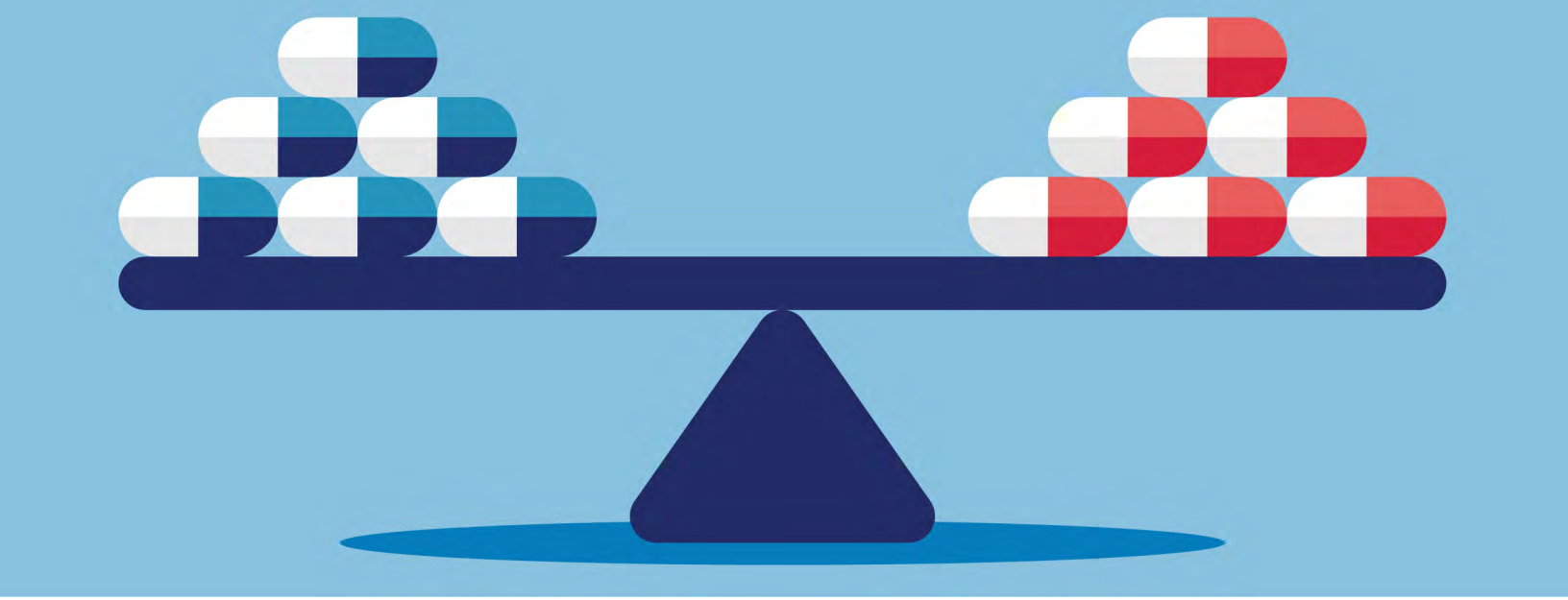
JULY 27 | Issued a draft guidance Clinical Considerations for Studies of Devices Intended to Treat Opioid Use Disorder to help drug companies design clinical studies evaluating devices intended to treat opioid use disorder and to further FDA's Overdose Prevention Framework goal of advancing evidence-based treatment for those with substance use disorders

JULY 28 | Approved the second branded OTC naloxone nasal spray to treat opioid overdose

AUGUST 25 | Provided a grant to fund a new clinical practice guideline detailing dental pain management strategies for children issued by the American Dental Association Science and Research Institute, the University of Pittsburgh School of Dental Medicine, and the Center for Integrative Global Oral Health at the University of Pennsylvania School of Dental Medicine[12,13]

12 Freeman PR, McAninch J, Dasgupta N, et al, 2023, Drugs Involved in Kentucky Drug Poisoning Deaths and Relation with Antecedent Controlled Substance Prescription Dispensing, Subst Abuse Treat Prev Policy, 18(1):53, doi:10.1186/s13011-023-00561-y.

13 Carrasco-Labra A, Polk DE, Urquhart O, et al, 2023, Evidence-based clinical practice guideline for the pharmacologic management of acute dental pain in children: A report from the American Dental Association Science and Research Institute, the University of Pittsburgh School of Dental Medicine, and the Center for Integrative Global Oral Health at the University of Pennsylvania, J Am Dent Assoc, 154(9):814-825.e2, doi:10.1016/j.adaj.2023.06.014.



Ensuring the Quality, Safety, and Effectiveness of Generic Medications

FDA's generic drug program continued to lead many safety and surveillance activities to ensure the quality of generic medications before and after they are approved and throughout the time these medications are available for sale in the United States. The program tracked and evaluated reports relating to generic medication quality, adverse events, and therapeutic effects. Effective postmarket monitoring is essential to ensuring these 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 (those 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 drug program substantially increases the availability of high-quality, safe, and effective medications that are generally more affordable in the United States by promoting competition. More than 32,000 generic medications are currently approved by FDA, and 90 percent of the prescriptions filled in the United States are generic medications. Increasing the availability of generic medications helps create competition in the marketplace, which can reduce the cost of

treatment and increase access to these medications for more patients. Overall, 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 of new generic medications approved in 2019, 2020, and 2021 are estimated at more than $45 billion.

