Report to Congress

Changing the Future of Drug Safety: FDA Initiatives to Strengthen and Transform the Drug Safety System

Department of Health and Human Services
Food and Drug Administration
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/s/
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Foreword

In 2007, Congress passed landmark drug safety legislation as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The drug safety provisions of FDAAA give the Food and Drug Administration (FDA) important new drug safety authorities and also mandate that the agency establish novel programs to prevent and detect adverse drug reactions to enhance drug safety.

These provisions recognize the enormous changes in medication use that have occurred since Congress enacted the requirements for drug efficacy in 1962.[1] For several decades thereafter, the major focus of drug development was demonstration of efficacy—resulting in the availability of a large number of effective drugs to treat acute and chronic illnesses. Today, millions of people depend on medications to sustain their health. However, the consequences of this success are that many Americans are exposed to multiple prescription drugs each year (on average, more than ten), and many individuals, particularly the elderly, take more than five separate medications on a chronic basis. Because of such widespread use, an unanticipated drug safety problem can rapidly evolve into a public health threat, as illustrated by the recent problems with the blood thinner heparin.

The broad and growing exposure of the U.S. population to medications requires an aggressive approach to prevention and detection of safety problems, as well as the capacity for rapid response. FDA expects that postmarket surveillance will ultimately require a level of staffing and organizational structure similar to that used for premarket review. FDA anticipates that the new authorities enacted in FDAAA will enable the agency to promptly deal with safety problems once detected.

The FDAAA legislation also calls on FDA to apply new scientific and technological advances to build a new postmarket drug safety system. This new system will enable a seamless flow and integration of information gathered during biomedical research, clinical testing, and, once a drug is approved, throughout postmarket surveillance. In addition, FDA is already using electronic health information to develop faster, more robust methods of surveillance that can detect previously unrecognized adverse events. The emerging "science of safety"—understanding the cause of adverse events at the molecular level—is expanding FDA's ability to prevent drug safety problems that cannot be identified during clinical testing. Finally, FDA, under FDAAA, is implementing new tools to manage risks associated with drug products through the use of Risk Evaluation and Mitigation Strategies (REMS).

This report describes FDA's progress through December 2008 in the broad area of drug safety. The Center for Drug Evaluation and Research (CDER) has created a new initiative, *Safety First/Safe Use*, as a framework for integrating many of the new drug safety activities under way, including implementation of the drug safety provisions of FDAAA, follow-up actions resulting from recommendations in the Institute of Medicine's (IOM) report *The Future of Drug Safety*,

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[1] The 1962 Kefauver-Harris Drug Amendments, for the first time, required drug manufacturers to prove to FDA the effectiveness of their products before marketing them.

and commitments under the Prescription Drug User Fee program. CDER has begun implementing *Safety First*, which addresses many of these mandates and recommendations. Concurrently, CDER is planning *Safe Use*, which will involve capitalizing on the capabilities and expertise of others through partnerships to help bring about the safer use of medicines.

New medicines will continue to be developed, and older drugs will continue to exhibit new risks and benefits. Patients and consumers deserve a vigilant, responsive drug safety system that applies the best possible science and technologies to rapidly identify and understand the risks of medication use.

Executive Summary

In September 2007, Congress passed and the President signed the Food and Drug Administration Amendments Act (FDAAA). In addition to reauthorizing drug user fees, medical device user fees, and statutes affecting pediatric uses of drugs, FDAAA gave the Food and Drug Administration (FDA) new authorities in many areas, including drug safety. FDAAA also authorized increased funding from appropriations and user fees for drug safety.

Among other provisions, FDAAA directed the Secretary of Health and Human Services to issue a report responding to recommendations contained in a 2006 report issued by the Institute of Medicine (IOM) entitled, *The Future of Drug Safety—Promoting and Protecting the Health of the Public*.[2] Specifically, Section 919 directs the Secretary to include in that report an:

1. update on the implementation by FDA of its plan to respond to the IOM report; and

2. assessment of how FDA has implemented the recommendations described in the IOM report and the requirement under Section 505-1(c)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (added by FDAAA) regarding working relationships between the offices responsible for reviewing drugs and the offices responsible for postapproval safety.

This report has been developed to meet this FDAAA requirement. It also explains how FDAAA has affected FDA efforts to improve and enhance the drug safety system.

As the report outlines, the drug safety system has three fundamental components.

- Detection of risks
- Analysis and evaluation of the risks
- Management of risks, including risk communication

Each of these components is being strengthened through technical, management, procedural, and cultural changes at FDA, which are described in the report.

This is not FDA's first response to the 2006 IOM report. In January 2007, FDA provided an initial response to the IOM report, including a table that listed each IOM recommendation, FDA's response to the recommendation, and the status of activities relevant to each recommendation. That table has been recreated in the Appendix of this report and updated to reflect the status of specific activities FDA has undertaken related to the IOM's recommendations through the end of December 2008.

[2] http://www.iom.edu/.

Implementing FDAAA

FDAAA provides FDA with additional authorities and resources with regard to both pre- and postmarket drug safety. The statute contains important new authorities to require postmarket studies and clinical trials, safety labeling changes, and risk evaluation and mitigation strategies (REMS). These new requirements are enforceable, and FDAAA gives FDA the authority to impose civil penalties, among other enforcement tools, for violations. The new safety authorities in Title IX, Subtitle A of FDAAA took effect on March 25, 2008.

Between March 25 and December 31, 2008, FDA approved 29 drugs with required postmarket safety studies or clinical trials. In the past, these types of studies would have been undertaken voluntarily, as postmarket commitments; now, they are required, and the established time frames for the conduct of the studies are enforceable.

During the same time frame, FDA has used its new authorities to require safety label changes for eight classes of drugs and three individual drugs. For example, FDA required sponsors of all conventional antipsychotic medications to add a Boxed Warning and other warnings to their prescribing information indicating a risk of mortality in elderly patients treated for dementia-related psychosis. FDA also required the makers of fluoroquinolone antimicrobial drugs for systemic use to add a Boxed Warning to their prescribing information indicating an increased risk of developing tendinitis and tendon rupture in patients taking these drugs. Manufacturers of fluoroquinolones and antimicrobial drugs were also required to develop a Medication Guide for patients. Additionally, FDA required sponsors of erythropoeisis stimulating agents (ESAs) to add information to their labeling about risks of increased mortality and/or poorer outcomes in patients with certain types of cancer taking ESAs and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should not be initiated.

Between March 25 and December 31, 2008, FDA approved 25 REMS, 4 of which included elements to assure the safe use of the product. ("Elements to assure safe use" is the phrase used in FDAAA for restricted distribution elements.)

As required by Section 505-1(c)(2), FDA has used a team-based approach to making decisions about the need for and content of REMS. Staff members responsible for premarket review and for postmarket safety are involved.[3] This team-based approach to decision making is now being used in all drug safety activities as described in more detail in other sections of the report.

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[3] For purposes of applying FDAAA, FDA has interpreted *teams* to mean staff from CDER's Office of New Drugs and Office of Surveillance and Epidemiology. It should be noted that both offices share responsibility for premarket and postmarket safety and collaborate routinely on the need for and content of a REMS, whether they are required at the time of or after approval. In the Center for Biologics Evaluation and Research (CBER), the offices are the Office of Blood Research and Review/Office of Vaccines Research and Review/Office of Cellular, Tissue and Gene Therapies and the Office of Biostatistics and Epidemiology.

Managing the Drug Safety System

As part of FDA's January 2007 response to the IOM report, FDA identified a series of management initiatives designed to strengthen drug safety. To provide a framework for these activities and other drug safety efforts, CDER launched an initiative called *Safety First/Safe Use*.

The *Safety First/Safe Use* initiative has two parts. *Safety First* refers to steps CDER is taking to strengthen and modernize its internal policies and processes for managing significant drug safety issues. Specific objectives of CDER's *Safety First* initiative are listed here.

- Create and maintain a collaborative, multidisciplinary, team-based approach to the review of drug safety.
- Apply world-class project management to ensure FDA focuses the same attention on postmarket safety issues as it does on premarket review.
- Align policies and processes to ensure that the most appropriate and best-qualified experts lead and have an equal voice in regulatory decisions.
- Build the scientific, administrative, and technological capacity to carry out the provisions of FDAAA and the Prescription Drug User Fee Act (PDUFA).
- Ensure that significant postmarket safety issues are highest priority.

Safe Use involves CDER's long-term investment in partnering with other components of the healthcare system to ensure that drugs are used safely and appropriately. Although CDER's *Safe Use* initiative will continue to evolve, two objectives identified to date:

- Collaborate with other stakeholders in the healthcare system to devise effective, efficient steps to make sure drugs are used as appropriately as possible in ways that minimize medical errors and manage risks aggressively.
- Develop a cutting-edge pharmacovigilance system using electronic health data for evaluating drug performance.

FDA has already begun working with a variety of organizations to implement risk communication tools and explore new approaches to minimize medical errors. Other activities are planned.

Transforming CDER's Workplace

Among the objectives of *Safety First/Safe Use*, two objectives have been the focus of significant effort: (1) transforming CDER's workplace to better manage drug safety and (2) building the capacity for postmarket monitoring. During the past two years, CDER has undertaken an extensive self-evaluation with the goal of identifying what is working and what needs improvement. As a result of this effort, substantial changes have been and continue to be made to the way CDER is organized and functions.

To effectively identify and address workplace culture issues in CDER, a consultant from the Center for Professional Development, Inc., administered an organizational effectiveness survey

in December 2007. A total of 1,100 CDER employees (41 percent of staff) completed the survey. The overall rating of satisfaction with CDER's workplace was encouraging. However, surveyed staff identified many opportunities to improve work style and processes. CDER is pursuing these opportunities.

To ensure that CDER gets the very best effort from its staff, it formed a Workplace Culture Team (WCT), comprising staff from many levels and occupations throughout the center. The WCT has identified and launched more than 20 projects designed to improve the workplace culture.

During 2008, CDER's senior management team participated in 360-degree staff assessments, after which they participated in follow-up coaching and facilitated feedback sessions with their subordinates. A multidisciplinary Review Team Summit was held in fall 2008 for supervisors and team leaders to discuss the challenges and opportunities CDER is facing and to develop strategies to improve working interactions.

FDA has assessed and is improving how FDA's reviewing and approving offices and its safety monitoring offices interact.[4] A team-based approach to drug review integrates staff from CDER's Office of New Drugs (OND) and its Office of Surveillance and Epidemiology (OSE). The interactions are managed by dedicated regulatory health project managers.

Finally, CDER is establishing new positions with a specific focus on safety. There are now deputy directors for safety (DDS) as well as safety regulatory health project managers (safety RPMs) in each OND review division.

Tracking/Addressing Safety Issues

CDER is applying the management techniques it brings to new drug review to the management of drug safety issues. Work plans and timelines are being established to ensure that safety issues are resolved in an efficient and timely manner. CDER is also clarifying how it manages its advisory committees.

Postmarket safety issues are tracked in a database by the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). An application within DARRTS provides a platform for managing activities involved in evaluating safety issues, tracking due dates, and archiving essential documents generated during the evaluation of a safety issue (e.g., related reviews, correspondence, and FDA communications generated during the evaluation of the safety issue). Modifications to DARRTS, slated for 2009, will enable detailed tracking of postmarket requirements (e.g., studies and clinical trials).

OND and OSE share responsibility for the review of postmarket safety information for drugs and therapeutic biologics. In 2007, 79 joint safety meetings were held between OSE and the 17 OND review divisions, and in 2008, 82 joint meetings were held.

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[4] See previous footnote.

CDER is listing all drugs with related Public Health Advisories, Healthcare Professional Sheets, Early Communications, Medication Guides, or other safety information pages on its Web site,[5] and the center developed a consolidated drug safety Web page, as required in Section 915 of FDAAA. In addition, to fulfill the requirements of Section 921 of FDAAA, CDER developed a Web page for quarterly reports on potential signals of serious risks identified from adverse event reports.

FDA has made a number of changes to how it manages advisory committees. Additionally, the agency issued a number of guidances that improve and clarify advisory committee operations and processes.

In January 2007, CDER launched a pilot program to review systematically, collaboratively, and regularly the safety profiles of approved new molecular entities (molecules that are approved for the first time). The pilot is providing valuable information about the required resources and appropriate methods for conducting such a systematic review. The pilot is also informing implementation efforts for Section 505(r)(2)(D) of the FD&C Act, added by Section 915 of FDAAA, which requires FDA to prepare summaries of adverse events reported for drugs at a specified time after approval.

Increasing Capacity for Postmarket Safety Monitoring

As part of FDA's effort to meet the requirements in FDAAA, CDER is expanding its human capacity and exploring methods and tools to enable it to capitalize on existing large postmarket databases. CDER is aggressively recruiting more epidemiologists, statisticians, medical officers, safety evaluators, statistical programmers, data managers, and experts in other disciplines to assist in effectively accessing and analyzing new safety data.

FDA's centers (e.g., CDER, the Center for Biologics Evaluation and Research, the Center for Devices and Radiologic Health) are involved in a number of pilot projects that are exploring ways to leverage the power of existing large databases and the capabilities of information technologies to access and analyze possible safety signals. For example, FDA is working with the Centers for Medicare & Medicaid Services (CMS) and the Assistant Secretary for Planning and Evaluation (ASPE), Department of Health and Human Services (HHS), on a pilot project on drug safety surveillance using Medicare and Medicaid data.

Strengthening the Science of Drug Safety

During the past two years, FDA has undertaken a variety of projects to advance the scientific infrastructure of its drug safety systems. As noted in FDA's January 2007 response to the IOM report, CDER's work is targeting science at every stage of a drug's life cycle. FDA's Critical Path Initiative and the Reagan-Udall Foundation, which was created under FDAAA, are two efforts with important roles to play in strengthening the science of drug safety.

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[5] See http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.

The Critical Path Initiative, launched in 2004, has as its key focus modernizing the sciences that support FDA-regulated product development, evaluation, manufacturing, and use. In June 2008, the Office of Critical Path Programs issued a list of the Critical Path activities FDA had launched, or participated in, during 2007. Many of the activities on that list, as well as activities launched before and since,[6] will lead to new tools to help improve pre- and postmarket drug safety; CDER is involved in many of these activities. This long-term, agency-wide initiative is advancing agency and center collaborations to strengthen drug safety.

Title VI of FDAAA created the Reagan-Udall Foundation to identify unmet scientific needs in the development, manufacture, and evaluation of the safety and effectiveness of FDA-regulated products, including postmarket evaluation, and to establish scientific projects and programs, including funding, to address those needs. These activities will directly support CDER's effort to strengthen the science of safety. The Foundation is a private, independent, nonprofit entity.

Advancing Premarket Drug Safety Prediction

CDER is developing tools to advance drug safety, from the earliest stages of drug development through the entire period of use of the drug. Tools that prove useful during drug development may also contribute to safe use after a drug is on the market. A biomarker is one example of such a tool. CDER is involved in a number of efforts to identify and qualify biomarkers for use in drug development that will help improve premarket drug safety (with some important implications for postmarket use). Areas of interest include identifying and validating possible biomarkers to:

- improve liver injury risk prediction during drug development and therapy;
- reduce muscle and renal injury during development and therapy;
- identify the potential for vascular injury; and
- minimize drug-related phospholipidosis, a condition where excess lipids accumulate in cells.

Advancing Postmarket Drug Safety Prediction

Tools that help identify potential postmarket risks are critical to improving drug safety because it is impossible to learn from a premarket trial of even thousands of people everything about how a drug will perform once on the market. Once approved, a drug is often used by millions of people, many of whom may not have the indicated condition, may be taking other medications, or may belong to special population groups (e.g., geriatric, pediatric). A number of specific areas of interest are under investigation, usually as collaborative projects involving FDA and other organizations. Some examples are listed here.

- Improving warfarin dosing.
- Evaluating dual antiplatelet therapy with cardiac drug eluting stents.

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[6] The Office of Critical Path Programs is finalizing the Critical Path Activities List for 2008.

- Identifying gender-related differences in QT effects (pharmacologic effect on cardiac repolarization) and drugs with the potential of causing torsade de pointes (a specific variety of ventricular tachycardia.
- Evaluating the effects of over-the-counter skin products, such as sunscreens, on the absorption of dermally applied estradiol, in an in-vitro and an in-vivo model.
- Detecting and confirming gender-related safety signals, using the electronic healthcare data from the Department of Defense.
- Using narcotics safely in pregnant and lactating women.
- Qualifying imaging biomarkers to monitor neoadjuvant chemotherapy in breast cancer patients to identify responders, using positron emission tomography.

Advancing Signal Detection and Analysis

In line with the agency's mission to protect public health, FDA not only reviews large safety databases in marketing applications, but also evaluates large amounts of data as part of postmarket surveillance (e.g., through MedWatch and other mandatory and voluntary adverse events reporting programs). It is critically important that FDA use this information efficiently and effectively to rapidly detect potential drug safety signals.

Bioinformatics (the application of information technologies to the field of biology) is an area of substantial long-time focus at FDA. It is important that FDA capitalize on available information technologies to transition from a paper-based to an all-electronic environment for managing the information it receives, evaluates, manages, stores, and shares (i.e., along the entire drug information supply chain). Numerous bioinformatics projects are under way to improve FDA's ability to detect possible drug safety signals, efficiently receive and analyze drug safety information, and communicate important drug safety information to the public, as mandated by FDAAA Sections 915 and 921. Some key projects are listed here.

- FDA is developing the new MedWatch*Plus* reporting portal and FDA Adverse Events Reporting System (FAERS) data repository.
- The agency is in the process of implementing electronic drug establishment registration and drug listing for manufacturers of human drug products and veterinary drugs.
- The Sentinel Initiative[7] was launched in May 2008 with the goal of adding a proactive component to FDA's postmarket drug safety monitoring system.

[7] The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety. http://www.fda.gov/oc/initiatives/advance/reports/report0508.html.

Ensuring Quality Manufacturing

Another critical aspect of drug safety is drug quality. If a drug is not manufactured in such a way to ensure that it has the necessary identity, strength, quality, and purity, consumers are at risk. FDA may approve a drug based on the risk–benefit profile of the drug when properly manufactured. However, if the drug is not properly manufactured, the risks may be entirely different, and the drug may not provide the expected benefits.

FDA continues to modernize its approaches to regulatory oversight of drug products manufacturing and quality under the Pharmaceutical Quality for the 21st Century initiative. This program encompasses cross-cutting activities and systems in the quality program's review, compliance, and inspection units.

Examples of the most recently initiated or completed activities related to quality systems approaches include:

- launching an initiative to use risk modeling to select the most appropriate sites for routine current good manufacturing practice (CGMP) surveillance;
- beginning a pilot program to inspect active pharmaceutical ingredient manufacturing sites in developing nations, in collaboration with fellow regulators; and
- sharing best practices for review and use of scientific information to enhance work products within the centers.

To address globalization of the industry, FDA is working in tandem with other global regulators and recently opened offices in Asia, Europe, and Latin America.[8] This approach will help address the challenges drug manufacturers and regulators face to ensure the quality of imported drugs and drug ingredients. FDA will continue to implement regulatory system changes that improve the quality of new, biotech, and generic drugs consumed by the American public.

