U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY PRIORITIES 2019

May 2020
www.fda.gov

Table of Contents

Introduction

The National Center for Health Statistics reports that, in 2018, nearly 25 percent of Americans used three or more prescription drugs every 30 days. Meanwhile, sales of non-prescription or "over-the-counter" (OTC) medicines exceeded 35 billion dollars.

While these numbers represent the essential health benefits conferred by prescription and OTC medicines for many millions of people, they also point to an ever-growing national exposure to the risks associated with these medicines. No medicine is entirely without risk, and adverse events (side effects), incorrect or inappropriate use of drugs, manufacturing issues, or criminal tampering are only some of the safety issues that can emerge in association with any drug product.

Management of emerging drug safety issues has become more complex, requiring multidisciplinary collaborations across the Center for Drug Evaluation and Research (CDER) in the Food and Drug Administration (FDA). **CDER Drug Safety Priorities 2019**—our fifth annual CDER Drug Safety Priorities report—describes the scope and scale of the Center's drug safety oversight programs, detailing the evolving and wide-ranging nature of our safety operations, with updates on several of the year's key milestones and achievements.

The work described in this report has continued to fuel the ongoing modernization and response capabilities of our safety surveillance, and represents substantive contributions to protection of the public health. But with millions of drug products in the marketplace at all times, safety issues continue to arise with unprecedented frequency, demanding swift and comprehensive innovations in how we identify, assess, and address safety concerns.

To meet this growing need, I established the Drug Risk Management Steering Committee in July 2019. The group was tasked with developing recommendations for a unified, integrated concept of operations for postmarket safety activities, and to lay the groundwork for the launch of the CDER Drug Risk Management Board. Going forward in 2020, the Board will meet the burgeoning complexity of drug safety concerns, capitalizing on and enhancing the synergies that already exist in many of CDER's collaborative efforts—ensuring seamless alignment in facilitating rapid analysis and resolution of safety issues.

This report details a number of programs shaping CDER's drug safety operations, including the Sentinel System, our electronic safety surveillance system; the Safe Use Initiative, working to minimize preventable harm from medications; our ongoing activities to help address the national opioid crisis; our work in addressing unexpected impurities in medicines, and our use of mobile apps and social media platforms to better understand drug safety risks as they are experienced in the "real world," together offering a portrait of CDER's multi-tiered drug safety enterprise in action throughout 2019.

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Safety Surveillance and Oversight of Marketed Drug Products

Pharmacovigilance

FDA maintains a robust practice of postmarket surveillance and risk evaluation programs to identify new adverse events that did not appear during the product development process, or to learn more about known adverse events. Evaluations are based on more than two million adverse event reports submitted every year to the FDA Adverse Event Reporting System (FAERS) database by patients, family members, and health care providers through the MedWatch program, as well as by regulated industry. FAERS contains adverse event reports, as well as reports of medication error reports and product quality complaints that result in adverse events that were submitted to FDA, allowing identification of safety concerns and recommendations to improve product safety and protect the public.

The 21st Century Cures Act, signed into law in 2016, included a requirement that FDA develop best practices for drug safety surveillance. In November 2019 the agency posted a draft document to seek public comment, Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. This document outlines our approach for timely postmarket analyses of drugs and biologics, including a high-level overview of tools, methods, and signal detection and evaluation activities, using varied data sources for drug safety surveillance, and to provide an overview and broader context of our overarching effort and commitment in this area.

The best practices document incorporates the guiding principle that postmarket safety surveillance is a dynamic and constantly evolving field. By using a risk-based approach, FDA considers the nature of a drug, its potential adverse events, the intended population, and the potential for serious outcomes, as well as the impact on individuals and the overall potential impact on the health of the public. When information is uncovered that may change the benefit-risk profile of a product, FDA will investigate the issue and consider appropriate action, including labeling changes, issuing drug safety communications, requiring postmarketing studies, requiring a risk evaluation and mitigation strategy, or, rarely, market withdrawal of the product. FDA continuously monitors the safety of the product even if we have determined that one of the above actions is not necessary.

FDA Adverse Event Reporting System Public Dashboard

The FDA Adverse Event Reporting System (FAERS) is a database that contains adverse event reports, as well as reports of medication errors and product quality complaints that resulted in adverse events that were submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance of drug and biologic products.

Improving data access and transparency are core concepts underlying the work of FDA and driving the development of the FAERS Public Dashboard, a highly interactive, user-friendly web-based tool that allows public access to human adverse event drug reports received by FDA and contained in the FAERS database. Data may be viewed in a customizable, searchable format. Dashboard users can view the summary of the adverse event reports received on specific drugs from 1968 to the present (or within a specific timeframe).

The data in the FAERS Public Dashboard is updated quarterly, and is current through December 31, 2019.

Medication Error Prevention and Analysis

FDA works to increase the safe use of drug products by minimizing use errors related to product naming, labeling, design, and packaging, including a focus on how proprietary names (commonly known as brand names) can contribute to confusion in the marketplace.

Phonetic and Orthographic Computer Analysis (POCA)

FDA analyzes a drug's proposed proprietary name to ensure it does not look or sound like the name of other drugs, helping sponsors develop proprietary names that do not cause or contribute to medication errors.

FAERS reports are submitted voluntarily by the public via the MedWatch Program, and are required to be submitted by the pharmaceutical industry. The FAERS database has more than 15 million reports, from 1968 through 2018, and now receives nearly two million reports every year.

"The FAERS Public Dashboard presents data in a more user-friendly format that allows people to search and organize based on a wide range of criteria, such as what reports did we get in a given year, what reports did we get focused on a specific drug … and what were the outcomes that were seen? We have had many requests to improve data access and transparency, and this Dashboard is a response to that."

Janet Woodcock, M.D., Director, CDER

To assist in this analysis, FDA uses the Phonetic and Orthographic Computer Analysis (POCA) software, which performs comparisons and flags any possible conflicts or potential confusions with the names of marketed drug products—both in how names sound and how they can appear in handwritten prescriptions. The POCA system is comprised of two applications, a search engine component and a prescription simulation component called RX Studies.

In 2019:

- FDA continued to use the POCA search engine in conducting proprietary name reviews to evaluate written and phonetic similarities of a proposed proprietary name to other proprietary and non-proprietary names.
  - The POCA search engine can also conduct target comparisons of proposed suffixes to the existing suffix component of biological nonproprietary names.
- FDA revised the RX Studies System to allow studies to assess potential errors with proposed proprietary names prescribed using Computerized Prescriber Order Entry systems (CPOE), the electronic systems that allow prescribers to enter and send prescriptions for medications using a computer application rather than paper, fax, or telephone.
  - This modification to the RX Studies functionality allows FDA to design CPOE simulations aligned with the technological advances made in recent industry and practice improvements. It helps simulate real-world situations for the assessment of potential name confusion and simulate potential medication prescribing errors in CPOE systems.

Modernizing the Human Factors (HF) Program

Human Factors studies examine how people interact with a medical product, which can include drug-device combination products. Important goals of such studies are to minimize use-related hazards and risks and then confirm that these efforts were successful, allowing individuals to use the device safely and effectively.

Combination products are two or more components packaged as a single product by physically, chemically, or otherwise combining or mixing and producing as a single entity. Examples include drug/device combinations such as prefilled drug delivery/device systems, auto-injectors, metered-dose inhalers, nasal sprays, transdermal systems ("skin patches"), or biologic/device combinations which can include prefilled delivery/device systems such as a vaccine or other biological product in a prefilled syringe, auto-injector, or nasal spray. There are numerous kinds of combination products that are described in detail on the FDA website.

In 2019, FDA updated and modernized internal databases to accommodate Human Factors activities, and developed a draft guidance, Bridging for Drug-Device and Biologic-Device Combination Products. This guidance provides recommendations to industry on the process of establishing the scientific relevance of information developed in an earlier phase of the development program, or in another development program, to support the combination product for which an applicant is seeking approval. Once the applicant has established the relevance of such information, the applicant may be able to leverage that information to streamline the development program.

Learn more about the FDA's Human Factors program here.

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 their benefit-risk balance
- Adjustments, made as appropriate, to risk minimization strategies to further improve the benefit-risk balance

FDA's primary risk management tool is communicating through FDA-approved product labeling, often referred to as the "package insert" or the "prescribing information," which includes a summary of the essential information needed by health care providers for the safe and effective use of the drug.