OGD's Safety Surveillance of Generic Medications

The Office of Generic Drugs 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 recalls. We analyzed generic medication quality and adverse event reports that may suggest potential therapeutic inequivalence and trends, followed generic medication distribution patterns, and identified emerging safety issues. We assisted generic drug applicants in developing, implementing, and maintaining REMS for all generic medications requiring a REMS and monitored those applicants' compliance with the relevant REMS.

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, health care professionals, pharmacists, and medication safety-focused organizations.

Highlights of OGD's safety and surveillance work in FY23 include:

Drug Safety Alerts

AUGUST 1 | Provided input that supported a Drug Safety Alert and Class I recall for Lupin Pharmaceutical's prescription oral contraceptive Tydemy (drospirenone/ethinyl estradiol/levomefolate calcium) due to concerns of potential reduced effectiveness related to decreased levels of ascorbic acid, an inactive ingredient, in the product

SEPTEMBER 18 | Provided support in developing a Drug Safety Alert with Questions and Answers for health care professionals describing the change in therapeutic equivalence rating for Accord Healthcare Inc.'s (Accord) generic of Prograf (tacrolimus) oral capsules to prevent organ rejection. We also presented research results with simulations comparing peak and trough blood tacrolimus

concentrations for the Accord generic and the Prograf reference listed drug (RLD), commonly known as the brand-name drug. Results of the clinical pharmacokinetics study conducted at BioPharma Services Inc. were made publicly available on ClinicalTrials.gov (NCT04725682).

Guidance and Policy Activities

DECEMBER 13 | Provided instrumental support in developing and publishing the final guidance on Study Data Technical Conformance Guide – Technical Specifications Document Technical Specifications Guidance

AUGUST 4 | Provided instrumental support in developing and publishing the final guidance on Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs). Staff in the OGD Office of Safety and Clinical Evaluation made significant contributions to the guidance.

Stakeholder Outreach

NOVEMBER 9 | Joined a panel discussion on Complex Generics: An Inside look from the Agency as part of the Science and Regulatory Track at the GRx+Biosims 2022 Generic + Biosimilar Medicines Conference

NOVEMBER 29 | OGD staff, in collaboration with the CDER Office of Communications developed the educational webinar FDA Safety Topics: The Safety Evaluation and Surveillance of Generic Drugs for health care professionals

APRIL 4 | Presented Bioavailability (BA)/Bioequivalence (BE) Study Safety Reporting for Generic Drugs at the FDA-sponsored public meeting Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using International Council for Harmonisation (ICH) E2B(R3) Standards

APRIL 12 | Presented Providing an update on Risk Evaluation and Mitigation Strategies (REMS) for Generic Drugs: Use of a Drug Master File (DMF) and REMS Modifications at the CDER Small Business and Industry Assistance (SBIA) Generic Drugs Forum 2023-Celebrating 10 Years

JUNE 15 | Collaborated with the Center for Research on Complex Generics to organize and host the workshop Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generic Products with experts in the generic drug industry. Provided a forum to discuss the assessment of risks related to forming NDSRIs in certain medications; strategies to prevent or mitigate the formation of such impurities; potential impact on bioequivalence of reformulating generic products (e.g., with antioxidants) to address *N*-nitrosamine-related risks; and approaches to efficiently address these issues

JUNE 29 | Presented BA/BE Study Safety Reporting for Generic Drugs on Reporting of Pre- and Postmarket Safety Reports to FDA Adverse Event Reporting System (FAERS) using ICH E2B Standards at the Drug Information Association's Global Meeting

AUGUST 10 | Published Global Postmarket Pharmacovigilance: A Generic Drug Perspective summarizing results of a global regulatory research study underwritten with support from CDER's Office of Global Policy and Strategy through a unique ORISE Global Safety Fellowship that included information from the FDA, Health Canada, United Kingdom Medicines and Healthcare products Regulatory Agency, and SwissMedic[14]

Generic Drug REMS Highlights

The OGD REMS team continued to serve as experts on the statutory and regulatory requirements and recommendations in FDA guidance documents related to ANDAs subject to a REMS. We assisted in developing, implementing, managing, and evaluating related activities submitted to ANDAs. Throughout FY23, we actively participated in CDER's cross-office efforts to:

- Evaluate established REMS materials aiding in the approval of 15 new ANDAs subject to REMS
- Evaluate and approve various Shared System (SS) REMS modifications affecting 94 approved ANDAs

JANUARY 5 | Aided in developing and publishing Format and Content of a REMS Document Guidance for Industry

APRIL 3 | Collaborated on issuing notices to applicants in line with the announcement FDA Moves Forward with Mail-back Envelopes for Opioid Analgesics Dispensed in Outpatient Settings, which affected 328 Opioid Analgesic ANDAs and New Drug Applications (NDAs)

APRIL 9 | Evaluated and approved the Thalidomide SS REMS to prevent the risk of embryo-fetal exposure and to inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for thalidomide

JUNE 1 | Evaluated and approved a SS REMS for PS-Mycophenolate to mitigate the risk of embryo-fetal exposure

SEPTEMBER 8 | Evaluated and approved eliminating the Lotronex and Alosetron REMS once we determined they were no longer necessary to ensure the benefits of these drugs' use outweigh the serious risks of ischemic colitis and serious complications of constipation

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

14 Dalsey T, Kim E, Chazin H, et al, 2023, Global Postmarket Pharmacovigilance: A Generic Drug Perspective, Therap Innov & Regul Sci, 57:1180-1189.

