The Future of Drug Safety —

Promoting and Protecting the Health of the Public

FDA's Response to the Institute of Medicine's 2006 Report

U.S. Department of Health and Human Services
Food and Drug Administration (FDA)
January 2007

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I. INTRODUCTION

The safety of drugs and other medical products regulated by the Food and Drug Administration (FDA) has always been a key focus of FDA's commitment to its mission to protect and promote the public health. Recently, rapid advances in science and technology have resulted in increasing complexity of medical products. These advances, combined with increased attention to safety-related issues by consumer advocates, health professionals, academic researchers, and members of Congress have created an opportunity for FDA to reassess its efforts to ensure that its drug safety program is the best possible. As a result, in 2004 and 2005, the FDA and the Department of Health and Human Services (HHS) announced a series of steps to address drug safety issues. One such step was the recent creation of the Drug Safety Oversight Board.[1] Another step was FDA's request that the Institute of Medicine (IOM) convene a committee to assess the U.S. drug safety system and to make recommendations to improve risk assessment, surveillance, and the safe use of drugs.[2] To gather information, the IOM interviewed FDA staff and interested persons outside of FDA and conducted public meetings. On September 22, 2006, the IOM released its report entitled *The Future of Drug Safety — Promoting and Protecting the Health of the Public*.[3] The IOM report makes substantive recommendations about how we, the FDA, can improve our drug safety program and about what actions other parts of government should take to create a more robust and comprehensive system for better ensuring the safe use of medical products.

Completing our review of the IOM report has presented a timely opportunity for reporting on our commitment to strengthening drug safety. In reviewing the IOM report, we find we are in substantial agreement with most of the IOM recommendations directed to the Agency. Driven by available science, we are fully committed to strengthening our drug safety program just as rapidly and efficiently as available resources allow. The initiatives described in this report are among the highest priorities of the recently confirmed Commissioner.

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[1] See http://www.fda.gov/cder/drug/DrugSafety/DSOBmeetings/default.htm.

[2] See Appendix A for a more detailed summary of the Statement of Task for IOM.

[3] See the IOM report at http://www.iom.edu/.

Much of our commitment, although directed to drugs, also has applicability to other medical products regulated by the FDA. Our other medical product centers have ongoing safety activities that can inform our efforts to improve the drug safety program. For example, FDA's Center for Devices and Radiological Health (CDRH) recently completed an in-depth assessment of its postmarketing surveillance and enforcement program. This CDRH assessment and resulting recommendations are being carefully evaluated for their Agency-wide applicability.[4]

In the discussion that follows, we first describe our commitment to drug safety.[5] We then address the IOM recommendations in the context of our ongoing drug safety initiatives. The IOM report presents an array of 25 recommendations, 14 of which were directed to FDA.[6] In this paper, we set forth our commitment to transforming the drug safety system, the actions we have taken or plan to take to fulfill this commitment, and our responses to the IOM recommendations addressed to FDA and HHS,[7] organized around three themes:

(A) The science supporting our drug product safety system
(B) Communication and information flows
(C) Operations and management

We address each theme in turn.[8] We believe that the actions discussed here are consistent with FDA's commitment to a high-quality drug safety system and necessary to strengthen FDA's drug safety program within the framework of America's quickly changing healthcare system.

II. FDA'S COMMITMENT TO THE DRUG SAFETY SYSTEM

In addition to commissioning the IOM report in 2005, FDA began its own ongoing assessment of its drug safety program. As part of the assessment, we have received extensive input from external stakeholders and launched a number of initiatives that will enhance the system.

The U.S. drug safety system and the medical product safety system in general are on the verge of major transformations driven by the rapid evolution of science, technology,

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[4] For more, see http://www.fda.gov/cdrh/postmarket/mdpi-report.html and http://www.fda.gov/cdrh/postmarket/mdpi-recommendations.html.

[5] Our campaign for drug safety includes 18 recently initiated actions that respond to the IOM's recommendations, 8 items separately announced earlier this month as part of our proposed recommendation for reauthorization of the Prescription Drug User Fee Act (which, if enacted, would take effect in October 2007), and 14 new items announced here. Together these actions constitute a commitment to drug safety and a comprehensive suite of responses to IOM's recommendations to FDA.

[6] 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.

[7] See Appendix B for a table that summarizes the IOM report's recommendations and our specific responses.

[8] In some cases, the IOM recommendations relate to more than one theme; they are addressed under all themes when relevant.

and the healthcare system. FDA recognizes that its processes and scientific methods must keep pace with and harness the benefits of this rapid evolution. We believe that the major themes of the IOM recommendations are generally consistent with this evolution.

Specifically, new scientific discoveries are generating an emerging ***science of safety*** that will help prevent adverse events by improving the methods used in the clinic to target a specific drug for use in patients for whom benefits relative to risks are maximized. This new science will also give us the tools to prevent adverse events by rapidly identifying drug safety problems before they can cause injury. This new science combines a new understanding of disease and its origins at the molecular level (including of adverse events resulting from treatment) with new methods of signal detection, data mining, and analysis that are enabling researchers to generate hypotheses about and confirm the existence and cause of safety problems, as well as about the unique genetic and biologic features of the person that will determine how he or she responds to treatment. This science of safety encompasses the entire life cycle of a product, from premarket animal and human safety testing to widespread clinical use beyond original indications. This kind of life-cycle approach to benefit and safety should be used for all medical products so that safety signals generated at any point in the process will robustly inform regulatory decision making.

New drugs, devices, and diagnostics present the greatest opportunity currently available to improve healthcare and the way medicine is practiced; but all medical products pose potential risks. The FDA is challenged to make sure that it consistently balances access and innovation against the steps taken to improve our approach to safety issues. The Agency's efforts to improve drug safety must not dampen the process of medical innovation that could itself enable safer approaches to drug development and drug use. Stimulating the development of products that can be used safely and effectively by patients suffering from unmet medical needs is important. Safety and innovation, as well as efficiency in drug development, do not necessarily conflict but are dependent on one another. A more modern, efficient, and risk-based drug development process will improve FDA's ability to detect safety-related problems earlier. FDA will not achieve enhanced safety programs without also pursuing innovation in the way that drugs are developed.

