DRUG SAFETY

Highlights of FDA's report, *Advances in FDA's Safety Program for Marketed Drugs*

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

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

The U.S. Food and Drug Administration (FDA) has taken many actions in recent years to enhance its postmarket drug safety program. As a result, FDA's Center for Drug Evaluation and Research now oversees the safety of marketed drugs with the same emphasis it has for premarket safety review. Efforts include the development of new scientific tools to help detect potential drug safety issues after a drug is on the market and new methods for planning, managing, tracking, and communicating about those issues.

This brief document highlights information from a larger 20-page FDA report from April 2012 titled *Advances in FDA's Safety Program for Marketed Drugs*. The report is a comprehensive compilation of information describing FDA's current drug safety program and its multi-faceted work to help ensure a safety system that includes thorough scientific rigor across the entire lifecycle of FDA-approved drugs.

The complete report is available at:
http://www.fda.gov/DrugSafetyReport2012

FDAAA

Key catalysts for positive change at FDA

Although FDA initiated formal planning of long-term safety changes as early as 2004,[1] many of FDA's actions associated with assuring marketed drug safety were enhanced by new authorities provided in the Food and Drug Administration Amendments Act of 2007 (FDAAA). Some of FDAAA's provisions were stimulated by a 2006 report from the Institute of Medicine (IOM),[2] which noted that FDA devoted more attention and resources to premarket drug safety review than to postmarket drug safety. Since FDAAA was passed in September 2007, FDA has made significant advances in four major areas to enhance its focus on postmarket drug safety:

Safety First:
An FDA initiative establishing internal policies and procedures that give premarket drug safety review and postmarket safety monitoring an equal focus.

Safe Use:
FDA's effort to help make sure that medicines are used safely and appropriately and to help Americans avoid preventable medication errors.

Strengthening Drug Safety Science:
From developing the Sentinel System, a national electronic system for monitoring FDA-approved medical products, to a wide variety of advances in specific safety sciences, to leveraging resources by collaborating with other government agencies, FDA has strengthened its overall capabilities in utilizing drug safety science to protect public health.

Drug Safety Communications:
FDA's communications program, which provides updated drug safety information and earlier and more useful information to patients and physicians about emerging drug safety issues.

Enhancements in these four areas are the pillars upon which FDA has built its strengthened postmarket safety program. Highlights of each are discussed in further detail on the following pages.

[1] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108370.htm
[2] Institute of Medicine, The Future of Drug Safety: Promoting and Protecting the Health of the Public, September 2006, available online at http://www.iom.edu/Reports/2006/The-Future-of-Drug-Safety-Promoting-and-Protecting-the-Health-of-the-Public.aspx

SAFETY FIRST

A team approach involving all disciplines at FDA

In 2008, to ensure equal priority between premarket drug safety review and postmarket safety, FDA launched an internal program called Safety First, a key initiative that has helped create FDA's current drug safety program. This effort included:

The Equal Voice Initiative, which assures that all relevant disciplines are involved in drug-related decisions, including drug safety, and each viewpoint is fully considered.

Increased and enhanced safety staffing. Since 2007, FDA has doubled the size of the staff of its Office of Surveillance and Epidemiology (OSE), the office primarily responsible for postmarket drug safety monitoring. Additionally, the Office of New Drugs (OND) established specific safety positions within each of its 18 divisions that review applications for new drugs. Each division's deputy director for safety and safety regulatory project manager ensure that postmarket safety issues that arise related to the drugs approved in their division are handled effectively.

Changes under Safety First have made a measurable difference. Employee surveys show increased job satisfaction, high sense of purpose and accomplishment, trust in their supervisors, and confidence that their supervisors listen to them.

Implementation of FDAAA's drug safety provisions

FDA also used the Safety First program organizational tool to implement the provisions of FDAAA, which have helped modernize the Agency's postmarket drug safety capabilities. These provisions include new authorities for FDA to:

- Require manufacturers to conduct safety studies and clinical trials upon or after drug approval. Prior to FDAAA, these studies were conducted by manufacturers as voluntary commitments. Since 2008, FDA has required more than 385 postmarketing drug safety studies;
- Require manufacturers to change a drug's label to include new safety information. Prior to FDAAA, FDA did not have authority to order such label changes. Since 2008, FDA has required new safety labeling 65 times;
- Require manufacturers to implement special risk management programs called Risk Evaluation and Mitigation Strategies (REMS) for its product if FDA believes it is necessary to assure that the drug's risks do not outweigh its benefits. Many of these programs have a simple requirement to provide information sheets, called Medication Guides, to patients; others have more complex requirements such as patient registries, prescriber education, and restricted product distribution. Since 2008, FDA has required 64 REMS programs with these more complex requirements.

SAFE USE

Reducing preventable harm from medications

Through the Safe Use Initiative, FDA has identified many forms of preventable harm related to 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.[3] FDA instituted the Safe Use Initiative to identify areas of preventable drug harm, caused by inappropriate use, such as unintentional overdose or inappropriate prescribing.