Expanding Safety Communication and Information Flows

In the January 2007 response to the IOM report, FDA outlined a series of efforts it was undertaking to improve communication and information flows. Efforts include conducting a comprehensive review of current public communication tools, improving internal communications, and posting reviews of new drug applications, supplements, and assessments of postmarket safety studies. In addition, FDA has convened a number of advisory committee meetings since January 2007.

The scope of FDA activities has been substantially augmented by new resources and requirements resulting from FDAAA. The agency is developing new and expanding existing

[8] See FDA's Action Plan for Import Safety at http://www.fda.gov/oc/initiatives/advance/imports/.

drug safety communication projects, some involving extensive collaboration with other organizations.

- FDA established a risk communication advisory committee.
- Between January 1, 2007, and December 31, 2008, CDER issued 17 Public Health Advisories (PHAs),[9] 39 Information for Healthcare Professional Sheets (HCPs),[10] and 1 Science Review.[11]
- From August 2007 to December 31, 2008, CDER issued 17 Early Communications to notify the general public that (1) important new postmarket safety information had been received; (2) the center intended to review, or was in the process of reviewing, that information; and (3) specific time frames had been identified for completion of the safety reviews.
- CDER launched a quarterly *FDA Drug Safety Newsletter*.[12]
- The center created a Web site for consumers on postmarket studies on drug exposure during pregnancy and related fetal effects.[13]
- The Medication Safety and Effectiveness Health Education Initiative was developed and launched.
- FDA facilitated public access to information on clinical trials in accordance with Title VIII of FDAAA.
- The MedWatch Partners Program Plan of Action has begun.
- The agency is exploring the possibility of an FDA/AMA *Network of Nodes* to develop and sustain relationships for better communication between FDA and medical specialty societies. (The Network of Nodes would be launched in 2009 conjunction with FDA's *Safe Use* initiative.)

Conclusions

Working to ensure the safety and effectiveness of drugs and other medical products regulated by FDA has always been a critical component of the agency's mission to protect and promote the public health. As this report explains, new authorities and resources provided by FDAAA are making it possible for FDA to invest substantial resources in an effort that will strengthen existing pre- and postmarket drug safety processes and procedures. To achieve this, the pre- and postmarket components of drug safety must work together, creating a seamless flow and integration of information gathered during biomedical research, clinical testing, and—after approval—during treatment. FDA is also reevaluating its overall approach to risk management and working to improve and expand the ways it communicates about drug safety. The goal is improving safety throughout a drug's entire period of use. The many efforts outlined in this

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[9] HCPs are posted with the specific drug; see www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.
[10] See http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.
[11] A science review was issued on bupropion (http://www.fda.gov/cder/drug/infopage/bupropion/TE_review.htm).
[12] See http://www.fda.gov/cder/dsn/default.htm.
[13] See http://www.fda.gov/cder/regulatory/pregnancy_labeling/default.htm.

report, both on an agency level and in the centers, are bringing results today while laying the foundation for continued progress in the future.

Report to Congress
Changing the Future of Drug Safety—
FDA Initiatives to Strengthen and Transform the Drug Safety System

Introduction

In September 2007, Congress passed and the President signed the Food and Drug Administration Amendments Act (FDAAA).[14] Section 919 of Title IX of FDAAA directs the Secretary of the Department of Health and Human Services (HHS) to respond to recommendations contained in a 2006 report issued by the Institute of Medicine (IOM) entitled *The Future of Drug Safety—Promoting and Protecting the Health of the Public*.[15] Section 919 directs the Secretary to include in the report an:

1. update on the implementation by the Food and Drug Administration (FDA) of its plan to respond to the IOM report; and

2. assessment of how FDA has implemented the recommendations described in the IOM report and the requirement under section 505-1(c)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (added by FDAAA) regarding working relationships between the offices responsible for reviewing drugs and the offices responsible for postapproval safety.

The following report has been developed to meet this FDAAA requirement. The report summarizes efforts by FDA to respond to the IOM recommendations and concerns. It also describes FDA efforts to implement related provisions of FDAAA that have expanded FDA's ability to act on key IOM recommendations. In addition, the report describes efforts to bring the same level of structured focus and capacity to postmarket safety review that has previously been devoted to premarket safety review. Many of the activities described here have been made possible with the added resources and authority from FDAAA. The required assessment of the working relationships between the offices responsible for reviewing and approving drugs and the offices responsible for monitoring postapproval safety can be found in section II, as well as in other sections of this report that address the culture of the Center for Drug Evaluation and Research (CDER).

This is FDA's second response to the 2006 IOM report. In January 2007, FDA provided an initial response to the IOM report, describing related activities that were planned and under way.[16] In that response, activities were grouped into the three major areas:

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[14] Pub. Law 110-85, September 27, 2007.

[15] http://www.iom.edu/.

[16] See http://www.fda.gov/oc/reports/iom013007.pdf. In that response, FDA committed to provide an update on the status of the activities described in the report. This report fulfills that commitment.

- agency operations and management initiatives to implement improved safety oversight;
- science supporting the drug product safety system; and
- communications and information flows key to ensuring drug safety and safe use.

For consistency, these same general themes are used here in discussing efforts through December 31, 2008.

The appendix of this report contains a detailed table updating the specific activities FDA has undertaken (some under way; some completed) that respond to specific IOM recommendations.

Although there are many efforts throughout the agency to strengthen the safe use of all medical products regulated by FDA, this report focuses primarily on activities under way in CDER through the end of December 2008 related to drugs, including therapeutic biological products. Where appropriate, related efforts in the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), or FDA's National Center for Toxicological Research (NCTR) are also discussed.

This report is organized as follows:

Section I gives some background on the initial IOM report of 2006 as well as the evolution and expansion of postmarket safety efforts following enactment of FDAAA.

Section II highlights the new safety authorities in FDAAA.

Section III describes the management and organizational changes within the framework of the *Safety First Safe Use* initiative that are changing the culture in CDER.

Section IV summarizes selected efforts to advance the science of drug safety.

Section V describes major steps in CDER to improve safety-related communication and information flows across offices, with other centers, and with key outside stakeholders.

Section VI contains a brief summary and conclusions.

I. Background—Strengthening the Drug Safety System

The safety of drugs and other medical products regulated by FDA has always been a key focus of the agency's mission to protect and promote health. However, rapid advances in science and technology have resulted in increasing use of complex medical products. These advances have outpaced improvements in the medical product safety system. Increased attention to safety-related issues by consumer advocates, health professionals, academic researchers, and Congress have provided FDA the opportunity to transform the medical product safety system into the most modern and effective system possible.

A September 2006 report by the Institute of Medicine (IOM) provided the groundwork for many of FDA's most recent initiatives. In 2005, FDA asked the IOM to convene a committee to assess the U.S. drug safety system and make recommendations to improve risk assessment, surveillance, and the safe use of drugs. To gather information, IOM interviewed FDA staff and interested persons outside of FDA and conducted public meetings. On September 22, 2006, IOM released the report entitled *The Future of Drug Safety—Promoting and Protecting the Health of the Public*.[17] The 2006 IOM report made 25 recommendations about how FDA could improve its drug safety program and what actions other parts of government should take to create a robust and comprehensive system for ensuring the safe use of medical products. Of the 25 recommendations, 14 were directed to FDA, primarily CDER.[18] The other 11 recommendations were directed to the Administration, Congress, and the Secretary, Health and Human Services. In reviewing the IOM report, CDER found that it was in substantial agreement with most of the IOM recommendations directed to FDA.

In January 2007, FDA issued a report responding to the IOM recommendations,[19] addressed within the context of ongoing drug safety initiatives, organized around the three themes:

- operations and management;
- science supporting the drug product safety system; and
- communication and information flows.

In September 2007, Congress strengthened FDA's capacity to ensure drug safety with the enactment of FDAAA.[20] FDAAA reauthorized the Prescription Drug User Fee Act (PDUFA), which allows FDA to continue to collect fees from drug companies to help fund reviews of new drugs. FDAAA also authorized increased funding from appropriations and user fees for drug

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[17] Id.

[18] The IOM report was organized into five major chapters: Chapter 3: A Culture of Safety; Chapter 4: The Science of Safety; Chapter 5: Regulatory Authorities for Drug Safety; Chapter 6: Communicating About Safety; and Chapter 7: Resources for the Drug Safety System. IOM recommendations to FDA include 3.4, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.12, 4.13, 5.4, and 6.2; recommendations to HHS include 3.2, 3.3, and 4.3; recommendations to Congress include 3.1, 3.5, 4.11, 5.1, 5.2, 5.3, 6.1, and 7.1. The Appendix to this report provides a detailed update on FDA work, organized by IOM recommendation.

[19] http://www.fda.gov/oc/reports/iom013007.pdf.

[20] Pub. Law 110-85, September 27, 2007.

safety. The new law also reauthorized medical device user fees and statutes affecting pediatric uses of drugs.[21]

Sections of FDAAA contain new provisions to enhance drug safety.

- Title VI created the Reagan-Udall Foundation, a private, independent, nonprofit entity, and charged it with advancing the mission of FDA to modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety.
- Title VIII of FDAAA mandated expansion of the existing ClinicalTrials.gov registry to make safety information on drugs undergoing premarket study available to the public on the Internet.
- Title IX established a number of new FDA authorities and expectations for postmarket safety information (see following section). Title IX also provided for enhanced postmarket pharmacovigilance activities.[22]

A number of FDAAA provisions respond directly to recommendations in the September 2006 IOM report on drug safety. With the increased resources and new authorities provided under FDAAA, the agency has launched a number of efforts to strengthen its drug safety programs. *Safety First/Safe Use* is a key initiative in CDER that is providing a broad framework for CDER's activities in response to the IOM recommendations and new FDAAA authorities. This initiative incorporates efforts that were already under way and builds on FDAAA's new statutory authorities.

After a brief discussion of FDAAA, the report describes how the *Safety First/Safe Use* initiative has created a long-term framework for agency activities. The examples of specific activities described are part of FDA's effort to advance the science of drug safety, implement the safety provisions of FDAAA, and respond to the recommendations in the 2006 IOM report.

II. Implementing Safety-Related Sections of FDAAA

FDAAA provides FDA with additional authorities and resources with regard to both pre- and postmarket drug safety. FDAAA contains important new authorities to require postmarket studies and clinical trials, safety labeling changes, and risk evaluation and mitigation strategies (REMS). These new requirements are enforceable, and FDAAA gives FDA the authority to

[21] Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

[22] Section 905 of FDAAA requires FDA (in collaboration with public, academic, and private entities) to develop methods to obtain access to disparate sources of data and validated methods to link and analyze safety data from multiple sources.

impose civil penalties for violations. The new safety authorities in Title IX, Subtitle A, of FDAAA took effect on March 25, 2008.[23]

As a result of the new authorities, FDA was able to require postmarket studies or clinical trials, when necessary to:

- assess a known serious risk related to use of a drug;
- assess signals of serious risk related to use of a drug; and/or
- identify an unexpected serious risk when available data indicate the potential for a serious risk related to use of a drug.

Between March 25 and December 31, 2008, FDA approved 29 drugs with required postmarket safety studies or clinical trials to be performed after drug approval. These required studies and trials, which have time frames for completion from months to five years, address a range of risks (e.g., pulmonary adverse effects, macrovascular events, and long-term safety). Each of the required studies and trials has a date for the protocol submission, a start date, and a date for submission of a final report. In the past, these kinds of studies would have been undertaken voluntarily; FDAAA gives FDA the authority to require the studies, and the established time frames for conduct of the studies are enforceable.

As of December 31, 2008, FDA has used its new authority to require safety labeling changes for eight classes of drugs and three individual drugs. In one case, FDA used this new authority to require manufacturers of all conventional antipsychotic medications to add a Boxed Warning and other warnings to their drugs' prescribing information about the risk of mortality in elderly patients treated for dementia-related psychosis, similar to the Boxed Warning and Warning added to the prescribing information of the atypical antipsychotic drugs in 2005. In another case, FDA required the makers of fluoroquinolone antimicrobial drugs for systemic use to add a Boxed Warning to their prescribing information indicating an increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones. Additionally, manufacturers were required to develop Medication Guides for patients. FDA also required manufacturers of erythropoeisis stimulating agents (ESAs) to add information to their labeling about risks of increased mortality and/or poorer outcomes in patients with certain types of cancer taking ESAs and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should not be indicated. FDA expects that these changes will be made promptly as a result of the use of the new labeling authority, thus increasing the safe use of these drugs.

FDA has also been using its new authority to require REMS, when necessary, to ensure that the benefits of a drug outweigh its risks. Before FDAAA, FDA approved certain drug and biological products with Risk Minimization Action Plans (RiskMAPs), which were developed to manage risks that require additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required reporting. Because many of the purposes of a RiskMAP can be met with a REMS and because REMS have additional enforcement provisions under FDAAA, we anticipate that most products that would have previously been approved with

[23] The provisions of Subtitle B took effect upon enactment on September 27, 2007.

a RiskMAP will, instead, be approved with a REMS. In some cases, a REMS consists only of a Medication Guide and a timetable for submissions of assessment of the REMS. In other cases, more extensive REMS have been required to communicate the risks of a drug and manage the risks in such a way as to ensure safe use. (*Elements to assure safe use* is the phrase used in FDAAA for restricted distribution elements.) By December 31, 2008, FDA had approved 25 REMS, 4 of which included elements to assure safe use. All of these new authorities are powerful tools for enhancing drug safety.

Section 919 of FDAAA requires FDA to conduct an assessment of how FDA has implemented the recommendations described in the IOM report and the requirement under section 505-1(c)(2) of the Act (added by FDAAA) regarding working relationships between the offices responsible for reviewing drugs and the offices responsible for postapproval safety. Section 505-1 contains several provisions that require those offices to consult on implementation of the REMS provisions. For purposes of applying FDAAA, for CDER, FDA has interpreted "the office responsible for reviewing the drug and the office responsible for postapproval safety with respect to the drug" to mean staff from CDER's Office of New Drugs and Office of Surveillance and Epidemiology. It should be noted that both offices share responsibility for premarket and postmarket safety and collaborate routinely on the need for and content of a REMS, whether REMS are required at the time of or after approval. [24] In CBER, the offices are the Office of Blood Research and Review/Office of Vaccines Research and Review/Office of Cellular, Tissue and Gene Therapies and the Office of Biostatistics and Epidemiology.

To fulfill this responsibility, CDER and CBER representatives are included in cross-disciplinary working groups that have been created to develop policies and procedures to help implement the FDAAA provisions involving postmarket studies and trials, safety label changes, and REMS. Having input from both CDER and CBER helps to ensure consistent implementation of FDAAA across the agency.

In CDER, each significant safety issue is reviewed by cross-disciplinary teams that include representatives from OND and OSE, and other offices as needed, working together to determine the appropriate regulatory response, including whether to exercise the new authorities. In addition, numerous other activities described below are under way to enhance the working relationships between these offices. Similarly, CBER has created cross-disciplinary teams who work collaboratively on implementing the FDAAA safety provisions.

FDAAA contains numerous other provisions that will enhance drug safety. Where they are pertinent to the discussion, they are described below. In many cases, there are separate

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[24] OND has the primary responsibility for review of periodic safety reports and most other clinical regulatory submissions. OSE has the primary responsibility for review of 15-day alert reports, direct reports of adverse drug experiences, reports of medication errors, and the authority to grant waivers of postmarket safety reporting requirements. OND and OSE both have responsibilities for the review of proposed REMS and the evaluation and modification of existing REMS. OND, through its offices and divisions, has the final decision-making and signatory authority for biologics licensing applications (BLAs) or new drug applications (NDAs) assigned to it for review.

requirements for FDA to report to Congress on its implementation activities, and they will not be addressed further here.

III. Improving Management of the Drug Safety System

As part of FDA's January 2007 response to the IOM report, CDER identified a series of management initiatives designed to strengthen drug safety. Efforts include engaging external management consultants to help the agency and CDER develop a comprehensive strategy for improving organizational culture, making specific organizational and management changes to increase communications among review and safety staff, and improving the use of advisory committees (see the Appendix). To provide a framework for these activities and other drug safety efforts, CDER launched the *Safety First/Safe Use* initiative.

The *Safety First/Safe Use* initiative has two parts. *Safety First* refers to steps CDER is taking to strengthen and modernize its internal policies and processes to manage significant drug safety issues. FDA has been tremendously successful in developing a world-class premarket review process,[25] enabling FDA to approve safe and effective medical products effectively and efficiently, without sacrificing the quality of its reviews. During the past 16 years, additional resources and commitments resulting from PDUFA have brought unprecedented accountability to new drug review and institutionalized project management, prioritization, and tracking for premarket drug review. CDER is currently applying these same management processes and principles to postmarket safety review.

Specific objectives of CDER's *Safety First* initiative are to:

- create and maintain a collaborative, multidisciplinary, team-based approach to the review of drug safety;
- apply world-class project management to ensure FDA focuses the same attention on postmarket drug safety issues as it does on its premarket review;
- align policies and processes to ensure that the most appropriate and best-qualified experts lead and have an equal voice in regulatory decisions;
- build the scientific, administrative, and technological capacity to carry out the provisions of FDAAA and PDUFA; and
- ensure that significant postmarket drug safety issues are our highest priority.

Safe Use is the phrase CDER is using to describe its long-term investment in partnerships with other components of the healthcare system to ensure that drugs are used safely and appropriately. Drug development does not end at the point a product is approved for marketing; it continues throughout the product life cycle. Modern drug regulation requires CDER to interact with the

[25] Premarket review of drugs and therapeutic biologics is performed in CDER; CBER performs premarket review of other biological products (e.g., blood products, vaccines).

healthcare system to discover the consequences of drug use after marketing and to feed that information back into drug development. CDER is just beginning to build both the human and scientific capacity to lead such an effort under the *Safe Use* initiative. Although it will continue to evolve, CDER's *Safe Use* broad objectives are to:

- collaborate with other stakeholders in the healthcare system to devise effective and efficient steps to make sure drugs are used as appropriately as possible and in ways that minimize medical errors and manage risks aggressively; and
- develop a cutting-edge pharmacovigilance system for evaluating drug performance using electronic health data.

FDA has already begun working with a variety of organizations to implement risk communication tools and to explore new approaches to minimize medical errors. Other activities are planned.

Activities are under way both in the centers and at the agency level. For example, the Sentinel Initiative, announced in May 2008, is a long-term, agency-wide effort to capitalize on the power of existing large data sources (e.g., Medicare data, large health insurance claims databases, electronic health records) to augment FDA's existing postmarket pharmacovigilance activities and add an active surveillance component to the program. As described in the Sentinel Report,[26] a number of activities (e.g., public- and private-sector pilot projects) already are under way in CDER and other agency centers that will directly support the creation of such a system (see section IV and the attachment of this report for more on Sentinel). The Sentinel Initiative will fulfill many of the mandates in FDAAA Section 905 to establish a postmarket risk identification and analysis system.

