U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY PRIORITIES 2017

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Introduction

Americans now take more prescription medicines than at any time in the nation's history. While this represents an increased use of lifesaving treatments and improved access to newly-developed medicines and needed therapies, risks related to the growing use of medicines are various and complex. Be it an adverse event (side effect) related to a drug, a problem stemming from inappropriate or incorrect use, a manufacturing-related issue such as contamination, or criminal tampering or counterfeiting, confronting a drug safety concern calls for interdisciplinary scientific teamwork, proactive decision making, and regulatory action to protect the public health.

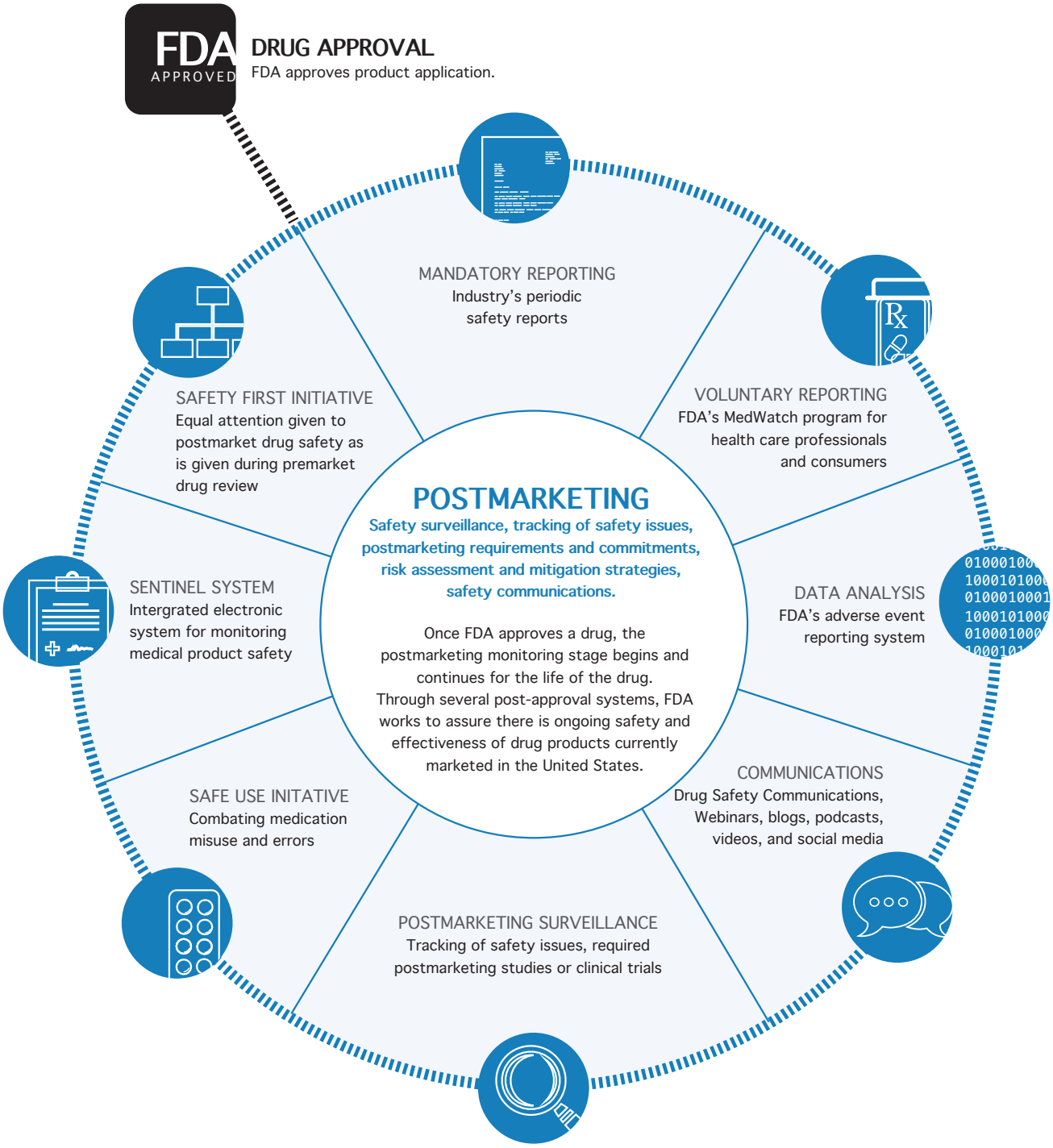
Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Recognizing and understanding a drug-related safety risk, and deploying the regulatory action needed to address that risk, is a key aspect of the mission of the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA). A range of initiatives, programs, and partnerships support CDER's overall drug safety mission, including the fully operational review platform for generic medicines, policy development for real world evidence, progress in regulating compounded medicines, and continued efforts to confront the nation's devastating opioid crisis on a number of medical and public health fronts.

Within the larger framework of CDER's drug safety enterprise, the Center's longstanding safety programs such as the Safe Use Initiative, the FDA Adverse Event Reporting System (FAERS), and the Sentinel System continue to advance their important work. These and many other interconnected efforts – depicted in the infographic on the following page – maintain, improve, and expand CDER's safety-related surveillance and regulatory activities on an ongoing basis.

As CDER pursues a wide-ranging agenda of safety surveillance and regulation, the Center's mission continues to be strengthened by scientific collaborations and partnerships across the FDA, with our many federal health and medical partners, and with stakeholder organizations. *CDER Drug Safety Priorities 2017* illustrates the multidisciplinary nature of CDER's drug safety operations, offers updates from a number of initiatives and programs, and presents key safety-related milestones and achievements of 2017.

FDA Drug Safety Surveillance and Regulatory Activities, Programs, and Initiatives



Safety Surveillance and Oversight of Marketed Drug Products

The Office of Surveillance and Epidemiology (OSE) evaluates 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 and 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.

"Everything someone in OSE does is tied to our four core functions."

Gerald Dal Pan, M.D., OSE Director

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.

Pharmacovigilance	• Detect and assess potential safety-related concerns and issues for all marketed drug and therapeutic biologic products
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
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
Risk Management	• Determine the need for risk evaluation and mitigation strategies (REMS) • Review proposed REMS • Review REMS assessments and REMS modifications

OSE has supported 7,446 safety reviews, of which 2,860 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 included in one or more of OSE's core functions.

The selected projects below highlight OSE's ongoing efforts to modernize drug safety in 2017.

Pharmacovigilance / Pharmacoepidemiology

FDA and PatientsLikeMe (PLM) signed a research collaboration agreement (RCA) in April 2015. Under this collaboration, PLM and the FDA have systematically explored the potential of patient-generated data to inform and enhance regulatory review activities and surveillance related to benefit-risk assessment and risk management.

- Several pilot studies have been completed, including evaluation of PLM's coding of patient-reported adverse drug events, demographics and other characteristics of the PLM community, quality of MedWatch reports submitted to FDA by PLM, and whether patients discuss medication errors on the PLM platform.
- This RCA expires in April 2018. A complete report of FDA's findings will follow after the completion of all ongoing projects.

OSE is exploring social media, patient-generated data, and advanced computing technologies to better understand how these tools can support drug safety oversight and regulation.

OSE is evaluating the use of advanced technologies such as text mining and machine learning methods to aid FDA drug safety evaluators in identifying reports most likely to demonstrate a causal relationship to a suspect medication.

- These models would enable FDA safety evaluators to focus on reports more likely to contain valuable medication-related adverse event information.
- Collaborative research between OSE, Stanford University, and the University of California, San Francisco (UCSF), conducted under the FDA Centers of Excellence in Regulatory Science and Innovation (CERSI) program, demonstrated that such models can be produced. Results of this research were published in March 2017.
- Applying these models to all FDA adverse event reports has the potential to streamline manual review processes and greatly reduce reviewer workload.

