FDA | U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY PRIORITIES 2018

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Introduction

The National Center for Health Statistics reports that, in 2015, the number of prescription drugs ordered or provided during patient visits at doctor's offices approached 4 billion—a number that continues to rise. While this represents rapid advances in medical research and health care that are making more and better medicines available to people in need, the inherent risks related to an ever-growing national exposure to prescription drugs are as diverse as they are complex. No medicine is entirely without risk, and adverse events (side effects), the 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.

Recognizing and promptly addressing drug-related safety concerns is a core element in the mission of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). **CDER Drug Safety Priorities 2018** details the range of CDER's safety work and provides updates on the year's safety-related achievements and milestones.

This year's report describes established and emerging safety programs across the Center, including the FDA Adverse Event Reporting System (FAERS), the Sentinel System (our electronic safety surveillance system), the Safe Use Initiative that works to mitigate preventable harm from medications, and our ongoing activities to help address the national opioid crisis. In some of our newest activities, CDER is investigating the use of mobile apps, social media, and electronic prescribing data to better understand drug safety risks while also ensuring patient privacy. Our response to the discovery of impurities in a widely used high blood pressure drug is detailed on page 16, vividly illustrating CDER's multi-tiered drug safety enterprise in action.

Managing drug safety problems as they arise requires interdisciplinary scientific teams working to understand the nature of each unique problem and implement solutions leading to the necessary regulatory actions that help to protect the public health. **CDER Drug Safety Priorities 2018** offers a portrait of several of our critical drug safety programs and initiatives, and describes the wide-ranging and collaborative nature of our safety work as reflected through some of the year's key safety-related milestones and achievements.
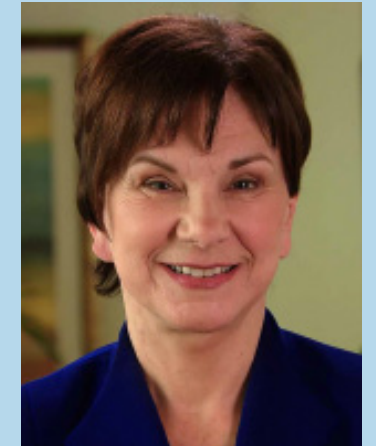
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology's Four Core Functions

1	**Pharmacovigilance**	• Detect and assess potential safety-related concerns and issues for all marketed drug and therapeutic biologic products
2	**Pharmacoepidemiology**	• Review drug safety-related epidemiologic study protocols and study reports required of manufacturers as post-marketing requirements • Develop and conduct safety-related observational epidemiological studies, often in conjunction with outside collaborators
3	**Medication Error Prevention and Analysis**	• Review proposed proprietary drug names and proper name suffixes • Review of labels and labeling, including Instructions for Use • Review Human Factors study protocols and reports • Medication error signal surveillance and analysis
4	**Risk Management**	• Determine the need for risk evaluation and mitigation strategies (REMS) • Review proposed REMS • Review REMS assessments and REMS modifications

Safety Surveillance and Oversight of Marketed Drug Products

The Office of Surveillance and Epidemiology (OSE) within FDA's Center for Drug Evaluation and Research (CDER) evaluates and characterizes the safety profiles of drugs available to the American public using a variety of tools and disciplines. OSE is committed to continuing the modernization of safety surveillance of drug products, maintaining a system of post-marketing surveillance and risk assessment programs to identify and characterize adverse events and medication errors that may not have appeared during the drug development and approval process. OSE staff also review strategies to minimize the risks of certain drugs and assessments of the effectiveness of those strategies.

OSE's four core functions—pharmacovigilance, pharmacoepidemiology, medication error prevention and analysis, and risk management—operate across multiple disciplines to review and assess drug product safety.

Through October 2018, OSE has supported 6,159 safety reviews, of which 2,964 were part of biweekly surveillance, across a variety of different product applications and amendments. These reviews are typically conducted by multiple OSE divisions across a range of scientific and technical specialty areas—but all are included in one or more of OSE's core functions.

The selected projects described below highlight OSE's ongoing efforts to continue its work in modernizing drug safety throughout 2018.

Medication Error Prevention and Analysis

As part of its drug safety program, FDA analyzes proposed proprietary names (commonly referred to as brand names) to ensure they do not look or sound like the names of other drugs. 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 confusion with the names of marketed products—both in how names sound and how they appear when written. The POCA system is comprised of two applications, a search engine component and a prescription simulation component called RX Studies.

In 2018:

• FDA continued to use the POCA search engine in conducting proprietary product name reviews, to evaluate written and phonetic similarities of a proposed proprietary name to other proprietary names.

• New POCA tool features enable reviewers to compare a proposed suffix (the last few letters in a drug product's proposed name) to existing drug names to avoid proposed suffixes that would create similarity to other drug names. The search engine can also conduct target comparisons of proposed suffixes to the existing suffix component of biological nonproprietary names. These automated features are expected to improve review efficiency for both FDA and the pharmaceutical industry.

Biological products are a diverse category of products that may be produced through laboratory-based biotechnology in a living system such as a microorganism, plant cell, or animal cell. Examples of biological products include therapeutic proteins (such as filgrastim, a bone marrow stimulant for use in cancer patients), monoclonal antibodies (proteins that can enhance natural immune function to fight cancer), and vaccines.

- OSE revised the RX Studies System to assess potential errors with proposed proprietary names using a Computerized Prescriber Order Entry System (CPOE). This will better capture the type of errors being reported due to the use of electronic prescribing.

  ◦ The RX Studies application enables the design and conduct of studies on proposed proprietary drug names. Handwritten and verbal samples are distributed through the RX Studies application to volunteer health professionals in the FDA. Volunteers reply with their interpretations of the proposed proprietary names within the RX Studies application. Responses are then analyzed to see if proposed drug names might cause confusion due to phonetic or written similarities with existing drug names.

  ◦ RX Studies does not currently address the creation and use of CPOE in inpatient or outpatient environments—meaning that assessments and regulatory decisions concerning proposed proprietary drug names are not necessarily reflective of the current prescribing environment. To fill this gap, OSE developed a computerized method to determine written and phonetic similarities between proposed proprietary drug names that might increase the risk of confusion and medication errors in the CPOE environment. This modification allows OSE to design CPOE simulations that align with recent advances in industry and practice—helping to simulate real world situations for the assessment of potential name confusion, and simulate medication prescribing errors in CPOE systems.

JUNE 19-20, 2018
Global Regulators Meeting on Safety of Drug Container Labels

- Container labeling is an important aspect of product safety review, to reduce and prevent the potential for medication errors.

- OSE led a global summit for international regulators on drug container labeling and packaging safety, an event cosponsored by FDA and the International Medication Safety Network (IMSN), an alliance of patient safety organizations and advocates from over 20 countries. The World Health Organization (WHO) attended the meeting in alignment with the main theme of the WHO's Global Patient Safety Challenge: Medication Without Harm.