Research Related to Tacrolimus Oral Capsules

FDA completed the analysis of research and associated regulatory decision-making that altered the therapeutic equivalence rating of an approved generic tacrolimus oral capsule product manufactured by Accord. Tacrolimus oral capsules are approved for prevention of organ rejection in adult patients receiving kidney, liver, or heart transplants, and in pediatric patients receiving liver transplants. In 2012, the Agency revised its bioequivalence recommendations for generic tacrolimus oral capsules based upon an updated classification of tacrolimus as a narrow therapeutic index drug, which means the drug has a narrow window between its effective dose and that at which it produces adverse toxic effects. We also conducted research and funded several studies to assess whether tacrolimus oral capsules approved before 2012 may pose any therapeutic equivalence risks relative to the RLD product Prograf oral capsules.

Drugs with a narrow therapeutic index have a narrow window between their effective doses and those at which they produce adverse toxic effects.

The data generated from our research suggested the generic tacrolimus oral capsule product manufactured by Accord, which was approved prior to 2012, might have characteristics that could produce peak blood concentrations of tacrolimus that are higher than with the RLD product, which could cause adverse events. To assess this potential safety risk with Accord's generic products, we conducted a clinical pharmacokinetics study with BioPharma Services Inc. (BioPharma). Our research, including the results of BioPharma's clinical study and related data analysis, modeling, and simulation research, indicated that the peak blood concentrations from the Accord generic were higher than from the RLD product, posing a potential increased risk of toxicity. Our research also indicated there were no significant differences in the trough blood levels with Accord's tacrolimus oral capsules compared to the RLD product, indicating no increased risk for organ rejection. Thus, for patients who have been stable on Accord's tacrolimus oral capsule product, there was no evidence it would not be effective in preventing organ rejection.

While we are not aware of postmarketing issues regarding safety or efficacy for Accord's tacrolimus oral capsules, the results of this research supported a decision by the Agency to change the therapeutic equivalence rating for Accord's tacrolimus oral capsules from AB to BX, indicating this product is no longer recommended to be automatically substitutable at the pharmacy for Prograf oral capsules. This change, effective September 18, 2023, reflects our commitment to make regulatory decisions that ensure automatically substitutable generic products are as safe and effective as their RLD products, and that such regulatory decisions are continually based on the most current scientific thinking and evidence from ongoing research.

Research Related to *N*-Nitrosamines

In FY23, FDA conducted research on strategies to reduce or prevent the occurrence of *N*-nitrosamine impurities in drug products that include small molecule nitrosamines and NDSRIs. These impurities may increase the risk of cancer if patients are exposed to them above AI limits and over long periods of time.