Among the objectives of *Safety First/Safe Use*, two objectives have been the focus of especially significant effort: (1) transforming CDER's workplace management to better manage drug safety and (2) building the capacity for postmarket monitoring.

A. Transforming the CDER Workplace

Since March 2007, CDER has undertaken an extensive self-evaluation with the goal of identifying what is working and what needs improvement. As a result of this effort, substantial changes have been and continue to be made in the way the center is organized and functions.

- Improving workplace culture

To effectively identify and address workplace culture issues in CDER, a consultant from the Center for Professional Development, Inc. (CPD), administered an organization effectiveness survey in December 2007. A total of 1,100 CDER employees (41 percent of total staff) completed the survey. In February 2008, CDER's Senior Management Team met with CPD to

[26] The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety. http://www.fda.gov/oc/initiatives/advance/reports/report0508.html.

review the results. Although finding an encouraging overall rating of satisfaction with CDER's workplace, surveyed staff identified opportunities to improve work style and processes. CDER is pursuing these opportunities.

Another aspect of CDER efforts to improve how it can get the very best from its entire staff is through the formation of a Workplace Culture Team (WCT). The WCT, comprising nominated staff from many levels and occupations throughout CDER, began meeting in March 2008 to advise and advocate for workplace transformation efforts. The WCT has identified and launched more than 20 projects designed to improve the workplace culture. CDER's goal is to improve staff interactions and create a sense of community; to ensure the consistent communication of important information, including day-to-day administrative information; and to encourage staff participation in training and other professional enhancement activities.

CDER has planned a number of different communications activities for staff and management. CDER arranged for a communications training course, designed specifically for CDER by CPD, to be given in each office. During 2008, the CDER senior management team participated in 360-degree staff assessments. They also received follow-up coaching and facilitated feedback sessions with subordinates. The office directors and division directors participated in a similar process in the fall of 2008. CDER senior management team members, office directors and their deputies, and division directors attended a retreat in July 2008 to review and align workplace culture activities. A multi-disciplinary Review Team Summit was held in the fall 2008 for supervisors and team leaders to discuss the challenges and opportunities CDER is facing and to develop strategies to improve how we work together.

- Applying a team-based approach to drug safety review

CDER has established a team-based approach to drug review that incorporates staff from OND and OSE, and other offices as needed. On June 16, 2008, a memorandum of agreement (MOA) took effect between OND and OSE, documenting CDER's commitment to the timely resolution of drug safety issues and affirming CDER's collaborative, multidisciplinary team-based approach to the review of drug safety over the course of a drug's life cycle. The MOA affirms the center's *equal voice* philosophy—that all appropriate expertise should be brought to bear in the resolution of drug safety issues. This MOA provides the foundation for new processes to ensure that each team member has an opportunity to express his or her view, with an avenue for promptly raising unresolved differences of opinion between disciplines through the management chain for prompt resolution. Existing processes address differences of opinion between an individual and his or her chain of command and differences of opinion between an individual and the review team. [27] CDER believes that a team-based approach will help ensure that the most appropriate and best-qualified experts lead or have equal voice in regulatory decisions.

- Establishing new safety positions

[27] See CDER MAPP 4151.2 Documenting Differing Professional Opinions and Dispute Resolution–Pilot Program http://www/fda.gov/cder/mapp/4151.2.pdf.

CDER has also established new positions with a specific focus on safety. There are now deputy directors for safety (DDSs) as well as safety regulator health project managers (safety RPMs) in each OND product review division. These individuals serve as focal point experts for developing working review teams that include members of OND and OSE and other offices as needed to address postmarket safety issues emerging within their particular drug groups.

The DDS and safety RPM in each OND division and staff from OSE coordinate and oversee the development and tracking and follow-up of all postmarket safety activities and liaise with the Drug Safety Oversight Board (DSB) staff on issues that need discussion or need a risk communication. The DDS provides oversight, coordination, and technical medical expertise on postmarket safety activities, facilitating interactions between OND and OSE. Each DDS is charged with new drug division-level implementation of all CDER and FDA safety-related initiatives, including *Safety First* and *Safe Use*, and ensuring that staff members are informed and engaged about these and other related initiatives.

The OND safety RPM or the OSE safety RPM, as decided by the review team, serves as the focal point and coordinator for all new drug division-level activities related to postmarket safety activities, including required postmarket studies and clinical trials, REMS, and safety labeling changes. Activities include developing and coordinating materials to assist the review team. The safety RPMs also develop materials for congressional briefings and for publication in the *Federal Register*. They also support staff during safety application reviews.

Postmarket safety issues, including required postmarket studies, labeling changes, and REMS, are tracked by the Document Archiving, Reporting and Regulatory Tracking System (DARRTS), FDA's postmarket safety and postmarket commitment safety database. Modifications made to DARRTS, targeted for spring 2009, will enable detailed tracking of postmarket requirements (e.g., studies and clinical trials).

B. A Framework for Tracking/Addressing Safety Issues

CDER is bringing the same management techniques it brought to new drug review to the management of drug safety issues. Work plans and timelines are being established to ensure that drug safety issues are resolved in an efficient and timely manner. CDER also is clarifying how it manages its advisory committees.

- Safety management and tracking with DARRTS

In early 2007, the safety issue application within DARRTS was launched. This application provides a platform for managing activities related to evaluating a drug safety issue (e.g., tracking due dates, archiving essential documents, such as reviews, correspondence, and FDA communications generated during the evaluation of a safety issue). The system will continue to be developed to respond to the needs of the safety teams in OND and OSE and to document the flow of work related to the authorities conferred on FDA under FDAAA, Title IX (i.e., postmarket studies and trials, safety label changes, and REMS described in Section II, above).

- Safety meetings

OND and OSE share responsibility for the review of postmarket safety information for drugs and therapeutic biologics. Because of the joint nature of these responsibilities, OND and OSE concurred that there is a fundamental need for regularly scheduled interactions to exchange information. Since late 2006, each OND review division and the OSE staff assigned to monitor that division's drug groups have met regularly (generally, every other month) to share information about emerging issues, develop strategies to identify and analyze safety signals, coordinate their activities, and share decision making about next steps on specific issues. Safety issues are tracked and monitored regularly to ensure that concerns are fully addressed and not lost to follow-up. In 2007, there were 79 joint safety meetings held between OSE and the 17 OND review divisions, and in 2008 there were 82.

- Quarterly reports on new safety information or potential signals

FDAAA Section 921 requires that FDA conduct regular, bi-weekly screening of the Adverse Event Reporting System (AERS) database and post a quarterly report on the AERS Web site of any new safety information or potential signal of serious risks identified through AERS. The first report was posted in September 2008, covering the first quarter of the year (i.e., January through March 2008).[28] CDER currently lists all drugs with Public Health Advisory information, Healthcare Professional Sheets, Early Communications, Medication Guides, or other safety information pages on its Web page.[29] To fulfill the requirements of FDAAA Section 915, CDER developed a consolidated drug safety Web page,[30] as well as a Web page containing reports on the AERS screening consistent with the requirements of Section 921.[31] CDER's quarterly *Drug Safety Newsletter* also contains a list of recent drug safety communications.

- Managing advisory committees

FDA has made a number of changes to how advisory committees are managed. Goals were to clarify conflict of interest issues and improve public access to the information provided to advisory committee members prior to meetings. FDA issued a number of guidances that improve and clarify advisory committee operations and processes.[32]

  - Draft guidance for the public and FDA staff on *Convening Advisory Committee Meetings* (August 2008)

  - Guidance for FDA advisory committee members and staff on *Voting Procedures for Advisory Committee Meetings* (August 2008)

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[28] The second and third quarters were posted in February 2009.

[29] See http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.

[30] See http://www.fda.gov/cder/drugSafety.htm.

[31] See http://www.fda.gov/cder/aers/potential_signals/potential_signals_2008Q1.htm#list.

[32] Guidances are available on CDER's guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

- Guidance for industry on *Advisory Committee Meetings - Preparation and Public Availability of Information Given to Advisory Committee Members* (August 2008)

- Guidance for the public, FDA advisory committee members, and FDA staff on *Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees* (August 2008)

- Guidance for the public, FDA advisory committee members, and FDA staff on *Public Availability of Advisory Committee Members Financial Interest Information and Waivers* (August 2008)

- New molecular entities (NMEs) pilot

NMEs are unique compounds that have not previously been approved by the FDA. As part of CDER's effort to strengthen and standardize safety evaluation processes, it launched a pilot program in January 2007 to systematically and collaboratively review the safety profiles of selected approved NMEs. The pilot will help determine whether such reviews should apply to all or only a specified subset of NMEs. The pilot also will inform implementation efforts for Section 505(r)(2)(D) of FD&C Act, which requires FDA to prepare summaries of adverse events reported for drugs at a specified time after approval.

On March 18, 2008, CDER launched a Web site about the NME pilot program and issued a progress report on the program.[33] The report contains information on the findings from the first NMEs that were evaluated under the pilot program, with links to completed reviews related to the evaluations. In some cases, the NME evaluations identified safety issues that led to labeling changes. A description of completed regulatory actions is included in the report. The pilot is expected to provide valuable information about the required resources and appropriate methods for conducting such a systematic review.

Section 915 of FDAAA created 505(r) of the FD&C Act, which includes a requirement (505(r)(2)(D)) for FDA to prepare, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number. FDA is working to implement this provision and will use the experience from the NME pilot to inform its work.

C. Increasing Capacity for Postmarket Safety Monitoring

As part of FDA's effort to meet the requirements in FDAAA, CDER is expanding its human capacity and exploring methods and tools to enable the center to capitalize on existing large postmarket databases.

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[33] For more on the pilot and to view a report on progress to date, see the Web site about the program at http://www.fda.gov/cder/drug/postmarketing_safety/default.htm.

- Adding expertise

CDER is aggressively recruiting more epidemiologists, statisticians, medical officers, safety evaluators, statistical programmers, data managers, and expertise in other disciplines to help effectively access and analyze new safety-related data. These staff members are being recruited into CDER under its new organizational structure, which includes, for example, separate divisions in OSE devoted to risk management, medication error prevention and analysis, epidemiology, and pharmacovigilance (two divisions are devoted to this topic[34]).

- Leveraging other data sources and available information technologies

FDA centers are involved in a number of pilot projects that are exploring ways to leverage the power of existing large databases and the capabilities of information technologies to detect possible drug safety signals. The pilots described here, and others listed in the attachment of the Sentinel report and discussed in Part C of the next section, will also inform the goals of the Sentinel System.

  - FDA, Centers for Medicare & Medicaid Services (CMS), Assistant Secretary for Planning and Evaluation (ASPE) Pilot on drug safety surveillance (using Medicare and Medicaid data)

FDA and CMS, with the assistance of ASPE, have launched a pilot project that will use Medicare and Medicaid data to test the ability to confirm safety signals of specific drug products. FDA and CMS have assembled a team, including experts from FDA, CMS, and other relevant stakeholders (e.g., epidemiologists, medical doctors, information technologists, and project managers), to study adverse drug events previously identified through FDA's AERS.

  - Observational Medical Outcomes Partnership with FNIH, FDA, PhRMA)

Under a partnership involving FDA, the Foundation of the National Institutes of Health, and the Pharmaceutical Research Manufacturers of America, a series of experiments are being conducted to assess the value, feasibility, and utility of observational data to identify and evaluate the safety risks and potential benefits of prescription drugs. A range of analytical methods will be used in addition to currently available tools and data sources. Researchers will also test approaches for creating the infrastructure for accessing and managing the required data, including multiple claims and electronic health records data sources.

  - eHealth Initiative (Connecting Communities for Drug Safety Collaboration with HealthCare System and Regenstrief Institute/Indiana Network for Patient Care)

FDA is serving as advisor on the eHealth Initiative (eHI) pilot study, which is exploring opportunities for using clinical information captured in the electronic databases of two large health information exchanges to identify and assess safety signals associated with marketed

[34] The Divisions of Pharmacovigilance I and II.

pharmaceuticals. Specific goals include testing and evaluating the value and utility of using electronic health information to detect and evaluate drug safety signals and to develop a set of replicable tools and methods that can be widely disseminated and used nationwide to support the assessment of the risks and benefits of drug treatments.

Long-term goals of eHI include contributing to and supporting the creation of an active drug safety surveillance system; establishing a learning laboratory for patient safety that allows for the testing of various hypotheses in communities; fostering an ongoing dialogue on how to improve drug safety with several key stakeholders in the safety process: patients, physicians, communities, the pharmaceutical industry, and regulators; and providing a structure that enables ongoing collaboration among these parties.

FDA has also increased its access to automated healthcare data and to experts who have experience in using these data to answer important drug safety questions. Additional studies were funded through CDER's existing epidemiology contracts with Harvard Pilgrim Health Care, Vanderbilt University, Kaiser Research Foundation of California and Ingenix. New relationships were fostered with the Veterans Administration and the Department of Defense, enabling collaborative research on safety questions of mutual interest. FDA has also partnered with the Agency for Healthcare Research and Quality (AHRQ) to co-sponsor research on important drug safety issues through the Centers for Education and Research on Therapeutics (CERTs). In August 2008, FDA issued a request for proposals (RFP) to expand its pharmacoepidemiology research program to include risk management evaluation, methods research, and theme-based programs. Awards will be made in 2009.

IV. Strengthening the Science of Drug Safety

Since 2006, FDA has undertaken a variety of projects to advance the scientific infrastructure of its drug safety systems. As noted in FDA's January 2007 response to the IOM report,[35] CDER's work targets science at every stage of the drug life cycle. Projects have included exploring potential premarket methods for analyzing benefit and risk and for managing preclinical risk; strengthening methods and tools for postmarket safety surveillance; developing new scientific approaches for detecting, understanding, predicting, and preventing adverse events; and ensuring quality manufacturing. Selected efforts are highlighted here. The Appendix provides a detailed accounting of the status of our specific IOM commitments in relevant areas.

Of note, two initiatives, FDA's Critical Path Initiative and the Reagan-Udall Foundation, which was created by FDAAA, have important roles to play in strengthening the science of drug safety. The Critical Path Initiative, launched in 2004, has as its key focus to help strengthen the sciences that support FDA-regulated product development, evaluation, manufacturing, and use. As part of this FDA-wide initiative, numerous public-private partnerships have been formed to address specific scientific hurdles. In June 2008, the Office of Critical Path Programs issued a list of the Critical Path activities, many of them collaborations with other federal agencies and other

[35] http://www.fda.gov/oc/reports/iom013007.pdf.

interested stakeholders, FDA had launched, or participated in, during 2007.[36] Most of the activities on that list, as well as activities launched before and since, are leading to new tools to help improve pre- and postmarket drug safety, and CDER staff are heavily involved in many of the activities.[37]

Title VI of FDAAA created the Reagan-Udall Foundation to advance the mission of FDA to modernize medical, veterinary, food, food ingredient, and cosmetic product development; accelerate innovation; and enhance product safety. The Foundation is a private, independent, nonprofit entity. Appointed in November, 2007, the Board includes 14 voting members representing relevant stakeholders (e.g., general pharmaceutical, medical device, food, cosmetic and biotechnology industries; academia; patient or consumer advocacy groups; healthcare professionals; other relevant experts). The FDA Commissioner serves as one of several non-voting members. The statutory mission of the Foundation is to identify unmet scientific needs in the development, manufacture, and evaluation of the safety and effectiveness of FDA-regulated products, including postmarket evaluation, and to establish scientific projects and programs, including funding, to address those needs. This effort will directly support CDER's efforts to strengthen the science of safety.

A. Advancing Premarket Drug Safety Prediction

As this section illustrates, it is important to be able to predict possible risks related to the use of a drug from the earliest stages of drug development through the entire period of use of the drug. To do this, additional tools that can help identify possible risks during drug development are needed to both strengthen protections for study participants and make more effective use of drug development resources. For example, discovering early on that a candidate product causes hepatotoxicity (liver injury) and most likely will not be approved means resources can be redirected to more promising candidate products. FDA is working in a number of areas to improve the ability to identify and analyze drug benefits and risks. More systematic approaches to risk–benefit assessment and the identification of better biomarkers are two areas of agency focus.

In 2006, FDA began work toward the long-term goal of developing more systematic quantitative approaches to ***risk–benefit assessment***. During a 2006 workshop hosted by the IOM, it became clear that developing a more systematic approach to risk–benefit assessment will involve many facets, including, for example:

- identifying candidate analytic methods and tools;
- identifying regulatory decisions that would realize the greatest value from application of these methods; and

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[36] The Office of Critical Path Programs is finalizing a Critical Path Activities List for 2008.

[37] Examples include the Oncology Biomarker Qualification Initiative (launched 2006) and the Cardiac Safety Research Consortium (launched 2006). For a complete listing of Critical Path activities launched during 2006 and 2007 and for more information on the Critical Path Initiative, see http://www.fda.gov/oc/initiatives/criticalpath/.

- building the IT, data, and analytic infrastructure to more easily apply more quantitative and systematic approaches.

In November 2007, FDA held a two-day meeting, which was designed to support FDA staff in (1) determining the applicability of current tools to regulatory decisions, (2) identifying research projects that might lead to greater confidence in current tools, and (3) identifying gaps in current tools that may lead to new tool development. The agency will continue to explore the application of analytic tools and issues related to effective communication of benefits and risks.

FDA believes the tools that prove useful during drug development may also contribute to safe use after a drug is on the market. A ***biomarker***[38] is an example of such a tool.

A biomarker might be used to:

- diagnose a disease;
- individualize drug dosing during clinical testing or treatment; or
- identify people at high risk of a side effect during clinical testing or treatment.

Patients with a gene called HLA-B*5701 are at greater risk of experiencing serious allergic reactions from abacavir (a drug to treat HIV and AIDS) than those without this gene. Testing patients for this *biomarker* enables healthcare professionals to avoid giving abacavir to patients with a high risk for this side effect.

CDER is involved in a number of efforts to identify and qualify biomarkers for use in drug development, and examples of projects targeting premarket drug safety (with important implications for postmarket use) are highlighted here.[39]

- Liver injury risk prediction

The possibility of hepatotoxicity (drug-induced liver injury) is a priority concern during drug development. Some drugs have not been approved because clinical studies provided evidence of hepatotoxicity or of potential hepatotoxicity, resulting in termination of the study. Several drugs have not been approved in the United States because European marketing experience revealed their potential for liver injury. Hepatotoxicity discovered after approval for marketing also has limited the use of many drugs. Liver injury has been the most frequent single cause of safety-related drug marketing withdrawals during the past 50 years. FDA is working with industry, academia, and others to broaden our understanding of the biochemical and genetic basis of drug-induced liver injury. These efforts will help identify people who may be more prone to this adverse effect.

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[38] A measurable characteristic that *reflects* (mechanistic, diagnostic or predictive) physiological, pharmacological, or disease processes in animals or humans.

[39] For additional projects, see the 2006 and 2007 Activities Lists on FDA's Critical Path Initiative Web page at http://www.fda.gov/oc/initiatives/criticalpath/.