- The meeting brought together FDA staff, representatives of other drug regulatory agencies, IMSN members, and invited speakers for sharing of experiences and discussion of ways to improve medication safety globally.

  ◦ Some international regulators have already implemented packaging and labeling changes, achieving some success in reducing medication errors related to approved labeling.

  ◦ One of the meeting's goals was to move forward in creating a minimum set of best practices for labeling and packaging aimed at reducing medication errors. Another goal was to promote the use of safe technologies to reduce medication errors, with discussion targeting the need for an international barcode standard.

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 is minimizing use-related hazards and risks and then confirm that these efforts were successful and users can use the device safely and effectively.

Per the Prescription Drug User Fee Act reauthorization for fiscal years 2018-2022 (commonly known as PDUFA VI), FDA committed to establish submission procedures for Human Factors protocols no later than September 30, 2018. Beginning in October 2018, FDA will review and provide comment on the protocols for Human Factors studies of combination drug-device and biologic-device products within 60 days.

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 or "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.

- OSE updated and modernized internal databases to accommodate Human Factors activities.

- OSE published draft guidance in September, intended to assist sponsors of drug and biological products that are subjects of product reviews. The guidance describes submission procedures for human factors information submitted to FDA. By standardizing procedures for human factors submissions, FDA hopes to help sponsors streamline the submission process.

Risk Management

FDA approved the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) on September 18, 2018, which applies to all opioid analgesics intended for outpatient use. The REMS program requires that training be made available to all health care providers who are involved in the management of patients with pain, including nurses and pharmacists.

Also in September, FDA approved the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain, as well as safety labeling changes that require companies to include new safety information regarding the Opioid Analgesic REMS in the *Boxed Warning* and *Warnings and Precautions* sections of prescribing information.

FDA issued two new guidances that relate to Shared System (SS) REMS in 2018. A SS REMs encompasses multiple prescription drug products and is developed and implemented jointly by two or more product sponsors. This provides a single portal for REMS participants to engage in and undertake the activities of the program. Learn more about SS REMS here.

The first guidance, Development of a SS REMS, provides general recommendations for industry on the development of a SS REMS, whether voluntary or required. This guidance provides information about the benefits that SS REMS may provide, and the process for developing them among multiple prescription drug products (including biological products). In providing clarity on the development process for SS REMS, FDA can allow for a better planning process related to REMS development while also facilitating the development of SS REMS.

The second guidance, Waivers of the Single Shared System REMS Requirement, describes the factors FDA will consider in evaluating a request for a waiver of the single shared system requirement.

FDA Adverse Event Reporting System Public Dashboard

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

Improving data access and transparency are core concepts underlying the work of OSE 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. At the time this report is issued FAERS data is current through September 30, 2018.

The Sentinel System

If a potential safety concern is identified in FAERS, further evaluation is performed, which might include conducting studies using other large databases, such as those available in the Sentinel System.

The Sentinel System is sponsored by the FDA to proactively monitor the safety of FDA-regulated medical products and complement FAERS safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multifaceted effort to develop a national electronic system. Sentinel collaborators include data and academic partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise.

Sentinel monitors drug safety by leveraging data across health care databases (with care taken to protect personal health information). Sentinel analyzes emerging risks associated with FDA-regulated medical products, enabling FDA to assess medical product safety under real-world conditions. Sentinel complements existing FDA post-marketing monitoring capabilities, and allows evaluation of safety issues more rapidly than has been possible in the past.

Sentinel's distributed data approach allows its data partners to maintain physical and operational control over electronic data in their existing databases through a standardized data structure called the Sentinel Common Data Model. 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.

The Sentinel System supports many safety inquiries, including but not limited to those related to medication errors, risk mitigation strategies, generic drugs, and pregnancy safety. The Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program allows public and private entities access to the Sentinel System. In addition, the Sentinel Common Data Model and tools for querying the data are publicly available on the Sentinel Initiative website.

2018 Sentinel System Updates

FEBRUARY | The Tenth Annual Sentinel Initiative Public Workshop brought together stakeholder communities to discuss a variety of topics on active medical product surveillance and current and emerging Sentinel projects. This year, FDA expanded the Sentinel Annual Meeting to include training on the Sentinel System's analysis tools, which addressed advanced topics including Sentinel's analytic capabilities and methods of identifying unexpected safety concerns. Recordings of the presentations are available at the Workshop website.

APRIL | An Industry Day event was held to address the public in response to a Request for Information (RFI) issued by FDA in December 2017 in anticipation of the third Sentinel Contract. FDA outlined the goals of the third five-year contract and hosted approximately a dozen potential contractors who responded to the RFI and shared their scientific capabilities and solutions. The next contract for the Sentinel Initiative is set to be awarded in Fiscal Year 2019.

MAY | The Duke Margolis Center for Health Policy led a workshop in collaboration with FDA to consider potential opportunities to improve the efficiency of outcome validation in the Sentinel System, particularly as it relates to the Active Post-Market Risk Identification System (ARIA). ARIA represents a set of querying tools combined with electronic health care data in the Sentinel Common Data Model to conduct safety assessments. The agenda, meeting summary, and presentations can be found here.

JULY | A public webinar took place in cooperation with the Duke Margolis Center for Health Policy on planned next steps to advance the Sentinel System by exploring how innovative technologies such as natural language processing, machine learning, and computable phenotyping could support more efficient and automated processes.

DECEMBER | A public workshop explored opportunities to implement signal detection capabilities in the Sentinel System. To continue advancing and modernizing the Sentinel data infrastructure, FDA sought broad stakeholder input on methodological approaches for signal detection, as well as the opportunities and challenges to implement these approaches in Sentinel's distributed data network. Stakeholder input received at this workshop will further inform the agency's thinking around these priority issues and support strategic planning in the Sentinel System.

Real-World Evidence and Real-World Data in Drug Safety Surveillance

Real-world data (RWD) and real-world evidence (RWE) play an increasing role in health care decisions.

- Real-world data comes from many sources—not only electronic health records, but also claims and billing activities, disease registries, patient-related activities in out-patient or in-home settings, and mobile health devices.

- Over the past decades, the use of computers and other electronic tools to gather and store massive amounts of health-related data has seen exponential increase. This data holds potential to allow us to better design and conduct clinical trials in the health care setting to answer questions previously thought infeasible. With the development of sophisticated, new analytical capabilities, we are better able to analyze these data and apply the results of our analyses to medical product development, safety evaluation, approval for marketing, and postmarket safety oversight.

- The health care community can use these data to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice.

- Medical product developers are using RWD and RWE to support clinical trial designs and observational studies to generate innovative treatment approaches.

"Real-world data consists of data relating to patient health status and/or the delivery of health care collected from a variety of sources … by using this information, we can gain a deeper understanding of a medical product's safety and benefits, its additional treatment implications, and its potential limitations."

