S. HRG. 110–384

DRUG USER FEES: ENHANCING PATIENT ACCESS AND DRUG SAFETY

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

ON

EXAMINING ENHANCING PATIENT ACCESS AND DRUG SAFETY RELATING TO PRESCRIPTION DRUG USER FEES, INCLUDING **S. 484**

MARCH 14, 2007

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STATEMENTS

MARCH 14, 2007

ADDITIONAL MATERIAL

DRUG USER FEES: ENHANCING PATIENT ACCESS AND DRUG SAFETY

WEDNESDAY, MARCH 14, 2007

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:21 a.m., in Room SD–430, Dirksen Senate Office Building, Hon. Edward M. Kennedy, chairman, presiding.

Present: Senators Kennedy, Mikulski, Brown, Enzi, Burr, Coburn, and Allard.

OPENING STATEMENT OF SENATOR KENNEDY

The CHAIRMAN. We will come to order. I thank our witnesses today for their understanding and their patience. We will get started on our hearing.

So I welcome our committee's members and our distinguished witnesses today on today's hearing on improving the drug user fee program and enhancing drug safety. Patients across the Nation look with hope to our biotechnology, our pharmaceutical research to develop medical breakthroughs for the illnesses they face. Every day that such breakthroughs are delayed is another day of hope denied for patients afflicted with cancer, Parkinson's disease, spinal cord injury, or other serious illnesses.

We in Congress have a responsibility to see that the FDA has the expertise, the information and resources it needs to make the right decisions as quickly as possible for the patients who need such treatments. Obviously, the need for swift review does not mean that drugs should be rushed to the market regardless of proper safety precautions. A review conducted with inadequate regard for safety subjects patients to unacceptable risks of serious side effects or even death.

The user fee program that the committee considers today is an attempt to strike the right balance. Its goal is to give the FDA the support it needs to review new drugs as swiftly as proper regard for safety allows. Most drugs are now approved first in the United States, due in part to the user fee program, which has reduced both review times and approval times for new drugs. I commend FDA and the biotechnology and pharmaceutical industries for having reached agreement on recommendations to Congress for the renewal of this essential program.

All of us are committed to moving this authorization through Congress as quickly as possible. The user fee program, however,

demonstrates the failure by Congress to give FDA the funds it needs to do the job that the American public counts on it to do. Congress ought to correct this failing so the FDA does not have to rely excessively on user fees for its basic budget.

Thorough reviews are essential in assuring drug safety, but the commitment to safety does not stop when the initial review is completed. As the recent Institute of Medicine report emphasized, there must be a life cycle approach to drug safety that includes both a thorough initial review and ongoing reviews to oversee safety through the life cycle of the drug.

Part of the ongoing responsibility for assuring safety is to take effective action to protect patients from unacceptable risks that are detected after drugs reach the market. The approach described by the IOM is at the heart of the bipartisan legislation that Senator Enzi and I have introduced on drug safety. Our legislation gives FDA clear authority to reduce label changes after drug approval to make certain that additional safety studies are conducted where needed. Our proposal includes a structure to oversee safety that is flexible enough to be tailored to the unique characteristics of each new drug and strong enough to protect patients from unacceptable risks.

I will include the rest of my statement in the record and ask Senator Enzi if he would say a word.

[The prepared statement of Senator Kennedy follows:]

PREPARED STATEMENT OF SENATOR KENNEDY

I welcome our committee members and our distinguished witnesses to today's hearing on improving the drug user fee program and enhancing drug safety.

Patients across the Nation look with hope to our biotechnology and pharmaceutical research to develop medical breakthroughs for the illnesses they face. Every day that such breakthroughs are delayed is another day of hope denied for patients afflicted with cancer, Parkinson's disease, spinal cord injury, or other serious conditions.

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The approach described by the IOM is at the heart of the bipartisan legislation that Senator Enzi and I have introduced on drug safety. Our legislation gives FDA clear authority to require label changes after drug approval, and to make certain that additional safety studies are conducted where needed. Our proposal includes a structure to oversee safety that is flexible enough to be tailored to the unique characteristics of each new drug, and strong enough to protect patients from unacceptable risks.

The same goal of improving safety and protecting patients also underlies the legislation that our colleague, Senator Dodd, has introduced with Senator Grassley on the issue. Senator Dodd was among the first to recognize that Congressional action is needed to improve drug safety, and I commend him for his vision and leadership in this important area.

Although there are significant differences in our two bills, their basic goal is identical—to see that consumers receive the best, most effective, and safest drugs possible. Our bills also share the goal of giving patients and doctors access to the best possible information about risks and benefits when they choose among different drugs to treat a disease. I look forward to working with Senator Dodd, and all the members of the committee on these important issues.

It's an honor to welcome all of our distinguished witnesses to today's hearing, but it is a particular pleasure to welcome Dr. Andrew von Eschenbach for his first hearing in which the word "Acting" has been removed from his title as Commissioner of FDA. The agency needs a strong, effective and **confirmed** leader, and I commend our colleagues, and particularly the skillful chairmanship of Senator Enzi, for enabling FDA once again to have a confirmed Commissioner at the helm.

We are also graced today by the presence of one of his illustrious predecessors as Commissioner, Dr. Mark McClellan. I understand that he comes to us after attending a conference that IOM convened on this issue on Monday.

I also welcome, Ms. Kim Witczak, who will describe in personal terms the tragic loss that can occur when we fail to get it right on drug safety.

I also welcome Diane Dorman of the National Organization for Rare Disorders and Dr. Bruce Burlington of Wyeth Pharmaceuticals who will provide valuable perspective from the viewpoints

of patients and the pharmaceutical industry on this important issue.

Your recommendations will help guide our committee and Congress as we take up the vital work of renewing the drug user fee program and giving FDA the resources and authority it needs to do the job that American families are counting on it to do.

OPENING STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman. I appreciate your holding this important hearing. We are here today to talk about reauthorizing the prescription drug user fee program, more widely referred to as "PDUFA." The prescription drug user fee program is a tried and tested program. It's a successful partnership between industry and the Food and Drug Administration. FDA must meet rigorous timeframes for the review of important new drug therapies for patients. Through fees on drug manufacturers, PDUFA has enabled the partners to meet these deadlines while still preserving patient safety.

However, where we are today is not where we need to be tomorrow. We are not a rear view mirror country. We are a pedal to the metal country. We are always optimistic. We are looking to the future and at how to make things better.

While the PDUFA program is a strong system the public can count on, it can and should be improved. In the early 1990s, AIDS and cancer advocates picketed in the front of the Parklawn Building at the FDA demanding faster access to lifesaving drugs. At that time new therapies were being approved in other countries, while there was a significant lag of time before they were approved in the United States. Americans were dying because of this drug lag.

While the drug lag has now shifted to other countries and most drugs are now approved first in the United States, patients still want safe drugs, but don't want to suffer or die while waiting for them. Increasing access to lifesaving drugs initially drove the goals of the drug user fee program, resulting in even faster approvals. This has had a tremendous effect on the number of available new therapies, particularly for such conditions as AIDS and cancer.

We are now at a point at which approvals are probably as fast as they can or should be and attention is turning back to safety issues. Of course, a drug that is never approved is completely safe, but this is not a tradeoff that Americans are willing to make. So now our challenge is getting back to basics and moving toward a model in which increasing access also includes an increased focus on activities directed toward identifying and managing safety issues.

We can and should achieve these goals, increasing both access and safety. This improved, integrated approach entails rapid premarket evaluation of innovative new therapies combined with tracking and evaluating safety issues in the postmarket setting over the entire lifespan of the product. An example of the drugs that should be continually monitored are those that have turned fatal diseases into chronic conditions. The safety issues associated with a drug that is taken for years are different than one that's taken for a week. On the one hand, patients with a life-threatening

disease may be more willing to take a drug with risks, but if they may be on that drug for years they also want to know about side effects and weigh safety and access differently.

I believe the FDA needs new authorities to acquire and evaluate safety information and act on it promptly. Senator Kennedy and I have introduced legislation to grant the agency those new authorities. Our proposal creates robust systems to collect, assess, evaluate, and respond quickly to safety information.

In addition to the new authorities, I believe we need to examine the persistence of some of the very conditions that led to the enactment of PDUFA. The users fees were never intended to supplant appropriations. They were intended to supplement appropriated funds. While the industry has committed ever-increasing amounts of money, the agency has committed to meeting ever more ambitious performance goals. As part of the reauthorization of this program, we must ask ourselves what sort of commitment we, the Congress, need to make to this agency. We must review our financial commitment to the program and be open to rethinking what we have agreed to do in the light of evidence that funding is currently not sufficient to do all we require of the FDA.

I have a number of statements from outside groups and I would ask unanimous consent that they be entered in the hearing record.

[The prepared statement of Senator Enzi follows:]

PREPARED STATEMENT OF SENATOR ENZI

Thank you, Mr. Chairman, for holding this important hearing. We are here today to talk about reauthorizing the Prescription Drug User Fee program, or more widely referred to as PDUFA.

The Prescription Drug User Fee program is a tried and tested program. It is a successful partnership between industry and the Food and Drug Administration (FDA). FDA must meet rigorous timeframes for the review of important new drug therapies for patients. Through fees on drug manufacturers, PDUFA has enabled the partners to meet the deadlines, while still preserving patient safety. However, where we are today is not where we need to be tomorrow.

We are not a "rear view mirror" country. We are a pedal to the metal country—always optimistic and looking to the future—always looking at how to make things better. While the PDUFA program is a system the public can always count on, it can and should be improved.

In the early 1990's, AIDS and Cancer advocates picketed in front of the Parklawn Building at the FDA demanding faster access to life saving drugs. New therapies at that time were being approved in other countries, and there was "drug lag" of sometimes years before they were approved in the United States. Americans were dying because of this "drug lag."

While the "drug lag" has now shifted to other countries and most drugs are now approved first in the United States, patients still want safe drugs but don't want to die waiting for them. Increasing access to life saving drugs initially drove the goals of the drug user fee program resulting in ever faster approvals. This has had a tremendous effect on the number of available new therapies, particularly for conditions such as AIDS and cancer.

We are now at a point at which approvals are probably as fast as they can or should be, and attention is turning back to safety issues. A drug that is never approved is completely safe. But this is not a tradeoff that Americans are willing to make. So now our challenge is getting back to basics and moving towards a model in which access includes an increased focus on activities directed toward identifying and managing safety issues. We can and should achieve both goals—access and safety.

This better approach entails rapid pre-market evaluation of innovative new therapies combined with tracking and evaluating safety issues in the postmarket setting over the entire life span of the product. An example is the many drugs which have turned fatal diseases into chronic conditions. The safety issues associated with a drug that is taken for years are different than one that is taken for a week. On the one hand, patients with a life threatening disease may be more willing to take a drug with risks, but if they may be on that drug for years, they also want to know more about side affects and weigh safety and access differently.

I believe the FDA needs new authorities to acquire and evaluate safety information and act on it promptly. Senator Kennedy and I have introduced legislation to grant the agency those new authorities. Our proposal creates robust systems to collect, assess, evaluate, and respond quickly to safety information.

In addition to the new authorities, I believe we need to examine the persistence of some of the very conditions that led to the enactment of PDUFA. The user fees were never intended to supplant appropriations—they were intended to supplement appropriated funds. The industry has committed ever-increasing amounts of money. The agency has committed to meet ever more ambitious performance goals. As part of the reauthorization of this important program, we must ask ourselves what sort of commitment we, the Congress, need to make to this agency. We must review our financial commitment to the program and be open to rethinking what we have agreed to do in light of the evidence that funding is currently not sufficient to do all we require of FDA.

I have a number of statements from outside groups. I ask Unanimous Consent that they be entered into the hearing record.

Again, I thank the Chairman for holding this hearing and the witnesses for agreeing to participate. I look forward to hearing your testimony today.

[Information referred to may be found in Additional Material.]

The CHAIRMAN. It will be so ordered.

Senator ENZI. And again, I thank you for holding this hearing.

The CHAIRMAN. Thank you very much.

We always try to accommodate our members' schedules and I know that Senator Mikulski, who has a special interest obviously in the FDA, wishes to be recognized to say a word. We welcome her, her comment, because I know she has to——

STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Senator, if you wanted to go right to the questions, I would be happy to come after you and Senator Enzi.

The CHAIRMAN. Well, we were going to hear from Dr. von Eschenbach, so maybe——

Senator MIKULSKI. Fine. I think that's well taken.

I must go to a Defense Appropriations hearing. The Army's testifying and of course the issues of Army medicine from acute care all the way through to long-term care will be very much on the agenda.

To my colleagues and also to our director of FDA, first of all, FDA is very important I think to the Nation and certainly to me as the Senator from Maryland. I think that there is among the constellation of Federal agencies—this is one of the most important agencies because it stands sentry over the safety of our food supply and the safety over our drug supply.

There are those who question whether the agency can do both. That will not be the purpose of this hearing, but I think it should be the purpose of further discussion.

The concerns that are being raised are: Does FDA have the right resources? I believe we have all fought for the right resources and we will be looking at the framework for that. But what I'm talking about today is the right leadership. Now, Dr. von Eschenbach, I supported your nomination. I believe you are a professional. I knew your work at the National Cancer Institute. But we need your help and we need your leadership.

What I am deeply concerned about is, No. 1, the perception that FDA has been politicized, and where it has been particularly focused has been on the Office of Women's Health, that first of all we felt that Dr. Wood was pressured out when she was head of the FDA of Women's Health because she spoke out on Plan B. We feel that the office was downgraded when your predecessor's predecessor put in a veterinarian to head up the Office of Women's Health.

Then No. 3, most recently you have said that you were going to downgrade the financing of this office. And yet we do know that there are gender differences or certain drugs that do pertain particularly to women, both for acute care and then long-term care, chronic management. Certainly the hormone replacement therapy shows what I'm talking about. So we need to hear from you your commitment, No. 1, to an agency that is not political and that, No. 2, it's not perceived as political; and then also to reinstitute the Office of Women's Health that has strong support from all the women in the Senate, and my colleague Senator Snowe and I have been particular leaders on that.

No. 3, we are also looking for an independent way of reviewing the drugs, particularly in a postdrug surveillance. I could list from acne drugs to Vioxx to others. We need your help and we need your leadership. You come from an outstanding background of clinical practice. I know it from the research and being at NCI. Now help us create once again the confidence that we have in FDA where we work on the right resources, but we need the right leadership.

I will have other questions if my time permits, and if not I will be willing to follow up with these with you in any way that you deem appropriate in the most collegial way.

The CHAIRMAN. Thank you. Thank you very much, Senator Mikulski. Those are good.

I would hope that in your comments you can include responses to those questions, if you would.

We are glad to have you back here, Dr. von Eschenbach. As a physician, you know this is essential to have as many effective medicines as possible, treat patients under the care, and as a cancer survivor and a former patient you know it's just as important patients have confidence in the safety of the medicines they rely on to improve their health and extend their lives. We look forward to hearing your perspective and recommendations on the drug user fee and on the important drug safety issues and any other comments that you wish to make.

We thank you for coming back to the committee and for all of your help to the committee that you continue to provide. Thank you.

STATEMENT OF ANDREW VON ESCHENBACH, M.D., COMMISSIONER OF FOOD AND DRUGS

Dr. VON ESCHENBACH. Thank you very much, Mr. Chairman, Senator Enzi, and other members of the subcommittee.

Let me begin by first thanking you all for the tremendous support and commitment that you have made to the Food and Drug Administration as we continue to serve the American people by protecting and promoting their health. Let me say at the outset, in response to Senator Mikulski's comments——

The CHAIRMAN. Is your mike on? There you go. Thank you.

Dr. VON ESCHENBACH. Thank you, sir.

Let me say at the outset that as I have come to the Food and Drug Administration both in the role of Acting Commissioner and now as the confirmed Commissioner, I am adamantly committed to the fact that this agency will be both a science-based and a science-led organization with regard to its decisions in order to promote and protect the public health.

I'm pleased to be here today to both propose and emphasize the importance of reauthorizing the Prescription Drug User Fee Act, commonly known as PDUFA. This is the fourth time that Congress will consider PDUFA reauthorization, having first passed the PDUFA package in 1992 and the third reauthorization having occurred in 2002.

Today's proposal builds on that past experience and includes significant modifications that will further improve the program and assure the funds provided by these fees not only enhance the efficiency of processing of applications for new drugs and biologics, but more importantly contribute to the safety of those products. The new proposal, referred to as PDUFA IV, outlines the fee structure and the services supported by those fees and includes application fees, establishment fees, and product fees, and a separate provision for providing for reviews of direct-to-consumer advertising.

Let me state and emphasize that these are fee for service, much like any fee paid to process any application. They in no way will or do affect the decisions regarding those applications. Although funds are largely used to support personnel costs, this is an administrative accounting function and reviewers typically have no direct knowledge of the source of those funds.

With regard to the structure of PDUFA IV, there are a few key points I would like to emphasize this morning. First, I am also grateful for the cooperation of industry to arrive at a proposal that's satisfactory to industry and the FDA and, most importantly, a proposal that is good for the American people. The proposal provides a revenue stream that is much more aligned with the services we will be providing. For example, it provides for additional revenues that support drug application consultation meetings at all stages of drug development. These are labor-intensive meetings, but they are good for industry because they can prepare better applications. They are good for the FDA because they enhance our efficiencies. And they are good for the American people because they get products to patients more quickly.

The fees also now better match the full cost of the personnel required, and this is important because it will assure the industry of our ability to meet goals. It will help the FDA to avoid any unexpected shortfalls, and the structure is good for the public because it leverages public funds with private funds to ensure a strong drug review system.

PDUFA IV builds on the foundation that was established in PDUFA III to use these fees to directly address issues with regard to safety. It enhances the utilization of resources that are dedicated to the safety of these products throughout their entire life cycle. For example, in the premarket arena PDUFA IV will help to minimize the risk of adverse events by funding development of guidance documents that will assist in the development of clinical trial and trial designs that will improve our ability to define efficacy as well as safety.

In the postmarket arena, PDUFA IV triples the PDUFA investment in postmarketing safety that will provide and enable more tools to help detect and mitigate unforeseen and unexpected risks after drugs are approved and are available to wide diverse populations.

Every drug has benefits and risks, but effective risk management requires us to learn about these products long after their approval and utilization. Safety initiatives included in PDUFA IV include, among others, developing epidemiologic best practices to survey populations, expanding our database and database mining resources, developing and validating risk management tools, improving communication and coordination between the various components, and, most importantly, eliminating our 3-year limitation on the use of funds to monitor drugs in the postmarketing setting, which will enable us to track drugs throughout their entire life cycle.

Mr. Chairman, as I conclude I must emphasize that PDUFA III expires on September 30, 2007 and in order to maintain this trajectory of continuous improvement and this process and maintaining the infrastructure that's been established it is critical that reauthorization occur seamlessly without any gap between the expiration of the old law and enactment of PDUFA IV. FDA is ready to work with you and other members of this committee to accomplish this outcome.

We value the input from Congress, patients, and the medical community as we are engaged in a continuous, ongoing effort to de-

velop and refine drug safety initiatives, including the continued effort as recently announced in our response to our Institute of Medicine study that we commissioned and in launching our drug safety commitment.

We thank you for your support and your commitment to the mission of FDA as we all collectively continue to protect and promote the health of the American people.

Thank you and I'm happy to entertain your questions.

[The prepared statement of Dr. von Eschenbach follows:]

PREPARED STATEMENT OF ANDREW VON ESCHENBACH, M.D.

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 1993 to only 6 months in fiscal year 2006. For standard NDAs, the median approval time was 22 months in fiscal year 1993. By fiscal year 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 fiscal year 2000, meetings scheduled at the request of drug sponsors grew by 72 percent, up to 2,288 meetings in fiscal year 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 premarket and postmarket review, discussed below, we are recommending that PDUFA fees be increased by approximately $100 million, to an estimated total of $393 million in fiscal year 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.

Last, 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.

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 3 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

[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 fiscal year 2008, the first year of PDUFA IV.

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 one-time 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 postmarketing 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 postmarket 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 decisionmaking.

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 workforce, 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.

The CHAIRMAN. Thank you very much.

I will be glad to recognize Senator Mikulski first and then Senator Enzi, if she has to go.

Senator MIKULSKI. Well, Senator, thank you for the courtesy. And I know we have a vote at 11:15 and I'm going to dash to my hearing.

Dr. von Eschenbach, do you want to respond to the points that I made, particularly about the Office of Women's Health? And then I have one other question about the after-drug surveillance. But most of all this perception of politicization and also that somehow or another the Office of Women's Health has become a flashpoint and therefore it at times seems administratively punished.

Dr. VON ESCHENBACH. Thank you, Senator. I first of all absolutely share with you your passion and your commitment to addressing the issues that are unique to women with regard to the issue of both effectiveness as well as risks associated with drugs and pharmaceuticals. And to that point, one of the important initiatives that I proposed in the 2008 budget was to enhance the effort that is currently under way and currently has been supported by the women's health initiative with regard to doing research in our Center for Toxicologic Research in Arkansas that is specifically looking at the genetic basis for gender differences and specifically the reason why——

Senator MIKULSKI. Doctor, I don't want to interrupt. I really—I want to make sure that we view this as a courteous—but the question is, that in the budget, we were talking about the women, the Office of Women's Health losing 25 percent of its funding. And the office was meant to go across lines to ensure that perspective was there, just the way Senator DeWine made sure children were being included.

Dr. VON ESCHENBACH. Well, I do not understand the source of that perception or misperception, because in fact we have not finalized, and we are in the process of submitting that to Congress this week—our plan for the 2007 budget. I was referring to the proposal that I testified to with regard to our 2008 budget and the commitment to an initiative specifically addressing women's health.

Let me state, Senator, that there is no intention whatsoever to minimize or reduce our commitment to addressing issues related to women's health, nor any effort to minimize the important role and the resources that are operative in the Office of Women's Health. This is not my intent and it is not what our plan is currently considering.

Senator MIKULSKI. Well, I appreciate that answer. Senator Snowe and I would like to know specifically then what are the resources that are needed that should be specified in both the authorizing and then also as we go forth in the appropriations. Senator Snowe is not a member of this committee, but I told her that we were going to have this conversation.