In August 2007, FDA entered a two-year Cooperative Research and Development Agreement (CRADA) with Entelos, Inc. to develop a computer model of drug-induced liver injury (DILI). The goal is to use this platform to guide the development of clinical biomarkers and preclinical assays to identify patient types and drug combinations that increase the risk of DILI.

In October 2007, FDA published a draft guidance for industry entitled *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*. In conjunction with PhRMA and the American Association for the Study of Liver Diseases, FDA held a meeting in March 2008 on detecting and investigating DILI during clinical trials and to discuss the draft guidance. Comments are being carefully considered as part of guidance finalization.

In a related effort, FDA's National Center for Toxicologic Research (NCTR) has joined with CRADA partner BG Medicine, Inc. in a study using new genomics technologies to discover new biomarkers predictive of liver injury. Such early preclinical biomarkers are needed because biomarkers currently being used are not adequate to accurately predict liver injury in humans. Biomarkers are needed that will help identify the potential for liver injury ***before*** it happens, rather than after damage has already occurred. Successful development of these biomarkers will result in improved safety assessments of potential new drugs and, ultimately, safer postmarket use. Candidate products with the potential for liver injury may be identified before they are tested in people in clinical studies, and patients who have the genetic characteristics that may make them more prone to liver injury can be identified before they are treated with a drug that could injure them.

- Muscle and renal injury

Drug-induced muscle injury (e.g., cardiac, skeletal) is also of concern both during preclinical and clinical drug studies and postmarket use. Muscle injury can be evident in various forms, including myalgias, creatine kinase elevations, rhabdomyolysis, and phospholipidosis. In some cases, muscle injury in study participants has resulted in termination of clinical studies, or treatment of an affected patient has been discontinued. FDA is involved in several collaborative efforts to gain a better understanding and improve predictors of potential drug-induced muscle injury.

FDA has a multi-center (CDER, CDRH, NCTR) study under way to develop gene expression and protein biomarkers that are predictive of renal, cardiac muscle, and skeletal muscle injury associated with drug therapies. This work is a component of the Critical Path Institute's (C-Path's) Predictive Safety Toxicology Consortium. Goals of the study include (1) comparing the sensitivity and specificity of five biomarkers to other measures of renal injury, including histopathology, clinical chemistry markers, metabonomic analysis, and urinary proteins; (2) identifying gene expression and protein markers of dilated cardiomyopathy, cardiac hypertrophy, and skeletal muscle injury; and (3) working with the International Life Sciences Institute's Health and Environmental Sciences Institute Committee on Application of Biomarkers of Toxicity to better define baseline levels of biomarkers (e.g., cardiac troponin T) in animal models.

- Vascular injury

CDER, in collaboration with industrial CRADA partners, is investigating the predictive power of acute-phase proteins for detecting microvascular injury induced by drugs, known as phosphodiesterase IV inhibitors. These drugs are used to treat asthma and other congestive disorders. If successful, this project will provide drug developers and FDA with a better understanding of the pathogenesis of respiratory vascular injury and with methods for early detection of this adverse event in preclinical and clinical studies of phosphodiesterase inhibitors.

- Phospholipidosis

In collaboration with industrial CRADA partners, CDER is conducting studies to help provide a mechanistic interpretation of the development of phospholipidosis in relation to effects on target tissue pathology and function. Phospholipidosis is a lipid storage disorder in which excess phospholipids accumulate within cells, an adverse drug reaction with some drugs. This project involves genomic analysis of target tissues and investigation of the sensitivity and specificity of lipid biomarkers of phospholipidosis.

B. Advancing Postmarket Drug Safety Prediction

Tools that help identify potential postmarket risks are critical to improving drug safety because a premarket trial of even thousands of people will not demonstrate all of the effects of a drug once it is approved and being used by millions of people. Reasons for this include (1) many people taking the drug may not have the relevant condition, (2) many may be taking other medications, or (3) they may belong to special population groups (e.g., geriatric, pediatric). Sometimes, tools are useful in risk management both pre- and postmarket; often new predictive/detective tools are developed once a drug has been approved and experience can be gained from real-world use.

- Warfarin

There is wide inter-individual variation in response to warfarin, making it difficult to identify the correct dose. The optimal dose varies greatly from person to person, and the consequences of under- or over-dosing can be significant. Too little warfarin puts a person at increased risk of forming blood clots and having a stroke; too much warfarin puts the person at risk for a potentially devastating bleeding event—bleeds in the gastrointestinal track and brain are the most common major events.

FDA has been collaborating with the C-Path Institute and the University of Utah on the Cardiovascular Drug Safety and Biomarker Research Program[40] to establish an evidence-based framework for determining the clinical utility of cardiovascular biomarkers, including genetic variants, that determine the anticoagulation response to warfarin. CDER believes a pharmacogenetic algorithm may improve the therapeutic efficacy and safety of warfarin dosing.

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[40] See www.fda.gov/oc/initiatives/criticalpath/biomarker.html.

In a related project, sponsored by the National Heart, Lung, and Blood Institute and other leaders in the field, CDER is involved in developing a protocol for a trial that would identify and validate an algorithm for dosing warfarin. Initial goals are to identify (1) specific elements of a clinical trial design; (2) which dosing algorithms to evaluate; (3) how other factors such as age, gender, and weight might influence patient response to warfarin; (4) patient enrollment; (5) what single nucleotide polymorphisms (SNPs) to measure; (6) how the in vitro diagnostic and clinical data might be collected, analyzed, and shared; and (7) what information would facilitate development of new genetic diagnostic tests for specific genotype-based dosing and drug-label recommendations.

Based on the information gained from these efforts, in August 2007, FDA updated the labeling for warfarin products. The updates are based on the analysis of recent studies indicating that people respond to warfarin differently depending, in part, on whether they have variations of certain genes. The dosage and administration of warfarin must be individualized for each patient according to the particular patient's response to the drug. Specific dose recommendations are described in the warfarin product labeling, along with the new information regarding the impact of genetic information on the initial dose and the response to warfarin. Ongoing warfarin therapy should be guided by continued monitoring. Additional efforts are under way to provide more specific dosing algorithms in the warfarin labeling for patients with various genotypes.

- Dual antiplatelet therapy (DAPT) with cardiac drug eluting stents

Drug-eluting stents (DESs) are widely used, but there are limited data on whether a patient should continue DAPT after one year to decrease incidence of late stent thrombosis, myocardial infarction, and death. A large trial is needed to explore the benefits of DAPT beyond one year.

Under the Cardiovascular Safety and Research Consortium (launched September 2006[41]), FDA (CDER, CDRH, the Office of Combination Products, and FDA's Office of Women's Health (OWH)), and other partners are working toward the development of a placebo-controlled, multicenter clinical study of safe and effective dual antiplatelet regimens for use with DESs past one year. Immediate goals are to issue a request for proposals, choose a contract research organization to refine the protocol, and begin trial enrollment. Ideally, enrollment will be completed in 12 months.

In March 2008, FDA issued a draft guidance for industry containing recommendations for sponsors seeking to develop DESs, which involve input from both CDER and the CDRH. That guidance is being finalized.

An additional effort under way involves a retrospective evaluation into risk factors for late stent thrombosis (CDER, CDRH, OWH, and Agency for Healthcare Research and Quality).

[41] http://www.fda.gov/bbs/topics/NEWS/2006/NEW01467.html and www.cardiac-safety.org.

- Other safety-related research under way in 2008

The evaluation of the Safety of Key Inhaled and Intravenous Drugs in Pediatrics (SAFEKIDS) initiative, which will be officially launched in early 2009,[42] focuses on evaluating the neurocognitive and neurobehavioral effects of sedatives and anesthetics in children exposed to these agents for required medical or surgical procedures. Recent data from non-clinical studies in juvenile rodents and primates have demonstrated that exposure to certain sedatives and anesthetic agents may result in neurodegenerative changes (apoptosis and necrosis), as well as learning and behavioral deficits. There are no studies or data in humans to date that have specifically examined whether pediatric exposure to sedatives and anesthetics is associated with adverse neurological outcomes. More clinical and non-clinical research is urgently needed to fully elucidate what, if any, are the neurological and developmental effects in pediatric patients exposed to these agents during surgical and other procedures.

- Efforts in the Office of Women's Health (OWH)

OWH[43] regularly sponsors intramural research to advance the sciences related to women's health. For fiscal year 2008, OWH funded more than $2 million worth of research projects, targeting drug product safety. Five new studies were funded in fiscal year 2008 to support drug safety.[44]

  - Evaluate gender-related differences in QT effects and drugs with the potential of causing torsade de pointes (a specific variety of ventricular tachycardia).
  - Evaluate the effects of over-the-counter skin products, such as sunscreen, on the absorption of dermally applied estradiol, in an in-vitro and an in-vivo model.
  - Detect and confirm gender-related safety signals using the electronic healthcare data from the Department of Defense.
  - Identify safer use of narcotics in pregnant and lactating women.
  - Qualify imaging biomarkers to monitor neoadjuvant chemotherapy in breast cancer patients to identify responders using positron emission tomography (PET).

C. Advancing Signal Detection and Analysis

As part of its mission to protect health, FDA not only reviews large safety databases in marketing applications, the agency also evaluates large amounts of data as part of postmarket surveillance (e.g., through MedWatch and other mandatory and voluntary adverse events reporting programs). It is imperative that FDA use available tools to manage this information efficiently and effectively with the goal of rapidly detecting potential drug safety signals.

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[42] SAFEKIDS was launched on March 13, 2009; http://www.fda.gov/bbs/topics/NEWS/2009/NEW01973.html.
[43] See http://www.fda.gov/womens/programs.html.
[44] For more information, see http://www.fda.gov/womens/registries/registries.html#products.

Bioinformatics (the application of information technologies to the field of biology) is an area of substantial long-time focus at FDA. It is important that FDA capitalize on available information technologies (IT) and tools to transition from a paper-based to an all electronic environment for managing the information it receives, evaluates, stores, and shares (i.e., along the entire drug information supply chain). Numerous projects are under way as part of a long-term FDA effort to become a wholly electronic environment. FDA's Bioinformatics Board (BIB), in the Office of the Commissioner, approves and oversees most information technology projects, but individual projects are cross-agency efforts involving representatives from FDA centers and relevant offices. Use of IT technologies will improve the agency's ability to detect possible drug safety signals, efficiently receive and analyze drug safety information, and communicate important drug safety information to the public, as mandated by FDAAA sections 915 and 921. The efforts described here represent activities at different places along the information supply chain.

- MedWatch*Plus* portal/FAERS

FDA launched an important effort to modernize the way it collects, reviews, and analyzes adverse event reports and other safety information for ***all*** FDA-regulated products. The effort has three parts:

  - ***MedWatch*****Plus** will expand the current MedWatch system, incorporating all FDA-regulated products.
  - There will be a ***single Web-based portal*** (entry way for all reporters for all products) for submitting reports to the agency. A logical, user-friendly rational questionnaire is being developed that will help users complete and submit their reports easily and consistently. FDA is partnering with NIH to develop the rational questionnaire and Web portal.
  - A unified ***data repository, FAERS*** (FDA Adverse Event Report System), will make it possible for all FDA centers to use a common system for the monitoring and analysis of adverse event, product problem, and product use error reports submitted to FDA.

The safety information reported to FDA will go directly into the FAERS database, which agency staff can access using data mining and other analytical tools to identify and track safety signals and other important safety information and quickly spot potential safety problems.

The MedWatch*Plus* portal and FAERS system will be made available in stages, with the first release expected in 2009. At that time, the public will be able to use the Internet to access the MedWatch*Plus* portal to report safety concerns about human/animal food, animal drugs, and cosmetics, thus fulfilling the mandatory reporting requirements of the Dietary Supplements and Nonprescription Drug Consumer Protection Act of 2006 and FDAAA Reportable Foods and Early Recall Warnings for pet food. The second release, expected in late 2009, will involve the integration of existing electronic reporting systems for drugs, devices, and biological products. The third release, in 2011, will integrate remaining reporting systems. To help develop and integrate this new system, FDA recently awarded a five-year contract to SRA International, Inc.

- Electronic drug establishment registration and drug listing for manufacturers of human drug products and veterinary drugs

Section 510 of the FD&C Act (and FDA regulations) requires most owners and operators of domestic and foreign drug manufacturing-related establishments to register their establishments and submit listing information to FDA on their products, such as ingredients, labeling, and manufacturing information. New provisions in FDAAA require that this information be submitted electronically.

In July 2008,[45] FDA launched a pilot program that will make it possible for manufacturers to electronically submit to FDA their establishment registration and drug listing information. Beginning in June 2009, this information must be submitted electronically. Having this information available electronically and in a standardized structured product labeling (SPL) format that the agency can easily process, review, and archive will greatly improve FDA's ability to identify serious adverse drug reactions, inspect facilities used for drug manufacturing and processing, and monitor drug products imported into the United States. Electronic registration and listing will also make it easier for companies to meet their registration and listing requirements. In the past, manufacturers who were required to submit this information submitted it in paper form. Electronic filing will be available for the first time for all manufacturers of human drug products, including OTC and biological drug products, as well as veterinary drugs.

- Sentinel Initiative

In May 2008, FDA launched the Sentinel Initiative.[46] The ultimate goal of the initiative is to create and implement a nationwide electronic system for monitoring medical product safety, the Sentinel System. Once implemented, the Sentinel System will enable FDA to partner with existing data owners (e.g., CMS, insurance companies with large claims databases, owners of electronic health records) to query their databases, according to strict privacy and security safeguards, for information about medical product safety. Data sources would remain at their original locations and continue to be maintained by the owners, who would run requested queries and, with the appropriate tools, convey the result of their queries to FDA for analysis. Once in place, this new system is expected to strengthen FDA's ability to monitor the performance of a product throughout the entire period of use, enhancing health protection.

This system will satisfy certain requirements of Section 905 of FDAAA, which directed FDA to develop methods to obtain access to disparate data sources and to establish a postmarket risk identification and analysis system. The law sets a goal of access to data from 25 million patients by July 1, 2010, and access to data from 100 million patients by July 1, 2012. The law also requires FDA to work closely with partners from public, academic, and private entities.

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[45] See the draft guidance describing the new submission and pilot program on the CDER Web page at http://www.fda.gov/cder/guidance/OC2008145(2).pdf.

[46] The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety. http://www.fda.gov/oc/initiatives/advance/reports/report0508.html.

The Sentinel System, which is a long-term project that will be implemented in stages, ultimately could facilitate data mining and other research-related activities. The Sentinel report describes a number of public- and private-sector pilot projects already under way that will directly inform the goals of the Sentinel Initiative (see also section III.C of this report).

FDA's first step has been to create a broad public forum for discussion of issues related to developing and implementing the Sentinel System. Next steps will include exploring what kind of public–private partnership would best ensure the success of the initiative and evaluating the privacy and security safeguards that will be needed.

D. Engaging Outside Experts on Safety Signal Analysis

In the PDUFA IV goals letter from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives,[47] FDA promised to increase the rigor of scientific analysis of postmarket drug safety signals. A number of activities are under way as part of this effort. For example, FDA is working to define best practices to be applied when FDA scientists analyze epidemiologic data. FDA also held two public workshops to solicit outside expertise on ongoing internal research and development work. These activities are also responsive to the IOM's recommendations and new requirements in FDAAA.

- Public meeting, Maximizing the Public Health Benefit of Adverse Event Collection Throughout a Product's Marketed Lifecycle, January 29, 2008

The meeting's goal was to solicit information and views from interested persons on best research approaches and methods for assessing the public health benefit of collecting, analyzing, and reporting adverse events. Input from this workshop was used to publish a request for information (RFI) in April 2008 to determine the types of outside organizations that might be interested in, and have the relevant capabilities for, conducting the research described above. A request for proposals (RFPs) and eventual award of a contract will follow in 2009.

- Public workshop, Developing Guidance on Conducting Scientifically Sound Pharmacoepidemiologic Safety Studies Using Large Electronic Healthcare Data Sets, May 7, 2008

The workshop's goal was to solicit information and views from interested persons on best practices and principles for the design and evaluation of pharmacoepidemiologic safety studies using large electronic healthcare data sets. Input from this workshop is being used to draft a guidance for industry and provide consistent review criteria for FDA to use in evaluating protocols and study reports submitted to the agency (the guidance is in the early drafting stage).

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[47] See http://www.fda.gov/oc/pdufa4/pdufa4goals.html.

E. Ensuring Quality Manufacturing

Another critical aspect of drug safety is drug quality. Consumers are at risk if a drug is not manufactured in such a way that ensures that it has the necessary identity, strength, quality, and purity. FDA may approve a drug based on the risk–benefit profile of the drug when properly manufactured. However, if the drug is not properly manufactured, the risks presented by a drug may be entirely different, and the drug may not provide the expected benefits. For example, the recent worldwide problems (including serious adverse events and possibly deaths) caused by contaminated heparin were a result of poor drug quality. FDA is charged with overseeing pharmaceutical companies' manufacturing, quality assurance, and distribution systems.

Since 2004, FDA has been implementing a modernized regulatory system for product quality. Many projects have been launched and completed under the initiative, which is now known as Pharmaceutical Quality for the 21st Century. This program encompasses cross-cutting activities and systems in the quality program's review, compliance, and inspection units. The agency's quality initiative has a number of important goals.

- Provide the regulatory policy framework to enable industry adoption of technological advances that promote drug quality assurance.
- Provide the regulatory policy framework to facilitate increased reliance on quality systems that will continually improve the quality of drugs and drug manufacturing.
- Enhance the consistency and coordination of FDA's drug approval and drug quality regulatory programs, in part, by integrating enhanced quality management systems into review and inspection processes.
- Encourage implementation of risk-based approaches that focus both industry and agency attention on critical areas. Ensure that regulatory review and inspection policies are performed by well-trained staff who are well-versed in state-of-the-art pharmaceutical science.

Examples of most recently initiated or completed activities related to applying quality systems approaches to agency business processes and regulatory policies concerning review and inspection activities include:

- launching an initiative to use risk modeling to select the most appropriate sites for routine CGMP surveillance;
- beginning a pilot program to inspect active pharmaceutical ingredient manufacturing sites in developing nations in collaboration with fellow regulators; and
- sharing best practices for review and use of scientific information to enhance work products within the centers.

As part of this effort, FDA has continued its outreach efforts on quality systems. A number of workshops have been held to solicit public input on related issues. Workshops are held in the United States and in other countries (e.g., Dublin in 2007; Shanghai and Beijing in 2008). Furthermore, the 3rd Annual CDER Workshop on CMC (21st Century Pharmaceutical [Chemistry] Manufacturing and Control Strategies—A Changing Paradigm) took place on

October 20–21, 2008. FDA also has developed a number of guidance documents describing FDA's expectations about how to implement quality systems.[48]

FDA continues to develop and improve regulatory approaches toward ensuring the quality of new, biotech, and generic drugs used by the American public. On July 2, 2008, FDA announced a pilot program with industry involving the voluntary submission of quality (chemistry, manufacturing, and controls) information for biotechnology products in an expanded change protocol, consistent with the principles of quality by design and risk management in pharmaceutical manufacturing.[49] The purpose of the pilot program is to gain more information on, and facilitate agency review of, quality by design, risk-based approaches for manufacturing biotechnology products.