The emerging science of safety also offers a way to partially solve a fundamental dilemma: the trade off between safety and access. A clear example of this trade off occurs when FDA, after analysis of adverse events, considers whether to withdraw a drug from the market for safety reasons. While withdrawal of the drug would avoid further adverse events, it would also deprive patients for whom the drug is effective of its benefits. If, however, new science enables us to determine that the adverse events are restricted to a small, identifiable segment of the population, public health could be improved by making the drug available to others who could benefit without undue risk.

The new science of safety, by its very nature, will require an interdisciplinary team approach to assessment, incorporating experts in genetics, cell biology, and other basic sciences with clinical pharmacologists, clinicians, statisticians, epidemiologists, and informatics experts. We agree with the IOM that adequately incorporating the input from these various experts will require a much more formalized, semi-quantitative approach to benefit and risk analyses and continuing reorganization of regulatory processes. We regard improving our approaches to risk and benefit analysis to be one of the important facets of the science of safety that urgently requires additional development.

In addition, new uses of information technology are providing us novel opportunities to learn more about the outcome of medical product use in the healthcare system. As health information technology becomes more widespread, we will be able to perform active surveillance of outcomes from product use in new ways. It is critical that FDA be able to take advantage of these opportunities. Passive surveillance systems (e.g., MedWatch) are useful for early signal generation from a broad segment of the exposed population, but such systems are not always helpful in establishing accurate incidence rates, evaluating causality, understanding risk factors, or elucidating patterns of use. FDA is aggressively seeking ways to make use of new and emerging information sources with current resources.

Information technology is also creating new methods for risk communication. It has been well documented that a major source of drug safety problems is lack of timely, relevant safety information at the point of care—the bedside, the clinic, and the pharmacy. We are working with many partners to create new avenues for effective risk communication on drug safety and to develop technology solutions—for example, e-prescribing systems—to help minimize errors and promote the safe use of products. These solutions will also generate data that can be used to update postmarketing risk assessments.

Today, FDA regulates medical products in a globalized environment. Medical products are discovered, developed, authorized, marketed, transported, promoted, and used by practitioners, patients, and other consumers throughout much of the world. Because of this, much important information regarding the safety of these products can, and does often, originate outside the United States. FDA, for many years, has leveraged its scientific and human resources dedicated to product safety with those of many sophisticated foreign counterpart regulatory authorities. FDA does this through well-established bilateral relationships, including confidentiality arrangements with specific foreign regulatory authorities, which allow rapid exchange of emerging safety information and discussion of developing concerns. In addition, FDA is involved in formal harmonization initiatives, such as the International Conference on Harmonisation (ICH) with counterpart regulatory authorities and the regulated industry. Through these formal initiatives, international harmonization of safety-related definitions, reporting intervals, and reporting content and format have been realized, resulting in more efficient and more useful worldwide information on product safety to regulators.

Finally, the entire healthcare system—of which drugs and FDA are only a part—is rapidly evolving toward a culture that explicitly focuses on safety and quality, and this rapid evolution should stimulate and be catalyzed by FDA's efforts. The landmark IOM report *To Err is Human* (November 1999) and the March 2001, IOM report *Crossing the Quality Chasm,* described a roadmap for improving healthcare quality, including patient safety. The future medical product safety system must establish robust links with the quality and safety managers and researchers within the healthcare system to allow a continuous web of information exchange and feedback.[9] We must also ensure that safety information is relayed to healthcare stakeholders, patients, and other consumers in a timely and effective manner and that information learned in the context of healthcare is rapidly available to us.

[9] IOM's reports are available at http://www.iom.edu/.

Our very concepts of healthcare are changing as we envision a future in which healthcare will be personalized, predictive, preventive, and more participatory, all of which have significant ramifications for a new era in drug safety led by FDA. To take full advantage of this rapid evolution in science, technology, and healthcare, FDA must make fundamental changes to its scientific assessment processes. And making fundamental changes to long-standing practices will entail a culture shift within FDA. We believe that these changes must occur broadly, beyond traditional safety evaluation functions. A transformation to a life-cycle approach across all medical product centers involves, at some level, staff throughout the Agency. Whether an individual's work relates directly to safety, to the conduct of risk and benefit analyses, or relates only very indirectly to these areas, individual performance affects the Agency's ability to fulfill its mission. The Agency will take actions across organizational lines, both within and outside of the Centers. Our foremost challenge will be to bring about the cultural changes within FDA that allow us to participate effectively in the ongoing transformation of the healthcare system.

We have already taken some steps to meet this challenge. Of note, for example, is the Critical Path Initiative, launched in 2004. This initiative builds heavily on coordinated cross center communication and activities, as well as on extensive collaboration with stakeholders in academia, other agencies, the public health community, and industry.[10] These activities focus on a life-cycle approach, and a number of specific activities are consistent with and in furtherance of the IOM's recommendations.

III. FDA'S SPECIFIC SAFETY INITIATIVES

Ongoing and new FDA actions align with many of the key IOM recommendations. These actions are described below, organized around the following three themes that we believe capture the critical elements of the IOM recommendations:

A. Strengthening the science that supports our medical product safety system at every stage of the product life cycle from premarket testing and development through postmarket surveillance and risk management

B. Improving communication and information flow among all stakeholders engaged in promoting the safe use of medical products

C. Improving operations and management to ensure implementation of the review, analysis, consultation, and communication processes needed to strengthen the U.S. drug safety system

Some of the actions, designated as ***Recently initiated***, were begun as a result of FDA's own assessment of the drug safety system. Others, designated as ***New***, have been initiated since our receipt and review of the IOM report. Whether we will be able to implement these actions in a timely way is contingent on the availability of resources requested for fiscal year 2007.