OSE is exploring social media for pharmacovigilance and adverse event surveillance.

- Collaborative research between OSE, Epidemico, Inc., and other partners was conducted that explored text mining of social media data for pharmacovigilance, with an objective of determining whether specific product-related adverse events were reported in social media before they were reported to FAERS.

- The analysis concluded that an efficient semi-automated approach to social media monitoring may provide earlier insights into certain adverse events, but more work is needed to identify additional uses for social media data in pharmacovigilance and to determine how they can be applied by regulatory agencies.
- *Evaluation of Facebook and Twitter Monitoring to Detect Safety Signals for Medical Products: An Analysis of Recent FDA Safety Alerts* was published in April 2017.

The FDA Adverse Event Reporting System (FAERS) Public Dashboard went live online on September 28, 2017.

The FAERS Public Dashboard is a highly interactive, user-friendly web-based tool that allows access to human adverse event drug reports received by FDA and contained in the FAERS database. FDA anticipates that the increased availability of FAERS data to the general public will prompt consumers, health care professionals, and other members of the public to submit more detailed and complete reports. Complete and detailed reports are immensely helpful to the Agency when identifying safety signals and choosing particular products for further scrutiny.

Improving data access and transparency are core concepts that drove the development of the new FAERS Public Dashboard.

Medication Error Prevention and Analysis

OSE revised the Phonetic and Orthographic Computer Analysis (POCA) software program to better capture the shift in the type of errors that are being reported due to the use of electronic prescribing.

- Many medicines have names that sound similar or look similar when written, a problem that has led to sometimes critical confusions for health care professionals. POCA determines the orthographic (written) and phonetic (spoken) similarity between two drug names.
- Medication errors related to written or spoken similarities in the names of drugs can include medicines incorrectly dispensed at a pharmacy or incorrectly administered in hospitals or clinics. For example, pharmacists might mistakenly interpret letters or words on a hand-written prescription, or nurses might incorrectly interpret physician orders for hospitalized patients.
- POCA is a central component of FDA's safety review of proposed drug product proprietary names. POCA can compare a proposed drug name against multiple other drug names found in several different data sources contained in the software. POCA uses computer algorithms to assess the similarity of names when spoken or written and assigns a percent similarity score to a given pair of names.

Risk Management

OSE evaluated the relationship between drug development program characteristics and postmarket safety outcomes.

- This study explored the relationship among drug development (the premarket phase) characteristics, and a number of postmarket safety outcomes, including safety-related withdrawals and updates to the Boxed Warning, Contraindications, Warnings and Precautions, Adverse Reactions, and Drug Interactions sections of the drug product label.
- These findings underscore the importance of a robust safety surveillance system throughout a drug's lifecycle, and for practitioners and patients to remain updated on drug safety profiles.
- This study was published in December 2017.

The Sentinel System

The Sentinel System is the FDA's national, integrated electronic system for monitoring drug safety by leveraging data across health care databases (with care taken to protect personal health information).

Sentinel enables FDA to proactively assess medical product safety under real-world conditions, and complements existing FDA post-marketing monitoring capabilities, and allows evaluation of safety issues more rapidly than has been possible in the past.

The Sentinel System analyzes emerging risks associated with FDA-regulated medical products.

The Sentinel System uses a distributed data approach in which data partners maintain physical and operational control over electronic data in their existing databases, achieved 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—and allowing that data to be collected securely with full patient privacy safeguards in place. (Data transmitted to the Sentinel Operations Center is confined to what is minimally necessary to conduct a safety analysis. Patient privacy is protected by removing all personally identifiable information and using datasets that have been aggregated into groups of people, rather than individuals.)

Read more about the background and development of Sentinel here.

How does FDA use the Sentinel System during the review of new drug product applications?

When conducting drug product evaluations before approval for marketing, FDA may identify serious safety concerns. Continued safety monitoring after a drug is approved and on the market (among other postmarketing actions) may be deemed necessary as a requirement for approval. In these cases, FDA assesses whether the Sentinel System's Active Risk Identification and Analysis (ARIA) system is sufficient to meet the specific safety monitoring need. If so, the Agency begins planning for a future ARIA study. The ARIA system is a key aspect of the regulatory planning process to monitor serious safety concerns identified in the review of new drug applications.

The 9th Annual Sentinel Initiative Public Workshop was held February 2, 2017. Convened by the Duke-Margolis Center for Health Policy at Duke University and supported by a cooperative agreement with FDA, this event brought the stakeholder community together to discuss a variety of topics on active medical product surveillance, including future improvements to the Sentinel System.

In addition to considering the Sentinel System during the review of new drug applications, FDA may use the System to examine safety issues not seen during the approval process but identified after a drug is approved.

Who can access Sentinel resources?

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.

FDA hosted a public workshop in July 2017 that offered training for the public on the Sentinel System. The training helped users understand the kinds of questions that can be asked using health care claims data generally and within the FDA Sentinel System specifically, allowing an understanding of the capabilities of the Sentinel System.

Sentinel System Updates

The Sentinel Initiative Final Assessment Report was completed and posted in September 2017. This independent assessment characterizes the developing maturity of the Sentinel System since its inception.

As a component of FDA's commitment to transparency and communication with the public about the capabilities and regulatory impact of the Sentinel System, CDER has developed a webpage dedicated to highlighting how ARIA analyses have been used by FDA.

How Real-World Evidence Will Help to Advance Drug Safety Science

- There are several kinds, or "levels", of medical evidence that FDA product reviewers evaluate to assess the safety profiles of new drugs.
- This evidence is based on data produced by different types of studies designed to provide information on a drug's therapeutic action, effectiveness, and safety. Currently, evidence generated in traditional randomized controlled trials (RCTs) are considered the most reliable.

Although traditional RCTs remain the gold standard for providing the highest level of medical and scientific evidence needed to support FDA drug product approval decisions, they are often conducted in specialized and controlled research settings. They are also time-consuming and often require millions of dollars and many years to complete. And at the end of a drug development program, RCTs can leave critical questions unanswered, particularly about the effects or impacts of a drug after it is used by hundreds of thousands of people over an extended period of time.

"As the breadth and reliability of real-world data increases, so do the opportunities for FDA to make use of this information."

Scott Gottlieb, MD, FDA Commissioner

CDER's ability to look at drug product data in this post-marketing period — drug use in the "real world" — has been enhanced over the last decade by powerful new scientific computing and data storage technologies. With vast amounts of health-related information now available for analysis, this "real-world data" can help FDA and others such as researchers and regulated industry, to answer post-marketing drug safety questions that could not be previously addressed.

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

RWD comes from both within and outside the health care setting, including electronic health records, medical claims and billing data from health plans, medical product or disease registries, as well as data gathered from wearable personal devices or through health applications ("apps") on mobile devices.

Electronic health records and claims data tell us about conditions or diseases people have, the stages of their disease, the treatments they are receiving, and how they are responding to those treatments. Mobile devices and apps may provide additional information on mobility and activity levels.

Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

RWE may go beyond current post-marketing surveillance capacities, eventually becoming applicable across all phases of drug development. For example, RWE could potentially help to support new indications for existing drugs already being marketed by providing evidence about how a drug works in populations not studied in the original RCT, or how a drug works when used with other drugs. Importantly, RWE can be derived from randomized clinical trials but those trials can be designed to be more integrated into clinical settings, with the goal of providing evidence on how a medical product works in patient care settings.

"Being able to take advantage of data other than those in traditional clinical trials increases our options for research and helps us to gather more information."