Labeling is sufficient for most drugs to ensure that the benefits outweigh the risks. In a limited number of cases, FDA may determine that a risk evaluation and mitigation strategy will also be needed to ensure that the benefits of the drug outweigh its risks.

In 2019 FDA conducted a series of four internal meetings to reflect on progress made and lessons learned in the 10 years since the REMS authorities were implemented. Discussions focused on improving the quality and efficiency of assessing the effectiveness of individual REMS programs, continuing our REMS standardization and integration efforts, and working with outside stakeholders to develop approaches that allow for integration of REMS program requirements into existing and evolving health IT systems.

- Three drugs, all designated as breakthrough therapies, were approved with a REMS to ensure the benefits outweigh the risks of these products: Spravato (esketamine hydrochloride), Zulresso (brexanolone), and Turalio (pexidartinib).
- Five shared-system REMS were approved which provide access to generic versions of brand products that are approved with a REMS. A shared system REMS encompasses multiple prescription drug products,

REMS is a drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS.

A breakthrough therapy is a drug intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition.

- To meet FDA breakthrough criteria, preliminary evidence must indicate that the drug may demonstrate substantial improvement over existing therapies on one or more medically significant end-points, such as substantial treatment effects observed early in the drug's development.
- If a drug is designated as a breakthrough therapy, FDA will expedite the development and review of that drug.

including brand product and generic products, and is developed and implemented jointly by two or more sponsors. For more information about the REMS approved for these products visit REMS@FDA.

- Two new guidances on the assessment of REMS programs were issued. These draft guidances provide a framework for companies to develop a REMS Assessment Plan at the same time the REMS program is being developed in order to improve the quality of the information used to assess the effectiveness of a REMS program. FDA is currently working to finalize these draft guidances based on submitted public comments.
  - *REMS Assessment: Planning and Reporting* describes how to develop a REMS Assessment Plan by considering how the REMS program goals, objectives and REMS design may impact the types of metrics and data sources that could be used to assess whether the program is meeting its risk mitigation goals.
  - *Survey Methodologies to Assess REMS Goals That Relate to Knowledge* provides recommendations on conducting REMS assessment surveys to evaluate patient or health care provider knowledge of REMS-related information, such as the serious risks and safe use of a medication. The draft guidance discusses general principles and recommendations related to conducting REMS assessment knowledge surveys, including study design, survey data collection and processing and data analysis.

The Sentinel System

"FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval."

Janet Woodcock, M.D., Director, CDER

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) comprised currently of 17 partner institutions. Sentinel collaborators include data and academic partners that provide access to healthcare data and scientific, technical, and organizational expertise. Distributed data networks allow secure access to multiple data sources, achieving far larger sample sizes than could ever be achieved through a single source, while assuring that data is collected securely with full patient privacy safeguards in place.

Sentinel monitors drug safety by analyzing emerging risks associated with FDA-regulated medical products, enabling product safety assessment under real-world conditions and providing unparalleled capabilities for investigation of new safety signals from spontaneous reporting systems like FAERS and other sources of safety information.

Sentinel can also be used 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 pre-specifying a specific target. (While promising, the results of these data mining approaches need to be corroborated by further studies.)

Sentinel also supports many safety inquiries, including but not limited to those related to medication errors, risk mitigation strategies, generic drugs, and pregnancy safety.

The Sentinel System has transformed the way researchers monitor the safety of 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 real-world data (RWD) and real-world evidence (RWE).

- **RWD** are data relating to patient health status or the delivery of health care routinely collected from a variety of sources, such as electronic health records (EHR) and insurance claims data.
- **RWE** is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.
- **The Sentinel System** capitalizes on the potential in RWD and RWE by accelerating access to and broadening the use of RWD—in turn facilitating the generation of RWE.

FDA now 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, by making it possible to analyze emerging risks associated with FDA-regulated medical products, enables the FDA to assess medical product safety under real-world conditions.

The Sentinel System Five-Year Strategy includes five goals:

- Enhance and expand the Sentinel System's operational foundation.
- Augment the System's safety analysis capabilities by leveraging advances in data sciences and signal detection.
- Leverage the System to accelerate access to and broader use of RWD for RWE generation.
- Broaden the System's stakeholders to pursue the vision of a national resource.
- Disseminate knowledge and advance regulatory science to encourage innovation and meet the FDA's scientific needs.

2019 Highlights

JANUARY | Major goals associated with the future of the Sentinel System were presented in the Sentinel System Five-Year Strategy: 2019-2023, a roadmap charting the development of the Sentinel System through five strategic aims including expansion of the Sentinel System's operational foundation, augmenting the System's safety analysis capabilities and signal detection, and leveraging the System to accelerate access to and broader use of RWD for RWE generation.

APRIL | The Eleventh Annual Sentinel Initiative Public Workshop convened on April 3 and brought together stakeholder communities to discuss a variety of topics on active medical product surveillance and current and emerging Sentinel projects, followed by a public training on Sentinel on April 4. FDA hosted the first International Regulator's Forum for other regulatory agencies on April 5, which was developed in response to requests from regulatory agencies for further information on how FDA operationalizes and implements

the Sentinel System to inform regulatory decision making. Recordings of the presentations are available at the Workshop website.

AUGUST | A public training on Sentinel's Cohort Identification and Descriptive Analysis (CIDA) tool was held at the University of Pennsylvania. The training was comprised of presentations and optional hands-on exercises exploring CIDA's capabilities. During the training, participants were guided through the process for answering epidemiological questions related to medical product safety using Sentinel's tools.

SEPTEMBER | The third Five-Year Sentinel Contract was awarded to two consortiums, one led by Harvard Pilgrim Health Care and the other by Deloitte Consulting, which established three distinct coordinating centers: The Sentinel Operations Center, Innovation Center, and the Community Building and Outreach Center. These three Sentinel centers will widen participation to a broader array of scientific expertise, translate new technologies from fields such as data science and big data, develop new approaches to using electronic health records and cultivate a robust scientific community to uncover novel ways to leverage the system's core capabilities beyond drug safety.

Other RWD/RWE Activities in 2019

To facilitate use of mobile technology (phones, fitness trackers, etc.) and direct input of RWD by patients, FDA developed the MyStudies mobile app which can be used to collect data entered by patients (with personal information protected) for clinical trials and RWE studies.

FDA has posted the computer code and a technical roadmap that allows researchers and app developers to customize and use the MyStudies app. While the MyStudies app was developed by FDA and private sector partners, its underlying code is "open source," meaning the app's computer code is freely available for use or modification by users or other developers. Although the app bore the FDA brand while its functionality was tested in a pilot study, it can now be rebranded by researchers and developers who would like to customize the app for use by their own institutions and studies.

Two demonstration projects were underway in 2019 using the MyStudies mobile application.

- **Improving Outcomes in Limited Juvenile Idiopathic Arthritis (Limit-JIA) Trial** will test how using a safe biologic treatment soon after diagnosis affects the medical course of a child with limited JIA. About half of children diagnosed with limited JIA (four joints or less affected at the time of diagnosis) will extend to five or more joints and/or eye inflammation over the course of their childhood. These children sometimes progress to severe disease that is very hard to treat. What is learned from this study can help doctors and families make better decisions about early treatment in limited JIA. The FDA MyStudies app,

rebranded for this trial, is being used to capture the eye inflammation endpoint as well as information related to medication use.

- **Study of a Prospective Adult Research Cohort with Inflammatory Bowel Disease (SPARC–IBD)** is a multicenter study of adult IBD patients which will collect and link data, including patient-reported outcome data using the FDA MyStudies app. Data will be used for research, with the goal of finding predictors of response to treatments and predictors of relapse that will lead to precision medicine strategies and new therapeutic targets that will improve the quality of life of patients with IBD. For this study the MyStudies app has been rebranded as IBD PROdigy, and will enable registry participants to contribute patient reported outcomes quarterly and after procedures.

FDA also conducted RWD/RWE seminars, public meetings, and guidance development in 2019. Highlights include:

Two Small Business and Industry Assistance webinars.

- **March 15 |** Framework for FDA's RWE Program
- **May 9 |** An Introduction to FDA MyStudies

MAY 9 | A draft guidance was issued, Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics. This guidance is intended to encourage industry and applicants seeking product approvals who are using RWD to generate RWE as part of regulatory submissions to provide information on their use of RWE in a simple, uniform format.