Scott Gottlieb, M.D., FDA Commissioner

> **"By better leveraging real-world data, we can enable more efficient medical product development by integrating greater complements of safety and benefit information gleaned from clinical care. This is especially true when it comes to our important obligation to continue to evaluate products in the postmarket setting."**
>
> Scott Gottlieb, M.D., FDA Commissioner

RWD/RWE 2018 Activities

JUNE 10 | FDA Budget Matters: A Cross-Cutting Data Enterprise for Real-World Evidence posted online. Dr. Scott Gottlieb, FDA Commissioner, noted that FDA's Fiscal Year 2019 Budget request seeks to establish the building blocks and data assembly for an interoperable real-world data platform that will allow different groups to meaningfully share data. FDA's overall goal is the creation of a national utility that can be accessed by qualified research partners to inform a host of important clinical questions.

AUGUST 28 | FDA and Sentinel System scientists published a paper describing the first use of artificial intelligence technologies in the Sentinel System to identify cases of anaphylaxis, a serious allergic reaction that sometimes occurs after treatment with drugs. This paper explores a major challenge in the use of RWD for assessing drug safety: ensuring that health outcomes can be accurately defined using the data available in real-world settings. Evaluating Automated Approaches to Anaphylaxis Case Classification using Unstructured Data from the FDA Sentinel System was published in *Pharmacoepidemiology and Drug Safety*.

SEPTEMBER 19 | Remarks by FDA Commissioner to the National Academy of Sciences on the Impact of Real-World Evidence on Medical Product Development.

Sources of Real World Data: Electronic health records, insurance claims, patient registries, digital health applications.

Real World Evidence: Clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of real world data.

Real World Data: Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

NOVEMBER 7 | In order to allow researchers and developers to customize and use the newly created MyStudies app, FDA posted links to computer source code and a roadmap. MyStudies is designed to facilitate the input of real-world data directly by patients. A whitepaper describes the MyStudies app in detail, including concept, development methods, design, and testing.

The MyStudies app is an example of FDA using technology to bridge initiatives and respond to stakeholder feedback by:

- Expanding clinical information available for clinical trials and studies while directly capturing the perspective of patients—patients can securely enroll and participate in large scale clinical trials or registries involving multiple health care systems or data sources.

- Publicly releasing the source code and documentation so the app and patient data storage system can be reconfigured and rebranded by other organizations conducting clinical research.

- Aiding researchers and industry in collecting real-world patient-level data that, when linked to existing electronic health data, will promote efficiencies in drug development and drug safety monitoring processes.

NOVEMBER 19 | Harnessing Real-World Evidence for Safety and Innovation, remarks by the FDA Commissioner at a public meeting sponsored by the Reagan-Udall Foundation for the FDA, to discuss Expanded Access Programs and identify the challenges and opportunities in utilizing real-world evidence from these programs for regulatory decisions.

DECEMBER 6 | Framework for FDA's Real-World Evidence Program issued with accompanying statement from the FDA Commissioner on FDA's new strategic framework to advance use of real-world evidence to support development of drugs and biologics.

> **"Our hope is that the collection of more real world data directly from patients, using a secure app, will lead to more efficient product development and assist with safety monitoring."**
>
> Scott Gottlieb, M.D., FDA Commissioner

> **"The new real-world evidence strategic framework is intended to advance the collection of data that are appropriate, consistent and provide information and knowledge that can better inform regulatory decision-making … part of our new Framework is to explore strategies for filling the gaps with other sources of RWD, which may include the use of mobile technologies, electronic patient reported outcome tools, wearables, and biosensors … this Framework … is another milestone in our effort to advance the use of RWD and RWE to better inform patients and providers."**
>
> Scott Gottlieb, M.D., FDA Commissioner

This investigation is led by a dedicated task force whose mandate is to oversee the investigation and track new developments and information from manufacturers. This multidisciplinary team of chemists, toxicologists, medical doctors, pharmacists, investigators, communication specialists, and analytical lab staff coordinates across the FDA, and acts on the newest available information.

Unexpected Impurities in Blood Medications: FDA's Ongoing Multidisciplinary Response

On June 19, 2018 the FDA learned that some generic versions of the prescription drug valsartan, a medication for treating elevated blood pressure and heart failure, contained unexpected impurities that posed a safety concern.

The "sartans" are drugs in the angiotensin II receptor blocker (ARB) class. "Sartans" is a term derived from a portion of their names that they all share. Examples of ARBs include the drugs candesartan, irbesartan, losartan, olmesartan, and valsartan.

The impurities in these products, N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) are probable human carcinogens—cancer-causing chemicals. NDMA was the first impurity to be discovered in some valsartan products. During the FDA's investigation of valsartan products, the agency learned of a second impurity, NDEA. These impurities may be generated when specific chemicals and reaction conditions are present in the drug product manufacturing process.

With further testing that included other drugs in the same class as valsartan, NDEA has also been found in some irbesartan and losartan products. All products found to contain these impurities above acceptable levels have been recalled and are no longer available in the U.S. Lists of valsartan and irbesartan products affected by the recall are available on the FDA website. As this report is being prepared, there is one lot of losartan affected. Our investigation and testing activities are ongoing, and updates will be available on a continuing basis.

ARB Impurities and Recalls:
Timeline for FDA Response and Updates

JULY 13 | Initial press release issued.

JULY 18 | First update issued. Updates have been regularly issued in the months since. In that same time frame the FDA has shared new and developing information across other communication channels known to reach consumers and health care providers, such as social media, newswires, and email listservs.

JULY 27 | FDA shared our scientists' estimate of the theoretical risk that the NDMA impurity in valsartan could pose to patients. We estimate that if 8,000 people took the highest valsartan dose (320 mg) from NDMA-affected medicines daily for four years (the amount of time we believed the affected products had been on the U.S. market), there may be one additional case of cancer over the lifetimes of these 8,000 people, beyond the average cancer rate among Americans. This estimate represented the highest possible level of NDMA exposure—in other words, it was a measure of risk under the most extreme circumstances. Most patients who were exposed to the impurity through the use of valsartan received less exposure than this worst-case scenario.

The FDA continues to improve its procedures for guarding against impurity risks. The agency will use the information from our investigation into the sartans to strengthen our oversight.

In March 2018 the FDA issued a **guidance** for manufacturers that describes risk assessments that manufacturers can use to evaluate the presence of genotoxic impurities, lays out the conditions under which risks of impurities can occur, and the steps that manufacturers should take to test for these potential impurities.

The *active pharmaceutical ingredient* in a drug product, or API, is the chemical ingredient that exerts the therapeutic or medical effect of the drug. Pills or tablets also have other ingredients that are medically inactive, such as binders or dyes.

AUGUST 22 | FDA scientists developed a test to detect and measure NDMA in valsartan active pharmaceutical ingredient and publicly shared this method to help manufacturers and regulators detect NDMA in valsartan API and tablets.

