

CENTER FOR DRUG EVALUATION AND RESEARCH

# DRUG SAFETY PRIORITIES 2021





# Table of Contents

|   |    |
|---|----|
| Introduction from Center Director.....  | 5  |
| COVID-19.....   | 6  |
| Safety Surveillance and Oversight of Marketed Drug Products .....                               | 14 |
| Nitrosamine Impurities in Medicines: FDA’s Continuing<br>Multidisciplinary Response.....        | 22 |
| Continued Efforts to Address the Misuse and Abuse of<br>Opioid Drugs and Other Substances ..... | 24 |
| Ensuring Quality, Safety, and Effectiveness of Generic Drugs.....                               | 28 |
| Safe Use Initiative: Collaborating to Reduce Preventable<br>Harm from Medications .....         | 33 |
| Compounded Drugs: Continuing Oversight and Stakeholder Outreach .....                           | 38 |
| Communicating Drug Safety: Global Outreach Through Diverse<br>Tools and Technologies.....       | 41 |



## Introduction

The past year had its challenges with much of our focus still directed toward the response to the Coronavirus Disease 2019 (COVID-19) pandemic. During this period, we continued to advance the Food and Drug Administration's (FDA) public health and consumer protection mission. **CDER Drug Safety Priorities 2021**—[our seventh annual report](#)—illustrates the broad range of safety efforts undertaken based on multidisciplinary collaborations and partnerships, and presents updates on the year's safety-related achievements and milestones.

In addition to assessing the safety of drug products used for COVID-19 and protecting consumers from unsafe, unapproved, and fraudulent products, we maintained our robust postmarket surveillance and risk evaluation programs. We were able to rapidly analyze and resolve drug safety issues when they arose through coordinated activities that included experts across multiple scientific disciplines. We continued to protect the public from contaminated products by inspecting facilities to the extent we were able during the pandemic, issuing warning letters and risk alerts, and working to improve the quality of compounded drugs. On the heels of historic highs in the number of drug overdose deaths, we redoubled our efforts to address the opioid crisis and to reduce inappropriate use and the harm from controlled substances abuse or misuse. We also continued our work on other drug 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 work to address unexpected, and potentially cancer-causing impurities in medicines. We continued outreach to transparently communicate a broad variety of drug safety information to the public. Our many accomplishments over the past year reflect the best of CDER's commitment to public health and safety.



**Patrizia Cavazzoni, M.D.**  
Director, Center for Drug  
Evaluation and Research (CDER)



## COVID-19

COVID-19 continued to present a major threat to public health worldwide in 2021. The FDA recognized the increased demand for certain products during this emergency and remained committed to facilitating access to safe and effective medical products to help address critical needs of the American public. The Agency's safety focus included monitoring and evaluating drugs for COVID-19; taking actions against unsafe, fraudulent, and unapproved products; and keeping the public informed. The latest COVID-19 news from the FDA can be found [here](#).

*The highlights below detail key drug safety actions CDER worked on in 2021.*

### **Assessing the Safety of Products Used for COVID-19**

To protect the public during the pandemic, CDER monitored and assessed the safety of novel and repurposed medicines used for COVID-19. We conducted surveillance using multiple data sources for safety concerns and medication errors related to products used to treat or prevent COVID-19, provided guidance on how to adapt risk evaluation and mitigation strategies (REMS) programs during a pandemic, offered recommendations for labels and labeling to minimize medication errors, and collaborated with other agencies and organizations to study the effects of drugs used to treat COVID-19. The Agency also enhanced communications with the public and industry.

## Surveillance

- Reviewed safety data, including adverse event reports and observational studies, as part of the overall benefit-risk assessment for products submitted for COVID-19 under an EUA and new drug application (NDA) approval
- Conducted surveillance on case reports in FAERS, medical literature, the National Poison Data System, prescription and nonretail sales, and other data sources; and evaluated newly identified safety concerns and medication errors related to products used to treat or prevent COVID-19
- Conducted searches and reviews of observational study literature on the impact of drugs used to treat or prevent COVID-19
- Reviewed and provided feedback on the quality and feasibility of proposals for Real World Data (RWD) analyses to inform the effectiveness of COVID-19 therapies
- Reviewed proprietary names (commonly known as brand names), container labels, carton labeling, Fact Sheets, and Dear Health Care Professional letters related to multiple COVID-19 therapies
- Undertook an in-depth research project exploring the effects the COVID-19 pandemic was having on opioid use and addiction

## Safety Assessment in Population-Based Data Sources

- Examined use of systemic corticosteroids and concomitant therapies, clinical and demographic characteristics, COVID-19 severity, and outcomes in COVID-19 outpatients using data from [Sentinel System](#) and three other large U.S. databases
- FDA's [Sentinel System](#) initiated activities designed to:
  - Describe racial and ethnic distribution of testing, hospitalization, and death from COVID-19, and evaluate associations between race and ethnicity and COVID-19 severe disease and in-hospital death among patients younger than 65 years
  - Inform safety surveillance activities by characterizing utilization patterns and baseline characteristics of patients receiving products under EUA, including monoclonal antibodies, baricitinib, and tocilizumab
- FDA's [Sentinel System](#) also continued to carry out activities in the following areas:
  - Built and enhanced infrastructure to analyze health care claims and electronic health record data to support epidemiological studies of COVID-19

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FDA continued to support public-private partnerships of clinical trials conducted through the [Coronavirus Treatment Acceleration Program \(CTAP\)](#) that were testing new treatments for COVID-19 to gain valuable knowledge about their safety and effectiveness and enable treatments supported by research to be available as quickly as the scientific evidence supported them.

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To assist the public in searching for information related to adverse events with drugs and therapeutic biological products approved under an Emergency Use Authorization (EUA) during COVID-19, FDA launched in 2021 the [COVID-19 EUA FAERS Public Dashboard](#), which provides weekly updates. During public health emergencies, the FDA may in certain circumstances use an EUA to authorize use of unapproved drugs or unapproved uses of approved drugs for life-threatening conditions when there are no adequate, approved, and available options and other conditions are met. FAERS, the FDA Adverse Event Reporting System, is a database containing adverse event reports, medication error reports, and product quality complaints resulting in adverse events submitted to FDA and supports the Agency's postmarketing safety surveillance program.

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- Developed and applied new capabilities to conduct near real-time monitoring of critical drugs in the inpatient setting to assess changes in utilization over time and by geography to inform the potential for drug shortages
- Described the course of illness among hospitalized COVID-19 patients, including their characteristics, health care utilization, disease progression, and outcomes
- Assessed the occurrence of coagulopathy and its risk factors among hospitalized COVID-19 patients
- Examined the natural history of COVID-19 disease in pregnant women, including medication utilization, disease severity, and clinical outcomes of COVID-19
- Completed two studies describing risk factors for COVID-19-related deaths and hospitalizations in Medicare beneficiaries, one in community-dwelling beneficiaries and another in those residing in nursing homes
- Completed a study to examine whether the active use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) to treat high blood pressure at the time of SARS-CoV-2 infection was associated with an increased risk of COVID-19 hospitalization or more severe COVID-related outcomes

### ***Collaboration with Other Organizations and Communication with the Public and Industry***

- Led collaboration with the American College of Medical Toxicology (ACMT) to create a Toxicology Investigators Consortium (Toxic) COVID-19 Sub-Registry, an enhanced data collection tool within the Toxic network, to focus on identifying potential adverse events related to COVID-19 drug products
- Led collaboration with the Veterans Administration (VA) and CMS to develop infrastructure and conduct near real-time surveillance of EUA products in the CMS Medicare and VA populations
- Contributed to the FDA's Center for Biologics Evaluation and Research (CBER)-led guidance called Policy for Certain REMS Requirements During the Tocilizumab Shortage
- Responded to Congressional and media inquiries related to the safety of products used to treat or prevent COVID-19, multiple inquiries on individual approved REMS requirements during COVID-19, and multiple inquiries on the feasibility of conducting remote [human factors](#) studies during COVID-19

## Warnings about Hand Sanitizers

Hand sanitizer is recommended for use when soap and water are not available, and since the beginning of the pandemic, the FDA has remained vigilant and continued to take action when safety and quality issues arose with certain [hand sanitizer products](#). The Agency is especially concerned with:

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

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In 2021, the FDA worked to protect the public from poor-quality, unsafe, and unapproved hand sanitizer products, in particular, those contaminated with methanol and associated with deaths in the United States, including by:

- Creating the first-ever country-wide import alert for Mexican firms
  - Seeking the voluntary recall of more than **190** hand sanitizer products
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- Seeking the voluntary recall of more than 190 hand sanitizer products

**JANUARY 19** | FDA issued a [guidance](#) outlining the Agency’s policy for drug manufacturers and compounders to test alcohol or isopropyl alcohol for methanol contamination prior to using the alcohol to produce drugs, including hand sanitizer products.

**JANUARY 26** | FDA [placed](#) all alcohol-based hand sanitizers from Mexico on a countrywide [import alert](#) to help stop products that appear to be in violation from entering the United States until the Agency is able to review the products’ safety.