Some actions that require additional resources have been recently proposed by FDA, after discussions with industry, in the reauthorization of PDUFA (PDUFA IV). Recommended actions proposed under PDUFA IV are designated as ***PDUFA IV Proposal***. These FDA proposed actions will require congressional action to provide the

[10] For more on the Critical Path Initiative, see http://www.fda.gov/oc/initiatives/criticalpath/.

necessary resources for implementation. Although the proposed PDUFA IV safety initiatives represent a much smaller investment of resources than would be required to fully implement the IOM recommendations, the Agency's proposed recommendations for PDUFA reauthorization, if adopted, would provide the needed increased resources for drug safety and added flexibility to FDA in the use of fee funding to address the entire drug life cycle and our commitment to drug safety. FDA believes it has the statutory and regulatory authority needed to carry out its commitment to ensure drug safety.

Appendix B provides a chart that describes FDA's response to each specific IOM recommendation directed to FDA or HHS. We do not respond to the recommendations appropriately directed to other government decision makers. These may be addressed in other forums.

Finally, the actions described below are not the final word on FDA's commitment to drug safety. They are only our initial response to the IOM recommendations. Other longer term actions may be considered based on available resources and emerging experience.

A. STRENGTHENING THE SCIENCE THAT SUPPORTS OUR MEDICAL PRODUCT SAFETY SYSTEM

The scientific assessment of the risks associated with using medical products is at the core of efforts to improve safety, and FDA is committed to strengthening the science that supports our medical product safety system.[11] The IOM recommended that FDA's commitment to research and science be strengthened by increased emphasis within the Office of the Commissioner. FDA's recently confirmed Commissioner will be taking this recommendation into account as his new management team is established with the intent to provide increased Office of the Commissioner management focus on fostering and promoting regulatory science. As a first step, the Commissioner proposed the creation of the Office of Chief Medical Officer, which will oversee scientific operations for FDA. In addition, the Commissioner has requested that the FDA Science Board 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. (***New and Recently initiated***)

Many of the PDUFA IV recommendations are designed to give FDA resources to enhance its internal and external epidemiologic and informatics capabilities. We will use these resources to hire the necessary experts and to employ outside resources to strengthen our drug safety program. Use of new scientific tools and data resources will help transform FDA's drug safety system. The Agency is aggressively exploring improved methods of benefit and risk analysis and risk management and better surveillance methodologies and tools and is stimulating, under its Critical Path Initiative, scientific projects that will help modernize safety assessments.

[11] The IOM recommendations that relate to the science of drug safety include (1) taking a systematic approach to risk and benefit analyses in both the pre-approval and post-approval settings (IOM Recs. 4.1, 4.5, 4.13, 5.4); (2) building internal and extramural epidemiologic and informatics capabilities to improve postmarket assessments of drugs (IOM Recs. 4.2, 4.6); (3) evaluating the performance of Risk Minimization Plans (RiskMAPs) post approval (IOM Rec. 4.4); (4) strengthening the commitment to building the Agency's scientific research capacity (IOM Rec 4.7); and (5) partnering with other public and private organizations to conduct confirmatory drug safety and efficacy studies (IOM Rec. 4.3).

The FDA scientific activities described below are organized into three general categories: (1) those relating to improving benefit and risk analysis and risk management, (2) surveillance methods and tools, and (3) incorporating new scientific approaches into FDA's understanding of adverse events

1. Upgrading methods of benefit and risk analysis and risk management

- Developing and incorporating new quantitative tools in the assessment of benefit and risk

  - 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 meantime, we have introduced several training courses to help medical reviewers conduct better safety assessments. (***Recently initiated***)
  - In 2006, CDER created the Quantitative Safety and Pharmacoepidemiology Group (QSPB) to promote science-based, data-supported, regulatory decisions on the safe use of drugs. 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. (***New***)
  - CBER (Center for Biologics Evaluation and Research) has implemented an integrated approach to benefit and 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 products and public health safety issues (e.g., it is being used for a quantitative assessment of risks of transmissible spongiform encephalopathy (mad cow disease) in plasma derived Factor VIII products). (***New***)

- Developing and validating risk management and risk communication tools

Under the PDUFA IV proposals, 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) 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. (***PDUFA IV Proposal***)

- Conducting a pilot program beginning in 2007 for routine new molecular entity postmarketing evaluations to assess their utility

CDER is conducting a pilot developed by its Office of Surveillance and Epidemiology (OSE) and its 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. Postmarketing evaluations of NMEs will incorporate data from the Adverse Events Reporting System (AERS), data mining analysis, epidemiologic data, postmarketing clinical trial information, and a review of the Periodic Safety Update Reports (PSURs), or U.S. Periodic Report, to identify potential safety concerns early in the product life cycle. (***New***)

2. Strengthening methods and tools of safety surveillance

- Maximizing the public health benefit of adverse event information (AE) collection throughout the product life cycle

During the first year of PDUFA IV, if it is enacted, 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. (***PDUFA IV Proposal***)

- Upgrading AERS II

We are upgrading AERS II, the second release of the Adverse Events Reporting System database, a Web-accessible computer system, to add signal detection and tracking tools. These tools will allow safety reviewers to more efficiently and effectively identify and track safety signals from submitted adverse event reports. (***Recently initiated***)

- Expanding safety database resources

FDA has been working to expand significantly its access to safety information, as the following examples demonstrate:

- *Data use agreement with the Agency for Healthcare Research and Quality (AHRQ)*

  FDA has entered into a data use agreement with AHRQ to use data from the Centers for Medicare & Medicaid Services (CMS) to conduct a collaborative research project to develop data structures and methodologies for identifying and analyzing adverse drug events. The study will include three projects involving the use of four drugs in the Medicare beneficiary population. In addition to studying safety issues relating to these specific drugs, the goal of this program is to gain familiarity with CMS data, in anticipation of the availability of Medicare Part D data in the near future. (***Recently initiated***)

- *FDA and Veterans Health Administration (VHA) to share information and expertise*

  The Veterans Health Administration (VHA) and FDA are working under a recently signed memorandum of understanding 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. (***Recently initiated***)

