



CENTER FOR DRUG EVALUATION AND RESEARCH

U.S. Food and Drug Administration

U.S. Health and Human Services

DRUG SAFETY UPDATE – 2014

Initiatives, Programs, Innovation and Ongoing Work

April 2015

2014 marked another strong year for FDA's Center for Drug Evaluation's (CDER) new drug approvals, with many of its 41 novel new drugs offering innovative treatments for patients in need. Equally important as these drug development and review successes is CDER's continued expansion of drug safety oversight and safety science, encompassing all phases of the drug product lifecycle — from premarket development, to the review and approval process, to ongoing monitoring after products are on the market.

As 2015 unfolds, CDER's advances in monitoring drug safety reflect synergies created by a growing range of resources, including bioinformatics and systems pharmacology, pharmacovigilance, pharmacogenomics, and improved adverse event surveillance. Several key programs—representing only a fraction of FDA's overall drug safety portfolio—are highlighted below.

PREMARKET

- ***Modernized review and approval methods to ensure safety.*** CDER's 21st Century Review guides CDER's performance and accountability standards when reviews of new drugs involve multiple offices. CDER's 21st Century Review makes the review process more organized and integrated and allows sufficient time at the end of the process to confirm that concerns from all contributing disciplines have been heard and addressed by the decision maker. The procedures also help to ensure timely identification of drug safety issues during the review period, to allow for appropriate communication with sponsors, and to determine if further action is needed to address these issues.
- ***Earlier and better understanding of safety information during new product review.*** CDER's JumpStart program—recognized as an HHS Innovates "Secretary's Pick"—is a bioinformatics platform that runs clinical trial data analyses early in the review process to evaluate data composition, quality and other parameters. JumpStart allows reviewers to better understand incoming data and spot safety signals earlier in the review process. Like 21st Century Review, JumpStart encourages multidisciplinary collaboration, which improves both quality and speed of communication with sponsors to resolve data issues or questions.

POSTMARKET

- ***Incorporating "active surveillance" into the safety tool box.*** FDA's Sentinel Network is a national, integrated electronic system for monitoring medical product safety through shared health care databases (with care taken to protect personal health information). Sentinel, one of the first active surveillance infrastructures focused on characterizing safety issues related to pharmaceuticals and other medical products, partners 50-plus healthcare and academic organizations in a fully operational surveillance system.
- ***Drug Safety Communications (DSCs) remain key elements in FDA drug safety education and outreach.*** CDER's Office of Communications (OCOMM) has fully redesigned the DSC format,

creating a single primary safety message that targets both consumer and professional audiences and assists prescribers, patients and health care agencies in making informed choices about drug therapies. The DSC web page is one of the most visited on the FDA website, with millions of page views every year. OCOMM also deploys various digital tools (e.g., blog posts, social media applications, Tweets) to effectively carry drug safety information to different audiences.

COMPOUNDING

Increased oversight of compounded drugs in 2014. After the 2012 outbreak of fungal meningitis associated with contaminated compounded sterile drugs, CDER actively strengthened efforts to inspect compounders and take appropriate regulatory and enforcement actions. In calendar year 2014 CDER directed and evaluated findings from over 100 inspections of compounders throughout the United States. Problems were identified in a majority of these inspections, prompting numerous compounders to initiate voluntary product recalls and, in some cases, to stop sterile production. As problems are identified at compounding pharmacies across the country during 2015 and beyond, CDER will continue to vigorously pursue inspection and enforcement efforts. CDER has also made significant progress in implementing the Compounding Quality Act and publishing policy documents applicable to compounding pharmacies and outsourcing facilities. In 2014, FDA published three final guidance documents, three draft guidance documents, one proposed rule, and announced the members of the newly reconstituted Pharmacy Compounding Advisory Committee. So far in 2015, FDA has issued four draft guidance documents related to human drug compounding and repackaging, and a draft memorandum of understanding between a state and the FDA addressing certain distributions of compounded human drug products. FDA also held the first meeting of the reconstituted Pharmacy Compounding Advisory Committee on Feb. 23-24, 2015. On March 6, 2015, FDA established a public docket to receive information, recommendations, and general comments on matters related to the Agency's regulation of human drug compounding that are not specific to documents or issues that are the subject of other dockets.

ORGANIZATIONAL INNOVATION AND ONGOING WORK

Structuring and re-structuring the CDER workforce to meet ever-evolving safety needs is critical for success. Here are some examples:

- ***Office of Pharmaceutical Quality (OPQ)***, fully reorganized for a January 2015 launch, centralizes review of the quality of new and generic drugs from early development through postmarket availability. The OPQ reorganization establishes (among a number of safety-related assets) the Office of Process and Facilities with process and facility inspection divisions and the Office of Surveillance for postmarket inspections and safety surveillance in conjunction with the Office of Regulatory Affairs.
- ***Office of Surveillance and Epidemiology (OSE)*** is integral to CDER drug safety efforts by evaluating the safety profiles of drugs using a variety of tools and disciplines throughout the

product lifecycle. OSE maintains a postmarket surveillance system and operates a risk assessment program to identify adverse events that did not appear during the drug development process, helping to identify drug safety concerns and recommend actions to improve product safety.

