参考8

European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
JANUARY 2008 PLENARY MEETING
MONTHLY REPORT (抄)

The Committee for Medicinal Products for Human Use (CHMP) held its January plenary meeting from 21-24 January 2008.

CENTRALISED PROCEDURE

Initial applications for marketing authorisation

The CHMP adopted three positive opinions by consensus on initial marketing authorisation applications:

- **Effentora** (fentanyl citrate), from Cephalon U.K., for the treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain. EMEA review began on 21 March 2007 with an active review time of 204 days.

- **Pradaxa** (dabigatran etexilate mesilate), from Boehringer Ingelheim International, for the prevention of venous thromboembolic events. EMEA review began on 21 February 2007 with an active review time of 205 days.

- **Thalidomide Pharmion** (thalidomide), from Pharmion Ltd, for the treatment of multiple myeloma. EMEA review began on 21 February 2007 with an active review time of 177 days. Thalidomide is the 45th orphan medicine to receive a positive opinion.

  A separate press release and a question-and-answer document explaining the grounds for the positive opinion and the risk management plan approved by the CHMP are available.

Negative opinion

The CHMP adopted a negative opinion recommending the refusal of a marketing authorisation for **Lenalidomide-Celgene Europe** (lenalidomide), from Celgene Europe. Lenalidomide-Celgene Europe was intended to be used for the treatment of anaemia due to myelodysplastic syndromes. It was designated as an orphan medicine. EMEA review began on 28 September 2005 with an active review time of 176 days.

A separate question-and-answer document with more detailed information about the negative opinion is available here.

Summaries of opinion for these medicinal products are available on the EMEA website http://www.emea.europa.eu/htms/human/opinion/opinion.htm. Further information will be included in the European Public Assessment Report (EPAR) once the European Commission has granted final approval.

Re-examination procedure under Article 9(2) of Regulation (EC) No. 726/2004

Following the re-examination of the negative opinion adopted in September 2007, the CHMP confirmed its previous position and adopted a final negative opinion for **Mylotarg** (gemtuzumab ozogamicin), from Wyeth Europa Limited. Mylotarg was intended for the re-induction treatment of CD33-positive acute myeloid leukaemia adult patients in first relapse who are not candidates for other intensive re-induction chemotherapy regimens (e.g. high-dose Ara-C).

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A separate question-and-answer document with more detailed information on the grounds for the final negative opinion is available here.

The EMEA has been formally requested by Pharming Group N.V, to re-examine the negative opinion for **Rhucin** (recombinant human C1 inhibitor) intended to be used in the treatment of acute attacks of angioedema in patients with hereditary angioedema, adopted during the CHMP meeting on 10-14 December 2007.

The EMEA has been formally requested by Neurochem Luco II SARL, to re-examine the negative opinion for **Kiacta** (eprodisate disodium) intended to be used in the treatment of amyloid A (AA) amyloidosis, adopted during the CHMP meeting on 10-14 December 2007.

Withdrawal

The EMEA has been formally notified by Marvel Lifesciences Ltd of its decision to withdraw its applications for centralised marketing authorisation for the medicines **Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel** (insulin human). These medicines were expected to be used for the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis and for the initial control of diabetes mellitus and diabetes mellitus in pregnancy. A separate press release with more information is available. The question-and-answer document will be available in the near future.

Post-authorisation procedures

New contraindications

The CHMP recommended the addition of a new contraindication for rosiglitazone-containing medicines (**Avandia, Avandamet, Avaglim**), stating that rosiglitazone must not be used in patients with an acute coronary syndrome. The CHMP also recommended the inclusion of a new warning stating that rosiglitazone is not recommended in patients with ischaemic heart disease and/or peripheral artery disease.

A separate press release on these changes is available here.

In addition the CHMP agreed to change the product information for Avaglim (rosiglitazone maleate/glimepiride) to delete the contraindication for its use in combination with insulin.

