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Food and Drug Administration
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STATEMENT BY

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BEFORE THE

**COMMITTEE ON HEALTH, EDUCATION, LABOR, AND
PENSIONS**

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Andrew von Eschenbach, Commissioner at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the Agency's success in implementing the Prescription Drug User Fee Act (PDUFA) and to emphasize the importance of reauthorizing this law well in advance of its September 30, 2007, expiration date. I will summarize highlights of our proposal for PDUFA IV and take this opportunity to share my vision for the future of FDA's drug safety program and to present a few of the initiatives and opportunities that we have embraced.

BACKGROUND

FDA's review of new drug applications (NDAs) and biologics license applications (BLAs) is central to FDA's mission to protect and promote the public health.

In 1992 Congress enacted PDUFA, intending to reduce the time necessary for new drug application review, and subsequently has reauthorized it twice. The most recent reauthorization of PDUFA directed FDA to consult with the House Committee on Energy and Commerce, the Senate Committee on Health, Education, Labor, and Pensions, appropriate scientific and academic experts, health care professionals, patient representatives, consumer advocacy groups, and the regulated industry in developing recommendations for PDUFA reauthorization. We have complied with these requirements in preparing our PDUFA IV proposal.

PDUFA ACHIEVEMENTS

PDUFA has produced significant benefits for public health, including providing the public access to 1,220 new drugs and biologics. During the PDUFA era, FDA reviewers have approved:

- 76 new medicines for cancer;
- 178 anti-infective medications (including 56 for treatment of HIV or Hepatitis);
- 111 medicines for metabolic and endocrine disorders;
- 115 medicines for neurological and psychiatric disorders; and
- 80 medicines for cardiovascular and renal disease.

In addition, PDUFA implementation efforts have dramatically reduced product review times.

While maintaining our rigorous review standards, we now review drugs as fast as or faster than anywhere in the world. The median approval time for priority new drug and biologic applications has dropped from 14 months in fiscal year (FY) 1993 to only six months in FY 2006. For standard NDAs, the median approval time was 22 months in FY 1993. By FY 2006 median approval times had declined to 16.2 months for standard NDAs.

FDA GOALS FOR PDUFA IV

1. SOUND FINANCIAL FOOTING

User fees have provided substantial resources to FDA, but these resources have not kept up with the increasing costs of the program due to inflation or the expanding review workload.

The PDUFA III provision for adjusting fees has not adequately accounted for actual growth in costs and workload. Therefore, we are proposing changes for the PDUFA IV financial provisions to correct for these shortcomings.

For example, in PDUFA IV we recommend changing the calculation of inflation adjustment to include the actual FDA rate of increase in costs of salary and benefits per full-time employee (FTE) over the most recent 5-year period.

Additionally, the surrogates and workload adjusters should more accurately reflect Agency activity. The workload adjuster contained in PDUFA III did not provide adequate accounting of the volume of FDA review activities. For example, since FY 2000, meetings scheduled at the request of drug sponsors grew by 72 percent, up to 2,288 meetings in FY 2006-- this translates to more than nine formal meetings per business day. PDUFA IV would include adjustments for the growth in the number of meetings and special protocol assessments for investigational new drug applications, and labeling supplements and annual reports for the NDA and BLA workload surrogates.

To pay for these proposals for sound financial footing, as well as for enhancements to pre-market and post-market review, discussed below, we are recommending that PDUFA fees be increased by approximately \$100 million, to an estimated total of \$393 million in FY 2008.¹ This amount would be adjusted in later years based on measured changes in inflation and workload.

2. ENHANCE PROCESS FOR PRE-MARKET REVIEW

For PDUFA IV, FDA recommends enhancements in two areas for the pre-market review process: 1) expanding implementation of Good Review Management Practices (GRMPs) developed under PDUFA III and 2) additional initiatives designed to help expedite drug development. In the area of GRMPs, we propose to further implement the principles and

goals outlined in the 2005 *Guidance for Review Staff and Industry on Good Review Management Principles and Practices for Prescription Drug User Fee Act Products* (2005 Guidance), enhancing the efficiency and effectiveness of our review process. One area that we will focus on is developing a planned timeline for the review of the application with attention to important work such as 1) discussion of labeling and post-marketing study commitments; 2) decision-making; and 3) documentation of such decisions in the administrative record by the signatory authority. By providing such a timeline, applicants will better understand FDA's review plan and when to expect feedback from the Agency on important issues such as application deficiencies, labeling, and post-marketing study commitments.

The PDUFA IV proposal also includes increased user fees to fund additional staff resources to further enhance the science base of our review processes, including developing guidance documents to assist in clinical drug development. By clarifying the Agency's expectations on important topics such as clinical trial design, we can allow the industry to focus their efforts on useful trials and decrease less useful experimentation. Increased resources will also free up reviewer time enabling greater participation in scientific training and research collaborations that will ultimately help clarify regulatory pathways for development of promising future therapies.

Lastly, the PDUFA IV proposal allocates funds to further improve the information technology (IT) infrastructure for Human Drug Review and increase the efficiency of the review process.