My second question—and I appreciate that. Let's go to postdrug surveillance. One of the things that concerned me when the vaccine came out to prevent cancer through sexually transmitted diseases and Merck was that you need to take three shots at about $460 a pop, and we were talking about 9-year-olds getting this. I was concerned that, regardless of, now you have approved this, what does this mean in terms of surveillance, postdrug surveillance, to a vaccine for not an infectious—an infectious disease like a parasite?

There was a lot of concern, particularly in the pediatric community and adolescent health community. We all want to prevent cancer. You have been one of the leading researchers. But then here was a new concept, a vaccine to prevent cancer, and the vaccine was going to be given to children who might be sexually promiscuous with then no post anything surveillance. Could you tell us how this would work in this particular situation?

Dr. VON ESCHENBACH. The vaccination against the virus, human papilloma virus, which would then mitigate and prevent the risk of subsequent diseases associated with that virus, including cancer,

FDA approved that vaccine based on the demonstration of its effectiveness and its safety. Now, what we also need to do is continue to monitor and track that vaccine as a process of research, because there are still unanswered questions.

Senator MIKULSKI. But how would it work? If we do PDUFA IV, how then would you have the tools to do that? We are talking about 9-year-olds getting a vaccine against sexually transmitted, in case they engage in sexual promiscuity. It's not like a 21-year-old.

Dr. VON ESCHENBACH. There are research projects that would address a sub-population of the overall population, that would be able to define subsequent questions that still need to be answered. For example, the need for revaccination or unexpected adverse events.

Senator MIKULSKI. Well, would PDUFA pay for this or is this done through other ways?

Dr. VON ESCHENBACH. Well, the primary responsibility rests with the sponsor and with the producer of the vaccine to carry on ongoing trials regarding subsequent——

Senator MIKULSKI. Is that mandatory? Is that mandated?

Dr. VON ESCHENBACH. With regard to that specific vaccine, I would have to answer that for the——

Senator MIKULSKI. I don't think it is. Now, you see, this then comes back to—I know my time is up and the Chairman and the Ranking Member have been very courteous. What then do we leave on the drug company? This is a nonjudgmental phase and what then does FDA's responsibility for ongoing monitoring or mandating that as subject to an ongoing post-clinical distribution review? Do you see what I'm saying?

Dr. VON ESCHENBACH. Yes.

Senator MIKULSKI. So, and again, so Merck has got this vaccine out. Several governors are rushing to make it mandatory. I'm not getting into that policy debate, but if you have got a 9-year-old taking this type of vaccine I think we need to be able to follow that, and I think that needs to be a mandated process. And then it's the question of then who pays for it or what kind of partnership.

My time is up, but you see where I'm heading here?

Dr. VON ESCHENBACH. Yes, ma'am.

Senator MIKULSKI. And where PDUFA comes in. So I think we have a lot of good work to do and I really look forward to working with my chairman and the ranking member. This is one of the most important public policy issues we will be addressing.

Thank you so much.

Dr. VON ESCHENBACH. Thank you, Senator.

The CHAIRMAN. Thank you, Senator. Very important.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

We began this reauthorization process for PDUFA with a November 2005 meeting and there have been extensive negotiations between the agency and industry since that time, as well as further public participation in the process. Now, as you mentioned, we are facing disastrous consequences if this program is allowed to expire on September 30th. But so far we haven't received all of the PDUFA IV proposal. We got part of it yesterday and we are still missing the second half, which outlines the agency performance goals.

I was hoping we would get to see that before this hearing and be able to study it to make this hearing as worthwhile as possible. Can you give me a timeframe as to when we are going to get that final problem resolved and when we will see the final proposal?

Dr. VON ESCHENBACH. Senator Enzi, we continue to work directly with you, your staff, the rest of the committee staff, continuing to move this process through the administrative structure to get all of the details and all of the final parts and pieces of this proposal before you. Clearly, there is a great deal of complexity that's been associated with this particular process and we are trying to expedite that as quickly as possible.

I would expect that this will occur within a matter of perhaps a few weeks, to have the entire package before you.

Senator ENZI. September 30th is coming up fast, and we can't do our work until you have done your work. So I hope you will put a lot of emphasis on getting that done.

Dr. VON ESCHENBACH. It's an extremely high priority for us at the FDA and we are working with other parts of the process to get this to you as rapidly as possible, while at the same time being certain that we have addressed all of the specific issues and details that are necessary in order to make certain that the proposal is sound.

Senator ENZI. I will have a considerably more detailed question to nail that timeframe down a little bit better as a written question.

I would like to hear more about how the FDA will use some of the large patient databases to conduct drug safety studies. Can you tell me how this is happening now and how that's going to change under PDUFA IV?

Dr. VON ESCHENBACH. This is an extremely important part of our ongoing commitment to a comprehensive approach to product safety, including not just drugs and biologics, but devices. And that's the opportunity to look at the full life cycle.

With regard to postmarketing, there are opportunities for us now to access databases that are being developed, for example, in large health care plans, where there is significant information regarding the utilization of drugs and particularly combinations that patients may be taking, the ability to detect signals of adverse outcomes that might be occurring in that diverse population.

What we will be doing is first of all partnering with those kinds of health care systems, currently United Health. We have signed a memorandum of understanding with the Veterans Administration. We will be working with the Center for Medicare and Medicaid Services. By accessing those databases and then bringing to that modern tools of information technology, including sophisticated data mining, things that are operative in other areas, like banking and finance, we will begin to have a system in place that will actively, not just simply passively but actively, early on be able to give us insights into unexpected adverse outcomes that are occurring in a real world population, if you will.

Senator ENZI. Thank you. I have several other questions, but I will submit those in writing and get some more definite answers.

The CHAIRMAN. Just quickly, Commissioner, when do we expect to get the MDUFA, you know, the device industry? A long history

of complexity in getting that aspect approved. But are you somewhat hopeful that this is moving ahead? I thought we had that behind us.

Dr. VON ESCHENBACH. I have been working very directly, have worked very directly with the industry in an effort to continue to accelerate that process. Mr. Chairman, we currently have a proposal that has met and addressed all of the major issues. There appears to be one particular area that still needs further resolution.

But again, as with PDUFA, it's an area in which we want very much to accelerate that process. I cannot give you a specific time line on that, but it is a high priority.

The CHAIRMAN. If you think there's a way Senator Enzi and I we can be helpful, because this is a key aspect and is enormously important, please let unknow.

On the issues of dividing, separating drug review and drug safety programs at FDA, some of us have mentioned that. Maybe we could get your position on that. There are some on the committee that feel that that's the best way to go. Others think that—and a patients' group, that that may slow down some of the potential drugs. Your view?

Dr. VON ESCHENBACH. I agree, Mr. Chairman, in principle with the need for a very distinct and very clear focus on both sides of the equation, the efficacy and the adverse events that could occur with the drug. However, I do not believe that those two processes should be separated. I believe that with the new tools that are emerging in molecular medicine we actually will benefit in the future from having much greater integration of those two aspects of understanding the drug. There are animal models that are being developed, for example, that will enable us to see both sides of that issue almost simultaneously as we apply a drug.

I do believe that it's important that we create systems within that environment that allows for vigorous and, even if not necessarily aggressive, debate of both sides of that equation. But that should all be done within an integrated framework rather than silos that would actually, I think, in the long run perhaps do more harm than good.

The CHAIRMAN. Just finally, that Institute of Medicine report on drug safety raised concerns over the culture at FDA, and the report described an organizational culture in crisis. You had indicated that you were going to try and deal with this issue. Could you comment about what steps you have taken to try and deal with this?

Dr. VON ESCHENBACH. Yes, sir. We have taken a number of steps to address the issue, beginning with the construct, Mr. Chairman, that I believe that the ideal opportunity for us is to create an environment in which we actually promote and stimulate diversity of thought, diversity of perspective, and an aggressive debate and discussion of those various aspects within the decisionmaking process regarding drugs.

Structuring that in an environment that allows that to occur, putting processes and mechanisms in place, are what we are currently engaged in as we speak. We are looking at opportunities for conflict resolution. We have taken responsibility and ownership to continue to promote this within the Office of the Commissioner. I have recently established within the Deputy Commissioner for Pol-

icy an Office of Integrity and Accountability that will look at our internal issues with regard, for example, as to how we manage conflict of interest.

We are developing guidances for our advisory committee functions so that we can bring a richness of information and insight and input into that decisionmaking process.

So it is a multifactorial approach to a culture of diversity of thought that results in the best decision for the American people.

The CHAIRMAN. Thank you. We had a very good hearing the other day on follow-on biologics, and if you at the agency have some views on that we would like to have them, but we need them rapidly. But we appreciate any guidance you can help us with.

Dr. VON ESCHENBACH. I look forward to that.

The CHAIRMAN. Thank you.

Senator Burr.

SENATOR BURR

Senator BURR. Thank you, Mr. Chairman.

Welcome, Dr. von Eschenbach. It's my understanding that PDUFA IV negotiations are complete. We haven't received everything. Let me ask you, if the Kennedy-Enzi bill were in fact passed, would you have to renegotiate PDUFA IV?

Dr. VON ESCHENBACH. The negotiation of the package that has been finalized and negotiated did not include provisions that may be contained in the outcome of Senator Kennedy and Senator Enzi's bill.

Senator BURR. So the answer is you would have to go back and renegotiate the entire user fee.

Dr. VON ESCHENBACH. We would have to find additional resources.

Senator BURR. Thank you.

Do you agree that the Kennedy-Enzi bill incorporates many of the drug safety tools that the FDA currently has under its existing RISKMAP program?

Dr. VON ESCHENBACH. We have been continuing to be anxious to provide technical support for Senator Kennedy and Senator Enzi's bill. I believe that there are opportunities for us with regard to our RISKMAP program to continue to enhance our ability to make certain that with certain products we have in place a very well-defined trajectory of being able to monitor and modulate drugs that are of concern.

Senator BURR. Well, there are no Risk Evaluation Mitigation Strategies, "REMS" for the acronym. REMS must include a drug label. You currently require a drug label at the FDA?

Dr. VON ESCHENBACH. Yes, we do.

Senator BURR. It requires quarterly and annual reports on adverse events. You currently do that through MEDWATCH, and are there any other?

Dr. VON ESCHENBACH. We have an adverse events reporting system which we are continuing to improve, of which MEDWATCH is a component as part of our passive surveillance.

Senator BURR. They have pharmacovigilance statements and justifications indicating whether routine adverse events are adequate or whether postmarketing studies or clinical trials are needed. You

currently have the capabilities at the FDA and do exercise the requirement of postmarketing studies as needed. Is that correct?

Dr. VON ESCHENBACH. Yes, sir. We are working with companies to develop postmarketing studies that would be necessary for particular drugs.

Senator BURR. The last requirement that they have within REMS is a timetable for periodic assessment of REMS, which since there's no REMS you currently don't have that. It says REMS may include MEDGUIDE or patient package insert. We currently require a package insert, don't we, at the FDA for pharmaceuticals?

Dr. VON ESCHENBACH. Yes, sir.

Senator BURR. Communication plan to health care providers. Do we currently have a communication plan to health care providers?

Dr. VON ESCHENBACH. Yes, sir, we have the means to do that.

Senator BURR. Postapproval studies. Again, we concluded you do have that capability today and do utilize it.

Dr. VON ESCHENBACH. Yes, sir.

Senator BURR. Post-approval clinical trials, is that a power that exists at the FDA today?

Dr. VON ESCHENBACH. We can ask for clinical trials, yes, sir.

Senator BURR. Pre-clearance of direct-to-consumer ads. It's my understanding that that's negotiated in PDUFA IV.

Dr. VON ESCHENBACH. Yes, sir. We have a provision for fees that would enable us to enhance that opportunity to screen and advise.

Senator BURR. A 2-year ban on direct-to-consumer advertising, that's currently not something that you have at the FDA and currently something that probably would reach a constitutional test; you would agree?

Dr. VON ESCHENBACH. There may be constitutional questions with regard to first amendment rights.

Senator BURR. Restrictions on distribution or use. You currently have the ability to put restrictions on use and distribution. You do have some restrictions on use and distribution based upon certain products?

Dr. VON ESCHENBACH. Yes, sir.

Senator BURR. That would also include training, wouldn't it?

Dr. VON ESCHENBACH. It could.

Senator BURR. A system to implement, monitor, and evaluate the restrictions on distribution and use. So you do have a tracking mechanism now that tells you if people are following the restrictions that you put on distribution and use?

Dr. VON ESCHENBACH. We can access that kind of data.

Senator BURR. Let me just say, I think you have all the tools that are currently in this bill. They may not be statutorily, but you have got regulations that cover it. I had, I know, with Dr. Coburn a very lengthy conversation in 1997 when we passed FDAMA with Dr. Kessler.

Our attempt was to try to set up a surveillance mechanism post-approval. We thought surveillance was the absolute key and at that time Dr. Kessler felt that MEDWATCH was the correct tool. I think over time we have seen that MEDWATCH was not as effective as Dr. Kessler might have thought. There's still a need for a surveillance program today, but I would suggest that the Kennedy-

Enzi bill is not a surveillance program; it is taking FDA regulation and statutorily putting it in the law.

Does the FDA currently have the authority to require postmarket studies?

Dr. VON ESCHENBACH. In certain circumstances.

Senator BURR. Looking at the numbers from an FDA notice published in the Federal Register as of September 30, 2006, only 3 percent of the NDA companies delayed postmarket studies. Now, I found that to be extremely low. Is that a correct assumption on my part?

Dr. VON ESCHENBACH. There are a variety of reasons why there is the potential for delay in the institution of studies and one of the——

Senator BURR. So the 3 percent should not be a great concern?

Dr. VON ESCHENBACH. I think it would depend on the particular study and the importance of it.

Senator BURR. Do you think that the press coverages of the drug safety issue really display the facts of how well the FDA executes the regulations that are at your disposal?

Dr. VON ESCHENBACH. Well, I think when one looks at the entire portfolio there are extraordinary stories of effectiveness and efficiency with regard to the FDA's activity. Having said that, as with all of our issues, I am constantly committed to a process of improvement and looking for better ways to improve. So the input as to how we can do that is certainly welcome.

Senator BURR. Thank you. My time has expired. Mr. Chairman.

The CHAIRMAN. Senator Brown.

STATEMENT OF SENATOR BROWN

Senator BROWN. Thank you, Mr. Chairman.

Thank you, Dr. von Eschenbach. Nice to see you again. There are two reasons people give, some people give, to oppose making the results of clinical trials publicly available. One is that the individuals will be scared away from taking the drugs because of the warnings—one of the arguments that is made is individuals are not sophisticated enough to really understand the description and analysis of the clinical trials. I think that's frankly pretty insulting to the American people.

The second reason is that clinical trials would disclose commercial information proprietary to the drug maker. My answer to that is that the drug—my understanding is that the bill would not require the release of the results until after the drugs approval, on the market.

Could you give me your thoughts on especially what we do with stage 2 and stage 3 clinical trials?

Dr. VON ESCHENBACH. I think it's very important that we continue to pursue a strategy of open sharing of data and information regarding the utilization of these drugs. I think there are complexities with regard to the messaging of that so that people fully understand risk as well as benefit. Oftentimes that is something that does require management in the context of a doctor-patient relationship and understanding a particular drug in particular circumstances and the value equation of risk versus benefit.

So as we do that in a broad disseminated way, I think there are clearly important safeguards that we have to have in place to make certain that the public accurately interprets the information by virtue of the fact we have appropriately communicated it. So I do not have any opposition to communicating data. I do want to be certain we are doing it in the proper and appropriate way.

Senator BROWN. That sort of leads me to the whole issue of direct-to-consumer advertising. My father was in general practice for 50 years and retired in the early 1990s. He told me that when drugs came to market in the old days, well until DTC was allowed and became so common—that a drug would come on the market, that it would be in a medical journal, that a few drug reps—there weren't nearly as many then—would come to their offices and doctors would talk among themselves.

So that a new drug coming on the market, it's use would slowly increase, and over time, over the first year or two, the public would, even with the mistakes that can always happen in clinical trials and with little injury if there was a drug with a problem, the public would become aware of it, as well as the medical community. There would be significantly fewer people damaged by that drug.

Today, obviously, a drug comes to the market with the drug reps, with direct-to-consumer advertising, and all that happens. The use just starts off with the marketing campaign at a very high level.

My understanding is the Kennedy-Enzi bill, which I think makes major progress both on the clinical trial release of information and on the whole direct-to-consumer advertising by giving you the option of delaying for 2 years, why would we not just directly say that we cannot—that no drug maker can do direct-to-consumer advertising within the first year or the first 2 years, until we have had a chance to see what the reaction to this drug is in the general public?

Dr. VON ESCHENBACH. One of the things I think is occurring, Senator, is a really significant change in the culture of medicine. I think patients have become much more active participants in their care. They are much better informed, because for example of the Internet and access to information.

So I think the earlier we get information out to patients in the proper and appropriate way, I think the greater opportunity we have for them to be even better informed participants.

Senator BROWN. Is direct-to-consumer advertising the proper way, your words, compared, contrasted to how consumers can get their information other ways? Is the direct-to-consumer advertising a little too one-sided to encourage them to push their doctors to prescribe this instead of letting it play out in the population a while longer?

Dr. VON ESCHENBACH. I concur that direct-to-consumer advertising has to be done appropriately. The information has to be accurate and factual. I think we have seen situations in which it's heightened, for example, disease awareness with regard to, for example, depression. It's also led patients to better understand the options and choices that might be available.

But at the same time, I fully concur with you that it's only a part of the communication set.

Senator BROWN. Is the FDA equipped, are you equipped, to make those decisions drug by drug, that this one we should allow direct-to-consumer advertising the day that it's on sale, but these others we should delay 2 years before we allow? Is that a decision you can make drug by drug by drug?

Dr. VON ESCHENBACH. At this point we can make decisions regarding the accuracy of the information that's being provided and whether it in fact is appropriate.

Senator BROWN. My understanding is that pre-clearance hasn't been done particularly effectively either, though. Is the burden a little too great? My understanding from hearings in the past, if I could, Senator Kennedy, is that the FDA really has not been able to—just in a cursory sort of way, pre-approve those advertisings.

Dr. VON ESCHENBACH. Well, one of the things with PDUFA IV is to enhance our resources and our ability to specifically address our ability to preview and prescreen and to help make certain that that advertising is in fact appropriate.

Senator BROWN. But if we are not given the resources—and as I said, I think the Kennedy-Enzi bill has made major progress in this, PDUFA IV. But if you don't have the resources to really screen this advertising, wouldn't it be better to err on the side of safety and say for the first year in this huge marketing campaign, the first year we are not, at least we are not going to allow the direct TV to consumer advertising?

Dr. VON ESCHENBACH. I think that would have to be balanced by what potential down side might there be by not informing patients of the availability of a particular opportunity. So I don't know that I know that value equation at this point, but it's certainly something I think we need to discuss and address.

Senator BROWN. Thank you, Dr. von Eschenbach.

The CHAIRMAN. Senator Coburn.

Senator COBURN. I think Senator Allard was here before me.

The CHAIRMAN. We still use the old-fashioned rule, seniority, unless there's somebody who has an appointment or schedule conflict and we try to recognize them. The old-fashioned, old-fashioned way.

SENATOR COBURN

Senator COBURN. Dr. von Eschenbach, thank you for your service. It is a tough job.

The Kennedy-Enzi bill would give the FDA authority to impose restrictions on the use of a drug, including, as I read the language, a restriction on off-label use. Is that your understanding?

Dr. VON ESCHENBACH. We are in the process of providing technical assistance with regard to Senator Kennedy and Senator Enzi's bill——

Senator COBURN. But as it is written now, that is what it would do, correct?

Dr. VON ESCHENBACH. I would not be able to say that specifically, sir.

Senator COBURN. Well, I will say it specifically. It would.

Dr. VON ESCHENBACH. To me that's——

The CHAIRMAN. I think if the Senator would yield, I don't think that's our understanding of the legislation. I will ask the staff to

explain it if you want to go through that, but that's not what our understanding is.

Senator COBURN. All right, thank you. I will take that under advisement.

The problem I have with what I see coming is that the FDA's going to be interfering with the practice of medicine and that highly concerns me. Your background is oncology. Have there not been hundreds of times when you have used an off-label cancer therapeutic drug and achieved a great benefit?

Dr. VON ESCHENBACH. Yes.

Senator COBURN. There is no question about it. And the reason for that is because companies can not afford to do a clinical trial for every significant disease. And with that there is an informed consent, is there not, when you are using a drug off-label?

Dr. VON ESCHENBACH. There's an opportunity within the context of that individual patient and that doctor, as you well know as a physician, to be able to make a therapeutic decision that utilizes what's available in an effort to serve that patient's individual needs.

Senator COBURN. You bet. And I am very worried about what this bill will do to that. I will just tell you that.

The Kennedy-Enzi bill also would give authority to the FDA to restrict which providers can prescribe drugs. Now, you already have that?

Dr. VON ESCHENBACH. I am sorry, sir?

Senator COBURN. Which providers can prescribe drugs? You already have that. You did that with Symlin, much to the negative detriment of people in rural America and in small towns, because they do not have access to an endocrinologist or a diabetologist. So therefore a drug, even, granted, with a narrow therapeutic index, is made available only if you live in a big city, which really has a constitutional question of a different class of citizen because you do not have access.

The question I would raise, as I look at Symlin and its therapeutic index and insulin and I also look at Coumadin and its therapeutic index, I would wonder why the FDA wouldn't want to restrict what doctors could prescribe Coumadin.

Dr. VON ESCHENBACH. Well, I think that there is, as you well appreciate, a spectrum in which we approve a drug but under certain circumstances want to continue to define the utilization of that drug to populations in whom we believe that the safety and efficacy relationship is appropriate and not go beyond or outside of that where we do have reason to believe there will be significant adverse events.

On the other hand, there are drugs that are appropriate for large populations and in which patients can make individualized decisions about the utilization of that drug without any additional restrictions on that practice of medicine.

Senator COBURN. What do you think would happen if aspirin was a new drug today and had to go through the FDA?

Dr. VON ESCHENBACH. In terms of whether it would be approved?

Senator COBURN. First of all, it would not be approved, would it? Five-hundred thousand to six-hundred thousand cases of GI bleeding a year with deaths from aspirin; transfusion reactions that lead

to death from aspirin; kidney damage significant in this country from aspirin usage. It would have a tough time getting approved, correct?