JULY 11-12 | A public workshop, Leveraging Randomized Clinical Trials to Generate Real-World Evidence for Regulatory Purposes, brought stakeholders together to explore key considerations for utilizing aspects of RWD to generate RWE. This workshop is a part of the FDA's ongoing efforts to explore the utility of RWE and will inform policy development in this area.

OCTOBER 3 | A public meeting, Developing Real-World Data and Evidence to Support Regulatory Decision-Making, considered development of RWE for regulatory use, including initiatives to improve and assess data quality, use of mobile technologies and sensors, and evaluation of observational methods to draw causal inference about product effectiveness. Stakeholders attending the meeting included representatives from the pharmaceutical industry, health care delivery, academia, patient organizations, standards development organizations, and members of the general public.

Small Business and Industry Assistance (SBIA) is often the first stop for a small pharmaceutical business interested in working with the FDA. SBIA's goal is to help small pharmaceutical business and industry navigate the wealth of information that the FDA offers and to provide assistance in understanding the regulation of human drug products.

The Framework for FDA's Real-World Evidence Program details the agency's current uses of RWD for evidence generation, and describes the program for evaluating RWD/RWE for use in regulatory decision-making.

Nitrosamine Impurities in Medicines: FDA's Continuing Multidisciplinary Response

In June 2018 the FDA learned that certain generic versions of valsartan, a high blood pressure and heart failure drug, contained unexpected impurities that posed a potential safety concern. These impurities, known as nitrosamines, including N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA), are potentially cancer-causing substances that can be generated when certain other chemicals and reaction conditions are present in the drug product manufacturing process.

Since that time, several more drug products in the same class as valsartan (angiotensin II receptor blockers, or ARBs), as well as ranitidine (a medicine used to prevent and relieve heartburn associated with acid indigestion and sour stomach, most commonly known by the trade name Zantac), have been found to contain small amounts of nitrosamines.

NDMA is a common contaminant found in water and foods including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of NDMA. The FDA does not expect NDMA 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 NDMA at-or-below the acceptable daily intake limit every day for 70 years is not expected to have an increased risk of cancer.

The FDA's response to the discovery of nitrosamine impurities in drug products has been a constant and comprehensive effort, supported by an internal working group led by a multidisciplinary team of chemists, toxicologists, physicians, pharmacists, communication specialists, investigators and analytical laboratory staff from across the FDA and in collaboration with global regulators. The agency is using a systematic approach to identify medicines with nitrosamines above acceptable daily intake limits and removing them from the market. Detailed information about nitrosamine impurities in medications, including information for patients, health care professionals, and industry, can be found on the FDA website.

The FDA has made consistent and significant progress in addressing nitrosamine impurities in medicines throughout 2019. The agency has better testing methods than ever before—improved technology that enables our scientists to detect even trace amounts of impurities in drug products. Adhering to the FDA's strict standards for safety, effectiveness and quality, our scientific teams make every effort to help keep the U.S. drug supply as safe as possible. The highlights below detail key actions taken in 2019.

"We remain steadfast in making sure we minimize risks to patients who rely on these medications … and ensure affected medications are removed from the U.S. supply chain … we're making significant advances in our efforts to protect patients from unnecessary exposure to these impurities."

Janet Woodcock, M.D., Director, CDER

ARBs

All FDA updates and announcements on ARB investigations, oversight, and recalls in 2019 are available online. Highlights of efforts addressing ARB impurities and testing include:

MARCH 1 | Update posted on ongoing investigation into ARB drug products including reports on finding a new nitrosamine impurity in certain lots of losartan and product recall. The recalled losartan tablets contain NMBA (N-Nitroso-N-methyl-4-aminobutyric acid), which is known to cause cancer in animals and is a potential human carcinogen. This was the first ARB recall resulting from the presence of NMBA—the third type of nitrosamine impurity detected in ARB medicines.

APRIL 4 | Statement issued by former FDA Commissioner Scott Gottlieb, M.D., and CDER Director Janet Woodcock, M.D, detailing FDA's response to the issue of drug impurities—seeking at all times to minimize risks to patients, ensure access to safe medicines or acceptable alternative therapies, and ensure all affected medications are removed from the U.S. supply chain.

AUGUST 28 | Statement from CDER Director Janet Woodcock, M.D. on FDA's ongoing efforts to resolve safety issue with ARB medications, including clarification of actual risk to patients, enhanced oversight of manufacturing data, and the expanding investigation.

Ranitidine

The full timeline of announcements, statements, and actions related to ranitidine products is available online. Key actions addressing NDMA impurities in ranitidine products include:

"When the FDA needs to demonstrate the quality and performance of a drug product, the agency employs a variety of novel analytical techniques. These techniques help to assess specific information about a drug or drug product, such as its chemical structure, purity, and quantity of active ingredient."

David Keire, Ph.D., Deputy Director, OTR

"The FDA is planning to test other drugs based on how they are made or structural chemical elements that may put them at risk for nitrosamine impurities."

David Keire, Ph.D., Deputy Director, OTR

SEPTEMBER 13 | The FDA announced that some versions of ranitidine—including some products commonly known by the brand-name Zantac—contain low levels of NDMA. The agency also released technical details regarding its testing methods.

SEPTEMBER 26 | An alert to health care professionals and patients was issued regarding a recall of certain dosage forms of over-the-counter (OTC) ranitidine tablets that may contain low levels of NDMA. The agency recommended that consumers taking OTC ranitidine consider using other OTC products approved for heartburn and gastric acid reflux.

OCTOBER 2 | Update issued noting that FDA is continuing to test ranitidine products from multiple manufacturers and is assessing the potential impact on patients who have been taking ranitidine. The agency also asked ranitidine manufacturers to conduct their own laboratory testing to assess NDMA levels in their ranitidine products and to send samples of ranitidine products to FDA to be tested by our scientists.

OCTOBER 28 | Alert issued to health care professionals and patients regarding three voluntary recalls of ranitidine. The agency recommended that consumers taking OTC ranitidine consider using other OTC products approved for their condition.

NOVEMBER 1 | Statement issued by Janet Woodcock, M.D., CDER Director, announcing the release of a summary of results after testing numerous ranitidine products. An announcement was also issued regarding FDA laboratory testing for presence of NDMA in ranitidine products, noting that NDMA had been observed in nizatidine (often known by its brand-name, Axid, also used for indigestion and gastric acid reflux). FDA posted laboratory results showing NDMA levels in all ranitidine and nizatidine samples tested to date. (The methods FDA used in the laboratory testing are available here.) The FDA found estimated risk from NDMA levels in ranitidine and nizatidine products to be similar to levels expected through consumption of common foods like grilled or smoked meats. Also posted were extensive questions and answers related to ranitidine.

NOVEMBER 8–22 | FDA maintained ongoing public communications regarding three different voluntary ranitidine recalls.

DECEMBER 4 | Update issued announcing that the FDA asked manufacturers of ranitidine and nizatidine products to expand their testing for NDMA to include all lots of the medication before making them available to consumers. If testing shows NDMA above the acceptable daily intake limit as established by the agency, the manufacturer must inform the agency and should not release the lot for consumer use.

For more information on the FDA's laboratory techniques to detect impurities in drug products, see CDER Scientists Use Modern Measurement Tools for Quality Assurance and Comparability of Complex Drugs.

Detecting Nitrosamines in Drug Products—FDA Innovations in Testing and Analysis

The FDA's Office of Testing and Research (OTR) within the Office of Pharmaceutical Quality in CDER is the front line for FDA's testing of drug products and drug substances for nitrosamine impurities. OTR has successfully developed and implemented methods to determine the presence of nitrosamine compounds. David Keire, Ph.D., Deputy Director, OTR, discusses nitrosamines in drug products, how FDA detects these impurities, and how the agency's innovations have enhanced laboratory analysis when looking for nitrosamine impurities.

How do nitrosamine impurities get into ARBs and ranitidine drug products?

For ARBs, the nitrosamine compounds were impurities related to the synthesis of the drug substance. For ranitidine, initial evidence points to NDMA being a breakdown product of the drug substance that can happen under certain manufacturing conditions. As reports and testing data come in from pharmaceutical firms and other regulators, we have followed each lead to verify if the information is relevant to U.S. marketed products that could reach consumers. Importantly, we also know that many drugs tested do not have any detectable nitrosamine impurities.