Updated Safety information

The CHMP finalised a safety review carried out to evaluate the evidence suggesting an increased risk of serious and potentially fatal cardiovascular events (heart attack, stroke, heart failure, and sudden death) when epoetins are administered to treat anaemia in patients with chronic kidney disease. The results of two studies and a meta-analysis recently published, suggest that treatment of anaemia with epoetins in patients with chronic kidney disease may under some circumstances be associated with an increase in the risk of mortality and cardiovascular morbidity. In addition, data from recent clinical trials also showed a consistent unexplained excess mortality in patients with anaemia associated with cancer who have been treated with epoetins. Following CHMP request, the MAHs of the centrally authorised epoetins (**Aranesp (darbepoetin alfa), Neorecormon (epoetin beta), Dynepo (epoetin delta), Mircera (methoxy polyethylene glycol-epoetin beta) and Binocrit/Epoetin Alfa Hexal/Abseamed HX575 (recombinant human erythropoietin alfa)** have amended sections 4.1, 4.2, 4.4 and 5.1 of their SPC through a type II variation to include these warnings. The CHMP adopted these variations by consensus.

The CHMP recommended the inclusion of a warning in the prescribing information for **CellCept** (mycophenolate mofetil) related to cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, reported in patients treated with CellCept. Physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms.

- The CHMP recommended the revision of section 4.1 of the SPC of abacavir containing products (**Ziagen II/45, Kivexa II/18 and Trizivir II/46**) to inform prescribers that screening for carriage of the HLA-B*5701 allele should be performed before initiating treatment with abacavir, and abacavir should not be used in patients known to carry the HLA-B*5701 allele.

Summaries of opinions for all mentioned products, including their full indication, can be found here

Withdrawal

The EMEA has been formally notified by Ipsen Ltd of its decision to withdraw the application for an extension of indication for the centrally authorised medicine **NutropinAq** (somatropin). NutropinAq was expected to be used for the treatment of children with severe idiopathic short stature (short height not explained by growth hormone deficiency or other medical conditions) with a predicted adult height of at least one standard deviation score below the target height. A separate press release with more information is available. The question-and-answer document will be available following the CHMP February 2008 meeting.

OTHER INFORMATION ON THE CENTRALISED PROCEDURE

Lists of Questions

The Committee adopted eight Lists of Questions on initial applications (one under the mandatory scope, and seven under the optional scope) and one List of Questions on a "line extensions" application (in accordance with Annex II of Commission Regulation (EC) No. 1085/2003).

Detailed information on the centralised procedure

An overview of centralised procedures since 1995 is given in **Annex 1.** The post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 2.** The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting in December 2007 is provided in **Annex 3.**

Applications for marketing authorisation for orphan medicinal products

Details of those orphan medicinal products that have been subject of a centralised application for marketing authorisation since the December 2007 CHMP plenary meeting are provided in **Annex 4.**

Name Review Group (NRG)

See procedural announcement on submission of proposed invented names and new NRG meetings schedule.

Statistical information on the outcome of the checking of acceptability of proposed invented names for medicinal products processed through the centralised procedure will be provided after adoption of the NRG conclusion by the CHMP.

REFERRAL PROCEDURES

Referral procedures started

The CHMP started a referral procedure for **medicinal products containing a fixed combination of dextropropoxyphene and paracetamol,** intended for the treatment of pain, because of safety concerns related to overdose. The procedure was initiated by the European Commission under Article 31 of Directive 2001/83/EC, as amended.

The CHMP started a referral procedure for **Ribavirin iQur,** 200 mg hard capsules, 200 mg, 400 mg, 600 mg film-coated tablets, (ribavirin), from iQur Pharmaceuticals, because of disagreements on the grounds for approval of the medicine in the context of the decentralised procedure. Ribavirin iQur is

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参考9

The Future of Drug Safety —

Promoting and Protecting the Health of the Public

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

Copies of this report are available on the FDA Web page at http://www.FDA.gov/

U.S. Department of Health and Human Services
Food and Drug Administration (FDA)
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TABLE OF CONTENTS

The Future of Drug Safety — Promoting and Protecting the Health of the Public

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

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

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[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.