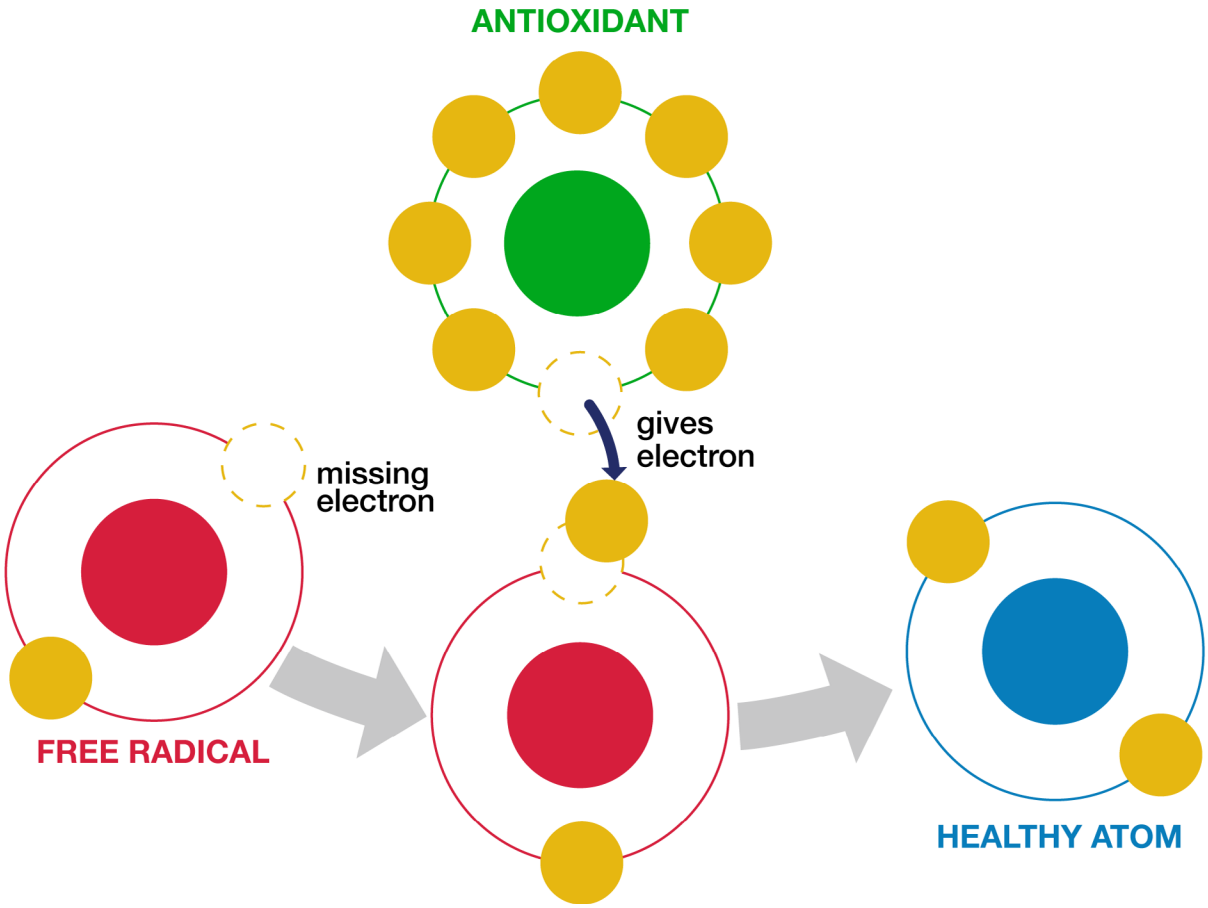
One proposed strategy to mitigate these risks involved incorporating an antioxidant into the drug product formulation. However, it was unknown which antioxidants could be suitable, at what concentrations they might be effective, and whether those concentrations of the relevant antioxidant might alter the bioavailability, or bioequivalence, of a generic drug product. To address these knowledge gaps, we used innovative techniques and approaches to conduct research. For example, our scientists 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 mutagenicity potential of *N*-nitrosamine impurities. We also conducted research to assess the effect of certain excipients in metformin drug products 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 LC-HRMS analytical platform that can be broadly utilized for NDSRI analysis across a diverse range of drug products. The results from our research have developed powerful tools to study *N*-nitrosamines, identified underlying risk factors contributing to these contaminations, elucidated how NDSRIs occur in drug products, and provided insights about how to prevent their occurrence.

OGD's Division of Pharmacology/Toxicology Review (DPTR) also continued to collaborate with scientists at FDA's National Center for Toxicologic Research on in vitro and in vivo testing to inform compound-specific risk of NDSRIs, resulting in publications that detailed the enhanced bacterial mutagenicity testing conditions necessary for the hazard evaluation of nitrosamines and NDSRIs. DPTR also participated in a panel session in the Generic Drug Science and Research Initiatives Public Workshop in May 2023. Also in May, DPTR nitrosamine experts in the joint FDA-Health and Environmental Sciences Institute (HESI) Research Roadmap Planning on Hazard and Risk Assessment of Nitrosamine Impurities in Drugs workshop to discuss pharmacology/toxicology research needs with industry and academic experts.

FDA also funded research conducted by experts outside of FDA, including a study to evaluate the impact of several antioxidants on the in vitro permeability of four biopharmaceutics classification system (BCS) III model drugs using a Caco-2 monolayer system. This research was complemented by studies performed under an FDA grant to the Centers of Excellence in Regulatory Science and Innovation (CERSI), a joint undertaking among the University of California-San

Francisco (UCSF), Stanford University, and the Agency. The CERSI research focused on assessing the potential effect of antioxidants on the functionality of three intestinal transport proteins: P-gp, BCRP, and OATP2B1. These data will provide fundamental information to inform the need for in vivo bioavailability or bioequivalence studies for certain drug products that are reformulated to add certain antioxidants to mitigate formation of nitrosamine impurities.

Antioxidant Mechanism of Action



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 and 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; hospitals; and patients, caregivers, consumers, and the organizations representing them. SUI supports many of its collaborations through funding and participating in research studies seeking to reduce preventable medication-related harm and by maintaining a continuous announcement to solicit proposals for this research. Ongoing projects in FY23 include investigation of a Transition of Care program in patients at high risk for readmission due to a history of multiple admissions, examination of whether instruction to pharmacists incorporated into the Electronic Health Record (EHR) as part of the electronic prescription will reduce errors in administering pediatric liquid medications, and assessment of hospital needs specific to direct-acting anticoagulant prescribing.