How many nitrosamine testing methods have the FDA labs developed? Were modifications needed when testing different drug products?

We have developed 10 methods capable of measuring seven nitrosamine compounds in eight ARBs or ranitidine. The initial tests were for NDMA. As subsequent nitrosamines were discovered or predicted, new methods were developed or modified to accommodate characteristics of the new drug product, drug substance, or nitrosamine. As each of these methods were validated, they were made available online to pharmaceutical companies. While in many cases the same method could be used for a new drug as was used for a drug that was tested earlier, modifications had to be made to the method for testing ranitidine because of different formulations or drug substance properties.

Have nitrosamine impurities likely always existed, but improved technology enables FDA labs to detect even trace amounts of these impurities in the drug products?

Analytical methods for detecting nitrosamine compounds were available as they are found in foods, beverages, and the water supply. However, because there was little precedent for the presence of excessive nitrosamines in drug products like the ARBs, specific targeted testing for nitrosamines like NDMA was not performed. Some of the screening tests often used in drug quality control could detect nitrosamines—if we were looking for nitrosamines. However, other methods not looking for nitrosamines lacked the sensitivity to measure nitrosamines at or near the levels of concern ("acceptable daily intake"). Current technology is much more sensitive and faster than ever before. While the presence of nitrosamines in the diet was widely known, improved technology has shown that they may have been present at low levels and undetected in drugs developed and approved with older test methods. The FDA is planning to test other drugs based on how they are made or structural chemical elements that may put them at risk for nitrosamine impurities.

Is the FDA working on additional nitrosamine tests or studies?

To test the hypothesis that ranitidine breaks down to NDMA in the stomach, FDA scientists collected laboratory data with ranitidine present under conditions that simulated human stomach gastric fluid. The results did not show any increase in NDMA under normal simulated gastric conditions. However, to assure that there is no other biologic mechanism that could form NDMA from ranitidine in humans, the FDA designed and plans to initiate a small trial involving humans. This important study should provide a definitive answer to the question of the chemical stability of ranitidine in the human body.

Are other classes of drugs susceptible to nitrosamine impurities?

Testing data collected from pharmaceutical firms, international regulatory partners, and the FDA has offered clues to factors that can lead to the formation of nitrosamines in the drug supply chain. Importantly, we also know that many drugs tested have no detectable nitrosamine impurities. However, with newer and more sensitive test methods for examining drug manufacturing processes and materials for nitrosamines, we expect there may be other drugs impacted. Recent research is also shedding light on which drugs are at higher risk, and the FDA is prioritizing a list of drugs with risk factors for testing. We expect more data will be available in 2020 to assess the extent of the presence of nitrosamines in the drug supply.

A timeline of FDA activities and significant events addressing opioid misuse and abuse going back many years is available here.

Continued Efforts to Address the Misuse and Abuse of Opioid Drugs

The misuse of opioid drugs is one of the most critical national public health crises of the last 20 years. Between 1999 and 2018, over 200,000 people died in the United States from overdoses related to prescription opioids. In one recent period between July 2016 and September 2017, opioid overdoses increased by 30 percent in 45 states. In the midwestern U.S. alone, opioid overdoses increased by 70 percent in the same time period. While it is encouraging to note that total drug overdose deaths in the United States dropped just over 4 percent from 2017 to 2018 – the first decrease in more than two decades – we still have much work to do as deaths from drug overdoses remain at historically high levels.

A key focus of FDA's work throughout 2019 was implementing the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act), passed on October 24, 2018. The Act provided the FDA with new authorities for confronting the opioid crisis, enabling the agency to support and facilitate the development of evidence-based opioid analgesic prescribing guidelines for acute pain, strengthening FDA and U.S. Customs and Border Protection (CBP) coordination and capacity and restricting entrance of illicit drugs, and safety-enhancing packaging and disposal.

The SUPPORT Act has enabled FDA to revise regulatory procedures to permit a mandatory recall for a controlled substance if there is a reasonable likelihood the drug could cause serious adverse health consequences or death, and to more vigorously promote the development of non-addictive drugs to treat pain. The FDA is also considering whether to use SUPPORT Act authority to require that opioids be dispensed with "disposal technologies" (for example, mail-back pouches) to help get unused medications out of home medicine cabinets. This might also help reduce the flow of opioid drugs at risk of "diversion"—opioids that find their way to the streets and other illicit venues for sale.

On February 26, the FDA announced the agency's 2019 policy and regulatory agenda for continued action to address the opioid epidemic. The agency's efforts are currently organized around four principal areas of effort: reducing misuse and abuse of opioids, supporting recovery from opioid use disorder (OUD) and reduction of overdose deaths, research and innovation in novel non-addictive pain treatments, and strengthening enforcement against illicit opioids. Actions, activities, and updates from 2019 are highlighted below.

Reducing Misuse and Abuse of Opioid Drugs

MARCH 27 | An FDA Commissioner's statement was issued on new steps to strengthen safety requirements aimed at mitigating risks associated with transmucosal immediate-release fentanyl (TIRF) products. The agency is pursuing efforts to continue to evaluate the effectiveness of Risk Evaluation and Mitigation Strategies (REMS) programs for opioid products, including methods for data collection and assessment tools.

APRIL 25 | The FDA launched *Remove the Risk*, an education campaign to help Americans understand the important role they play in removing and properly disposing of unused prescription opioids from their homes.

MAY 30 | The FDA issued a statement regarding the agency's request for information from the public on requiring fixed-quantity blister packaging for certain opioid pain medicines—an action that can help decrease unnecessary exposure to opioids. The agency is considering using new authority under the SUPPORT Act to mandate that certain oral dosage forms of immediate-release formulations of opioid analgesics (indicated for treatment of acute pain) be made available in short-duration packaging for dispensing in outpatient settings.

JUNE 11-12 | The FDA convened a public meeting to seek input on the clinical utility and safety concerns associated with the higher range of opioid analgesic dosing (both in terms of higher strength products and higher daily doses) in the outpatient setting in order to better understanding current clinical use and situations that may warrant use of higher doses of opioid analgesics.

DECEMBER 19 | The National Academies of Sciences, Engineering and Medicine announced publication of Framing Opioid Prescribing Guidelines for Acute Pain in January 2020. This report, commissioned by the FDA, addresses how evidence-based clinical practice guidelines for prescribing opioids for acute pain might help mitigate the opioid overdose epidemic. To meet this challenge, the report presents a framework to evaluate existing clinical guidelines for prescribing opioids for acute pain, recommends indications for which new evidence-based guidelines should be developed, and recommends a future research agenda to inform and enable healthcare organizations to develop and disseminate evidence-based clinical practice guidelines for prescribing opioids to treat acute pain indications.

The FDA requires Risk Evaluation and Mitigation Strategy (REMS) programs to ensure the benefits of a medication outweigh its risks. In regard to opioids, REMS program requirements help the agency strike a balance between reducing new cases of opioid use disorder (OUD) by decreasing exposure to opioids, while still allowing appropriate access to patients with a legitimate medical need for these medicines.

"The FDA remains committed to addressing this national crisis on all fronts, with a continued focus on decreasing exposure to opioids and preventing new addiction; supporting the treatment of those with opioid use disorder; fostering the development of novel pain treatment therapies; and taking action against those who contribute to the illegal importation and sale of opioid products."

Janet Woodcock, M.D., Director, CDER

Throughout 2019 the FDA continued to work with and support the non-profit Partnership for Drug-Free Kids/ Center on Addiction to expand outreach nationwide of an FDA-sponsored healthcare prescriber (HCP) opioid education campaign called "Search and Rescue." The campaign provides resources and tools to aid HCP opioid decisions, communications with patients, and prescribing practices, through paid and unpaid media outreach as well as collaboration with other organizations, including the American Medical Association Opioid Task Force, the American Society of Addiction Medicine, and Boston Children's Hospital. Expanded outreach included launch of a text-message program providing information about opioids to parents of children and teens who receive prescriptions for them. Between January 1 and October 31, 2019, visits to the campaign website reached nearly 115,000, more than double the number in 2018, including more than 21,000 downloads or active links to campaign materials.