Dr. VON ESCHENBACH. I think you are making the important point, doctor, that there is no drug that's absolutely——

Senator COBURN. Right.

Dr. VON ESCHENBACH [continuing]. Always safe, nor is there a drug that under every circumstance is always effective. What we are looking for is that appropriate balance between the benefit to be obtained and the circumstances in which it's being administered versus what potential risks there might be.

Senator COBURN. Well, one of my concerns is, for example, with Accutane, I am a certified provider for Accutane, done all the stuff and done that. But I live in a small town. I cannot prescribe Symlin because I am not an endocrinologist. My patients do not have that. Prior to coming here, I took care of about 400 diabetics. I cannot give them one of the latest drugs because you have decided that I am not capable of making those decisions, which gets back to the problem is the FDA interfering in the practice of medicine.

So one of the things I am worried about is carrying this logic on further with the Kennedy-Enzi bill and what it will do in terms of interfering additionally in the practice of medicine. I think the charge under the Federal Food, Drug, and Cosmetic Act is safety first and efficacy second, and I see us moving in the direction far beyond that.

I will stop with that. I want to answer one other thing. I am not a big fan of direct-to-consumer advertising, but I am a big fan of the Constitution, and there is no authority in the Constitution for the government to say what a company can advertise and what it cannot. It may have to be accurate and we can hold them accountable. But this idea of saying that the Congress is going to tell who has a first amendment right and who does not needs to get out of our head. It will never pass muster with the courts. It sounds great. It is a great political play. But drug companies have the right to advertise their product just like everybody else, unless they come to a negotiated agreement that they will not.

But we have no business taking away or delaying a first amendment right on advertising. I would just take this further, just for a second. The way drugs used to be marketed is very competent, well-trained individuals, most of them pharmacists, would come in and teach a doctor about the drug and about its side effects and about its drug-drug interactions. And drugs were utilized, maybe not as fast as they were, but because we had confidence in the people who were teaching us then we would utilize drugs very quickly if we had a significant need and they provided a new solution.

I have a lot of confidence in you, Dr. von Eschenbach, but I think it is very important that we are very frank with you. We do not put a lot of laws on the books for things you already have the authority to do and take judgment out of the FDA. I think your scientific judgment most times is very, very good.

Dr. VON ESCHENBACH. Thank you, sir.

The CHAIRMAN. Senator Allard.

STATEMENT OF SENATOR ALLARD

Senator ALLARD. Well, thank you, Mr. Chairman.

It's a challenging day. You just got it from a physician. Now you are going to have to listen to a veterinarian.

I'm glad to hear that you stressed the fact that you use good science and you want to make science-based decisions. I'm certainly very appreciative of that fact, and I know that you employ a lot of veterinarians within the FDA and, unknown to most of the populace, I think we are very highly educated and have got a lot of training in pharmacology. My experience includes both private practice as well as a health officer, which surprises some people now and then.

But I am in a profession where perhaps more, I think more so than in human medicine, for example, cost gets to be more of a consideration when you move forward. So I obviously am very concerned about policies and what-not in the FDA that raise the cost of the drugs, but also I want to make sure that they are properly licensed and processed.

Some of the things that I have a hard time understanding is that when a drug's been out on the market for 30 or 40 years—and we have some of those—sometimes as a practitioner, if we are talking about drug resistance, for example, we have found out that going to a very old antibiotic that hasn't been used much for years, you might be better able to deal with the resistance problem than maybe some of the newer products. So I think they are still useful out there, but they have an extensive history of being used clinically and a lot of scientific articles written about it.

I don't understand sometimes the relicensing that you are requiring on many of those projects, when you have such a broad database already out there. And it is a concern that gets raised to me by my profession, and I would like to have you address that.

Dr. VON ESCHENBACH. Yes, sir. Thank you, doctor. One of the important aspects of our addressing drugs that have been out on the market for a long period of time, as you point out, but are unapproved in that they never went through the regulatory process, is to really take a risk management approach to that, a risk mitigation approach to that. Where we identify and are identifying drugs that with their application do in fact raise serious concerns, those are the drugs that we are really addressing from the point of view of requiring them to go through the appropriate processes before we would allow that appropriate use.

Senator ALLARD. So you are looking at some of the adverse reaction reporting data and then using that as a selection for a review on a particular drug that was approved earlier?

Senator COBURN. Also the circumstances for which the drug is being currently recommended. For example, if it's being recommended in a pediatric use, in a pediatric formulation, we would look at that in terms of that presenting a unique risk to that population.

Senator ALLARD. Well, you have a real challenge as far as my profession is concerned because we use off-label drugs a lot. I'm pleased to hear a physician talk about that, because we deal with such a wide variety of species. And minor use is important. Occa-

sionally compounding may be important, which we write instructions to the pharmacist to do something. So that becomes very important, I think. I just hope that you remain sensitive to that.

I have had reported to me that pharmacies, to sometimes just do a color change on the label, have to go through a whole relicensing process and everything. And if that's true, it seems rather frivolous to me. I can understand if they are changing print size or something like that that it might be an issue.

But I would like to more fully understand what you require when you have a relabeling and everything, if you are actually requiring them to retest and go through a relicensing if they are just changing some of the labels, like the color for example, is something like that a minor change? I would like to have an explanation.

Dr. VON ESCHENBACH. I would be happy to provide for you, Senator, for the record the framework in which those decisions are made. But let me say at the outset that I concur with you with regard to the fact that for a practitioner—veterinarian, physician, or pharmacist—in the context of a particular patient with a prescription, that the idea of being able to create the right compound or the right medication for that patient is a perfectly appropriate part of practice.

I think our concerns at the FDA are primarily focused on the other end of the spectrum, where that process is being used essentially as a drug manufacturing process for widespread utilization, and that's the area of compounding that we have great concerns with.

Senator ALLARD. So describe for me how the post-market safety enhancements would work with the Enzi-Kennedy drug safety legislation?

Dr. VON ESCHENBACH. As I indicated, we are in the process of engaging in technical assistance with regard to addressing the provisions of the bill. What we are working toward, what we are looking forward to, as I indicated in my testimony, is to address the full life cycle of a drug and begin to really utilize the opportunities in postmarket surveillance, particularly with the databases that are now becoming available, and to do that in a way that we can pick up early signals of adverse events and really be able to do that in a risk mitigation strategy that is not simply a blanket coverage, but really gives us an opportunity to look at risk across the entire spectrum.

Senator ALLARD. Can you describe the need for increases in user fees to more adequately cover FDA's costs and what these increases will be used for?

Dr. VON ESCHENBACH. If I understand your question, Senator, it's with regard to how these fees will be used?

Senator ALLARD. Yes.

Dr. VON ESCHENBACH. They are specifically intended to be a fee for service that is compartmentalized to enable us to address the ability to have the resources to efficiently process applications. We have broken them down in terms of establishment fees, product fees, and application fees.

Senator ALLARD. Do you have as part of your objectives, to try and reduce the rules and regulations that impact private practice, whatever that might be?

Dr. VON ESCHENBACH. Well, we are not in any stretch of the imagination in any way lessening our rigor, discipline, and precision and the rules of our regulatory process. That is not something that we would ever embrace in an effort to make the process more efficient.

Senator ALLARD. But you would agree that rules and regulations will outdate and may not be as pertinent today as they were 20 years ago and you ought to look for some of the outdated rules and regulations? Also, you may need new rules and regulations. But I do think you need to have a balance on both ends of that. That's my point.

Dr. VON ESCHENBACH. Yes, I fully concur with that, Senator.

Senator ALLARD. Thank you.

Dr. VON ESCHENBACH. Thank you.

The CHAIRMAN. Thank you very much.

I think that this has been a good discussion. Obviously, what we are interested in, Senator Enzi and I, is to be sensitive to the dangers that have been out there, whether the agency really has the authority and the power to get these companies to make the changes that they are supposed to. Your only ability to get them to change is if you are going to withdraw the drug and that hasn't been used. Otherwise, the idea that they are going to do more clinical trials or take these other steps, there's not been a very dramatic record of willingness to follow along on these safety items. At least I haven't seen it. Maybe it's out there.

When you look at the dangers in Vioxx, for example, the delay that it took 14 months because of the tensions between the company and the FDA prior to your watch, we begin to understand the necessity of making sure we are going to have adequate safety. I go back a while. I still remember Thalidomide and what happened in that danger, and we have seen these problems with antidepressants and the rise of suicides among younger children and real kinds of dangers.

I mean, this idea that we have got an agency that is not going to put a very, very high level and priority in terms of safety, we want to get these various products out as fast as we can. I'm a great believer we are in the life science century; we ought to get them out.

Postmarketing surveillance can do a great deal. It's taken us a long time to get to this point. The Europeans have been after this for a long, long period of time. We have been reluctant. Industry's been reluctant. Now they are for it and we are trying to do it in such a way that's going to be responsive to the particular kind of item, giving that kind of flexibility and authority to the agency.

But it's clearly, if we are able to get—and obviously we are able to get information technology with higher technology on there and greater kind of reporting, greater kind of breadth in terms of the coverage. It's enormously important.

I just talk from a personal point of view, having a son who was a chronic asthmatic, went to a school in Massachusetts and had an asthma attack and was unable to get through that asthma attack, went to the Lawrence Hospital in Lawrence, a first-rate hospital. They weren't authorized to give the kind of drug to him. He finally had to go back to Children's Hospital. They gave the drug. He was

in for 5 days in a very difficult kind of health condition, but survived.

Because of the high toxicity of that particular kind of chemical, there were five different areas around the country that had the authority to use that with those kinds of indicators on it. But it had high, high kinds of possible toxicity.

He's been able to survive. He's done very, very well. We are going to try and bring the best that we have in terms of American medicine out to make sure that it's going to be applicable to the sickest individuals. We want to give maximum flexibility, but we also want to have maximum safety for people. And even though there are some who might think that the idea that we have the Institute of Medicine's recommendations in terms of direct advertising, it's a good deal different. Some would think it would be more dramatic than actually the ones that we have on it.

But we want to make sure in these that the—and I would think most people would feel that having an agency, that you would feel a lot more comfortable in getting matters out into the public and get them out there faster and quicker if they have various safety guidelines on it. If you are not going to be able to get those safety kinds of conditions on it you are going to have to do a good deal more to make sure that mistakes aren't made.

That's the balance that we are trying to do and it seems to me that we have a pretty good balance if we take what's been the lessons of history with the FDA and their power and how their suggestions and recommendations, how they have been treated in the past. We want to make sure that they have the best in terms of science, you are going to be able to get the best and the newest drugs out to the people in the most timely way, but it's going to be done understanding the issues on safety.

Senator Enzi has voted early. Doctor, we want to thank you. We will have others. We appreciate very, very much and look forward to hearing from you on the biologics. I thank you very much for your presence here today.

We will introduce our next panel and represent a broad and important range of experience, critical issues, drug safety. Kim Witczak is showing courage today coming to our committee to tell of an irreplaceable loss, calling on us to respond by improving drug safety. We commend her for her courage.

The committee is honored to be hosting not only the current FDA commissioner, but also a distinguished predecessor, Mark McClellan, whose wisdom and experience on drug safety will be of enormous value to our committee's consideration.

We will hear from Dr. Bruce Burlington, who served with great distinction at FDA for many years. He now comes from Wyeth Pharmaceuticals. We look forward to his perspective on user fees and congratulate him on his leadership in negotiating agreements between FDA and industry.

And Ms. Diane Dorman, who for many years has been a tireless champion of the rights of patients. Her views on this matter are of major importance in developing the right policy on safety.

We will have a brief recess. As soon as Senator Enzi returns, he will start the hearing, and I will be right back.

[Recess from 11:28 a.m. to 11:37 a.m.]

Senator ENZI [presiding]. I will call the hearing back to order again so that we can have the testimony from the witnesses and meet the next deadline that we will have on doing some voting here at the same time.

Ms. Witczak.

STATEMENT OF KIM WITCZAK, FOUNDER OF WOODYMATTERS

Ms. WITCZAK. Thank you. Thank you, Mr. Chairman, members of the committee. Thank you for inviting me to testify here today. I am here to represent the voice of thousands of families who live every day with the consequences of the current drug safety system. Behind me I have Matthie Downing. She's also a family member. She lost her 12-year-old daughter.

Unfortunately, I know firsthand what it's like to lose someone because of unsafe drugs. On August 6, 2003, my life changed forever. I became a widow. My husband of almost 10 years was found dead hanging from the rafters of our garage, of Zoloft-induced suicide at age 37. Woody was not depressed, nor did he have a history of depression or any other so-called mental illness.

Woody had just started his dream job as vice president of sales with a start-up company 2 months prior and was having trouble sleeping, which is not uncommon for new entrepreneurs. So Woody went to his general practitioner and was given Zoloft for insomnia. Five weeks later, Woody took his own life.

No cautionary warning was given to him or me about the need to be closely monitored when first going on this drug or dosage changes. In fact, I was out of the country on business for the first 3 weeks. When I returned from business, I found Woody sitting in the fetal position in our kitchen floor with his hands wrapped around his head like a vice crying, going "Kim, help me, help me; I don't know what's happening to me; my head's outside my body looking in; I'm losing my mind."

Never once, never once, did we question the drug. Why would we? It was FDA-approved, heavily advertised as safe and effective, and it was given to him by his doctor.

From the beginning, something didn't add up about Woody's death. So my brother-in-law, Eric Swan, who's here, and I started researching the only thing that made Woody change during this extremely short period of time, and it was Zoloft. As a result, we established WoodyMatters Web site as a place, a concept and a place for information for consumers.

Our journey for the truth has led us to the FDA, HHS, Congress, and the courts. In fact, this is our 25th trip out here since Woody died. In our battle for Woody, we were able to get confidential internal drug company and FDA documents made public that the suicide risk was known since the late 1980s. In fact, according to a 1990 internal FDA memo, Dr. David Graham expressed concern that he didn't think Eli Lilly adequately addressed the suicide risk with Prozac.

In 1991 the FDA held a public hearing on antidepressant-induced suicidality in adults on Prozac. At that time the FDA determined that further studies were needed to look at suicidality. The drug companies never conducted them and FDA never followed up on it.

Meanwhile, by the end of 1991 the FDA received over 17,000 adverse event reports through the MEDWATCH. Fast forward. More antidepressants enter the market with millions of adults and now children taking the drugs. By 2004, the mounting public pressure and other countries reporting the link between antidepressants and suicide, the FDA held another public hearing on antidepressants and children. It ultimately led to a black box warning for children under 18 and the FDA agreed to look at clinical trials to see if the risk existed for adults.

Just this past December 2006, 15 years after the first hearing, the FDA held another hearing to share their findings for the adults. It's interesting to note it is literally the same people conducting the review and approve the drugs in the first place. After reviewing the original clinical trial data, the FDA recommended that the black box warning be extended to adults 25 and under. My husband still would not be under that warning. He was 37.

How many unnecessary deaths happened between that time period of 15 years? This I am afraid is our current drug safety system at work.

One thing that was particularly hard for me to discover was the side effect that killed my husband was known very early in the clinical trial. I obviously hope that you amend the bill to include phase 2 and even phase 1 trials. It seems to me that if a drug is tested on a human being and there are side effects that emerge, life-threatening side effects, it belongs to all of us. This is vital information that the doctor-patient decision needs to have for the risk-benefit. Woody would have appreciated knowing this information as he was given Zoloft for sleep issues.

I would also like to see a separate and independent Office of Drug Safety, as Senator Dodd and Grassley have proposed. It is telling that the current office is called Surveillance and Epidemiology, not exactly a clear message to the public. A separate office with power to regulate and not just negotiate is vital. In the mean time, there should be posters hanging around the FDA that say "Safety First," like on every construction site in America.

I have offered an idea and a solution in my written statement that addresses the power struggle between the pre- and the post-market offices.

Let's talk technology. The FDA needs to be funded into a 21st century organization. Its Web site is in drastic need of updating. It's confusing and needs to be redone, making it consumer-friendly and searchable. A separate section needs to be dedicated specifically to drug safety and all the names that the drugs use. A lot of times I hear the FDA using the actual chemical name as opposed to what it is marketed to the consumer as.

The MEDWATCH system needs to be updated in electronic reporting so that it is easy to use by doctors and consumers. It needs to be promoted to the public so they know it exists. There is a survey that was done and only 2 percent of the public knows that MEDWATCH, the FDA even has a MEDWATCH system.

I believe if DTC advertising is a must or is going to be here to stay, that we need an 800 number or the medwatch.gov Web site should be required at the end of every drug commercial, that consumers know that they can write to the FDA and report, because

the real clinical trial happens when millions of people take the drugs. Consumers need to be a part of the drug safety system and the FDA has to be able to use that and search it.

You, in a sense, are the board of directors and we are the shareholders. We need you to fix this system, this agency, to protect us.

In conclusion, as you guys debate FDA reform I want you to remember Woody, for his story represents countless of Americans who have personally paid the price. Your decisions have real life consequences. When I leave Washington and go back to Minneapolis, I will go back to an empty house of shattered dreams. I will never grow old with Woody and have children with him. All I have are pictures and memories of a life cut too short. But you have the ability and the responsibility to change this. Please bring the FDA back to the gold standard it once was.

Thank you.

[The prepared statement of Ms. Witczak follows:]

PREPARED STATEMENT OF KIM WITCZAK

Mr. Chairman, Senator Enzi, members of the committee, thank you for inviting me to testify today.

I am here today to represent the voice of thousands of families who live every day with the consequences of the current drug safety system. Unfortunately, I know first hand what it feels like to lose someone because of unsafe drugs. On August 6, 2003, my life changed forever. I became a widow.

My husband of almost 10 years was found dead hanging from the rafters of our garage of Zoloft-induced suicide at age 37. Tim Witczak, known to most as Woody, was not depressed nor did he have a history of depression or any other so-called mental illness. Woody had just started his dream job as Vice President of Sales with a start up energy efficient lighting company a couple months prior and was having difficulty sleeping which is not uncommon for new entrepreneurs. So Woody went to see his general physician and was given Zoloft for an insomnia diagnosis. Five weeks later, Woody took his own life. His doctor gave him a 3-week Pfizer-supplied sample pack that automatically doubled the dose after week one. No cautionary warning was given to him or me about the need to be closely monitored when first going on drug or dosage changes. In fact, I was out of the country on business for the first 3 weeks he was on Zoloft. When I returned, I found Woody one night in the fetal position on our kitchen floor with his hands wrapped around his head like a vise, crying, "Help me, help me!" "I don't know what is happening to me. I am losing my mind. It's like my head is outside my body looking in."

Never once did we question the drug. Why would we? It was FDA-approved, heavily advertised as safe and effective, AND it was given by Woody's doctor that he has seen for years and trusted.

From the beginning, something didn't add up about Woody's death. So my brother-in-law, Eric Swan and I started researching the only thing that made Woody change during this extremely short period of time—Zoloft.

In our battle for Woody, we were able to get confidential internal drug company and FDA documents made public that showed the side effect that killed my husband and many others was known in the original clinical trials from the 1980s. In fact, according to a 1990 internal FDA memo, Dr. David Graham expressed concern that he didn't think Eli Lilly adequately addressed the suicide risk with Prozac. In 1991, the FDA held a public hearing on the antidepressant-induced suicidality in adults taking Prozac. At that time, the FDA determined that further studies were needed to look at suicidality. The drug companies did not conduct studies even though protocols were created. Subsequently in the years to follow, more antidepressants entered the market with millions of adults and now children taking the drugs. With mounting pressure and other countries reporting the link between antidepressants and suicide, the FDA held another public hearing in 2004 on children and antidepressant-induced suicidality. It ultimately led to a blackbox warning for children under 18 and the FDA agreed to review clinical trials to see if the risk exists for adults. In December 2006, 15 years after the first public hearing, the FDA held another hearing to share their findings on a link between antidepressants and suicide in adults. [It is interesting to note that it's literally the same people conducting the review and approved the drugs in the first place.] After reviewing the original

clinical trial data, the FDA recommended that the blackbox warning further be extended to adults 25 and under. The FDA acknowledges that the suicide risk exists in people taking antidepressants—adults and children. Why would you confuse the public by not warning ALL people of the suicide risk? If my husband were still alive, the current FDA recommended blackbox warning would not cover him because he was 37 years old.

Our journey for the truth has led us to the FDA, HHS, Congress and the courts. In fact, this is our 25th trip out here since Woody died. Unfortunately, Woody's story is not an isolated case (or anecdotal story). I have been working with many other families who have lost loved ones due to unsafe drugs and they could tell similar stories. WoodyMatters was founded to give a voice to Woody and our activism. The Web site also gives other families a chance to tell their stories and get information.

I tell Woody's story in the hope that you will use the once-in-5-year opportunity of PDUFA extension to make fundamental reforms in FDA, so that other families will not have to suffer what I and so many others have endured.

To be blunt, the draft agreement reached between the industry and the FDA is totally inadequate.

First, let me say for the record that consumers, most legitimate patient groups, and the Institute of Medicine are deeply troubled by the whole user-fee program. The FDA is one of America's most vital public agencies, and its duty is to ensure the quality and safety of over a fifth of our economy. Its client is the American public, and therefore it ought to be funded totally out of the general Treasury. If user fees are needed in lieu of general appropriations, then there should be no conditions attached on how that money is spent. I support legislation that Rep. Maurice Hinchey proposed in the last Congress, which breaks the morale-destroying conditions that are part of the current PDUFA system.

If breaking those ties is not possible, then we need increased resources for safety and the post-approval drug monitoring process—and we need specific goals for the use of those resources, just like industry gets on the pre-approval side.

The Institute of Medicine report did not give one specific number for the cost of its various recommendations, but it appears to be between $100 million and $200 million. The draft industry-FDA agreement provides for only about $29 million for increased safety. Some of that $29 million is said to be earmarked (we would like to see the specific language of how that will be done) for some very worthy improvements. For example,

- The proposal would no longer limit how long user fees could be spent on a specific drug's post-market approval safety issues (it eliminates the current 2- to 3-year limit), since, as the FDA says, "current data show that safety issues can arise after a drug has been on the market for 8 or more years";
- PDUFA IV monies could be used to "obtain access to additional databases and increase program staffing with epidemiologists, safety evaluators, and programmers who can use these new resources."