**MARCH 25** | FDA [warned](#) consumers and health care professionals not to use Durisan Antimicrobial Solutions Hand Sanitizer manufactured by Sanit Technologies LLC doing business as Durisan in Sarasota, Florida, due to microbial contamination. Durisan voluntarily [recalled](#) its hand sanitizer product on March 24 and [expanded the recall](#) on April 16.

**JUNE 16** | FDA issued a [Drug Safety Communication](#) warning that symptoms such as headache, nausea, and dizziness can occur after applying alcohol-based hand sanitizers to the skin. These symptoms are likely to have occurred because of vapors from the hand sanitizer, potentially from exposure in enclosed spaces or places with poor air circulation. FDA received increasing reports of these side effects since the start of the COVID-19 pandemic and alerted consumers and health care professionals to use hand sanitizers in a well-ventilated area or if using in an enclosed area such as a car, to open a window to improve ventilation until the hand sanitizer is dry and the vapors have cleared.

**OCTOBER 4** | FDA [tested](#) certain ArtNaturals Scent-Free Hand Sanitizer labeled with “DIST. by ArtNaturals Gardena, CA 90248” and found unacceptable levels of benzene, acetaldehyde, and acetal impurities. FDA urged consumers not to use this product.

**NOVEMBER 2** | FDA issued a [Drug Safety Communication](#) warning that getting alcohol-based hand sanitizer in the eyes from splashing or touching the eyes can result in serious injury, including severe irritation and damage to the surface of the eye. Such eye injuries had become much more frequent, especially in children, likely due to the marked increase in the use of alcohol-based hand sanitizer during the COVID-19 pandemic. FDA recommended mitigating alcohol-based

hand sanitizer in the eyes by immediately and thoroughly rinse them under gently running water such as from a sink tap, water bottle, or emergency shower for at least 15-20 minutes.

A more complete timeline of FDA announcements, statements, and actions related to hand sanitizers, including those products consumers should not use, can be found [online](#).

## Taking Actions Against Fraudulent Unapproved Products for COVID-19

The FDA has continued to actively monitor for any firms marketing products with fraudulent COVID-19 prevention and treatment claims. The Agency exercised its authority to protect consumers from firms selling unapproved products and making false or misleading claims, including by issuing warning letters or pursuing injunctions against products and firms or individuals that violate the law.

- Issued 26 warning letters to companies marketing products fraudulently claiming to treat COVID-19 and to internet pharmacies selling unapproved medications claiming to treat it. More than 80 percent of the recipients complied with these warning letters.
- Worked with the Department of Justice and the FDA's Office of the Chief Counsel to successfully obtain injunctive relief against one company that did not comply with our warning letters.

## FDA Issued Specific Compounded Drug Concerns Related to COVID-19

Compounded drugs are not FDA-approved, which means they have not undergone premarket review for safety, effectiveness, or manufacturing quality. The Agency recommends FDA-approved drugs be used to treat patients whenever possible; compounded drugs should only be used to meet the needs of patients whose medical needs cannot be met by an FDA-approved drug. The FDA had [concerns](#) about the use of the following drugs prepared by compounders to treat patients with COVID-19:

- The FDA was aware of products containing thymosin being offered to patients for the treatment of COVID-19; however, thymosin is not approved to treat any condition, including COVID-19. Therefore, the Agency warned that it would take appropriate action against compounders that produced thymosin. Thymosin alpha-1 is not a component of an approved drug, and thymosin does not meet

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Methanol, or wood alcohol, is a substance that can be toxic when absorbed through the skin and can be life-threatening when ingested; 1-propanol can cause skin irritation or serious damage to the eyes, and may be harmful if inhaled and life-threatening when ingested.

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- FDA recommended that the approved drug [Veklury \(remdesivir\)](#) be used to treat patients who were prescribed remdesivir rather than a compounded version of the drug. The FDA was [concerned](#) that complexities related to the quality and sourcing of the remdesivir active pharmaceutical ingredient (API) and formulation of the drug product could make these drugs particularly challenging to compound. The Agency was concerned that patients would receive substandard or low-quality compounded remdesivir products which could result in harm.

FDA

## Postmarketing Drug Surveillance



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



Manufacturers must evaluate received adverse event reports associated with their marketed products and report certain serious adverse health effects to FDA for evaluation.



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



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



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

Visit [www.fda.gov/drugs](http://www.fda.gov/drugs)  
to learn more.



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## Safety Surveillance and Oversight of Marketed Drug Products

### Pharmacovigilance

The FDA maintains a wide-ranging practice 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 or to learn more about known adverse events. These reviews and evaluations are based on detailed assessment of a variety of data. For example, [FAERS](#) is a database that contains adverse event and medication error reports that have been submitted to the Agency by patients, family members, and health care professionals through the MedWatch program. It also includes information required to be submitted by regulated industry under the Code of Federal Regulations and the FD&C Act. The reports allow the FDA to identify safety concerns and develop recommendations to improve product safety and protect the public.

The FDA's risk evaluation program includes:

- Surveillance, assessment, and review of epidemiologic data using various data sources, including Sentinel
- Review of protocols and studies submitted by industry
- Surveillance and review of the published scientific literature

When information is uncovered that may change the benefit-risk profile of a product, the FDA will investigate the issue and consider appropriate action, including requesting or requiring labeling changes, issuing Drug Safety Communications and other safety information, requiring postmarketing studies, requiring a REMS, or rarely, requesting a market withdrawal of the product. The FDA continuously monitors the safety of all drug products while they are being marketed, even if the Agency has determined that one of these actions is not necessary at a specific point in time.

## FAERS Public Dashboard

Improving data access and transparency are core concepts underlying the FDA's work and they are key factors driving the development of the [FAERS Public Dashboard](#). This dashboard is an interactive, user-friendly, web-based tool that allows the public to access information about adverse drug event reports received by FDA and contained in the FAERS database. Data is updated quarterly, and may be searched and viewed in a customizable format. Dashboard users can view a summary of the adverse event reports received on specific drugs during time periods dating from 1968 to the present.

## Medication Error Prevention and Analysis

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

## Selected Updates

- OSE and the Reagan-Udall Foundation for the FDA convened a [public meeting](#) to explore perspectives on the risk of medication errors related to the content and format of information on investigational drug container labels, the prevalence and nature of medication errors, and practices that might minimize the potential for such errors.

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

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A REMS is a drug safety program that the FDA can require for a certain relatively small number of drugs with serious safety concerns to help ensure the benefits of the drug outweigh its risks. REMS are designed to reinforce drug use behaviors and actions that support that drug's safe use.

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- OSE collaborated with the Center for Devices and Radiologic Health (CDRH) and the Center for Veterinary Medicine (CVM) to analyze and mitigate medication errors associated with device incompatibility and pet exposure to human drugs that result in animal fatalities.

## Risk Management

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

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

The FDA's primary risk management tool is FDA-approved product labeling, often referred to as the "package insert" or the "prescribing information," and the required "Drug Facts" labeling of nonprescription drugs, which includes a summary of the essential information needed by health care professionals or nonprescription drug consumers for the safe and effective use of the drug. [Medication Guides](#) are also part of drug labeling and they contain FDA-approved information that can help patients avoid serious adverse events. Labeling is sufficient for most drugs to ensure that the benefits outweigh the risks. In a limited number of cases, the FDA may determine that a [REMS](#) will also be needed.

## REMS Public Dashboard

The FDA launched the [REMS Public Dashboard](#), an interactive, web-based tool that allows analysis of REMS data in a user-friendly fashion. The intention of this tool is to expand access to data and report-generating capabilities on REMS programs for research organizations, academia, and industry. Improving data access and transparency are core concepts that drove the development of this dashboard. The FDA anticipates this increased transparency will help meet the policy and regulatory needs of existing and future REMS programs. Data used in this dashboard are pulled from existing REMS data files submitted by drug companies and REMS program administrators. The dashboard does not include all data about REMS drugs, for example, risk information and the indication for use. The FDA is continuing to explore other data sources to augment the information in this database.

## ***Modernizing and Improving REMS Assessments***

The FDA continues its efforts to modernize and improve REMS assessments. The improvement efforts focus on: (1) improving REMS assessment planning; (2) clarifying FDA expectations by expanding the review of REMS assessment methodological approaches, study protocols, other analysis plans and assessment approaches; (3) improving the efficiency of our reviews; and (4) enhancing our enforcement actions and tools.

Additionally, the FDA launched improvements to the review processes for REMS Assessment Reports and REMS Assessment Methodologies, which were incorporated into CDER's workflow management system in 2021. Highlights include automated workflow steps and data collection, improved collaboration across offices, divisions, teams and disciplines, and improved transparency of the review process.

## ***New REMS Approvals***

The FDA approved a REMS for three separate NDAs in 2021:

**APRIL 6** | FDA approved a [shared system REMS](#) for macitentan because it has a risk of serious birth defects if used during pregnancy. Macitentan is a prescription medication used to treat pulmonary arterial hypertension, which is high blood pressure in the arteries of the lungs.

**MAY 14** | FDA approved a [REMS](#) for Empaveli (pegcetacoplan) because the medication can increase the chance of having serious infections, which may quickly become life-threatening and cause death if not recognized and treated early. Empaveli is a prescription medication used to treat adults with a disease called paroxysmal nocturnal hemoglobinuria.