AUGUST 30 | Statement issued from FDA Commissioner Scott Gottlieb, M.D. and CDER Director Janet Woodcock, M.D. on FDA's ongoing investigation into valsartan impurities and recalls, with an update on FDA's findings as of that time.

SEPTEMBER 13 | Press release issued announcing test results showing NDEA for the first time in several batches of valsartan API.

OCTOBER 11 | A redeveloped version of the testing method, to detect both NDMA and NDEA impurities, was publicly posted.

OCTOBER 30 | The pharmaceutical company ScieGen recalled irbesartan found to contain NDEA. This was the first non-valsartan drug product the agency found containing the NDEA impurity.

NOVEMBER 9 | The pharmaceutical company Sandoz recalled one lot of losartan containing NDEA.

NOVEMBER 21-27 | FDA alerted patients and health care professionals to voluntary recalls, by pharmaceutical companies Mylan and Teva, of valsartan containing NDEA. Both Mylan's and Teva's recalls involved API manufactured by Mylan. With this recall, Teva recalled all their unexpired valsartan-containing products remaining on the U.S. market. We also updated lists of valsartan products under recall and valsartan products not under recall. FDA reminded patients that not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

We encourage patients and prescribers to check the FDA updates on ARB recalls frequently for potential changes in the recall status of their medicine. We are continuing to update this information on a regular basis and are also providing consumer updates on our social media platforms to ensure broad reach.

The FDA continues to investigate and test all ARBs for the presence of NDMA and NDEA and is taking swift action when it identifies these impurities at above-acceptable levels. FDA has also posted questions and answers to assist health care professionals and patients.

Health care professionals, patients, and consumers have been rightly concerned about the impurities affecting ARB drugs.

Since the first news of a recall, the FDA has received more than 7,500 inquiries from patients, physicians, nurses, pharmacists, and academicians. We take these inquiries very seriously and strive to answer all of them. CDER has a skilled group of pharmacists and nurses who manage a **toll-free number** (855-543-3784) and answer email inquiries (**druginfo@fda.hhs.gov**) from the public. The public wants to know how to get safe ARB products, what to talk about with their pharmacists, if they should stop taking their medications and how to calculate their risk for cancer if they have been taking affected valsartan for several years. It was these questions, in part, that prompted the FDA to conduct its analysis of the risk that NDMA posed.

Advancing Efforts to Address the Misuse and Abuse of Opioid Drugs

In January 2018, FDA Commissioner Dr. Scott Gottlieb, working in collaboration with senior leaders from across the FDA, identified four priority areas to serve as focal points for additional policy activity throughout the year, presented as the Healthy Innovation, Safer Families: FDA's 2018 Strategic Policy Roadmap.

Among the Roadmap's goals is one of the highest policy priorities of the Department of Health and Human Services and the FDA—advancing efforts to address the crisis of misuse and abuse of opioid drugs that is harming American families.

As opioid addiction continues to claim American lives at a staggering rate, this crisis represents one of the most pressing public health emergencies facing the FDA. The agency's understanding is growing about the evolution of the opioid crisis, from one mostly involving prescription drugs to one increasingly fueled by illicit substances purchased online or on the street. The FDA is identifying steps to reduce avoidable exposure to prescription opioid drugs, and reduce the amount of opioid drugs at risk of "diversion"—finding their way to the streets and other illicit venues for sale—by helping to ensure that patients are prescribed opioid drugs only when properly indicated and for dosages and durations of use that are medically appropriate.

FDA's multi-disciplinary science-based efforts include supporting development of opioid drugs with improved formulations that are harder to manipulate and abuse, advancing the development of drugs and devices that can treat pain and are less likely to lead to addiction, and strengthening enforcement activities targeting those who unlawfully market or distribute controlled substances and other unapproved drugs, including enhanced efforts aimed at the interdiction of opioids being illegally shipped into the United States.

These efforts are congruent with the FDA's four priority areas for addressing the prescription opioid crisis:

- Decreasing exposure and preventing new addiction

- Supporting treatment of those with opioid use disorder

- Fostering the development of novel pain treatment therapies

- Improving enforcement and assessing benefit/risk

FDA is also continuing its work to facilitate treatment options and the development of therapies to address opioid use disorder as a disease. This means helping more people secure medication-assisted treatment (MAT) for addiction, an approach that involves the use of medications in combination with counseling and behavioral therapies. MAT requires us to break the stigma often associated with some of the medications used to treat addiction. It also requires us to find new and more effective ways to advance the use of medical therapy in the treatment of opioid use disorder.

FDA's concerted efforts in confronting the opioid crisis continued throughout 2018, and included a wide range of actions and activities. Highlights include:

- **JANUARY 11 |** The 2018 Strategic Policy Roadmap was announced by the FDA Commissioner, Dr. Scott Gottlieb. The Roadmap provides an overview of some of the key priorities the agency will pursue to advance its public health mission including the FDA's Opioid Policy Work Plan.

- **FEBRUARY 15 |** Duke-Margolis Center for Health Policy sponsored a Public Workshop: Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids, which convened experts and speakers from FDA, Duke University School of Medicine, and Duke-Margolis Center for Health Policy to examine strategies and tools used to support safe opioid prescribing, how data and health IT can advance these efforts, and how stakeholders are addressing barriers to implementation and potential unintended consequences.

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

- **MARCH 14** | FDA Keynote Address, Recently Released Policies for Fighting the Opioid Epidemic, presented at the Abuse-Deterrent Formulations Summit by Douglas Throckmorton, M.D., Deputy Director for Regulatory Programs, CDER.

- **APRIL 4** | FDA Commissioner speech at the National Rx Drug Abuse and Heroin Summit, In Search of More Rational Prescribing.

- **APRIL 17** | FDA hosted a public meeting on Patient-Focused Drug Development for Opioid Use Disorder (OUD), in collaboration with National Institute of Drug Abuse (NIDA). In addition to NIDA, FDA is also working closely with patient advocacy and community organizations to encourage participation from individuals with OUD. This meeting aligns with FDA's ongoing work aimed at reducing the impact of opioid abuse and addiction.

- **APRIL 20** | FDA issued the draft guidance, "Opioid Dependence: Developing Buprenorphine Depot Products for Treatment," which focuses on ways drug companies can more efficiently explore innovations in depot buprenorphine products.

- **MAY 16** | FDA approved Lucemyra (lofexidine hydrochloride), the first non-opioid treatment for the mitigation of withdrawal symptoms associated with abrupt discontinuation of opioids.

A scalable, patient-centered approach for "right-sizing" opioid prescribing is a project co-funded by CDER's Safe Use Initiative and the Office of Surveillance and Epidemiology.