- **Office of Drug Security, Integrity and Response (ODSIR)** within the Center’s Office of Compliance protects patients from unsafe, ineffective, or poor quality drugs by improving the security of the drug supply chain. On November 27, 2013, the Drug Supply Chain Security Act (DSCSA) was signed into law, providing a new federal framework for an electronic, interoperable system to trace drug products as they are distributed within the United States. The Act also enhances CDER’s ability to protect consumers from drugs that may be counterfeit, stolen, or intentionally contaminated. Key DSCSA requirements take effect in 2015 and CDER will continue to ensure efficient implementation and compliance by supply chain stakeholders.
- **Office of Generic Drugs (OGD)** has seen several advances including a major reorganization in 2014, which included the establishment of the Clinical Safety and Surveillance Staff (CSSS) to provide oversight of generic postmarket safety and surveillance (with many other OGD staff) and coordination with other CDER Offices. The CSSS and other OGD staff are responsible for detecting and responding to complex issues related to the therapeutic equivalence of generic drugs to the reference (branded) drug, as well as formulation-related safety issues. Last year, as part of the processes under CDER’s Safety First Initiative (see below), OGD safety staff worked on many other potential safety issues involving generic products. As part of the Regulatory Science component of the Generic Drug User Fees Amendments (GDUFA) of 2012, OGD staff also oversaw many internal and extramural research activities related to the safety and postmarket surveillance of generic drugs.
- **Safety First Initiative**, launched in 2008, continues to ensure drug safety throughout the product lifecycle by giving equal focus and attention to postmarket drug safety as is given during the premarket drug review. The Initiative also helps implement FDA’s postmarketing safety authorities provided under the Food and Drug Administration Amendments Act of 2007 (FDAAA). Multidisciplinary inter-office teams assess significant drug safety issues that arise in the postmarket period, identify the appropriate actions, and monitor sponsors’ responses to those actions.
- **Safe Use Initiative (SUI)** facilitates public-private collaborations within the healthcare community to reduce preventable harms of medication use. Improper medication use increases the risk of harm from medication, often resulting in thousands of preventable injuries or deaths each year. SUI seeks to reduce these preventable harms by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use. CDER is in a unique position to facilitate this collaborative process given the Agency’s intersection with industry, the healthcare system,

and other government agencies directly involved with public health. SUI stakeholders include other Federal agencies such as the Drug Enforcement Agency (DEA) and the Centers for Disease Control and Prevention (CDC), pharmacies and hospitals, healthcare professionals, professional licensure and oversight boards, insurers, and patients and consumers.

- **Safety Research Investigation Group (SRIG).** On March 10, 2015, CDER's SRIG issued a report for stakeholders, "Assessing CDER's Drug Safety-Related Regulatory Science Needs and Identifying Priorities." The report supports CDER's continuing efforts to assess safety-related research needs, strategize internal research efforts, and communicate key safety-related research needs that would benefit from collaboration with external research partners such as other FDA Centers, government agencies, and academia. The SRIG helps CDER to assess and maximize the value of safety research, identify gaps in ongoing safety research, and facilitate efforts to close those gaps.

CDER has helped to create and develop more than 20 public-private collaborations that offer extensive amounts of technical experience and expertise. These collaborations are all serving to protect public health by advancing drug safety. Key examples include:

- **Critical Path Initiative (CPI)** — a joint effort of industry, academia, professional societies, trade associations, advocacy groups, and the federal government — supports a national effort to transform the ways that FDA-regulated medical products are developed, evaluated, and manufactured.
 - **Critical Path Institute (C-PATH)**, a public-private partnership under the auspices of CPI, accelerates drug product development through the creation of drug development tools (DDTs) which aid in safety evaluation of new therapies. One set of vital DDTs are biomarkers — distinct chemical, genetic, or molecular indicators that point to a particular condition or biological process. Identifying a specific biomarker (usually in a blood sample) can alert drug developers and FDA reviewers to potential drug safety-related concerns.
 - **ECG Warehouse**, also established under the CPI and co-sponsored by FDA and the Duke Clinical Research Institute, develops tools for early identification of potential adverse effects that drugs and devices may have on heart rhythms. Tapping a vast database ("warehouse") of ECGs collected by FDA from clinical trial data submitted as part of new drug applications, ECG patterns help identify which patients are at increased risk for potentially life-threatening cardiac arrhythmias, in turn shaping development of safer drugs.
- **Innovation in Medical Evidence Development and Surveillance (IMEDS)**, a public-private partnership created under the auspices of the Reagan-Udall Foundation, builds on progress made in research methodologies by the FDA's Sentinel Network. IMEDS advances the science

needed to support the generation of postmarket evidence about drug products, including safety surveillance and safety evaluations.

FDA has taken many steps to establish parity between premarket drug safety review and evaluation of drug safety in the postmarket setting. Moving forward, all of our safety efforts will remain thorough, systematic, and scientific as they continue to support our parallel efforts to advance innovation and to help ensure that safe and effective new therapies are available to the American public.