**MAY 21** | FDA approved a [shared system REMS](#) for lenalidomide because the medication can cause birth defects or death to unborn babies if used during pregnancy. Lenalidomide is a prescription medication used to treat multiple myeloma and other types of cancer of white blood cells, and a condition called myelodysplastic syndromes.

## **The Sentinel System**

The [Sentinel Initiative](#), launched in 2008, began as a Congressional mandate for the FDA to establish a public-private partnership to develop an electronic medical product safety surveillance system using existing data. The principal operational component of the Sentinel Initiative is the Sentinel System, a network of databases (technically known as a [distributed database](#)) that included [13 partner institutions](#) with 14 data marts as of October 2021.

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

When safety concerns arise, FDA staff can use Sentinel to assess potential risks that may be associated with FDA-regulated medical products, enabling product safety assessment under real-world conditions. Sentinel provides unparalleled capabilities for investigation of new safety signals that arise from spontaneous reporting systems like FAERS and other sources of safety information. FDA is developing Sentinel's capacity to detect unsuspected potential safety concerns using new approaches that scan thousands of health outcomes, looking for unexpected safety signals after product exposure. Such analyses mine large amounts of health care data without prespecifying a specific target medical product. Sentinel also supports inquiries on many different regulatory questions, including those related to medication errors, risk mitigation strategies, generic drugs, biosimilars, and drug safety in specific patient groups such as children and pregnant patients.

The Sentinel System has transformed the way researchers monitor FDA-regulated medical products. Now one of the FDA's leading evidence-generation platforms, Sentinel proactively monitors medical product safety and serves to advance the science of RWD and RWE.

The [Sentinel System Five-Year Strategy 2019–2023](#) is a roadmap charting the development of the Sentinel System through five strategic aims intended to expand the Sentinel System's operational foundation, augment its safety analysis and signal detection capabilities, and leverage the system to accelerate access to and broader use of [RWD](#) for [real world evidence](#) (RWE) generation. To advance these aims, the FDA established three centers as part of the Sentinel System: the [Sentinel Operations Center](#) (SOC), the [Sentinel Innovation Center](#) (IC), and the [Community Building and Outreach Center](#) (CBOC). The SOC continues to focus on conducting medical product assessments and enhancing the infrastructure of the Sentinel System to support FDA's regulatory needs. The IC carries out work to advance analytic tools and accelerate novel data source acquisition and evaluation, and the CBOC focuses on building the Sentinel System user community and engaging stakeholders.

FDA routinely uses RWD made available through the Sentinel System to generate evidence about drug safety, drawing on data from insurance claims, hospital stays, outpatient doctor visits, and pharmaceutical dispensing data. Sentinel also queries data from partners with electronic health record information to address questions in the context of 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 FDA to assess medical product safety, describe medical product utilization, and characterize medical events under real-world conditions.

## 2021 Highlights

In 2021, FDA's Sentinel System supported numerous activities to protect and promote public health during the [COVID-19 pandemic](#) (see the COVID-19 section of this report). To support these activities, Sentinel has enhanced its data infrastructure by building a database with near real-time data from six Data Partners and incorporating use of several additional data sources derived from electronic health records. Sentinel is also collaborating with the Reagan-Udall Foundation and Friends of Cancer Research on the COVID-19 [Evidence Accelerator](#), a forum for stakeholders across the health care spectrum to share RWD and generate ideas on COVID-19. Additional Sentinel highlights include:

**MAY** | On May 13th, the Sentinel System deployed a fully redesigned public website to improve the usability and findability of information and to better serve the Sentinel community. Some major new features include:

- A Google Search engine directly integrated into the [website interface](#) to improve the relevancy of results for the site's global search.
- [Sentinel Training Center](#): A single location for easy access to the video recordings and materials of key Sentinel trainings and workshops.
- [Engage with Sentinel](#): A dedicated space that encourages the community to stay informed, get involved, and engage with the Sentinel Initiative.
- [Drug Assessments](#): Information is now provided on drug assessments conducted in the Active Risk Identification and Analysis (ARIA) system and other Sentinel data resources in a new table structure that consolidates analytic code, results, communications, and regulatory outcomes for all queries associated with the same underlying safety question.

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FDA published in September 2021 a draft guidance document on [Benefit-Risk Assessment for New Drug and Biological Products](#). The guidance clarifies for drug sponsors and other stakeholders how considerations about a medication's benefits, risks, and risk management options factor into certain premarket and postmarket regulatory decisions that the Agency makes about NDAs and BLAs.

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- [Sentinel Initiative YouTube Channel](#): Incorporates major webinars, trainings, and workshops into a single, publicly available repository.

**AUGUST** | Investigators disseminated Sentinel work at the [37th International Conference on Pharmacoepidemiology and Therapeutic Risk Management \(ICPE\)](#), leading two symposia and providing 14 oral presentations and scientific posters.

**SEPTEMBER** | FDA enhanced the Sentinel System infrastructure by releasing a new version of the Sentinel Common Data Model (SCDM): v8.o.o. This improvement expands Sentinel's data capture and precision and allows for its use by international partners. Key enhancements in this new version include the addition of a prescribing table and a provider table. This SCDM upgrade also introduces technical efficiencies designed to ensure the Sentinel System will match the growing volume of health care data provided by data partners.

**NOVEMBER** | The [Thirteenth Annual Sentinel Initiative Public Workshop](#) was held virtually on November 8 and 9, bringing together stakeholder communities on a variety of topics on active medical product surveillance and current and emerging Sentinel activities. Sessions featured key leads from each CDER Sentinel coordinating center to discuss past and current activities as well as to advance and transform Sentinel's data infrastructure into a national resource for evidence generation. Sessions also highlighted the past, present, and future of Sentinel and RWE.

**DECEMBER** | Throughout the year, the [Sentinel Innovation and Methods Seminar Series](#) brought leading experts to present on various topics, including feature engineering, natural language processing, advanced analytics, and data interoperability. This seminar series engaged Sentinel's scientific community by sharing information on emerging technologies and advances in methods relevant to Sentinel's work.

## Drug Safety Modernization

CDER's Drug Risk Management Board (DRMB) is a cross-CDER board responsible for three key objectives: (1) facilitating and coordinating decisions around major product safety issues; (2) providing clear and consistent guidance enabling an appropriate response to major safety issues; and (3) systematically communicating decisions and resulting actions across the Center and to other stakeholders as appropriate. In addition, the DRMB facilitates and coordinates all new and existing marketed product safety initiatives across CDER, including the modernization of the Center's framework capabilities for safety surveillance of marketed products.

CDER continues to support implementation of the [Newly Identified Safety Signal](#) (NISS) process, a major modernization initiative achieved in April 2020, which allows for a standardized, interdisciplinary approach to systematically identify, evaluate, and resolve both clinical- and quality-related safety signals. The Lifecycle Signal Tracker (LiST) workflow tool was developed to support the NISS process, providing the ability to capture and manage all safety signals for marketed drugs. The NISS Manual of Policies and Procedures (MAPP) and LiST not only support CDER's commitment to drug safety, but also its commitment under Prescription Drug User Fee Act (PDUFA) VI for timely and effective evaluation and communication of postmarketing drug safety issues. In March 2021, FDA contracted with a third party to assess how data systems and processes support the review, oversight, and communication of postmarketing drug safety issues to meet this commitment. The NISS MAPP and LiST also address recommendations made in the 2015 Government Accountability Office report.

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In November 2021, the FDA released FAERS II to replace the previous version of FAERS to support our internal postmarket stakeholder community. FAERS II is a one-stop shop solution for case intake and processing, safety surveillance, and analytics for approved drugs. This modernized pharmacovigilance toolkit will improve regulatory processes and data quality to better support lifecycle safety tracking.

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## Nitrosamine Impurities in Medicines: FDA's Continuing Multidisciplinary Response

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

Since then, several more drug products have been found to contain unacceptable levels of nitrosamines, including the heartburn drugs ranitidine and nizatidine, the type 2 diabetes drug metformin, the tuberculosis drugs rifampin and rifapentine, and the smoking cessation drug varenicline. On [November 18, 2021](#), FDA provided information to industry on possible mitigation strategies to reduce the risk of NDSRIs in drug products.

## Varenicline

All FDA updates and actions on varenicline in 2021 are [available online](#). Key actions addressing N-nitroso-varenicline impurities in varenicline products include:

**JULY 2** | FDA [alerted](#) the public about Pfizer's voluntary recall of nine lots of the smoking cessation drug varenicline to the warehouse level because it may contain levels of a nitrosamine impurity, called N-nitroso-varenicline, above FDA's acceptable intake limit of 37 ng per day.

**JULY 16** | To ensure patient access to varenicline, FDA [announced](#) it would not object to certain manufacturers temporarily distributing varenicline tablets containing N-nitroso-varenicline up to the FDA's interim intake limit of 185 ng per day until the impurity could be eliminated or reduced to acceptable levels. The agency continues to evaluate data.

**JULY 19** | Pfizer expanded its voluntary [recall](#) of varenicline to 12 lots to the consumer level.

**AUGUST 18** | Pfizer expanded its voluntary [recall](#) to include four additional lots of (16 total) to the consumer level.