But all too much of the new "safety money" is spent on "let's just do more of what we are doing," let's hold forums and symposia, let's develop "papers." For preapproval, industry gets specific, rapid deliverables. In postapproval safety, we get placebos. That's a strong statement, but look at the draft agreement: The industry gets 90 percent of new drug applications decided within a certain number of days, and requests for meetings answered within 2 weeks. What does the consumer public get? We get sentences like:

> ". . . FDA would use these funds to continue to enhance and improve communication and coordination between pre- and post-market review staff."

We get phrases like:

> "Potential activities in this area might include integration of certain proposed recommendations made by the [IOM]."

And

> "a public workshop to identify best practices in this emerging field, ultimately developing a document that addresses epidemiology best practices . . ."

I urge you to amend the PDUFA agreement and/or section 107 of S. 484, to spell out additional resources for *specific* safety achievements *such as*:

- Give the FDA the computer resources to detect dangers faster. S. 484 calls for the FDA to submit a strategic plan for information technology within a year. The FDA has told consumers that they need $20 million a year to implement their modernization plan, and that at the end of 2006 vendors would no longer serve over half their IT equipment because it is so outmoded. But I urge this committee to require regular progress reports from the FDA on how they are

using this money. I just had an opportunity to see the heavily censored "Breckenridge Institute" analysis of the FDA's efforts to modernize the Adverse Event Reporting System. The report describes incompetence and waste that is breath-taking. It describes a culture that explains how **antidepressants** and so many other drugs have been on the market for so long with so little **safety** action **taken**. As the Breckenridge analysts say,

> "One of the root causes of the confusion and delay surrounding the AERS II system from 2003 onward is a lack of effective leadership and management on the part of CDER's Office of Information Technology . . . CDER's culture can be characterized as one in which managers at all organizational levels fail to move from the *awareness* of organizational problems, to the kind of action that will produce positive change."

Please, I urge this committee—*the Board of Directors of the FDA*—to make sure that the agency starts to move to action, and stops wasting precious time and money.

- Within the next 5 years make sure the FDA's computers can use the goldmine of information available from Medicare part A, B and D data to detect what is dangerous and what works;
- Do more to ensure the timely pre-clearance not just of TV ads, but of all advertisements and informationals, including ads on the Internet and at continuing medical education displays. My career is in advertising, and I can tell you that a goal of 30 to 45 days for pre-clearance of TV ads is much too long and will not work for industry. I oppose direct-to-consumer advertising of drugs, but if you are going to do it, do it right, and that means doing it in a timely manner;
- The lying and falsification of data in the Ketek case is outrageous and you hear rumors of similar trial distortions (why is it that so many trials, especially Phase IV postapproval trials come in favorable to the people paying for the trial?). Spend PDUFA safety money to double the number of trials and investigational review board applications audited to ensure the ethical treatment of enrollees, and the integrity of the data;
- Investigate all serious adverse event reports within 15 days; also program FDA computers so they can better detect patterns or clusters of adverse event reports to determine if REMS action should be taken. Clusters of AERs should trigger studies and trials to determine if there is fire where there is so much smoke;
- Spend some money to actively recruit non-conflicted advisory committee members. As others have said, with about 125 medical schools in this Nation, we ought to be able to develop a "library" of experts who are conflict free and willing to serve. Without spending some money to recruit these people, it is too easy for the FDA to complain that they do not exist. As we can find more conflict-free experts, you can amend Title IV of S. 484 to require a gradually rising percentage of conflict-free advisors.
- Spend money to take action (which may include the levying and collection of civil monetary penalties provided by S. 484) against at least 50 percent of the applicants who have failed to complete follow-up safety studies or trials. When the FDA was first reviewing anti-depressants in 1991, it ordered follow-up safety studies that were never done—and are part of the tragedy of Woody's story.

As I indicated above, I oppose direct-to-consumer advertising of drugs, because there are so many side effects and dangerous consequences that we do not know about until a drug has been on the market for years and even decades. To encourage overuse and the medicalization of every problem leads to the death and injury of many who may not really have needed a particular drug. Vioxx is a prime example. *If there is advertising, then the law should require that each ad include a 1-800-number where consumers are advised to report adverse side effects.* Currently, it is very difficult for consumers to use the FDA Web site to search for dangers in drugs. The whole Web site needs to be re-designed to be made easier for the public—starting with the use of the commonly advertised name of drugs. The public does not know the nearly unpronounceable, multi-syllable chemical name of drugs; the simple step of using the advertised name would be a huge improvement.

One other key point: there is nothing in PDUFA or that I can see in S. 484 that addresses the key FDA problem: the internal culture to "approve drugs quickly/consider safety slowly."

We all want life-saving drugs approved quickly, but the FDA is out-of-balance and must give more attention to postapproval safety.

You *can* legislate culture and staff morale, by improving the transparency of the agency and of the approval process.

First, I urge you to strengthen S. 484's Title III: report the results of all trials, within a year of the last trial on the specific drug, whether it is submitted for approval or not. In addition, trials of drugs that are currently on the market should gradually be included so that there is a public library of the scientific trials conducted in the last decade or so.

Dr. Steven Nissen, President of the American College of Cardiology testified before this committee on November 16, 2006:

> When drugs show serious toxicity in patients, the results are rarely published. Accordingly, other companies subsequently expose patients to closely-related drugs without knowing that their competitors' study of a similar agent showed significant harm. *I am aware of a class of drugs where more than a dozen compounds showed serious toxicity, resulting in termination of development, but without a single publication of results* [emphasis added]. In my view, when a patient volunteers to participate in a drug or device study, there is an implicit moral obligation that the patient's participation will benefit medical science. When studies are not published, we learn nothing from the experiment and make the same mistakes over and over again.

In other words, fellow citizens have 12 times been subject to danger as human guinea pigs on a chemical or biologic that was dangerous, had toxic effects, and was a scientific dead end. That is outrageous. If Phase 1 results were made public, then after the first failure, 11 other sets of volunteers—probably over 200 people—would not have been endangered, and the cause of science would have been advanced.

Publishing Phase 1 results can also speed drug discovery at lower cost. I find it ironic—and sad—that the pharmaceutical industry complains about the high cost of research, yet the results of unsuccessful trials that waste millions and endanger volunteers are hidden. The FDA's PDUFA discussion published in the Federal Register of January 16, 2007 says:

> "Our experience and insight, gained through years of review, can help the industry avoid wasting scarce research and development resources on clinical trials that are not likely to produce results because of flawed designs."

True! And imagine how much more would be saved if the world scientific community could see the results of Phase 1 trials. If there is a proprietary secret, the patents surrounding the whole drug process provide some protection. But it is immoral to continue human guinea-piggism in the name of proprietary secrets and without advancing the cause of science.

If you have questions about making Phase 1 results public, I urge you to at least amend S. 484's GAO study about whether to report late Phase 2 trial results, and instead make it a study of whether to report Phase 1 results.

I obviously hope you will amend S. 484 to report all Phase 2 trials. That should be a *given* in the name of science and to facilitate meta-analysis studies of safety and effectiveness.

S. 484 provides for publication of a trial result 2 years after the final completion of the trial. I understand that this is to allow time for publication in peer-reviewed medical journals. But I also understand that the world of medical journal reporting is changing rapidly to be quicker and more electronic, and that some are urging that the great journals concentrate on discussions of the implications of findings from one or more trials, and not be a slow, front-line source of basic trial data. Certainly in cases where the trial or study has raised concerns about aspects of a drug on the market, a way should be found to make that data public for further study by the world scientific community.

Mr. Chairman, Senator Enzi, I particularly appreciate the provision in S. 484 that requires both a technical and a more-laypersons descriptions of the results of clinical trials. A relatively "user friendly" version will empower patients and patient advocates to understand better the drugs that are available and whether they want to "dig into" the more technical explanation.

There is a second major transparency step that Congress should legislate: make the details of all FDA approval decisions public within a month or two of approval, so the world can see what the issues are and what needs more study. By legislating disclosure you *can* instill a climate of scientific openness and dissent so the staff's morale is restored. Those who say that having pro and con data public about a drug will confuse the public and cause drugs not to be used are just saying that we consumers and—even worse—our family physicians are too dumb to understand or too stupid to handle complexity. They obviously have never lost a loved one to a drug reaction. It is an arrogant argument, and it is an insensitive argument—and it certainly doesn't fit with all the talk I hear from Washington about patient empowerment and "shopping" for health care.

I would like to see a separate and independent Office of Drug Safety, as Senator Dodd and Grassley have proposed. It is telling that the current office is called Surveillance and Epidemiology—not exactly a clear message to the general public! The public needs to hear a clear message about this office—a message like you see on construction sites: Safety First! The Commissioner and many others oppose such a separate office, saying it would be a duplicate bureaucracy and slow up approvals.

I would like to offer a solution: Give the head of Drug Safety (currently the head of the Office of Surveillance and Epidemiology) the authority—*and the responsibility*—to say he believes there are enough safety questions about a drug, pre- or post-
approval, that the drug should not be approved, or if approved, that REMS (as established by S. 484) should be adjusted, or that it should be pulled from the market. If the head of the Office of New Drugs disagrees, the two Office heads present their cases to the Commissioner within a date certain, say a week, and he makes a decision within a day. This would not slow down the process, but it would make a career professional physician-scientist *responsible* for standing up for safety when he thinks the facts justify it. Today, there appears to be little or no accountability for the woeful saga of Ketek and other questionable drugs. This process should, of course, be very public, with reports to Congress on the details of when such disagreements have arisen and how they were resolved. In addition, points of contention should be subject to Advisory Committee review and comment by national and international experts.

Under my idea, there would be no separate bureaucracy. No new expense. The two offices would still work together. But there would be accountability. Doesn't that bridge the argument pro and con about a separate Office of Drug Safety?

There is a great deal more I could say. But in conclusion, I think transparency and openness is the key to restoring the FDA as the world's "gold standard" in drug approvals and safety. Dr. David Ross, currently with the NIH, recently left the FDA with, I gather, a great deal of sadness and frustration. He has described the FDA decision-model as very military and one that squelches dissent. Once a decision is made, no more questions! And as he says, that can be necessary on a battlefield. But the FDA is a scientific organization, and the heart of any such organization is open-mindedness, willingness to look at new data, and flexibility. If the culture of the FDA became one of openness, there would be fewer future drug disasters, and I gather it would be a much better place for scientists to work.

Mr. Chairman, Senators, it is said the history of the FDA is written in the tombstones of drug and food safety disasters.

Stop the march of tombstones.

Do what is right for the American public.

Give us a strong, well-funded FDA.

Senator ENZI. Thank you. I know that was difficult. It was well done.

Dr. McClellan.

STATEMENT OF MARK McCLELLAN, M.D., PH.D., AMERICAN ENTERPRISE INSTITUTE

Dr. MCCLELLAN. Senator Enzi, thank you for the opportunity to join the committee today on issues, as you just heard from Ms. Witczak, that are so important to our Nation. Thanks to your bipartisan leadership, this year holds an historic opportunity for strengthening the ability of the FDA to help Americans live longer and better lives through access to safe and effective medicines that keep getting better. And for the first time, we have the opportunity to use new 21st century tools to make transformational improvements in drug safety in the United States.

I want to highlight two key points in making the most of this unique opportunity. First, the FDA will need significantly greater appropriations to improve postmarket safety. The FDA is overstretched and a lack of trained staff and technical capabilities to perform the oversight necessary on thousands of prescription drugs is an even more pressing issue than providing the FDA with new

regulatory authorities. This need has broad support, for example from the Coalition for a Stronger FDA.

As PDUFA and the appropriations process go forward, all of these stakeholders appreciate your support that you reiterated today to give the FDA the resources it needs to do its tough job.

The tight FDA budget and the high cost of medications also highlight the need for finding ways to achieve needed drug safety improvements at a lower overall cost, and that leads to my second point: Building on the elements in your drug safety proposals, it is feasible to implement an active population-based surveillance system for prescription drugs, to identify and follow up on the drug safety problems faster and more effectively than in the past. The core feature of this approach is putting together existing population-based electronic data on prescriptions linked to information on complications, such as hospitalizations for particular diagnoses or deaths.

The data sources include health insurance databases maintained by large private health insurers and by Medicare, some State Medicaid programs, and potentially other government programs. Virtually all of these data with appropriate privacy protections are already being used piece by piece for safety studies, but they have not been put together to answer drug safety questions as quickly and completely as possible.

Over time this infrastructure could be augmented by additional clinical data, such as electronic medical records and computerized information from networks such as the NIH's emerging consortium of academic medical centers that have received clinical translational science awards.

To assure focus on the most pressing public health questions, it could be guided by the FDA, with reliance on the FDA's expert advisory groups, with a process for public input. The analysis of the public-private electronic drug safety data could be performed by expert groups such as the Centers for Education and Research on Therapeutics, the CERTs, and academic medical programs that focus on drug safety and effectiveness issues, such as MIT's Center for Biomedical Innovation.

This electronic drug surveillance system would require some limited additional resources, but it's likely to be less costly overall and it definitely gets us more for the money than what we are doing now. Data like these are increasingly being used, but they are being used separately, incompletely, and inconsistently by health plans, government agencies, and drug manufacturers. With legislative support, a public-private collaboration to use health IT for drug safety would significantly reduce the duplicative and rising costs of case-by-case efforts and one-off risk management plans by drug manufacturers. It could also achieve safety improvements that are not possible through the efforts of individual drug manufacturers, such as understanding whether the risks of a particular drug extend to other drugs in the same class.

Senator Enzi, members of the committee, we know that no drug is or ever will be completely safe. Every drug will have side effects and, while we can do much to improve the science of predicting and avoiding risk, no feasible pre-market testing will enable us to identify and fully understand all of the risks in actual practice.

With your continued leadership, we can give the American public much more confidence that they will not be exposed to preventable risks. The 21st century should be an era of electronic health care, to improve quality and avoid excess health care costs. When it comes to drug safety, we need to do better than just seeing the tip of the iceberg of a safety problem after it has already hit us. We are past the time when our core strategy for postmarket safety should be relying on the hope that overly busy health professionals will file individual reports on adverse events involving drugs. Health IT for drug safety, Senator Enzi, is an idea whose time has come.

Thank you for your leadership.

[The prepared statement of Dr. McClellan follows:]

PREPARED STATEMENT OF MARK MCCLELLAN, M.D., PH.D.

INTRODUCTION

Mr. Chairman, Senator Enzi, and members of the committee, thank you for the opportunity to testify today, as the committee takes steps to improve our current system for monitoring the safety of drugs. This year is a critical year for strengthening the ability of the Food and Drug Administration (FDA) to help Americans live longer and better lives through access to safe and effective medicines that keep getting better.

As you and others have noted, there are opportunities to improve the pre-market process for evaluating the safety of drugs, particularly through new resources that would enable FDA to develop better information tools for evaluating the safety data it receives as well as better scientific tools for evaluating preclinical and clinical safety. But the greatest opportunities for improvement are in the postmarket process. Consequently, I will spend the bulk of my time outlining steps I believe we can use to improve the postmarket process for evaluating drugs after they are approved for marketing.

With the highly-publicized drug safety incidents involving Vioxx (a selective anti-inflammatory drug) and newer antidepressants (selective serotonin re-uptake inhibitors, or SSRIs) in 2004, followed by the Institute of Medicine's recommendations for a range of changes to enhance postmarket drug safety at FDA in 2006, it is clear that our current system of monitoring the safety of marketed drugs can be significantly improved. I want to thank the Chairman and Senator Enzi, and the other members of this committee and the Congress, for your leadership to address this challenge as effectively as possible. Your leadership, in conjunction with hard work by the FDA and new ideas from patient advocacy groups, product developers, and other stakeholders, has created a unique and unprecedented bipartisan opportunity to achieve a fundamentally more effective system for monitoring drug use and aggressively addressing the questions about safety that inevitably arise in the postmarket setting.

Legislation to improve post-market drug safety involves a combination of better information on drug risks, new regulatory authorities, organizational reforms, and additional resources to carry out these new steps effectively. Significant new resources for FDA to support drug safety programs are absolutely essential to this strategy. Now is also the best opportunity we have ever had to move to a 21st century, electronic approach to monitoring and acting on potential drug safety problems, one based on much more complete and timely information than is available to FDA today. In particular, building on the elements to improve safety information in the legislation proposed by Senators Kennedy and Enzi, it is feasible to implement much more active, complete population-based monitoring of adverse events associated with prescription drugs, to identify and follow up on drug safety problems much faster and more effectively than in the past. This system, which would draw on public and private electronic prescription and health information which has not yet been put together in a comprehensive strategy for drug safety, would directly address the delays in developing and addressing safety "signals" that have resulted in delays in resolving drug safety problems like Vioxx. While this public-private collaborative system would require limited additional resources, it would significantly reduce the duplicative and rising costs of case-by-case efforts by drug manufacturers and health plans to address safety issues—efforts that are also incomplete and inconsistent. It could also achieve safety improvements that are not possible through

imposing more regulatory requirements on drug manufacturers or making organizational changes at the FDA.

KEY QUESTIONS AND OBJECTIVES FOR IMPROVING THE DRUG SAFETY SYSTEM

With this unique opportunity to make fundamental enhancements in drug safety, it's important to keep asking some key questions as we consider possible solutions.

First, **will the proposed steps have the greatest impact on reducing the likelihood of another Vioxx or SSRI-type event?**

In evaluating approaches to enhance drug safety, there are at least three main areas to consider. None of these alone are sufficient to achieve success, but if all are addressed together, the result can be fundamental improvements in our postmarket monitoring system:

• *Regulatory authority:* Pending legislation and the IOM recommendations appropriately recognize the need to review and consider updating FDA's regulatory authority to require drug manufacturers to take appropriate and effective steps to mitigate risks associated with marketed drugs. FDA's current selective application of RiskMAP tools is a necessary component of postmarket monitoring, for drugs that present special issues that cannot be addressed through standard labeling and communication. Given the limited resources available to the agency to oversee these authorities, and the already high costs of our health care system, a key principle at FDA is efficient regulation: achieving the regulatory goal of addressing safety risks without imposing excess costs or unnecessary burdens. In addition, the elements described below—sufficient resources and better information—can help achieve the intended goal of a new authority more effectively and with less burden.

• *Resources and technical capabilities:* FDA needs the manpower, technical skills, and technical support to carry out their increasingly complex oversight requirements effectively. Inadequate resources even for existing FDA activities, let alone enhanced drug safety activities, is now widely regarded as a significant problem. As I will discuss, in addition to providing more resources to FDA—and a relatively small amount of additional funding, properly spent, can go a long way—there are significant opportunities for public-private collaborations with expert academic groups to augment FDA's capabilities on drug safety.

• *Good Information:* Regulatory decisions, like other policy decisions, can only be as good as the information on which they are based. Too often, we have faced important questions about drug safety that have major consequences—whether a drug should be on the market, and which patients should use it—without information that is nearly as good as it could be and should be. Today, as prescription drug information is increasingly electronic, there are growing opportunities to use more data more effectively for postmarket safety.

Second, **will the proposed steps achieve the maximum improvement in safety at the lowest cost?** Of course, no one wants to put a price on health. But we have consistently imposed very tight budgets on the FDA, and many people are also concerned about the impact of regulatory burdens that may increase the time and cost of making lifesaving drugs available to the patients who need them. Consequently, in making policy decisions about drug safety, it's important to ask whether a particular safety goal is being achieved at the lowest feasible cost to taxpayers, and to the consumers and patients who will ultimately be using the drugs. By considering all the tools available to improve safety—new regulatory authority for the FDA, as well as new resources and better information—we can achieve major improvements in postmarket safety while minimizing additional costs and difficulties in access to valuable medications.

I want to be clear that additional resources will be required to provide adequate support for postmarket monitoring. But if designed carefully, an enhanced post-market safety system can make tight budget dollars go much further toward achieving the goal of maximizing benefits from medications and avoiding inappropriate drug use, and may lead to significant cost savings from addressing safety questions more completely and efficiently.

To be maximally effective, the improved drug safety system would:

• Recognize, based on pre-market testing and other biomedical knowledge, potential areas of risk for drugs, particularly new drugs coming on the market, to help avoid safety problems in the first place and focus postmarket monitoring on identifying true safety signals rather than random associations.

• Identify safety "signals"—whether potential risks are actually observed—much more quickly and reliably.

• Permit significantly better and more timely monitoring of how drugs are used in practice.

• Enable post-market clinical trials and other costly, sophisticated clinical studies to be focused more quickly and effectively on instances where a safety signal is real, but whether a drug has caused the signal cannot be determined from monitoring drug use and patient outcomes alone.

Finally, because the 21st century should be an era of electronic health care to improve quality and avoid excess health care costs, an ideal safety system should be based on and should foster effective health information technology (IT). We are past the time when our core strategy for postmarket safety should be relying on the hope that overly busy health professionals will file individual reports on adverse events involving drugs. "Health IT for drug safety," and catalyzing the movement to electronic data systems more broadly, is an idea whose time has come.

It is possible, by building on the steps in pending legislation, to make major progress toward this fundamentally enhanced drug safety system this year. In the next sections, I describe how both the current system and proposed administrative and legislative changes can help get there, and some specific, feasible ways to build on these steps to make sure we get the most out of the unique opportunity we face today.

CURRENT DRUG SAFETY SYSTEM AND PROPOSED IMPROVEMENTS

While most of my testimony addresses postmarket issues, I would like to commend the committee for seeking to make some important enhancements in the premarket setting to avoid drug safety problems later. In particular, while there isn't and won't be any completely safe drug, improving the science of pre-market evaluation of drugs can help reduce the risk that patients will have serious adverse events without delaying or reducing access to needed cures. Improving the science of drug safety includes such steps as supporting the development of better preclinical and clinical techniques for predicting whether a drug will cause serious risks such as liver and cardiac toxicity. These drug side effects often complicate and add to the costs of drug development programs. It also includes the development of new clinical trial designs such as adaptive approaches that can surface more information more efficiently about the safety and effectiveness of drugs. New technologies such as pharmacogenomics can also help target drugs more effectively to patients, so that they will be more likely to realize benefits and avoid side effects of new drugs. Building on its "Critical Path" initiative, FDA has recently reported on plans outlining these and other scientific improvements, and these steps are reinforced by the proposed legislation. However, I also want to emphasize that these improvements will only be realized if sufficient additional resources accompany the new emphasis on better science for developing drugs. These investments will be well worth it: a more robust scientific base for pre-market drug evaluation will provide a better understanding of potential areas of risk for drugs, and which patients may actually face those risks, particularly for new drugs coming on the market. It will help focus our postmarket monitoring on identifying true safety signals rather than random associations.

