Ensuring Drug Safety: Where Do We Go From Here?
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Dr. Janet Woodcock
U.S. Food and Drug Administration
Acting Deputy Commissioner for Operations
Testimony

INTRODUCTION

Mr. Chairman and members of the Committee, I am Dr. Sandra Kweder, Deputy Director of the Office of New Drugs at the Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss drug safety and the drug approval process.

Because of the importance of these issues, you are holding two hearings over the course of three days. Dr. Janet Woodcock, FDA's Acting Deputy Commissioner for Operations, will appear at your hearing on March 3. We have one written statement to address both hearings.

SAFETY IS A HIGH PRIORITY

Let me begin with a few words about safety, and I will return to this issue throughout our written testimony. Modern drugs provide unmistakable and significant health benefits. FDA's drug review process is recognized worldwide as a gold standard. Indeed, we believe that FDA maintains the highest standards for drug approval. There have been significant additions to those standards during the last several decades, in response to advances in medical science. Currently, FDA approves drugs after they are studied in many more patients and undergo more detailed safety evaluation than ever before. FDA grants approval to drugs after a sponsor demonstrates that their benefits outweigh their risks for a specific population and a specific use, and that the drug meets the statutory standard for safety and efficacy. However, no amount of study before marketing will ever elucidate all the information about effectiveness or all the risks of a new drug. Therefore, post-marketing surveillance is extremely important.

Adverse effects that are not detected during clinical trials are identified after approval through post-marketing clinical trials, spontaneous reporting of adverse events, or observational studies based on more widespread use of the product following approval. That is why Congress has supported and FDA has created a post-market drug safety program designed to collect and assess adverse events identified after approval for all drugs we regulate.

This program serves as a complement to the pre-market safety reviews required for approval of prescription drugs in the U.S. FDA also evaluates and responds to adverse events identified in ongoing, post-market clinical trials that test approved drugs for other indications. We also evaluate and respond to events reported by physicians, their patients, or drug manufacturers. With this information, we make label changes and take other

regulatory action as needed.

It is important to emphasize that all approved drugs pose some level of risk, such as the risks identified in clinical trials and listed on the labeling of the product. Unless a new drug's demonstrated benefit outweighs its known risks for its intended population, FDA will not approve the drug. However, we cannot anticipate all possible effects of a drug based on data from the clinical trials that precede approval.

NEW FDA INITIATIVES TO STRENGTHEN DRUG SAFETY

November 2004 Five-Step Plan

At FDA, we are constantly striving to improve our processes and methods, and thereby better serve the public health. Recent developments have prompted us to refocus our drug safety efforts and take additional steps to identify drugs that may have unacceptable risk profiles.

On November 5, 2004, Acting Commissioner Crawford announced a five-step plan to strengthen FDA's drug safety program. First, it called for FDA to sponsor an Institute of Medicine (IOM) study to evaluate the current drug safety system. An IOM committee will study the effectiveness of the U.S. drug safety system, with an emphasis on the post-marketing phase, and assess what additional steps FDA could take to learn more about the side effects of drugs as they are actually used. We will ask IOM to examine FDA's role within the health care delivery system and recommend measures to enhance the confidence of Americans in the safety and effectiveness of their drugs.

Second, Dr. Crawford announced that CDER would implement a program for addressing differences of professional opinion. I am pleased to report that CDER recently put this program into effect. Currently, in most cases, free and open discussion of scientific issues among review teams and with supervisors, managers and external advisors, leads to an agreed course of action. Sometimes, however, a consensus decision cannot be reached, and an employee may feel that his or her opinion was not adequately considered. Such disagreements can have a potentially significant public health impact.

In an effort to improve the current process, CDER has formalized a program to help ensure that the opinions of dissenting scientific reviewers are formally addressed and transparent in its decision-making process. An ad hoc panel, including FDA staff and outside experts not directly involved in disputed decisions, will have 30 days to review all relevant materials and recommend to the Center Director an appropriate course of action.

Third, CDER will conduct a national search to fill the currently vacant position of Director of the Office of Drug Safety (ODS), which is responsible for overseeing the post-marketing safety program for all drugs. CDER is seeking a candidate who is a nationally recognized drug safety expert with knowledge of the basic science of drug development and surveillance, and a strong commitment to protecting the public health. CDER is working with the Office of Personnel Management on this search.

