

# Advances in FDA's Safety Program for Marketed Drugs

Establishing Premarket Safety Review and Marketed Drug Safety  
as Equal Priorities at FDA's Center for Drug Evaluation and Research



**Center for Drug Evaluation and Research**  
U.S. Food and Drug Administration  
U.S. Health and Human Services

## **Introduction**

In today's modern regulatory environment, the role of the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) in working to ensure drug safety includes two equally important areas: premarket review and postmarket monitoring.

FDA's safety assessment of medicines does not diminish after drugs are approved for marketing. Although the premarket phase of study is very intensive, much work still remains to monitor approved drugs over time. No drug is risk-free, and it is not uncommon for new information to be discovered after a drug is on the market and being used by larger numbers of patients. Such information helps provide a better picture of drug risks, enables FDA to give health care professionals and patients the latest information on potential or newly identified risks, and strengthens FDA's ability to safeguard patients against unacceptable risks.

In this report, FDA describes the actions CDER has taken in recent years to enhance the quality, accountability, and timeliness of its postmarket drug safety decisions. As a result, FDA now oversees the safety of both innovator and generic marketed drugs with the same rigor and focus as for premarket drug review. These efforts include the development of important new scientific tools to enhance detection of potential drug safety issues that occur once a drug is on the market and new methods for planning, managing, tracking, and communicating about those issues.

### **Working to ensure safety throughout a drug's entire life cycle**

FDA's Center for Drug Evaluation and Research monitors and reviews safety information throughout a drug's entire life cycle, from marketing application through approval and after the drug is marketed, addressing any new safety issues that are identified. Adverse reactions may become apparent only after a drug is marketed and used more widely, under more diverse conditions (e.g., concurrent use with other drugs) or when the drug is prescribed for uses for which it was not approved (i.e., "off-label" uses). In some cases, medication errors can occur because the name of the drug is confused with the name of another drug, so that the patient receives the wrong medicine. In other cases, factors that influence the selection, prescribing, preparation, or administration of the medication can lead to medication errors and adverse events. As new safety information related to a drug becomes available postmarket, a multidisciplinary team reviews the data to evaluate whether there is an emerging drug safety concern.

Interpreting postmarket safety data is complex, involving analysis and detailed review of a wide range of information, including spontaneous reports of adverse drug events, controlled clinical trials and epidemiologic studies, active surveillance efforts, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse events, the pharmacology of the drug in relation to the identified safety concern, and other relevant information. Decisions about how to address a safety concern and interpret the available data often are a matter of judgment, about which reasonable and informed persons with relevant expertise may disagree. Experts within FDA engage in robust and comprehensive discussions regarding potential drug safety issues, considering all points of view before making a decision on how to proceed.

### **Key catalysts for positive change at FDA**

By the early 2000s, methods and techniques used in the science of evaluating drug safety had greatly evolved beyond those used in the 1980s and 1990s. These included stronger capabilities for predicting potential adverse effects from drugs, such as dangerously abnormal heart rhythms and liver toxicity, which were key safety issues for certain drugs during that time period. As a result, FDA began conceptualizing changes needed to keep up with these important advances.

A key step towards implementing those early concepts for change formally began in November 2004, when the Agency launched a comprehensive plan to strengthen its safety program for marketed drugs.<sup>1</sup> Among a variety of other innovative ideas, the plan included an FDA request that the Institute of Medicine (IOM) study and conduct a complete review of FDA's postmarket drug safety system.

The Agency's enhanced postmarket safety system of today has its roots in the launch of this plan. However, in 2007, with passage of the Food and Drug Administration Amendments Act (FDAAA), which greatly revised laws governing Agency responsibilities, FDA was given a wide array of new authorities in drug safety to help further implement the goals of its 2004 plan and strongly effect change.

Some of the important safety provisions in FDAAA were stimulated by the IOM report requested by FDA. The report, issued in 2006, identified opportunities for development of more effective scientific tools at FDA to detect and evaluate emerging drug safety issues once a drug is on the market. The report also noted that FDA needed additional legal authorities (many of which FDAAA provided) and resources to effectively address drug safety issues.

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<sup>1</sup> <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108370.htm>

## **Implementing FDAAA: Enhancements to FDA's drug safety program**

Since FDAAA was passed in September 2007, FDA has accomplished a comprehensive set of enhancements that have strengthened and modernized the Agency's drug safety program. These include:

- New capabilities for detecting and responding quickly to drug safety issues that emerge after marketing;
- Enhanced quality, speed, and transparency of FDA's decisions about how to address specific drug safety issues;
- Earlier and more effective drug safety communication to the public; and
- Stronger protection of patients from preventable medication errors.