FY23 Studies

Several SUI-supported studies were completed and published in FY23, including:

JANUARY 6 | Preventable Harm from Pediatric Outpatient Medication Errors: Measure Development. This study furthered knowledge on existing measures of outpatient pediatric medication errors, including errors in medications administered at home, and assessed the gap between current measures and needs. Development of medication error measures is necessary in defining and establishing quality-improvement programs; however, quality measures in pediatrics have lagged those in other areas. The project incorporated input from

stakeholders, including health care providers, parents, and patients. A systematic literature review of 142 studies was also completed, which included studies that measured ambulatory medication errors in patients under 26 years. Measures included assessments of errors in prescribing, dispensing, administering (via health care personnel or caregivers at home), and monitoring for adverse effects. Thirty-one (22 percent) measures included an assessment of validity or reliability (e.g., use of a validated scoring tool), and 42 (30 percent) included an outcome measure (e.g., hospitalization, preventable adverse drug events). The results of the systematic literature review have been published in the official journal of the American Academy of Pediatrics.[15]

SEPTEMBER 23 | A Scalable, Patient-centered Approach to "Right-sizing" Opioid Prescriptions. This study collected data from patients undergoing elective surgical procedures and those seen in the Emergency Department for acute pain at the University of Pennsylvania Health System (UPHS). Understanding how much medication patients use can inform postoperative prescribing to reflect actual patient need. Patient-reported data on pain intensity, management, and quantities of opioids prescribed and taken were collected prospectively using an automated text-messaging system to generate data for UPHS' 30 highest volume surgical procedures. These data were used to engage attending surgeons and providers in the development of procedure-specific opioid prescribing guidelines and a 6-month automated clinician feedback intervention to encourage guideline adherence. Results demonstrated that patients treated by clinicians randomized to the feedback intervention had a 24.6 percent increase in the probability of receiving a guideline-adherent prescription compared with treatment by control clinicians. Since implementation, there have been 32,000 fewer opioid pills prescribed for postoperative pain without compromising pain management outcomes. Eight peer-reviewed publications have been supported by this contract.[16-23]

15 Rickey L, Auger K, Britto MT, et al, 2023, Measurement of Ambulatory Medication Errors in Children: A Scoping Review, Pediatrics, 152(6):e2023061281, doi:10.1542/peds.2023-061281.

16 Agarwal AK, Ali ZS, Sennett B, et al, 2021, An Automated Text Messaging Program to Inform Postoperative Opioid Prescribing, NEJM Catal Innov Care Deliv, 2(2), doi:10.1056/CAT.20.0440.

17 Agarwal AK, Lee D, Ali Z, et al, 2021, Patient-Reported Opioid Consumption and Pain Intensity After Common Orthopedic and Urologic Surgical Procedures with Use of an Automated Text Messaging System, JAMA Netw Open, 4(3):e213243, doi:10.1001/jamanetworkopen.2021.3243.

18 Howard SD, Agarwal A, Delgado K, et al, Opioid disposal rates after spine surgery, Surg Neurol Int, 12:472, doi:10.25259/SNI_856_2021.

19 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.

20 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.

21 Agarwal AK, Lee D, Ali Z, et al, 2022, Effect of Mailing an At-home Disposal Kit on Unused Opioid Disposal After Surgery: A Randomized Clinical Trial, JAMA Netw Open, 5(5):e2210724, doi:10.1001/jamanetworkopen.2022.10724.

22 Lee D, Agarwal A, Ali Z, et al, 2022, Real-Time Measurement of Patient Reported Outcomes and Opioid Use Following Urologic Procedures using Automated Text Messaging, Urology, 170:83-90, doi:10.1016/j.urology.2022.07.059.

23 O'Sullivan LR, Shofer FS, Delgado MK, et al, 2023, Are There Differences in Postoperative Opioid Prescribing Across Racial and Ethnic Groups? Assessment of an Academic Health System, Clin Orthop Relat Res, 481(8):1504-1511, doi:10.1097/CORR.0000000000002596.

The following projects are ongoing:

- Leveraging the EHR to Promote Pharmacy Adoption of Dosing Best Practices and Reduce Parent Errors in Administering Pediatric Liquid Medications
- Assessment of a Pharmacist-led Interprofessional Transitions of Care Program Targeting Patients with Multiple Recent Hospital Admissions: The ICARE Program
- Reducing Preventable Medication Errors through Minimizing Work Distractions: Evaluating Data from Smart Pump Usage in Health Systems across the Midwest
- Oral Anticoagulation Surveillance and Improvement through Stewardship (OASIS)

Compounded Medications: Continuing Oversight and Stakeholder Outreach

FDA's compounding program continued to protect patients from unsafe, ineffective, and poor-quality compounded medications in FY23, 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, 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 approved medications. Oversight and enforcement activities included the issuance of 11 warning letters to facilities that compound human drugs, oversight of more than 35 recall events, and entry of a consent decree against an Oklahoma-based outsourcing facility prohibiting the company from directly or indirectly distributing adulterated drugs in interstate commerce.

FDA received reports about increased demand for certain drugs and developed two immediately in effect guidance documents that describe FDA's regulatory and enforcement priorities regarding the compounding of certain drug products:

- Compounding Certain Ibuprofen Oral Suspension Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act
- Compounding Certain Beta-Lactam Products in Shortage Under Section 503A of the Federal Food, Drug, and Cosmetic Act

In June, CDER issued a draft guidance on Prohibition of Wholesaling Under Section 503B of the Federal Food, Drug, and Cosmetic Act. This draft guidance

describes FDA's interpretation of, and policies concerning, the prohibition on wholesaling in section 503B of the Federal Food, Drug, and Cosmetic Act. This draft guidance also describes examples of how FDA intends to apply section 503B's wholesaling provision.