Fourth, in the coming year CDER will conduct additional workshops and advisory committee meetings to discuss complex drug safety and risk management issues. Most recently, for example, the Agency conducted a three-day Advisory Committee meeting that examined COX-2 selective non-steroidal anti-inflammatory drugs and related medicines. The Committee held its meeting on February 16-18, 2005, and heard presentations from more than twenty-five experts. At the end of the meeting, the Advisory Committee issued recommendations that the Agency is promptly and carefully reviewing before taking further action.

Finally, FDA intends to publish final versions of three guidances that the Agency developed to help pharmaceutical firms manage risks involving drugs and biological products. These guidances should assist pharmaceutical firms identify and assess potential safety risks not only before a drug reaches the market and but also after a drug is already on the market. FDA expects to publish the final guidances in the second quarter of 2005.

February 2005 Drug Safety Announcement
On February 15, 2005, HHS Secretary Leavitt and Acting Commissioner Crawford unveiled a new, emboldened vision for FDA that will promote a culture of openness and enhanced oversight within the Agency. As part of this vision, FDA will create a new independent Drug Safety Oversight Board (DSB) to oversee the management of drug safety issues, and will improve transparency by providing emerging information to health providers and patients about the risks and benefits of medicines.

Under this proposal, FDA will enhance the independence of internal deliberations and decisions regarding risk/benefit analyses and consumer safety by creating an independent DSB. The DSB will oversee the management of important drug safety issues within CDER. The DSB will be comprised of individuals from FDA who were not involved in the initial review of the drug, as well as medical experts from other HHS agencies and government departments (e.g., the National Institutes of Health and Department of Veterans Affairs). CDER’s Deputy Director will serve as the Chair of the DSB. The DSB also will consult with other medical experts and representatives of patient and consumer groups.

FDA will also increase the transparency of the Agency;s decision-making process by establishing new and expanding existing communication channels to provide drug safety information to the public. These channels will help ensure that established and emerging drug safety data are quickly available in an easily accessible form. The increased openness will enable patients and their health care professionals to make better-informed decisions about individual treatment options. The Agency is also proposing a new Drug Watch webpage that will include emerging information about possible serious side effects or other safety risks for previously and newly approved drugs. This resource will contain valuable information that may alter the benefit/risk analysis for a drug or affect patient selection or monitoring decisions. The web resource may also contain information about measures that patients and practitioners can take to prevent or mitigate harm. This information resource will significantly enhance public knowledge and understanding of

safety issues by discussing emerging or potential safety problems even before FDA has reached a conclusion that would prompt a regulatory action. As always, FDA is committed to maintaining patient privacy as it implements these measures.

As FDA develops these communication formats, the Agency will solicit public input on how FDA should manage potential concerns associated with disseminating emerging information prior to regulatory action. The Agency will also issue draft guidance on procedures and criteria we will use to identify drugs and information that will appear on the Drug Watch webpage. In addition, FDA will actively seek feedback from health care professionals, patients and consumers on how best to make this information available to them.

Increased Funding for the Office of Drug Safety

FDA has a longstanding commitment to provide a strong resource base for ODS. As the graph set forth below demonstrates, we have steadily increased the financial and human resources dedicated to post-market drug safety over the past decade.

The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. The Administration's proposed budget for ODS will increase by $6.5 million, including $1.5 million in user fees, for a total fiscal year 2006 ODS funding level of $33.4 million. PDUFA resources will represent nearly one-third of the ODS budget for the coming year. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.

THE DRUG APPROVAL PROCESS

Pre-Approval Focus on Safety

FDA's focus on safety begins at the earliest stages of drug development, when we review a product under an investigational new drug (IND) application. During the IND period, products must complete three phases of clinical (human) trials. Phase I studies involve the initial introduction of an IND drug into humans to assess the most common acute adverse effects and examine the size of doses that patients can take safely without a high incidence of side effects. However, before beginning human trials, the sponsor must perform extensive animal toxicity studies. Researchers closely monitor these studies. They may conduct Phase I trials in patients, but often rely on healthy volunteer subjects. In general, these studies yield initial safety data and useful information to establish the appropriate dose of the drug.

Phase II includes the early controlled clinical studies conducted to obtain additional information on appropriate dosing, as well as preliminary data on the effectiveness of the drug for a specific indication in patients with the disease or condition. This phase of testing also helps identify short-term side effects and risks possibly associated with the drug. Phase II studies are typically well controlled, closely monitored and conducted in studies that usually involve several hundred patients. In these studies, researchers compare results of patients receiving the drug with those who receive a placebo, a different dose of the test drug, and/or another active drug. At the conclusion of these studies, FDA and the sponsor meet to determine if the drug's development should advance to Phase III and how to design and conduct further trials.