## **Executing necessary changes**

FDA has made significant advances in four major areas to execute FDAAA provisions and effect necessary changes in postmarket drug safety. These are:

- 1. Safety First:** FDA created Safety First, a set of internal organizational and cultural changes in the Center for Drug Evaluation and Research, to create a strong drug safety infrastructure for postmarket monitoring and surveillance, and to respond to new safety information identified in the postmarket setting. Safety First was designed to ensure that postmarket drug safety is given as much attention as premarket safety review and to enhance the quality and timeliness of specific postmarket drug safety decisions. This program has provided needed expertise and capacity and a commitment to FDA's drug safety program, new ways of prioritizing and addressing safety issues, and the addition of many new safety officials on staff.
- 2. Safe Use:** As an external public outreach complement to Safety First, FDA instituted the Safe Use Initiative, which identifies areas of preventable drug harm caused by inappropriate uses of medicine. This non-regulatory effort comes from the collaboration of a wide array of sectors of the health care community to enhance the safe and appropriate use of FDA-regulated drugs. As many as 1.5 million Americans are injured or killed each year by inappropriate use (including errors and misuse) of FDA-regulated drugs.<sup>2</sup> Through the Safe Use initiative, FDA is building public and private coalitions throughout the health care community to increase the safe use of drug products and reduce preventable drug harm for all Americans.

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<sup>2</sup> Institute of Medicine, Preventing Medication Errors. July 2006, available online at <http://www.iom.edu/Reports/2006/Preventing-Medication-Errors-Quality-Chasm-Series.aspx>.

- 3. Strengthening Drug Safety Science:** FDA has advanced a variety of scientific tools and capabilities to strengthen its ability to monitor, assess, and manage drug safety, both during drug development and after a drug is marketed. The Agency's Sentinel Initiative is developing the Sentinel System, a national electronic system for monitoring the safety of FDA-approved medical products. An effort to bring drug chemistry and pharmacology to bear on understanding drug safety by using the tools of systems pharmacology and bioinformatics is underway. Other major actions to advance drug safety monitoring include enhanced capabilities of statistical analysis, expansion of a dedicated program to conduct epidemiologic studies, new capabilities to study drug safety through pharmacogenomics (i.e., "personalized medicine"), improved adverse event surveillance, and leveraging government resources by partnering with other government agencies.
  
- 4. Drug Safety Communications:** FDA has strengthened its drug safety communications to provide earlier and more useful information to patients and health care professionals about drug safety issues as they emerge. In 2011, FDA issued 68 Drug Safety Communications (DSCs) to the public—an average of more than one DSC a week. By comparison, the Agency issued 39 DSCs in 2010. FDA's Drug Safety Communication webpage is one of the most visited pages on the Agency's website, with over 8 million page views last year.

These four above areas are the pillars upon which FDA built its strengthened postmarket drug safety system and are discussed in further detail below:

### **The Four Pillars of FDA's Strengthened Postmarket Drug Safety System**

#### **1. Safety First: Enhancing the quality, timeliness, and transparency of safety decisions throughout a drug's life cycle:**

FDA developed a series of internal initiatives collectively called the Safety First program, which was launched in 2008. The overarching goal of Safety First is to ensure that FDA gives the same priority to the oversight of the safety of marketed drugs as it does to premarket safety review. More specific objectives of Safety First include:

- Prioritizing postmarket safety issues according to their degree of risk to patient safety;
- Enhancing the quality and timeliness of specific drug safety decisions so that FDA responds quickly and appropriately to emerging safety issues;
- Ensuring that drug safety decisions are made collaboratively, using a team model that considers all relevant scientific viewpoints; and

- Implementing the drug safety authorities and responsibilities authorized by Congress in FDAAA.

Some of the most important changes under Safety First are described below.

### **A roadmap for change**

In implementing the policy of giving equal priority to postmarket safety and premarket safety review, FDA created a clear pathway for addressing a life cycle approach to drug safety issues, beginning with the premarket review of safety data through the detection, analysis, and communication of any postmarket safety issue that emerges. This pathway includes:

- **Prioritizing risk.** A new policy on prioritizing postmarket safety issues, to make sure the most significant potential risks are given the highest priority and addressed as rapidly as possible;
- **Expert review.** Assignment of each significant safety issue to a multidisciplinary team of FDA experts who provide timely evaluations of potential risk and recommend appropriate action based on all relevant viewpoints;
- **Scientific expert advice.** Guidelines for when to seek advice from additional internal and external experts on safety issues;
- **Public communications.** New frameworks for early communication of potential drug safety issues to the public, including updates as more information becomes available;
- **Timelines.** Timelines for decisions to assure that even complex and controversial issues are addressed in a timely way;
- **Rationale for decisions.** Procedures for documenting the reasons for final decisions, including the reasons why some viewpoints or recommendations were not followed; and
- **Oversight and accountability.** A tracking system to make sure that the evaluation and resolution of each safety decision for a significant postmarket safety issue is following the roadmap.