CDER also continues important outreach and training efforts to spur adoption of quality best practices among compounders. The Compounding Quality Center of Excellence continues to provide free training to compounders. Its 2023 annual conference convened stakeholders from across the compounding industry to discuss emerging trends and best practices, good manufacturing practice requirement topics, progress made in the outsourcing facility industry over the past 10 years, and ways to address remaining challenges. More than 900 people attended the virtual conference.

Actions Against Fraudulent Products

FDA continued to vigilantly monitor online marketplaces and retail stores in FY23 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. We issued 59 immediate public notifications to alert consumers and retailers about FDA's testing results indicating the presence of a hidden drug ingredient. Products containing hidden drug ingredients were promoted for sleep aid, pain relief, weight loss, and sexual enhancement/energy. We also identified a trend of hidden drug ingredients for Viagra and Cialis, medications used to treat erectile dysfunction, in tainted energy products.

Additional compliance activities related to health fraud included:

OCTOBER 28, 2022 I Issuance of warning letters to Amazon, Walmart, and Latin Foods Market regarding the availability of products marketed with variations of the names "Artri" or "Ortiga"; in FY22 FDA warned consumers not to use these products because they may contain dangerous hidden active pharmaceutical ingredients not listed on the product label

APRIL 26 I Warning teens and young adults about the dangers of using selective androgen receptor modulators (SARMs), chemical substances that mimic the effects of testosterone and anabolic steroids; online marketplaces and influencers are using social media to make SARMs seem like a safe and effective way to improve physical appearance and ability although they are not FDA approved

APRIL 28 I Warning consumers not to use Apetamin, which is a potentially dangerous product promoted and sold through social media, targeting people seeking to gain weight and achieve a certain physique

MAY 1 I Warning consumers not to use Nose Slap and Soul Slap products,

inhalants that primarily contain ammonia, marketed for alertness and energy boosting

AUGUST 18 | Issuance of warning letters to six companies selling unapproved products marketed to treat molluscum, a common skin condition

SEPTEMBER 12 | Issuance of warning letters to eight companies for manufacturing or marketing unapproved eye products; ophthalmic drugs in the warning letters were illegally marketed to treat conditions such as conjunctivitis, cataracts, and glaucoma

OCTOBER 2 | Warning consumers about heavy metal poisoning associated with certain unapproved ayurvedic products

Communicating Drug Safety: Global Outreach Through Diverse Tools and Technologies

CDER's Office of Communications (OCOMM) supports critical aspects of drug product safety to protect and promote public health using a broad range of communication tools and technologies. Throughout FY23, OCOMM continued to develop and expand this mission through 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 platforms
- Respond to inquiries from the public about a range of topics related to human medications
- 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

Communicating Drug Safety Across Multiple Audiences and Platforms

Drug Safety Communications (DSCs) provide clinically important emerging postmarket safety information associated with human prescription and nonprescription medications to patients, caregivers, health care professionals, and the public. These 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 a class of medications or affect a special population of patients. They contain actionable recommendations for patients and health care professionals and their purpose 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 topics offered. Other channels through which the information is disseminated include FDA's Facebook page, X (formerly Twitter) feeds, and LinkedIn page; podcasts; and targeted outreach to media, health care professionals, patient advocacy groups, and other stakeholders. Throughout FY23, DSC information was widely reported, including by Reuters, Healio, MedPage Today, Medscape, and multiple other trade press publications.

Two of the three DSCs issued in FY23 involved high-profile issues or drug products that related to addressing continuing concerns about misuse, nonmedical use, addiction, and overdose of opioids and prescription stimulants as noted below:

APRIL 13 | FDA updates prescribing information for all opioid pain medicines to provide additional guidance for safe use. As part of its ongoing efforts to address the nation's opioid and overdose crises, FDA required several updates to the prescribing information of opioid pain medications to provide additional guidance on their use. Based on our review of available data, we also required a new warning about opioid-induced hyperalgesia. This condition can be difficult to recognize and may result in increased opioid dosages that can instead worsen pain and increase the risk of respiratory depression.

MAY 11 | FDA updating warnings to improve safe use of prescription stimulants used to treat ADHD and other conditions. To address continuing concerns of misuse, abuse, addiction, and overdose of prescription stimulants, FDA required updates to the Boxed Warning and other sections of the prescribing information to ensure consistency across the entire class of these medications. These included requiring warnings against patients sharing their medications with those for whom they are not prescribed and using unapproved methods of taking the medications such as snorting or injecting, all of which are major contributors to nonmedical use and addiction.

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

In conjunction with each DSC, OCOMM issued Drug Safety Podcasts, providing an additional platform where patients and consumers can find emerging safety information about medications. The three podcasts issued in FY23 generated more than 16,081 engagements and are available on FDA's website, Apple Podcasts, Google Podcasts, Spotify, and ReachMD.