Support Recovery from Opioid Use Disorder and Reduce Overdose Deaths

JANUARY 17 | Statement issued on the FDA's unprecedented efforts to support development of over-the-counter naloxone to help reduce opioid overdose deaths. The agency is seeking to work with industry partners who are interested in developing these OTC naloxone products.

FEBRUARY 6 | FDA In Brief issued after the agency finalized a new policy to encourage innovation and development of new buprenorphine treatments for opioid use disorder (OUD). The FDA is prioritizing new efforts to advance the development and use of safe and effective medications to treat OUD including new guidance aimed at supporting the development of novel medicines as well as novel medical devices such as digital health tools; advancing new policies to promote the adoption of safe and effective OUD treatments, and working with partner organizations/stakeholders to reduce the stigma associated with medications to treat OUD.

APRIL 19 | The FDA approved the first generic naloxone hydrochloride nasal spray, commonly known as Narcan, a life-saving medication that can stop or reverse the effects of an opioid overdose.

Nalaxone is a drug that can reverse the overdose effects of opioids, usually within minutes. Although any person administering naloxone should also seek immediate medical attention for the patient, wider availability of naloxone and quick action to administer it can save lives.

- Since naloxone is currently available only by prescription, or through a standing order that allows pharmacists to dispense the drug, a potential way to improve access is to make naloxone available for over-the-counter (OTC) sale.
- The FDA is actively working to facilitate development and availability of OTC naloxone products.
- OTC drug packaging includes the consumer-friendly Drug Facts Label (DFL). To encourage drug companies to enter the OTC market and increase access to naloxone, the FDA developed a model naloxone DFL with easy-to-understand pictograms on how to use the drug.
- This is the first time the FDA has proactively developed and tested a DFL for a drug to support development of an OTC product. Drug manufacturers can use this model labeling to obtain approval for OTC naloxone and increase its access, which in turn should jumpstart the development of OTC naloxone products to promote wider access to this critically important medicine.
- Extensive information on the agency's naloxone work, including consumer updates, Commissioner's statements, meeting minutes, and draft DFLs are available online.

Research and Innovation in Novel Non-Addictive Pain Treatments

SEPTEMBER 17 | A public meeting, Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction, was held where stakeholder input was heard on the approval process for new opioids. Stakeholders discussed how FDA might best consider the existing range of available therapies, among other factors, in reviewing applications for new opioids to treat pain. FDA also sought input on potential new incentives for industry aimed at fostering the development of new therapeutics to treat pain, as well as new treatments for addiction.

SEPTEMBER 30 | CDER's Office of Communications (OCOMM) awarded a contract for an opioid-related research project titled *An Exploratory Assessment of Substances Used as Adjuncts or Alternatives to Prescription Opioids* to better understand the knowledge, experiences, attitudes, perceptions and behaviors of consumers who currently use or recently used prescription opioids in conjunction with the following four substances: gabapentinoids, benzodiazepines, kratom, and cannabidiol (CBD). This study will involve 144 in-depth interviews with patients in inpatient treatment facilities across the U.S. to explore a number of questions, including who is using, misusing, and abusing these alternative and adjunct substances, how and why they are using them, how they are obtained, side effects and drawbacks, and substance use trajectories.

Currently, most states allow pharmacists to dispense naloxone with a *standing order* from the state health department physician. This allows a pharmacist to dispense naloxone without a prescription for an individual patient.

While abuse-deterrent opioids are not abuse- or addiction-proof, they are a vital step toward products that may help reduce abuse. The FDA fully supports efforts to better understand the impact of these products in the real-world setting and to discuss current data and methods for evaluating ADF products.

FDA is Encouraging Development of Prescription Opioids with Abuse-deterrent Formulations (ADFs) to Help Combat the Opioid Crisis

Previous research conducted by CDER's Office of Communications (OCOMM) found significant misunderstanding among health care providers about ADFs, in turn limiting prescribing of these drugs whose aim is to deter abuse of prescription opioids. Ongoing research is exploring and assessing the knowledge, attitudes, and behaviors related to ADFs among prescribers and dispensers/pharmacists. Findings from focus groups with opioid prescribers and pharmacists completed in 2019 will form the basis of the subsequent survey phase to begin in 2020 and an experimental phase to follow in 2021.

- Opioids with ADFs are designed to prevent—or make more difficult—actions such as crushing tablets to enable snorting, smoking, or intravenous (IV) injection.
- ADFs have physical or chemical properties intended to either hamper manipulation of a tablet, or make abuse of a manipulated product less rewarding.
- "Abuse-deterrent" does not mean a product is impossible to abuse or that abuse-deterrent properties fully prevent addiction, overdose, and death—but ADFs are a step toward products that may help reduce abuse.
- The science of abuse deterrence is relatively new, and both the formulation technologies and the methods for evaluating those technologies are rapidly evolving.
- The FDA supports the development of opioid medications with progressively better abuse-deterrent properties, which includes working with individual drug makers, developing testing methods for both innovator (often known as "brand name") and generic products, and publishing guidance on the development and labeling of abuse-deterrent opioids.

Strengthen Enforcement Against Illicit Opioids

FEBRUARY 12 | Statement issued describing the FDA's efforts to increase enforcement and interdiction targeting illegal, unapproved, counterfeit and potentially dangerous products shipped illegally through international mail facilities (IMFs). Tens of millions of packages are estimated to contain FDA-regulated products, and a high percentage of these products are illegal. The FDA's efforts to combat this public health emergency extend to stopping the spread of illicit opioids and further securing all aspects of the supply chain for legitimate medications, including opioids.

APRIL 2 | Illicit substances, frequently including opioids, can be purchased online with increasing frequency and ease. Illegal online pharmacies, drug dealers, and other criminals often use the internet due to significantly reduced risks of detection and legal repercussions. A vital step to address this public health emergency is the adoption of a more proactive approach by internet stakeholders to crack down on internet traffic in illicit drugs. Responding to this aspect of the opioids crisis, the FDA held the second Online Opioid Summit, expanding collaboration with internet stakeholders to crack down on illicit drugs sold online.

JUNE 19 | Announcement on the FDA's benefit-risk framework for evaluating opioid analgesics and announcing the issue of a draft guidance, Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework, which describes the application of the benefit-risk assessment framework the agency uses in evaluating applications for opioid analgesic drugs.

SEPTEMBER 30 | FDA and the Drug Enforcement Administration (DEA) issued first-of-its-kind joint warning letters to four online networks, operating a total of 10 websites illegally marketing unapproved and misbranded versions of opioid medicines.

In recent years 86 percent of packages suspected of containing FDA-regulated products and pulled for FDA review indeed contained illegal, illicit, unapproved, counterfeit and/or potentially dangerous drugs.

Easy online access to illicit opioids has emerged as an urgent public health concern.

- According to a 2015 study by Carnegie Mellon University, revenues from online illicit drug sales grew from between $15-17 million in 2012 to $150-180 million in 2015.
- A January 2018 U.S. Senate report established the ease with which average Americans can now purchase illicit opioids online.
- The National Association of Boards of Pharmacy found that when searching online for prescription opioids across the three major search engines, nearly 91 percent of the first search results led users to an illegal online drug seller offering prescription opioids.

The FDA remains committed to addressing the opioid crisis on all fronts. With a focus on decreasing exposure to opioids and helping prevent new cases of opioid use disorder (OUD), the agency is encouraging more appropriate prescribing, supporting the treatment of those with OUD and promoting the development of improved—and more inexpensive—forms of medications to treat OUD, fostering the development of novel pain treatment therapies that are not as addictive as opioids as well as opioids that are more resistant to abuse and misuse, and taking action against those who contribute to the illegal importation and sale of opioid products.

THE OPIOID EPIDEMIC BY THE NUMBERS

130+
People died every day from opioid-related drug overdoses[3] (estimated)

10.3 m
People misused prescription opioids in 2018[1]

47,600
People died from overdosing on opioids[2]

2.0 million
People had an opioid use disorder in 2018[1]

81,000
People used heroin for the first time[1]

808,000
People used heroin in 2018[1]

2 million
People misused prescription opioids for the first time[1]

15,349
Deaths attributed to overdosing on heroin (in 12-month period ending February 2019)[2]

32,656
Deaths attributed to overdosing on synthetic opioids other than methadone (in 12-month period ending February 2019)[2]

SOURCES

1. 2019 National Survey on Drug Use and Health. Mortality in the United States, 2018
2. NCHS Data Brief No. 329, November 2018
3. NCHS, National Vital Statistics System. Estimates for 2018 and 2019 are based on provisional data.