Finally, researchers design Phase III trials for a larger number of patients and build on the data gained from the first two phases of trials. These studies provide the additional information about safety and effectiveness needed to evaluate the overall benefit-risk relationship of the drug. Phase III studies also provide the basis for extrapolating the results to the general population and provide essential information for the package labeling. Once the results of all the clinical trials are available, the sponsor of the application (usually the manufacturer of the product) analyzes all the data and submits a new drug application (NDA) or biologics license application to FDA for review.

Post-Approval Risk Assessment
Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA on their drug. Also during this period, we continuously receive adverse event reports through our MedWatch system from other sources such as health care providers and patients. Safety experts review and analyze the reports to establish the frequency and seriousness of the adverse events. Our response to information from this ongoing surveillance depends on an evaluation of the aggregate public health benefit of the product compared to its evolving risk profile. FDA carefully considers the seriousness and the frequency of reported adverse events as well as the estimated number of patients who benefit from the drug. The occurrence of a rare event, even a serious event, may or may not, by itself, be sufficient to take a drug product off the market. Adverse event reports do not solely provide all the data necessary to identify any potential risks that may be associated with a specific product or class of products; however, over time, they provide us with another piece to a complex puzzle.

If the public health benefit of the product outweighs its known risks for the intended population and intended use, FDA allows the continued marketing of the drug. Often, as more becomes known about the potential risks or benefits of a product, its label will be revised so that it better reflects information on appropriate use. For example, FDA may ask the manufacturer to revise the labeling to add information on adverse reactions not previously listed, to add new warnings describing conditions under which the drug should not be used, or to add new precautions advising doctors of measures to minimize risk. FDA often issues Public Health Advisories and information sheets for health care providers and patients that discuss the new safety information. In the event of reports of death or life-threatening injury, FDA and the sponsor may consider restricting the

distribution of the product or removing it from the market. Our action will depend on the frequency of the reports, the seriousness of the diseases or conditions for which the drug provides a benefit, the availability of alternative therapy, and the consequences of not treating the disease.

The issue of how to detect and limit adverse reactions can be challenging. How to weigh the impact of these adverse drug reactions against the benefits of these products on individual patients and the public health is multifaceted and complex, and involves scientific as well as public health issues.

STATUTORY CHANGES TO DRUG APPROVAL AT FDA

FDA was founded in response to concerns about safety, and attention to safety pervades everything that we do. In the Federal Food, Drug and Cosmetic Act of 1938, Congress gave FDA the authority to review the evidence that a drug was safe for its intended use. In 1962, Congress added a requirement that drug sponsors also demonstrate that a drug is effective, using adequate and well controlled studies. Thus, drug safety means that the demonstrated benefits of a drug outweigh its known and potential risks for the intended population and use. In recent years, Congress has enacted legislation that provides significant additional tools to improve our focus on safety: the Prescription Drug User Fee Act (PDUFA) and the Food and Drug Administration Modernization Act (FDAMA).

In 1992, Congress enacted PDUFA. This landmark legislation provided significant resources for FDA to hire more medical and scientific reviewers to conduct pre-market reviews, to hire support personnel and field investigators to speed the application review process for human drug and biological products, and to acquire critical information technology infrastructure to support our review process.

In 1997, following the success of PDUFA I, Congress reauthorized the program for an additional five years when it enacted FDAMA of 1997. With PDUFA II came higher expectations for product reviews and additional goals designed to reduce drug development times.

In 2002, Congress reauthorized PDUFA for a third time. PDUFA III places great emphasis on ensuring that user fees provide a sound financial footing for FDA's new drug and biologic review process and, for the first time, gives FDA authority to expend PDUFA resources on risk management and drug safety activities during the approval process and during the first two to three years following drug approval. Mr. Chairman, your Committee played a significant role in creating and reauthorizing PDUFA, and on behalf of my colleagues at FDA and countless patients throughout America who benefit from the therapies approved under the PDUFA process, I thank you for your efforts.

One of the primary goals of PDUFA was to address the significant delay in U.S. patients' access to new medicines. The objective was to increase benefits to patients, without increasing risks. Before PDUFA, drug lag was a serious concern for U.S. patients and practitioners. Life-saving drugs were available to patients in other countries months and sometimes years before they were available in the U.S. Because of the additional

resources and process improvements implemented since PDUFA I became law, the average FDA drug review time has declined by more than 12 months.