To address globalization of the industry, FDA is working in tandem with other global regulators and recently opened offices in Asia, Europe, and Latin America.[50] This approach will help address the challenges drug manufacturers and regulators face toward ensuring the quality of imported drugs and drug ingredients. Recent events, such as the heparin contamination episode, demonstrate that international cooperation among regulators and industry can address these challenges.

V. Expanding Safety Communication and Information Flows

In the January 2007 response to the IOM report, FDA outlined a series of efforts to improve communication and information flows. These included conducting a comprehensive review of current public communication tools, improving internal communications, and posting reviews of NDA supplements and assessments of postmarket safety studies. In addition, FDA has convened a number of advisory committee meetings since January 2007.[51] Details of FDA's work to date in these areas are provided in the Appendix.

The scope of these activities has been substantially augmented by new resources and requirements resulting from FDAAA. Consequently, as part of the *Safety First Safe Use* initiative, as well as other initiatives, the agency is expanding existing and developing new drug safety communication projects, some involving extensive collaboration with others.

A. Efforts Under Way

When the IOM issued its 2006 report, FDA had already launched a number of efforts to strengthen the drug safety system. In the year following the IOM report, FDA began additional

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[48] See guidances on *Quality Systems Approach to Pharmaceutical CGMP Regulations*; *Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP*; and *INDs–Approaches to Complying with CGMPs for Phase I Drugs.*

[49] See the *Federal Register***,** Vol. 73, No. 128, Wednesday, July 2, 2008, p 37973**.**

[50] See FDA's Action Plan for Import Safety at http://www.fda.gov/oc/initiatives/advance/imports/.

[51] For example, meetings have been held on Avandia, Tysabri for Crohn's Disease, Trasylol, and cardiovascular studies for antidiabetic agents.

activities in response to the IOM recommendations. In some cases, because of new authorities in FDAAA, FDA has begun other efforts. Some activities are highlighted here.

- Established a risk communication advisory committee

In 2007, FDA established the Risk Communication Advisory Committee (RCAC),[52] comprising external experts to provide advice on strategies and programs to better communicate with the public about both the risks and benefits of FDA-regulated products so as to facilitate optimal use of the products. This Committee was codified in Section 917 of FDAAA. Committee tasks include reviewing and evaluating research relevant to public risk communication by FDA and to the use of our communications by other entities. The Committee is also facilitating the sharing of risk and benefit information with the public to enable people to make informed independent judgments about use of FDA-regulated products.

RCAC met three times during 2008. At the first meeting, on February 28–29, 2008, the Committee heard presentations and discussed how FDA's risk communication programs relate to its responsibilities. FDA's proposed template for press releases announcing product recalls was also discussed with a view to incorporating best practices for risk communication. The Committee met on May 15–16, 2008, for presentations and discussion on how to produce a report mandated by FDAAA (Section 901(d(5)) on direct-to-consumer (DTC) advertising, including how it relates to communicating to subsets of the general population, such as the elderly, children, and racial and ethnic minority communities. Of special interest, the Committee discussed how to increase access to health information and decrease health disparities in special populations. The Committee also discussed studying the appropriateness of televised DTC ads containing a statement encouraging consumers to report negative side effects of prescription drugs to MedWatch (this is currently required for print DTC prescription drug ads). The Committee met a third time in mid-August to discuss the scientific basis for translating principles of risk communication into practice in situations of emerging and uncertain risk associated with FDA-regulated products.[53]

- Expanding drug safety communication approaches

In a final guidance[54] formalizing its commitment and current efforts to ensure communication of the latest safety information to healthcare professionals, patients, and other consumers, FDA explained that it communicates on specific issues in a variety of ways, including Public Health Advisories, Healthcare Professional Sheets, and Early Communications.

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[52] For more on RCAC, see http://www.fda.gov/oc/advisory/OCRCACACpg.html.

[53] The first meeting in 2009 took place February 26 and 27.

[54] http://www.fda.gov/cder/guidance/7477fnl.pdf.

- Between January 1, 2007, and December 31, 2008, CDER issued 17 Public Health Advisories (PHAs),[55] 39 Information for Healthcare Professional Sheets (HCPs),[56] and 1 Science Review.[57]
- Beginning in August 2007, CDER has been providing to the general public *Early Communications (ECs)*[58] about Ongoing Safety Reviews. From August 2007 to December 31, 2008, CDER issued 17 Early Communications. FDA uses Early Communications to notify the general public (1) that important new postmarket safety information has been received; (2) that FDA intends to review, or is in the process of reviewing that information; and (3) the specific time frame identified for completion of the safety review.

Drugs with active safety alerts (e.g., PHAs) are denoted on the Index to Drug-Specific Information on FDA's Web site.[59] In addition, FDA's *MedWatch* program sends these communications to 102,000+ listserv subscribers and to more than 130 partner organizations, many of which also distribute the information to their members.

Informal feedback from practitioners and leaders in the healthcare community has been positive. FDA is aware that healthcare institutions and systems, such as the Veterans Health Administration (U.S. Department of Veterans Affairs), regularly distribute these communications to their clinical staff and online medical information distributors, such as ePocrates, routinely alert their subscribers to newly released risk communications. Healthcare systems, private and governmental, have altered their formularies and recommendations in response to the information CDER has provided.

Examples of recently updated and newly created methods for communicating vital safety information to healthcare practitioners, patients, and consumers include the following:

- Consolidated Web page for drug safety information

  FDAAA Section 915 requires the creation of an FDA Web page that consolidates all drug safety information for patients and practitioners in one place. The Web page should also include a list of all drugs that have approved REMS (formerly known as RiskMAPs, risk minimization action plans).

  FDA had already begun taking steps to build more transparency into its risk management efforts before FDAAA was enacted in September 2007. For example, Medication Guides, alerts, product recalls, and warning letters were already available on FDA's main Web page.[60] Also, CDER had developed an extensive drug safety Web page on the CDER home

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[55] HCPs are posted with the specific drug; see www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.
[56] See http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.
[57] A science review was issued on bupropion (http://www.fda.gov/cder/drug/infopage/bupropion/TE_review.htm).
[58] For an example posted in June 2008, see http://www.fda.gov/cder/drug/early_comm/TNF_blockers.htm.
[59] See http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm.
[60] See at http://www.FDA.gov.

page.[61] At a 2-day public workshop in June 2007 sponsored by FDA and AHRQ entitled, "Implementation of Risk Minimization Action Plans (RiskMAPs) to Support Quality use of Pharmaceuticals: Opportunities," the role of risk management in drug development and the challenges faced by various stakeholders were discussed. At the public meeting, the need for transparency was stressed, along with the need for better access to information. Participants examined creative paths to ensure that this would be accomplished. It was recommended at the meeting that there be public posting of a list of drugs that have Medication Guides, a list of drugs with risk management programs, along with a standard list of risk management components that could be used to monitor program progress.

With the enactment of FDAAA, this project has evolved to accommodate the new requirements. Although the agency has begun posting approved REMS by individual product on the Web page at Drugs@FDA, a list of products with approved REMS is included on the new, consolidated Web page, along with links to patient labeling and packaging, drugs with Medication Guides, most recent safety information, alerts, product recalls, warning letters, and other relevant safety information that could be of interest to patients and practitioners.[62]

– Encouraging voluntary reporting to FDA

As mentioned previously, in September 2007, FDA and NIH signed an MOU to develop a rational reporting questionnaire for MedWatch that will make voluntary reporting to FDA easier and quicker and improve the quality and consistency of reports FDA receives. FDA hopes that this Web-based, user-friendly questionnaire will encourage more voluntary reporting.

– Launched *FDA Drug Safety Newsletter*

In September 2008, FDA published the fourth issue of its quarterly *Drug Safety Newsletter*, which provides information for healthcare professionals about the findings of selected postmarket drug safety reviews, important emerging drug safety issues, and safety information about recently approved new drugs. The newsletter is intended to complement other FDA tools for communicating drug safety information to the public. In addition, FDA hopes the newsletter will raise awareness of the importance of reporting adverse drug events and stimulate additional reporting by healthcare professionals.

- Efforts in the Office of Women's Health (OWH)

FDA's OWH maintains a consumer-friendly Web site containing a range of useful drug safety and medical health information. The Office also communicates with more than 4,500 groups and individuals, providing electronic updates about FDA and on safety-related issues on a quarterly basis. OWH collaborates with several hundred external groups to distribute consumer health

[61] See http://www.fda.gov/cder/.
[62] See http://www.fda.gov/cder/drugSafety.htm.

information about FDA-regulated products to their members. Examples of recently updated and newly created methods for communicating important safety information to healthcare practitioners, patients, and consumers include the following.

– A Web site for consumers on postmarket studies on drug exposure during pregnancy and related fetal effects.

– Consumer fact sheets tested by focus groups.

Consumer fact sheets, which are created and focus-group tested, help explain things consumers should know about FDA-regulated products (e.g., buying drugs online; generic drugs; how to use medications wisely; medications and pregnancy; medications and menopause). All materials are free and available in English and Spanish. They can be downloaded from FDA's OWH Web site as well as ordered in bulk through the Federal Consumer Information Clearing House. Some of these are also translated into multiple languages.

– Medication Safety and Effectiveness Health Education Initiative

OWH and the Health Research Services Administration's (HRSA) Office of Pharmacy Affairs have developed and implemented a Medication Safety and Effectiveness Health Education Initiative, targeting community and migrant health centers and individuals with special healthcare needs, including HIV/AIDS. OWH provides free consumer information, disseminated as part of an educational tool kit to HRSA grantees. OWH and HRSA are also collaborating in the development of a Web-based course and information portal for pharmacists, nurses, and other health professionals working at more than 6,000 urban and rural underserved areas across the country.

– Medication brochures for patients and health practitioners

OWH has created and posted medication brochures for use by patients and health practitioners on a variety of issues (e.g., birth control, cholesterol, depression, high blood pressure, HIV, menopause, smoking cessation). The brochures, which have been tested by focus groups, provide reliable, easy-to-read information on benefits and side effects for all FDA-approved medicines for these specific health problems.

– Exhibitions

OWH exhibits at more than 60 medical, professional, and health issue related meetings each year to distribute consumer health information.

B. New Communication Tools

Since 2006, FDA has been working to redesign its entire Web site to make it more user-friendly for all audiences, especially for consumers. Although redesign activities are not yet complete, some substantive changes have already been implemented, including a new FDA home page that

makes it easier for the public to find and evaluate safety information related to medical products. FDA is making the specific safety information outlined in Section 915 of FDAAA available on this consolidated Web page, as soon as it is ready for posting.

FDAAA has provided FDA with new authorities and resources that are making it possible for the agency to develop new communication tools. For instance, CDER launched a series of new communication activities that support ongoing efforts to make public access to drug safety information more transparent and efficient. Some key activities are described here.

- Facilitating public access to information on clinical trials

In its 2006 report, IOM recommended that industry sponsors be required to register, in a timely manner, at ClinicalTrials.gov. IOM also recommended that, at a minimum, sponsors be required to register all phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to FDA as part of a new drug application or supplemental drug application, or if the data are to fulfill a postmarket commitment. A summary of efficacy and safety results of the studies should also be posted.

This IOM recommendation was not directed to FDA. However, Section 801 of FDAAA mandates expansion of the existing ClinicalTrials.gov registry to include additional information about applicable clinical trials of drugs, biologics, and devices (as defined in the law). It also mandates establishment of a clinical trial results database and requires, beginning not later than 12 months after enactment of FDAAA (i.e., by September 27, 2008), including the basic results information described in the law. Additional statutory provisions outline processes for adding information about serious and frequent adverse events observed in a trial and for expanding the registry and results database. (Section 915 requires a link to the database from the consolidated FDA Web page as well.)

FDA and NIH are working together to implement the various provisions under Title VIII of FDAAA. Seven FDA-NIH working groups have been established, and much has been accomplished.

- The clinical trials registry has been expanded to accept a broader scope of trials and more required information New registrations-submission of more data items.
- Existing records for ongoing trials (~13,000) have been updated.
- Links have been established from the clinical trials registry to specified FDA and NIH (NLM) results information.
- FDA developed a certification form to accompany investigational and marketing applications and submissions.[63]
- FDA issued a draft guidance entitled, C*ertifications to Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The*

[63] See http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674_508.pdf.

Public Health Service Act, Added by Title VIII of FDAAA[64] to clarify the certification process.

- FDA updated template letters for investigational and marketing applications to advise sponsors and applicants of the new requirements in Title VIII.
- FDA is currently working with NIH to provide clarification of the requirements for the expanded clinical trial registry and the basic results database via rulemaking. Basic results materials have also been made available for comment on the NIH Web site.[65]

- Developed a prescription drug labeling training module for health professionals.

In January 2006, FDA unveiled a major revision to the prescription drug labeling format. To manage the risks of medication use and to reduce medical errors, the newly designed package insert provides the most up-to-date information in an easy-to-read format that draws healthcare practitioners and patient attention to the most important pieces of drug information before a product is prescribed.

To help inform health professionals about the new labeling, CDER's Office of Training and Communications, in partnership with FDA's Office of Special Health Issues, has developed a new, accredited educational module called An Introduction to the Improved FDA Prescription Drug Labeling.[66] The primary audiences for the course are physicians, nurses, and pharmacists. The course is designed to give health professionals a better understanding of the revised prescription drug labeling, the format changes that were made, and why they were necessary. The goal of this training module is to make information about the revised labeling clearer and more easily understood. Continuing education credit is offered for health professional groups. The program received an award of excellence from the National Association of Government Communicators at their May 2008 meeting.

- Developed MedWatch Partners Program Plan of Action

In November 2007, FDA's MedWatch Program began fact-finding discussions with current and potential healthcare partner organizations. These discussions sought to obtain feedback on how to expand the MedWatch Program to meet the needs of healthcare partner organizations and to strengthen the communication between the healthcare community and FDA. This project involved telephone interviews and face-to-face consultations with representatives from health professional organizations. FDA received valuable feedback, benefited from the exchange of ideas, and was encouraged by the thoughtfulness and breadth of concrete suggestions made during the discussions. FDA is currently reviewing recommendations made during the

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[64] See http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html.

[65] See http://prsinfo.clinicaltrials.gov/fdaaa.html.

[66] See http://www.fda.gov/cder/learn/CDERLearn/prescriptionLabeling/default.htm. The interactive training module launched on December 3, 2007.

discussions to develop a plan of action for building and sustaining meaningful partnerships with external stakeholders.

- Prepare MedWatch safety labeling summaries

To help ensure the timely dissemination of safety information for FDA-regulated drugs and biologics to healthcare professionals and consumers, MedWatch staff prepare monthly summaries of drug products with safety labeling changes and make them available via the MedWatch Web site and by sending notification to over 130,000 individual e-list subscribers, to the 106 healthcare professional organizations who are MedWatch Partners and to a variety of drug reference resource providers who include this new safety information into the reference sources used by clinicians in day-to-day care. In 2006, there were 919 changes made to 480 package inserts, and in 2007, there were more than 1,200 labeling changes made to 495 package inserts, including 77 boxed warnings and 85 medication guides. In 2008, FDA made 1157 changes to 561 package inserts, including 56 boxed warnings and 60 medication guides. FDA is exploring how best to convert its current manual process to an electronic process using Structured Product Labeling and DailyMed.

- Created new Web communication for health professionals

In December 2007, FDA created a new listserv for healthcare professionals to receive FDA updates. The listserv provides the most recent announcements, particularly related to safety, medical product approvals, opportunities to comment on proposed rules, upcoming public meetings, and other information of interest to health professionals. The list has more than 13,000 members.

The MedWatch listserv, which has been operational since 2000, provides timely new safety information through Early Communications to both healthcare professionals and their patients. Early Communications focus on emerging safety issues, alerts about new prescribing information, Class I recalls, market withdrawals, and public health advisories. The listserv continues to add new subscribers; currently nearly 102,000 healthcare professionals, patients, and consumers receive these alerts and notifications.

- Exploring FDA/AMA Network of Nodes

FDA and the American Medical Association (AMA) are exploring the possibility of developing a Network of Nodes that would create and sustain relationships to facilitate communication between FDA and medical specialty societies. The Network of Nodes would be launched in 2009 in conjunction with FDA's *Safe Use* initiative. Prior to the launch in 2009, FDA plans to pilot the Network of Nodes concept with a few interested specialty societies.

VI. Summary and Conclusions

The safety and effectiveness of drugs and other medical products regulated by FDA have always been key to the agency's mission. As this report explains, the new authorities and resources

provided by FDAAA are making it possible for FDA to invest substantial resources in an effort to strengthen existing premarket, and augment its postmarket, drug safety processes and procedures. The pre- and postmarket components of drug safety must interact to enable a seamless flow and integration of information gathered during biomedical research, clinical testing, and therapy. FDA is also evaluating its overall approach to risk management and working to improve and expand the ways it communicates about drug safety. The goal is improving safety throughout a drug's entire period of use.

For the past decade, FDA has been working to move from the paper-based organization of the past to an electronic-based environment for the future. This effort continues unabated. Capitalizing on the power of available information technologies will help FDA to strengthen the science of drug safety signal detection, analysis, and risk communication, helping to protect and promote public health.

Many of the projects described in this report were already under way at FDA when IOM issued its 2006 report on improving drug safety. However, the IOM report identified additional significant opportunities for change that FDA is working to complete; in some cases, FDAAA broadened or added to these opportunities. The efforts outlined here—both on an agency level (e.g., Sentinel Initiative, MedWatch^{Plus}) and in the centers (e.g., CDER's *Safety First/Safe Use* initiative, drug safety communication activities)—are all prospering today while laying the foundation for greater progress in the future.

Attachment: IOM Recommendations—FDA Actions Update

Accessible text version of this attachment

In 2005, the Food and Drug Administration (FDA or agency) commissioned the Institute of Medicine (IOM) to convene a committee of experts to assess the U.S. drug safety system and make recommendations to improve risk assessment, surveillance, and safe use of drugs. On September 22, 2006, the IOM issued its report on that study.[1] The report included 25 recommendations related to improving the drug safety program and creating a more robust and comprehensive system for better ensuring the safe use of medical products. Fourteen of the recommendations in the report were directed to FDA.

After reviewing the IOM report and recommendations, FDA issued its response in January 2007 stating that it was in substantial agreement with the majority of the recommendations directed to FDA.[2] The agency also described a series of specific actions it was taking, or planned to take, to improve medical product safety and committed to track those actions and report their progress in 1 year.[3] The following table shows the IOM recommendations, agency actions, and status of those actions as of July 2008. IOM recommendations are listed in the far left column with FDA actions and status updates in the adjacent columns.

In September 2007, while FDA was working on its safety initiatives, the President signed the Food and Drug Administration Amendments Act of 2007 (FDAAA)—sweeping legislation that contained many provisions directed at improving medical product safety. FDAAA established new authorities for FDA to ensure medical product safety and specified actions to improve collaboration between drug review and drug safety staff at FDA. Section 919 of FDAAA directs FDA, within 1 year of enactment, to issue a report assessing how it has implemented the recommendations in the IOM report. This Report to Congress fulfills that commitment.