Ensuring Quality, Safety, and Effectiveness of Generic Drugs

The FDA's generic drug program has substantially increased the availability of affordable, high-quality drugs in the United States. There are more than 10,000 generic drugs currently approved, and 9 out of 10 prescriptions filled in the United States are for generic drugs. Generic drugs have saved the healthcare system over a trillion dollars in the past decade.

Increasing the availability of generic drugs helps to create competition in the marketplace, which helps reduce the cost of treatment. This makes medicines more affordable and increases access to healthcare for more patients.

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

- Active ingredients (the ingredients that treat your condition or symptoms)
- Strength
- Dosage form (for example: tablet, capsule, cream, patch, liquid)
- Route of administration (for example: oral, topical, inhalation or injection]
- Conditions of use
- Labeling (with certain exceptions)

OGD monitors and evaluates generic drug safety from the time a generic product is approved for marketing until it is no longer available for sale in the U.S.

Effective surveillance of generic drug safety is essential to making sure that FDA-approved generic drugs provide the same therapeutic effect and safety as brand-name drugs.

In 2019, OGD presented its scientific approach in conducting safety evaluations to several major stakeholder audiences, including:

JANUARY 28 | *Updates in Generic Drug Pharmacovigilance* presented at the Drug Information Association (DIA) Pharmacovigilance and Risk Management Strategies Conference.

JULY 17 | Generic Drugs—Bioavailability/Bioequivalence Trials Safety Reporting, a presentation at Electronic Submissions of Adverse Event Reports using International Committee on Harmonisation Standards public meeting (session II). This public meeting provided the pharmaceutical industry and other interested parties with information on the plans, progress, and technical specifications to upgrade electronic submission standards for premarket and postmarket safety surveillance programs managed by the FDA.

Safety Surveillance of Generic Drugs—OGD's Clinical Safety Surveillance Staff

OGD's Clinical Safety Surveillance Staff (CSSS) is a team of physicians, pharmacologists, pharmacists, and other scientists that perform and coordinate pre-approval and post-approval generic drug safety surveillance activities. The CSSS analyzes adverse event report content and trends from the FDA Adverse Event Reporting System (FAERS), follows generic drug distribution trends, and reviews serious adverse events from bioequivalence studies and periodic safety reports submitted by drug companies. The CSSS may also identify emerging safety issues through published literature, calls from patients or healthcare professionals to FDA's Drug Information call center, or information shared by pharmacies and drug safety focused organizations.

An example of the CSSS in action in 2019 involves the anti-diarrhea drug loperamide, with many generic versions available on the market. Despite the addition of a warning added to the medicine label and previous public communications, FDA continued to receive reports of serious heart problems and deaths with much higher than the recommended doses of loperamide, primarily among individuals intentionally misusing or abusing the product.

The CSSS was closely involved with and supported changes in loperamide tablet packaging to promote safe use, detailed in a Drug Safety Communication issued September 20, 2019, FDA Limits Packaging for Anti-Diarrhea Medicine Loperamide (Imodium) to Encourage Safe Use. FDA is continuing to work with manufacturers to use blister packs or other single dose packaging and to limit the number of doses in a package.

The CSSS continues to participate in the FDA task force that is addressing issues related to the presence of nitrosamine impurities in angiotensin II receptor blocker and ranitidine products.

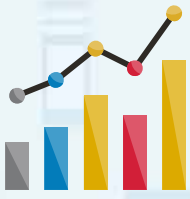
Postmarketing Surveillance of Generic Drugs

Once a generic medication is available for prescription or over-the-counter use, FDA continues to monitor its safety, efficacy, and quality.

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

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

Generic drug manufacturers will often propose changes to their products after they are approved; FDA evaluates these changes to ensure the drugs are still safe and effective.



FDA monitors FAERS (the FDA Adverse Event Reporting System) and reviews MedWatch reports to investigate concerns related to generic drug product quality and therapeutic inequivalence.

Visit www.FDA.gov/GenericDrugs to learn more.

U.S. FOOD & DRUG ADMINISTRATION

Safe Use Initiative: Collaborating to Reduce Preventable Harm from Medications

More than a million Americans are injured or killed each year due to preventable medication errors.

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. Too many people, however, 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 with foods that can increase the risk of side effects.

FDA believes that many of these medication-related risks are manageable if partners committed to the safe use of medications work together. FDA's Safe Use Initiative (SUI) works to create and facilitate public and private collaborations within the healthcare 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, healthcare professionals and professional societies, pharmacies and hospitals, and patients, caregivers, consumers, and their representative organizations.

SUI enables many of its collaborations through funding as well as actively participating in research projects that seek to reduce preventable harm from drugs, and maintains an open and continuous announcement to solicit research proposals.

SUI projects target many kinds of preventable medication-related harm from a range of approaches.

Projects Completed in 2019

Improving Safe Use of Fluoroquinolone Antibiotics through Development of an Innovative Educational Program. Fluoroquinolone (FQ) antibiotics have been among the most widely prescribed antibiotics in the world. However, reports of serious adverse events related to their use began to emerge several years ago. The FDA issued Drug Safety Communications in 2016, and updated the Boxed Warning that appears in the product labeling of all FQ drugs in 2016 and again in 2018. In a recently completed project, SUI partnered with WebMD to decrease potentially inappropriate FQ use in order to reduce adverse events. Physicians who prescribed more FQs than others in their specialty were provided with feedback about their prescribing relative to their same-specialty peers and/or educational materials regarding FQs. Over 11,000 physicians participated, and a statistically significant reduction in FQ prescribing was observed in physicians who were provided with individualized feedback or educational materials. Physicians who also enrolled in a separate continuing education module achieved the highest reduction in potentially inappropriate prescribing. Compared to non-participant controls, primary care physicians, urologists, and physician assistants and nurse practitioners all achieved significant reductions in FQ prescribing. WebMD also provided consumer-level education materials on FQs via their website and magazine. As a result of this project, an estimated 85,000 potentially inappropriate FQ prescriptions were never written.

FDA Health Care Professional Communication Project. Safety information changes over time. For doctors to provide the best care, they need the most current information—but they receive far more information than they have time to read and digest. This project sought to discover what sources of information and what formats are most likely to be read by physicians. A message about a recent FDA Drug Safety Communication was placed on Medscape, a state board of medicine newsletter, and a primary care specialty daily briefing newsletter. The message was available in both text and video formats. The number of individuals clicking on the message and the time spent on the site were measured. Medscape reached a higher percentage of physician viewers than the other two sources, but the rate of viewing was low for all three sources. Roughly 60.6 percent of physicians preferred the text format. The findings from this project will assist FDA in understanding how to best reach physicians with important safety information.

Pragmatic Risk Score for Severe Hypoglycemia. SUI partnered with Kaiser Permanente to develop a practical tool for health care providers to identify which diabetic patients may be at an elevated risk of hypoglycemia (low blood sugar). Using a set of six questions, patients can be stratified into high, intermediate, or low risk for severe hypoglycemia. The questions will help healthcare providers to identify the 11 percent of diabetics who are at high to moderate risk of experiencing severe low blood sugar. Work from the first phase of the project was published.

Projects Ongoing in 2019

Assessing the Impact of a State Intervention on High-Risk Prescribers. SUI is partnering with Brandeis University and the New York State Department of Health to reduce adverse events related to use of prescription opioids. This project will identify "high-risk" prescribers—those who write prescriptions for high doses or co-prescribe with medications which increase the risk of adverse events—and target these individuals for an educational intervention to facilitate safer prescribing practices. This project offers the potential to provide a cost-efficient model for reducing preventable harm from high-risk opioid prescribing practices that could be used by other states.

National Standardization of Intravenous (IV) and Oral Liquid Medications. In this SUI-funded project, the American Society of Health-System Pharmacists (ASHP) is working to reduce medication errors by creating standard concentrations of IV and oral liquid medications. A nationwide expert panel has proposed standards for IV medications while a second panel is focusing on liquid medications. Further work includes developing an app for oral liquid measurement, and disseminating and promoting the adoption of the new standards to decrease dosing errors.