### **Generating a strong spirit of collaboration**

Safety First was used by FDA to help establish a policy of inclusion and respect for all scientific voices as an essential part of sound regulatory science-based decision making. The 2006 IOM report on drug safety identified opportunities for

more effective handling of low morale and discord between and/or within premarket drug reviewers and postmarket drug safety evaluators at FDA.

To address these issues, FDA's Center for Drug Evaluation and Research created a multidisciplinary team approach to drug safety decisions, which has helped generate strong collaboration among all of the offices involved in drug safety. These include the Office of New Drugs (OND), primarily responsible for premarket drug safety, and the Office of Surveillance and Epidemiology (OSE), primarily responsible for monitoring postmarket drug safety data. Other offices involved in this multidisciplinary approach are the Office of Biostatistics, the Office of Clinical Pharmacology, the Office of Translational Science, the Office of Pharmaceutical Science, the Office of Compliance, and the Office of Generic Drugs.

Since 2008, FDA has undertaken a series of organizational and management actions to help ensure that 1) all scientific viewpoints are freely expressed, understood, and brought into the drug safety decision-making process, and 2) significant safety issues are managed by multidisciplinary teams that include representatives from OND, OSE, and all other relevant CDER offices.

**The Equal Voice Initiative:** FDA created the Equal Voice Initiative in response to observations that all relevant offices within CDER sometimes did not have equal input with regard to safety decisions. The goals of Equal Voice are to assure that:

- All relevant viewpoints are brought into the drug safety decision-making process;
- Each professional viewpoint has been fully expressed, understood, and considered;
- Drug safety decisions are made in a mutually respectful professional environment; and
- All participants in drug safety decisions reach alignment on the appropriate decision. In cases in which alignment cannot be reached, CDER has developed processes to resolve professional differences within a scientific discipline and across scientific disciplines.

To create the more inclusive, respectful culture envisioned by the Equal Voice Initiative, FDA has instituted training in dispute resolution, held town hall meetings, and provided other avenues for broad input on Equal Voice goals. To put these goals into practice, Equal Voice establishes that each scientific discipline has the lead in decisions related to its expertise. Where drug safety decisions are to be made, Equal Voice requires that the lead office or decision-maker invite the input of all relevant disciplines and organizational components into the process of evaluating risk and of determining the appropriate response

(for example, adding a warning or withdrawing a drug). If there is disagreement, the decision is escalated up the organizational chain in each office to include increasing levels of senior staff, to the point at which alignment can be reached. As a result, all scientific and professional viewpoints of CDER staff involved in safety decisions, across all offices of the Center, are considered with the same amount of respect and priority.

- **Multidisciplinary teams and joint decision-making:** In June 2008, FDA established two new policies for handling significant safety issues. Each new significant safety issue is managed by a multidisciplinary team including members of OND and OSE. Once a significant safety issue is identified, OND and OSE, with other CDER offices as needed, jointly determine and reach alignment on the steps needed to resolve the issue.
- **Restructuring and expansion of OSE:** In 2006, FDA modified its reporting structure such that the office directors of OSE and OND would each report directly to the center director. This important managerial change helped establish parity between these two important offices that lead drug safety efforts at FDA. Since 2007, when OSE staff numbered 123 employees, the Office has nearly doubled in size, expanding to a current total of 245 employees to handle the Agency's enhanced emphasis on postmarket drug safety.
- **New safety staff in OND:** The Office of New Drugs established specific safety positions within each of its 18 divisions that review applications for new drugs. Each division's deputy director for safety and the safety regulatory project manager ensure that postmarket safety issues that arise related to the drugs approved in their division are handled effectively.

### **Meaningful and measurable change**

The organizational and culture changes instituted by FDA under Safety First have made a measurable difference. Results from the 2011 CDER employee viewpoint survey showed a notable increase in job satisfaction from the 2008 survey, as well as high scores on questions that reflect the sense of purpose and accomplishment those employees feel. The surveys also show high scores on employee trust in their supervisors and confidence that their supervisors listen to what they have to say. CDER scored high in such major index areas as the "Overall Satisfaction" and "Best Places to Work." CDER continues to pay attention to and work on improving areas where the survey scores were not as high as desired, such as having a reasonable workload, having sufficient resources, and meeting training needs.

## Safety First's implementation of FDAAA's drug safety provisions

The Safety First Initiative has successfully implemented many new authorities to monitor postmarket drug safety. The following is a list of the most significant safety provisions under FDAAA and the status of their implementation:

- **Postmarket studies and clinical trials:** FDAAA granted FDA the authority to require manufacturers to conduct postmarket safety studies and clinical trials at the time of or after the approval of a drug. These studies can be required to assess a known serious risk, to assess a signal of a serious risk, or to identify an unexpected risk when there is evidence of the potential for such a risk. Prior to FDAAA, these studies were conducted as voluntary commitments by manufacturers. Since 2008, FDA has required more than 385 postmarket drug safety studies. FDA published a final guidance on implementation of this authority in March 2011.<sup>3</sup> FDA tracks manufacturer progress on these required studies and annually reports these tracking results to Congress<sup>4</sup> and in the *Federal Register*.
- **Required labeling changes:** FDAAA granted authority to FDA to require a change in a drug's label to include new safety information. Prior to FDAAA, FDA did not have authority to order such label changes if the company did not voluntarily make the change. Since 2008, FDA has required new safety labeling 65 times using its FDAAA authority, generally for whole classes of drugs (e.g., providing safety information on the adverse effects on newborns of antipsychotic drugs taken during pregnancy). FDA published a draft guidance on implementation of this authority in April 2011 and is working to finalize this guidance.<sup>5</sup>
- **REMS authorities:** Under FDAAA, FDA has authority to require manufacturers to implement special risk management programs, called risk evaluation and mitigation strategies (REMS), for their products if FDA believes such a program is necessary to assure that the drug's benefits outweigh its risks. REMS programs utilize tools that go beyond routine labeling. Their requirements may range from the relatively simple, such as education for patients in the form of written information called Medication Guides, to the more complex, such as required training or certification for health care providers, patient monitoring, restricting use to particular health care settings, requiring medical tests as a condition for dispensing, or enrollment in a patient registry. Since 2008, FDA has required 64 REMS programs with these more complex requirements. FDA is well aware of the need for patients to promptly receive their medications as well as the workload issues of health care professionals. For these reasons,

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<sup>3</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>

<sup>4</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM291520.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf>

FDA designs REMS programs to maintain patient access to needed drugs and to avoid unduly burdening the health care system. For example, because FDA could require a REMS, FDA was able to approve a new drug, Sabril (vigabatrin), for the treatment of epilepsy. This drug has a risk of new and worsening vision loss, including permanent vision loss. This REMS program's goals are to ensure that patients and health care professionals are informed about the drug's risks, patients' vision is monitored, and problems are detected as early as possible.<sup>67</sup>

- **Quarterly online reports:** In accordance with FDAAA, on a quarterly basis FDA posts two types of online reports and summaries related to adverse event reports.
  - As required by FDAAA, FDA has been conducting twice-monthly screenings of AERS and posting the required quarterly reports since the first quarter of 2008.<sup>8</sup> The reports list any potential signals of serious risks or new safety information that were identified using the AERS database during the indicated quarter.
  - Since June 2010, FDA has posted online summary information about ongoing and completed postmarket safety evaluations of adverse experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007.<sup>9</sup> The evaluations are done to determine if there are: any new serious adverse events not previously identified during product development; known side effects reported in unusual numbers; or potential new safety concerns now that the products are being used in the general population.

## **2. Safe Use: Reducing preventable harm from medications:**

In 2009, FDA launched the Safe Use Initiative to reduce preventable drug harm caused by inappropriate use, such as unintentional overdose or inappropriate prescribing. The Safe Use Initiative has established partnerships with other federal agencies, health care professionals, consumers, and others interested in drug and patient safety, to create collaborative efforts that include a wide variety of different sectors of the health care community. Through these collaborative, non-regulatory efforts, the Safe Use Initiative supports the regulatory work of FDA to address postmarket drug safety. Below are several examples of the Safe Use Initiative's activities:

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<sup>6</sup><http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187533.pdf>

<sup>7</sup><http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187533.pdf>

<sup>8</sup><http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm>.

<sup>9</sup><http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm>

- **Preventing acetaminophen toxicity:** Acetaminophen, used for treating pain and fever, is an active ingredient in more than 600 prescription and over-the-counter medications. Daily dosing in excess of the recommended maximum labeled dose is associated with serious liver injury and death. Acetaminophen overdose is the most common cause of drug-induced liver injury leading to liver transplant in the United States. FDA has an ongoing public education campaign, is participating in education coalitions, and has taken and is considering taking new regulatory actions. As an outgrowth of FDA's regulatory actions, Safe Use is working closely with the National Council for Prescription Drug Programs in gaining agreement from stakeholders, including data software vendors and pharmacies, to remove the abbreviation "APAP," a common abbreviation for acetaminophen, from prescription labels and replace it with "acetaminophen." In addition, the coalition is working to ensure that the liver warning is displayed on all prescription vials that contain acetaminophen. Adoption of these recommendations will increase consistency of information on the drug vial label, reduce consumer confusion, and potentially eliminate some overdose problems. In addition, Safe Use provides FDA advisors to the Acetaminophen Awareness Coalition's "Know Your Dose" campaign.
- **Antipsychotic use in elderly with dementia-related psychosis:** Both conventional and atypical antipsychotics are associated with an increased risk of death in elderly patients treated for dementia-related psychosis. The Safe Use Initiative has teamed up with the Centers for Medicare and Medicaid Services (CMS) to examine CMS' claims data for elderly patients with dementia and to determine if these drugs remain associated with preventable harm. Using the data obtained from CMS, the Safe Use Initiative will collaborate with CMS and health care professionals, state and federal agencies, and consumer organizations to develop interventions that promote safe prescribing and the safe use of medications in our nation's elderly.
- **Medication adherence:** The National Consumers League (NCL) leads "Script Your Future," a nationwide multimedia campaign to improve public health by raising consumer awareness of the importance of medication adherence. The Safe Use Initiative has joined in supporting the efforts of this broad cross section of public and private stakeholders.
- **Prescription opioids:** Errors in the prescribing and use of opioid analgesics can increase risk and lead to serious harm, including death. The harm caused by these errors and other types of misuse is preventable. To increase the safe use of opioid analgesics, the Safe Use Initiative formed the Opioids Patient Prescriber Pain Treatment Agreement Working Group. This collaboration comprises thought leaders and experts from patient advocacy organizations, pain management specialists, safe prescribing advocates, health literacy experts, and others. It is part of a larger, multi-pronged, multi-agency effort