Janet Woodcock, M.D., Director, CDER

Potential Benefits of RWD/RWE in Regulatory Decision-Making

- Inform therapeutic development and safety surveillance.
- Improve the efficiency of conducting clinical trials in support of regulatory decisions
- Fill important evidence gaps that are not typically addressed with traditional RCTs (for example, real-world uses of products in patients with multiple illnesses).

Recognizing the increasing role played by both RWD and RWE in health care, Congress mandated, in the 21st Century Cures Act, that FDA publish a framework for a program to evaluate the potential use of RWE to support regulatory decision making for new indications of approved drugs or to satisfy post-marketing study requirements.

An example of using RWD to generate evidence about drug product safety is the Innovation in Medical Evidence Development and Surveillance System, or IMEDS.

IMEDS is a public-private partnership formed by the Reagan-Udall Foundation for the Food and Drug Administration.

A resource that can be used by both public and private-sector organizations, including regulated industry, IMEDS facilitates evaluations of drugs and medical products in collaboration with multiple healthcare data partners who participate in the Sentinel System and the Analytic Center that also operates the Sentinel System activities. Two private sector sponsors completed queries within the first 12 months since the launch of the program.

Through the Sentinel System, FDA routinely uses information from large amounts of electronic healthcare data – real-world data – to better inform regulatory decisions. The IMEDS framework allows private-sector organizations to gain access to data from the Sentinel System while protecting patient privacy and keeping health care information secure. IMEDS also makes the Sentinel System's scientific methods and tools available to organizations outside of FDA who want to conduct important research to advance patient safety.

IMEDS provides distinct advantages for FDA, regulated industry, and foreign regulators, including a large underlying database of privacy-protected information about medical products currently used by millions of patients, detailed descriptions of analyses, publication of findings, and structured querying tools and data quality checking procedures that have been proven to be reliable through FDA use.

Real-world data enables FDA to use more diverse sources of data than data generated solely in traditional RCTs, and to develop better understandings of how drug products behave when taken by millions of people. This will also further and enhance the Agency's options for research – and could increase the speed and efficiency of clinical trials.

As CDER continues to explore the roles of RWD and RWE in drug safety oversight, highlights of FDA's work with RWD and RWE from 2017 are included on the next page.

Programs and Initiatives

- As part of a data analytics initiative at FDA called Information Exchange and Data Transformation (INFORMED), the Oncology Center for Excellence is collaborating with Flatiron Health to examine how RWD can be used to gain insights into the safety and effectiveness of new cancer therapies.
    - In June 2017, FDA announced a partnership with CancerLinQ, the American Society of Clinical Oncology's "big data" initiative. FDA and CancerLinQ will be using real-world, aggregated, de-identified patient care data from oncology practices to understand a variety of issues related to the appropriate use of newly approved therapies. By working with these real-world data to explore questions around the use of new oncologic agents, FDA will better understand how to evaluate the relevance and quality of these data.
- The FDA My Studies App was developed as part of the FDA-Catalyst program within the Sentinel Initiative. This mobile device application can support informed consent and study enrollment as well as secure data collection from patients at multiple study sites or data partners in real-time. This allows researchers to leverage the combined power of existing electronic health data as well as additional data provided directly by patients.
    - The application has an associated web-based study design portal that allows for creation, distribution, and modification of questionnaires on mobile phones with Android (Google) and iOS (Apple) operating systems. The portal makes the app reusable by different research teams.
    - As an initial proof of concept for RWD supporting drug safety and effectiveness research, pregnant women used the app to provide information on exposures to prescription and over-the-counter drug use as well as healthcare outcomes during the last quarter of 2017.

Publication

Multidimensional Evidence Generation and FDA Regulatory Decision Making: Defining and Using "Real-World" Data. Jonathan Jarow, M.D., Lisa LaVange, Ph.D., and Janet Woodcock, M.D. Journal of the American Medical Association, August 22/29, 2017.

Public Presentations

Collection of Patient Provided Information through a Mobile Device Application for Use in Medical Product Safety Surveillance, American Medical Informatics Association Joint Summits on Translational Science, March 2017

Engaging Patients in Evidence Generation, National Academy of Medicine's Clinical Effectiveness Research Innovation Collaborative, April 2017

Developing a Mobile App for Studies of Medication Safety, International Conference on Pharmacoepidemiology and Risk Management, August 2017

Examining the Impact of Real-World Evidence on Medical Product Development, National Academies of Science, Engineering and Medicine, September 19–20, 2017. Dr. Scott Gottlieb delivered the keynote address. Dr. Janet Woodcock presented on "The Regulator's Perspective".

"There's little doubt that the new sources of data now open to researchers, clinicians, and patients hold enormous potential for improving the quality, the safety, and the efficiency of medical care."

Janet Woodcock, M.D., Director, CDER

THE OPIOID EPIDEMIC BY THE NUMBERS

IN 2016...

116
People died every day from opioid-related drug overdoses

11.5m
People misused prescription opioids[1]

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

2.1 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]

948,000
People used heroin[1]

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

170,000
People used heroin for the first time[1]

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

504 billion
In economic costs[3]

Sources: [1] 2016 National Survey on Drug Use and Health, [2] Mortality in the United States, 2016 NCHS Data Brief No. 293, December 2017, [3] CEA Report: The underestimated cost of the opioid crisis, 2017

Updated January 2018. For more information, visit: http://www.hhs.gov/opioids/

Fighting the Opioid Crisis: New Tools, New Approaches

The crisis of opioid analgesic abuse and misuse is one of the nation's most pressing public health challenges. The abuse of prescription opioid drugs has created the most lethal drug misuse, abuse, and overdose epidemic in U.S. history.

In announcing the formation of the Opioid Policy Steering Committee (OPSC) on May 23, 2017, FDA Commissioner Dr. Scott Gottlieb emphasized the need for additional tools and strategies to examine regulatory and policy actions that FDA can take to combat this crisis. The steering committee will direct targeted focus on evaluating efforts the Agency can take to reduce the number of new cases of opioid addiction.

The OPSC has a broad mandate to use the Agency's full authorities in reducing the scope of the opioid epidemic. Within that mandate, Dr. Gottlieb asked the Committee to consider its activities in the context of three pivotal questions:

- Should FDA require some form of mandatory medical education to ensure that prescribers are properly informed about prescribing recommendations, understand how to identify patients at risk of opioid abuse, and how to get addicted patients into treatment?
- Should FDA take additional steps to ensure that the number of opioid analgesic doses an individual patient can be prescribed is more closely tailored to the medical indication (the diagnosis or condition)?
- Is FDA using the proper policy framework to adequately consider the risk of abuse and misuse as part of the drug review process for the approval of opioid medicines?

In establishing a framework for operationalizing these questions, the Commissioner subsequently established four priorities which serve as organizing precepts to guide FDA's opioid activities going forward.

- Decreasing exposure and preventing new addiction
- Treating those with opioid use disorder
- Developing novel pain treatment therapies
- Improving enforcement and assessing benefit-risk

These priorities align with both U.S. Department of Health and Human Services Strategic Priorities, as well as with other national activities, including the Office of National Drug Control Policy recommendations, the National Pain Strategy, and the Comprehensive Addiction and Recovery Act (CARA).

"Addressing the epidemic of opioid addiction is my highest public health priority … I believe it is within the scope of FDA's regulatory tools – and our societal obligations – to take whatever steps we can, under our existing legal authorities, to ensure that exposure to opioids is occurring under only appropriate clinical circumstances, and for appropriate patients."

Scott Gottlieb, M.D., Commissioner, FDA

In establishing these four priorities, Dr. Gottlieb committed the FDA to working across the full scope of the Agency's regulatory capacities and obligations by:

- Updating and extending product labeling; exploring how opioid products are packaged, stored, and discarded, and ensuring that training is available for health care providers—including consideration of mandatory education for physicians and other health care professionals who prescribe opioid pain medications.