**AUGUST 23** | FDA posted its [laboratory results](#) showing N-nitroso-varenicline levels in varenicline products currently available for the U.S. market.

**SEPTEMBER 17** | FDA alerted the public that Pfizer expanded its voluntary [recall](#) to the consumer level to include all lots of varenicline 0.5 mg and 1 mg tablets. Pfizer recalled these lots due to the presence of unacceptable N-nitroso-varenicline levels.

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



## Continued Efforts to Address the Misuse and Abuse of Opioid Drugs and Other Substances

The misuse and abuse of illicit and prescription opioids and the risks of addiction, overdose, and death are a public health crisis in the United States. From 1999 to 2019, approximately 500,000 people died from an overdose involving any opioid, including prescription and illicit opioids. In 2020, 191 people died every day in the United States from opioid overdose, according to provisional data from the [Centers for Disease Control and Prevention \(CDC\)](#). The estimated number of overdose deaths from opioids increased from 50,963 in 2019 to 69,710 in 2020. The COVID-19 pandemic has exacerbated the opioid crisis and the FDA has continued to prioritize addressing this public health crisis. Actions, activities, and updates from 2021 are highlighted below.

### ***Support Recovery from Substance Use Disorder (SUD) and Reduce Overdose Deaths***

**MARCH 4** | FDA approved changes to the prescribing information for all opioid pain relievers and medicines indicated to treat opioid use disorder (OUD) to add new recommendations about patient access to naloxone for the emergency treatment of opioid overdose. These changes were instituted to help ensure that health care professionals

discuss the availability of naloxone and assess each patient's need for a naloxone prescription when opioid pain relievers or medicines to treat OUD are being prescribed or renewed. This information was originally announced in a [Drug Safety Communication](#).

**APRIL 30** | FDA announced the [approval](#) of a higher dose naloxone hydrochloride nasal spray product to treat opioid overdose. The newly approved product delivers 8 milligrams (mg) of naloxone into the nasal cavity. FDA had previously approved 2 mg and 4 mg naloxone nasal spray products. A higher dose of naloxone provides an additional option in the treatment of opioid overdoses.

**OCTOBER 18** | FDA announced the [approval](#) of Zimhi (naloxone) injection as an additional option to treat opioid overdose. Zimhi is administered using a single-dose, prefilled syringe that delivers 5 mg of naloxone solution through injection in the muscle or under the skin.

**OCTOBER 18** | The FDA, in partnership with the Reagan-Udall Foundation for the FDA and the National Institute on Drug Abuse, held a public workshop called [A Practical Research Agenda for Treatment Development for Stimulant Use Disorder](#). The workshop allowed stakeholders to provide input on a proposed practical research agenda that focuses on innovation in clinical trial design and endpoints for the evaluation of potential treatments for stimulant use disorder.

### ***Strengthen Enforcement Against Illicit Opioids and Inappropriate Opioid Use***

**FEBRUARY 1** | FDA provided an [update on the pilot program](#) with the National Telecommunications and Information Administration (NTIA) and three domain name registries to help reduce the availability of unapproved opioids illegally offered for sale online. The 120-day pilot program ended in 2020, and the update reported that nearly 30 websites illegally offering opioids for sale became inaccessible to the public.

Naloxone is a medicine that can be administered by individuals with or without medical training to help reduce opioid overdose deaths. If naloxone is administered quickly, it can counter the opioid overdose effects, usually within minutes. Currently, most states allow pharmacists to dispense naloxone through a standing order from the [state health department](#). This allows a pharmacist to dispense naloxone without a prescription for an individual patient.

The pilot program was an effective tool in maximizing the impact of FDA's efforts to limit the illegal sale of unapproved opioids online and the collaboration will continue to help prevent illegal online opioid sales.

**FEBRUARY 16** | FDA issued a [warning letter](#) to AcelRx Pharmaceuticals, Inc. for the false and misleading promotion of Dsuvia (sufentanil sublingual tablet), a potent opioid pain medication. AcelRx disseminated promotional communications that undermined key prescribing conditions required for the safe use of this opioid. Dsuvia was approved with a [REMS](#) with special restrictions requiring that it only be prescribed in a certified medically supervised setting by health care professionals trained to properly administer it. However, the promotional communications at issue promoted the product as simple to administer: just "Tongue and Done." This promotion dangerously undercut FDA-required conditions on the proper administration of the drug, which requires particular diligence to minimize the risk of serious or even fatal adverse events.

**SEPTEMBER 9** | FDA hosted its [third summit](#) to continue to enhance collaboration with internet stakeholders, government entities, academia, and other important partners to maximize the scope of our efforts to address the illegal availability of opioids online. Discussions at the summit focused on new ways to continue to combat the online component of the opioid crisis.

### ***Supporting Safe Use of Opioids and Other Substances***

**MARCH 1** | FDA approved [hydrocodone bitartrate](#), the first FDA-approved generic opioid with an [abuse-deterrent formulation](#). This means that product has properties that are expected to reduce, though not totally prevent, abuse of the drug when chewed and taken orally, or crushed and snorted or injected.

**MARCH 25** | FDA issued a [Drug Safety Communication](#) warning that the abuse and misuse of the over-the-counter (OTC) nasal decongestant propylhexedrine (Benzedrex) can lead to serious harm such as heart and mental health problems that could result in hospitalization, disability, or death. Propylhexedrine is safe and effective when used as directed; however, reports of individuals abusing and misusing it have increased in recent years.

**JUNE 7-8** | FDA held the public workshop [Morphine Milligram Equivalents: Current Applications and Knowledge Gaps, Research Opportunities, and Future Directions](#). The purpose was to bring stakeholders together to discuss the scientific basis of morphine milligram equivalents (MME) for opioid analgesic prescribing, with the goals of providing an understanding of the science and data underlying existing MME calculations, considering gaps in these data, and discussing future directions to refine and improve the scientific basis of MME application.

**JUNE 28–29** | Through a cooperative agreement with FDA, the Duke-Margolis Center hosted the private workshop called [Exploring Options for Safe and Effective In-Home Opioid Disposal](#). The purpose was to bring together regulators, academic researchers, clinicians, patient advocates, and other stakeholders to explore available in-home opioid disposal options, and the potential benefits and impact of FDA requiring opioid manufacturers to provide a safe, in-home disposal option when opioids prescriptions are dispensed.

**JULY 12–13** | Through a cooperative agreement with FDA, the Duke-Margolis Center hosted a public workshop called [Safe Use of Benzodiazepines: Clinical, Regulatory, and Public Health Perspectives](#). Its purpose was to bring together regulators, academic researchers, clinicians, patient advocates, and other stakeholders to discuss epidemiological and abuse liability data of polysubstance use, patient and clinician perspectives and experiences, and gaps in data and understanding about the safe use.

**JULY 21** | FDA issued a Consumer Update, [Accidental Exposures to Fentanyl Patches Continue to Be Deadly to Children](#), to warn patients, caregivers, and health care professionals about the dangers of accidental exposure to the fentanyl patch, and how to properly store and dispose of the product.

**AUGUST 4** | Researchers from FDA published a systematic review titled [Patient-Reported Opioid Analgesic Use After Discharge from Surgical Procedures: A Systematic Review](#). It describes published literature on patient-reported opioid analgesic use after surgical procedures and gives methodologic recommendations for future studies to help support their use in condition- and procedure-specific evidence-based opioid analgesic guidelines.

**OCTOBER 13–14** | Through a cooperative agreement with FDA, the Duke-Margolis Center for Health Policy [convened](#) a public workshop, [Reconsidering Mandatory Opioid Prescriber Education Through a Risk Evaluation and Mitigation Strategy \(REMS\) in an Evolving Opioid Crisis](#). The purpose was to give stakeholders an opportunity to provide input on aspects of the current opioid crisis that could be mitigated in a measurable way by requiring mandatory prescriber education as part of a REMS.

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The FDA is involved in ongoing education and outreach campaigns to help support the safe use of opioids. [Remove the Risk](#) aims to raise awareness among patients and consumers about the serious dangers of keeping unused prescription opioids and to provide information about safe disposal of these medicines. Through a CDER collaboration with Partnership to End Addiction, [Search and Rescue](#) aims to provide health care professionals with the tools and resources they need to help patients avoid prescription drug misuse, abuse, and addiction.

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## Ensuring Quality, Safety, and Effectiveness of Generic Drugs

The FDA's generic drug program continued to substantially increase the availability of affordable, high-quality drugs in the United States. More than 10,000 generic drugs are currently approved by the FDA, and nine of 10 prescriptions filled are for [generic drugs](#). Importantly, generic drugs have saved the health care system more than \$2 trillion in the past decade.

Increasing the availability of generic drugs helps to create competition in the marketplace, which helps reduce the cost of treatment and increase access to medicines for more patients. The [Office of Generic Drugs \(OGD\)](#) follows a [rigorous review process](#) to ensure that, compared to the brand-name drug, a generic drug has the same:

- Active ingredients (the ingredients that treat a condition or symptoms)
- Strength
- Dosage form (e.g., tablet, capsule, cream, patch, or liquid)
- Route of administration (e.g., oral, topical, inhalation, or injection)
- Conditions of use
- Labeling (with certain exceptions)

OGD evaluates generic drug safety before these drugs are approved and continues to monitor and evaluate their safety throughout the time they are available for sale in the United States. Effective postmarket surveillance is essential to making sure that FDA-approved generic drugs provide the same therapeutic effect and safety as brand-name drugs.