New Projects in 2019

Core Elements of Anticoagulation Stewardship. 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 because they can be challenging for health care providers to manage. This project aims to improve care for anticoagulation patients by identifying best practices in quality and safety, and by helping healthcare providers identify areas where they can implement these strategies. The project will produce three important documents, including one to identify best practices in the care of anticoagulation patients, a health care provider self-assessment tool, and a report to identify and prioritize gaps in current regulations, standards, quality measures, and treatment guidelines, and provide recommendations from subject matter experts to guide future enhancements.

Manganese Contamination in Neonatal Parenteral Nutrition. Manganese (Mn), a trace element in neonatal parenteral (given by IV) nutrition, is typically added to parenteral nutrition (PN) in a multi-trace element mixture. However, due to Mn being present as a contaminant in other PN ingredients, infants typically receive higher than needed doses. Known to deposit in the neonatal brain, Mn may have an effect on neurodevelopmental outcomes. This project will test 18 PN components to identify contaminant sources of Mn. In the second phase, a randomized trial of 20 infants will test whether a "no Mn added strategy" results in more appropriate doses of Mn (as evidenced by normal Mn levels). This pilot project could decrease a potential harm related to PN and improve the care of premature infants, a highly vulnerable population.

Compounded Drugs: Continuing Oversight, Policy Development, and Stakeholder Outreach

Human drug compounding is generally a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, 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 medical need for certain patients, they also can present a risk to patients.

- ✓ **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.**

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, FDA has developed a novel approach to engage outsourcing facilities and help them produce the highest quality drugs.

The Compounding Quality Center of Excellence, launched in 2019, is designed to enhance collaboration with, and provide educational programs for, outsourcing facilities with the goal of improving the overall quality of compounded medicines.

Through the Center of Excellence, FDA will explore new ways to engage and collaborate with outsourcing facilities, including 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.

FDA also worked in 2019 to advance policy priorities related to drug compounding, including development of the statutorily required lists of bulk drug substances (also known as active ingredients) that compounders and outsourcing facilities can use to compound drugs. (These lists are also known as the "503A bulks list" and the "503B bulks list" after sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, which specify the criteria under which certain compounders may compound drug products using bulk drug substances.)

The agency placed six bulk drug substances on the 503A bulks list of substances that compounders can use to compound drugs through a final rule. This rule also identifies four bulk drug substances not included on the 503A bulks list and therefore cannot be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act. FDA also issued a Federal Register notice identifying nine bulk drug substances the agency considered and is proposing not to include on the 503B bulks list.

What is the difference between 503A and 503B compounders?

Section 503A of the FD&C Act …

- addresses compounding by a licensed pharmacist in a state-licensed pharmacy, or federal facility, or by a physician. These compounders are limited to compounding medications to fill individual patient-specific prescriptions, among other conditions.

Section 503B of the FD&C Act …

- addresses outsourcing facilities—a category of compounders established in 2013 by the Drug Quality and Security Act. Outsourcing facilities are inspected by FDA according to a risk-based schedule and are subject to increased quality standards.

FDA worked closely with our partners across the agency throughout 2019 to take regulatory and enforcement actions targeting compounded drugs with the greatest potential to cause harm, including:

- 102 inspections conducted
- 19 warning letters issued advising compounders of significant violations of federal law
- 38 letters issued referring inspectional findings to state regulatory agencies
- Consent decrees of permanent injunction obtained for four compounding pharmacies, in collaboration with the Department of Justice

Other resources related to human drug compounding can be found online at FDA.gov:

- Compounding inspections, recalls, warning letters, and related press releases are here.
- Compounding Risk Alerts are here.
- Consumer and Health Care Professional Information is here.

Common questions and answers related to drug compounding are available here.

Communicating Drug Safety: Global Outreach Through Diverse Tools and Technologies

CDER's Office of Communications (OCOMM) supports FDA's mission to protect and promote public health through a broad range of communications tools and technologies. Throughout 2019, OCOMM has 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 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
- Conduct risk communications research

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

Across all Drug Safety Communications (DSCs), online visitors spent an average of four minutes on DSC content. In comparison, most users generally stay on websites for less than 15 seconds.

Communicating Drug Safety Across Multiple Audiences

Drug Safety Communications (DSCs) provide updates and critical new and evolving information for patients, caregivers, pharmacists, healthcare providers, and the public, regarding potential risks of FDA-approved drugs. DSCs address urgent issues affecting a large number of patients, describe potentially serious or life-threatening adverse events or other cautions related to use of a drug or class of drugs, and contain actionable recommendations for patients and health care professionals.

The DSC home page is consistently one of the most visited pages on the FDA's web site. These key safety messages are also broadly circulated through many other channels, including listservs, email newsletters, social and traditional media, podcasts, as well as targeted outreach to media, healthcare professionals, advocacy groups and other stakeholders. Throughout 2019, DSC information was reported by the Associated Press, CNN, NBC News, Wall Street Journal, Bloomberg News, New York Times, and Washington Post.

Nine DSCs were issued in 2019, generating nearly 200,000 unique pageviews on the DSC website. ("Unique pageviews" refers to the number of times a visitor to the DSC website viewed the page one or more times.)

Among the DSCs issued, several were high-profile issues, including:

- Breathing difficulties associated with the widely-prescribed nerve pain medicines gabapentin and pregabalin
- Uncontrolled pain, psychological distress, withdrawal symptoms, and suicide resulting from sudden discontinuation or rapid dose decrease of opioid pain medicines
- Injuries caused by sleepwalking from taking certain prescription insomnia medicines
- Increased risk of death with the gout medicine febuxostat (Uloric)

DSCs issued in 2019 were widely shared via social media on FDA's Facebook page, Twitter feed, and LinkedIn page. LinkedIn—with a greater potential for specifically targeting healthcare professionals—saw 6,019 "click-throughs" to the full DSC. Across all DSCs issued during the year, visitors spent an average of four minutes on DSC content. In comparison, most users generally stay on websites for less than 15 seconds.

Drug Safety Podcasts provided emerging safety information about drugs in conjunction with the release of Drug Safety Communications. Nine podcasts

issued in 2019, and are available online and in Apple Podcasts as FDA Drug Information Updates.

Drug Information Webinars offer free, live, online continuing education for physicians, physician assistants, nurse practitioners, nurses, pharmacists, and pharmacy technicians. The webinars often center on drug safety or safety-related topics. In 2019, *An Overview of Pharmacovigilance in the FDA Center for Drug Evaluation and Research* was presented on March 26, and remains online and available to interested professionals.

Responding to Public Inquiries

Public inquiries are received via phone, email, letters, and through social media platforms such as Facebook and Twitter. Expert responses are developed and facilitated by a team of pharmacists, nurses, and other health professionals who field questions from consumers, healthcare professionals, journalists, research organizations, non-profits, regulated industry, other government agencies, and academia, as well as queries from international stakeholders in government and research institutions.

In June 2018 the FDA learned that certain generic versions of valsartan, a high blood pressure and heart failure drug, contained unexpected impurities known as nitrosamines, which are potentially cancer-causing substances.

- Since that time, several more drug products in the same class as valsartan, as well as ranitidine (a medicine used to prevent and relieve heartburn and acid indigestion, most commonly known by the trade name Zantac), have been found to contain small amounts of nitrosamines.
- In the first three quarters of 2019, OCOMM's web team charted over two million unique pageviews on www.fda.gov related to nitrosamine impurities, with online visitors searching for and viewing FDA updates, press releases, and recall notifications. The drug information team responded to nearly 10,000 nitrosamine-related inquiries from patients, health professionals, academicians, and consumers, received by mail, email, phone, and via social media.

FDA received and managed over 60,000 public inquiries between January 1 and September 30, 2019.