¹ The exact amount will be determined when we have the final-year workload data for PDUFA III. That number would be used to calculate the exact fee amounts for FY 2008, the first year of PDUFA IV.

3. MODERNIZE AND TRANSFORM THE POST-MARKET DRUG SAFETY SYSTEM

FDA would use the proposed PDUFA IV funds to strengthen the drug safety system, particularly the Agency's efforts to address the full life cycle of drug products. This effort includes the initiatives identified as most critical by our Office of Surveillance and Epidemiology (OSE) and provides resources that will facilitate collaboration between the Office of New Drugs and OSE, as recommended by the Institute of Medicine (IOM).

Our recommendations for PDUFA IV would triple the amount of user fee revenue available to improve the post-market drug safety system. We also propose to eliminate the current statutory time limit that restricts user fee funding of drug safety activities to the first three years that a drug is on the market, so that PDUFA IV fees could fund drug safety activities on a marketed product at any time in the drug's life-cycle. Eliminating the statutory time limitation will enable assessments of drug products over time to adequately manage drug risks, regardless of approval date.

As part of this effort, we would adopt new scientific approaches to improve the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events associated with drugs and biological products. In addition, FDA would use these funds to continue to enhance and improve communication and coordination between pre- and post-market review staff, a recommendation proposed by IOM in their September 2006 Report.

More specifically, PDUFA IV fees would allow FDA to procure external research to determine the best way to maximize the public health benefits associated with the collection and reporting of adverse events throughout a product's life cycle. Such studies would attempt to answer such central questions as: 1) the number and types of safety concerns that

are discovered by various types of adverse event collection; 2) the age of the medical products at the time such safety concerns are detected; and 3) the types of actions that are subsequently taken and their ultimate effect on patient safety.

The increased funds in PDUFA IV also would allow FDA to gain input from academia, industry, and others in the public to identify epidemiology best practices. This would inform our development of a guidance document that addresses epidemiological best practices and scientifically sound observational studies using quality data sources.

Another critical part of the transformation of the drug safety program supported under PDUFA IV would be maximizing the usefulness of tools used for adverse event detection and risk assessment. PDUFA IV funds would be used to obtain access to additional drug safety information such as population-based epidemiological data and other types of observational databases, as well as to hire additional epidemiologists, safety evaluators, and programmers.

PDUFA IV also would allow us to 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 or two risk management programs and one major risk management tool.

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. By making such information available to industry, we would promote effective and consistent risk management and communication.

To ensure the best collection, evaluation, and management of the vast quantity of safety data received by FDA, we would use the additional PDUFA IV funds to improve our safety-related IT systems. We would improve our IT infrastructure to support a safety workflow tracking system, access to externally linked databases, and enhance the Agency's surveillance tools.

4. REVIEW OF DIRECT-TO-CONSUMER (DTC) ADVERTISING

We also are proposing a new program to assess fees for advisory reviews of DTC television advertisements. Research has shown benefits associated with DTC prescription drug television advertising, such as informing patients about the availability of new treatment options and encouraging patients to see a physician about an undiagnosed illness. However, some have expressed concerns that DTC advertisements may overstate benefits or fail to fairly convey risks.

Currently, companies have the option of submitting their planned advertisements to FDA for advisory review before public dissemination. This approach provides the benefit of FDA input on whether or not the advertisements are accurate, balanced, and adequately supported, enabling advertisements to be changed, if necessary, before they are shown to the public.

Companies recognize the benefits this advisory review mechanism offers. However, though FDA's DTC advisory review workload has been steadily increasing, our staffing for this activity has remained relatively level. As a result, it is impossible for FDA to review all of the DTC television advertisement advisory submissions it receives in a timely manner.

Therefore, we propose creating a separate program to assess, collect, and use fees for the advisory review of prescription drug television advertisements. These user fees would not be funded by application, product, or establishment fees assessed under PDUFA. Instead, these new fees would be assessed separately and collected only from those companies that intend to seek FDA advisory reviews of DTC television advertisements. This program would provide for increased FDA resources to allow for the timely review of DTC television advertisement advisory submissions and ensure FDA input on whether or not the advertisements are accurate, balanced, and adequately supported.

To ensure stable funding for the program in case the number of advisory submissions fluctuates widely from year to year, the program would assess a onetime participation fee to be placed in an operating reserve. The program would then charge fees each year for each advisory review requested. These new fees would provide sufficient resources for FDA to hire additional staff to review DTC television advertising submissions in a predictable, timely manner. FDA anticipates collecting \$6.25 million in annual fees during the first year of the program (and a similar amount to go into an operating reserve fund) to support 27 additional staff to review DTC television advertising. Advisory review fee amounts would be adjusted annually for inflation and to take into account increases in workload. As part of this program, FDA is proposing to commit to certain performance goals including review of a certain number of original advisory review submissions in 45 days and resubmissions in 30 days. The goals would be phased in over the 5 years of the program to allow for the recruitment and training of staff.