As the table that follows illustrates, FDA has made significant progress in the three key areas identified in its initial response: Operations and Management, Science of Drug Safety, and Communication and Information Flows. FDA has also included notations in the table where new authorities and/or resources from FDAAA have resulted in changes and/or additions to our efforts to strengthen the FDA's drug safety programs.

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[1] *The Future of Drug Safety—Promoting and Protecting the Health of the Public.* http://www.iom.edu/.

[2] *The Future of Drug Safety—Promoting and Protecting the Health of the Public, FDA's Response to the Institute of Medicine's 2006 Report*, p. 1.

[3] Id. at 17.

IOM RECOMMENDATIONS AND FDA Safety Initiative— One Year Update

IOM Recommendations	FDA Actions	Status
3.1 Amend FD&C Act to require that the FDA Commissioner, currently appointed by the President with the advice and consent of the Senate, also be appointed for a 6-year term of office.	**Not directed to FDA**	
3.2 Secretary of HHS appoint an external Management Advisory Board to advise the FDA Commissioner in shepherding CDER (and all of FDA) to implement and sustain the changes necessary to transform the Center's culture by improving morale and retention of professional staff, strengthening transparency, restoring credibility, and creating a culture of safety based upon a lifestyle approach to risk-benefit.	**FDA is engaging external management consultants to help CDER/FDA develop a comprehensive strategy for improving CDER/FDA's organizational culture.** [4]	CDER had begun planning Center organizational changes to effect a change in its culture prior to its January 2007 response to the IOM report. Since that time, the center has done the following. • CDER's senior management team (SMT) began laying the foundation for this work in November 2006, when they embarked on a course of action to strengthen the SMT and to develop their vision for CDER. • In September 2007, CDER awarded a contract to the Center for Professional Development, Inc. (CPD). The period of performance is September 21, 2007 to September 20, 2009. • The SMT meets regularly, including quarterly 2-day off-site meetings, to manage the change process. • Led by experts from CPD and working with a cross section of Center staff, CDER has defined and validated its vision for the desired culture changes. Regular meetings with the CDER Workplace Culture Team (WCT) continue to take place.

[4] The actions listed are those most relevant to the specific IOM recommendation. Other related actions may not be listed.

IOM Recommendations	FDA Actions	Status
		• The CPD is required to assess and diagnose the current culture at CDER by evaluating all relevant data. The CPD developed a custom organizational effectiveness survey to give all CDER employees an opportunity to provide feedback on CDER's culture. Nearly half of CDER's employees responded to the survey, which demonstrates a high level of interest and confidence in the culture transformation process. • The survey results were reported to the SMT and CDER employees in early February 2008. CDER will use the results to identify areas where improvements are needed. • The CPD plans to repeat the survey in 18 months to measure what improvements have been made and determine what future actions are needed.
	On January 19, 2007, the Commissioner proposed the creation of the Office of Chief Medical Officer, which will oversee scientific operations for FDA.	The Commissioner created the position of Chief Scientist and filled it in April 2008.
3.3 Secretary of HHS direct FDA Commissioner and CDER Director, with the assistance of the Management Advisory Board, to develop a comprehensive strategy for sustained cultural change that positions the agency to fulfill its mission, including protecting the public health.	**See response to 3.2**	**See progress in 3.2**

IOM Recommendations	FDA Actions	Status
3.4 CDER appoint an OSE staff member to each NDA review team and assign joint authority to OND and OSE for post approval regulatory actions related to safety.	**In 2007, FDA initiated two pilot projects to (1) evaluate various models for involving OSE staff in reviews, including the logistics and value of having an OSE staff person participate in each biologics license application (BLA) and new drug application (NDA) review; and (2) evaluate various models for more significant involvement of OSE in postmarket decision making. The agency is committed to ensuring that safety staff has a strong voice in pre- and postmarket safety decision making.** **As described above, FDA has already created two process improvement teams that have made recommendations about specific ways to increase communications between review staff and drug safety staff. Their recommendations to (1) establish an Associate Director for Safety and a Safety Regulatory Project Manager in each OND review division within CDER; and (2) conduct regular safety meetings between OSE and all of the OND review divisions have been implemented.**	Progress on these proposed actions has been substantial since 2006. Significant operational changes have been made in CDER respecting the involvement of safety staff in drug reviews. To provide a framework for these activities and other drug safety efforts, CDER launched *Safety First Safe Use*. The *Safety First Safe Use* initiative has two parts. *Safety First* refers to steps CDER is taking to strengthen and modernize its internal policies and processes to manage significant drug safety issues. Specific objectives of CDER's *Safety First* initiative include: • Create and maintain a collaborative, multidisciplinary, team-based approach to the review of drug safety; • Apply world-class project management to ensure FDA focuses the same attention on postmarket safety issues as it does on premarket review; • Align policies and processes to ensure that the most appropriate and best-qualified experts lead and have an equal voice in regulatory decisions; • Build the scientific, administrative, and technological capacity to carry out the provisions of FDAAA and the Prescription Drug User Fee Act (PDUFA); and • Ensure that significant postmarket safety issues are CDER's highest priority. Recently, under the *Safety First* initiative, a memorandum of agreement was finalized and signed in July 2008 by OND, OSE, and CDER's Director. The agreement affirms CDER's commitment to a multidisciplinary, team-based approach to the review of drug safety that ensures that the best-qualified experts lead or have an equal voice in regulatory decisions. CDER is in the process of identifying all internal processes that need to be adjusted or developed to ensure that this "equal voice" philosophy is embodied in center operations. OND has established the positions of Deputy Director for Safety and Safety Regulatory Project Manager in each review division. Recruitment to fill these positions is under way with approximately half of the positions now

IOM Recommendations	FDA Actions	Status
	Another outgrowth of the process improvement teams discussed above is the creation of new procedures to improve the decision making processes related to postmarket drug safety. These procedures will address issues such as how decisions are made to request further studies and labeling changes. **The proposed performance goals under PDUFA IV also include provisions for enhancing and improving communication and coordination between OSE and OND in CDER, the Office of Biostatistics and Epidemiology, and the premarket product review offices in CBER, including activities to assess the impact and value of routinely including postmarket review staff on premarket review teams.** *** * *** **CDER is creating a standard operating procedure for presenting postmarket safety issues to an Advisory Committee (AC) or other body. This new procedure will articulate the division of responsibility between OND and OSE for planning presentations, Advisory**	occupied. During the application approval process, OND and OSE work closely together on certain aspects (trade name reviews, REMS, and labeling review) of the NDA/BLA review. OSE becomes involved at the pre-NDA or pre-BLA stage of review and attends and provides input at preapproval milestone meetings, which occur throughout the NDA/BLA review cycle. OSE staff attends preapproval safety conferences, during which OND and OSE staff discuss complex safety issues and make recommendations for postmarket studies and trials and other possible postmarket safety activities. In addition, reviewers from OND and OSE together evaluate proposed proprietary names, REMS proposals, and proposed patient labeling. The recently signed MOA gives OSE sign-off authority for certain postmarket actions dealing with medication errors, proposed proprietary name review, and epidemiological studies. The implementation of the transfer of this responsibility from OND to OSE is under way. Within CDER, both OND and OSE collaborate regularly on safety reviews with the Office of Biostatistics and Epidemiology and other offices in CDER, and also ensure cross-center coordination by involving CBER in many of the implementation activities for *Safety First* and FDAAA. *** * *** OSE and OND have jointly worked on several postmarket safety issues in the past year that have gone to Advisory Committees. The standard operating procedure will formalize this process. It was discussed at a recent Advisory Committee meeting.

IOM Recommendations	FDA Actions	Status
	Committee configuration, and a process for compiling background materials for Advisory Committees.	
3.5 Congress should introduce specific safety-related performance goals in the Prescription Drug User Fee Act IV in 2007.	**The proposed recommendations for PDUFA IV included the following safety-related performance goals (changes, as reflected in the status update, have been made to these goals as a result of FDAAA):** • **FDA would develop a plan to (1) identify, with input from academia, industry, and others from the general public, risk management tools**	• FDA held a public workshop on June 25 and 26, 2007, to identify ways to implement RiskMAPS (now Risk Evaluation and Mitigation Strategy - REMS) to support the quality use of pharmaceuticals. • Following the workshop, CDER and the Office of Special Health Issues began developing materials for a RiskMAP Web site. As a result of Sections 901 and 915 of FDAAA, this project has evolved to accommodate new requirements (e.g., Risk Evaluation and Mitigation Strategies (REMS)). A consolidated Web page containing drug safety information for patients and practitioners will be available soon to fulfill the requirements of Section 915. (See additional discussion on Section 915 below.) • Building on the input from this workshop and new authorities from

IOM Recommendations	FDA Actions	Status
	and programs for the purpose of evaluation; (2) conduct assessments of the effectiveness of identified Risk Minimization Action Plans (RiskMAPS) (under FDAAA called REMS) and current risk management and risk communication tools; and (3) conduct annual systematic review and public discussion on the effectiveness of one to two risk management programs and one major risk management tool (codified in FDAAA in Section 901(f)(4)) • **FDA would post reports of these discussions on its Web site.** • **In addition, FDA would hold a public workshop to obtain input from industry and other stakeholders regarding the prioritization of the plans and tools to be evaluated.** *** * *** • **FDA would publish a request for proposals from outside research organizations that would be interested in conducting research on determining the best way to maximize the public health**	FDAAA, CDER is also developing a process for quality assessment and has been conducting inspections of several risk management programs each year. CDER is finding that risk management programs are being implemented. • FDA is in the early planning stages of a public meeting to take place during 2009 with the purpose of obtaining outside input on the priority, frequency, and methodology for evaluating elements to assure safe use. The focus of the meeting will be, among other things, to obtain outside input on the priority for evaluating REMS, how frequently they should be evaluated, and what specific tools should be evaluated. * * * A public meeting was held on January 29, 2008 ("Maximizing the Public Health Benefit of Adverse Event Collection Throughout a Product's Marketed Lifecycle"). The goal of the meeting was to solicit information and views from interested persons on best research approaches and methods for assessing the public health benefit of collecting and reporting all adverse events. • The input from this workshop was used to publish a request for information (RFI) (April 29, 2008) to determine the types of outside

IOM Recommendations	FDA Actions	Status
	benefits associated with collecting and reporting serious and nonserious adverse events (AEs) occurring throughout a product's life cycle. Central to addressing this question are determining the number and type of safety concerns discovered by AE collection, the age of products at the time safety concerns are detected by AE collection, and the types of actions that are subsequently taken to protect patient safety.	organizations that may be interested in, and have the capability to, conduct the research described above. The RFI will be followed by a request for proposal (RFP), which is planned for fiscal year 2008, and the eventual award of a contract in fiscal year 2009. • Title VI of FDAAA establishes a conduit for private funding through the Reagan-Udall Foundation that may prove supportive of FDA drug safety activities. The Foundation is to identify unmet scientific needs in the development, manufacture, and evaluation of the safety and effectiveness of FDA regulated products, including postmarket evaluation, and establish scientific projects and programs, including funding, to address those needs.
		Relevant to additional databases, see progress in 4.1
	• **FDA would use PDUFA funds to obtain access to additional databases and to hire the additional epidemiologists and programmers needed to use these databases.**	With regard to the hiring of additional epidemiologists: During the July 2008 hiring fair, OSE hired eight epidemiologists. One additional epidemiologist was hired through an advertised position, bringing the total hired to nine.
	• **FDA, with input from pharmacoepidemiologists in academia and industry, would develop guidance on conducting scientifically sound pharmacoepidemiologic**	On May 7, 2008, FDA held a meeting entitled "Developing Guidance on Conducting Scientifically Sound Pharmacoepidemiologic Safety Studies Using Large Electronic Healthcare Data Sets" to discuss how to conduct scientifically sound pharmacoepidemiologic studies using observational data, based on large automated healthcare data sets. • Topics discussed at the meeting included best practices on designing and evaluating pharmacoepidemiologic studies and providing consistent review criteria for FDA to use in evaluating protocols and study reports

IOM Recommendations	FDA Actions	Status
	studies using observational data based on large healthcare data sets. FDA would hold a public workshop the first year of PDUFA IV to identify best practices for observational epidemiologic studies using large healthcare data sets. CDER and CBER would then jointly develop and issue a draft guidance document that recommends epidemiology best practices for this type of study.	submitted by industry. • Using input from both the internal and public meetings, the working group has begun writing the draft guidance and anticipates publication of the draft for comment in fiscal year 2010. Plans are to finalize the guidance in fiscal year 2011.
	• Under PDUFA IV, to improve safety assessments supporting NDAs and BLAs, FDA would develop guidance for industry on how to test, detect, and prevent safety problems during drug development. For example, FDA would develop the following guidances: **- *Guidance on clinical hepatotoxicity* to make recommendations on how to evaluate a drug for possible hepatotoxicity during drug development**	• In October 2007, FDA published draft guidance for industry on *Drug-Induced Liver Injury: Premarketing Clinical Evaluation.* The comment period closed on December 24, 2007. Only one comment was received. • In conjunction with PhRMA and the American Association for the Study of Liver Diseases (AASLD), FDA held a meeting on March 26 and 27, 2008, on detecting and investigating drug-induced liver injury during clinical trials. • Approximately 250 people attended the meeting. • The comments on the initial draft guidance as well as input from the transcripts will be taken into consideration when revising the guidance. • The goal is to publish a final guidance by the end of 2008. A large effort has been under way at FDA during the past several years to encourage the development and use of new trial designs, including enrichment designs. As part of this effort, a series of guidances are being drafted that will provide specific guidance on innovative trial designs. The agency has also launched a long-term effort to modernize the clinical trial enterprise. Planned guidances include the following: • Adaptive Trial Designs—publication of a draft is anticipated in 2008.

IOM Recommendations	FDA Actions	Status
	and how FDA will review an application to look for signs that a drug may be a significant hepatotoxin. **- *Guidance on enriched trial designs* to focus on approaches to enrich the clinical trial population to better define the efficacy and safety of the drug under development.**	This guidance would explain FDA's perspective on the use of adaptive trial designs during drug development. Topics to be addressed include the definition of adaptive trial designs, recommended designs, and how the statistical issues should be addressed in analyzing trials. • Non-Inferiority Trials—publication of a draft is anticipated in 2008. This guidance would describe FDA's perspective on the design of non-inferiority (NI) trials. Topics expected to be addressed include how to select the active control, how to document the effect size of the active control versus placebo, and how to establish the non-inferiority margin of interest. • Multiple Endpoints in Clinical Trials—publication of a draft is anticipated in 2009. This guidance would describe FDA's perspective on the appropriate procedures and analyses for trials with multiple endpoints (e.g., a trial with multiple co-primary endpoints). • Enriched Trial Designs—publication of a draft is anticipated in FY 2010. This guidance would focus on approaches to enrich the clinical trial population to better define the efficacy or safety of the drug under development. Other product-specific guidances that are in development outline the use of novel trial designs. For example, guidances on rheumatoid arthritis and systemic lupus erythematosus, which are expected to issue in draft in 2008, will provide guidance on the use of novel trial designs.
* * *	*** * ***	* * *
In addition, IOM recommends that FDA prepare a summary analysis of the adverse drug reaction reports not	**This IOM recommendation was codified in FDAAA in Section 915.**	FDA is working to implement the requirements of FDAAA Section 915 by developing an integrated Web site with links to drug safety information. Among the types of information that will be available: • A list of approved REMS, and links to a list of Medication Guides, withdrawal letters, alerts, guidances and regulations related to drug safety, among other information relevant to drug safety. • Between January 1, 2007, and July 1, 2008, FDA issued 16 Public

IOM Recommendations	FDA Actions	Status
previously identified, potential new risks, or known risks reported in the unusual number not previously identified within 18 months of drug launch or after exposure of 10,000 persons, whichever is later. Reports should be publicly available and posted on the agency's Web site.		Health Advisories, 26 Healthcare Professional Sheets, and one science review. • Beginning in August 2007, FDA began providing to the general public *Early Communications (ECs)* about ongoing safety reviews. From August 2007 to July 1, 2008, FDA issued 14 ECs. FDA uses EC to notify the general public (1) that important new postmarket safety information has been received; (2) that FDA intends to review, or are in the process of reviewing, that information; and (3) what specific timeframe has been identified for completion of the safety review. • Drugs with active safety alerts are denoted on the Index to Drug-Specific Information on the FDA Web site. • Since September 2007, CDER has been listing in its quarterly *Drug Safety Newsletter* recent FDA drug safety communications.
4.1 Conduct a systematic, scientific review of the AERS system, identify and implement changes in key factors that could lead to a more efficient system, and systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals.	**The Adverse Events Reporting System (AERS) database, a Web-accessible computer system is being upgraded to add signal detection and tracking tools. These tools will enable safety reviewers to more efficiently and effectively identify and track safety signals from submitted adverse events reports.**	• A contractor was selected in March 2008 to integrate the components of the new MedWatch^{Plus} portal/FDA Adverse Event Reporting System (FAERS) project. FDA awarded the 5-year contract to SRA International, Inc. • Demonstrations of commercial products to meet FDA needs began in July 2008. • Selection of a final commercial product or suite of products is expected in October 2008. • AERS data analysis and preparation for migration to the new system (FAERS MedWatch^{PLUS}) is under way in parallel with commercial product analysis and selection. • The FAERS functional pilot is planned to begin in December 2008. • FAERS Release 1 in 2009 will accommodate drugs and biologics. • FAERS Release 2 will address devices and combination products.

IOM Recommendations	FDA Actions	Status
		• FAERS Release 3 will address remaining products. • MedWatch^{PLUS} will be operational in 2009 for all FDA-regulated products.
	• **During the first year of PDUFA IV, FDA would publish a request for proposals from outside research organizations who would be interested in conducting research on determining the best way to maximize the public health benefits associated with collecting and reporting serious and nonserious adverse events occurring throughout a product's life cycle. Central to addressing this question are determining the number and type of safety concerns discovered by AE collection, the age of products at the time safety concerns are detected by AE collection, and the types of actions that are subsequently taken to protect patient safety.**	**See progress in 3.5**
	• **Under the proposed PDUFA IV recommendations, FDA would use PDUFA funds to obtain**	

IOM Recommendations	FDA Actions	Status
	access to additional databases and to hire the additional epidemiologists and programmers needed to use these databases.	**Relevant to hiring additional epidemiologists, see 3.5**
	*** * ***	* * *
	Access to types of data other than spontaneous reports would expand FDA's capability to conduct targeted postmarket surveillance, to look at effects of classes of drugs, and to detect signals. Access to data other than spontaneous reports is essential to the transformation of the drug safety program.	Regarding access to other databases, FDA has been engaged in many activities, including pilot programs, to obtain access to other databases to look at effects of classes of drugs and detect signals. FDA has launched a number of pilots (see examples in Section III of the report) in collaboration with other organizations to explore methodologies and tools for accessing additional databases to conduct targeted postmarket surveillance, look at effects of classes of drugs, and detect signals. • Examples of pilots under way include: – Pilot with CMS data – eHealth Initiative – Meningococcal Vaccine Study and CDC Vaccine Safety Data link – AHRQ DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) research network
	• **On March 7 and 8, 2007, FDA sponsored a public meeting to explore opportunities for linking private sector and public sector postmarket safety monitoring systems to create a virtual integrated, interoperable, nationwide medical product safety**	After the March 2007 public meeting to explore the possibility of a nationwide system to monitor product performance, FDA began laying out its vision creating a nationwide distributed data network that would enable targeted queries, under appropriate personal security safeguards, of large databases to monitor product safety. The data sources would be at remote locations and continue to be maintained by their owners. Creation of such an active system would ultimately enable the tracking of safety, outcome, and use information for all FDA-regulated products and augment FDA's mostly passive safety monitoring system.