- Exploring ways to expand access to naloxone and facilitate the switch to over-the-counter naloxone.

Naloxone is a medication that blocks the effects of opioids, especially in overdose. When given intravenously, naloxone works in about two minutes. When injected into a muscle, it works within five minutes. It may also be sprayed into the nose.

- Supporting development of new opioid analgesic products that are harder to manipulate and abuse (known as abuse-deterrent formulations or ADFs), and facilitating research that can inform benefit-risk assessments for these products.

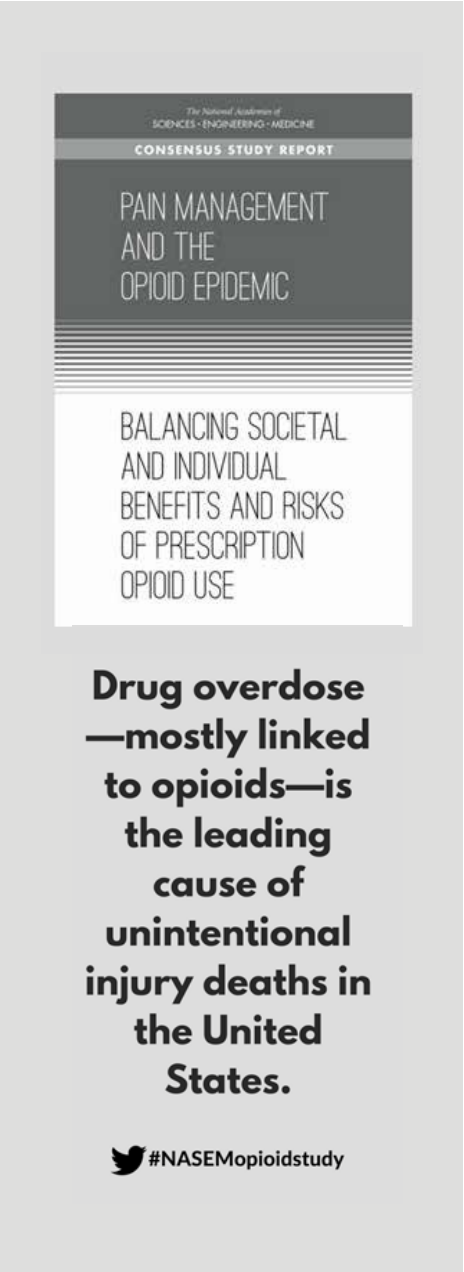
Opioid analgesic products are often manipulated – crushed, powdered, or liquefied – for purposes of abuse. Abuse-deterrent formulations (ADFs), are intended to make manipulation of the product more difficult or make abuse less rewarding. An opioid medicine with abuse-deterrent properties is not less addictive and does not mean there is no risk of abuse, but rather that it may be more difficult to manipulate the product for abuse than it would be without such properties.

- Updating FDA's risk-benefit framework to take measure of the risks associated with misuse and abuse of opioids, and using this information to inform our decisions, including recommending that products be withdrawn from the market.

To better understand the state of the science regarding prescription opioid abuse and misuse, the evolving role that opioid analgesics play in pain management, and other actions the Agency should consider in addressing the opioid crisis—with particular emphasis on strengthening its benefit-risk framework for opioids— the FDA commissioned a study by the National Academies of Science, Engineering and Medicine. The study, Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use, was issued on July 13, 2017. The FDA is now considering and implementing the report's recommendations. The Agency has added a more structured risk-benefit analysis to reviews of opioid products, and will solicit additional feedback to supplement the report's recommendations.

The FDA is actively continuing to incorporate new and emerging public health information and insights to help identify which tools are best suited for application to prescription opioid assessment, and to ensure that FDA acknowledges and includes the public health effects of opioids into its regulatory decision-making framework.

As the Agency takes further steps, it will consider the benefits of opioid pain relievers for patients with severe and chronic pain, as well as the adverse effects of opioids affecting both individual patients and overall public health. By ensuring that the FDA's decision-making tools are matched to the reality of how opioids are used—and misused or abused—the Agency can do more to confront this pressing national crisis.



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Milestones and Highlights 2017

Operating within its regulatory authorities and consistent with its public health mission, and with contributions from throughout CDER and the larger Agency, the FDA has maintained vigorous and sustained efforts aimed at addressing the challenge of opioid abuse, misuse, and addiction. A complete timeline of FDA opioid-related activities can be found here.

Important milestones, actions, and achievements of 2017 are described below.

Regulatory Actions, Research Activities, Reports and Publications

April 20. FDA announced the restriction of the use of opioid medicines codeine and tramadol in children because these medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years. The FDA also recommended against the use of codeine and tramadol medicines in

breastfeeding mothers due to possible harm to their infants. FDA required several changes to the labels of all prescription medicines containing these drugs.

May 9. Draft revisions released for *FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain*. The revised Blueprint contains a high-level outline of the core educational messages that will be included in the educational programs developed under the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS). The Blueprint focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics.

June 8. FDA requested that Endo Pharmaceuticals remove its opioid pain medication, reformulated Opana ER (oxymorphone hydrochloride), from the market based on concerns that the benefits of the drug for patients no longer outweighed its risks when abused. This is the first time FDA has taken steps to remove a currently marketed opioid pain medication from sale due to the public health consequences of abuse.

July 6. Following the FDA's request, Endo announced it would voluntarily remove reformulated Opana ER from the market.

July 6. *The Journal of the American Medical Association* published a Viewpoint article by Drs. Scott Gottlieb and Janet Woodcock, Marshaling FDA Benefit-Risk Expertise to Address the Current Opioid Abuse Epidemic. This article describes FDA's approach to assessing the benefits and risks of opioid drug products, and outlines a structured approach that includes extensive additional review of the risks related to the potential misuse and abuse of opioids.

July 13. The National Academies of Science, Engineering, and Medicine released *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,* a consensus report sponsored by FDA which outlines the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management. Learn more, and watch a short video, about the report here.

August 21. FDA announced that through the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), a multi-site research collaboration between FDA, academia and health insurers, the Agency is conducting research to learn more about medication effects by linking healthcare records for mothers and babies. MEPREP is currently conducting a three-year epidemiologic study to evaluate

a potential association between neural tube defects and maternal exposure to prescription opioid analgesics.

September 20. FDA issued a Drug Safety Communication alerting health care providers and patients that the medications to treat opioid addiction, buprenorphine and methadone, should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). Buprenorphine and methadone are both used as part of Medication-Assisted Treatment (MAT) regimens (the use of medicines in combination with counseling or behavioral therapies). Although the combined use of buprenorphine or methadone and benzodiazepines increases the risk of serious side effects, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks. In concert with the Drug Safety Communication, Dr. Gottlieb issued a statement in which he identified MAT as "one of the major pillars of the federal response to the opioid epidemic in this country."

"We must do everything possible to address the staggering human toll caused by opioid use disorders, and ensuring patients receive proper treatment for both addiction and coexisting mental health conditions is a critical step in that effort."