## ***Presenting Generic Safety Surveillance Activities to Stakeholders in 2021***

In 2021, OGD presented its scientific approach to conducting safety evaluations and postmarketing surveillance, and engaged with several major stakeholder audiences.

**JANUARY 27** | Presented Update on Safety Surveillance for Generic Drugs at the [Drug Information Association Pharmacovigilance and Risk Management Strategies Conference: FDA Updates in Pharmacovigilance session](#).

**APRIL 29** | Presented and participated in panel discussions at the [CDER Small Business and Industry Assistance \(SBIA\) Generic Drugs Forum 2021: Lifecycle of a Generic Drug](#) for the following sessions:

- [Postmarketing Safety Surveillance of Generic Drug Products – An Update](#)
- [Premarket Review of Expedited Serious Adverse Event Reports from IND-Exempt BA/BE Studies](#)
- [Risk Evaluation and Mitigation Strategies \(REMS\) for Generic Drugs](#)

**SEPTEMBER 22** | Presented Comparative Analyses for Generic Oral Inhalers at the [CDER Small Business and Industry Assistance Advancing Generic Drug Development: Translating Science to Approval](#).

## ***Safety Surveillance of Generic Drugs: OGD's Division of Clinical Safety and Surveillance***

OGD's Office of Safety and Clinical Evaluation's (OSCE) Division of Clinical Safety and Surveillance (DCSS) consists of a multidisciplinary staff of physicians, pharmacists, epidemiologists, nurses, and other scientists who perform and facilitate broad preapproval and postmarket generic drug safety and surveillance activities for OGD. OSCE was newly established in 2021 as part of a reorganization within OGD and was formed through the realignment of certain clinical, pharmacology/toxicology, and safety review staff. This realignment of these suborganizations places scientists and other staff with expertise in drug safety under one group within OGD for resource efficiency.

Together, the DCSS staff support CDER's Postmarket Safety Modernization efforts, including through 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](#). They also initiate Generic Drug User Fee Amendments (GDU-FA)-related postmarket safety research, and perform generic drug safety and surveillance outreach through presentations and publications to generic drug stakeholders, including patients, health care providers, pharmacists, and drug safety-focused organizations.

### ***DCSS Safety and Surveillance Highlights in 2021***

**JANUARY** | The DCSS was instrumental in the publication of the CDER Alert, [FDA updates vinca alkaloid labeling for preparation in intravenous infusion bags only](#). Throughout 2021, the DCSS, along with colleagues in OGD's Office of Regulatory Operation's Division of Labeling Review continued work on requesting that all ANDA holders of the chemotherapy drug products vincristine sulfate, vinblastine sulfate, and vinorelbine tartrate remove instructions for using them with a syringe and add use with minibags in order to address the risk of fatal neurologic injury or death related to the accidental spinal rather than intravenous administration of these cancer medicines.

**JUNE** | The DCSS collaborated with CDER's Office of Medical Policy in updating the "Safety Reporting Requirements for BA and BE Studies" portion of the draft guidance for industry, [Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies](#).

**SEPTEMBER** | The DCSS contributed to the investigation that supported FDA's [public notification to pharmaceutical companies](#) regarding data integrity concerns with clinical and bioanalytical studies conducted by Synchron Research Services and Panexcell Clinical Lab in support of ANDAs and NDAs.

The DCSS collaborated with CDER's Office of Medical Policy in updating the draft guidance for industry, [Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices](#).

The DCSS Clinical Team reviews Bio-Investigational New Drug Applications (Bio-INDs) and serious adverse events from Bio-INDs and non-IND bioequivalence/bioavailability studies that support Abbreviated New Drug Applications (ANDAs). In addition, the clinical reviewers are responsible for assessing Health Hazard Evaluations for potential recalls. The DCSS Data Team analyzes generic drug quality and therapeutic equivalence adverse event reports and trends, follows generic drug distribution patterns, and identifies emerging safety issues. The DCSS REMS Team assists generic drug applicants in developing and maintaining REMS for applicable generic drugs.

## ***DCSS Risk Evaluation and Mitigation Strategies (REMS) Highlights in 2021***

The DCSS REMS Team assists in developing, implementing, managing, and evaluating REMS-related activities submitted to ANDAs. For OGD, a generic drug that is the subject of an ANDA is subject to certain elements of the REMS required for the applicable listed drug. The DCSS REMS Team serves as experts on the statutory and regulatory requirements and recommendations in FDA guidance documents related to ANDAs containing a REMS or subject to a REMS. Throughout 2021, the DCSS REMS Team actively participated in CDER's cross-office efforts to:

- Evaluate and approve 3 separate system REMS
- Evaluate established REMS materials to aid in the approval of 25 ANDAs subject to REMS
- Evaluate and approve various REMS modifications, ultimately affecting 135 approved ANDAs

Information on approved REMS for NDAs and ANDAs is available at [FDA REMS](#).

## ***Generic Substitution and Safety of Generic vs Brand-Name Drugs: OGD's Office of Research and Standards***

As part of GDUFA-funded research projects, the FDA is conducting ongoing research to evaluate generic substitution, including clinical studies of substitution in patients, medical informatics data analysis to evaluate generic utilization and substitution, and patient and provider perceptions impacting generic substitution.

In 2021, the FDA completed a study investigating the bioequivalence of a generic immunosuppressive drug product tacrolimus and its reference product. The FDA is currently analyzing the results of this study to determine its impact on generic substitution. The FDA also investigated the feasibility of using Sentinel data to investigate generic performance in terms of therapeutic equivalence with the reference product and compared the outcomes of solid organ transplantation between these two formulations.

During 2021, ongoing research efforts were focused on evaluating the substitutability of approved generic products and their corresponding reference products. Research in collaboration with the Yale University-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI) was completed to characterize whether users of different generic levothyroxine products used to treat underactive thyroid had equivalent clinical outcomes, in particular thyroid stimulating hormone (TSH) levels. Preliminary results showed there were no significant differences among the various generic levothyroxine products and no need to caution against switching between different generic products. A second study with the Yale-Mayo CERSI was designed to control for unobserved confounding that is ubiquitous in observational studies. Previous efforts had successfully controlled for observed confounding factors such as age and other demographic factors. The preliminary results showed the global treatment effect was not significantly different between generic levothyroxine and brand levothyroxine products following adjustment for confounding effects.

Other ongoing research efforts include monitoring postmarket performance of a first generic, Wixela Inhub, an approved generic version of Advair Diskus used to treat asthma and chronic obstructive pulmonary disease (COPD). Research has also been initiated to evaluate the application of pharmacogenomic (PGx) information for BE purposes. PGx information can be applied in BE studies for generic drug development to further enhance subject safety and BE study design. The ongoing research will help determine when PGx information should be used to identify subjects vulnerable to serious adverse events, minimize carryover effects in a crossover study, and ensure balanced groups in a parallel study.



## Safe Use Initiative: Collaborating to Reduce Preventable Harm from Medications

Millions of Americans depend on prescription and OTC medications to sustain their health on a daily basis, with more than four billion prescriptions written annually. However, too many people suffer unnecessary injuries and some die as a result of preventable medication errors, which can include medicines dispensed in error, medicines taken for too long or not long enough, or inappropriately mixed with other medicines or foods that can increase the risk of side effects.

The FDA believes that many of these medication-related risks are manageable if partners committed to their safe use work together. FDA's Safe Use Initiative (SUI) works to create and facilitate public and private collaborations within the health care community that can help to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing, and evaluating interventions along with partners and collaborators. Current and potential partners in Safe Use programs and projects include federal agencies; health care professionals and professional societies; pharmacies and hospitals; and patients, caregivers, consumers, and their representative organizations.

SUI enables many of its collaborations through funding and actively participating in research projects that seek to reduce preventable drug harm.

Safe Use maintains an open and continuous announcement to solicit research proposals and its projects target many kinds of preventable harm and involve a range of approaches.

### ***Projects Completed in 2021***

**Manganese Contamination in Neonatal Parenteral Nutrition.** Parenteral nutrition (PN), which is the administration of nutrition through a vein, has become standard and essential to the care of preterm newborns in the neonatal intensive care unit. Health benefits of PN include positive nitrogen balance, weight gain, and reduced neurodevelopmental impairment. However, the daily provision of PN to preterm newborns involves numerous safety risks, including side effects from ingredient formulations not ideally suited for this vulnerable population. One example is the trace element manganese, which is added to PN. However, the [first part of this project](#) found neonatal PN contains significant quantities of manganese not intentionally added during its preparation. In the second part of the project, a prospective clinical trial was conducted to determine whether preventing potential harm from PN manganese overexposure can be done reliably and safely through creative product selection during the PN compounding process. Data collection has been completed and reporting is underway.