IOM Recommendations	FDA Actions	Status
	network. Such a Sentinel Network could integrate existing and planned private and public sector databases to enable the collection, analysis, and dissemination of safety information about medical products to healthcare professionals and patients at point of care (e.g., in the clinic, where this information is needed to make informed decisions about safe and effective treatments). FDA will engage the public and private sectors in a discussion of opportunities for public- and private-sector collaboration on activities that could develop the data collection and risk identification and analysis components of such a potential network.	Also, in Section 905 of FDAAA, Congress directed FDA to collaborate with others to access large databases to enable the agency to add an active component to its mostly passive postmarket surveillance processes. Specific aggressive deadlines are set forth (see new Section 505 (k)(3) of the Federal Food, Drug, and Cosmetic Act). FDA announced the Sentinel Initiative in May 2008. (http://www.fda.gov/oc/initiatives/advance/reports/report0408.pdf). The Sentinel report describes what such a system could look like and recommends an organizational plan for creating such a system. The Sentinel Initiative will fulfill several of the requirements in FDAAA to capitalize on the potential of existing databases to create an active system for monitoring medical products. Recent steps in the initiative include: • FDA has created a broad public forum to discuss issues related to the implementation of the Sentinel System. Seven meetings have been held with potential stakeholders. ▪ FDA is in the process of publishing several Requests for Proposals (RFPs) to do research on specific issues that have been identified. ▪ Near-term goals include establishing a public–private partnership and making progress on the pilot with CMS using Medicare data, and identifying a sustainable governance structure for the public–private partnership that will be overseeing the development and implementation of the system. Other Sentinel-related activities under way: • On January 24, 2008, Brookings held the "Brookings Roundtable on Postmarket Evidence." Participants explored the need, feasibility, and technical hurdles to establishing a postmarket surveillance system. • A June 2008 meeting sponsored by Brookings continued discussions of Sentinel that began in January. • Since 2006, FDA has been an active and key participant in the IOM Sectoral Strategies Roundtable on Evidence Based Medicine. In the fall of 2007, FDA recommended to the Roundtable the development of a

IOM Recommendations	FDA Actions	Status
		"sentinel system" (for more information, see http://www.iom.edu/CMS/28312/RT-EBM.aspx). FDA is participating in the development of a national priority list of safety problems that could be researched as part of broad collaborations. **See progress in 4.2**
4.2 To facilitate formulation and testing of drug safety hypotheses, CDER should increase intramural and extramural programs that access study data from large automated healthcare databases, include program studies on drug utilization patterns and background incidence rates for adverse events of interest, and develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings.	**FDA would use PDUFA funds to obtain access to additional databases.** **See response in 4.1** **In addition, outside of PDUFA IV, FDA has embarked on other initiatives to obtain access to data:** • **Data use agreement with the Agency for Healthcare Research and Quality (AHRQ)** • **FDA and Veterans Health Administration (VHA) agreement to share information and expertise** • **Active monitoring and analysis of influenza vaccine safety**	**See progress in 4.1** • FDA has added funds to its existing epidemiologic study contracts with HMO Research Network, Kaiser Permanente of California, Ingenix, and Vanderbilt University to conduct additional drug safety studies. FDA is also planning to issue a new RFP in 2008 to expand this program to include more funding for studies, as well as additional sites for collaboration. The award of the new contracts is expected in September 2008. • FDA conducted a pilot study to evaluate the use of data from Medicare Parts A and B (Centers for Medicare & Medicaid Services); the analyses were completed during the last quarter of 2007, and FDA is writing up the results. In the interim, FDA has initiated an inter-agency agreement to work with CMS on pilot studies of several drug safety issues using data from Parts A, B, and D, as well as providing funding for linking Medicaid data from all 50 states together in a format suitable for conducting medical product safety surveillance. The pilot studies were initiated in June 2008; the Medicaid data initiative is planned for fiscal year 2009. • FDA has initiated an interagency agreement with AHRQ to provide funding for collaborative research in four defined areas with the AHRQ-supported Centers for Education and Research on Therapeutics (CERTs). These areas include (1) comparative effectiveness of antipsychotic agents, with special attention to safety; (2) safety risks of biologic immune modulators; (3) methods work in safety outcomes and confounders, and (4) characterization of key national drug use scenarios. This funding opportunity announcement was sent to the 14 CERTs sites for limited competition in March 2008 and is expected to be

IOM Recommendations	FDA Actions	Status
		awarded by September 2008. • FDA is actively sharing safety information with the VHA and DoD.
	***	***
	Many of the Critical Path initiatives will also help in the formulation and testing of drug safety hypotheses.	In addition to assisting with Sentinel, the Critical Path Initiative is assisting other activities to support testing of drug safety hypotheses. For an overview as well as detailed descriptions of specific projects, see the Critical Path Web page at http://www.fda.gov/oc/initiatives/criticalpath/. Specific examples include the following: • Develop and qualify techniques for predictive toxicology; • Identify cardiovascular risk of drugs, including drug eluting stents; • Prevent drug-induced liver injury; • Use pharmacogenomic and other information to guide safer and more effective use of drugs (40 voluntary genomic data submissions received so far); • Use new scientific tools to enhance blood safety; and • Enhance the long-term safety of gene therapy. Related efforts: • Created Cardiac Safety Research Consortium (CSRC). A research team is evaluating normal values for electrocardiogram) ECG parameters using data from the ECG Warehouse. This project should lead to more efficient study designs. • Formed the CSRC Publications Committee to produce a series of white papers on topics of general interest related to evaluation of cardiac safety. The Publications Committee has produced a first draft of a paper on points to consider in evaluating oncology products for effect on QT. • Established a CRADA between Entelos, Inc. and FDA to develop a computer model of drug induced liver injury. The goal is to use this

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		model to guide the development of clinical biomarkers and preclinical assays to identify patient types and drug combinations that increase the risk of developing liver injury. • Developed and published draft guidance, *Premarket Evaluation of Drug Induced Liver Injury*. A public meeting to discuss this guidance is scheduled for March 2008. **See progress in 3.5** • Expanded existing contract with the C-Path Institute to identify gaps in knowledge about the genetic basis of common ADEs. The workgroup is in the process of identifying a list of potential products/therapies. The next step is to organize a public meeting to identify most useful candidates and possible partners to perform studies. • In January 2008, FDA and Duke University launched the Clinical Trial Transformation Initiative, a collaboration of a broad variety of stakeholders (e.g., academia, patient groups, research organizations, pharmaceutical industry) to evaluate the current clinical trial enterprise in the United States and propose and support efforts to modernize that enterprise, making it safer and more efficient. An initial project proposed for action is improving the focus of suspected unexpected serious adverse reaction (SUSAR) reporting in clinical trials. – This project will be the first phase of a long-term project to use empirical evidence to focus the serious adverse reaction reporting system on the most effective methods for identifying true adverse events caused by therapies. – The initial phase will address the issue of SUSARs that must be reported in an expedited fashion in the current regulatory system. – The goal will be to improve the ability of the system, including investigators, institutional review boards, regulatory groups in industry, and the FDA to obtain the type of adverse event data that is most informative in the most efficient manner. See http://www.fda.gov/oc/initiatives/criticalpath/.

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4.3 The Secretary of HHS working with the Secretaries of Veterans Affairs and Defense should develop a public–private partnership with drug sponsors, public and private insurers, for-profit and not-for-profit healthcare provider organizations, consumer groups, and large pharmaceutical companies to prioritize, plan, and organize funding for confirmatory drug safety and efficacy studies of public health importance. Congress should capitalize the public share of this partnership.	**The Veterans Health Administration (VHA) and FDA are working under a recently signed memorandum of understanding (MOU) to allow sharing of certain information related to the use of drugs, vaccines, other biological products, and medical devices. The purpose of the project is to enhance knowledge and efficiency through the sharing of information and expertise between FDA and VHA regarding medical product safety, effectiveness, and patterns of use.**	**See progress in 4.2**
4.4 CDER should assure the performance of timely and scientifically-valid evaluations (whether done internally or by industry sponsors) of Risk Minimization Plans (RiskMAPs).	**FDA would develop a plan to (1) identify, with input from academia, industry, and others from the general public, risk management tools and programs for the purpose of evaluation; (2) conduct assessments of the effectiveness of identified Risk Minimization Action Plans (RiskMAPS) and current risk management and risk communication tools; and (3)**	**See progress in 3.5**

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	conduct annual systematic review and public discussion of the effectiveness of one to two risk management programs and one major risk management tool. FDA would post reports of these discussions on its Web site. In addition, FDA would hold a public workshop to obtain input from industry and other stakeholders regarding the prioritization of the plans and tools to be evaluated.	
4.5 Develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the pre-approval and post approval settings.	**On May 30 and 31, 2006, FDA and IOM held a workshop to hear about new proposals in quantitative benefit-risk assessment. FDA is continuing to explore the possible use of best practices in this area, with a goal of ultimately identifying and testing quantitative tools that could be of use. In the interim, FDA has introduced several training courses to help medical reviewers conduct better safety assessments.**	In 2006, FDA began work toward the long-term goal of more systematic quantitative approaches to risk-benefit assessment, with a workshop hosted by the IOM. Developing a more systematic approach will involve many facets, including, for example: • Identifying candidate analytic methods and tools; • Identifying regulatory decisions that would realize the greatest value from application of these methods; and • Building the IT, data, and analytic infrastructure to more easily apply more quantitative and systematic approaches. In November 2007, the Agency held a 2-day meeting ("Assessing Drug Benefits and Risks in Regulatory Decisions: Framing the Need, Evaluating the Tools, and Deciding Next Steps") as follow-up to the May 2006 workshop. The November meeting was designed to support FDA staff in determining the applicability of current tools to regulatory decisions, research projects that will lead to greater confidence in current tools, and gaps in current tools that may lead to new tool development. The agency is currently developing a white paper summarizing the meeting discussions. In addition, FDA is planning to hold a public meeting later in 2008 to continue to explore the application of analytic tools and issues related to effective communication of benefits and risks.

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	In 2006, CDER created the Quantitative Safety and Pharmacoepidemiology Group (QSPG) to promote science-based, data-supported, regulatory decisions on the safe use of medicinal therapeutics. This group of internal experts will develop quantitative methods for safety evaluation, develop and disseminate best practices for reviews of safety aspects of study protocols during product development, and provide consistency in review practices and analytical approaches across review divisions to the extent possible.	The Quantitative Safety and Pharmacoepidemiology Group (QSPG), created in 2006, have successfully completed a number of projects, and several new efforts are under way. Several accomplishments and ongoing efforts are described below. • The QSPG has developed a curriculum for core competencies in safety review (pre- and post-marketing) for clinical, epidemiological and statistical reviewers in the Office of New Drugs (OND), the Office of Biostatistics (OB), and the Office of Surveillance and Epidemiology (OSE). Courses currently offered include the following: – Introduction to the use of MedDRA terminology for adverse event analysis; – Advanced Signal Detection; – Introduction to submission data standards: The CDISC (Clinical Data Interchange Standards Consortium, http://www.cdisc.org/) Model; – Principles for data collection, retrieval, and analysis for pre- and post-market safety assessment; and – Identification, Testing and Use of analytical tools for pre- and postmarket safety review. • QSPG continues to enrich the curriculum and has provided training on introductory and advanced safety signal detection to approximately 240 reviewers from OND, OSE, and OB. • To ensure clinical and statistical staff readiness to request and review standardized clinical trial data, didactic and practical training courses were offered to approximately 150 reviewers. • QSPG has also held several workshops on statistical methods of particular importance in the assessment of epidemiologic safety data. • An effort is under way to establish partnerships with academic

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		institutions to leverage targeted expertise not yet available within the FDA. • The QSPG developed a proposal to obtain additional staffing and other resources to increase the internal capacity of the FDA in quantitative safety; the proposal was positively received. Two of the proposed resources (personnel and IT infrastructure) were allocated (January 2008). Subsequently, QSPG has been aggressively recruiting and hiring staff with the specific skills necessary to provide safety-related quantitative support to OSE, OND, and OCP as well as to build a coordinated quantitative safety research program within CDER. • A guidance for industry on Meta-Analysis of Safety Data is under development, and FDA expects to publish the draft by December 2009. • QSPG has recently entered into an interagency collaboration with the National Cancer Institute to explore ways to improve the manner by which safety data is collected through the use of patient reported outcomes tools. • QSPG has been working with OSE to develop a curriculum to provide additional quantitative safety-related training to the OSE staff.
	* * * **FDA and the National Toxicology Program of the National Institute of Environmental Health Sciences are developing and validating an animal model to examine factors that may increase the risk of cancer that has been associated with various gene therapies. The model can be used by sponsors to test modifications to gene therapy vectors to mitigate cancer risk while preserving effectiveness. In**	* * * The collaboration between FDA and the National Toxicology Program to develop an animal model is ongoing.

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	November 2006, FDA provided a new, risk-based guidance to sponsors on long-term follow up of such therapies. **CBER (Center for Biologics Evaluation and Research) has already implemented an integrated approach to benefit risk analysis, including cross-cutting product safety teams, and has built a quantitative risk assessment unit that it uses for scientific and modeling support of its more mathematically complex, highest priority product and public health safety issues (e.g., quantitative assessment of risks of transmissible spongiform encephalopathy (mad cow disease) in plasma-derived Factor VIII products).** **See response 4.2 for Critical Path initiatives** **See response 5.4 Pilot for NMEs** **FDA is strengthening and standardizing the process used by safety evaluators in OSE. These safety evaluators critically review adverse event reports that have**	Since January 2007, OSE has developed and implemented discipline competencies and staff development plans for safety evaluators and a tracking system.

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	been submitted to the agency's AERS reporting system by sponsors of approved applications, healthcare professionals, consumers, and other sources. The goal of this initiative to strengthen the safety evaluation process is to identify best review practices and develop a quality assurance system including standardized methodologies, training and mentoring, workload prioritization, and management tools to optimize the use of resources to ensure efficient risk management.	• OSE is conducting in-house training for safety evaluators and clinical and statistical staff: an introductory course is designed to provide a basic understanding of the scope, structure, characteristics, and maintenance of MedDRA (Medical Dictionary for Regulatory Activities) and the relevant regulations concerning its use. In addition, the training provides an overview of coding with MedDRA and applications of MedDRA in data retrieval and analysis, including use of Standardized MedDRA Queries in safety signal detection and case identification. The following is a link to the MedDRA training that is being offered: http://www.meddramsso.com/mssoweb/training/courses.htm. • Other training and staff development programs that are in place include: OSE Tools and Methodology courses, AERS and WebVDME training manuals for adverse event signal evaluation and detection, an ongoing Safety Evaluators Best Practices Work Group for safety data evaluation and analysis principles, processes and procedures, and Safety Evaluators mentorship resources. • Standard review templates including a methodology section were introduced in early 2007. In addition, OSE has established a new employee mentoring check-list and has identified several mentors (eight experienced safety evaluators) for new employees. OSE will be evaluating the mentor program on a regular basis. In addition, OSE has drafted a standard operating procedure for managing the receipt and triage of AERS data.
	*** * *** **CDER is now implementing an**	* * * CDER's Associate Director for Safety Policy and Communication Staff collaborated with the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) working group in CDER's Office of Business

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	electronic system to track postmarket drug safety issues. This system, which will replace multiple office- and division-specific systems, will enable CDER reviewers and managers to prioritize more effectively their work on safety issues and ensure that different organizational units have the same information.	Process Support to develop a postmarket drug safety tracking system. • The DARRTS Safety Issue Application was launched in January 2007. This application is used for monitoring serious peri- and postmarket safety issues that have the potential to lead to a significant regulatory action, including, but not limited to, the withdrawal of the drug product or an indication, the institution of a REMS, a significant labeling change such as the addition of a boxed warning, or the need for a postmarket safety study or trial. The system is also used for planning joint safety meeting agendas and to identify postmarket safety issues that would benefit from risk communication messages being sent to healthcare professionals and the public by the Safety Policy and Communication Staff. • Use of the tracking system will help ensure timely resolution of postmarket safety issues and facilitate the communication of safety information to the public and other health-related stakeholders. In August 2008, a work plan functionality was added to the DARRTS safety issue application. This work plan enables OND and OSE staff to more easily plan for and monitor postmarket safety issues, enhancing efficiency and improving communication among CDER staff working on such issues. Additional functionalities, such as reviewer reminders, will be added in future updates.
4.6 Build internal epidemiologic and informatics capacity to improve the postmarket assessment of drugs.	**See response 3.5 and 4.2 for access to databases**	**See progress in 3.5 and 4.2**

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4.7 Commissioner should demonstrate commitment to building the agency's scientific research capacity by: Appointing Chief Scientist in OC to oversee, coordinate, and ensure quality and regulatory focus of FDA's intramural research programs. Designate FDA's Science Board as the extramural Advisory Committee to the Chief Scientist. Include research capacity in the agency's mission statement. Apply resources to support intramural research approved by the Chief Scientist. Ensure adequate funding to support intramural research program is requested in the agency's annual budget request to Congress.	**The Commissioner asked the FDA Science Board to undertake a comprehensive formal review of scientific needs and activities across the agency. The vast majority of FDA scientific programs are related to regulated product safety.** **See response 3.2**	Upon the recommendation of the Commissioner, the FDA Science Board performed an extensive review of agency operations with the goal of identifying possible gaps and scientific needs. After approximately 6 months of program review, including meeting with agency and center staff, the Science Board report subcommittee presented the report to the full Science Board in early December 2007. The report is available on the Advisory Committee Web page at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_00_index.html. • The Science Board unanimously accepted the report. (Two additional reviews of the National Center for Toxicological Research (NCTR) and the Office of Regulatory Affairs (ORA), which were not included in the initial investigation, were presented to the Science Board at its May 30, 2008 meeting. Final versions of both reviews have been accepted by the Science Board and transmitted to the agency.)
4.8 FDA should have its advisory committees review all NMEs either prior to approval or soon after to advise in the process of ensuring drug	**See response 5.4 Pilot for NMEs**	CDER has implemented the provision in FDAAA Title IX Section 918 that requires FDA to refer to an Advisory Committee prior to approval, or state in the approval letter why the NME was not referred. If FDA does not refer such a product to an Advisory Committee, FDA is required to summarize the reasons in the approval letter. To date, when an NME has not been referred to an Advisory Committee, the reasons have been summarized in