to address the public health concerns around the inappropriate use, misuse, and abuse of opioid analgesics.

- **Research opportunities:** By creating opportunities for innovative research in areas of preventable drug harm and ways to increase safe use of drugs or drug classes, the Safe Use Initiative continues to promote FDA's mission to protect public health. The Safe Use Initiative has created funding opportunities for ten innovative research projects addressing preventable drug harm in a wide variety of areas, such as opioid prescribing, gluten content of drugs, effects on celiac disease, antibiotic usage and *Clostridium difficile* susceptibility, and improving the safe use of medications in Americans with diabetes. Safe Use continues to find ways to foster collaboration and research around increasing the safe use of and reducing the preventable harm from FDA-regulated drugs.

There are many other examples of Safe Use Initiative programs. For a more complete list, visit

<http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm188762.htm>.

### **3. Strengthening drug safety science: New capabilities for detecting, investigating, managing, and monitoring drug safety issues:**

Over the past several years, FDA has developed a variety of new drug safety tools and capabilities to detect, investigate, manage, and monitor drug safety issues. Below are some key examples:

**The Sentinel Initiative:** Although FDA had been planning new electronic advanced capability for monitoring drug safety prior to the passage of FDAAA,<sup>10</sup> FDAAA specifically authorized the Agency to establish a system for postmarket risk identification and analysis. As a result of this planning and FDAAA's provision of new authorities for implementation, FDA launched the Sentinel Initiative,<sup>11</sup> a long-term program to create a national electronic system for securely accessing health care data to monitor the safety of drugs and other FDA-regulated medical products. Once completed, the system will be called the Sentinel System. Much of the development of FDA's Sentinel System is being conducted via FDA's Mini-Sentinel pilot program, a large-scale working model of the eventual full-scale Sentinel System.<sup>12</sup> The Mini-Sentinel System enables FDA to assess medical product safety issues, by utilizing secure access to the electronic health care information of more than 125 million patients, provided by 17 data partners nationwide. For a summary overview of the Sentinel Initiative, visit <http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf>

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<sup>10</sup> <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm113621.htm>

<sup>11</sup> <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm089474.htm>

<sup>12</sup> MiniSentinel website available online at <http://mini-sentinel.org/>

**Advancing risk evaluation during drug development:** FDA has made strides in advancing the evaluation of potential risks into the development of new drugs, so that risks are identified early and risk management strategies are considered when FDA is deciding whether to approve a drug. For example, FDA issued guidance to industry in 2005 on how sponsors could design, conduct, analyze, and interpret clinical studies to assess the potential of a drug to cause serious and potentially fatal heart problems;<sup>13</sup> in 2008, on how sponsors could demonstrate that a new anti-diabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk;<sup>14</sup> and in 2009, to assist the pharmaceutical industry and other investigators who are conducting new drug development in assessing the potential for a drug to cause severe liver injury.<sup>15</sup>

**Statistical analysis:** The Office of Translational Science's Office of Biostatistics (OB) employs more than half of FDA's statisticians. OB provides CDER's safety scientists with safety evaluation support throughout the full life cycle of FDA-approved medical products and now has a team of biostatisticians dedicated exclusively to postmarket safety evaluation. OB supports CDER in quantitative safety and efficacy evaluation of drugs and therapeutic biologics through a full-cycle review approach.

In October 2009, OB established a new division, called the Division of Biometrics VII (DBVII), focused on full-cycle drug safety evaluation. This division has expertise in evaluating randomized trials designed primarily to evaluate safety, design and analysis of observational studies (including propensity score and marginal structural models expertise), meta-analyses, signal detection, survey methodology, Bayesian methods in drug safety, data-mining techniques, time series analysis, graphical and computational methods for quantitative safety evaluation, and analyses of registry and health care databases. DBVII has performed a variety of safety evaluations of significant regulatory importance, two of which are described below.