### ***Projects Ongoing in 2021***

**A Scalable, Patient-centered Approach to “Right-sizing” Opioid Prescriptions.** Patient-reported data on the use of opioid pain medications after specific procedures are lacking, and many studies have found that more pills are prescribed than are actually needed. This project is collecting data from patients undergoing elective surgical procedures and those seen in an emergency department for acute pain. Information on the number of doses of opioid pain medication used, the number of days of medication used, and how patients feel about their ability to treat their pain is being collected. Understanding how much medication most patients actually used will enable standard orders for surgeries to be revised to reflect actual need. The project will ensure patients are provided enough medication to treat their pain, while attempting to minimize the number of leftover pills that could be diverted, misused, or abused. To date, several thousand patients have been enrolled and data collection is ongoing. Two articles have been published, which can be viewed [here](#) and [here](#).

In a second phase of this project, prescriber “report cards” are being tested to further “right-size” prescribing. This aim will test the effect of providing prescribers comparative feedback on their patients’ quantity of unused pills using a stepped-wedge cluster randomized trial. Report cards will contain information on pills prescribed and those actually

used by patients for each surgical provider for each common procedure. The hypothesis is that compared with usual care, monthly feedback will prompt prescribers to reduce the amount of opioid tablets prescribed, thereby reducing the amount of pills left over, but will not impact ability to manage pain. Multiple surgical subdivisions are participating in this phase of the project.

**Suicide-Related Risks Associated with Prescription Opioid Deprescribing.** Concerns exist that abrupt discontinuation or rapid/unsupported tapering of opioid pain medication may result in unintended consequences, including suicides. However, the scope of suicides and suicide attempts after opioid deprescribing, as well as which patients are most vulnerable, are largely unknown. This project assesses overdose and suicide-related outcomes associated with prescription opioid deprescribing in a large, multisite, nationally representative, observational study using data from six health systems. A further aim of the study is to identify factors that can reduce associated risks and reduce preventable harm related to opioid deprescribing.

**Perioperative Medication Safety Self-Assessment for Hospitals and Ambulatory Surgical Centers (ASCs) and Targeted Risk-Reduction Tool Development.** Preventable harmful medication errors in perioperative settings are a common cause of morbidity and mortality in the United States, with the frequency of medication errors varying widely depending on detection and measurement strategies. Systematic identification and characterization of perioperative medication errors is essential to enable targeted interventions such as resources that enable health care providers and institutions to identify and manage shortcomings to reduce preventable harm. This project involves the development, testing, and implementation of a perioperative medication safety evaluation of systems and practices in U.S. hospitals and ambulatory surgical centers using a self-assessment instrument. Additionally, the Institute for Safe Medication Practices (ISMP) will apply findings to create a tool for general use by health care providers and institutions to perform these self-assessments. Data collection is currently underway. Results will be presented at a future national meeting.

**Leveraging the Electronic Health Record (EHR) to Promote Pharmacy Adoption of Dosing Best Practices and Reduce Parent Errors in Administering Pediatric Liquid Medications.** This project is examining whether an instruction to pharmacists incorporated into the EHR as part of the electronic prescription will reduce errors in administering pediatric liquid medications. These instructions specify

that the prescription should be in “mL only” units and that an appropriate-sized dispensing device should be given to the patient. Follow-up with patients checking that the appropriate dispensing device was given will assess the effectiveness of the instructions to the pharmacist and if the intervention reduces dosing errors made by parents.

**Evaluation of Stimulant Abuse in the United States: A Mosaic Epidemiology Study.** Stimulant abuse is increasing dramatically; however, compared to opioid abuse, little is known about this emerging public health issue. This project will use several databases to characterize stimulant abuse, including examining demographics, drugs of interest, motivations, and behaviors, as well as trajectories of use.

**Mentored Implementation and Dissemination of Anticoagulation Stewardship (MIDAS) Program.** Anticoagulants are essential medicines to reduce the risk of blood clots and strokes, but they are also a major source of preventable harm due to the risk of excessive bleeding and the challenge they pose for health care professional management. This project is examining the ability of an anticoagulation stewardship program to reduce preventable harm from anticoagulants using a Mentored Implementation Program, using a Stewardship Guide and Self-assessment developed in a previous FDA-funded project. In this new effort, paired physician-pharmacist teams will serve as mentors for five diverse hospitals that will conduct self-assessments at the beginning of the program, create an interdisciplinary team, and work with the mentors to create an individualized implementation plan. Mentoring will take place monthly over a 12-month period. The hospitals will share lessons learned with each other and provide updates quarterly. A content development committee will use the implementation plans and lessons learned to create a “playbook” which other institutions can use to create and carry out their own Anticoagulation Stewardship Implementation Program.

**Preventable Harm from Pediatric Outpatient Medication Errors: Measure Development.** This project seeks to develop an understanding of current measures in outpatient pediatric medication safety and assess the gap between current measures and needs. Measure development is a necessary step in defining and establishing quality improvement programs. Quality measures in pediatrics have lagged behind measure development in other areas. The project will include a systematic literature review and input from stakeholders such as health care providers, parents, and patients. The literature review has been completed and a manuscript is in preparation.

## ***New Projects in 2021***

**Assessment of a Pharmacist-led Interprofessional Transition of Care Program Targeting Patients with Multiple Recent Hospital Admissions: the ICARE Program.** Transitions of care (TOC) programs can decrease the rate of 30-day hospital readmission and 30-day emergency department utilization in high-risk patients. Previous studies have examined the impact of TOC services on outcomes related to specific disease states. One gap in the current literature is an examination of the impact of a TOC program on patients at high risk for readmission due to a history of multiple admissions. In order to decrease the rate of 30-day readmissions and improve patient care during care transitions, the investigators are implementing the ICARE (Identify at admission, Counsel before discharge, secure Access to medications, Reach out for follow-up, Engage community providers) TOC program. Using this approach, the investigators will develop a pharmacist-led hospital-community collaborative TOC program to decrease medication-related harm in patients at high risk for hospital readmission due to multiple recent admissions.



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FDA's compounding program aims to protect patients from unsafe, ineffective, and poor-quality compounded drugs, while preserving access to lawfully marketed compounded drugs for patients who have a medical need for them.

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## Compounded Drugs: Continuing Oversight and Stakeholder Outreach

[Human drug compounding](#) is generally a practice in which a licensed pharmacist or a licensed physician combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. Although compounded drugs can serve an important role, they also can [present a risk](#) to patients.

Compounded drugs do not undergo FDA premarket review for safety, effectiveness, and quality, and therefore may present a greater risk of harm to patients than FDA-approved drugs. To help mitigate these risks, the FDA has developed a novel approach to engage [facilities that compound sterile drugs](#) and help them produce the highest quality drugs.

The [Compounding Quality Center of Excellence](#), launched in 2019, is designed to enhance collaboration with outsourcing facilities, compounders, and other stakeholders with the goal of improving the overall quality of compounded medicines. An [FDA Voices article](#) published in 2021 highlighted the Agency's continued collaboration with drug compounders. One area of engagement includes supporting in-person and online trainings on current [good manufacturing practice \(CGMP\)](#) requirements. These requirements for outsourcing facilities are particularly important because their compounded drugs reach many patients across the country.

In 2021, the FDA advanced the implementation of the Compounding Quality Center of Excellence, including by:

- Developing and holding multiple instructor-led virtual and self-guided online CGMP and compounding policy trainings for outsourcing facilities
- Holding the second annual conference in [September 2021](#) to convene outsourcing facilities and other stakeholders to enhance collective learning in areas that can help to bolster the quality of compounded drugs
- Engaging in research to better understand the outsourcing facility sector and its needs to inform current and future program areas for the Center

The FDA also took important steps to implement and enforce federal law related to drug compounding. In September 2021, the FDA's actions led to a [consent decree](#) against a Florida-based compounder, Premier Pharmacy Labs Inc., prohibiting it from manufacturing and distributing drugs due to insanitary conditions. The FDA inspected the firm and found it manufactured and distributed drugs, including those intended to be sterile, that were adulterated because they were made under insanitary conditions and in violation of good manufacturing practice requirements under the FD&C Act.

In September 2021, the FDA [alerted](#) patients and health care professionals not to use products intended as sterile from Prescription Labs Inc., doing business as Greenpark Compounding Pharmacy in Houston, Texas. During an inspection, FDA investigators observed conditions that could cause compounded drugs to be contaminated or otherwise pose risks to patients.

In October 2021, the FDA issued a [Compounding Risk Alert](#) highlighting concerns with compounding of drug products by medical offices and clinics under insanitary conditions. Adverse events have been reported, but it is likely that these events are underreported. The FDA also noted increasing awareness of businesses such as intravenous (IV) hydration clinics, medical spas, and mobile IV infusion services that are compounding drugs under conditions that may not meet section 503A of the FD&C Act or comply with state regulations.

The FDA also advanced development of the lists of bulk drug substances that may be used in compounding through a meeting of the Pharmacy Compounding Advisory Committee and publications in the Federal Register. Additionally, the FDA published a [revised draft guidance](#) on compounding in hospital and health-system settings.