Scott Gottlieb, M.D., Commissioner, FDA

- **Medication-Assisted Treatment (MAT)** is the use of FDA-approved medications, in combination with counseling and behavioral therapies, to provide a "whole-patient" approach to the treatment of opioid use disorder (OUD).
- MAT offers the potential to help individuals with an OUD to reduce or stop use of opioids.
- Studies have concluded that MAT is the most effective way to deal with OUD – better than either medication or behavioral therapies used independently.
- Three FDA-approved MATs are available: methadone, buprenorphine, and naltrexone. Individuals receiving one of these treatments can cut their risk of death in half.
- Health care providers and patients face challenges when determining how best to treat OUD when the MAT drugs contain methadone or buprenorphine (which are also opioids).
    - Some patients with OUD might have a coexisting chronic condition, such as a mental health disorder, which may require separate treatment using medications that, when combined with the MAT drugs methadone or buprenorphine, may pose serious risks.
    - The Drug Safety Communication alerted health care providers and patients to this risk, and how to address these risks while continuing to maintain MAT.
- Labeling for the MAT drug buprenorphine was strengthened to emphasize that patients may require treatment indefinitely and should continue treatment for as long as they benefit.
- New labeling for MAT drugs recommends that health care providers develop a treatment plan to closely monitor, and taper and discontinue, if possible, use of benzodiazepines in individuals on MAT regimens – while considering other treatment options that the benzodiazepines might have been initially prescribed to address.

September 28. FDA issued letters notifying 74 manufacturers of immediate-release (IR) opioid analgesics intended for use in the outpatient setting that their drugs will now be subject to a more stringent set of requirements under a Risk Evaluation and Mitigation Strategy (REMS) for opioid analgesics. The REMS requires that training be made available to health care providers who prescribe IR opioid analgesics, including training on safe prescribing practices and consideration of non-opioid alternatives. The extended-release/long-acting (ER/LA) opioid analgesic manufacturers also received letters detailing additional modifications to the approved REMS.

A public docket was established to solicit suggestions and comments from patients, health care professionals, industry representatives, and others, on questions relevant to FDA's Opioid Policy Steering Committee.

September 29. A public docket was established to solicit suggestions, recommendations, and comments from interested parties, including patients, patient representatives, health care professionals, academic institutions, regulated industry, and other interested organizations, on questions relevant to FDA's Opioid Policy Steering Committee (OPSC). FDA hopes to better understand areas of focus important to the public and to identify and address opioid product and policy issues that need clarification. The docket closed on December 28, 2017, and responses are now being reviewed.

November 21. A final guidance was issued, General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products. This guidance recommends studies that a pharmaceutical manufacturer seeking approval of a generic opioid product should conduct and submit to FDA, to demonstrate that its generic opioid product (in pill form to be taken orally) is no less abuse-deterrent than its brand name drug counterpart with respect to all potential routes of abuse.

Public Meetings and Workshops

May 9-10, 2017. *Training Health Care Providers on Pain Management and Safe Use of Opioid Analgesics – Exploring the Path Forward* was a public meeting held to discuss and hear feedback on issues and challenges associated with federal efforts to support training on pain management and safe prescribing, dispensing, and safe patient use of opioid analgesics for health care providers.

July 10-11, 2017. *Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities,* a public workshop, explored ways to improve the analysis and interpretation of existing data on ADFs, and discussed opportunities and challenges for collecting and/or linking additional data to improve national surveillance and research capabilities in this area. Dr. Gottlieb offered opening remarks at this two-day workshop.

This workshop is discussed in greater depth in a CDER Conversation, *Measuring the Impact of Opioid Analgesic Formulations with Properties Designed to Deter Abuse in the Real World.*

December 11-12, 2017. *Packaging, Storage, and Disposal Options to Enhance Opioid Safety – Exploring the Path Forward,* a public workshop, explored the role of packaging, storage, and disposal options within the larger landscape of activities aimed at addressing abuse, misuse, or inappropriate access of prescription opioid drug products. Dr. Gottlieb also offered opening remarks at this workshop.

Advisory Committee Meetings

A number of Advisory Committee meetings related to opioid drug products were held in 2017. All addressed complex and pressing opioid-related issues, including the key meetings described below.

FDA Advisory Committee meetings addressed complex opioid-related issues in 2017, including abuse-deterrent products and benefit-risk considerations in the use of prescription opioid-containing cough and cold products in pediatric patients.

March 13-14. A joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee discussed safety issues for Opana ER (oxymorphone hydrochloride) extended-release tablets, indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The committees discussed pre- and post-marketing data about the abuse of Opana ER and the overall risk-benefit of this product, including discussion of generic versions of oxymorphone ER and oxymorphone immediate-release (IR) products.

July 26. A joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee discussed a new drug application for oxycodone hydrochloride extended-release oral tablets with the proposed indication of management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time. The product has been formulated with properties intended to deter abuse, with data submitted to support these abuse-deterrent properties. The committees discussed the overall risk-benefit profile of the product and whether the data submitted demonstrated abuse-deterrent properties for the product.

September 11. The Pediatric Advisory Committee met to discuss use of prescription products containing hydrocodone or codeine for the treatment of cough due to colds in pediatric patients. The discussion included current practice for the treatment of cough in children and benefit-risk considerations in the use of prescription opioid-containing cough and cold products in pediatric patients.

September 14. A joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee discussed Butrans (buprenorphine) transdermal system, evaluating Butrans in pediatric patients ages 7 through 16 for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The committees discussed findings of a clinical study of Butrans conducted in pediatric patients, and whether those findings support additional labeling.

Other Meetings

January 25. Industry Meeting on Modifying extended-release (ER) / long-acting (LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) allowed FDA to invite affected industry sponsors to inform them, and hear feedback about, the Agency's intention to require a REMS for immediate-release (IR) opioid analgesic products intended for use in the outpatient setting, in addition to all ER and LA opioid analgesics to ensure the benefits outweigh the risks of misuse, abuse, addiction, overdose, and death.

April 27. Use of Cough Suppressants in Children was an expert roundtable to discuss the experience of health care professionals with the use of cough suppressants in children 18 years of age and younger, particularly opioid-containing cough medicines, as well as the data available to support recommendations made by various professional societies regarding the treatment of cough in children.

Product Approvals

January 9. Arymo ER (morphine sulfate extended-release tablets), an extended-release (ER) opioid analgesic, is the eighth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling.

January 17. Vantrela ER (hydrocodone bitartrate extended-release tablets), an abuse-deterrent extended-release formulation product.

April 20. RoxyBond (oxycodone hydrochloride tablets), the first immediate-release (IR) ADF product.

November 30. Sublocade, a medication-assisted treatment (MAT) option for moderate-to-severe OUD. This once-monthly injectable buprenorphine product is for treatment of OUD in adult patients who have initiated treatment with a transmucosal (absorbed through a mucus membrane, typically under the tongue) buprenorphine-containing product. Sublocade is indicated for patients that have been on a stable dose of buprenorphine treatment for a minimum of seven days.

Safe Use Initiative: Reducing Preventable Harm from Medications

CDER's Safe Use Initiative (SUI) collaborates throughout the health care system to develop interventions designed to measurably reduce preventable harm from medications. SUI develops, implements, and evaluates a range of interventions, working with various partners committed to safe and appropriate medication use.

Preventable medication-related errors can arise due to a number of reasons. For example, medicines may be dispensed in error, may be taken for too long or not long enough, or may be inappropriately mixed with other medicines or with foods that can increase risks of side effects.

SUI enables many of its collaborations by funding as well as actively participating in projects that will develop innovative methods to encourage research that seeks to reduce preventable harm from drugs, and maintains an open and continuous announcement to solicit research proposals.

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

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

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. These individuals will be targeted for an educational intervention to facilitate safe prescribing practices. This project offers potential to provide a cost-efficient model for reducing preventable harm from high-risk opioid prescribing practices that could be used by other states.