Research shows that a majority of patients undergoing surgery have pain medication left over after surgery—and that many patients need less than half the number of pills prescribed. Leftover opioids may remain in homes for long periods and are at risk for being diverted, misused, and abused. This project aims to develop opioid prescriptions for 12 common procedures or diagnoses commonly encountered in emergency departments. After having a procedure or receiving a diagnosis, patients will answer questions via text message about the number of pills used, the number remaining, and their ability to control pain. Using this information, the "right-size" prescription—one which provides enough pills for a patient to control their pain but with a minimal number left over—will be developed. This prescription will then become the standard for all future patients undergoing the same procedure. Subsequent patients will be monitored via text to verify that the new prescription is adequate and that they continue to be able to control their pain. The project goal is to reduce the number of opioids prescribed and the number of pills left over while having minimal or no effect on the patients' ability to control their pain.

- **JUNE 27** | FDA invited Internet stakeholders, including government entities, academic researchers, and advocacy groups, to attend a one-day Online Opioid Summit to discuss ways to collaboratively take stronger action in combatting the opioid crisis by reducing the availability of illicit opioids online. A critical step in addressing this public health emergency is the adoption of a far more proactive approach by internet stakeholders to crack down on internet traffic in illicit drugs. The Summit agenda and links to presentations are here.

- **JULY 9** | FDA hosted a public meeting on Patient-Focused Drug Development for Chronic Pain to hear patients' perspectives on chronic pain, views on treatment approaches, and challenges or barriers to accessing treatments for chronic pain.

- **AUGUST 6** | FDA issued the draft guidance, "Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment," intended to assist sponsors in developing drugs for medication-assisted treatment of opioid use disorder and address the clinical endpoints acceptable to demonstrate effectiveness of such drugs.

- **SEPTEMBER 18** | FDA took important steps to encourage appropriate and rational prescribing of opioids through final approval of new safety measures governing the use of immediate-release opioid analgesic medications.

- **SEPTEMBER 20** | Duke-Margolis Center for Health Policy Public Workshop: Expanding Access to Effective Treatment for Opioid Use Disorder: Provider Perspectives on Reducing Barriers to Evidence-Based Care. A project supported through a cooperative agreement with FDA, this workshop's objective was to generate active discussion with providers and health system stakeholders on the range of therapies to treat opioid use disorder (OUD), current barriers to appropriate use of these medications, and opportunities to further reduce stigma and expand access to effective pharmacotherapies as part of an evidence-based approach to OUD treatment.

- **OCTOBER 23** | FDA announced efforts to advance new ways to increase the availability of naloxone as one means for reducing opioid overdose deaths, explored in a Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 17-18, 2018.

On October 23 FDA launched a global operation to crack down on websites selling illegal, potentially dangerous drugs, including opioids. In partnership with international regulatory and law enforcement agencies, FDA targeted 465 websites that illegally sell potentially dangerous, unapproved versions of opioid, along with other, prescription drugs to U.S. consumers. This effort was part of Operation Pangea XI, the eleventh annual International Internet Week of Action (IIWA), a global cooperative effort led by Interpol to combat unlawful sale and distribution of illegal and potentially counterfeit medical products through the internet.

- **OCTOBER 24** | Statement from FDA Commissioner issued on how new regulatory authorities will assist the agency in more forcefully addressing the opioid crisis, included as part of the newly enacted Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act.

- **NOVEMBER 2** | Statement from FDA Commissioner issued on the agency's approval of Dsuvia and the FDA's future consideration of new opioids.

- **NOVEMBER 8** | FDA Commissioner provided remarks at National Comprehensive Cancer Network-American Society of Clinical Oncology Workshop affirming FDA's commitment to a comprehensive process to develop a formal and transparent benefit/risk framework for how FDA evaluates the safety and efficacy of opioid medicines.

- **NOVEMBER 13** | FDA Commissioner addressed the National Academies of Sciences, Engineering, and Medicine Committee on Evidence-based Clinical Practice Guidelines for Prescribing Opioids for Acute Pain.

In late 2018, FDA began work on a multi-year, mixed-method research project to explore and assess the knowledge, attitudes, and behaviors about abuse-deterrent formulation opioids (ADFs) among opioid prescribers and dispensers/pharmacists. This includes the related terms "addiction" and "abuse deterrence," and to explore possible alternative language for describing these products. The three phases will involve focus groups, followed by a survey aimed at getting more representative findings, with the culmination an experimental study in which ADF-related content, including related to the terminology, will be compared experimentally. Led by CDER's Office of Communications, the Project Advisory Group—which will be intimately involved in all research tasks throughout this project—consists of several experienced social and behavioral scientists, as well as opioid and ADF subject matter experts, including physicians from CDER's Office of New Drugs and Office of Surveillance and Epidemiology.

THE OPIOID EPIDEMIC BY THE NUMBERS
2016 and 2017 Data

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

11.4 m People misused prescription opioids[1]

42,249 People died from overdosing on opioids[2]

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

2.1 million People had an opioid use disorder[1]

17,087 Deaths attributed to overdosing on commonly prescribed opioids[2]

886,000 People used heroin[1]

19,413 Deaths attributed to overdosing on synthetic opioids other than methadone[2]

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

15,469 Deaths attributed to overdosing on heroin[2]

SOURCES
1. 2017 National Survey on Drug Use and Health, Mortality in the United States, 2016
2. NCHS Data Brief No. 293, December 2017
3. NCHS, National Vital Statistics System. Estimates for 2017 and 2018 are based on provisional data.

Updated September 2018. For more information, visit: http://www.hhs.gov/opioids/ — HHS.GOV/OPIOIDS

Safety Surveillance for 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 in turn helps to make treatment 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 brand-name drugs , generic drugs:

- Contain the same active/key ingredients
- Have the same strength
- Use the same dosage form (for instance, a tablet, capsule, or liquid)
- Use the same route of administration (for example, oral, topical, or injectable)

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

OGD maintains a robust pre- and postmarketing program for evaluating generic drug safety. Effective postmarketing surveillance of generic drugs is essential to ensure that, when substituted for the brand-name drug, the FDA-approved generic drug is safe and effective.

OGD's Clinical Safety Surveillance Staff (CSSS) facilitates broad surveillance projects with an interdisciplinary team of physicians, pharmacists, epidemiologists, chemists, and other scientists. CSSS tracks and evaluates reports relating to generic drug product quality, adverse events, or differing therapeutic effects from the brand-name drug. The process path that a generic drug safety issue takes—from the point a safety concern emerges to a decision about what action to take—is depicted in the infographic on the next page.

In addition to its ongoing work in generic drug safety surveillance, the CSSS worked throughout 2018 to present its scientific approach in conducting safety evaluations to several major stakeholder audiences.

Regulatory Science—
OGD's Office of Research and Standards

OGD's Office of Research and Standards funds grants and contracts to address the methodology issues associated with generic drug postmarketing surveillance, including clinical effectiveness and safety issues of drugs on the market. More information on research to support safety surveillance of generic drugs can be found at the FDA's Generic Drug Science & Research website.

Communicating Generic Drug
Safety Surveillance in 2018

APRIL 11 | Challenges in Generic Drug Safety and Surveillance was presented at the FDA Small Business and Industry Assistance Generic Drugs Forum 2018. The presentation discussed the overall generic drug development framework and highlighted an example of different patient perceptions related to brand versus generic olanzapine orally disintegrating tablets.