FDA'S COMMITMENT TO THE DRUG SAFETY SYSTEM

New drugs, devices, and diagnostics present a significant opportunity to improve health care. In general, the number of lives saved and extended by new therapies vastly outweighs the risks that the treatments themselves pose. Nevertheless, ensuring the safety of drugs and other medical products regulated by FDA has always been a key focus of our commitment to protect and promote the public health. In the past few years, FDA has reassessed its drug safety programs because of the rapid advances in science and technology resulting in increasing complexity of medical products as well as the increased attention to safety-related issues by consumer advocates, health professionals, academic researchers, and Members of Congress.

FDA has a proud, 100-year record of being the world's gold standard and we have maintained this record by our willingness to look internally to see what transformations are necessary to sustain this standard. For this reason, the Agency asked IOM to study the effectiveness of the U.S. drug safety system, with an emphasis on the post-marketing phase, and to assess what additional steps FDA could take to learn more about the side effects of drugs as they are actually used.

On September 22, 2006, IOM released its report entitled *The Future of Drug Safety — Promoting and Protecting the Health of the Public*. The report recognized the progress and reform already initiated by the Agency. We have implemented an aggressive effort, including developing new tools for communicating drug safety information to patients, Through our Critical Path initiative, we are working to improve the tools we use and to more effectively evaluate products and processes, working with our health care partners.

The IOM report makes substantive recommendations about additional steps FDA can take to improve our drug safety program. We believe the proposed PDUFA fees provide FDA the resources needed to improve its record on drug safety. We have the regulatory and statutory authority needed to carry out our commitment to ensure drug safety as outlined in January of this year and hope to work with the Committee to evaluate any proposals to ensure that any legislation improves drug safety without new burdens and mandates that could drive up costs or harm patient access.

1. Strengthening the Science

First, I am committed to strengthening the science that supports our medical product safety system at every stage of the product life cycle, from pre-market testing and development through post-market surveillance and risk management. We will focus our resources on three areas of scientific activity: (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. As discussed above, we propose that these activities be supported, in part, by PDUFA IV funds.

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 combines an understanding of disease and its origins at the molecular level (including adverse events resulting from treatment) with new

methods of signal detection, data mining, and analysis. This approach enables researchers to generate hypotheses about and to confirm the existence and cause of safety problems, as well as explore the unique genetic and biologic features of individuals that will determine how he or she responds to treatment. This *science of safety* encompasses the entire life cycle of a product, from pre-market animal and human safety testing to widespread clinical use beyond original indications and should be used for all medical products so that safety signals generated at any point in the process will robustly inform regulatory decision-making.

2. Improving Communications

Second, I am committed to improving communication and information flow among all stakeholders to further strengthen the drug safety system. This will require a comprehensive review and evaluation of our risk communication tools with the benefit of Advisory Committee expertise, improving communication and coordination of safety issues within FDA.

One example of our efforts to improve communication is establishing a new advisory committee to obtain input to improve the Agency's communication policies and practices and to advise FDA on implementing communication strategies consistent with the best available and evolving evidence. We will include patients and consumers on the committee as well as experts in risk and crisis communication and social and cognitive sciences. Although IOM's report recommends legislation to establish this Advisory Committee, we intend to implement this recommendation more expeditiously through administrative procedures.

3. Improving Operations and Management

Finally, I am committed to improving operations and management to ensure implementation of the review, analysis, consultation, and communication processes needed to strengthen the U.S. drug safety system. We need to improve the culture of safety at FDA, and in the Center for Drug Evaluation and Research (CDER). Under my direction, 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.

CDER has employed process improvement teams comprising staff in various organizations including Office of Surveillance and Epidemiology (OSE) and Office of New Drugs (OND) to recommend improvements in the drug safety program. Their recommendations to (1) establish an Associate Director for Safety and a Safety Regulatory Project Manager in each OND review division within CDER and (2) conduct regular safety meetings between OSE and all of the OND review divisions are now being implemented. We are committed to providing the necessary management attention and support to effect sustained culture change in our drug safety program.

We have recently engaged external management consultants to help CDER 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.

CONCLUSION

PDUFA III expires on September 30, 2007, and I re-emphasize the importance of achieving a timely reauthorization of this law. FDA is ready to work with you to accomplish this goal. If we are to sustain our record of accomplishment under PDUFA III, it is critical that the reauthorization occur seamlessly without any gap between the expiration of the old law and the enactment of PDUFA IV. Any hesitation or delay in the reauthorization of this program could trigger sudden erosion in our work force, particularly among senior reviewers whose skills are in very high demand. The repercussions of such a loss would be with us for years to come.

At FDA, providing the American public with safe and effective medical products is a core component of our mission. We base decisions to approve a drug, or to keep it on the market if new safety findings surface, on a careful balancing of risk and benefit to patients. This is a multifaceted and complex process. The recent initiatives we have announced will improve our current system to assess and advance drug safety.

As always, we value input from Congress, patients and the medical community as we develop and refine these drug safety initiatives. Thank you for your commitment to the continued success of PDUFA and to the mission of FDA. I am happy to answer questions you may have.