It is important to emphasize that an recent study by Berndt, et al. of the National Bureau of Economic Research found no significant differences in the rates of safety withdrawals for drugs approved before PDUFA compared to drugs approved during the PDUFA era. This research confirms FDA's analysis on the same subject. In addition, we are now adding black box warnings sooner than we did before PDUFA. This indicates that PDUFA has been successful in both speeding access and preserving safety.

In general, PDUFA authorizes FDA to collect fees from companies that produce certain human drug and biological products. When a sponsor seeks FDA approval for a new drug or biologic product, it must submit an application accompanied by a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. Before PDUFA, taxpayers alone paid for product reviews through budgets provided by Congress. Under the PDUFA approach, industry provides additional funding in return for FDA's efforts to meet drug-review performance goals that emphasize timeliness but do not alter or compromise our commitment to ensuring that drugs are safe and effective before they are approved for marketing.

PDUFA III – GREATER EMPHASIS ON DRUG SAFETY

PDUFA fees are essential to our efforts to improve drug safety. Our trained health professionals work to help ensure and improve drug safety using a process of scientific review, monitoring, and analysis throughout the life cycle of the drugs we approve for marketing. A focus on safety initiates during the pre-marketing phase, when the earliest work on drug discovery begins. As the drug development process continues, we evaluate the safety of the therapeutic compound over a number of years during pre-clinical testing, clinical trials involving humans and eventually, with the submission of an NDA for FDA review. Thanks to PDUFA, we are able to commit far greater resources to our important safety responsibilities.

Under PDUFA III, Congress granted authority for FDA to expend user fees for post-market safety review. FDA made this a top priority during our PDUFA negotiations. Beginning with PDUFA III, for drugs approved after October 1, 2002, we can spend PDUFA resources on "collecting, developing, and reviewing safety information on drugs, including adverse event reports" for up to three years after the date of approval. The initiative to address drug safety for PDUFA III products helps FDA better understand a drug's risk profile, provide risk feedback to the sponsors and provide essential safety information to patients and health practitioners.

From October 1, 2002, through December 31, 2004, FDA reviewed 63 risk management plans for drug and biologic products. Twenty-eight of these related to applications submitted after PDUFA III took effect. We also conducted pre-approval safety conferences, risk management plan reviews, drug safety meetings, and meetings with sponsors to discuss proposed drug supplements.

In response to PDUFA III, FDA held a public meeting in April 2003 to discuss risk assessment, risk management, and pharmacovigilance practices. On May 5, 2004, based on the valuable information generated through the meeting process, we published three draft guidances on these important drug safety topics. FDA received extensive comments on these documents, and we expect to publish all three final guidances in the second quarter of 2005.

SAFETY ADVANCES IN FDAMA

Enacted in 1997, FDAMA has been an important addition to FDA's legal framework. FDAMA passed following a thorough Congressional examination of the Agency's policies and programs. It instituted a number of comprehensive changes, reaffirmed the Agency's vital role in protecting the public health and served as the vehicle for enacting PDUFA II.

Pediatric Exclusivity and Safer Use of Drugs in Children

For decades, children were prescribed medications that had not been studied for safety and efficacy in pediatric populations. As a component of FDAMA, Congress provided incentives to sponsors to conduct pediatric clinical trials. Section 111 of FDAMA authorized FDA to grant an additional six months of marketing exclusivity (known as pediatric exclusivity) to pharmaceutical manufacturers that conduct studies of certain drugs in pediatric populations. The objective of section 111 was to promote pediatric safety and efficacy studies of drugs. With the valuable information generated by these studies, the product labeling can then be updated to include appropriate information on use of the drug in the pediatric population. To qualify for pediatric exclusivity, sponsors must conduct pediatric studies according to the terms of a Written Request issued by FDA and submit the results of those studies in an NDA or supplement.

In 2002, Congress renewed this authority when it enacted the Best Pharmaceuticals for Children Act (BPCA). BPCA also mandates that FDA report to the Pediatric Advisory Committee, in a public forum, any safety concerns during the one-year period after we grant pediatric exclusivity. To date, we have reported safety concerns on 34 drugs at six separate public advisory meetings.