– *Active monitoring and analysis of influenza vaccine safety*

FDA's Center for Biologics Evaluation and Research (CBER) and the Centers for Disease Control and Prevention (CDC) are working closely using the Vaccine Safety Datalink (VSD) as a key database for active monitoring and analysis of influenza vaccine safety. A new initiative in collaboration with the CDC and Harvard will implement and assess the pilot testing of these and other databases to assess rapidly and prospectively the safety of seasonal flu vaccines and to be prepared to track selected adverse events related to pandemic vaccines, should they be administered widely. (***Recently initiated***)

In addition, under the proposed PDUFA IV recommendations, we would use PDUFA funds to obtain access to additional databases and to hire the additional epidemiologists and programmers we need to use these databases. Access to types of data other than spontaneous reports would expand FDA's capability to conduct targeted postmarketing 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. (***PDUFA IV Proposal***)

- Proposing a Sentinel Network

On March 7 and 8, 2007, FDA is sponsoring a public meeting to explore opportunities for linking private sector and public sector postmarketing safety monitoring systems to create a virtual integrated, interoperable Nationwide medical product safety 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 (i.e., 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. (***New***)

- Developing and issuing guidance on epidemiology best practices

FDA is leveraging its unique pharmacoepidemiologic expertise to identify best practices. Under the recent proposed PDUFA IV recommendations, FDA, with input from pharmacoepidemiologists in academia and industry, would develop guidance on conducting scientifically sound pharmacoepidemiologic studies using observational data based on large healthcare data sets. We 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. (***PDUFA IV Proposal***)

3. Developing new scientific approaches to detecting, understanding, predicting, and preventing adverse events

New scientific approaches will greatly improve our ability to detect, understand, and manage adverse events throughout the drug life cycle, both during drug development and during clinical uses. FDA has recently initiated a variety of drug safety activities with a wide group of collaborators, many as part of its Critical Path Initiative. Specific activities will improve the ability of animal testing to detect and predict organ damage; increase our ability to uncover toxicity problems during clinical development programs (before wide population exposure); improve our ability to understand whether less serious problems observed in small populations predict rare serious adverse events with broader exposure; enable us to understand the mechanisms of certain adverse events; and lead to development of screening tests that can prevent exposure of individuals susceptible to adverse events. Some examples include[12]:

- Developing and qualifying techniques for predictive toxicology

  Animal models are now used during drug development to predict whether drugs are likely to be toxic in humans. The FDA is involved in an ongoing scientific collaboration intended to yield more sensitive, specific, and informative tests for drug organ toxicity than the toxicology screening techniques currently in use. Such new tests would detect toxicity problems earlier than current approaches and could eventually be used for monitoring. (***Recently initiated***)

- Identifying cardiovascular risk of drugs

  Several projects are under way involving collaborations among FDA, academia, and industry to discover better methods to predict cardiovascular risks of drugs.

  - FDA has partnered with Mortara Instruments Inc., under a Cooperative Research and Development Agreement (CRADA), to design and build a repository to hold digital electrocardiograms (ECGs) used for drug approval; the ECG Warehouse now contains more than 400,000 ECGs. This database will facilitate regulatory review and research and aid in the development of evaluative tools that can be used in drug development and clinical decision making. (***Recently initiated)***
  - In a second phase to this effort, FDA and the Duke Clinical Research Institute (DCRI) have established a collaborative consortium, the Cardiovascular Safety and Research Consortium,[13] with members from academia, patient advocacy, other government and nonprofit organizations, and industry to coordinate and support a variety of research projects involving the ECG warehouse, such as evaluating drug effects on cardiac repolarization. Specific projects will look for more reliable means to measure drug effects on the QT interval of the ECG, to establish norms and to develop more sensitive assays for repolarization effects. (***Recently initiated***)

- Preventing drug-induced liver injury

[12] The detailed list of Critical Path activities currently underway with FDA participation is available on the Critical Path Web page; see http://www.fda.gov/oc/initiatives/criticalpath/.

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

FDA is collaborating with the National Institutes of Health (NIH), academia, industry, and other experts to develop a computer model or models that will help researchers identify appropriate criteria for triggering early clinical intervention that can identify patients most likely to suffer liver toxicity from specific compounds. Drug-induced liver injury is one of the most common severe adverse effects attributable to use of prescription drugs. Part of the collaboration would seek to identify any underlying genetic factors that would predispose individuals to this devastating toxicity (see also next subsection). (***Recently initiated***)

- Using pharmacogenomic information to guide safer and more effective use of drugs

Pharmacogenomics can help improve the safety (and effectiveness) of drugs on an individualized basis. Many adverse events are due to individual overdosing because of drug metabolism differences. FDA is working on several projects to better characterize these differences and reduce the frequency of such adverse events.

  - FDA is providing scientific and strategic input to the Predictive Safety Testing Consortium (PSTC), launched in March 2006, by the Critical Path Institute (C-Path) and 15 pharmaceutical industry partners. The goal is to validate preclinical (genomic) biomarkers of toxicity to use as experimental systems to test for the possibility of toxicity in humans. An innovative aspect of this consortium will be the sharing of data about preclinical and clinical genomic, proteomic and metabolomic biomarkers of drug-induced nephrotoxicity, hepatotoxicity, vascular injury, and genotoxic and nongenotoxic carcinogenicity for cross evaluation by other members of the consortium. The data will be combined with prospective studies to generate biomarker qualification packages for evaluation by the FDA. (***Recently initiated***)
  - FDA is also collaborating with C-Path and the University of Utah on the Cardiovascular Drug Safety and Biomarker Research Program to develop a pharmacogenetic algorithm to help personalize dosing of warfarin. Warfarin, a very effective blood-thinner used by roughly two million Americans annually, is the second most common drug implicated in emergency room visits for adverse drug events. Treatment is complicated because about one third of patients receiving warfarin metabolize it quite differently than expected, and many suffer serious adverse events. They experience significant cases of recurrent clots associated with strokes due to inadequate dosing, or serious bleeding due to excessive dosing. In addition to the human toll, strokes and serious bleeding are very costly to treat. By developing a pharmacogenomic algorithm for doctors to use to improve warfarin dosing, these adverse events could be significantly reduced, and the costs of treating them could be reduced by more than a billion dollars per year by one estimate. (***Recently initiated***)
  - On a related project, the National Heart, Lung, and Blood Institute (NHLBI) is sponsoring a clinical study, with input on the design from FDA and thought-leaders in the field, to determine how factors such as age, gender, and weight might influence patient response to warfarin and what information would lead to new pharmacogenetic dosing algorithms to reduce the adverse events associated with warfarin. The results of this study may inform drug label recommendations. (***Recently initiated***)