Separate from the DSCs but often centered on medication safety or safety-related topics, FDA's Drug Information Webinars offer free live online continuing education 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. Three safety-related webinars were conducted in FY23:

NOVEMBER 29, 2022 | The Safety Evaluation and Surveillance of Generic Drugs

MAY 23 | How to Avoid Medication Errors with Pen Injectors

SEPTEMBER 26 | Regulatory Framework for Human Drug Compounding

DSC Outreach

3 FY23 DSCS WERE VIEWED MORE THAN

63,000

times

REACHED MORE THAN:

49,000 DSC listserv subscribers

131,000 Drug Information listserv subscribers

404,000 MedWatch listserv subscribers

PUSHED TO MORE THAN:

664,000
LinkedIn followers

815,000
Facebook followers

339,000
X/Twitter followers

LinkedIn

75,227
impressions

466
reactions

1,161
clicks to the DSC

98
reposts

Facebook

22,845
impressions

300
engagements

X/Twitter

40,817
impressions

714
engagements

Responding to Public Inquiries

OCOMM continued its efforts to respond to public inquiries about human medications in FY23. Our office responded to more than 42,000 public inquires received via phone, email, letters, and through social media platforms such as Facebook and LinkedIn. Expert responses were developed 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, academia, and stakeholders from international government and research institutions.

Top Public Inquiries	
Recalls	4,633
Clinical Trials/INDs (non-Expanded Access)	1,985
Personal Import/Export	1950
Shortages	1568
Opioids	1355
Expanded Access	1287
GLP-1 Agonists	908
Drug Approvals	756
Registration & Listing	689

Public Inquiries Managed Between October 1, 2022-September 30, 2023	
Phone	25,684
Email	15,848
Letters	286
Social Media	410*
TOTAL	**42,228**

**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 X/Twitter, Facebook, LinkedIn, Instagram, and YouTube. Medication safety information is now actively shared with the public through several FDA platforms, including to more than 815,000 Facebook followers, 339,000 X/Twitter followers, and 664,000 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 monitors the comments and questions that users post on FDA's platforms to obtain immediate feedback on the Agency's actions and decisions.

The @FDACDERDirector account on X/Twitter had more than 3,400 followers in FY23, including those from media outlets, 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.

In FY23, the CDER Social Media team:

- Actively disseminated FDA information to followers on X/Twitter through more than 800 posts, Facebook through more than 235 posts, Instagram through more than 60 posts, and LinkedIn through more than 300 posts
- Provided information to more than 131,000 subscribers on our Drug Information listserv through messages sent
- Expanded social media outreach for COVID-19 communications, Facebook Events, DSCs, generics, biosimilars, Remove the Risk opioid disposal campaign, BESAFE Rx online pharmacy campaign relaunch, and a sunscreen campaign
- Added stories to Instagram to highlight MedWatch reporting, fentanyl disposal, signing up for listservs (including Drug Safety), National Adverse Event Day, and unapproved medications promoted for molluscum contagiosum

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. 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 drug companies. The database makes safety information available in near real-time, and stakeholders such as health care professionals, patients, and

health information technology and information vendors can search easily through a user-friendly portal. Stakeholders accessing the database are also able to provide feedback that assists FDA in continually upgrading how safety labeling information is organized and presented.

OCOMM published more than 5,800 Drug Safety-related Labeling Changes in FY23, including:

Safety-Related Labeling Changes*	
Adverse Reactions	1,121
Boxed Warnings	191
Contraindications	494
Drug Interactions	668
Patient Counseling Information and/or Medication Guides	1,112
Use in Specific Populations	1,022
Warnings and Precautions	1,197
TOTAL	**5,805**

**Between October 1, 2022-September 30, 2023.*

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 FDA offers and to assist their understanding of human drug product regulation. In FY23, our staff hosted the following training courses and informational webinars:

DECEMBER 7-8, 2022 I Presented Safety Considerations in Clinical Drug Development at the FDA Clinical Investigator Training Course (CITC) 2022

OCTOBER 11, 2022 I Presented Considerations for the Quality, Safety and Efficacy of Prophylactic Lipid Nanoparticle mRNA Vaccines at the FDA NanoDay Symposium 2022

JANUARY13 I Hosted webinar on Reporting Individual Case Study Reports (ICSRs) to FAERS Using ICH E2B R3 Standards

APRIL 19 I Hosted webinar on Dosage-Related Information in Labeling - Day 1

APRIL 20 | Hosted webinar on Dosage Modifications and Preparation- and Administration-Related Information in Labeling - Day 2

JUNE 6 | Presented Best Practices for Human Drug Product Recalls at the Regulatory Education for Industry (REdI) Annual Conference 2023

Educational and Outreach Campaigns

FDA continued its public outreach campaigns and education efforts to provide information to patients and health care providers about safe and effective biosimilar treatment options. This included videos and fact sheets for patients and a video series for health care professionals. We also collaborated with the Federal Trade Commission to develop a fact sheet explaining that FDA-approved biosimilars are as safe and effective as their original biological product and patients can expect biosimilars to have the same benefits and risks as the original biological product. To be FDA-approved, companies show that patients on biosimilars don't have any new or worsening side effects as compared to those on the original biological product.

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 FY23 traffic on CDER web pages (FDA.gov/drugs) 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 the platforms from which the traffic is coming; the 10 most-viewed CDER web pages—collectively accounting for almost 10 million page views; and the topics, questions, and documents generating the most online traffic. We also track trending topics on social media, and the leading subjects of stories carried on news media and other informational outlets, including newsfeeds and social media.