- *Rosiglitazone and Pioglitazone Meta-Analysis of CV Events:* Rosiglitazone, for treatment of type II diabetes mellitus, was re-evaluated for cardiovascular safety following the initial findings in 2007. DBVII conducted parallel patient-level meta-analyses across 52 studies to characterize the risk. Pioglitazone, another product in the same class, was evaluated as well. The statistical evaluation provided indirect comparison between these two products. In addition, DBVII provided independent assessment of 21 published observational

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<sup>13</sup> E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf>

<sup>14</sup> Guidance for Industry, Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf>

<sup>15</sup> Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

studies as well as the statistical support of a study performed on Medicare data. Based on the evaluations, Rosiglitazone had to undergo significant labeling changes and marketing restrictions, which limits its use to current users only.

- *Antidepressants and Suicidal Outcomes:* In 2006, CDER statisticians presented the FDA Psychopharmacologic Drugs Advisory Committee with a meta-analysis of 295 placebo-controlled trials of modern antidepressants, examining the association of these drugs with suicidal outcomes. Overall, the analysis did not show a relationship between these drugs and suicidal outcomes. However, a clear trend was found with younger patients having a higher risk of suicidal outcomes associated with these drugs compared to older patients. These findings were incorporated into a boxed warning for all antidepressants. Because of the overall rarity of the outcome, 40% of the trials did not have any outcome event. A series of Bayesian models were used to examine the sensitivity of the primary analysis method. The models were constructed similarly to those described in Kaizar et al (2006).<sup>16,17</sup>

**Epidemiology studies program:** FDA has expanded its program to conduct epidemiologic studies to answer important drug safety questions. When FDA staff identify an important safety issue for which an observational epidemiological study is appropriate, one option is that FDA epidemiologists and statisticians can work with outside collaborators who have both the access to large, population-based health care data and the expertise to use those data for drug safety studies. The addition of a statistics team dedicated to postmarket safety analysis has facilitated the expansion of this program. Three examples of epidemiology studies from this program are described below.

- *ADHD drugs and heart risks in young and middle-aged adults:* More than 1.5 million U.S. adults use stimulants and other medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD). These agents can increase heart rate and blood pressure, raising concerns about their cardiovascular safety. In order to examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults, a population-based cohort study using electronic health care records was conducted. Among young and middle-aged adults, current or new use of ADHD medications as

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<sup>16</sup> Overall background on the study can be found at <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf>. Reference: Kaizar E, Greenhouse J, Seltman H, Kelleher K 2006. Do Antidepressants Cause Suicidality in Children. *Clinical Trials* 3:73-98

<sup>17</sup> The results of the sensitivity analysis appear on slide 27 of the presentation: [http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4272s1-04-FDA\\_files/frame.htm](http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4272s1-04-FDA_files/frame.htm).

compared with non-use or remote use was not associated with an increased risk of serious cardiovascular events.<sup>18</sup>

- *ADHD drugs and heart risk in children and youth:* Adverse event reports have raised concerns that the use of drugs for ADHD increases the risk of serious cardiovascular events in children and young adults. FDA safety scientists identified serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke) from health plan data and vital records. This large study showed no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events.<sup>19</sup>
- *Medication Exposure in Pregnancy Risk Evaluation Program:* Although the number of prescription medications approved for use during pregnancy is limited, doctors in clinical practice must prescribe needed medicines to pregnant women to treat a variety of illnesses or conditions. Insufficient information exists about the use of drugs during pregnancy and associated outcomes in the infant and fetus. To overcome these challenges, the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) was established. MEPREP links health care records for mothers and their offspring (and birth certificate data) in each of the participating research sites. The 11 participating health plan-affiliated research sites within the 3 contract sites have health care information for 1,221,156 children delivered to 933,917 mothers. Nine publications are currently submitted or in preparation.<sup>20</sup>

**Pharmacogenomics:** Sometimes called “personalized medicine,” pharmacogenomics is the science of determining how genetic variability influences physiological responses to drugs, from absorption and metabolism to pharmacologic action and therapeutic effect.<sup>21</sup> With increasing knowledge of the molecular basis of drug action has come the recognition of the importance of an individual's genetic makeup in influencing drug response. This understanding of the genetic variations in drug response opens the door to personalized medicine by 1) identifying patients who are more prone to experience adverse events from a drug and 2) identifying patients who are more likely to benefit from a particular therapy. Below are three examples of FDA's use of pharmacogenomics in drug safety:

- **Warfarin:** Warfarin (Coumadin and generics), an anticoagulant, provides an example of the clinical use of pharmacogenomics to improve dosing. Warfarin

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<sup>18</sup> ADHD Medications and Risk of Serious Cardiovascular Disease in Young and Middle-Aged Adults. Habel L et al., JAMA December, 2011.