- Using new scientific tools to enhance blood safety

The CDC (Centers for Disease Control and Prevention) and FDA are working together to identify emerging threats to the nation's blood supply and facilitate the development, evaluation, and deployment of modern technologies that address them. Examples include nucleic acid amplification testing for HIV, hepatitis C, and, most recently, West Nile Virus. An ongoing effort targets new emerging threats such as Chagas disease and malaria. (***Recently initiated***)

- Enhancing the long-term safety of gene therapy

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 some gene therapies. The model can be used by sponsors to test modifications to gene therapy vectors to mitigate cancer risk while preserving effectiveness. In November 2006, FDA provided a new, risk-based guidance to sponsors on long-term follow up of such therapies.[14] (***Recently initiated***)

- Improving the science of drug development by providing guidance for industry

Under PDUFA IV, to improve safety assessments supporting new drug applications (NDAs) and biologics license applications (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 recommend how to evaluate a drug for possible hepatotoxicity during drug development and how FDA will review an application to look for signs that a drug may be a significant hepatotoxin. (***PDUFA IV Proposal***[15])
  - *Guidance on enriched trial designs* to make recommendations on ways to enrich the clinical trial population to better define the efficacy and safety of the drug under development. (***PDUFA IV Proposal***)

B. IMPROVING COMMUNICATION AND INFORMATION FLOWS

Improving our communication and information flows will further strengthen the effectiveness of the drug safety system.[16] This will require a comprehensive review and

[14] For the main and supplemental guidances, see http://www.fda.gov/cber/gdlns/gtclin.htm and http://www.fda.gov/cber/gdlns/retrogt1000.htm.

[15] We have been working on developing guidance on clinical hepatotoxicity for some time, and a workshop (see http://www.aasld.org/eweb/DynamicPage.aspx?webcode=07_Hepatotoxicity) was held on January 23 and 24, 2007, on this topic. The FDA issued a concept paper to provide a focus for discussion at the workshop. Eventually, we intend to develop a draft guidance in this area. The development of this guidance was recognized and is being proposed as a worthwhile performance goal under PDUFA IV.

[16] The IOM report recommends that we address information flows (1) within FDA, to inform and involve all key review disciplines and relevant experts, including Advisory Committees where needed; (2) to and from medical product sponsors, to ensure rapid and effective steps to provide label information that correctly conveys the product benefit and risk; and (3) across government and private partners in delivery of medical care to enable consumers and providers to maximize benefit and minimize risk. The IOM makes two specific recommendations on communication: (1) establish a new Advisory Committee on communication with patients

evaluation of our risk communication tools with the benefit of Advisory Committee expertise, improving communication and coordination of safety issues within FDA, and clearer guidance on public communication of information and availability of premarket and postmarket safety findings.

1. Conducting a comprehensive review of current public communication tools

We have 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 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 to 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. (***New***)

2. Establishing an Advisory Committee on communication

We are 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. We 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 legislation to establish a new Advisory Committee on communication with patients, but we intend to implement the IOM's recommendation more expeditiously through administrative procedures. (***New***)

3. Using fees to fund improvements in communication among staff on safety issues

Under the proposed recommendations for PDUFA IV, FDA would devote user fees to continue to enhance and improve communication and coordination among staff with different types of expertise. We have already put user fee funds toward supporting two CDER process improvement teams that recently completed their work and whose recommendations are being implemented (see section C2, below). Future funding will be used to develop additional ways to strengthen internal communications throughout CDER on safety issues. (***PDUFA IV proposal)***

4. Issuing drug safety information guidance

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

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and consumers (a recommendation actually directed to Congress but addressed here because we can take action without legislation) (IOM Rec. 6.1); and (2) develop a cohesive risk communication plan that reviews all risk communication activities of CDER and evaluates and revises as necessary our risk communication tools (IOM Rec. 6.2). In addition, in Chapter 4, The Science of Safety, the IOM report includes two recommendations that we consider related to communication and that we will address here: FDA should post all NDA review packages on the Agency's Web site (IOM Rec. 4.12) and FDA should make public the assessments of postmarketing safety studies (IOM Rec. 4.13).

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. (***Recently initiated***)

5. Publishing a newsletter on postmarket findings

In 2007, we plan to regularly publish a newsletter on the FDA Web site containing summaries of the results, including methods, of FDA postmarketing drug reviews. The summaries will not include confidential commercial or predecisional information. We believe it is important, particularly for healthcare professionals, for FDA to make readily available and easily accessible the results of our postmarketing 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 providers and to encourage reporting to the Agency. (***New***)

6. Posting reviews of NDA supplements and assessments of postmarket safety studies

FDA has determined that the IOM recommendation that FDA post all supplemental NDA review packages regardless of whether they have been requested under the Freedom of Information Act (FOIA) is inconsistent with our operations and management plan. Since 1998, FDA has committed to post all new NDA and BLA original approval packages, but has not had sufficient resources to post all supplement reviews. These are posted when FOIA requests are submitted. It is very easy to submit an FOIA request, which can be a very short letter. The fact that not all supplements are requested under FOIA suggests that many have little informational value to the public. FDA does not believe it should spend scarce resources posting materials that are very rarely requested.

Regarding posting assessments of postmarketing safety studies (IOM Rec. 4.13), FDA recognizes the importance of, and is committed to, communicating information about the safety of drugs in a timely, accurate, and meaningful way. However, many postmarketing 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 that is later determined to be erroneous could result in patients who could otherwise benefit from the drug not receiving it. Therefore, decisions to publicly disclose assessments of postmarketing safety studies have to be made on a case-by-case basis. As noted in item 5 above, FDA has committed to posting summaries of the results of FDA postmarketing reviews of adverse events in a public newsletter.