MAY 9 | Drug Information Association Pharmacovigilance and Risk Management Strategies 2017: Overview of the Generic Drug Program and Surveillance appeared in *Therapeutic Innovation and Regulatory Science*. The paper described the analyses that allow the FDA to determine that a generic drug will perform in a patient in the same way, with the same safety and efficacy profiles, as the brand name drug.

MAY 24 | Challenges in Generic Drug Safety and Surveillance: Opportunities for Research was presented at the Fiscal Year (FY) 2018 Generic Drug

Tracking and Managing Generic Drug Safety Issues

INCOMING GENERIC DRUG SAFETY ISSUES

- Mail/Email
- Media
- Patient and Physician Communications
- Internet
- Internal Questions and Concerns

CSSS Lead Clinical Safety Coordinator

Office of Research and Standards Liaison

Clinical Safety Surveillance Staff (CSSS)

CSSS Clinical Team

- Adverse Events
- Safety Reports
- FDA Database
- Consults

CSSS Data Team

Division of Labeling Review Liaison

OGD REVIEW AND ASSESSMENT

Liaisons from other CDER Offices

Monthly CSSS Safety and Surveillance Committee

Representative from OSE

Forwards Unresolved/Persistent Issues

OGD Division Directors and Associate Director for Regulatory Affairs

Bimonthly OGD Safety and Surveillance Committee

Immediate Office OGD

Representative from OPQ

FINAL DISPOSITION

Determine a Final Disposition

- Open a Tracked Safety Issue in Internal Database
- Track, Trend and Re-evaluate
- No Action Indicated

Regulatory Science Initiatives Public Workshop. This Workshop provided an overview of the current status of the regulatory science initiatives for generic drugs and offered an opportunity for public input on research priorities for FY 2019 and beyond. FDA used stakeholder input to develop the Regulatory Science Priority Initiatives for Fiscal Year 2019.

JUNE 26 | A session titled *Generic Drug Products: Comparison of Safety Profile with Branded Cousin* was presented at the Drug Information Association (DIA) Annual Meeting. An interview about this session was released as a podcast and on YouTube.

AUGUST 17 | A paper titled "Evaluation of Switching Patterns in FDA's Sentinel System: A New Tool to Assess Generic Drugs" was published in *Drug Safety*.

SEPTEMBER 20 | Generic Drug Development and Safety Evaluation was presented at the CDER Pediatric Advisory Committee Meeting. This presentation summarized the overall approach to generic drug development and safety surveillance as performed by the CSSS.

SEPTEMBER 25 | A podcast, Challenges in Generic Drug Safety and Surveillance, was posted by DIA on their *Driving Insights to Action* website. This podcast summarized efforts featuring multiple examples of past and ongoing safety surveillance efforts related to generic drugs conducted by CSSS.

> **"These efforts are part of our ongoing commitment to promote a framework that ensures that generic drug labels reflect up-to-date, science-based information to inform patients and providers, while also balancing the need to maintain a pathway for the development of generic drugs that is modern, efficient and low cost."**
>
> Scott Gottlieb, M.D., FDA Commissioner, and Janet Woodcock, M.D., CDER Director

On December 13, 2018, FDA Commissioner Scott Gottlieb, M.D. and CDER Director Janet Woodcock, M.D., issued a statement on efforts to modernize generic drug labels while maintaining the efficiency of generic development.

- The statement announced withdrawal of a proposed rule which, if finalized, would have allowed generic drug makers to independently update and distribute new safety information in drug labels (something that currently only branded drug makers can do).
- Manufacturers believed this change would impose significant new burdens and new costs that might raise the price of generic drugs to patients, potentially impacting patient access to generic medicines.
  ◦ The proposed rule would also result in labels for the same drug that varied between different generic manufacturers, leading to consumer and provider confusion.
- At the same time, the agency is taking important steps to update labels on certain generic cancer drugs with modern safety and efficacy information.
  ◦ This effort will help make sure that prescribers and patients have the most up-to-date information to guide treatment decisions and will broaden patient access to generic medicines.
- The statement provides background on the FDA's decision making process, the overarching public health considerations that were weighed, and outlines some of the current efforts the FDA is undertaking to help modernize generic labels.

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. 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.

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

Projects Completed in 2018

Improving Safe Use of Fluoroquinolone Antibiotics through Development of an Innovative Educational Program. Fluoroquinolone (FQ) antibiotics are 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 2018

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 2018

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 in 2018

Compounded drugs serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, such as a patient who has an allergy and needs a medication to be made without a certain dye, or an elderly patient or a child who cannot swallow a tablet or capsule and needs a medicine in a liquid dosage form that is not otherwise available.

However, compounded drugs are not FDA-approved, which means they have not been reviewed by FDA for safety, effectiveness, or quality before they are marketed. Poor compounding practices can result in serious drug quality problems, such as contamination or medications that do not possess the strength, quality, and purity they are supposed to have. This can lead to serious patient injury and death.

Since the widespread 2012 outbreak of fungal meningitis associated with contaminated compounded drugs, CDER has responded to numerous serious adverse events, including infections and deaths, related to compounded drugs that were contaminated or otherwise compounded improperly.

Congress provided FDA with new regulatory authorities through passage of the Drug Quality and Security Act (DQSA) in 2013, and FDA continues to make substantial progress on implementation of

> Compounding is generally a practice in which a licensed pharmacist, a licensed physician, or, in certain cases, 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.

the compounding provisions of federal law. In 2018, FDA continued its compounding facility inspections, regulatory and enforcement actions, policy development, state collaboration and coordination, and stakeholder outreach.

Compounding actions and activities through November 21, 2018 include:

- About 120 inspections of compounders conducted throughout the United States, many of which have been for-cause based on serious adverse events or product quality issues.

- More than 20 warning letters issued to compounders describing significant violations of the law that could put patients at risk.

- Oversight of about 50 recalls involving compounded drugs.

- Work with the Department of Justice in two civil enforcement actions and one criminal enforcement action.

- Established and advanced strategic policy goals as described in the 2018 Compounding Policy Priorities Plan.

- Issue of one draft guidance document, two revised draft guidance documents, seven final guidance documents, one final regulation, and one revised draft memorandum of understanding between FDA and states.

- One Pharmacy Compounding Advisory Committee meeting held.

- Four major research collaborations launched with the National Academies of Science, Engineering & Medicine and the University of Maryland and Johns Hopkins University Centers for Regulatory Science and Innovation, to help inform the public and the agency's policies regarding compounded drugs.

- One intergovernmental working meeting held with state boards of pharmacy on drug compounding, one federal partners meeting on drug compounding, and numerous listening meetings.

- Collaboration and coordination with state regulators on FDA inspections and enforcement.

- Four listening sessions held with more than 75 invited stakeholder groups, including pharmacy, hospital, and professional medical organizations, consumer and patient advocacy groups, and outsourcing facilities.