Even with these and other proposed pre-market reforms, there will inevitably be unresolved questions related to the safety of every drug that comes on the market. This is because no feasible amount of premarket testing in clinical studies can evaluate all real-world conditions of use—patients with multiple comorbidities, varying practice settings, possible use in off-label clinical indications, and the like. These real-world circumstances may affect both the benefits and risks of treatment, and with the growing potential of genomics and other steps toward personalized medicine, there will likely be more and more to learn in the postmarket setting about how drugs can be used most effectively in particular patients. Because it is not possible to replicate all of these settings and surface all of these real-world issues in pre-market testing, it is very important to have reliable and effective ways of learning more about the safety and effectiveness after drugs start to be used in clinical practice. Creating a true "life cycle" strategy for maximizing drug benefits and minimizing risks is a key challenge for the Nation's public health, and deserves the careful and deliberate consideration of this committee.

Right now, our postmarket surveillance is largely dependent on FDA's Adverse Event Reporting System (AERS) as well as limited use of existing electronic health databases. While these tools are important, it is feasible to achieve fundamentally better post-market safety monitoring, by building on some recent developments in electronic records of prescriptions, medical services, and patient outcomes.

FDA is currently working on an improved AERS system, AERS II, which will make it easier to collect reports from clinicians and enable better tools for evaluating this information once it is received by FDA, so that the most important safety signals can be surfaced more quickly. Pending legislation could also strengthen

FDA's authorities to compel drug manufacturers to take potentially costly further steps to support the collection of such data on their drugs. However, even with these enhancements, the potential to detect safety problems much earlier and more reliably will continue to be missed. AERS, with the required event reports from manufacturers that make up most of its data, is not routine and automatic. Rather, it depends on busy health care providers filing reports on a case-by-case basis, and then often requires further followup to obtain reasonably complete medical histories and utilization details. Only a small fraction of adverse events are captured with such a system, and they are not captured consistently.

Consequently, with regard to preventing future incidents like Vioxx and the SSRIs, if we remain unable to identify most adverse events in a consistent and timely way, it may still take years longer than necessary to confirm whether potential safety "signals" are real. Further, important issues such as whether the safety concerns are specific to an individual drug, versus broader drug class effects (e.g., is the enhanced cardiovascular risk with prolonged use also present in other cox-2 inhibitors, or perhaps in an even broader range of nonsteroidal anti-inflammatory drugs?) cannot be reliably studied using "one-off" event reporting on particular drugs. To solve these problems, we need a more comprehensive and routine system for identifying adverse events, not a system primarily dependent on case-by-case reporting requirements for individual drug manufacturers.

FDA has long recognized these limitations, and has taken steps to build a more active system for drug safety surveillance, similar to the systems that are in place when it comes to medical devices through FDA's MedSun initiative or for vaccines through the Vaccine Adverse Event Reporting System. In fact, FDA has purchased or obtained electronic data on prescription use, medical utilization, and complications for certain populations—health plan data, or Medicare Part B data linked to hospital use and other complications—to help evaluate certain individual drug safety questions. The recent PDUFA IV draft agreement provides some additional funding and staff to support this analysis, and pending legislation also supports the use of such electronic databases. Further, in its recent administrative actions, FDA has proposed some additional enhancements to its ability to obtain and analyze electronic population databases. Recently, FDA has also sought broad public comment and expert input to design a "Sentinel Network" that would begin to link each of these individual databases and authorities together—the makings of a true, systematic approach to identifying safety signals in a broad part of the U.S. patient population. However, current legislative authority and budget authority does not provide as much momentum as it could for achieving this system. Without such steps, it is unlikely that our drug safety system will have the data, resources, and analytic capabilities to minimize the risk of future post-market safety problems. At the same time, proposed legislation holds the potential to achieve fundamental improvements in post-market drug safety.

ESTABLISHING A ROUTINE ELECTRONIC SYSTEM FOR RELIABLE POST-MARKET DRUG SAFETY

In 2007, it is feasible to achieve fundamentally better post-market safety monitoring, by building on existing initiatives and proposals combined with recent developments in electronic tracking of medication use and patient results. This updated system would have:

1. Faster, More Reliable Detection of Potential Safety Problems ("Signal Detection") Using Better Data and Technical Support

The core feature of this approach is the creation of a public-private infrastructure to draw together relevant population-based, electronic data on prescriptions linked to information related to patient complications, such as hospitalizations for particular diagnoses or death. The data sources include insurance claims databases maintained by large private health insurers and by Medicare, some State Medicaid programs, and potentially other government programs including the VA. Virtually all of these data, with full patient privacy protections (e.g., full compliance with HIPAA requirements and other steps to assure confidentiality), are already being used for particular safety studies. But there is not yet an established system for reliably putting the power of these data sources together to answer drug safety questions as quickly and completely as possible. This infrastructure could potentially be augmented by additional clinical data sources as they become available, such as electronic medical records and computerized data from research networks such as NIH's emerging consortium of academic medical centers that have received Clinical Translational Science Awards (CTSAs).

While public and private stakeholders have already taken many steps to make this network a reality, recognition of the central value of this approach and limited new resource support through legislation would create the momementum to bring this surveillance or sentinel network for drug safety together now. For example, legislation could note that safety questions could be addressed through such a network, where it could provide more complete and efficient answers than RiskMAP requirements for a drug manufacturer, who would not have the capacity to develop this kind of comprehensive data.

To assure that the network's efforts focus on the most pressing safety questions from a public health standpoint, it could be guided by the FDA with reliance on the FDA's expert advisory groups. For example, in conjunction with a process for public input such as an advisory committee meeting or a public posting for comment, the FDA could identify the top safety questions to be answered using the data in the network, and outline the methods that would be used in the data analysis. These top questions would include adverse events that are suspected (but not proven) for new drugs as well as for existing drugs and drug classes, and severe, idiosyncratic adverse events (e.g., aplastic anemia, liver failure). FDA oversight of this process is appropriate and necessary, because FDA is charged with using all available information to reach appropriate conclusions about drug safety and effectiveness for purposes of labeling and marketing in the United States.

While FDA oversight of this process is necessary, carrying out the analyses of these data will require the ongoing participation of additional academic experts, even if additional resources enable the FDA to make needed enhancements in its statistical and epidemiologic capabilities. Interpreting observational data to identify safety "signals"—whether there is a significant and meaningful association between use of a drug and an important adverse event—is generally not straightforward. Fortunately, many groups with relevant expertise are available and are already working on these kinds of safety questions. These include: the Centers for Education and Research on Therapeutics (CERTs) which, with funding from the Agency for Healthcare Research and Quality (AHRQ), already conduct analyses using these data to address key issues on the effects of treatments, including questions of interest to FDA; academic programs that focus on drug safety and effectiveness issues, such as MIT's Center for Biomedical Innovation, and on learning more about treatment effects in routine clinical practice, such as Duke Medical Center's community-based clinical networks; and many other experts in the public and private sectors. Expert groups like these can form the backbone of an ongoing infrastructure for routinely answering priority safety questions using electronic population data quickly and effectively.

The reports from these analyses, using much larger population-based electronic data, have the potential to identify much more quickly whether there is a significant association between use of a drug and an adverse event. For example, according to calculations by Richard Platt (Principal Investigator of the HMO Research Network CERT), electronic and other data actually used to determine a significant association between Vioxx use and serious cardiovascular events took almost 3 years to detect a statistically significant association, based on the limited population data available for analysis at the time. If data from large health plans could have been pooled to provide more definitive evidence on this potential safety risk, as envisioned in this strategy, the significant association could potentially have been detected within just several months, enabling much faster action to address the safety problem. Moreover, if the safety monitoring infrastructure enables needed data to be put together for analysis more quickly when needed for priority safety questions, the "lag time" in obtaining the data needed could also be reduced compared to the situation today, when such data must be assembled on a "one-off" basis. This would provide additional speed in resolving possible safety questions, as well as lower costs compared to "one-off" studies by particular drug manufacturers or health plans that are less complete and consistent.

It is important to note that a significant association between use of a drug and an adverse event does not necessarily mean that the drug has caused the adverse event. Such associations may occur by chance, or because the patients actually taking a drug differ in ways that are important but hard to measure, compared to other patients who are not taking the drug. For example, patients in poorer health may be more likely to be treated with a drug, and also be more likely to have subsequent cardiovascular problems because of their health status not because of the drug. Consequently, until statistical methods can be enhanced, the more complete data developed as part of this drug safety infrastructure are generally not suitable for simply "fishing" for statistically significant associations between drugs and adverse events. Rather, as noted above, this system will be most useful for monitoring rare, serious adverse events that generally should not occur, and following up on questions where

a suspicion of a safety problem has already been raised but has not been resolved. Other sources of evidence, such as suspected signals based on pre-market clinical and biological data, can provide the needed guidance for this system. For example, pre-market and peri-market clinical evidence of a potential elevated risk of cardiovascular events with prolonged use of Vioxx suggested the possibility of a safety signal; with that clinical foundation, determining quickly whether a significant association does exist is important supportive evidence. In many cases, however, further clinical evaluation will be necessary to understand the implications of a clear "safety signal," as described below.

2. More Complete Monitoring of Patterns of Drug Use

In addition to providing much faster and more reliable evidence on the association between drug use and important adverse events, this drug surveillance network would also provide much better insights into how drugs are being used and how use is changing over time. For example, many new drugs over time may be used in indications other than those for which they were initially approved by the FDA. These "off-label" uses can provide important clinical benefits for many patients; at the same time, the quality of the evidence on their safety and effectiveness may be more limited than for approved indications. The same data used to provide much better evidence on potential safety problems can also provide a more complete picture on which types of patients are being treated, subject to the limitations on clinical detail in existing electronic databases. For example, even when new drugs are clearly beneficial for their approved indications, patients who are elderly, have multiple comorbid diseases, are taking other prescription medications, or are from racial or ethnic minority groups who are often underrepresented or cannot be represented in sample sizes large enough in pre-market clinical studies to determine if significant differences in risks or benefits exist for them.

The large populations incorporated in this surveillance network would permit more insights into how drugs are being used in different types of patients, and may highlight areas where risks or benefits may be greater, or where significant use is occurring and risks and benefits are unclear. This tracking of actual prescription drug use is, once again, likely to involve much more population data than are generally available to a drug manufacturer about which patients are actually using the drug, and so can provide insights about how drugs are being used that are not possible through a manufacturer RiskMAP.

3. Determination of Causal Relationships Through Better-Targeted Followup Studies

In many cases, establishing a statistically significant relationship between drug use and an adverse event may not be sufficient to determine that the drug caused the adverse event, even in light of prior evidence. Clinical trials in which patients are randomized to different treatments, or other sophisticated clinical studies, may be needed to provide definitive evidence. For example, a drug may have a significant association with an adverse event, but it may be due to the characteristics of the patients using the drug not the drug itself. In these cases, the enhanced drug surveillance described here will not settle the safety issue, but it can be very useful in identifying the most important questions for further clinical study and the most effective research methods for resolving the questions. Quickly identifying significant rates of adverse events, and better characterizing which patients are actually using the drug and experiencing the events, can guide the further clinical-epidemiologic studies and post-market clinical trials needed to reach a definitive conclusion. Because these clinical studies will be guided by much better evidence on drug use and adverse events, they can be designed and implemented more quickly and efficiently. Such trials can be very costly and time-consuming, and so targeting them effectively is an important public health goal.

Further, establishing the surveillance network to bring together FDA staff, academic investigators and other clinical experts, and much better postmarket data will itself lead to better post-market clinical studies. For example, the network could facilitate working with health plans to set up such studies, and could reduce the scope and cost of further data collection and analysis as part of the studies. It will also facilitate the development and validation of improved statistical methods for reaching conclusions using these improved data.

Because the building blocks for all three of these key steps toward an ideal postmarket safety system are already in place, it is feasible to implement this health IT-based system now. Private health plan data are already being used plan by plan for these purposes; some Medicaid programs already participate in safety studies; Medicare Part A and B data have also been used; and Medicare proposed using Part D data for such purposes last fall. Moreover, the resources required would also be relatively limited, and in any case it is less costly to build a post-market safety in-

frastructure that can be used routinely and quickly than to try to re-create it (less comprehensively) on a "one-off" basis through drug by drug RiskMAPs.

This approach is not intended to replace current adverse event reporting systems or planned improvements in those systems. But the key question is where the new postmarket requirements and efforts in the pending drug safety legislation should be focused. A relatively modest investment in an infrastructure including available electronic population data related to drug use and adverse events, plus a capacity for routine and transparent analysis of these data, would lead to a much more comprehensive capacity for identifying safety signals and acting on them effectively than we have today. It's time to move from a drug by drug approach to a systematic, routine, population approach to promoting drug safety in the United States.

This is also the best path for the future—a future that should include much more extensive use of electronic, interoperable, real-time clinical data systems for active safety surveillance. Indeed, not only is this approach a big step forward based on using electronic data today, but it provides a much stronger foundation into which more sophisticated data from electronic medical record systems can be added. Over time, the speed, clinical sophistication, and analytic sophistication of the postmarket network will continue to increase, with continuing benefits for the safety and effectiveness of drugs.

CONCLUSION

Chairman Kennedy, Senator Enzi, and members of the committee, your leadership has created the opportunity to make fundamental progress on enhancing drug safety and the effective use of drugs in the United States. As part of this effort, it is possible to learn more about the risks and benefits of drugs before they come to market, and to do a fundamentally better job of addressing the safety issues that will inevitably arise when drugs are on the market. This will require some new investments in drug safety, but most of all, it will involve a shared commitment between the public and private sector to build systems and collaborations that can surface and resolve drug safety questions as quickly as possible. With all of the advances that we are making in the more effective use of IT in healthcare, we should aim for nothing less than world class data for evaluating drugs through their life cycle. And we should not wait, so that better information on drug risks and benefits can enable the FDA, health care providers, and patients can get the most out of prescription drugs, and so that we make the most of this unique opportunity to prevent or mitigate future drug safety problems.

Senator ENZI. Thank you.

Dr. Burlington.

STATEMENT OF D. BRUCE BURLINGTON, M.D., EXECUTIVE VICE PRESIDENT, QUALITY, REGULATORY AND SAFETY, WYETH PHARMACEUTICALS

Dr. BURLINGTON. Senator Enzi, thank you very much for the opportunity to testify at this important hearing. I am the Executive Vice President of Business Practices and Compliance at Wyeth. Before joining Wyeth I worked for 17 years at the Food and Drug Administration in the Centers for Biologics, the Center for Drugs, and then the Center for Medical Devices. Last year I led the team from the Pharmaceutical Research and Manufacturers of America as we worked with the FDA on their proposed recommendations for reauthorization of the prescription drug user fee program.

I'm here today to urge Congress to adopt the FDA's recommendations and promptly reauthorize PDUFA. It's critical that Congress renew this PDUFA before the current law sunsets because by doing so it will ensure patients continue to have timely access to important and sometimes lifesaving new medicines.

By any measure, PDUFA has been a resounding success. Before Congress passed the first user fee act in 1992, regulators in foreign countries reviewed applications for new pharmaceutical products far before FDA. As a result, we had what we called the drug lag. Great Britain led the United States in the number of first introduc-

tions of new medicines by a 3 to 1 margin. Worse yet, patients in the United States waited, sometimes for 2, up to 5 years, after patients in other countries were already being treated with valuable new medicines.

The first three PDUFA laws helped the FDA fix this unacceptable state of affairs. PDUFA ensured that FDA had more staff and this led to substantial reductions in the time it took FDA to review and, when FDA decided it was appropriate, to approve new medicines for marketing. Perhaps the greatest evidence for the success of PDUFA is the increased access to new medicines for patients. According to FDA, between September 1993 and October 2006 the FDA approved more than 1,200 new medicines. They included many important advances for the treatment of cancer, cardiovascular diseases, renal disease, metabolic and endocrine disorders.

Congress was wise to require that PDUFA be reauthorized every 5 years. Each successive PDUFA agreement has allowed Congress and the FDA to address new needs and issues in the approval process. That is certainly true with respect to the current proposal.

Indeed, FDA's recommendations PDUFA IV contain several groundbreaking innovations which will further advance patient interests and drug safety. First, PDUFA would increase the annual user fee collections by some $87 million over those for the current year.

Second, $150 million over the 5 years of this new funding will be dedicated to further assuring the safety of medicines after they are on the market. This will allow FDA to hire 82 more employees specifically to work on postmarket surveillance and safety. It will permit the FDA to identify risks more quickly and accurately using modern techniques and tools, such as enhanced use of epidemiology studies and review of large medical databases.

Third, FDA will also be able to undertake research to identify which risk management and risk communication tools are the most effective. And FDA will run a pilot to test a major renovation of how they review proprietary names of medicines before they are used, so that we can reduce the potential for medication errors arising from drug name confusion.

Fourth, the FDA has proposed a new set of user fees exclusively for the review of direct-to-consumer television ads. The agency will hire 27 additional employees to oversee drug promotional activities. They will review ads in a thorough and timely manner before they are run. This will benefit patients by permitting the free flow of important medical information that is accurate, balanced, and useful.

Finally, the recommendations will advance the FDA's critical path initiative. The FDA will develop draft guidance in areas related to safety assessment, clinical trial design and the use of biomarkers. This will hopefully lead to new ways to develop drugs for critical diseases such as Alzheimer's, on which my company Wyeth is hard at work.

The proposed recommendations for PDUFA IV will materially improve the agency's review processes. More importantly, they embody critical new approaches for ensuring the safety of medicines throughout their life cycle.

We understand that the PDUFA reauthorization may become a vehicle for considering drug safety legislation such as S. 484, Enhancing Drug Safety and Innovation Act, introduced by the ranking member and Chairman Kennedy. Wyeth believes that S. 484 is a thoughtful effort to maintain the important balance of safety and providing patients access to new therapies. The REM system which we have heard described would bring the FDA closer to the risk management approach taken by the European Union. This is a desirable goal.

But risk mitigation elements in REMS may have far-reaching impact on the availability and use in medicines. So it is important that decisions on them should be approved only at the highest levels of the agency. Having said that, a statutory construct that is somewhat less prescriptive would be preferable. It would be better to have the law lay out principles and create a framework. This would guide FDA in developing specific criteria and processes by which they would apply risk mitigation tools. These should be put in place through rulemaking.

Under such a system, the FDA would have flexibility to vary risk management for medicines with different levels of risk and it would let them more easily adapt to new techniques for post-marketing risk evaluation as our knowledge evolves.

In conclusion, we urge Congress to reauthorize the Prescription Drug User Fee Act in a timely manner this year. In the interest of patients, the FDA, and drug safety, we can demand no less.

[The prepared statement of Dr. Burlington follows:]

PREPARED STATEMENT OF D. BRUCE BURLINGTON, M.D.

Thank you, Mr. Chairman and members of the committee. I bring to the hearing today a broad perspective on the Prescription Drug User Fee Act (PDUFA). Prior to joining Wyeth I spent more than 17 years at the Food and Drug Administration (FDA) where I had responsibilities in the Biologics and Drug Centers. I was the Acting Deputy Center Director for Medical Affairs when PDUFA was enacted in 1992. I finished my career at FDA by serving for 6 years as the Director of the Medical Device and Radiological Health Center during the period when Congress enacted the Food and Drug Modernization Act (FDAMA).

At Wyeth, I serve as the Executive Vice President for Business Practices and Compliance. I have had overall responsibility for regulatory submissions to the FDA, including New Drug Applications (NDAs) and Biologic License Applications (BLAs). I also was responsible for manufacturing quality assurance, drug safety and FDA compliance.

Wyeth is a member of the Pharmaceutical Research and Manufacturers of America (PhRMA), the trade organization which represents the research-based pharmaceutical and biotechnology industries. During the past year, I served as Chairperson of PhRMA's PDUFA reauthorization team, which met with FDA representatives to develop improvements to PDUFA. The outcome of those 9 months of intense discussions, the FDA's PDUFA IV proposal, will be the principle focus of my testimony today. I will also comment on drug safety proposals currently before Congress.

Reauthorization of PDUFA is one of the most important legislative issues facing Congress this year. By virtually any measure, PDUFA has been a resounding success. Since its enactment in 1992, PDUFA has delivered tangible and important benefits to patients, the FDA, and the pharmaceutical industry. PDUFA provides the FDA with critical additional resources to conduct rigorous reviews of new drug applications. As a direct result of PDUFA, important new medicines are now available to patients much more quickly.

In 1997, Congress built upon the early success of PDUFA when it adopted PDUFA II by passing FDAMA. PDUFA II further increased FDA's resources and provided improved interactions during the drug development process, which enhanced the drug approval process. In 2002, PDUFA III addressed FDA's need for a sound financial footing and provided additional resources for drug safety initiatives. PDUFA II and III also directed funding toward information technology so that

the FDA, industry, and, most importantly, patients could realize the significant efficiencies of electronic regulatory submissions.

Congress must continue to build on the success of PDUFA by passing PDUFA IV reauthorization legislation in a timely manner this year.

Throughout the 15 years of PDUFA's existence, the exacting standards by which FDA evaluates New Drug Applications have not been compromised or diluted. Indeed, user fees provide indispensable additional funds to FDA so that it can be more rigorous, and yet expeditious, in discharging its critical function of reviewing safety and effectiveness of potentially life-saving medications.

The level of evidence of safety and effectiveness needed for the approval of a new medication have not been reduced in any way. In fact, the extent of clinical studies and safety information in applications has increased markedly since PDUFA's inception. For instance, instead of assessing the general safety data base to address the chance that a drug might cause changes in heart rhythms, as was done in 1992, the drug industry now routinely submits additional studies of new drugs given at higher doses than therapeutic levels to specifically address this concern. When the FDA studies new applications, the outcome of its review is not affected in any way by PDUFA funding. The decision to approve or disapprove an application is predicated exclusively on the FDA's analysis of the science and the evidentiary data in the application.

Each successive reauthorization of PDUFA has focused on issues critical to the FDA's mission. Enhancements to PDUFA have always been carefully structured to be responsive to the needs of both the agency and the public.