C. IMPROVING OPERATIONS AND MANAGEMENT TO STRENGTHEN THE DRUG SAFETY SYSTEM

We agree we need to improve the culture of safety at FDA, and in CDER. Under the leadership of FDA's recently confirmed Commissioner, CDER has initiated a series of changes designed to effect a true culture change that will strengthen the drug safety system. CDER has moved to reinvigorate its senior management team and charged its members with the responsibility to lead the Center in an integrated manner that crosses organizational lines. Supported by external organizational consultants, the senior management team will address many of the concerns expressed by IOM including those

relating to a lack of mutual respect as well as tension between pre-approval and post-approval staff, the need for clarification of the roles and responsibilities of pre- and post-market staff so that drug safety is better integrated into regulatory decision making at all stages of the life cycle of a drug, and the need for improvement in the way scientific disagreements are handled and resolved. In addition, recognizing that culture change must grow from the ground up, CDER has employed process improvement teams comprising staff in various organizations including OSE and OND to recommend improvements in the drug safety program. As described in sections B.3 above and C.2 below, these teams have made important process improvement recommendations that are already being implemented, and these efforts are expected to continue. We are committed to providing the necessary management attention and support to effect sustained culture change in our drug safety program.[17]

Among the Commissioner's first goals are to ensure appropriate and timely implementation of the review, analysis, consultation, and communication processes needed to strengthen the drug safety system. Under his leadership, FDA is developing a comprehensive strategy for improving organization and creating a culture that values diversity; making specific process changes to increase communications among premarket and postmarket review staff, including specific drug safety goals in our recommendations for PDUFA IV; and improving the Agency's use of Advisory Committees.

1. Engaging external management consultants to help CDER/FDA develop a comprehensive strategy for improving CDER/FDA's organizational culture

In addition to the ongoing FDA activities to improve how our organization supports the individuals who work on safety issues in the FDA, we are enlisting the help of external experts in organizational improvement to help us identify additional opportunities for change and assist us with carrying out those needed changes. (***Recently initiated***)

2. Making specific organizational and management changes to increase communications among review and safety staff

- Process improvement teams have recommended specific organizational changes

  As described under B.3 above, we have 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 Program Manager in each OND review division within CDER and (2) conduct regular safety meetings between OSE and all of the OND review divisions are all now being implemented. (See also recommendations below to establish a safety tracking system and improve procedures for decision making.) (***New***)

[17] The IOM makes several recommendations to FDA relevant to Agency culture, operations and management. These include (1) creating an external Management Advisory Board to advise FDA on developing a comprehensive strategy for sustained cultural change (IOM Recs. 3.2,[17] 3.3); (2) making specific staffing changes concerning the role and responsibilities of OSE staff in pre- and postmarket reviews (IOM Rec. 3.4); and (3) making certain changes related to the operation of our Advisory Committees, particularly with regard to preventing conflicts of interest (IOM Recs. 4.8, 4.9, 4.10). Although recommendations 3.2 and 3.3 are specifically directed to the Secretary, this report discusses the organizational and management changes FDA intends to make to address the IOM recommendations pertaining to culture.

- Involving OSE personnel in new drug reviews

In 2007, FDA is initiating two pilot projects to (1) evaluate various models of involving OSE staff in reviews, including the logistics and value of having an OSE staff person participate in each BLA and NDA review and (2) evaluate various models for more significant involvement of OSE in postmarketing decision making. The Agency is committed to ensuring that safety staff have a strong voice in pre- and postmarketing safety decision making. (***New***)

Furthermore, the proposed PDUFA IV recommendations also include provisions for enhancing and improving communication and coordination between OSE and OND in CDER and 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. (***PDUFA IV Proposal***)

- Creating procedures to improve the decision-making processes related to postmarketing drug safety

Another outgrowth of the process improvement teams discussed above is the creation of new procedures to improve the decision-making processes related to postmarketing drug safety. These procedures will address issues such as how decisions are made to request further studies and labeling changes. ***(Recently initiated)***

- Creating an electronic postmarket drug safety tracking system

CDER is now implementing an 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. (***New***)

- Applying a quality systems approach to improve drug adverse event detection

We are strengthening and standardizing the process used by safety evaluators in OSE. These safety evaluators critically review adverse event reports that have 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. (***New***)

3. Improving our use of Advisory Committees

- Creating a standard operating procedure for presenting postmarket safety issues to an Advisory Committee or other body

This new procedure will articulate the division of responsibility between OND and OSE for planning, presentations, and Advisory Committee configuration and a process for compiling background materials for Advisory Committees. (***New***)

- Increase epidemiology expertise in Advisory Committee meetings

We also will 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 (DSARM) or brought in as special government employees. (***New***)

- Strengthening FDA Advisory Committee management

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 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, we 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. (***New***)

IV. CONCLUSIONS AND NEXT STEPS

To achieve its statutory mission to promote and protect the public health, FDA relies on experts in science, medicine, and public health and on cooperation with patients, other consumers, and industry. FDA agrees with the IOM that our mission requires us constantly "to balance expeditious access to drugs with concerns for safety" (IOM Report p. S-2). FDA is fully committed to doing its part to improve continuously the quality of the U.S. drug safety system. But a drug safety system of the highest possible quality should not be confused with a system in which drugs are risk free. Because there are some risks whenever anyone uses a medication, safety considerations involve complex judgments by the healthcare community, patients, and consumers, who must constantly weigh the benefits and the risks before deciding to use a medical product. The Agency agrees with the IOM that "understanding a drug's risk-benefit profile necessarily evolves over the drug's lifecycle" (IOM Report p. S-3).

The Agency has carefully considered the recent IOM recommendations, along with previous expert suggestions, for making needed advances in this system. FDA has begun to take the steps needed to (1) further scientific understanding of drug products' benefits and risks, (2) rely on this understanding for regulatory decisions about drug marketing, and (3) communicate this understanding to healthcare professionals, patients, and the public so that they can make prescribing decisions based on the best scientific information available.