- Four "compounding risk alerts" issued to inform health care professionals and patients of adverse events related to compounded drugs.

See our website to learn more about FDA's compounding work.

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. More than 100 staff members, including health care professionals, communications specialists, researchers, web and graphic designers, as well as senior strategists and advisors, 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 CDER's communication initiatives and tools

- Offer expertise on communication products across a variety of media

- Conduct risk communications research

CDER Trending Topics 2018, which appear on pages 38-39, reports activities between January 1-October 31, 2018. The Trending Topics metrics depict the extent of OCOMM's engagement across many online venues (search engines, online referrals, email, social media), illustrating the most viewed CDER web pages—collectively accounting for millions of online visits—and the topics, questions, and documents that generated the most online traffic. CDER also tracks the top ten trending topics on social media, as well as the top five media newsfeed topics, offering FDA leadership and senior managers a clear picture of what key issues are stimulating significant public interest.

These metrics illustrate the frequency with 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.

Communicating Drug Safety Across Multiple Audiences

Drug Safety Communications (DSCs) provide updates and critical new and evolving information for patients, caregivers, pharmacists, health care providers, and the public, regarding potential risks of FDA-approved drugs. These announcements involve new or emerging risks related to particular drug products, as well as cautions about potential medication errors. DSCs address urgent issues affecting patients and describe potentially serious or life-threatening adverse events, or other cautions related to use of a drug or class of drugs. DSCs contain actionable recommendations for patients and health care professionals that support more informed decision making and help prevent or mitigate drug-related harm.

The DSC home page is one of the most visited pages on the FDA's web site. The 13 individual DSCs posted in 2018 were viewed more than half a million times. These key safety messages were 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.

Drug Safety Podcasts and Director's Corner Podcasts are also available at ReachMD, with a reported 350,000 listeners weekly. ReachMD's content delivery platforms include websites, mobile apps, and internet radio with programming delivered both on demand and through 24/7 online streaming.

Drug Safety Podcasts provided emerging safety information about drugs in conjunction with the release of Drug Safety Communications. Eleven podcasts issued in 2018, and are available online and in iTunes.

Director's Corner Podcasts feature CDER Director Dr. Janet Woodcock. In exploring various topics, these podcasts frequently deal with drug product safety. Podcasts and transcripts are available online.

FDA Drug Topics Webinars offer free, live, online continuing education for physicians, physician assistants, nurse practitioners, nurses, pharmacists, and pharmacy technicians. Webinars often center on drug safety or safety-related topics. Six webinars produced in 2018 focused on drug safety initiatives and programs.

- JANUARY 30 | FDA Adverse Events Reporting System (FAERS) Public Dashboard
- MARCH 13 | FDA's MedWatch Adverse Events Reporting Program—Opportunities to Collaborate
- APRIL 10 | An Introduction to Drug Safety Surveillance and the FDA Adverse Events Reporting System (FAERS)
- JUNE 19 | Postmarketing Drug Safety and Inspection Readiness
- JUNE 26 | FDA's Web Resources Available to Health Care Providers Who Prescribe and Dispense Medications with Risk Evaluation and Mitigation Strategies (REMS)
- OCTOBER 9 | An Update to the FAERS Public Dashboard

Responding to Public Inquiries

OCOMM receives public inquiries via phone, email, letters, and through social media platforms such as Facebook. Over 60,000 such queries were received in Fiscal Year 2018 (between October 1, 2017 and September 30, 2018). Expert responses are developed and facilitated by a team of pharmacists, nurses, and other health professionals who field questions from consumers, health care professionals, journalists, research organizations, non-profits, regulated industry, and academia.

TOTAL QUERIES MANAGED IN FISCAL YEAR 2018 (OCTOBER 1, 2017-SEPTEMBER 30, 2018)	
Phone	44,334
Email	17,330
Letters	654
Social Media	1,297
TOTAL	**63,615**

In June 2018, the FDA learned of impurities found in the prescription drug valsartan, along with other drugs in the same class (known as angiotensin II receptor blockers, or ARBs). These impurities, which may be related to manufacturing processes, posed a safety concern in that they are probable human carcinogens—cancer-causing chemicals. (See Unexpected Impurities in Blood Pressure Medications: FDA's Ongoing Multidisciplinary Response on page 16.)

As the FDA launched a multifaceted response, including evaluations of manufacturing processes, development of laboratory tests designed to detect the impurities, and monitoring product recalls and safety reports, OCOMM's drug information team began to respond to ARB-related inquiries from patients, health professionals, academicians, and others.

The public wants to know how to discuss this issue with their doctors and pharmacists, if they should stop taking their medications, or how to understand their risk for cancer if they have been taking affected valsartan for several years. OCOMM's drug information pharmacists and nurses manage a toll-free number (855-543-3784) and answer email inquiries (druginfo@fda.hhs.gov). Since the first news of a product recall in June, OCOMM has received and responded to more than 7,500 ARB-related inquiries.

CDER Trending Topics

January - October 2018

📊 CDER WEB TRAFFIC

TRAFFIC VOLUME
www.fda.gov/drugs — Sessions*

Desktop	**9,309,881**
Mobile Devices (Tablets, Cell Phones)	**4,915,457**

TRAFFIC SOURCES
% of Sessions

Search Engines	**64**
Direct Sources (URLs)	**16**
Referrals	**14**
Email	**4**
Social Media	**2**

G TOP 5 GOOGLE SEARCHES
Clicks

1.	Valsartan/ Valsartan Recalls
2.	Recalls
3.	Levothyroxine Recalls
4.	Kratom
5.	Aimovig

*Sessions: the number of individual sessions initiated by all the users to our site with periods of inactivity of less than 30 mins.

HIGHEST VIEWED CDER WEB PAGES THIS PERIOD
Unique Pageviews†

1. Drug Recalls	**658,180**
2. Disposal of Unused Medicines: What You Should Know	**449,736**
3. FDA updates on valsartan recalls	**384,039**
4. Guidances (Drugs)	**334,388**
5. Drug Approvals and Databases	**301,691**
6. What's New Related to Drugs	**256,581**
7. National Drug Code Directory	**250,375**
8. Drug Master Files (DMFs)	**181,499**
9. Guidance, Compliance, & Regulatory Information	**179,682**
10. Medication Guides	**178,774**

†Unique Pageviews: The number of sessions during which that page was viewed one or more times.