The FDA's PDUFA IV proposal is carefully crafted and contains important new provisions and resources to:

- Enhance and modernize the FDA drug safety program;
- Add a new user-fee program to give FDA additional resources to review and provide advisory opinions on direct-to-consumer (DTC) television advertisements;
- Improve drug development; and
- Provide more stable financing for the program.

There can be no doubt that patients will be well-served by the improvements contained in the PDUFA IV agreement.

The substantial new funding provided to enhance and modernize the FDA drug safety system—nearly $150 million dollars plus additional information technology (IT) support—will continue to assure that FDA's pre- and post-market safety assessment system is the world's best. In addition, the PDUFA IV proposal incorporates many of the recommendations made by the Institute of Medicine in its report on the U.S. drug safety system which it issued last year.

The additional resources under the PDUFA IV agreement for postmarketing surveillance will allow the FDA to augment its reliance on the spontaneous reporting of adverse events through modernized techniques and resources, such as epidemiology studies and large medical databases, to identify risks more quickly and accurately. The FDA will be able to use new IT systems, secure access to electronic health records, employ new algorithms for detecting drug safety signals, and use new approaches to validate drug safety signals. The PDUFA IV agreement provides the funding for these initiatives.

The FDA's PDUFA proposal provides funds to develop guidance on best epidemiology practices that will serve as a base for agency, academia, and industry use. The guidance is intended to serve the public's interest by assuring that studies reporting drug-associated signals of risk do so based on defined scientific standards. It also provides funds necessary to identify which risk management and risk communication tools are effective. Moreover, the drug industry will benefit by having an array of risk management tools that work, simplifying the development of drug-specific risk management plans.

FDA will also conduct research during PDUFA IV to determine the best way to maximize the public health benefit associated with collecting and reporting adverse events. This will lead to a better deployment of drug safety resources.

A key patient safety initiative in PDUFA IV is effectively addressing the potential for medication errors arising from confusion in drug names. The FDA proposal allocates a portion of the user-fee funding to improving the trade name review process. Trade names are reviewed by the FDA to help ensure that new trade names are unlikely to be confused with existing trade names in an effort to reduce possible medication errors. FDA will now have additional resources to review trade names during drug development and provide industry with guidance on "good naming practices."

The FDA's PDUFA proposal also includes a new user fee for direct-to-consumer (DTC) television advertisements. In 2005, PhRMA issued a set of voluntary guiding

principles regarding DTC advertising. In those guiding principles, PhRMA member companies committed to submit all new DTC TV ads to FDA prior to public dissemination to ensure that FDA's suggestions could be addressed before the advertisement is seen widely by the public. The PhRMA principles are working but they will be enhanced by a strong and fully funded FDA drug advertising review program. The proposed new user fee will allow FDA to hire 27 additional employees in the Division of Drug Marketing, Advertising and Communications (DDMAC) and elsewhere to oversee drug promotional activities and to ensure that TV advertisements voluntarily submitted in accordance with the PhRMA principles are reviewed in a thorough and timely manner. This will benefit patients and the public health by permitting the free flow of important medical information that is accurate, balanced and useful.

The PDUFA IV agreement also enables the FDA to fully implement the good review management principles that were developed and piloted during PDUFA III. FDA will communicate to sponsors a timeline for discussing labeling and postmarket commitments in advance of the action date. This will improve the predictability of the drug review process and lead to postmarket studies that are more meaningful and appropriate for the new drug.

Under the agreement, funding is allocated for the purpose of advancing how FDA can expedite drug development under the agency's Critical Path Initiative. This will permit FDA staff to be directly involved in external activities such as partnerships and consortia that generate data and information that will be used to create new paradigms for drug development. FDA has also committed to developing draft guidance in areas related to safety assessment, clinical trial design, and the use of biomarkers. In addition, FDA will participate in workshops and other public meetings to explore new approaches to a structured model for benefit/risk assessment. The results of these interactions will be used to assess whether pilot(s) of such new approaches can be conducted during PDUFA IV.

Finally, it is important that we continue to assure that FDA is appropriately funded through a combination of appropriations and user fees so that the drug review program can address America's public health needs with the development of new medicines. During our discussions with the agency, a considerable amount of time was spent examining the increased workload within FDA, how it is measured, and how an appropriate workload adjuster can be constructed. The increases in funding to the program from the end of PDUFA III together with the new approach to workload adjustment will provide the sound financial footing needed to continue keeping FDA's drug and biological review program strong throughout the PDUFA IV years.

PDUFA is vital to ensuring that FDA has the necessary resources to perform its critical functions of fostering drug development and innovation and protecting the public health. The PDUFA IV proposal will provide FDA with substantial new funding and resources to enhance its oversight over drug safety and DTC advertising while ensuring that the drug review program is as robust and efficient as possible.

S. 484, "ENHANCING DRUG SAFETY AND INNOVATION ACT"

Wyeth believes the Kennedy-Enzi bill presents a thoughtful effort to maintain the important balance of providing safe drugs while not unduly delaying patient access to new therapies. The Risk Evaluation and Mitigation Strategy (REMS) system would bring FDA closer to the risk management approach taken by the European Union, a desirable goal.

To this end, a statutory construct that is somewhat less prescriptive and instead lays out principles and creates a framework to guide FDA in developing specific criteria for applying risk mitigation tools, through regulations, would be a preferable approach. Under such a system, FDA would be afforded the flexibility to develop varied programs for medications with differing levels of risk and to adapt to evolving technologies for post-marketing risk evaluation. Because the bill envisions broad latitude in developing REMS plans that may have far-reaching impact, it is important that these decisions be approved at the highest levels of the agency.

Additionally, the funding mechanism proposed in S. 484 conflicts with the PDUFA agreement so that matter would need to be reconciled before proceeding.

Senator Brown [presiding]. Thank you, Dr. Burlington.

Ms. Dorman, thank you for joining us.

STATEMENT OF DIANE EDQUIST DORMAN, VICE PRESIDENT, PUBLIC POLICY, NATIONAL ORGANIZATION FOR RARE DISORDERS

Ms. DORMAN. Thank you. Senator Enzi and members of the committee. Thank you for this opportunity to testify today regarding the reauthorization of the Prescription Drug User Fee Act and pending legislative proposals to enhance the postmarketing safety of prescription drugs.

The National Organization for Rare Disorders is a leading national nonprofit voluntary health agency dedicated to the identification, treatment, and cure of more than 6,000 known rare diseases that affect an estimated 25 million Americans. We appreciate the committee's continuing interest in our views on user fees, postmarket safety of prescription drugs, and the strength of the FDA. In addition to its own perspective, NORD plays a leadership role in the FDA Alliance as well as the Alliance for Drug Safety and Access. I will reflect some of the views of both during this testimony.

We are all aware that confidence in the FDA's judgments on the safety of a wide range of products has been greatly shaken. Congress needs to provide FDA with more authority, increased appropriations, and more consistent agency oversight. We join others in recommending that Congress enact the PDUFA IV reauthorization in a timely manner. It is necessary and important, but insufficient by itself.

NORD believes strongly that Congress should strengthen FDA's authority to assure postmarket drug safety, secure substantial additional nonuser fee appropriations, and provide consistent oversight to assure that the agency's leadership pursues independence and objectivity in its U.S. scientific and regulatory operations. We also believe that the FDA has secured several important improvements to the existing user fee program, but it has omitted other equally important potential improvements.

Our principal concern with the recommendations is how the program operates in conjunction with the Orphan Drug Act, which has led to the development and approval of more than 300 drugs and biologics for treatment of rare diseases. We do not want small companies deterred from pursuing promising orphan drug opportunities because modest revenues will be further diminished by product and facility user fees. This is a view that Congress has shared from the beginning of the user fee program and resulted in orphan drugs being totally exempt from application user fees.

We are not seeking exemption of all orphan drugs from product and facility user fees. Rather, we have the desire to assure that the purposes of both acts be maximized. We want your help in resolving this in a way that assures the continuing success of the Orphan Drug Act.

A second principal concern is that the $37.5 million in user fee funds dedicated to enhancing postmarket safety is inadequate. A substantially greater investment in additional user fees and appropriations will be needed to contribute to important CDER programs. Furthermore, we are also concerned that the PDUFA IV recommendations only allocate an additional $4 million for strengthening informational technology infrastructure for drug user

fees—for drug reviews. This is wholly inadequate given the sadly outmoded and inefficient computer systems now in place.

Like many public and private stakeholders, NORD has been deeply concerned that the FDA does not have adequate resources. We urge the committee to become activists for FDA funding, not only through PDUFA and other user fee programs, but through greater sustained appropriations.

The FDA Alliance specifically asks Congress to appropriate $2 billion for the FDA in fiscal year 2008, in addition to revenues for user fees. This is the amount needed to restore FDA to its fiscal year 2003 operating level, as well as fund the additional program responsibilities mandated by Congress in subsequent years.

Congress and the FDA must also address the need for sustained leadership that will help the agency shed recent unwanted blemishes. We are encouraged by the Senate's confirmation of Dr. von Eschenbach. He continues to be NORD's friend and a friend of the rare disease community.

Finally, NORD believes strongly that enactment of the Enhancing Drug Safety and Innovation Act is essential to improve the completeness of FDA's statutory authority, address clear deficiencies in agency practice and culture, and better secure public confidence in FDA's ability to protect the public health. The bill builds upon this foundation with essential duties, such as required pharmacovigilance, and additional requirements such as patient registries.

S. 484 also endows FDA with the critically important authorities to require postmarket studies and to compel labeling changes to reflect new safety information when sponsors fail to act in a timely or appropriate manner. I would like to add that NORD does not support efforts of some to establish a separate Center for Drug Safety. This would only serve to fragment the agency further and shrink already inadequate financial resources.

There are enhancements, however, that could strengthen its already important provisions. First, NORD believes that the Fair Access to Clinical Trials Act of 2007 sponsored by Senators Dodd and Grassley offers superior features such as increased civil monetary penalties.

Second, we would like to see postmarketing studies conducted for off-label uses. This is important because most patients with rare diseases and those in the pediatric population are treated off-label. By necessity, orphan drugs and biologics are tested on relatively small numbers of rare disease patients and therefore postmarket surveillance and studies are especially critical for gaining more widespread patient safety information over time.

Third, minor enhancements to the REMS paradigm are possible, such as omitting exceptions for current sponsor-controlled label changes.

Finally most importantly, NORD believes that S. 484 can provide for additional mechanisms to assure patient and provider input in the development of REMS plans.

In conclusion, rare disease patients are no different from most patients in their views and concerns about drug safety. We know safety can never be absolute, which is exactly why patients are so dependent on the thoroughness and competency of FDA's review

process and why FDA needs additional authority to oversee and act during the postmarket period.

Passage of S. 484 is a matter of urgency and one which benefits all stakeholders. Failure to enact it risks a repeat of the uneven and often disastrous safety decisions that have led to drug withdrawals, questionable sponsor practices, and apparent regulatory failures that have so badly eroded public confidence in the FDA.

Thank you.

[The prepared statement of Ms. Dorman follows:]

PREPARED STATEMENT OF DIANE EDQUIST DORMAN

INTRODUCTION

Chairman Kennedy, Senator Enzi, and members of the committee. Thank you for this opportunity to testify today regarding the reauthorization of the Prescription Drug User Fee Act (PDUFA) and pending legislative proposals to enhance the postmarket safety of prescription drugs.

I am Diane Dorman, Vice President for Public Policy of the National Organization for Rare Disorders (NORD). We are a leading national non-profit voluntary health agency dedicated to the identification, treatment and cure of rare diseases. There are more than 6,000 of these disorders, cumulatively affecting an estimated 25 million Americans. NORD has a long successful history working with Congress on the Orphan Drug Act of 1983, PDUFA and other healthcare-related legislation.

For these reasons, we appreciate the committee's continuing interest in our views on user fees, postmarket safety of prescription drugs, and the strength of FDA. In addition to its own perspective, NORD plays a leadership role in the FDA Alliance, as well as the Alliance for Drug Safety and Access (ADSA) and will reflect the views of both during this testimony.

We are all aware that confidence in the FDA's judgments on the safety of a wide range of products—from the food on our dinner tables to bestselling, blockbuster drugs, and the latest, breakthrough biotechnology therapies and medical devices—has been greatly shaken. The problems are systemic, cultural and financial. Congress needs to provide FDA with more authority, increased appropriations, and more consistent agency oversight. FDA, an agency that is hardworking and well meaning, needs to remember that regulated industries are "stakeholders," not customers and that it is the patients and consumers who may live or die and who are most at risk based on the quality and independence of its decisions.

We join others in recommending that Congress enact a PDUFA IV reauthorization in a timely manner well before the current law expires. The reauthorization is necessary and important, but insufficient by itself. NORD believes strongly that Congress has other, equally important tasks to fulfill in an equally timely fashion.

- Strengthen FDA's authorities to assure *post-market drug safety*;
- Secure substantial, additional *nonuser-fee appropriations* to adequately fund FDA; and,
- Provide *consistent oversight* to assure the agency's leadership pursues independence and objectivity in its scientific and regulatory operations.

COMMENTS ON THE PDUFA IV RECOMMENDATIONS, INCLUDING IMPACT ON ORPHAN PRODUCT DEVELOPMENT

Based on our review of the summary of PDUFA IV enhancements and recommendations, NORD believes that the FDA has secured several important improvements to the existing user-fee program. It has omitted other, equally important potential improvements. We would also caution that nothing can be certain about the PDUFA IV recommendations until actual legislative language has been made available to the public and to patients for review.

The PDUFA IV recommendations offer some clear improvements by:

- Allowing FDA to expend user-fee revenues for purposes of post-market risk management and scrutiny of products during the entire duration of their marketing, not restrained by the current limitation of 3 years postapproval;
- Creating dedicated user fees for the review of voluntary direct-to-consumer (DTC) television advertisements; and,
- Funding of guidance development and the revision of inflation and workload "adjusters" to account for actual submissions and the inflation-adjusted calculation of FDA's review costs.

NORD's principal concern with the FDA's PDUFA IV recommendations is how the program operates in conjunction with the Orphan Drug Act (ODA), which has led to the development and approval of more than 300 drugs and biologics for treatment of rare diseases. Since so much orphan drug development is conducted by small, start-up companies, there is an ever-present risk that user fees (or the perceived burden of user fees) present a potential barrier to innovation, research, product development and market entry.

In particular, we do not want small companies deterred from pursuing promising orphan drug opportunities because modest revenues will be further diminished by product and facility user fees. This is a view that Congress has shared from the beginning of the user-fee program and resulted in orphan drugs being totally exempt from application user fees.

The current waiver program administered by FDA for product and facility fees has chosen to interpret gross revenues of $10 million or greater as evidence that an entity and its affiliates are fully capable of developing and marketing orphan drugs without regard to the cost of user fees. We know that FDA believes that a higher threshold than $10 million in corporate gross sales will result in a significant expansion of waived products and a noticeable increase in the fees that would be charged to remaining companies. Nonetheless, this does not conform with any common sense view of what constitutes a small company in the bio-pharmaceutical industry and seems unrealistically low, especially with the higher fees that will be required under PDUFA IV.

We come to this issue with a desire to assure that the purposes of both acts be maximized. We do not seek the exemption of all orphan drugs from product and facility user fees, but neither do we feel confident that product and facility user fees are an inconsequential aspect of the development of orphan drugs for small populations or for which there is otherwise modest revenue potential. We seek Congress' help in resolving this in a way that assures the continued success of the Orphan Drug Act without undercutting the user-fee program.

A second principal concern is that the $37.5 million in user-fee funds dedicated to enhancing postmarket safety are inadequate. By comparison, the Institute of Medicine called for $100 million as a baseline investment in new funds for this purpose. This substantially greater investment in additional user fees and appropriations will be needed to permit the Center for Drug Evaluation and Research (CDER) to:

- Develop, validate, staff, deploy and utilize a wider and "smarter" range of postmarket safety tools and activities;
- Increase staffing in Office of Drug Safety and Office of Surveillance and Epidemiology; and,
- Broaden access to data, employment of new and improved data-mining techniques, and additional epidemiology contracts.

Similarly, we are concerned that the PDUFA IV recommendations only allocate an additional $4 million for strengthening the information technology infrastructure for drug reviews. This is wholly inadequate given the sadly outmoded and inefficient computer systems upon which CDER relies and the absence of resources to dedicate towards developing uniform standards. While improved IT related to drug safety is a purpose for which appropriated funds should also be requested, we are concerned that what FDA has in mind is a mere drop in the bucket towards the goals of enhancing post-market safety surveillance and boosting electronic pre-market submissions. As a point of reference, patient and consumers groups have been informed that roughly half of the agency's outmoded IT systems actually can no longer be serviced by commercial vendors. A large investment is clearly needed if IT is to contribute toward improved drug safety at anytime in the next few years.

NORD believes that other resource-starved and otherwise underemphasized enforcement activities need further support. While fees are levied upon submissions, this does not cover the needed level of activity in areas such as facility inspections and FDA's Bioresearch Monitoring Program (BIMO) inspections. The FDA must shift from reliance upon incomplete, unreliable passive surveillance and the Adverse Event Reporting System (AERS/AERS II) to more directed surveillance and FDA-conducted or mandated observational studies.

INCREASING FDA'S NON-USER FEE APPROPRIATIONS IS CRITICAL TO PROTECTING PUBLIC HEALTH AND ADVANCING INNOVATION

Like many public and private stakeholders, NORD has been deeply concerned that the FDA does not have adequate resources. We participated in the founding of The FDA Alliance, a broad-based, non-partisan coalition of consumers, patients, health care professionals, and industry, and I serve as a board member and the Alli-

ance's Vice President. With more than 100 members, including seven former FDA Commissioners, the FDA Alliance is an advocate for increased appropriated funding for FDA to enable the agency to effectively carry out its dual roles as a leading guardian of consumer health and safety and as an active leader in advancing global scientific and medical innovation.

As the Senate authorizing committee with jurisdiction over the FDA, we urge the committee to become activists for FDA funding—not only through PDUFA and other user-fee programs, but through greater, sustained appropriations. This is essential to the agency's proper functioning as a regulator of food safety, of drug and device safety, and of its critical oversight of the explosive innovation in fields as varied as nanotechnology, molecular diagnostics, pharmacogenomics, and material sciences.

The FDA Alliance specifically asks Congress to appropriate $2 billion for the FDA in fiscal year 2008, in addition to revenue from user fees. By our calculations, this is the amount needed to restore FDA to its fiscal year 2003 operating level, as well as fund the additional program responsibilities mandated by Congress in subsequent years. This would be an increase of $450 million over the fiscal year 2007 Continuing Resolution, a large but also prudent and overdue investment in strengthening the FDA, protecting the public health, and enhancing innovation.

As important as this user-fee reauthorization is, we cannot emphasize enough how dire the FDA's resource situation has become and how badly the agency is in need of an immediate and substantial infusion of additional appropriated dollars. In short, **PDUFA is a necessary and valuable component of FDA's funding, but it is not sufficient in itself and is simply no substitute for increasing FDA appropriations.**

LEADERSHIP IS URGENTLY NEEDED TO RESTORE AGENCY INDEPENDENCE AND CREDIBILITY

Congress and the FDA must also address a third, critical unmet need: sustained leadership that will help the agency shed recent and unwanted blemishes to its "gold standard" reputation for scientific independence and regulatory rigor. NORD has consistently represented to Congress and to the FDA that the agency's success cannot be measured by the speed of its work, but rather the completeness and scientific soundness of its work. I will not belabor the obvious examples of the crises in public confidence suffered lately by the agency, but there is clearly much work to do.

As the Institute of Medicine so forcefully concluded in its September 2006 report, "The Future of Drug Safety":

> "[R]ecent highly-publicized controversies . . . have contributed to a public perception that the drug safety system is in crisis . . . [and q]uestions [have] also surfaced about the independence of the scientific expertise relied on by FDA . . . and about the possibility of undue industry influence related to CDER's increasing dependence on PDUFA funding . . .
>
> . . . Many observe signs of an organizational culture in crisis."

These are views shared widely among patients, media and regulated industry: that only a strong FDA can sustain—or regain—public confidence in the food, drugs and devices it regulates.

We are encouraged by the Senate's confirmation of Dr. von Eschenbach, an accomplished clinical scientist and manager, to be Commissioner. We hope that he will steer the agency back towards a more vigorous and timely enforcement of science-based regulatory policy without concession to ideology or politics. We also recommend that Congress undertake two specific tasks to help assure this takes place:

- First, we believe that more consistent and focused oversight by the committee of the agency's enforcement activities and regulatory policies is needed. We have noted with concern that, over time and certainly since the last PDUFA reauthorization, the agency's responses to congressional requests for information may have become less timely. We consequently encourage the committee to undertake bipartisan oversight of priority FDA operations through the committee's investigative staff, sustained communications with agency scientific managers, and the appropriate use of the General Accountability Office and the HHS Inspector General.
- Second, we recommend that the committee enact revisions to the FDA's statutory mission in the Federal Food, Drug, and Cosmetic Act to reflect and reinforce the importance of scientific independence, integrity and objectivity. While this might be dismissed as a gesture, NORD believes that the Commissioner, political managers and career employees alike do or should take heed of the law and of congressional directives in undertaking their duties. That is why we agree with the IOM's recommendation that Congress change the agency's mission statement to further underscore the importance of science, independence, integrity and objectivity.

ENACTMENT OF S. 484 IS NEEDED TO STRENGTHEN FDA'S AUTHORITIES AND BETTER ASSURE POSTMARKET DRUG

Finally, NORD believes strongly that enactment of S. 484, the Enhancing Drug Safety and Innovation Act of 2007, is essential to improve the completeness of FDA's statutory authority, address clear deficiencies in agency practice and culture, and better secure public confidence in FDA's ability to protect the public health. We believe that the bill closely aligns with the Institute of Medicine's recommendations, and that Congress should do no less than what is proposed in the Enzi-Kennedy bill to address the many drug safety crises and failures that have transpired in the recent past.