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 on May 12 and July 26, 2016, recommending that FQ antibiotics be used only for patients with no other treatment options when treating sinus infections, bronchitis, and uncomplicated urinary tract infections. FDA also updated the Boxed Warning that now appears in the product labeling of all FQ drugs, detailing the serious adverse events reported with FQ use. To support and further this effort, SUI is partnering with WebMD to decrease potentially inappropriate FQ use in order to reduce adverse events. Physicians who prescribe more FQs than others in their specialty will be provided with feedback about their prescribing relative to their same-specialty peers and/or be given educational materials regarding FQs. The impact of these interventions will then be measured. WebMD is also providing consumer-level education materials on FQs via their website and magazine. By reaching both patients and prescribers, this project aims to reduce adverse events.

FDA Health Care Professional Communication Project. Safety information changes over time. Doctors need the most current information to provide optimum care – but they receive far more information than they can digest. This project sought to discover what sources of information and what formats are most likely to be read by physicians. Thirty-nine physicians from different geographic areas and a broad range of specialties participated, revealing that while physicians had positive regard for FDA, they were most likely to focus on communications from their specialty society sent via email with a subject line containing key words to alert them to the safety

information. The findings from this project will help FDA understand 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 high risk of hypoglycemia (low blood sugar). This tool will help healthcare providers devote their attention to the 11 percent of diabetics who are at high to moderate risk of experiencing severe low blood sugar. By partnering with the Transforming Clinical Practice Initiative (a part of the Centers for Medicare and Medicaid Services), SUI is moving this tool from the research setting to use in medical offices across the country.

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 intravenous (IV) and oral liquid medications. A nationwide expert panel has proposed standards for IV medications while a second panel works 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.

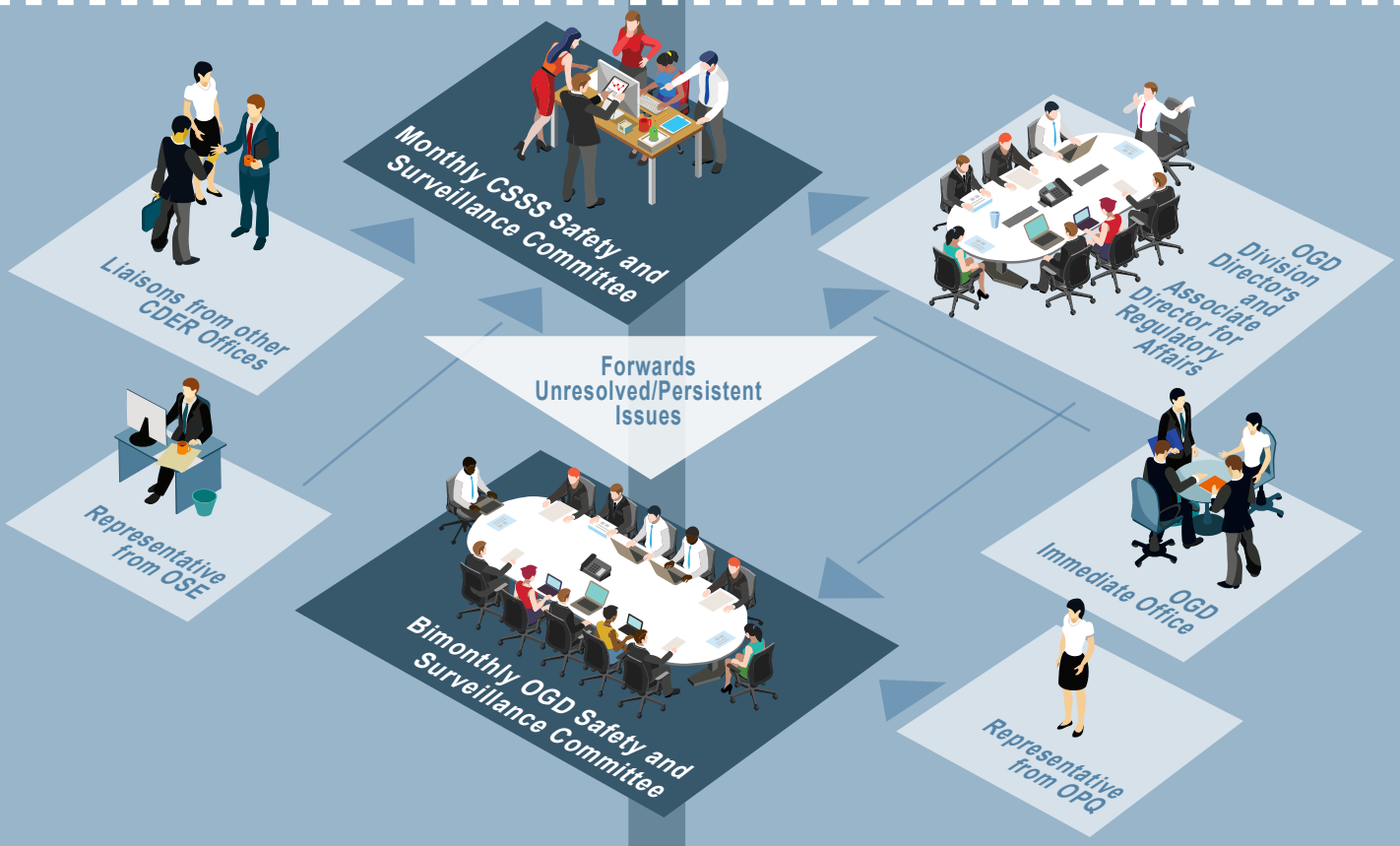
High-Alert Medication Safety Self-Assessment for Hospitals and Targeted Risk Reduction Tool Development. "High-alert medications" have an increased risk of causing significant patient harm when they are used in error. These include medications such as insulin, anticoagulants, opioids, cardiac drugs, and anesthetic agents. Strategies to prevent errors with these and other high-alert drugs are well known, but the extent to which healthcare institutions have adopted these best practices is unknown. In this SUI-funded project, the Institute for Safe Medication Practices (ISMP) has developed a self-assessment tool for hospitals to evaluate their level of implementation of these best practices. Participating institutions can then submit their results anonymously. By analyzing these data, ISMP will identify national opportunities to improve medication safety.

CDER's Safe Use Initiative enables many of its collaborations by funding as well as participating in projects that will facilitate innovative methods to encourage research that seeks to reduce preventable harm from drugs.

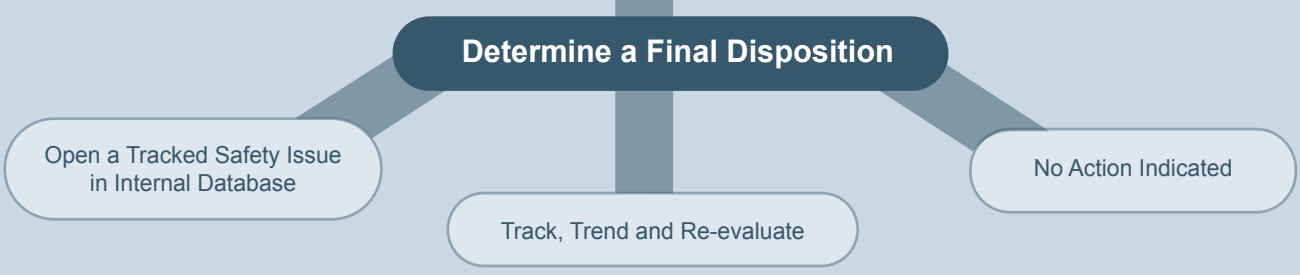
Tracking and Managing Generic Drug Safety Issues

INCOMING GENERIC DRUG SAFETY ISSUES

OGD REVIEW AND ASSESSMENT



FINAL DISPOSITION



Safety Surveillance for Generic Drugs

Established in 2014, CDER's Office of Generic Drugs (OGD) Clinical Safety Surveillance Staff (CSSS) facilitates collaborative projects with other CDER Offices, establishing coordinated partnerships that further CDER's commitment to generic drug quality, surveillance, safety and therapeutic equivalence.