<sup>19</sup> Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth. Cooper WO et al., New England Journal of Medicine. November 2011

<sup>20</sup> Andrade et al. Medication Exposure in Pregnancy Risk Evaluation Program. Maternal Child Health J. 2011 Oct 15. [Epub ahead of print]

<sup>21</sup> Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nat Rev Drug Discov. 2004;3(9):763-9.

has a narrow therapeutic window and a wide range of inter-individual variability in response, requiring careful clinical dose adjustment for each patient. Genetic variants in the warfarin target, the vitamin K epoxide reductase (VKORC1), as well as the warfarin-metabolizing enzyme cytochrome P450 2C9 (CYP2C9), influence the variation in patient response. Patients with certain variants of these genes eliminate warfarin more slowly and typically require lower warfarin doses. In those individuals, a traditional warfarin dose would more likely lead to an elevated International Normalized Ratio (INR), a longer time to achieve a stable warfarin dose, and a higher risk of serious bleeding events during the induction or dose-titration period of warfarin therapy. Genotype-based dosing recommendations were recently added to the drug's label.

- **Codeine:** Another example involves ultra-rapid metabolizers of codeine, who have multiple copies of the gene for cytochrome P450 2D6 (CYP2D6), the enzyme that converts codeine into its active metabolite, morphine. Nursing mothers who are taking codeine and are ultra-rapid metabolizers could have high levels of morphine in their breast milk, increasing the risk of morphine overdose in their nursing infant. Although most nursing mothers can take codeine safely after childbirth, health care practitioners should prescribe the lowest dose for the shortest period of time to relieve pain, and nursing infants should be carefully monitored when breastfeeding women receive this drug.<sup>22,23</sup>
- **Carbamazepine:** Pharmacogenomic studies have recently identified a genetic marker in patients, the human leukocyte antigen (HLA) allele HLA-B\*1502, which is associated with dangerous, sometimes fatal, skin reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) following treatment with the antiepileptic drug carbamazepine (Carbatrol, Equetro, Tegretol, and generics). Since the HLA-B\*1502 allele is found almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians, health care practitioners should screen patients with ancestry in at-risk populations for the HLA-B\*1502 allele prior to initiating treatment with carbamazepine. Patients who test positive for HLA-B\*1502 should not be treated with carbamazepine unless the expected benefit clearly outweighs the increased risk of SJS/TEN.<sup>24</sup> In weighing these risks and benefits, it is important to recognize that other anti-epileptic drugs are associated with these serious skin reactions as well.

Testing is available to identify the genetic variations that have been associated with warfarin, codeine, and carbamazepine toxicities.

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<sup>22</sup><http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124889.htm>

<sup>23</sup><http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124889.htm>

<sup>24</sup><http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm>

**Enhanced adverse event surveillance:** Due to increased societal awareness of the importance of drug safety and many efforts by FDA to encourage voluntary reporting of adverse events, the Agency has seen a steady rise in the number of adverse event reports submitted to FDA's Adverse Event Reporting System (AERS). In fact, in one recent five-year period, the number more than doubled, from 323,384 reports in 2005 to 673,259 in 2010. This increase has been beneficial to FDA scientists because it is providing a larger amount of information for their safety assessments. However, the growing volume has also created challenges in terms of information management. To address the increasing volume of adverse event reports, FDA has developed effective data mining algorithms to identify patterns of potentially drug-related adverse events that often might otherwise not be noticed in such a large number of reports. The output of data-mining analyses, along with other surveillance methods, enables FDA to effectively detect signals from these reports that may indicate new or increased risks from marketed drugs. FDA posts these signals on its drug safety website on a quarterly basis and provides quarterly updates to the signals.<sup>25</sup> In addition, in analyses of AERS data, FDA has developed methods to systematically examine the safety of newly approved drugs, which is particularly important since they have not been on the market for long periods of time nor used by extremely large populations of patients. Therefore, it is more likely that new safety issues may arise with such products. FDA posts these findings to the FDA website to keep the public informed.<sup>26</sup>

**Enhanced Safety Focus in OGD:** The Office of Generic Drugs (OGD) established a postmarket surveillance and safety team within the Division of Clinical Review. The safety team evaluates and tracks reports of potential inferior generic product quality, adverse events, and reports of different therapeutic effect compared to the relevant reference listed drug. The results of these investigations are further evaluated by an interdisciplinary team and, if a significant safety issue is identified, OGD works collaboratively with OSE, OND, and other CDER offices to resolve the issue.

**Collaboration with other federal agencies:** FDA has worked with other federal agencies to study important drug safety questions. Collaborations with the Veterans Administration (VA), the Department of Defense (DoD), and the Centers for Medicare and Medicaid Services allowed FDA to use large health care databases for epidemiological analyses. An example is presented below.