A. Key Features and Improvements to Postmarket Safety Through S. 484

Rather than delve into the specific provisions of S. 484, we believe that the committee should bear certain key principles in mind when it considers this legislation in the near future. First, the concept of "risk evaluation and management strategy" is based upon well-established FDA regulations, standards and practice. Minimal elements of the proposed "REMS," such as product labeling and adverse drug reaction reporting, are already in place today for all drugs. But the bill builds upon this foundation with essential duties such as required pharmacovigilance, and also provides FDA flexibility to add more requirements, such as patient registries, when called for by the risk-benefit profile of the given drug product.

Because NORD works globally on orphan drug issues, we also believe the committee should be aware that Europe requires REMS for all drug products in Europe.

We are aware of criticism of the scope and comprehensive reach of the REMS paradigm. But these critics fail or refuse to understand that S. 484 does not require a "one-size-fits-all" application of these safeguards. FDA has historically had great success in applying REMS requirements where the agency has exercised careful scientific judgment about balancing the risks and benefits of their application. First, it is the case that all drug products currently marketed are already held to some or all of the requirements. Second, REMS are particularly useful in challenging cases such as Tysabri, a novel, first-in-class biotechnology therapy for multiple sclerosis, a serious, life threatening disease. FDA's cooperative employment of appropriate "REMS" controls with the drug sponsor has led to the re-introduction of the therapy in the United States after its voluntary market withdrawal.

It is within the REMS paradigm that S. 484 also endows FDA with the critically important authorities to require postmarket studies and to compel labeling changes to reflect new safety information when sponsors fail to act in a timely or appropriate manner. The legislation also creates a publicly accessible registry of clinical trials and clinical trial results. These are vital changes to FDA authority that must be enacted to address past failings, to close loopholes in the law, and to secure patient access to safe and effective drugs and the information needed to use them.

B. Potential Enhancements to S. 484

There are enhancements to S. 484 that NORD believes could strengthen its already important provisions. First, NORD believes that the Dodd-Grassley Fair Access to Clinical Trials (FACT) Act of 2007 offers superior features in the organization and implementation of a clinical trial registry and disclosure database. Second, minor enhancements to the Kennedy-Enzi REMS paradigm are possible, such as omitting exceptions for current sponsor-controlled labeling changes to ensure FDA remains the ultimate arbiter of safety-related drug labeling. And finally and most importantly, NORD believes that S. 484 can provide for additional mechanisms to assure patient and provider input in the development of REMS plans—and the features of future PDUFA reauthorizations.

CONCLUSION

Rare disease patients are no different from most patients in their views and concerns about drug safety. We want innovative medicines as quickly as they can be tested, evaluated, proven, approved, and marketed. We can accept certain risks in new medications, if they are properly considered by FDA, accurately labeled by the sponsor, and correctly prescribed by health care professionals.

Safety can never be absolute, which is exactly why patients are so dependent on the thoroughness and competency of FDA's review process and why FDA needs additional authority to oversee and act during the postmarket period. Patients depend on the industry's skill in innovation and product development, but will necessarily be cautious without the assurance that FDA has thoroughly evaluated the safety and effectiveness of new therapies.

Although I cannot speak for industry, the credibility of FDA's review process should be every bit as important to them. Public confidence in FDA translates into patient and prescriber confidence in FDA-approved therapies. A strong FDA review process increases the value of approved products from both the patient and company perspective.

Seen this way, passage of S. 484 is a matter of urgency and one which benefits all stakeholders. Conversely, failure to enact S. 484 risks a repeat of the uneven and often disastrous safety decisions that have led to drug withdrawals, questionable sponsor practices, and apparent regulatory failures that have so badly eroded public confidence in FDA—and by extension in the safety and effectiveness of drug therapies.

The CHAIRMAN [presiding]. Thank you all very much.

I think all of us here on the committee believe that FDA ought to have greater resources. My friend Senator Hatch is not here. He and I for years and years have fought for additional resources over a long period of time. We ought to be able to get that help on modernizing all of that equipment at FDA, coordination of the various campuses. There's a wide variety of different things when you think about the responsibility that this agency has on health care, and we all bear responsibility that we haven't been able to give it the kind of funding it needs. We can imagine what that agency would be like if we didn't have the PDUFA and MDUFA. So this is something at least and a place where we can start.

We have a short time. There's a number of areas I would like to cover. I wanted to thank all of you for being here.

Dr. McClellan, just as you are a physician as well as a very dedicated public servant, you have looked at the legislation. When you were commissioner, did you feel that you would want some additional legal tools, that would be advantageous and helpful and useful to you in terms of drug safety?

Dr. MCCLELLAN. Mr. Chairman, when I was commissioner I was faced with the same issues that you have been hearing about today. Without adequate resources, it's very hard to do the planning necessary to do appropriate postmarket monitoring. I think the way that this committee is approaching the issue and the way that you are approaching it in your bill, of taking a comprehensive look at all the steps that are needed—information, resources, which are definitely needed, additional statutory authorities, and organizational issues—is the right way to approach this.

This is a once in 10-year opportunity and I truly commend you for taking this comprehensive look on getting all these issues on the table as you are.

I think there's a lot that could be done at the agency with additional resources and information that would make its job easier in terms of these postmarket activities, as I discussed in my testimony.

The CHAIRMAN. To Mr. Burlington, you testified that you thought the Enzi-Kennedy bill strikes a balance between safety and innovation. If you could just focus on that for just a moment. You have heard some of the discussion earlier today from the different sides. Maybe you could just elaborate on that point if you would, please.

Dr. BURLINGTON. Thank you, Mr. Chairman. I think it is important that we continue to make sure that when we look at safety tools that we ensure that there be access for products to patients who need them. We are always trying to get the right balance be-

tween safety information and the benefits. It's critically important that we keep benefits in view as we do so.

The CHAIRMAN. Well, just with regards to this balance, as we have talked about, are you satisfied with that legislation that we have done that? Do you think it's particularly weighted as being too overly burdensome, or do we hit about the zone that you would think that balances safety and innovation on this? Do you have a comment on that?

Dr. BURLINGTON. I do, Mr. Chairman. The legislation as it is drafted provides broad discretion to the Food and Drug Administration, as well as a tool kit, if you will, for mitigation strategies. The threshold for applying any one of those strategies is really quite low, and as a consequence it is very important that these be seriously reviewed, that they be not imposed on drug companies in such a way as to restrict access easily, but in fact should be very substantive determinations made at the most senior levels of the agency.

The CHAIRMAN. Kim, I regret I wasn't here for your testimony. I have a question—some have said that perhaps Congress should not take action on improving the drug safety, that the current system is adequate. Could you just respond to that? I think I saw you earlier during the course of the hearing when there was pretty good exchange by the other members on this issue, and I know you were listening carefully. Maybe you would comment on your own view.

Ms. WITCZAK. Sure, Mr. Chairman. I personally—right now I appreciate the first step on safety, but I don't feel that the current system is adequate in monitoring safety in the postmarket. Obviously, with the history—and the reason I gave the history of the antidepressant is to really show from 1991 and all the internal documents that have come out—I feel there's a lot more that could be done.

I think the ability to give the FDA more technology or to be able to search for postmarket safety data is needed. I would love to have an investigative attitude in regards to postmarket safety, almost like when a plane crashes the NTSB is out there and they are investigating all things. I understand that a lot of times you will hear these are anecdotal stories. But when you start seeing a trend emerge, whether it is the postmarket, the adverse events, I think we need to go out there and actually actively search and find these safety issues.

The CHAIRMAN. Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

I appreciate all of your testimony. I have questions, lots of questions, and I hope you will answer some of them in writing as I'm limited on time.

I will start with Dr. Burlington. I don't believe that user fees are a bad thing, but I am concerned about the ever-growing portion of the drug review program that is funded by user fees. It's been suggested that the appropriations trigger should be changed both to use a different base year and to use a more accurate inflator to change the amount from year to year. That would result in a significant increase in appropriated funds to the agency.

I'm interested in that idea, but I'm not convinced the larger appropriations alone would solve FDA's problems. What do you think?

Dr. BURLINGTON. Thank you, Senator. I believe that it would be preferable for the Food and Drug Administration to be fully and adequately funded out of appropriations. But this is the system we have today. User fees do provide very substantial resources to the agency to undertake their work and augment appropriations.

The concern that FDA is somehow unduly influenced by this I believe was commented on earlier by Commissioner McClellan. When I was at FDA, one didn't think about where the money was coming from. You understood that what your job was was to look at the safety and effectiveness and to try and reach the right balance in any determination you were making.

In terms of the specific question you raised about whether adjusting the trigger would be a mechanism to ensure greater appropriated funds, the way that Congress decides to allocate the available money is something obviously that you and the other members are far more expert in than I could be. I do think it is important that we not set up a mechanism whereby we would back FDA into having to give pink slips to a couple of thousand people currently supported by user fees and that we would then deprive American patients of the staff who are necessary, not only to look at new medicines, but also to continue to review and monitor the safety of those drugs on the market today.

Senator ENZI. Just to be clear on something, in your testimony you indicated that the Kennedy-Enzi bill is in conflict with the PDUFA agreement. I hope you meant that it would change the agreed upon dollar commitment, not that the two proposals are substantively in disagreement. Do I have that right? How much more do you think our bill would cost?

Dr. BURLINGTON. Senator, it is of concern that there is additional work that would undoubtedly fall to the agency under the Kennedy-Enzi bill. Exactly how much this would cost I'm not clear about. I suspect that the agency is much better able to develop a model for how much work that is going to be. But it is clear that there would be first year additional costs and that it is appropriate that there be a mechanism to fund those.

If you can find the appropriated dollars to do it, that would be best. If you can't find the appropriated dollars to do it, then yes, you would need to reconcile the user fee proposal which is in front of you today with the extra work that would be required to implement Kennedy-Enzi.

Senator ENZI. Thank you. I will have some more technical follow up questions on that. I appreciate that.

Dr. McClellan, we have all been working on some health information technology and I think that that information technology will answer a lot of the questions. I hear a lot about the total inadequacy of the FDA's technology infrastructure, which seems to me to be a precondition of getting a drug safety system nationwide. What sort of resources would it take to get the FDA's information technology up to par, up to date?

Dr. MCCLELLAN. Well, Senator, thank you again for your leadership with Senator Kennedy and others on getting to 21st century health IT. It's so important. With respect to the FDA's budget, I

think there are two pieces. One is the overall IT support at the agency. This is everything from doing e-mail to tracking correspondence to everything else besides dealing with adverse events and drug safety issues. The FDA does need substantial resources to modernize their overall IT support, and that's why so many groups from all across the spectrum of perspectives are all unified behind significant increases in resources—$500 million over 5 years, maybe $180 million if possible in this current round, much of which would go to modernizing the overall IT infrastructure at the agency.

With respect to postmarketing monitoring, it's a more contained problem. You need three things. You need adequate systems for the FDA to interact with the outside world in all these data systems that I described in my testimony. You need a system for bringing together all the different pieces that are out there now from health plans, Medicare, and other sources. It's all there. It's just not working together yet. And you need to fund keeping those pieces of data in place and usable for these efforts.

We are already spending a lot of money on those efforts. We are just doing it separately. Medicare is doing some analysis, FDA is buying data sets on a one-off basis. Drug companies, as part of their risk management plans, are doing single one-off analyses. If we put that together, we may even be able to save money in this.

So I think overall for that problem we are talking about low tens of millions of dollars, not an enormous new investment.

Senator ENZI. Thank you.

My time has expired. I will submit some additional questions.

The CHAIRMAN. Senator Brown.

Senator BROWN. Thank you, Senator Kennedy.

Ms. Witczak, thank you very much for coming. I'm sorry, we were on the floor and I didn't get back. But I have read your testimony. I, as you, am opposed to direct-to-consumer advertising. I think that we can do a better job regulating. Senator Coburn said—I'm not a lawyer, nor is he—but that there may be constitutional issues there.

You have suggested in your testimony that you have thought this through about some things we could do if we can't ban it, which I think we should at least have a 2-year ban on it. I don't know if this committee will accept that. But there are some things that we can do to regulate it. One of the things you mentioned which I thought was pretty intriguing is any advertisement has to, as you say, require each ad to include a 1–800 number where consumers are advised to report adverse side effects.

Elaborate on other ideas you might have that, if we are going to allow direct-to-consumer advertising in these huge multi-million, multi-tens of millions of dollars marketing campaigns, how we can perhaps steer them in a little different direction?

Ms. WITCZAK. Thank you for the question. Well, first of all I do think the fact—you know, I'm against DTC advertising. I have spent my entire career in advertising, so I kind of go against what is out there, because I think they should be held to a different standard. But I do believe that it is here to stay, and with that I think there are some things that we can do by requiring that 800 or MEDWATCH as a tag at the end. We have to listen to the side

effects anyway, but it really allows the consumer to actually bring forward their perspective, because we are the real clinical trials. I think a lot of direct-to-consumer advertising actually drives people to their doctor, because of the messages that they are out there promoting, especially like on the antidepressants and even on some of the sleeping medications. I think we are overprescribing. I mean, people are going for every little thing.

Because of that, I think there are some mechanisms that should be put into place. I do think that the idea of putting more moneys toward approving the advertising, I do think that it should be mandatory. Right now it's voluntary that they are going to get their messages approved. I think it should be mandatory.

But I do know that last year one of the companies ran a sleep medication ad during back to school and the FDA just sent out a memo in March telling them to pull it, to pull it, and it ran in September. So I think there needs to be better tracking inside the agency for communications that might be misleading or you want to change.

But I would really like to see that 800 number and bring the consumer into it.

Senator BROWN. Thank you for that.

Dr. McClellan, nice to see you again. I want to talk to you and shift for a moment if I could, Mr. Chairman, to another safety issue that's not really related to this bill, although I would like it to be, and that is the whole issue of antibiotic resistance. You and I have talked about that in the past in your position at the FDA. I think perhaps this bill can take that issue more seriously and including it in this bill—if I could pick your brain about any ideas you have. Maybe with better data collection, maybe with shifting the burden of proof to the industry.

If, for instance, a drug is approved for prophylactic use in an animal, an antibiotic, then the burden, I believe, is on the government to show that that could have an impact in creating or building antibiotic resistance in the human population. Talk that through with me. It's an increasingly serious problem with hospital infections, with what happens with this new XDR TB, this extremely multidrug-resistant TB that's beginning to kill people in pretty large numbers in the developing world and is as infectious as other forms of TB and is much, much, much more deadly. And we are not doing well enough with getting enough antibiotics in the pipeline. We know all that.

What can we do to preserve the safety of antibiotics by using the FDA, with data collection, with perhaps shifting that burden of proof to the industry rather than to the government to show what it might mean on the human population?

Dr. MCCLELLAN. A couple of things. In terms of the impact of animal drug use on human antibiotic resistance, which I think is the main point here, that is an issue that has been negotiated out by the FDA recently with industry, and I think those negotiations and the guidances that result from them are continuously subject to revision. So if there are better ways to do it, I think the FDA would be open to hearing about it, and I think you may not even need legislation to make sure that those most recent and up-to-date safety concerns are being addressed.

With respect to this legislation that's pending right now, taking a step back to this broader problem that we have, of not enough new antibiotics in the pipeline to give us confidence in the future that we will be able to treat very resistant organisms, which is the main point. I think having a better surveillance system on how drugs are actually being used in people would be very helpful.

The detection of safety problems more accurately and more quickly is a very important goal for using this network of databases that I described. But the same network can also help us get a better understanding of how antibiotics are actually being used in practice, what kinds of clinical indications are being treated using what specific medications. Well, if we can get a better handle on that, then good information puts you on the path to influencing how drugs are being used appropriately.

Something else that came up earlier in this hearing as well. Getting the health plans and these other groups to get information out about appropriate use. Health plans, as you know, can have a big impact. Medicare, private health plans, can have a big impact on which drugs are used and how. Bringing the FDA together more closely with these other parts of our health care system to promote better use of medication, getting the most for our money in drugs, including antibiotics, I think would be a very important side benefit of the kind of legislation that's being worked on here.

Senator BROWN. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Senator Burr.

Senator BURR. Thank you, Mr. Chairman.

Kim, I want to thank you for excellent testimony. We are all saddened at your loss. Your statement that the current system is deficient, I agree with totally. I think that you raise some good issues with the 800 number, with the recruitment process for advisory boards, and I would tell you we can't stop with the 800 number. It needs to be electronic means to contact as well, and I hope that we can do that. But I do thank you for your willingness to come.

Dr. McClellan, it's good to see you. If I can, I would like to shift because I have believed since 1997 when we did FDAMA, and when you were at the FDA I expressed this to you, that our real focus was that we needed a real surveillance program, one that looked at trends, one that did exactly what Kim said: When you identify something that looks like a problem, it sends you like a laser beam to figure out, are there more people that are experiencing this? Is this something that we didn't intend and that we didn't pick up in the original clinical trials?

We do a poor job of doing that. We have the ability today. We capture 99 percent of the scripts that were written yesterday, we capture today. We know exactly who took them. That's followed up in some way, shape or form with potentially an insurance claim that might detect an adverse reaction to that, probably processed within the same company or grouping of companies.

Why can't we tap into that? Why can't we process it? I realize that not every doctor's office is necessarily putting everything electronically. But the claim, the claim for insurance purposes, is. And it gives us a tremendous tool, whether it's Quintiles or any of the other companies. Is that feasible to do?

Dr. MCCLELLAN. Senator, I think it is. It is important you brought up FDAMA in 1997 because that was the last time we took a close look as a nation at what needed to happen fundamentally at the FDA to improve the safe and effective use of medications, to get them to patients fast, but, as Senator Kennedy highlighted as well, to make sure that we are avoiding safety problems wherever possible.

Back then, you couldn't do the kinds of things that you were just talking about now. Nice idea to have a surveillance mechanism in place, but we didn't have the same level of 99 percent electronic transactions involving prescriptions and all of the databases that are actually being used now piece by piece on a one-off basis to do exactly what you are saying.

What hasn't happened yet is putting it together in a national strategy for an infrastructure that on a routine and ongoing basis could conduct active surveillance and follow up on these issues. Now, I don't want to overstate this because just because you have got the data doesn't mean you can solve every safety problem. A lot of times you will see an association between a drug and an adverse event and it won't be the drug that caused the adverse event; it will be other factors, characteristics of the patient, other things.

But if you combine this kind of active surveillance system with good information that we have about drugs going to market, the areas where we want to look at potential risks, the kinds of things that Ms. Witczak highlighted, that for a long time nobody was able to put together real effectively, too long of a time, then you have a pretty good foundation for doing a much better job for preventing safety problems. And on top of that, you have a good infrastructure for conducting any necessary follow up clinical trials, randomized trials, other detailed clinical studies, which can be quite costly and time-consuming in the postmarket setting. You can target those more effectively and quickly.

So I do think this is the time and it's important for the committee to realize it's probably going to be another decade before we get another chance like this. And by that time, I sure hope we have gotten an electronic health care system.

Senator BURR. Mark, you hit on a real key. Usually when we are talking about trying to implement a surveillance mechanism like this we are deficient on the data and we have the means to do it. This time we have all the data that's being accumulated because we track the scripts that are written, we track the insurance claims that are paid. The data is there. It seems like the easy thing is to figure out how we bring this all under one umbrella, where we can tap into it, not for a determination but for trend lines that would give individuals at the FDA reason to ask additional questions of a manufacturer to look and search a database of patients that they might reach out to to see if anybody else is having similar things that they haven't in fact communicated.

That's why I'm a little bit standoffish on this legislation, because I don't see us going in the avenue of surveillance. I see us going in the avenue of taking the tools that the FDA currently has and they exercise in the ways that are historically influenced, and those need to shift, the paradigms need to shift.

Let me point to one area. Dr. Burlington, it's good to see you again. You talked about principle versus process. Under the REMS, drug companies would have to monitor providers. Providers are doctors and nurses. They would have to monitor pharmacists and they would have to monitor patients, for compliance with the restrictions. Not only is monitoring I think unworkable for the company; the company would be liable in this legislation.

So I go back to the innovation side that you didn't have concerns with and I ask you, if you present them with an unworkable situation and you hold them liable for the unworkable situation, will you have the degree of innovation tomorrow that you have today?

Dr. BURLINGTON. Senator, I share your concern that it does not sound very workable to ask the pharmaceutical industry to be policing the practice of medicine. I think that in many ways it is important for the pharmaceutical industry to take responsibility. We do look at safety as a very important issue. We work with the agency when issues arise in terms of putting in place marketing approaches or distribution approaches that will reduce the probability of having adverse events, serious adverse events. Those sometimes have included restrictions on the way products are used.

But in the end, it is not appropriate to ask a company to try and control how a doctor works with a patient.

Senator BURR. But that's what the legislation before us today actually does. It puts that requirement on doctors and nurses and pharmacists and patients. I'm not necessarily sure that at the end of the day we have any better information about adverse reactions. That is my big concern, and that's the objective that we are after.

REMS could also require a provider to be trained. Now, I represent a State with a tremendous rural population, as Mark knows because of his other hat of CMS grand poobah. One of the challenges I had was transportation. I couldn't get somebody from their home to a place that provided a service because transportation stood in the way. The question is how do we take this rural infrastructure of America and set up a training mechanism per drug, per manufacturer, where we don't at some point risk the chance of not being able to provide a medication that an individual needs? It may not be a lifesaving medication, but it may address a real chronic illness that they have, that there's no provider that's trained based upon FDA guidelines that were prescribed to them that can actually write the prescription.

Dr. BURLINGTON. Senator, the strategy of developing training for the use of a particular product is undoubtedly derivative from previous experience in the medical device arena, where, particularly for many complicated surgical devices, there currently is a requirement for training in how to use them before given physicians are authorized.

Now, of course that's not controlling what the physicians do. That's just setting up a requirement——

Senator BURR. And most of those procedures are not done in rural America.

Dr. BURLINGTON. Absolutely correct. I think to the extent that any sort of training program ought to be envisioned it ought to be very rarely used. It ought to be used only in the most extraordinary cases. It ought to be a determination at the most senior level of the

agency and one needs to be confident that that's what is necessary in order to maximize the benefit of the product. And then you need to develop mechanisms to make sure the training is available to those physicians who need to prescribe the product.

Senator BURR. Well, let me say I applaud the chairman and the ranking member for bringing drug safety up again. It's an issue that I have raised since 1997 when we passed FDAMA. It's something that I think we have the capabilities to do in a much more effective way today. Even if we didn't pass this legislation, I believe that with the right resources within the FDA today we could have a surveillance program that teaches us a lot more and that the partnerships between the applicants, the drug companies, and the FDA, the regulators, would raise the confidence level of the American people.