In this report, the Agency has identified specific actions it can take now in this regard. FDA will track each of the actions (18 recently initiated, 14 new, and 8 PDUFA IV) described here and will report in one year on our progress. It should be emphasized

that FDA does not view or treat drug safety in a vacuum but recognizes the need to integrate the specific initiatives in this report with a holistic program of product quality. Other FDA initiatives, such as Critical Path and our information technology modernization, will substantially contribute to the success of an ongoing commitment to ensure the safety and efficacy of the products we regulate. It is our goal to create an iterative process for improving the quality of the drug safety system by supplementing and expanding these actions as new funding becomes available and as new ideas for improvements to our drug safety system are evaluated and accepted. The Agency remains committed to working with renewed vigor to advance the scientific understanding and regulatory approaches needed for the safe use of marketed medical products.

APPENDIX A — STATEMENT OF TASK FOR THE IOM

(From Box p. S-1 of the IOM Report)

In response to growing public concern with health risks posed by approved drugs, the FDA has requested that the IOM convene an ad hoc committee of experts to conduct an independent assessment of the current system for evaluating and ensuring drug safety postmarketing and make recommendations to improve risk assessment, surveillance, and the safe use of drugs. As part of its work the IOM committee will

- Examine the FDA's current role and the role of other actors (e.g., health professionals, hospitals, patients, other public agencies) in ensuring drug safety as part of the U.S. healthcare delivery system
- Examine the current efforts for the ongoing safety evaluation of marketed drug products at the FDA and by the pharmaceutical industry, the medical community, and public health authorities
- Evaluate the analytical and methodological tools employed by FDA to identify and manage drug safety problems and make recommendations for enhancement
- Evaluate FDA's internal organizational structure and operations around drug safety (including continuing postmarket assessment of benefit and risk)
- Consider FDA's legal authority for identifying and responding to drug safety issues and current resources (financial and human) dedicated to postmarketing safety activities
- Identify strengths, weaknesses, and limitations of the current system
- Make recommendations in the areas of organization, legislation, regulation, and resources to improve risk assessment, surveillance, and the safe use of drugs

APPENDIX B — SUMMARY OF IOM RECOMMENDATIONS AND FDA ACTIONS

IOM Recommendations	FDA Actions	For more detail see Response section and page
3.1 Amend FD&C Act to require 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 life-style 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. [18] On January 19, 2007, the Commissioner proposed the creation of the Office of Chief Medical Officer, which will oversee scientific operations for FDA.	C.1, p. 16 A, p. 6
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.**	

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

IOM Recommendations	FDA Actions	For more detail see Response section and page
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 is initiating two pilot projects to (1) evaluate various models of involving OSE staff in reviews, including the logistics and value of having an OSE staff person participate in each BLA and NDA review and (2) evaluate various models for more significant involvement of OSE in postmarketing decision making. The Agency is committed to ensuring that safety staff have a strong voice in pre- and postmarketing safety decision making.	C.2, p. 15
	As described under B.3 above, we have 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 Program Manager in each OND review division within CDER and (2) conduct regular safety meetings between OSE and all of the OND review divisions are all now being implemented.	C.2, p. 15
	Another outgrowth of the process improvement teams discussed above is the creation of new procedures to improve the decision-making processes related to postmarketing drug safety. These procedures will address issues such as how decisions are made to request further studies and labeling changes.	C.2, p. 16
	The proposed performance goals under PDUFA IV also include provisions for enhancing and improving communication and coordination between OSE and OND in CDER and 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.	C.2, p. 16
	CDER is creating a standard operating procedure for presenting postmarket safety issues to an Advisory Committee or other body. This new procedure will articulate the division of responsibility between OND and OSE for planning, presentations, and Advisory Committee configuration and a process for compiling background materials for Advisory Committees.	C.3, p. 16

IOM Recommendations	FDA Actions	For more detail see Response section and page
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 include the following safety-related performance goals:** 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) 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. 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. FDA would use PDUFA funds to obtain access to additional databases and to hire the additional epidemiologists and programmers we need to use these databases. Access to types of data other than spontaneous reports would expand FDA's capability to conduct targeted postmarketing 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	A.1, p. 7 A.2, p. 8 A.2, p. 9

IOM Recommendations	FDA Actions	For more detail see Response section and page
	safety program.	
	FDA, with input from pharmacoepidemiologists in academia and industry, would develop guidance on conducting scientifically sound pharmacoepidemiologic studies using observational data based on large healthcare data sets. We 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.	A.2, p. 9
	Under PDUFA IV, to improve safety assessments supporting new drug applications (NDAs) and biologics license applications (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:	A.3, p. 12
	• *Guidance on clinical hepatotoxicity* to make recommendations on how to evaluate a drug for possible hepatotoxicity during drug development and how FDA will review an application to look for signs that a drug may be a significant hepatotoxin.	A.3, p. 12
	• *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.	A.3, p. 12
	The proposed performance goals under PDUFA IV also include provisions for enhancing and improving communication and coordination between OSE and OND in CDER and 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.	B.3, p. 13/C.2, p. 16

IOM Recommendations	FDA Actions	For more detail see Response section and page
In addition, IOM recommends that FDA prepare a summary analysis of the adverse drug reaction reports not 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.	See Rec 5.4	
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.	We are upgrading AERS II, the second release of the Adverse Events Reporting System database, a Web-accessible computer system, to add signal detection and tracking tools. These tools will allow safety reviewers to more efficiently and effectively identify and track safety signals from submitted adverse events reports. During the first year of PDUFA IV, if it is enacted, 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. Under the proposed PDUFA IV recommendations, we would use PDUFA funds to obtain access to additional databases and to hire the additional epidemiologists and programmers we need to use these databases. Access to types of data other than spontaneous reports would expand FDA's capability to conduct targeted postmarketing surveillance, to look at effects of classes of drugs, and to detect signals. Access to data	A.2, p. 8 A.2, p. 8 A.2, p. 9