The following resources related to human drug compounding can be found on FDA's website:

- [Compounding: Inspections, Recalls, and other Actions](#)
- [Compounding Risk Alerts](#)
- [Consumer and Health Care Professional Information](#)
- [Compounding and the FDA: Questions and Answers](#)



## Communicating Drug Safety: Global Outreach Through Diverse Tools and Technologies

CDER's Office of Communications (OCOMM) supports the FDA's mission to protect and promote public health through a broad range of communication tools and technologies. Throughout 2021, 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
- Respond to inquiries from the public about a range of topics related to human drugs
- Conduct social science and risk communications research

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

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## ***Communicating Drug Safety Across Multiple Audiences***

[Drug Safety Communications \(DSCs\)](#) provide important new or emerging safety information about marketed prescription and OTC drugs to patients, caregivers, health care professionals, and the public. DSCs communicate safety issues that, for example, may affect a large number of patients, describe potentially serious or life-threatening adverse events or certain other cautions related to use of a drug or class of drugs, and contain actionable recommendations for patients and health care professionals. DSCs also support more informed decision making by patients and health care professionals and help prevent or mitigate drug-related harm.

The [DSC home page](#) is consistently a highly visited page on the FDA's web site. The key safety information contained in the DSCs is also broadly circulated through many other channels, including large email listservs, including a [DSC-specific](#) list that allows patients and health care professionals to request [email alerts](#) about medicines or medical specialties of specific interest to them; social and traditional media; podcasts; and targeted outreach to media, health care professionals, advocacy groups, and other stakeholders. Throughout 2021, DSC information was widely reported, including by Bloomberg, Reuters, WNYT, and multiple trade press publications.

Eight DSCs were issued in 2021, generating nearly 206,000 unique pageviews. Among the DSCs issued, several involved high-profile issues or drug products, including:

- [Xeljanz, Xeljanz XR \(tofacitinib\)](#): Preliminary safety clinical trial results showed an increased risk of serious heart-related problems and cancer with this arthritis and ulcerative colitis medicine compared to tumor necrosis factor (TNF) inhibitors.
- [Xeljanz, Xeljanz XR \(tofacitinib\), Olumiant \(baricitinib\), Rinvoq \(upadacitinib\)—Janus kinase \(JAK\) inhibitors that treat certain chronic inflammatory conditions](#): Increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death communicated based on FDA review of the completed safety clinical trial results.
- Alcohol-based hand sanitizers (two DSCs): Symptoms such as [headache, nausea, and dizziness](#) can occur after applying alcohol-based hand sanitizers to the skin and breathing in the vapors. Splashing or touching the eyes after use of alcohol-based hand sanitizer can result in serious injury, including [severe irritation and damage to the surface of the eye](#).

More than a year after the OCOMM launched a distribution listserv that allows health care professionals, patients, and consumers to sign up to receive [email alerts](#) about DSCs on medications and medical specialties of specific interest to them, the listserv has over 31,000 subscribers across the

78 different DSC medication and medical specialty topics offered. Additionally, the DSCs are distributed through the [MedWatch Safety Alerts listserv](#), the [Division of Drug Information listserv](#), and to various targeted stakeholder organizations. DSCs issued in 2021 were also widely shared via social media on FDA's Facebook page, Twitter feeds, and LinkedIn page. LinkedIn, which has greater potential for targeting health care professionals, saw more than 2,000 "click-throughs" to the full DSCs. Across all DSCs issued during 2021, visitors spent an average of over two and a half minutes on DSC content. In comparison, most users generally stay on websites for less than 15 seconds.

[Drug Safety Podcasts](#) of each DSC provided an additional format for this emerging safety information. The eight podcasts issued in 2021, which generated more than 21,000 engagements, are [available on the FDA website](#) and on [Apple Podcasts](#), [Google Podcasts](#), [Spotify](#) and [ReachMD](#).

[Drug Information Webinars](#) offer free, live online continuing education (CE) for physicians, physician assistants, nurse practitioners, nurses, pharmacists, and pharmacy technicians. The webinars often center on drug safety or safety-related topics. Recordings of these webinars are posted online after the live session for home study.

**MAY 18** | [Safety Labeling Changes for Leukotriene Receptor Antagonists and Decisions Behind a Boxed Warning](#)

**JUNE 1** | [Enhanced Drug Distribution Security: 2023 and Beyond](#)

**OCTOBER 19** | [How FDA and ISMP Utilize Medication Error Reports to Improve Drug Safety](#)

**NOVEMBER 16** | [Fraudulent Products – Hidden Ingredients and Unproven Claims in Products Marketed as Dietary Supplements](#)

New Home Study CE Courses posted in 2021 include:

- [Overview of Risk Evaluation and Mitigation Strategies \(REMS\) for Health Care Providers](#)
- [An Overview of Naloxone and FDA's Efforts to Expand Access](#)

The FDA also issued several [Consumer Updates](#) related to drug safety information.

**NOVEMBER 3** | [Safely Using Hand Sanitizer](#)

**OCTOBER 28** | [Should You Give Kids Medicine for Coughs and Colds?](#)

**JULY 21** | [Accidental Exposures to Fentanyl Patches Continue to Be Deadly to Children](#)

**JUNE 14** | [Older Therapies Aren't Necessarily Better for Thyroid Hormone Replacement](#)

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Across all DSCs issued during 2021, visitors spent an average of over two and a half minutes on DSC content. In comparison, most users generally stay on websites for less than 15 seconds.

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# DRUG SAFETY COMMUNICATIONS OUTREACH



8 DSCS VIEWED NEARLY  
**206,000** TIMES

## REACHED OVER

**31,000** DSC LISTSERV SUBSCRIBERS

**117,000** DRUG INFORMATION LISTSERV SUBSCRIBERS

**400,000** MEDWATCH LISTSERV SUBSCRIBERS

## PUSHED TO OVER



**493,000**

FOLLOWERS



**783,000**

FOLLOWERS



**331,100**

FOLLOWERS



## LINKEDIN

**129,538**  
IMPRESSIONS

**712**  
REACTIONS

**2,072**  
CLICKS TO THE DSC



## FACEBOOK

**505**  
LIKES

**232**  
SHARES



## TWITTER

**163**  
LIKES

**180**  
RETWEETS



## Responding to Public Inquiries

OCOMM responds to public inquiries about all human drugs. These inquiries are received via phone, email, letters, and through social media platforms such as Facebook and LinkedIn. Expert responses are developed and facilitated by a team of pharmacists, nurses, and other health professionals who field questions from consumers, health care professionals, journalists, research and nonprofit organizations, regulated industry, other government agencies, academia, and from international stakeholders in government and research institutions. OCOMM received and managed more than 43,000 public inquiries between October 1, 2020, and September 30, 2021, mostly by phone.

## Social Media Engagement

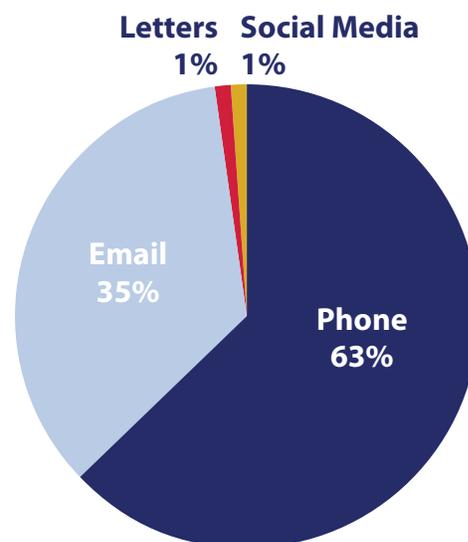
The CDER Social Media team has significantly expanded CDER's communications outreach by 'meeting people where they already are' on numerous social media platforms, including [Twitter](#), [Facebook](#), [LinkedIn](#), and [YouTube](#). Drug safety information is now actively pushed to more than 756,000 FDA Facebook followers, 327,000 Twitter followers, and 476,000 LinkedIn followers, facilitating exponential growth in the distribution of FDA's public health messages, safety communications, and drug safety warnings. In addition to posting content and engaging in two-way communication, the Social Media Team also performs social listening, monitoring the comments and questions users post on FDA's social media channels to obtain immediate feedback on FDA actions and decisions. The team also oversees 'live' tweeting of discussions occurring at meetings and workshops, providing real-time highlighted content to many more people than those attending in person.

On November 9, 2020, the team launched the [@FDACDERDirector](#) Twitter account to provide a head of Center perspective on CDER actions and initiatives, including those regarding drug safety. This account issued 187 tweets and has 2,503 followers from media, current and former FDA officials, consumers, health care providers, industry, stakeholder groups, health organizations, and other health and government leaders.

Between October 1, 2020, and September 30, 2021, the CDER Social Media Team:

- Actively disseminated FDA information to followers on Twitter through 956 tweets and Facebook through more than 320 posts
- Provided information to more than 117,000 subscribers on our Drug Information Listserv through 262 messages sent, generating more than 1.9 million URL "click-throughs" to FDA website content

## PUBLIC INQUIRIES MANAGED BETWEEN OCTOBER 1, 2020–SEPTEMBER 30, 2021



\*Facebook and LinkedIn

## TOP 10 PUBLIC INQUIRIES

|                                     |       |
|-------------------------------------|-------|
| COVID-19                            | 9,081 |
| Opioids                             | 1,334 |
| Nitrosamines                        | 1,182 |
| Investigational New Drugs (IND)     | 1,053 |
| Personal Import                     | 1,047 |
| Electronic Registration and Listing | 1,010 |
| Expanded Access/Right to Try        | 941   |
| Clinical Trials                     | 865   |
| Import/Export                       | 567   |
| OTC Monograph                       | 491   |



- Expanded social media outreach for COVID-19 communications, Facebook Events, and the [Remove the Risk](#) opioid disposal campaign, [BeSafeRx](#) online pharmacy campaign relaunch, information about [Biosimilars](#), and [Sunscreens](#).