👍 SOCIAL MEDIA

FACEBOOK
www.facebook.com/FDA

FDA Followers	**586,484**
CDER Engagement	
Posted Content	151
Replied to Comments	583
Public Likes/Shares	26,867

LINKEDIN*
www.linkedin.com/company/fda

Total Followers	**218,451**
SBIA Showcase Page	3,455
GADIS Group	679

*Estimated

TWITTER
www.twitter.com/FDA_Drug_Info

Total Followers	**245,518**
Tweets	688
Retweets	5,924
Likes	12,703

CDER Trending Topics

January - October 2018

📊 TRENDING TOPICS ON SOCIAL MEDIA*

ALS	632,225
Sunscreen	380,718
Kratom	334,163
Opioids	201,226
Expedited Reviews Pathway	114,684
Body Building Supplements	100,791
Drug Pricing	86,011
Biosimilars	59,967
Off-Label Marketing	52,373
Drug Disposal	41,159

*CDER Selected Topics on Brandwatch

TOP 5 MEDIA NEWSFEED TRENDING TOPICS MENTIONED*

1.	Expedited Review Pathways	**53,266**
2.	ALS	**52,540**
3.	Biosimilars	**24,062**
4.	Off-Label Marketing	**22,013**
5.	Sunscreen	**16,093**

*Brandwatch

📅 TOP 10 PUBLIC INQUIRIES
Total Inquiries for Period — 55,035

1.	Valsartan	**7,018**
2.	Opioids	**1,994**
3.	INDs/SPIs/EINDs	**1,827**
4.	Personal Importation	**1,641**
5.	Registration (DRLS)	**773**
6.	Fluoroquinolones	**706**
7.	Clinical Trials	**650**
8.	Gabapentin	**385**
9.	Prolia	**348**
10.	Kratom	**313**

Social Media Team

The OCOMM Social Media Program has significantly expanded CDER's communications outreach by "meeting people where they already are." Instead of hoping thousands of people will proactively visit FDA's website every day for information, or relying on traditional outreach activities, OCOMM actively pushes CDER information to over 500,000 FDA Facebook followers in the U.S., and almost 250,000 @CDER_Drug_Info Twitter followers. This allows CDER to reach an exponentially greater number with public health messages, safety communications, drug safety warnings, and information about new initiatives and new drug approvals.

By "live tweeting" Center meetings and workshops, the Social Media (SM) team provides highlighted meeting content to many more people than those who were able to attend in person. Live tweeting also puts CDER subject matter experts and Center activities at the top of trending topics on social media platforms. Twitter Chats allow CDER to engage with large stakeholder groups and major influencers that can expand the reach of CDER messages. In addition to posting content and engaging in two-way communication, the SM team performs "social listening" to obtain real-time feedback on any CDER action.

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, FDA may require a Drug Safety-related Labeling Change.

OCOMM manages the Drug Safety-related Labeling Changes (previously known as Safety Labeling Changes) program data and web access operations. 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 OCOMM 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 have continued in 2018.

SrLCs are made in one or more of seven sections in a drug's label. Over 3,000 new SrLCs were added to the SrLC database between January 1 and September 30, 2018.

SAFETY LABELING CHANGES IN 2018	
Adverse Reactions	597
Boxed Warnings	153
Contraindications	243
Drug Interactions	369
Patient Counseling information and/or Medication Guides	588
Use In Specific Populations	528
Warnings and Precautions	647
TOTAL	**3,125**

"Labeling" (otherwise 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 pharmacist. Labeling is also available online.

Risk Communications Research

Risk communications research activities within OCOMM continued throughout 2018. Data being generated will provide evidence that can be used to improve FDA and CDER communications, expanding distribution of content and materials to help target audiences understand the health and safety information that CDER provides. These research efforts also provide the public—including people with limited health literacy or who face disparities in accessing health services—opportunities to offer input on the effectiveness of CDER drug safety information.

In addition to providing evidence CDER can use to enhance its communications, OCOMM's research was shared through articles published or submitted for publication in peer-reviewed journals. OCOMM also presented throughout the year at several conferences, including the 2018 American Public Health Association Conference.

Research Activities in 2018

- As a new addition to its broad social and behavioral science research program, OCOMM began in 2018 a systematic process of monitoring, collecting, and analyzing the extensive amount of data that is available online and on social media platforms, and conducted several related projects using the processes developed. The overarching objectives for this social media research are to identify new and emerging topics and shifting trends related to prescription and OTC drugs, particularly concerning substances that may be used as adjuncts or alternatives to prescription opioids. The research will help to understand the social context surrounding substances being discussed online and through social media by "listening" to these conversations and gleaning information about the substances people report using, including how and why they are using these substances and the terminology used to describe them.

- In an effort to efficiently and effectively communicate about biological products that are demonstrated to be "biosimilar" to, or "interchangeable" with, an FDA-licensed biological product, OCOMM began a multiphase study that will include focus groups and interviews with likely prescribers of these medicines and their patients who will be recipients of these prescriptions. The study's aim is to better understand knowledge and attitudes about various aspects of these new drugs.

  ◦ In addition to general information collected from these audiences, prescribers and pharmacists will also be asked their opinions about several fact sheets CDER developed to educate prescribers about these medications. In 2018, focus groups were completed with healthcare professionals who prescribe these medicines and with pharmacists who dispense them. The in-depth findings from these groups were used to inform the second phase of the project, currently underway, to gather feedback on several informational materials CDER developed related to biosimilars and interchangeables.

- An ongoing multi-pronged study continued in 2018, aimed at enhancing FDA communications addressing opioids and other potentially addictive pain medications. Based on findings from earlier phases of the project—including in-depth interviews with prescribers, and focus groups with the general public, chronic opioid users, and friends and family of chronic opioid users—follow-up surveys were fielded among opioid prescribers and the general public, including chronic opioid users. Analysis and reporting from this study will be completed in early 2019.

- Detailed data analyses, including statistical modeling, and reporting were completed for a study investigating the effectiveness of various messages about medical countermeasure (MCM) drugs that might be used in the event of a chemical, biological or radiological terrorist attack or other health threats. The results of this experimental study, which will be completed in early 2019, will form the basis for developing guidelines for revising a large series of draft MCM-related messages and for developing effective communication materials for CDER to use in the event of public health emergencies.

- Research continued in exploring issues related to communicating benefits, risks, and of uncertainty and unintended consequences associated with prescription drug and drug safety information. Based on the findings from testing of recommended practices conducted through focus groups, individual interviews, and experimental surveys, the Framework for Communicating Benefits, Risks, and Uncertainties was finalized and is being used in the development of CDER's Drug Safety Communications. This framework and the associated recommended practices developed as part of this research will be shared in 2019 for use across all of FDA's various risk communications staff and teams.

Publications

Social Media Impact of the Food and Drug Administration's Drug Safety Communication Messaging About Zolpidem: Mixed-Methods Analysis appeared in *Journal of Medical Internet Research (JMIR) Public Health & Surveillance*, January 2018.

Family Caregivers' Facilitation of Daily Adult Prescription Medication Use appeared in *Patient Education and Counseling*, May 2018.

In August, OCOMM began developing a monthly report focusing on top opioid-related topics of conversation, particularly those related to misuse and abuse of prescription opioids. OCOMM also conducted social media research projects on several specific topics throughout the year. For more information on FDA's use of social media monitoring, see CDER Conversation: Monitoring Social Media to Better Understand Drug Use Trends.