The Safe Use Initiative has created partnerships with other organizations to enhance the safe and appropriate use of FDA-regulated drugs. Through the Safe Use Initiative, FDA is building public and private coalitions throughout the health care community and has identified many forms of preventable harm related to drugs. These include:

- Liver injury from acetaminophen, an over-the-counter and prescription painkiller;
- Misuse of prescription opioid painkillers;
- Diabetes and other risks from certain psychiatric medications in children; and
- Unintentional overdoses of over-the-counter and prescription drugs in children.[4]

As part of the Safe Use Initiative, FDA has created funding opportunities for ten innovative research projects addressing preventable drug harm and enhancing the safe and appropriate use of FDA-regulated drugs.

[3]Institute of Medicine, Preventing Medication Errors, National Academies Press, 2007, p. 124.
[4]FDA Safe Use Initiative, Opportunities for Collaboration. Available online at: http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm188762.htm

STRENGTHENING DRUG SAFETY SCIENCE

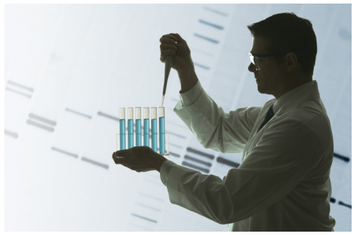
Developing, modernizing, and implementing new safety tools and capabilities

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. Following are some key examples:

The Sentinel Initiative: Although planned for some time prior to enactment of the law, FDAAA authorized FDA to establish a system for postmarket risk identification and analysis. The Agency calls this system, under development since early 2007, the Sentinel System, a national program for monitoring the safety of FDA-approved medical products. FDA's Mini-Sentinel pilot program is a large-scale working model of this system. Mini-Sentinel's 17 data partners nationwide generate secure information from electronic health care records of more than 125 million patients, providing FDA a new tool for postmarket drug safety.

Statistical Analysis: FDA uses advanced capabilities in the science of biostatistics to support CDER scientists in postmarket safety assessments. CDER now has a team of biostatisticians dedicated exclusively to postmarket safety evaluation and employs more than half of FDA's statisticians.

Epidemiology studies program: When FDA identifies a safety issue for which an observational epidemiological study is appropriate, an expanded FDA research program now enables epidemiologists and statisticians to work with outside collaborators who have secure access to large amounts of healthcare 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.



Pharmacogenomics: Sometimes called "personalized medicine," pharmacogenomics is the science of how a person's genetics affects their response to certain drugs. FDA is advancing science that helps determine how safe a drug is, based on results of a patient's genetic testing. Many such tests already now exist, including tests for the drugs warfarin (a blood thinner), codeine (a pain medicine), and carbamazepine (a drug used to help control epileptic seizures).

Adverse event surveillance: With greater awareness of the importance of reporting adverse events, the number of reports submitted to FDA's Adverse Event Reporting System (AERS) has more than doubled in a recent five-year period: from 323,384 in 2005, to 673,259 in 2010. This beneficial increase provides additional important data for FDA's safety assessments but has also created challenges in terms of information management. In response, FDA has developed effective data mining algorithms to identify potential adverse events that might otherwise not be noticed in such a large number of reports. In addition, FDA AERS analyses have helped to enhance safety monitoring of newly approved drugs, particularly important since new safety issues are more likely to arise with such products.

Collaboration with other Federal Agencies: FDA has worked with other Federal agencies to study important drug safety questions. Collaborations with the Veterans Administration, the Department of Defense, and the Centers for Medicare and Medicaid have enabled FDA to cost-effectively use large heath care databases for safety analyses.

ENHANCED COMMUNICATIONS

Earlier and more useful information

Since 2007, FDA has restructured its drug safety communications program to provide earlier and more useful information to patients and physicians about drug safety risks as they emerge. This effort includes a systematic approach to providing the public with information about possible new drug risks, discussing how FDA is addressing them, and offering safety advice for health care professionals and patients.

FDA's primary communication for drug safety issues is called the Drug Safety Communication (DSC). The document now has a single format, which has simplified and clarified our communications. In 2011, FDA issued 68 DSCs, up from 39 in 2010. These increased communications reflect the Agency's ongoing commitment to communicating postmarket safety issues. The DSC webpage[5] is one of FDA's most visited pages, receiving over 8 million page views in 2011.

FDA has also significantly advanced its communications in other ways. Recently, FDA issued an update to a Draft Guidance, titled *Drug Safety Information, FDA's Communication to the Public*, which provides the Agency's current thinking on how FDA makes drug safety decisions and communicates important drug safety issues.[6] Other significant advances in FDA's drug safety communications include:

- Greater transparency; FDA's new default position is to communicate safety issues as early as possible, unless there is a strong rationale for not communicating;
- Undertaking studies to help learn the most effective methods of communicating drug safety issues; and,
- Publishing articles in medical journals explaining the evidence and analyses used by FDA to make its benefit-risk assessments for specific drugs.

CONCLUSION

Like all other areas of science, drug safety science is dynamic and evolving. FDA recognizes that our ongoing success requires a constant ability to adapt to new information and new technologies. The important steps FDA has taken to establish parity between premarket safety review and postmarket drug safety establish FDA's 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, and better use of wireless technologies to transmit drug safety information from the point of care to FDA.

Moving forward, all of our safety efforts, while they will remain thorough, systematic, and scientific, will continue to be designed to support our 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.

[5] http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm

[6] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM295217.pdf

[ii] FDA Safe Use Initiative, Novel Interventions and Collaborations to Improve the Safe Use of Medications--Co-operative Agreements. Available online at: http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm277720.htm

FDA now gives the same priority to the oversight of the safety of marketed drugs as it does to premarket safety review.