To investigate concerns that the smoking cessation medication Chantix (varenicline) causes adverse neuropsychiatric events, FDA sponsored two observational studies of neuropsychiatric adverse events with Chantix. One

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<sup>25</sup><http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm>

<sup>26</sup><http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm>

was conducted by the VA Center for Medication Safety, and the other by the DoD U.S. Army Medical Command's Pharmacovigilance Center. The VA study examined and carefully compared medical records of 14,131 Chantix users and an equal number of users of nicotine replacement therapy, an alternative treatment to aide smoking cessation. The study found no significant difference in the rate of hospitalization for psychiatric disorders between the two groups of patients. Using a similar approach, the DoD study carefully compared medical records of 11,978 Chantix users and an equal number of users of nicotine replacement therapy. This study also found no significant difference in the rate of hospitalization for psychiatric disorders between the two groups. A strength of both studies was the inclusion of patients with pre-existing psychiatric disorders, since these patients were typically excluded from the clinical trials conducted with Chantix before it was approved (i.e., in premarketing trials). Based on these findings and other information, FDA determined that the current warnings in the Chantix drug label remain appropriate. FDA is continuing to evaluate the risk of neuropsychiatric adverse events with Chantix.<sup>27</sup> The manufacturer of Chantix, Pfizer, is conducting a large safety clinical trial of Chantix to assess neuropsychiatric adverse events as outcomes. Results from this trial are expected in 2017.

#### **4. Enhanced communications: Earlier and more useful communication about drug safety:**

Since 2007, FDA has substantially restructured its drug safety communication program to provide earlier, more consistent, and more useful information to patients and physicians about drug safety risks as they emerge. These changes reflect feedback from the public, which indicated a desire for FDA to make information available about potential drug risks as early as possible.

As part of its re-evaluation of drug safety communications, FDA has created a systematic approach to providing the public with information about possible new drug risks and how FDA is addressing them.

With this goal in mind, FDA has made several important changes:

- FDA's new default position is to communicate a safety issue to the public as early as possible, unless there is a strong rationale for not communicating;

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<sup>27</sup> <http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm>

- There is now a single format for communicating drug safety issues, called a Drug Safety Communication (DSC), as opposed to the multiple formats used in the past;
- FDA is undertaking studies of the most effective methods of communicating drug safety issues, from understanding what platforms are most useful for different types of communications (e.g., website postings, social media, press releases) to understanding what information different audiences need and in what form;
- FDA publishes articles in medical journals to explain the evidence and analyses used by FDA to make its benefit-risk assessments for specific drugs; and
- FDA regularly seeks advice from its internal Drug Safety Oversight Board, comprising representatives of the Agency's federal partners (Centers for Disease Control & Prevention, Veterans Administration, Centers for Medicare and Medicaid Services, Department of Defense, Indian Health Service, Agency for Healthcare Research and Quality, and National Institutes of Health) and its Risk Communication Advisory Committee of outside experts, created by FDAAA, on how to communicate drug risks.

FDA has carried through with its commitment to communicate early and often about new drug safety issues. In 2011, FDA issued 68 DSCs, up from 39 DSCs issued in 2010. These communications reflect the Agency's ongoing commitment to communicating postmarket safety issues. The DSC webpage<sup>28</sup> has now become one of the most visited pages on FDA's website, receiving more than 8 million page views in 2011.

Recently, FDA issued an update to the draft guidance "Drug Safety Information, FDA's Communication to the Public," which provides the Agency's current thinking on how FDA develops and disseminates information to the public on important drug safety issues, including emerging drug safety information.<sup>29</sup>

For more information on FDA's Drug Safety Communications, visit <http://www.fda.gov/drugs/drugsafety/ucm199082.htm>

## Conclusion

Efforts in recent years to enhance the Agency's emphasis on postmarket safety, such as the successful implementation of new regulatory authorities provided by FDAAA, key initiatives such as Safety First, Safe Use, and strengthened safety

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<sup>28</sup> <http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>.

<sup>29</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM295217.pdf>

science, and our enhanced public communications efforts, have all contributed to the Agency reaching equality between premarket and postmarket priorities. FDA's current drug safety program, which includes using a team-oriented approach to drug safety issues and providing all relevant disciplines an equal voice in developing solutions, has also helped the Agency reach its important safety objectives.

However, like all other areas of science, drug safety science is dynamic and evolving. FDA recognizes that ongoing success requires a constant ability to adapt to new information and new technologies. Efforts to date have created a safety system that includes thorough scientific rigor across the entire life cycle of FDA-approved drugs, which establishes our future ability to navigate the inevitable changes that occur when keeping pace with advances in science.

Future directions for improving the science of drug safety include enhanced review methodologies to analyze meta-analyses, better use of wireless technologies to transmit drug safety information from the point of care to FDA, continued advances in pharmacogenomics, innovative uses of secure access to safety data from electronic health care records, and improved toxicological methods to predict adverse events.

Moving forward, all FDA's safety efforts, while they will remain thorough, systematic, and scientific, will continue to be designed to support parallel efforts to advance innovation and to help ensure that safe and effective new therapies are available to the American public as efficiently as possible.