## SOCIAL MEDIA OUTREACH

| FACEBOOK  |         |
|---|---------|
| Facebook followers  | 756,252 |
| CDER posted content   | 320     |
| Replied to comments   | 319     |
| Public Likes/Shares   | 40,991  |
| LINKEDIN  |         |
| FDA page followers  | 476,704 |
| Small Business and Industry Assistance (SBIA) Showcase page followers | 15,350  |
| Global Alliance of Drug Information Specialists (GADIS) Group members | 1,094   |
| TWITTER   |         |
| Total followers   | 326,305 |
| Tweets  | 956     |
| Retweets  | 5,850   |
| Likes   | 9,885   |

## Drug Safety-related Labeling Changes

Not every safety concern can be identified at the time a drug product is approved for marketing. If new safety concerns emerge after a drug is marketed, the FDA may require a drug safety-related labeling change (SrLC). The [SrLC database](#) includes safety labeling changes FDA requires or orders drug manufacturers to make as well as labeling changes voluntarily submitted by product sponsors.

The database makes safety information available in near real-time and can be easily searched through a user-friendly portal by stakeholders such as health care professionals, patients, and health IT and information vendors. Stakeholders accessing the database provide valuable feedback that assists the FDA in continually upgrading how safety labeling information is organized and presented.

### SAFETY-RELATED LABELING CHANGES\*

|   |              |
|---|--------------|
| Adverse Reactions                                       | 1,204        |
| Boxed Warnings  | 374          |
| Contraindications                                       | 506          |
| Drug Interactions                                       | 754          |
| Patient Counseling information and/or Medication Guides | 1,206        |
| Use in Specific Populations                             | 1,178        |
| Warnings and Precautions                                | 1,280        |
| <b>TOTAL</b>  | <b>6,502</b> |

\*Between October 1, 2019–September 30, 2021



### **BeSafeRx Campaign**

FDA's [BeSafeRx](#) campaign helps consumers learn about how to safely buy prescription medicines online. Between October 1, 2020, and September 30, 2021, the BeSafeRx campaign received more than 2 million airings/placements, yielding an estimated 295 million impressions across TV, radio, and medical office and hospital waiting rooms.

- The campaign's TV public service announcements (PSAs) aired 21,471 times on 194 television stations and 10 television networks across the country, yielding approximately 113 million impressions.
- The radio PSAs aired approximately 53,229 times on 940 radio stations nationwide (including Nielsen, non-Nielsen and TTWN affiliates), 13 networks (including TTWN) and 1 program, yielding an estimated 167 million impressions.
- The video PSAs aired approximately 1,964,902 times in the waiting rooms of medical offices and hospitals across the country, yielding an estimated 14 million impressions.

## Online Communications

Drug safety news, announcements, and information are distributed to multiple audiences using a variety of digital and electronic media supported by a broad portfolio of services, including video production and photography, web graphics, online publications, posters, infographics, illustrations, and other materials. The online communications team also maintains web content such as drug safety information and safety-related regulatory policy documents on FDA web pages; manages public databases; and develops web and mobile applications, including optimizing applications for viewing formats such as smart phones and tablets.

Between January 1 and September 30, 2021, the traffic to CDER's web pages amounted to more than 19 million individual sessions. The metrics in the tables below depict the extent of this online engagement, including the platforms from which the traffic is coming; the 10 most-viewed CDER web pages – collectively accounting for more than five million online visits; and the topics, questions, and documents generating the most online traffic for the period. Also tracked are trending topics on social media, as well as the leading subjects of news stories and other informational outlets, and those carried via newsfeeds and social media.

### TEN MOST VIEWED CDER PAGES

|   | Unique Pageviews* |
|---|-------------------|
| 1. <a href="#">Drugs</a>  | 1,447,039         |
| 2. <a href="#">Drug Approvals and Databases</a>   | 835,899           |
| 3. <a href="#">FDA updates on hand sanitizers consumers should not use</a>  | 806,789           |
| 4. <a href="#">Drug Safety Communication: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems</a> | 540,315           |
| 5. <a href="#">High Blood Pressure–Understanding the Silent Killer</a>  | 527,434           |
| 6. <a href="#">National Drug Code Directory</a>   | 494,979           |
| 7. <a href="#">Q&amp;A for Consumers   Hand Sanitizers and COVID-19</a>   | 369,377           |
| 8. <a href="#">Disposal of Unused Medicines: What You Should Know</a>   | 309,431           |
| 9. <a href="#">FDA authorizes REGEN-COV monoclonal antibody therapy for post-exposure prophylaxis (prevention) for COVID-19</a>   | 271,163           |
| 10. <a href="#">Drug Disposal: Drug Take Back Locations</a>   | 238,498           |

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

### WEB TRAFFIC BETWEEN JANUARY 1– SEPTEMBER 30, 2021

| TRAFFIC VOLUME | SESSIONS*  |
|----------------|------------|
| Mobile         | 72,525,385 |
| Desktop        | 42,951,654 |
| Tablet         | 2,737,580  |

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

| TRAFFIC SOURCES | % OF SESSIONS |
|-----------------|---------------|
| Search Engines  | 67%           |
| Direct (URLs)   | 16%           |
| Referrals       | 9%            |
| Email           | 4%            |
| Social Media    | 4%            |

### TOP 10 GOOGLE SEARCHES LEADING TO FDA SAFETY CONTENT

|                       |
|-----------------------|
| 1. Hydroxychloroquine |
| 2. Benadryl           |
| 3. Hand sanitizer     |
| 4. Metformina*        |
| 5. Metformin          |
| 6. Loperamida*        |
| 7. Montelukast        |
| 8. Ketoconazole       |
| 9. Clopidogrel        |
| 10. Difenhidramina*   |

\* Spanish language searches.

## ***Risk Communications Research***

OCOMM undertakes a range of social and behavioral science research studies 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 communication, regulatory, and policy 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 FDA materials and messages, and exploratory pharmacovigilance studies conducted through monitoring and analysis of open-source data available online and through social media.

## ***Highlights of 2021 Research Programs and Projects***

### **Studies related to opioids and other abused drugs**

**Abuse-deterrent Formulation Opioids.** Throughout 2021, OCOMM social scientists and CDER opioid subject matter experts continued work on a three-phase project exploring and assessing the knowledge, attitudes, and understanding regarding abuse-deterrent formulation (ADF) opioids among prescribers and dispensers/pharmacists, including related to the ADF terminology. Based on findings from focus groups with opioid prescribers and pharmacists in the first project phase, a follow-up survey was completed in 2021 to obtain more representative data, including related to the terminology. The final third phase, which involves an experimental study, is underway.

**Substances Used as Adjuncts or Alternatives to Prescription Opioids.** Two additional studies are in progress exploring substances that may be used as adjuncts or alternatives to prescription opioids among both consumers with opioid/substance use disorder and health care professionals who prescribe these substances. Among the substances being explored are three classes of prescription drugs – opioids and benzodiazepines (among patients undergoing treatment and separately among prescribers) and gabapentinoids – and other substances often used with opioids – kratom and cannabidiol (CBD) (among patients undergoing treatment).

### **Proactive Pharmacovigilance Through Social Media Monitoring and Analysis.**

This novel research method aims to obtain an understanding of the social contexts and trends surrounding opioids and other prescription drugs, particularly their use for nonmedical or recreational purposes, being discussed in publicly available online discussion forums and on social media. In addition to developing monthly social media research reports concerning the misuse and abuse of prescription opioids, OCOMM completed an in-depth project exploring the effects the early days of the coronavirus pandemic had on opioid use and addiction, the findings from which were presented in several public meetings.

### **Other Studies**

**Biosimilar Products.** This project focuses on assessing educational materials FDA developed to most efficiently and effectively communicate with patients about biological products that are demonstrated to be biosimilar to an FDA-licensed biological product. The educational materials consist of an infographic, fact sheet, and a video public service announcement to be posted on FDA's website or disseminated to patients through other methods. This study is a follow-up to a related study that collected information about knowledge, awareness, and understanding of biological products and biosimilars from patients and health care professionals.

**Message and Materials Testing.** Several studies were undertaken in 2021 assessing a variety of FDA messages and materials, including sample drug safety announcements about the misuse and abuse of OTC medicines, proposed updates to the FDA's DSC web page and the communications' question-and-answer format, a draft Consumer Update article about children's OTC and homeopathic cough and cold products, and 20 commonly used technical regulatory terms and their plain language alternatives to determine comprehension by lay health consumers.

Information about these research efforts were presented publicly in 2021. This includes presentations at the [Drug Information Association's \(DIA's\) Biosimilar Conference](#) and the [FDA Science Forum](#).



**U.S. FOOD & DRUG**  
ADMINISTRATION

U.S. Food and Drug Administration

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