Finally, BPCA contains important, new disclosure requirements. Outside of BPCA, the Agency generally may not publicly disclose information contained in an IND, unapproved NDA, or unapproved supplemental NDA. Once FDA approves an NDA or supplemental NDA, the Agency can make public certain summary information regarding the safety and effectiveness of the product for the approved indication.

However, section 9 of BPCA gives FDA important new disclosure authority. BPCA requires that, no later than 180 days after the submission of studies conducted in response to a Written Request, the Agency must publish a summary of FDA's medical and clinical pharmacology reviews of those studies. Moreover, we must publish this information regardless of whether our action on the pediatric application is an approval, approvable, or not-approvable action. Thus under FDAMA, information on pediatric studies

conducted in response to Written Requests was not available until after the supplemental application was approved. In contrast, under BPCA, a summary of FDA's medical and clinical pharmacology reviews of pediatric studies is publicly available regardless of the action taken on the application. Since 2002, FDA has posted the summaries of these reviews for 41 products submitted in response to a Written Request on FDA's website at: http://www.fda.gov/cder/pediatric/Summaryreview.htm. This information provides a rich source of valuable safety information to allow pediatricians to make more informed decisions about whether and how to use these drugs in their patients.

Post-Marketing Safety Studies

On April 30, 2001, FDA's regulations implementing section 130 of FDAMA, which requires sponsors of approved drugs and biologics to report annually on the status of post-marketing commitments, became effective. These regulations modified existing reporting requirements for NDA drug studies and created a new reporting requirement for biologic products.

FDA may request that the sponsor conduct post-marketing studies to provide additional important information on how a drug works in expanded patient populations or to identify safety issues that occur at very low frequency or in special patient populations. The post-marketing safety study obligations in section 130 are of keen interest to patient and consumer advocates who track the completion of post-marketing commitments and FDA's efforts to review study results and modify drug labeling. The regulations implementing section 130 provide FDA with a mechanism to monitor study progress through the annual submission of study status reports. FDA posts the status of post-marketing studies on its public website and publishes an annual summary of industry's progress in fulfilling post-marketing commitments in the Federal Register.

CRITICAL PATH

On March 16, 2004, FDA released a report addressing the recent slowdown in innovative medical therapies submitted to FDA for approval: "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." The report describes options to modernize the medical product development process to try to make it more predictable and less costly. The report focuses on ways that FDA could collaborate with academic researchers, product developers, patient groups, and other stakeholders to make the critical path much faster, predictable, and less costly.

Enhancing the Safety of Medical Products

During drug development, safety issues should be detected as early as possible. However, because of limitations of current methods, safety problems are often uncovered only during clinical trials or, occasionally, after marketing. Despite efforts to develop better methods, some tools used for toxicology and human safety testing are outdated. Clinical testing, even if extensive, often fails to detect important safety problems, either because they are uncommon or because the tested population was not representative of eventual recipients. Conversely, some models create worrisome signals that may not be predictive of a human safety problem.

There are opportunities for developing tools that can more reliably and efficiently determine the safety of a new medical product. To meet this challenge, FDA has called for a new focus on modernizing the tools that applied biomedical researchers and product developers use to assess the safety and effectiveness of potential new products. Many of these tools—diagnostics such as pharmacogenomic tests and imaging techniques—would also be used after marketing to monitor safety in the real world clinical setting. The Critical Path report describes opportunities for FDA, working with academia, patient groups, industry, and other government agencies, to embark on collaborative research effort. The goal is to create new performance standards and predictive tools that will provide better answers about the safety and effectiveness of investigational products, to do this faster and with more certainty, and to enhance the safety of these products in the clinic.

In addition to improved safety tools, Critical Path also focuses on tools that will help individualize therapy. We enhance safety when the target population does not include individuals who cannot benefit from the treatment. For these individuals, drug exposure is all risk. Better tools for individualized therapy will help to identify patients who will respond to therapy. New science has provided the basic knowledge to make these tools a reality.

Critical Path is not a fundamental departure for FDA, but rather builds on the Agency's proven "best practices" for expediting the availability of promising medical technologies. While the report touches on all aspects of medical product development, identifying new tools to address drug safety challenges would represent a giant step down the Critical Path.

CONCLUSION

At FDA, providing the American public with safe and effective medical products is our core 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 decision process, involving scientific and public health issues. The recent initiatives we have announced will improve our current system to assess drug safety. Moreover, as we strive for continuous improvement, we will continue to evaluate new approaches to advance drug safety. As always, we value input from Congress, patients and the medical community as we develop and refine these drug safety initiatives.

Once again, thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.