The CSSS:

- Obtains and coordinates information regarding the safety and surveillance of generic drug products.
- Serves as OGD's liaison to CDER's Office of Surveillance and Epidemiology and other drug surveillance units within CDER.
- Interacts with external stakeholders such as physicians, pharmacists, patients, and patient advocacy groups to investigate reports of adverse events or therapeutic inequivalence of generic drugs.

CSSS evaluates post-marketing reports of potentially inferior generic product quality, adverse events and other safety concerns, and assess reports of different therapeutic effects compared to the relevant reference listed drug (the "brand name" drug). Results of these investigations are further evaluated by an interdisciplinary team, and if a significant safety issue is identified, that team works collaboratively with other relevant CDER offices to resolve the issue.

In addition to its post-marketing safety surveillance activities, the CSSS also reviews all expedited serious adverse event safety reports from pre-approval bioavailability (BA) and bioequivalence (BE) studies.

Pre-approval safety reports are required for all BA/BE studies conducted in the U.S. The CSSS's comprehensive review of this important safety data helps to flag early safety concerns related to generic drugs before they are submitted to FDA for approval. Any safety concerns are addressed through collaboration within OGD and across CDER to assure the safety of new generic drugs.

One of the CSSS's activities is addressing post-marketing safety concerns related to complex generic drug-device combination products. The FDA allows some differences in generic drugs (in inactive ingredients, but not in the active medication component) and delivery system devices (for example, inhalers, injectors, or patches), or both, as compared to the brand name drug. However, these minor differences in generic drug and device could lead to unexpected safety consequences.

A key example of this kind of challenge from 2017 involved a generic drug with two intravenous (IV) bag ports (rather than a single IV bag port used by the brand name drug). This difference raised concerns for potential confusion, risk of incompatibility issues, and potential adverse events in patients. The CSSS's collaboration activities led to the development of a new process for managing review of similar IV bags with different port configurations.

Compounded Drugs: Continuing Regulatory and Oversight Efforts

Compounding is 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.

Compounded drugs can 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, improperly compounded drugs, or drugs compounded under substandard or insanitary conditions, can pose critical health risks such as contamination or products that are either sub- or super-potent.

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 CDER with new regulatory authorities through passage of the Drug Quality and Security Act (DQSA) in 2013. CDER is working quickly to implement the compounding provisions of the DQSA, directing many new inspection and enforcement initiatives to protect the public from poor quality compounded drugs. Throughout

2017, CDER continued its efforts in compounding-related inspections and enforcement actions, policy development, state collaboration and coordination, and stakeholder outreach by:

- Conducting more than 140 inspections of compounders throughout the United States, many of which have been for-cause based on serious adverse events or product quality issues.
- Issuing more than 55 warning letters to compounders describing significant violations of the law that could put patients at risk.
- Overseeing about 40 recalls involving compounded drugs.
- Working with the Department of Justice to obtain favorable resolutions in two civil enforcement actions and three criminal enforcement actions.
- Issuing one revised draft guidance document, and four final guidance documents.
- Holding two meetings of the Pharmacy Compounding Advisory Committee.
- Holding one intergovernmental working meeting with states in addition to numerous one-on-one meetings and interactions.
- Collaborating and coordinating with state regulators on FDA inspections and enforcement.
- Holding seven listening sessions with over 50 stakeholder groups, including pharmacy, hospital, long-term care, and other medical organizations; consumer and patient advocacy groups; insurers, and outsourcing facilities.

Learn more about the FDA's compounding work here.

Throughout 2017, CDER continued its efforts in compounding-related inspections and enforcement actions, policy development, state collaboration and coordination, and stakeholder outreach.

Communicating Drug Safety: Strategic Outreach Through Diverse Tools and Services

CDER's Office of Communications (OCOMM) continued to support FDA's mission to protect and promote public health across a wide range of tools and platforms throughout 2017. With nearly 100 staff members including health professionals, communications specialists, and web and graphic designers, OCOMM:

- Provides strategic communication advice to CDER and Agency leadership
- Develops and coordinates overarching public communication initiatives and educational activities
- Devises and deploys comprehensive communication strategies that ensure consistent branding, messaging, and direction of CDER's communication initiatives and tools
- Offers expertise on communication products across a variety of media
- Conducts risk communications research

Communicating about drug safety is a key aspect of OCOMM's priorities. This is operationalized through many new and ongoing activities across a diverse portfolio of tasks and services, including external and internal communications, Web-based and social media, and responding to public and trade press inquiries related to drug products.

CDER Trending Topics 2017 on the following pages offers a snapshot of the year's topic and query traffic that populated the communications platforms CDER uses to disseminate health messages and respond to queries. These metrics illustrate the frequency with which safety-related issues are searched for, queried, are subjects of news stories and other informational outlets, reported by secondary sources, and carried via newsfeeds and social media. Searches that arrived at www.fda.gov/Drugs on desktop computers and mobile devices accounted for nearly 17 million individual sessions.

CDER Trending Topics

January - December 2017

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CDER WEB TRAFFIC

TRAFFIC VOLUME

www.fda.gov/drugs

	Sessions*
Desktop	11,533,158
Mobile Devices (Tablets, Cell Phones)	5,431,889

TRAFFIC SOURCES

	% of Sessions
Search Engines	70
Direct Sources (URL's)	16
Referrals	10
Email	2
Social Media	2

TOP 5 GOOGLE SEARCHES

Clicks (Data for Aug - Dec)

1. Eucrisa
2. Kratom
3. Triclosan
4. Recalls
5. Orange Book

*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.	Safe Disposal of Medicines: What you should know	546,998
2.	Drug Approvals and Databases	387,188
3.	National Drug Code Directory	359,531
4.	What's New Related to Drugs	311,506
5.	Guidances (Drugs)	291,467
6.	FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together	288,817
7.	Information for Healthcare Professionals: Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (marketed as Cipro and generic ciprofloxacin), ciprofloxacin extended-release (marketed as Cipro XR and Proquin XR), gemifloxacin (marketed as Factive), levofloxacin (marketed as Levaquin), moxifloxacin (marketed as Avelox), norfloxacin (marketed as Noroxin), and ofloxacin (marketed as Floxin)]	276,894
8.	Guidance, Compliance and Regulatory Information	212,142
9.	Medication Guides	208,333
10.	Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)	199,887

†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	539,681
CDER Engagement	
Posted Content	124
Replied to Comments	1,125
Public Likes/Shares	27,664

LINKEDIN

www.linkedin.com/company/fda

Total Followers	108,472
SBIA Showcase Page	2,063
GADIS Group	435

TWITTER

www.twitter.com/FDA_Drug_Info

Total Followers	235,283
Tweets	458
Retweets	5,904
Likes	5,003

CDER Trending Topics

January - December 2017

TRENDING TOPICS ON SOCIAL MEDIA*

ALS	627,455
Marijuana + FDA	311,690
Sunscreen	300,603
Kratom	191,239
Opioids	169,054
Expedited Reviews Pathway	83,064
Biosimilars	68,688
Drug Pricing	48,417
Body Building Supplements	44,043
Off Label Marketing	28,256

*CDER Selected Topics on Brandwatch

TOP 5 MEDIA NEWSFEED TRENDING TOPICS MENTIONED*

1. ALS	36,804
2. Expedited Review Pathways	33,009
3. Sunscreen	20,067
4. Biosimiliars	17,386
5. Off-Label Marketing	9,058

*Brandwatch

TOP 10 PUBLIC INQUIRIES

TOTAL NUMBER OF INQUIRIES	**57,305**
1. Personal Importation	1,329
2. INDs/SPIs/EINDs	1,290
3. Fluoroquinolones	947
4. Registration (DRLS)	853
5. Importation - Industry	845
6. OTC Products	781
7. Clinical Trials	671
8. Drug Disposal	444
9. PROLIA/Denosumab	345
10. EpiPen Recall	337

FDA | CDER | Office of Communications

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Public inquiries – over 50,000 in 2017 – received expert responses 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. These interactions may be in the form of phone, email, or mail.