FDA.gov Web Traffic | October 1, 2022–September 30, 2023		
Traffic Volume	**Users**	**Engaged Sessions***
Mobile	58,696,672	30,828,849
Desktop	40,513,161	38,595,145
Tablet	1,645,402	1,014,873

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

FDA.gov Web Traffic | October 1, 2022–September 30, 2023	
Traffic Sources	**% Of Sessions**
Search Engines	65
Direct (URLs)	22
Referrals	7
Email	4
Social Media	2

Top 10 Google Searches Leading to FDA Safety Content (with 2022 ranking noted)*	
1	Royal Honey (1)
2	XXX (New to list)
3	Orange Book (7)
4	Drugs@FDA (New)
5	Adderall Shortage (New)
6	Royal Honey VIP (Same rank)
7	FDA (New)
8	Montelukast (4)

Top 10 Google Searches Leading to FDA Safety Content (with 2022 ranking noted)*	
9	NDC Lookup (New)
10	FDA Orange Book (New)

** October 1, 2022 - September 30, 2023.*

Top 10 Most Viewed CDER Web Pages (with 2022 ranking noted)*	
CDER Web Pages	**Views****
1. Drugs (1‡)	2,597,600
2. Drug Approvals and Databases (2)	1,955,169
3. Drug Shortages (New to list)	1,006,629
4. High Blood Pressure – Understanding the Silent Killer (3)	762,922
5. Approved Drug Products with Therapeutic Equivalence Evaluations (New)	669,959
6. National Drug Code Directory (4)	620,557
7. FDA Announces Shortage of Adderall (New)	607,060
8. Novel Drug Approvals for FY23 (New)	454,192
9. La FDA actualiza las advertencies relativas al uso de la meformina, una medicina para la diabetes, en ciertos pacientes con una funcion renal deteriorada (5)	439,428
10. Public Notification: Royal Honey VIP contains hidden drug ingredient (7)	434,632

** October 1, 2022 - September 30, 2023.*

***The number of app screens or web pages users saw. Repeated views of a single screen or page are counted.*

‡ 2022 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 FY23 Research Programs and Projects

Studies Related to Opioids and Other Addictive Medications

Exploring health care providers' practices, perspectives, and experiences co-prescribing benzodiazepines and opioid analgesics. An OCOMM-led multidisciplinary cross-CDER research team completed data collection on the second of a two-phase qualitative study to enhance CDER's understanding of the context surrounding the prescribing of 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 prescribing benzodiazepines alone and in conjunction with opioids, tapering of benzodiazepines in patients taking them long term, and concerning guidelines used when prescribing these medications. These in-depth interviews were informed by findings from a series of focus groups with prescribers completed in 2022.

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 FY23 concerning the nonmedical use of prescription opioids and other substances used with them, we conducted a six-month trend report mid-year. Social scientists also completed

a detailed qualitative analysis of online and social media conversations occurring about marijuana as one of several research studies CDER conducted to address the administration's directive to explore whether marijuana should remain listed as Schedule I under the Controlled Substances Act. This six-month study involved manually analyzing hundreds of posts on publicly available online/social media platforms to provide context directly from users regarding marijuana, including its effectiveness for several therapeutic purposes such as anorexia, anxiety, nausea, and pain; nonmedical purposes; benefits and negative effects, experiences with access. CDER's final report submitted to DEA recommended down-scheduling to Schedule III.

Other Studies

Addressing Consumer Misinformation During Public Health Emergencies. As part of OCOMM's efforts to address misinformation in the public health arena, social scientists completed the first of two experimental studies among consumers to develop data aimed at identifying optimal message strategies for FDA to correct misinformation that surfaces about public health emergencies such as COVID-19. The findings from the first experimental study are being used to inform the follow-up experiment, and the finding from both will inform an evidence-based guidance on corrective messaging that FDA can employ when developing messages addressing misinformation on a broad array of issues, including the availability, safety, and efficacy of medications and other treatments and preventions.

Understanding HCP Misinformation. OCOMM social scientists began work on an exploratory research study to obtain an understanding of health care professionals (HCP) experiences with misinformation during a public health emergency, the ways in which they evaluate such information, and how they address misinformation with their patients. The aim of this study, in part, is to identify ways FDA can best support HCPs in addressing health misinformation with their patients.

Message and Materials Testing. Researchers conducted five studies as part of OCOMM's message and materials testing program. The main objectives of these studies are to obtain feedback from target consumer and/or health care professional audiences on a variety of communication materials to assess whether they are meeting their objectives, detect potential unintended effects, and identify suggestions for improvement. The message-testing studies completed in FY23 concerned an educational factsheet about biosimilars and interchangeable biosimilars, social media messages about the dangers of diversion and nonmedical use of prescription stimulants, an infographic about drug shortages, a Q&A web page about opioid drug disposal, and a draft Consumer Update about intoxicating cannabinoid products.

OCOMM social scientists made several internal and external presentations about the findings from their studies, including at the American Public Health Association annual conference, the annual Rx and Illicit Drug Summit, and the public FDA

Science Forum. In addition, a manuscript describing findings from an online/social media research study exploring the use of kratom to discontinue stimulants was published in the Journal of Addictive Medicines.[24]

24 Settle JR, Smith A, Rausch P, 2023, A social media analysis of kratom use to discontinue stimulants, J Addict Dis, doi:10.1080/10550887.2023.2292304.

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