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safety and efficacy or managing drug risks.		the approval letter. **See progress 5.4**
4.9 Advisory committees, and any other peer review effort such as mentioned for CDER-reviewed product safety, should include a pharmacoepidemiologist or an individual with comparable public health expertise in studying the safety of medical products.	**FDA will also increase the involvement, to the extent feasible, of pharmacoepidemiology and other experts in each Advisory Committee meeting when safety issues are an important component of the issues before the Committee. These individuals may be current members of the Drug Safety and Risk Management Committee or brought in as special government employees.**	FDA has increased the pool of epidemiologists available as special government employees (SGEs) for CDER Advisory Committees. **See response to 4.10**
4.10 FDA should establish a requirement that a substantial majority of AC members be free of significant financial involvement with companies whose interests may be affected by the committee's deliberations.	**Under the oversight of the FDA Commissioner, the agency will issue 3 guidances in 2007 making Advisory Committee operations more consistent, transparent, and predictable.** • **One guidance document will present new thinking about the criteria for granting waivers for conflicts of interest for members of all of our Advisory Committees.** • **A second guidance will**	FDA has made a number of changes to its processes for managing Advisory Committees. For example, FDA issued three guidances that will help improve and clarify the advisory committee operations and processes: • Draft guidance on *Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees* (March 2007); • Draft guidance on *Public Availability of Advisory Committee Members'*

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	address the disclosure of conflict of interest waivers. • **A third guidance will improve the release of Advisory Committee briefing materials to the public.** **In addition, FDA will make recruitment of potential members of Advisory Committees more transparent and open by issuing a standardized list of current and future Advisory Committee vacancies.**	*Financial Interest Information and Waivers* (October 2007); and • Guidance on *Advisory Committee Meetings — Preparation and Public Availability of Information Given to Advisory Committee Members* (February 2007). FDA has also begun making recruitment of potential members of Advisory Committees more transparent and open. For example, FDA added information on current vacancies to its Web site (http://www.fda.gov/oc/advisory/vacancies/acvacbycenter.html) so that individuals can readily access this information. The Web page is updated periodically. In addition, FDA publishes *Federal Register* notices soliciting nominations to Advisory Committee vacancies at least four times a year. This fiscal year nine notices were published. FDA also updated its Web site to include information on how to apply for membership to an FDA Advisory Committee (http://www.fda.gov/oc/advisory/vacancies/acvacmain.html).
4.11 Congress should require industry sponsors to register in a timely manner at www.ClinicalTrials.gov, at a minimum for all Phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA	**Not Directed to FDA, but FDAAA, Title VIII, requires extensive FDA and NIH effort to expand the clinical trials data bank and make substantive information related to clinical trial drugs available through links to both FDA and NIH Web sites.**	Although this IOM recommendation was not directed to FDA, FDAAA has provided related requirements, for example, to expand the existing ClinicalTrials.gov registry to: • Include additional information about applicable clinical trials of drugs, biologics, and devices; • Develop processes for adding information about serious and frequent adverse events observed in a trial and for expanding the registry and results database; and • Provide links in the data bank from a specific drug to relevant safety information, including, for example, related summary documents from Advisory Committee meetings on the drug, any public health advisories

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as part of an NDA, sNDA, or to fulfill a post-market commitment. Include a posting of structured field summary of efficacy and safety results of the studies.		regarding the drug or device that FDA may have issued, and other relevant information about the safety and effectiveness of the drug. These efforts will provide the public with substantial additional information and access to information about drugs that have been or are being studied in clinical trials. FDA and NIH are working closely to implement these provisions.
4.12 Post all NDA review packages on the agency's Web site, including all supplemental NDA review packages.	**Not accepted by FDA. However, Section 916 of FDAAA contains similar requirements: (1) post NDA new molecular entity (NME) and BLA action packages within 30 days of approval and (2) post all other action packages within 30 days of receiving the third Freedom of Information Act request for the package.**	FDA is attempting to comply with this provision in FDAAA in a timely manner. FDA is dedicating additional resources to improve the timeliness of posting of action packages: • Additional employees have been hired to perform disclosure reviews and Web posting. The employees are in various stages of training; and • Procedural changes were implemented to increase the efficiency of the disclosure and Web posting staffs interactions.
4.13 Review teams regularly and systematically analyze all postmarket study results and make public their assessment of the significance of the results with regard to the integration of risk and benefit information.	**FDA recognizes the importance of communicating information about the safety of drugs. However, many postmarket assessments contain recommendations that are the subject of ongoing discussions within FDA and other information that is predecisional in nature. Release of such information could have adverse public health impacts. For example, release of information about a safety signal**	For many years, FDA and sponsors have disseminated emerging drug safety information. The agency currently disseminates emerging drug safety information after having completed an analysis of available data and, in several cases, before having reached a decision about the need for a regulatory action. Agency communications about emerging drug safety information may help achieve certain longstanding public health goals, including enhanced vigilance on the part of healthcare professionals who may be prompted by the information to increase their reporting of safety observations to FDA. • In March 2007, FDA issued a final guidance that formalizes FDA's commitment and current efforts to ensure that it communicates to

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	that is later determined to be erroneous could result in patients who could benefit from the drug not receiving it. Therefore, decisions to publicly disclose assessments of postmarket safety studies have to be made on a case-by-case basis. **In the first quarter of 2007, FDA will issue a final guidance on communicating important drug safety information, including emerging drug safety information, to the public. This guidance formalizes FDA's commitment and current efforts to ensure that it communicates to healthcare professionals, patients, and other consumers the latest safety information with the potential to influence the way physicians prescribe and patients use medicines.** **In 2007, FDA planned to regularly publish a newsletter on the FDA Web site containing summaries of the results, including methods, of FDA postmarket drug reviews. The summaries will not include confidential commercial or predecisional information. FDA believes it is important, particularly for healthcare professionals, for FDA to make readily available and easily**	healthcare professionals, patients, and other consumers the latest safety information with the potential to influence the way physicians prescribe and patients use medicines. • The guidance is available on the FDA Web site at: http://www.fda.gov/cder/guidance/7477fnl.pdf. • A press release describing the agency's effort is available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01577.html. • During 2007, the Special Policy and Communication Staff (SPCS) issued four Early Communications to the public. SPCS also issued 10 Public Health Advisories and 21 Healthcare Professional Sheets in 2007. • In 2008 (through July 1), FDA issued six Public Health Advisories, six Healthcare Professional Sheets, and ten Early Communications. • FDA also publishes a quarterly newsletter for healthcare professionals, which contains emerging safety information. The first issue of FDA's quarterly newsletter, *Drug Safety News*, was published on September 18, 2007. The second and third issues followed in March 2008 and June 2008, respectively. See http://www.fda.gov/cder/dsn/default.htm.

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	accessible the results of our postmarket reviews of adverse events. In addition, this regular newsletter will contain information on emerging safety issues, as well as provide information on recently approved products both to inform healthcare professionals and to encourage reporting to the agency.	
5.1 The committee recommends that Congress ensure that the Food and Drug Administration has the ability to require such postmarketing risk assessment and risk management programs as needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug	**Not Directed to FDA. However, FDAAA gave FDA the authority to require risk management programs, now called Risk Evaluation and Mitigation Strategies (REMS).**	**See Section risk management plans in 3.5**

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product.		
5.2 Provide oversight and enact any needed legislation to ensure compliance by FDA and drug sponsors with provisions listed above (5.1). FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.	**Not Directed to FDA.**	However, FDAAA gave FDA many of the new enforcement authorities suggested in Section 5.1. Section 901 of FDAAA amended Section 505 of the FDCA to give the FDA new authorities to require postmarket studies and/or clinical trials, to require postmarket labeling changes based on new safety information, and to require Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits of a drug outweigh the risks. Violations of these new provisions are associated with misbranding charges and civil penalties. FDA is working on procedures for implementing these new enforcement authorities. With regard to direct-to-consumer (DTC) advertising addressed in this Section, FDAAA also gives FDA the authority to require television advertisements for drugs to be submitted to the FDA 45 days before dissemination for FDA review and recommendations. Although, in general, FDA cannot require changes, FDA can require specific disclosures about serious risks if FDA determines that the advertisement would be false or misleading without the specific disclosure. These provisions are also enforceable through misbranding charges and civil money penalties.
5.3: Amend FD&C Act to require product labels carry a special symbol such as the black triangle used in the UK or an equivalent symbol for new drugs, new combinations of active substances, and new systems of delivery of existing drugs. FDA should restrict DTC advertising during the period of time the special symbol is in	**Not Directed to FDA.** However, FDAAA, Section 904 states that FDA may consider use of a special symbol. "Not later than 1 year after the date of the enactment of this Act, the Commissioner of Food and Drugs shall submit to the Congress a report on how best to communicate to the public the risks and benefits of new drugs and the role of the risk evaluation and mitigation strategy in assessing such risks and benefits. As part of such study, the Commissioner	• FDA is working on the Report to Congress with regard to the use of a symbol. As part of the proposed Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products (65 FR 81082), which published on December 22, 2000, FDA included a provision to use a black triangle or another symbol on the professional label to denote the newness of a product. • After consideration of comments, in the final rule published on January 24, 2006 (71 FR 3922), FDA declined to adopt the use of symbols to emphasize or identify information in prescription drug labeling. • FDA determined that the use of an inverted black triangle would not be universally understood and could be confusing to both prescribers and patients, even with a concerted educational effort. • To communicate most effectively, the relative "newness" of a product to

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effect (recommended time: 2 years).	may consider the possibility of including in the labeling and any direct-to-consumer advertisements of a newly approved drug or indication a unique symbol indicating the newly approved status of the drug or indication for a period after approval."	healthcare professionals, FDA determined that it would be best to include prominently in the highlights section of the professional label the date a product was approved. FDA determined this approach would more clearly communicate both when a product became available and how long it has been on the market (Section 201.57(a)(3) and (d)(5)). • Absent evidence to the contrary, FDA believes that the recently revised current professional label with a highlights section and table of contents, that is now electronically available on the National Library of Medicine's DailyMed Web site, provides a readily accessible and useful source of information about the benefits and risks of new drugs. • When it comes to adding a symbol to consumer-directed materials, such as Direct to Consumer (DTC) advertisements, the potential for misinterpretation is greater. Consumers could easily interpret a symbol indicating a "new approval" to mean "new and improved," the latter interpretation being more common in advertising. Without rigorous testing of how a symbol used on DTC ads would be understood and interpreted, adding such a symbol has the potential to do more harm than good.
5.4 Evaluate all new data on NMEs no later than 5 years after approval. Sponsors will submit a report of accumulated data relevant to drug safety and efficacy, including any additional data published in a peer reviewed journal, and will report on the status of any applicable conditions imposed on	**CDER is conducting a pilot developed by its Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) to review systematically and collaboratively the safety profiles of new molecular entities (NMEs) on a regularly scheduled basis to determine whether these reviews should be initiated for all NMEs as suggested by IOM recommendation 5.4. NME postmarket evaluations will incorporate data from the Adverse**	As part of CDER's effort to strengthen and standardize safety evaluation processes, OSE and OND have implemented a pilot program, which began in January 2007, to review systematically, collaboratively, and regularly the safety profiles of approved NMEs (products that include an active substance that has never before been approved for marketing in any form in the United States) to determine whether these reviews should be regularly scheduled and initiated for all, or a specified subset of, NMEs. The purpose of the pilot program is to determine the value of the periodic systematic and collaborative review of the safety of marketed drugs. To examine the value of the reviews, a sample of NMEs with different durations of marketing and different extents of use were chosen for evaluation. The pilot program is also expected to provide valuable information about the required resources and appropriate methods for

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the distribution of the drug called for at or after the time of approval.	**Events Reporting System (AERS), data mining analysis, epidemiologic data, postmarket clinical trial information, and a review of the Periodic Safety Update Reports, or U.S. Periodic Report, to identify potential safety concerns early in the product life cycle.** **In Section 915 of FDAAA, Congress directed FDA to prepare, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number. FDA is working to implement this provision and will use the experience from the NME pilot to inform its work.**	conducting such a systematic evaluation. In March 2008, FDA issued a progress report describing the progress to date on the pilot program. (http://www.fda.gov/cder/drug/postmarketing_safety/progress_report.htm) Two of the conclusions about the review process in the progress report include: • The comprehensive reviews necessary to carefully examine a drug in the pilot program are most informative after the drug has been on the market for a year or more, or has had substantial use; and • The optimal timing within the lifecycle of a drug will merit consideration for future NMEs examined by the pilot program. FDA expects to issue a final report on the pilot program in the fall of 2008. The results of this pilot will be used to develop procedures to implement Section 915 of FDAAA.

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6.1 Enact legislation establishing a new Advisory Committee (AC) on communication with patients and consumers. The committee would be composed of members who represent consumer and patient perspectives and organizations. The AC would advise CDER and other Centers on communication issues related to efficacy, safety, and use during the lifecycle of drugs and other medical products, and it would support the Centers in their mission to "help get the public accurate, science-based information they need to use medicines and foods to improve their health."	**FDA is establishing a new Advisory Committee to obtain input to improve the agency's communication policies and practices and to advise FDA on implementing communication strategies consistent with the best available and evolving evidence. FDA will include on the Committee patients and consumers as well as experts in risk and crisis communication and social and cognitive sciences. The IOM report recommends that Congress enact legislation to establish a new Advisory Committee on communication with patients, but FDA believes it can implement the IOM's recommendation more expeditiously through administrative procedures.**	FDA has established a new Advisory Committee on Risk Communication. Although the IOM recommended a legislative approach, FDA decided that this recommendation could be implemented more expeditiously through administrative procedures. The new Advisory Committee was announced on November 5, 2007: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01739.html. Section 917 (121 Stat 960) of FDAAA created Section 567 of the Federal Food, Drug, and Cosmetic Act providing for such an Advisory Committee.
6.2 Office of Drug Safety Policy and Communication should develop a cohesive risk communication plan that includes, at a minimum, a review of all Center	**FDA has established a working group, chaired by CDER's Associate Director for Safety Policy and Communication, to develop a CDER risk communication strategic plan. In the process of developing this**	A plan to address current gaps in CDER's risk communication process has been completed. • The plan builds on recommendations of the IOM, input from other external stakeholders, new responsibilities and authorities under FDAAA, and other recent CDER safety initiatives. • The plan focuses on optimizing the use of CDER communication assets,

IOM Recommendations	FDA Actions	Status
risk communication activities, evaluation, and revision of communication tools for clarity, consistency, and priority-setting to ensure efficient use of resources.	**plan, CDER will identify, clarify, and define the purpose of each communication tool and streamline the use of tools to facilitate information flow. As part of this process, CDER is also evaluating the CDER Web site and will implement changes to make it more efficient and effective. In addition, FDA's recently established Bioinformatics Board in the Office of the Commissioner has taken steps to improve the public's ability to communicate with FDA. The Bioinformatics Board has initiated an agency-wide project to create a common portal for the collection of adverse event reports and consumer complaints about products for all FDA-regulated products. The scope of this project includes developing mechanisms to improve the ease and accuracy of reporting by the public and to improve the timeliness and quality of reports submitted to the FDA.**	including staff and supporting systems and tools, and the use of the best available science to create our messages, building and sustaining partnerships with key professional and patient groups, and monitoring and evaluating the accessibility and impact of our risk communication tools and channels. • One of the agency's key focuses under the Critical Path Initiative is to *harness bioinformatics to manage FDA product information.* FDA agency's Bioinformatics Board is helping to organize and harmonize agency information management systems. Using emerging information technologies will not only help the agency make its internal communications more efficient, but will also greatly improve communications with external parties, including the public, healthcare professionals, regulated industry, and other health-related organizations. • FDA has been working with NIH to create a common shared portal for the receipt of all adverse events reports and reports of problems related to FDA regulated products (MedWatch^{Plus} portal/FAERS initiative). • FDA expects to pilot test the portal in 2008 and implement it for use during 2009. **See also 4.1** A series of additional activities are under way, which are described in more detail in the report (see Section V). Activities include: • The FDA Prescription Drug Labeling training Module for Health Professionals; • MedWatch Partners Program; • MedWatch Safety Labeling Summaries; • Health Professional Web site and listserv; and • Network of Nodes.

IOM Recommendations	FDA Actions	Status
7.1 To support improvements in drug safety and efficacy activities over a product's lifecycle, Congress should approve substantially increased resources in both funds and personnel for the FDA.	**Not directed to FDA.**	Although not directed to FDA, through FDAAA, Congress provided FDA with additional resources to fund personnel and programs. FDAAA also provided additional funding to support drug safety activities.

Abbreviations and Acronyms

AC - Advisory Committee

ADS – Associate Director for Safety

AE - Adverse Event

AERS - Adverse Events Reporting System

AHRQ - Agency for Healthcare Research and Quality

ANDA - Abbreviated New Drug Application

BLA - Biologics License Application

CBER - Center for Biologics Evaluation and Research

CDC - Centers for Disease Control and Prevention

CDER- Center for Drug Evaluation and Research

CDISC - Data Interchange Standards Consortium

CERT - Centers for Education and Research on Therapeutics

CMS - Centers for Medicare & Medicaid Services

C-PATH - Critical Path Institute

CPD - Center for Professional Development, Inc.

CRADA - Cooperative Research and Development Agreement

CSRT - Created Cardiac Safety Research Consortium

DARRTS - Document Archiving, Reporting, and Regulatory Tracking System

DTC - Direct to Consumer (refers to DTC advertising)

DCRI - Duke Clinical Research Institute

EC – Early Communication

ECG - Electrocardiograms

FAERS - FDA Adverse Event Reporting System

FD&C ACT (also FDCA) - Federal Food, Drug, and Cosmetic Act

FDA - Food and Drug Administration

FDAAA – Food and Drug Administration Amendments Act of 2007

HHS - Department of Health and Human Services

HIV - Human Immunodeficiency Virus

IOM - Institute of Medicine

MedDRA - Medical Dictionary for Regulatory Activities

MOU - Memorandum of Understanding

NDA - New Drug Application

NHLBI - National Heart, Lung, and Blood Institute

NIH - National Institutes of Health

NME - New Molecular Entity (never before approved)

OC - Office of the Commissioner

OND - Office of New Drugs

OSE - Office of Surveillance and Epidemiology

PDUFA - Prescription Drug User Fee Act

PSTC - Predictive Safety Testing Consortium

QSPB - Quantitative Safety and Pharmacoepidemiology Group

REMS – Risk Evaluation and Mitigation Strategy, required by FDAAA, will now replace RiskMAP

RFI - Request for Information

RFP - Request for Proposal

RiskMAP - Risk Minimization Action Plan (no longer in use)

SRPM – Safety Regulatory Project Manager

SUSAR - Suspected Unexpected Serious Adverse Reaction

VHA - Veterans Health Administration

VSD - Vaccine Safety Datalink

WCT - Workplace Culture Team