PUBLIC QUERIES RECEIVED BY	
Phone	39,883
Email	16,269
Letters	942
TOTAL	**57,094**

Drug Safety Communications (DSCs) provide critical updates and vital new information regarding potential risks of FDA-approved drugs for patients, caregivers, pharmacists, health care providers, and the public. These messages and announcements involve new or emerging risks or cautions about potential medication errors, including issues affecting a large number of patients, potentially serious or life-threatening adverse events, or medication errors that may result in serious or life-threatening adverse reactions.

Twelve DSCs issued in 2017.

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 Drug Safety Communication web page is one of the most visited pages on the FDA's web site.

The DSC home page and the 12 individual DSC web pages received half a million page views in 2017—but outreach of this safety information was significantly greater as DSCs are more broadly circulated through many other channels, including listservs, email newsletters, podcasts, social and traditional media, and targeted outreach to media, healthcare professionals, advocacy groups and other stakeholders.

Drug Safety Podcasts provided emerging safety information about drugs in conjunction with the release of Drug Safety Communications. Twelve podcasts were issued in 2017, and are available online via RSS feed, and in iTunes.

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.

Director's Corner Podcasts featured CDER Director Dr. Janet Woodcock. Two Director's Corner Podcasts in 2017 focused specifically on safety issues, *Antibiotic Misuse and Resistance*, and *FDA's Adverse Event Reporting System (FAERS)*. The podcasts are available for download. Transcripts are also available at the same page.

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. Of seven webinars produced in 2017, four focused on drug safety concerns:

February 7. Collaborating with FDA – Get Involved with FDA's MedWatch Adverse Event Reporting Program

March 7. FDA Post-Marketing Drug Safety Surveillance

April 4. Fluoroquinolone Safety Labeling Updates

November 21. Tainted Products Marketed as Dietary Supplements

Safety Labeling Changes

Not every safety concern can be identified at the time a medicine is approved for marketing. If new safety concerns emerge after a drug is marketed, FDA may require a Safety Labeling Change.

The Safety Labeling Changes (SLC) program data and web access operations migrated to a new online platform managed by OCOMM in late 2016, making drug safety labeling information available in real time, and searchable through a user-friendly portal for stakeholders such as health care providers, pharmacists, patients, and health IT and information vendors. The new platform responded to rapid developments in web and database technologies, and has been continually refined throughout 2017.

"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.

Stakeholders accessing the database offered invaluable feedback throughout the year that has helped OCOMM to continually upgrade the manner in which data is organized and presented – including implementing an interactive calendar for reporting and introducing data format changes which more closely reflect the format of an actual prescription drug label.

SLCs are made in one or more of the eight sections in a drug label. Over 3,000 new SLCs were added to the SLC database in 2017.

SAFETY LABELING CHANGES IN 2017	
Adverse Reactions	572
Boxed Warnings	119
Contraindications	265
Drug Interactions	536
Patient Counseling Information, Patient Information, and/or Medication Guide	594
Use In Specific Populations	406
Warnings and Precautions	746
Physician Labeling Rule Conversions	95
TOTAL	**3,333**

A Safety Labeling Change (SLC) conveying new or revised information about a drug is applied to all products that contain that drug. A specific drug may be marketed in different forms (for example, as a liquid, tablet, for injection or inhalation, for topical application, or as part of a combination product) and in both brand-name and generic versions of products. The SLC database counts each of these labeling actions individually.

Risk Communications Research

OCOMM continued to conduct risk communications research activities throughout 2017. 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 several articles published or accepted for publication in peer-reviewed journals. OCOMM also presented throughout the year at several conferences, including the 2017 National Rx Drug Abuse & Heroin Summit, the Annual Meeting of the American Public Health Association, International Conference on Communication in Healthcare & the Health Literacy Annual Research Conference, and the National Communications Association.

The Physician Labeling Rule (PLR) governs the content and format of drug prescribing information ("labeling"). The goal of the PLR requirements is to enhance safe and effective use of prescription drug products by providing health care providers with clear, concise, easy- to-access information. Drug products approved on or after June 30, 2001 are required to convert from the older labeling format to PLR format. These conversions are considered safety labeling changes and are reflected in the table as "Physician Labeling Rule Conversions".

Research Activities in 2017

- 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 and patients of these medicines. The aim of this study 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.

- A multi-pronged study aimed at enhancing FDA communications addressing opioids and other potentially addictive pain medications, continued throughout 2017. 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, the general public, and chronic opioid users. Analysis and reporting from this study will be completed in early 2018.

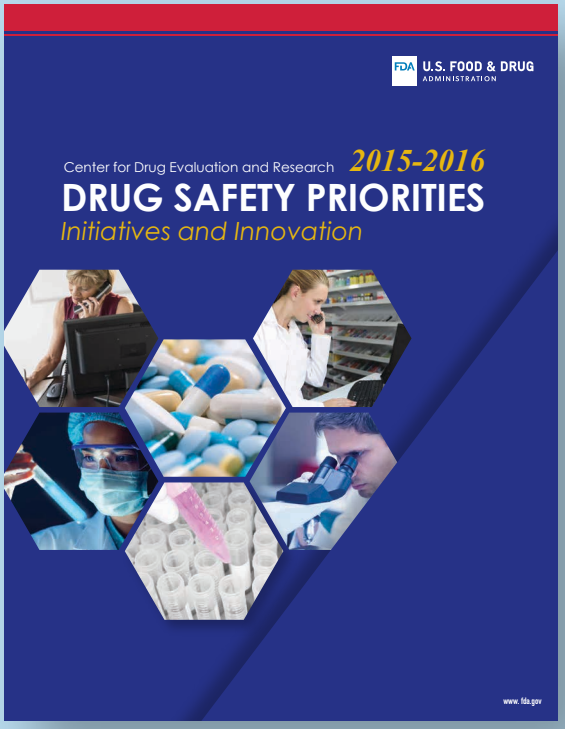
- Data collection was completed for a study investigating the effectiveness of various messages about medical countermeasure drugs that might be used in the event of a chemical, biological or radiological terrorist attack or other health threats. The results of the study, which will be completed in late 2018, will provide the basis 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 uncertainty and unintended consequences associated with prescription drug and drug safety information. Once testing is completed in 2018, the framework and the associated recommended practices being developed as part of this research will be shared for use across all of FDA's various risk communications staff and teams.

Publications

Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. *Journal of Health Communications,* May 2017. (Published online March 24, 2017.)

Patient and Physician Perceptions of Drug Safety Information: A Qualitative Study. *Drug Safety,* June 2017. (Published online February 28, 2017.)



Download the 2015-2016 version of the **Drug Safety Priorities Report**

https://www.fda.gov/downloads/Drugs/DrugSafety/ucm523486.pdf

With millions of Americans taking more medicines than at any time in history, an unanticipated drug safety problem can rapidly escalate to become a major public health threat—demanding a response rooted in multidisciplinary scientific teamwork. FDA has made great strides over the last decade in developing its drug safety enterprise, fueled by broad collaborations both within the Agency and with stakeholders representing academia, industry, and the public. To better describe these activities, we established an annual safety report with CDER Drug Safety Priorities 2015-2016: Initiatives and Innovation. Going beyond previous reporting efforts to offer a more comprehensive picture of FDA's drug safety portfolio, our 2015-2016 report joins the current one in offering updates on our many drug safety activities, research, publications, and other programs.

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