PUBLIC INQUIRIES MANAGED BETWEEN JANUARY 1-SEPTEMBER 30, 2019

Phone	42,420
Email	16,288
Letters	501
Social Media	842*
TOTAL	60,051

** Facebook and LinkedIn*

TOP 10 PUBLIC INQUIRIES

Nitrosamines	9,558
Opioids	2,475
Personal Import	1,955
Investigational New Drugs	1,519
Drug Registration and Listing	1,492
Expanded Access / Right to Try	1,366
Clinical Trials	1,176
Marijuana/CBD	1,161
Drug Shortages	1,036
Import/Export	903

2019 WEB TRAFFIC

TRAFFIC VOLUME	SESSIONS*
Desktop	11,930,306
Mobile	8,029,191

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

TRAFFIC SOURCES	% OF SESSIONS
Search Engines	58
Referrals	20
Direct (URLs)	16
Email	4
Social Media	2

TOP 10 GOOGLE SEARCHES

1.	Recalls
2.	Medication Disposal
3.	REMS
4.	Importing
5.	Losartan Recall 2019
6.	Zantac Recall 2019
7.	Expired medicine
8.	Ranitidine Recall
9.	National Drug Code lookup
10.	Drug Shortages

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, and custom-designed flow-charts, posters, infographics, and illustrations.

The online communications team also maintains web content, including drug safety information and safety-related regulatory policy documents on FDA webpages, manages public databases, and develops web and mobile applications (including optimizing applications for viewing formats such as smart phones and tablets).

The metrics displayed below depict the extent of online engagement between January 1 and September 30, 2019, including the ten most viewed CDER web pages—collectively accounting for over five million online visits—and the topics, questions, and documents generating the most online traffic for the reporting period.

Also tracked are trending topics on social media, as well as the leading media newsfeed topics, offering FDA leadership and senior managers a clear picture of the key issues stimulating significant public interest and, over time, which safety-related issues are searched for, are subjects of news stories and other informational outlets, are reported by secondary sources, and are carried via newsfeeds and social media.

TEN MOST VIEWED CDER PAGES

	Unique Pageviews*
1. Drug Recalls	1,409,032
2. FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan	853,938
3. Drug Approvals and Databases	807,350
4. Search List of Recalled Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan	603,006
5. FDA Updates and Press Announcements on NDMA in Zantac (Ranitidine)	554,712
6. Disposal of Unused Medicines: What You Should Know	551,033
7. National Drug Code Directory	367,029
8. Guidances (Drugs)	244,262
9. FDA's Assessment of Currently Marketed ARB drug products	223,667
10. Drug Safety and Availability	198,260

* *Number of sessions during which the page was viewed one or more times*

Social Media Engagement

The OCOMM Social Media team has significantly expanded CDER's communications outreach by "meeting people where they already are" with presences on numerous social media platforms, including Facebook, Twitter, YouTube, and LinkedIn.

Drug safety information is now actively pushed to over 600,000 FDA Facebook followers in the U.S., and over 250,000 Twitter 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" to obtain real-time feedback on FDA actions and decisions.

The team also oversees "live tweeting" of meetings and workshops, providing highlighted meeting content to many more people than those able to attend in person. Live tweeting (including "Twitter Chats") also positioned FDA's drug and drug safety subject matter experts at the top of trending topics on social media platforms.

In 2019 the Social Media Team:

- Actively pushed FDA information to nearly 260,000 followers on Twitter (708 tweets), over 600,000 followers on Facebook (223 posts), and over 100,000 subscribers on our Drug Information Listserv (305 messages sent), generating over 480,000 URL "click-throughs" to FDA content.
- Gained over 13,000 new followers on Twitter and nearly 2,000 new Listserv followers.

SOCIAL MEDIA OUTREACH

FACEBOOK	
Facebook followers	642,321
Posted content	223
Replied to comments	572
Public Likes/Shares	35,688
LINKEDIN	
Total followers	311,181
Small Business and Industry Assistance (SBIA) Showcase page	7,034
Global Alliance of Drug Information Specialists (GADIS)	814
TWITTER	
Total followers	259,168
Tweets	699
Retweets	7,077
Likes	10,468

A sunscreen quiz was launched on Twitter and Facebook to educate stakeholders on sun safety and proper use of sunscreens. FDA identified areas where additional educational outreach was needed which we will take into consideration when promoting sunscreens in the future.

TRENDING ON SOCIAL MEDIA*

1. ALS	447,175
2. Sunscreens	294,603
3. Kratom	283,642
4. Opioids	144,287
5. Expedited Review	98,548
6. Drug Pricing	95,561
7. Benzodiazepine	87,738
8. Biosimilars	53,882
9. Off-label marketing	28,340
10. Drug Shortages	24,298

** Reported by Brandwatch*

TOP MEDIA NEWSFEED TRENDING TOPICS ONLINE MENTIONS*

1. Expedited Review	68,922
2. ALS	51,566
3. Biosimilars	28,809
4. Off-Label Marketing	25,391
5. Drug Pricing	14,492

** Reported by Brandwatch*

- Leveraged expanded social media outreach for launch of the Remove the Risk opioid disposal campaign, BESAFE Rx campaign relaunch, Biosimilars campaign, and Sunscreen campaign.

The charts above detail the range of social media outreach in support of drug safety messaging and engagement in 2019. The Social Media Trending Topics and Top Media Newsfeed Trending Topics reflect numbers reported by an online and social media monitoring service that "crawls" more than 90 million publicly available websites.

Drug Safety-related Labeling Changes

"Labeling" (also known as the "package insert") is the detailed prescribing information that appears on the printed insert that accompanies a drug, either inside the product box, folded and glued to the bottle lid, or given to the patient by the dispensing pharmacists. Labeling for all medicines is also available online.

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, FDA may require a Drug Safety-related Labeling Change. The drug safety-related labeling changes (SrLCs) database includes safety labeling changes required or ordered by FDA per legislation, as well as labeling changes that are voluntarily submitted by product sponsors.

The database makes safety information available in close to real time, and is easily searched through a user-friendly portal for stakeholders such as health care providers, pharmacists, patients, and health IT and information vendors. Stakeholders accessing the database offer valuable feedback throughout the year that assists FDA in continually upgrading how safety labeling information is organized and presented.

The SrLC platform continues to keep pace with rapid developments in web and database technologies and refinements. In 2019, version 2.0 of the drug safety label database was released, offering improved search functions for end users while continuing to provide approved safety-related labeling changes from January 2016 forward. (Data prior to January 2016 will continue to be available on the MedWatch website.)

SrLCs are made in one or more of the sections of a drug's label. Nearly 5,000 SrLCs were made in 2019, a 13 percent increase over 2018.

Adverse Reactions	877
Boxed Warnings	232
Contraindications	388
Drug Interactions	552
Patient Counseling information and/or Medication Guides	892
Use in Specific Populations	908
Warnings and Precautions	952
TOTAL	**4,801**

Risk Communications Research

OCOMM undertakes a range of research studies, including pharmacovigilance studies conducted through social media monitoring and data analysis to gather real-world data and evidence related to numerous drug safety-related issues.

- The goal of risk communications research is to enhance understanding of our stakeholders' knowledge, perceptions, needs, desires, and behaviors related to a variety of drug and drug safety issues.
- Findings from these studies provide detailed and comprehensive evidence to inform policy, regulatory, and communication decisions aimed at enabling healthcare professionals, patients, and the public to make informed health decisions.

Highlights of 2019 research programs and projects include:

- **Exploration and assessment of health care prescribers' and pharmacists' knowledge, attitudes, and understanding regarding opioid analgesic abuse-deterrent formulations (ADFs)**. Findings from focus groups with opioid prescribers and pharmacists completed in 2019 will form the basis of the subsequent survey phase to begin in 2020.
- **Research on proactive pharmacovigilance through social media monitoring and analysis** identified new and emerging topics and shifting trends related to prescription and OTC drugs—particularly concerning prescription opioids and substances that may be used as adjuncts or alternatives to them—and to understand the social context surrounding substances being discussed in publicly available online discussions and on social media. OCOMM developed a series of monthly social media research reports in 2019, and a contract was awarded for a social media monitoring platform that will enhance OCOMM's ability to undertake this type of research.
- Several **message testing studies** included assessments of a patient-prescriber agreement form for Transmucosal Immediate-Release Fentanyl (TIRF); web content for FDA's BeSafeRx campaign to raise awareness of the dangers of buying prescription medicines from fake online pharmacies, and a notecard about safe disposal of unused medicines.

Publications

Patients' Knowledge of Key Messaging in Drug Safety Communications for Zolpidem and Eszopiclone: A National Survey, *Journal of Law, Medicine, and Ethics*, September 2019.

Multimodal Analysis of FDA Drug Safety Communications: Lessons from Zolpidem. *Drug Safety, Drug Safety*, November 2019.

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
www.fda.gov