IOM Recommendations	FDA Actions	For more detail see Response section and page
	other than spontaneous reports is essential to the transformation of the drug safety program. On March 7 and 8, 2007, FDA is sponsoring a public meeting to explore opportunities for linking private sector and public sector postmarketing safety monitoring systems to create a virtual integrated, interoperable Nationwide medical product safety 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 (i.e., 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.	 A.2, p. 9
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 these 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 Rec. 3.5) 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) to share information and expertise • Active monitoring and analysis of influenza vaccine safety Many of the critical path initiatives will also help in the formulation and testing of drug safety hypotheses: • Developing and qualifying techniques for predictive toxicology • Identifying cardiovascular risk of drugs • Preventing drug-induced liver injury • Using pharmacogenomic information to guide safer and more effective use of drugs	A.2, p. 8 A.2, p. 8-9 A.3, pp. 10-12

IOM Recommendations	FDA Actions	For more detail see Response section and page
	• Using new scientific tools to enhance blood safety • Enhancing the long-term safety of gene therapy	
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 health care 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 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.	A.2, p. 9
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) 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.	A.1, p. 7

IOM Recommendations	FDA Actions	For more detail see Response section and page
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 meantime, we have introduced several training courses to help medical reviewers conduct better safety assessments.	A.1, p. 7
	In 2006, CDER created the Quantitative Safety and Pharmacoepidemiology Group (QSPB) 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.	A.1, p. 7
	CBER (Center for Biologics Evaluation and Research) has implemented an integrated approach to benefit and 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., it is being used for a quantitative assessment of risks of transmissible spongiform encephalopathy (mad cow disease) in plasma derived Factor VIII products). See pilot for NMEs (Rec 5.4) See also critical path initiatives (Rec. 4.2)	A.1, p. 7
	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 some gene therapies. The model can be used by sponsors to test modifications to gene therapy vectors to mitigate cancer risk while preserving effectiveness. In November 2006, FDA provided a new, risk-based guidance to sponsors on long-term follow up of such therapies.	A.3, p. 12

IOM Recommendations	FDA Actions	For more detail see Response section and page
	We are strengthening and standardizing the process used by safety evaluators in OSE. These safety evaluators critically review adverse event reports that have 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. CDER is now implementing an 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.	C.2, p. 16 C.2, p. 16
4.6 Build internal epidemiologic and informatics capacity to improve the postmarket assessment of drugs.	See access to databases in Recs. 3.5 and 4.2	
4.7 Commissioner should demonstrate commitment to building the agency's scientific research capacity by: Appointing Chief Scientist in OC to oversee, coordinate, 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 agency's mission statement. Apply resources to support intramural research approved by the Chief Scientist. Ensure adequate funding to support	The Commissioner has requested that the FDA Science Board 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 Rec. 3.2	A, p. 6

IOM Recommendations	FDA Actions	For more detail see Response section and page
intramural research program is requested in the agency's annual budget request to Congress.		
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 safety and efficacy or managing drug risks.	See pilot for NMEs (Rec 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.	We also will 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 (DSARM) or brought in as special government employees.	C.3, p. 17
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 recently confirmed 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 address the disclosure of conflict of interest waivers. • A third guidance will improve the release of Advisory Committee briefing materials to the public.	C.3, p.17

IOM Recommendations	FDA Actions	For more detail see Response section and page
	In addition, we 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.	
4.11 Congress should require industry sponsors to register in a timely manner at clinicaltrials.gov, at a minimum, 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 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.	**Not Directed to FDA**	
4.12 Post all NDA review packages on the agency's web site, including all supplemental NDA review packages.	**Not accepted**	B.6, p. 14
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 postmarketing 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 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 postmarketing safety studies have to be made on a case-by-case basis. In 2007, we plan to regularly publish a newsletter on the FDA Web site containing summaries of the results, including methods, of FDA postmarketing drug reviews. The summaries will not include confidential commercial or predecisional information. We believe it is important, particularly for healthcare professionals, for FDA to make	B.6, p. 14 B.5, p. 14

IOM Recommendations	FDA Actions	For more detail see Response section and page
	readily available and easily accessible the results of our postmarketing 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 providers and to encourage reporting to the Agency. 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.	B.4, p. 13
5.1 The committee recommends that Congress ensure that the Food and Drug Administration has the ability to require such post marketing 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 product.	**Not Directed to FDA**	
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	**Not Directed to FDA**	

IOM Recommendations	FDA Actions	For more detail see Response section and page
authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.		
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 effect (recommended time: 2 years).	**Not Directed to FDA**	
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 the distribution of the drug called for at or after the time of approval.	CDER is conducting a pilot developed by its Office of Surveillance and Epidemiology (OSE) and its 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 postmarketing evaluations will incorporate data from the Adverse Events Reporting System (AERS), data mining analysis, epidemiologic data, postmarketing clinical trial information, and a review of the Periodic Safety Update Reports (PSURs), or U.S. Periodic Report, to identify potential safety concerns early in the product life cycle.	A.1, p.7
6.1 Enact legislation establishing a new Advisory Committee on communication with patients and consumers. The committee would be composed of members who represent consumer and patient perspectives and organizations. The AC would	We are 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. We 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	B.2, p. 13

IOM Recommendations	FDA Actions	For more detail see Response section and page
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.	Committee on communication with patients, but we believe we can implement the IOM's recommendation more expeditiously through administrative procedures.	
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 risk communication activities, evaluation, and revision of communication tools for clarity, consistency, and priority-setting to ensure efficient use of resources.	We have 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 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 to 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.	B.1, p. 13
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**	

ABBREVIATIONS

AC - Advisory Committee

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

CMS - Centers for Medicare & Medicaid Services

C-PATH - Critical Path Institute

CRADA - Cooperative Research and Development Agreement

DTC - Direct to Consumer (refers to DTC advertising)

DCRI - Duke Clinical Research Institute

DSARM - Drug Safety and Risk Management Committee

ECG - Electrocardiograms

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

FDA - Food and Drug Administration

FOIA - Freedom of Information Act

HHS - Department of Health and Human Services

HIV - Human Immunodeficiency Virus

IOM - Institute of Medicine

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

PSUR - Periodic Safety Update Report

QSPB - Quantitative Safety and Pharmacoepidemiology Group

RFP - Request for Proposal

RiskMAP - Risk Minimization Action Plan

VHA - Veterans Health Administration

VSD - Vaccine Safety Datalink