I'm not sure that we need legislation to do that. But where legislation can enhance, where it can provide the FDA with tools that possibly it doesn't explicitly have today, where it can be empowered to address direct-to-consumer advertising, which I think that the industry in total has handled in a very inappropriate way with some of the advertising that they choose—but by the same token, I also see that people throughout the country that never visit a doctor, saw an ad that talked about a medication that described their condition, and they went in and got blood pressure medicine and they are not the recipient of bypass surgery today, or they got a medication that saved them from an in-hospital incident.

So there is value to it. The tricky thing is finding the balance, and part of that is the responsibility of the industry on a voluntary basis. Part of it is the enforcement at the FDA, Mark, and I think you and I have talked about that in the past, in finding what we are comfortable with the FDA having control of and what the courts will allow us to do, which means a majority of it has to be voluntary.

Mr. Chairman, you have been very patient because I know I have exceeded my time. I appreciate your time on this and Senator Enzi's time and look forward to working with you on this.

The CHAIRMAN. Good. Well, we thank you very much, Senator Burr, and thank all of our panel. I think that this gets into, as we have all been wrestling with, on the one hand permitting the best in terms of the medical practice, but also understanding the issues of medical safety. Somebody has a bad liver and a particular drug may do potential damage to the liver. The FDA issues some rule or regulation with regard to that; does that interfere with a doctor's practice of medicine? Well, it does. It does. It's based upon science. Is that healthy or for the good? I would expect so, and certainly with regards to the individual who had the liver problem it's in their best interest.

So does it interfere with the practice of medicine? This is the balance. I don't know whether, Dr. McClellan, you want to make any general comments. I mean, I think all of us understand if discretion is taken to an excess that you can perhaps draw one conclusion and if not perhaps another.

But the hope is that we are providing the tools and the discretion for science, so that individuals who have that responsibility can

make a judgment. But what's your sense about whether we have this about right or not?

Dr. MCCLELLAN. Senator, I appreciate you are striving for balance. Let me also just add that I want to give a special thanks to your staff, Senator Enzi's staff, and other staff on the committee who have been working very hard to take a complex and challenging issue, realizing just how important this once in a decade opportunity is, to get it right, to take good ideas and modify them so you do get that balance right.

There are all kinds of influences on medical practice today. Some come from the FDA, as you said, through their announcements and the like. Many come through health care financing mechanisms, what health plans will pay for, what Medicare pays for, and other types of regulation.

One thing that I hope we can continue to do—your staff has really been helpful in making this happen—is view these safety steps and the further steps to improve access to safe and effective medicines as part of an overall effort to improve our health system. We often think of issues siloed, drug safety as an FDA responsibility. That's not all that it is. It's the responsibility of the FDA, it's the responsibility of the drug companies, but also, as Ms. Witczak said, it's something where consumers can help. It's something where health plans can help. It's all of our responsibility.

If we take a step back from just looking at one traditional way of dealing with this problem and instead use all the tools that are available through information from health plans and how they can influence, hopefully in a positive direction, medical practice—there's no question they do—the FDA, all of these different parties, I think you have a unique opportunity to have a huge impact on drug safety in the United States and improving access to medicines at the same time.

The CHAIRMAN. Thank you.

Ms. Dorman, do you want to make a comment whether you view the availability and the accessibility of those special drugs will be still available under this kind of a regime?

Ms. DORMAN. I think most definitely so. There are some people who have thought because people have rare diseases that their standards for how a drug reacts in their system is somewhat lower, and that has never ever been the case. Safety and efficacy is probably one of the most important things for people with rare diseases.

But in some respects, our position on how the FDA works and how drugs work is somewhat unique because patient populations are so small. So we want to just make sure that whatever occurs within this legislation or any type of legislation, that people think about the orphan products, the exclusivities, because there are 304 products on the market now to treat rare diseases, but yet there are over 6,000 rare diseases. Many of them do not have any treatment at all. So we want to ensure that those protections for these patients continue to be strong.

The CHAIRMAN. Well, certainly that whole orphan drug and the Hatch-Waxman, they made an enormous difference in a very, very positive way.

Very helpful panel. Thank you very, very much. Very appreciative. And I think we are going to have some questions we might

try and impose on you. So we will keep the record open for a period of 10 days.

Thank you very much.

[Additional material follows:]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF THE FDA ALLIANCE*

Chairman Kennedy, Senator Enzi and members of the committee, the FDA Alliance is pleased to provide this statement for the record of your hearing on FDA resources, user fees and drug safety.

The FDA Alliance is a broad-based, non-partisan coalition of consumers, patients, health care professionals, and industry. With more than 100 members, including seven former Commissioners of the Food and Drug Administration, the FDA Alliance is an advocate for increased appropriated funding for FDA to enable the agency to effectively carry out its dual roles as the leading guardian of consumer health and safety and as an active leader in advancing global scientific and medical innovation.

FDA is underfunded and understaffed. Its budget is woefully inadequate. A weakened FDA undermines consumer protection. The United States needs a strong FDA that is sized and modernized to carry out its responsibilities in the 21st century.

FDA receives minimal new funds each year. Its ability to fulfill its mission is compromised by increasing costs, evolving missions, expanding science, and changing technologies. The American people and the Congress expect more from the FDA than it can deliver without additional money.

User fees are an important component of the resources available to the FDA, but cannot substitute for a significantly increased appropriations and a long-term commitment by Congress to assure that the FDA has the resources it needs.

The U.S. Food and Drug Administration needs $2 billion in fiscal year 2008 appropriated budget authority. Adding in user fee revenues, this would result in a total budget of at least $2.45 billion. This modest budget increase would merely restore FDA to the capabilities it had in fiscal year 2003. Since then, FDA's budget has actually lost buying power.

An investment in FDA is long overdue. We need to preserve and sustain FDA's ability to protect Americans, advance innovation, and remain the regulatory "gold standard" worldwide.

Analysis done by FDA suggests that the agency appropriation is *underfunded by $300 million to $800 million*, compared to what is needed to accommodate its existing statutory program responsibilities and congressional mandates. An updated version of this analysis is appended to this statement and demonstrates that $2 billion in budget authority (plus user fees) is an appropriate target for immediate reinforcement of FDA and its mission.

For example, $2 billion in fiscal year 2008 *appropriated* funding (budget authority) is needed to sustain the public health and safety priorities given to FDA by Congress in such critical areas as:

- food safety counterterrorism/defense,
- pandemic preparedness,
- drug/patient safety,
- medical device, animal drug and generic drug reviews,
- BSE/Mad Cow Disease, and
- new technologies, such as nanotechnology.

Other key priorities include funding for improved and more capable information technology systems at FDA and restoring post-9/11 funding levels for the field force that inspects foods, imports and regulated manufacturing sites.

Much of the historic underfunding of FDA can be attributed to failure to fund the personnel costs required to fulfill the agency's mission. FDA spends more than 83 percent of its budget to support its workforce. The costs of maintaining and supporting staff have increased at a much faster rate than the agency's appropriated resources. By its own calculations, FDA needs inflation increases each year of at least 5.8 percent just to maintain its current service and staff level. Annual appropriations to FDA never include the full cost to the agency of pay and benefit increases or rising non-pay costs.

Currently, Congress appropriates *just $4.94 per American* per year (excluding user fees) to the FDA. At $2 billion in appropriated funds for fiscal year 2008, this would still represent only *$6.67 per American* to enable FDA to keep pace with its vital missions and services.

Congress should make a long-term commitment to upgrade FDA's appropriated funding. As the committee of jurisdiction overseeing the FDA, we ask you to be ad-

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*For more information, contact Steven Grossman, FDA Alliance, at *info@StrengthenFDA.org*.

vocates in the budget and appropriations process to assure that Congress provides needed funding to support the agency in carrying out its mission.

Providing $2 billion in appropriated funding in fiscal year 2008—and sustaining that level of budget authority and providing budget growth as needed for the next 4 fiscal years—will help the FDA fulfill its mandate and be innovative in its approach to regulation, oversight, inspections, approvals, and monitoring.

FDA Alliance. For More Information, contact Steven Grossman, at info@StrenghtenFDA.org

Total FDA Appropriated S&E Budget Authority, If...

1. Appropriated Budget Authority had increased at 5.8% per year over FY 2003 level, and
2. All funds for program increases had really been added to the Appropriation

UNDER THESE ASSUMPTIONS,
THE FY 2008 BUDGET AUTHORITY SHOULD BE $2 Billion,
WITH USER FEES SEPARATE AND ADDITIONAL

	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Amt if 2003 increased by 5.8% per year	**$ 1,373**	**$ 1,453**	**$ 1,537**	**$ 1,626**	**$ 1,720**	**$ 1,820**
Additions Shown in Budget, and then increased in Subsequent years at 5.8%						
1) Food Safety Counterterrorism/Defense		$ 20.5	$ 83.7	$ 94.4	*See Discussion Below Regarding FY 2007 Funding*	*See Discussion Below Regarding FY 2008 Funding*
2) Patient Safety		$ 3.0	$ 3.2	$ 3.4		
3) OTC Drugs		$ 0.7	$ 0.7	$ 0.7		
4) Generic Drugs		$ 8.0	$ 8.5	$ 9.0		
5) BPCA		$ 3.5	$ 3.7	$ 3.9		
6) Medical Device Review		$ 1.0	$ 26.6	$ 34.2		
7) Orphan Product Grants			$ 1.2	$ 1.3		
8) Influenza (transfer from OC)			$ 0.3	$ 0.3		
9) Medical Product Countermeasures			$ 5.0	$ 5.3		
10) BSE/Mad Cow Disease			$ 8.0	$ 8.5		
11) Drug Safety				$ 10.0		
12) Critical Path				$ 0.8		
13) DTC Advertising				$ 0.9		
14) Pandemic Preparedness				$ 20.0		
15) Tissues						
16) Animal Drug Review						
Total Additions		**$ 37**	**$ 141**	**$ 192**	**$ 203**	**$215**
What would have been:	**$ 1,373**	**$ 1,489**	**$ 1,678**	**$ 1,819**	**$ 1,924**	**$ 2,035**
Actual Appropriation: [1]	**$ 1,373**	**$ 1,195**	**$ 1,450**	**$ 1,487**	**$ 1,558**	
Difference		**$ (295)**	**$ (228)**	**$ (332)**	**$ (366)**	
Percent Difference		**-20%**	**-14%**	**-18%**	**-19%**	

[1] From S&E Budget Authority in All Purpose Tables in Congressional Budget Justifications

FY2007:

FY 2007 is calculated as a 5.8% increase over 2006, including prior year program additions

$1.819 billion X 1.058 = $1.924 billion

Program additions in H.J. Res 20, if any, cannot be identified until FDA submits its FY 2007 plan to the Appropriations committees.

FY2008:

Using the above calculation as a baseline and assuming no further program additions, FY 2008 would be calculated as a 5.8% increase over 2007

$1.924 billion X 1.058 = $2.036 billion

Based on analysis done by Frank Claunts for FDA, with revisions, updates and annotations by the FDA Alliance March 13, 2007

PREPARED STATEMENT OF THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS

The American Society of Health-System Pharmacists (ASHP) respectfully submits the following statement for the record to the Senate Health, Education, Labor, and Pensions (HELP) Committee hearing on "User Fees: Enhancing Patient Access and Drug Safety."

ASHP is the 30,000-member national professional and scientific association that represents pharmacists who practice in hospitals, health maintenance organizations, long-term care facilities, and other components of health systems. For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient outcomes. This includes working with patients to help them access the medications they need and to use them safely and effectively.

The Society has long-standing policies that express support for congressional action to provide the Food and Drug Administration (FDA) with increased authorities to require post-marketing studies on the safety of drugs that are in the public interest. ASHP policy has also supported broader authority for the FDA to require additional labeling or the withdrawal of certain products on the basis of review of such studies.

While ASHP is pleased that the PDUFA program continues to support the FDA's mission to protect and promote public health, we believe that the next reauthorization must go much further in this regard. As PDUFA has allowed faster drug approvals, manufacturers must bear some of the responsibility to provide support for drug safety initiatives. We are pleased that the reauthorization of the Prescription Drug User Fee Act (PDUFA) will address this issue, targeting resources to modernize the post-market drug safety system.

As we noted in our comments to the FDA early in the reauthorization process, critical elements of this reauthorization must include: (1) improved post-marketing safety regulation, (2) addressing the impact of direct-to-consumer advertising on medication-use safety, and (3) developing models of patient care that bring actual medication use into better alignment with medication-safety information. We believe that FDA's recommendations do attempt to address these key areas, however, some additional improvements can be made and we ask the committee to consider several points as it pursues a legislative strategy.

PRE-MARKET RISK ASSESSMENT

Restricted Drug Distribution

There are many concerns regarding the existing restricted drug distribution system (RDDS) framework. RDDS programs are developed for many reasons, most importantly to ensure that drugs with very high risks are prescribed, dispensed and administered safely. While these systems are necessary in appropriate circumstances to protect patients, there are many challenges associated with their administration, especially in the hospital setting, which compromise the quality of patient care.

ASHP recently conducted a survey (see attached) of its members who have experience with RDDS to better understand what hospital pharmacists and their patients are experiencing with regard to these programs. ASHP received 521 responses from hospitals and health-systems nationwide with 49 States represented. Most significant findings indicate that timely access to drugs for patients and care continuity are frequently or occasionally a problem in the vast majority of hospitals and health-systems. The findings also indicate that most hospital and health-system pharmacists believe that some aspects of RDDS programs can be standardized.

The reauthorization of PDUFA provides a unique opportunity to improve elements of FDA's oversight of these programs, improving patient care and reducing unnecessary burdens on the health care system. ASHP suggests that this PDUFA reauthorization provide for research on how well existing and new restricted drug distribution systems are achieving their goals. Additionally, new PDUFA reauthorization legislation should mandate that drug manufacturers and the FDA partner with professional organizations in conducting this research.

The Society also recommends that this PDUFA reauthorization direct the FDA Drug Safety and Risk Management Advisory Committee to craft recommendations to improve RDDS programs. The committee should analyze current FDA standards and recommend new policy in several key areas related to RDDS including: (1) feasibility of standardizing basic elements of all programs, (2) ensuring timely access to drugs for patients, (3) eliminating continuity of care problems, and (4) permitting exceptions from various RDDS program registration rules for those practitioners that meet pre-determined agency standards and requirements.

POSTMARKETING SURVEILLANCE

ASHP supports the elimination of statutory restrictions so that PDUFA fees could be used to assess safety issues postapproval, independent of a product's approval date and allow the agency to review the drug's safety in whatever timeframe risks

arise using all available resources. The Society does ask the committee to consider the following as it drafts its final PDUFA proposal:

Adverse Event Reporting and Assessment.—ASHP was pleased to see that the FDA's draft recommendations included an initiative to conduct research on maximizing the public health benefits associated with collecting and reporting adverse events throughout a product's life cycle. Additionally, we support access to population-based data to utilize signal detection as part of improved post marketing surveillance. Pharmacists are especially positioned to provide leadership in medication-error reporting programs and we would urge the committee to require FDA to include these health care professionals in its research efforts to improve the use of adverse events data that are collected and reported.

Drug Naming and Labeling.—ASHP is pleased that the FDA's draft recommendations suggest the development of new guidance materials to improve methods for naming and labeling drugs. With respect to measures to reduce medication errors related to look-alike and sound-alike names, we support the recommended pilot program to explore a different paradigm for proprietary name review. The agency recommends publishing three guidance documents in this area including: naming, labeling, and packaging. We urge the committee to require the inclusion of pharmacists as part of the agency's consultation in developing this guidance.

Effective Risk Communication Strategies.—While we are pleased that FDA has suggested a draft recommendation to expand the types of tools available for adverse event detection, this will have only limited impact if risk information is not made available to the public in some way. ASHP would suggest that the committee include in its PDUFA proposal a new research program which would examine methods and mechanisms for effective risk communication by health professionals, including looking at who—pharmacists, physicians, industry, etc.—and where—in the pharmacy, by telephone, via DTC—such communication is most effective.

DIRECT-TO-CONSUMER ADVERTISING

ASHP has long advocated for FDA to develop research to evaluate the medication-use safety implications of FDA policies and industry marketing practices related to direct-to-consumer (DTC) advertising of prescription medicines. We believe that FDA's draft recommendations for PDUFA IV in this area fall short. Data on the impact that DTC ads have on the appropriateness of medication use remains negligible. ASHP members have also supported policy that promotes delays in DTC promotion until postmarketing data are collected and assessed. ASHP suggests that in combination with this delay, it would be consistent with the FDA's public health mission for the agency to commission research on this topic.

INNOVATIONS IN HEALTH CARE PRACTICE

In order to fully address medication safety, it is critical to allot dedicated research funds to study innovations in health care practice that may improve the safety of medication use. Insufficient attention is given to evidence about how to use a medication safely, and by ignoring this critical element of research the government continues to miss an opportunity to identify and solve a significant portion of the drug safety problem. ASHP would encourage the committee to expand FDA's research base through PDUFA reauthorization, dedicating funds to research in this important area of drug safety.

CONCLUSION

We appreciate the opportunity to share our views on aspects of the PDUFA reauthorization. It is essential that the American public have confidence in our Nation's ability to maintain the integrity of our drug supply and protect patient health through appropriate drug approval and monitoring systems. ASHP and its members are committed to working with the Congress, FDA and other stakeholders to achieve this goal.

ASHP
Restricted Drug Distribution System Survey
March 2007

Methodology

- Administered via an email invitation, linking participants to an online survey instrument.
- Sent to 3,389 ASHP members (who are also primary members of the sections for Pharmacy Practice Managers Section or the Informatics Section).
- Fielded February 27, 2007 through March 5, 2007 (with one reminder to nonrespondents).
- 521 responses received; response rate is 15%.

Results

Please indicate which of the RDDS program drugs listed below are prescribed for patients seen at your hospital or health-system. Please check all that apply. Check "NONE" if appropriate.	
Answer	**Percentage**
Clozaril *(clozapine)*: Clozaril National Registry Program	66%
Thalomid *(thalidomide)*: S.T.E.P.S. Program	46%
Tikosyn *(dofetilide)*: T.I.P.S. Program	45%
Accutane, Amnesteem, Claravis, Sotret *(isotretinoin)*: iPLEDGE Program	30%
Aralast, Prolastin, Zemaira *(alpha-1-proteinase inhibitor)*	29%
Fosamax *(alendronate)*: Paget's Patient Support Program	29%
Tysabri *(nataluzimab)*: TOUCH Prescribing Program	26%
Tracleer *(bosentan)*: Tracleer Access Program (TAP)	25%
Suboxone *(buprenorphine)*	17%
Iressa *(gefitinis)*: Iressa Access Program	16%
Lotronex *(alosetron)*: Prescribing Program	10%
Mifeprex *(mifepristone)*	8%
Exjade *(deferasirox)*: EPASS Program	8%
Revlimid *(lenalidomide)*: RevAssist Program	8%
Nexavar *(sorafenib)*: REACH Program	6%
Ventavis *(iloprost)*	5%
Plenaxis *(abarelix)*: Plenaxis Plus Program	4%
Xyrem *(sodium oxybate)*: Xyrem Success Program	2%
Cystadane *(betaine)*	1%
Other	3%
None	14%
Total Responses: 521	

Overall, how often are these drugs prescribed in your hospital or health-system?	
Answer	**Percentage**
A few times a year or less	42%
At least two times a month	36%
One time per week or more	22%
Total Responses : 445	

Is your hospital or health-system pharmacy (inpatient or outpatient) registered to dispense products for one or more RDDS programs?		
Answer	**Bar**	**Percentage**
Yes		75%
No		25%
Total Responses: 512		

Do you believe that RDDS programs are necessary in some circumstances in order to protect patients from risk?		
Answer	**Bar**	**Percentage**
Yes		68%
No		32%
Total Responses: 375		

Do any of the RDDS programs you encounter compromise timely patient access to the drug?	
Answer	**Percentage**
Never	10%
Occasionally	67%
Frequently	23%
Total Responses : 374	

Do any of the RDDS programs you encounter compromise continuity of care?	
Answer	**Percentage**
Never	18%
Occasionally	62%
Frequently	20%
Total Responses : 375	

Do you think it is possible to simplify and improve RDDS programs?	
Answer	**Percentage**
Yes	56%
No	4%
Don't know	40%
Total Responses : 471	

Do you think it is possible to standardize some aspects of RDDS programs in order to reduce burden and simplify administration of such programs?	
Answer	**Percentage**
Yes	67%
No	5%
Don't know	28%
Total Responses : 465	

Do you believe practicing hospital and health-system pharmacists' input into the development of RDDS programs would yield better programs?	
Answer	**Percentage**
Yes	79%
No	2%
Don't know	18%
Total Responses : 467	

What is the average daily census at your organization?	
Daily census	**Percentage**
not applicable	4%
less than 50 beds	15%
51 to 99 beds	14%
100 to 199 beds	22%
200 to 299 beds	16%
300 to 399 beds	10%
400 to 499 beds	6%
500 or more beds	13%
Total Responses: 467	

What is your primary practice setting?	
Answer	**Percentage**
Community Hospital – non-teaching	51%
Community Hospital – teaching	25%
Academic/University Medical Center	10%
Government Hospital (State, County, Federal)	4%
Pediatric Hospital (any type)	2%
Other	9%
Total Responses: 467	

STATEMENT OF MICHAEL FITZPATRICK, EXECUTIVE DIRECTOR, NATIONAL ALLIANCE ON MENTAL ILLNESS (NAMI)

Chairman Kennedy, Senator Enzi and members of the committee, on behalf of the 210,000 members and 1,200 affiliates of the National Alliance on Mental Illness (NAMI), I am pleased to submit the following statement reform of the Food and Drug Administration (FDA) and on the Prescription Drug User Fee Act IV agreement. As the Nation's largest organization representing people with severe mental illness and their families, NAMI would like to express support for PDUFA IV.

Mr. Chairman, at the outset I would like to restate NAMI's thanks and strong support for the committee's moving so expeditiously to favorably report S. 558, the Mental Health Parity Act of 2007. This landmark legislation will bring about equitable insurance coverage for individuals living with mental illness and their families. The strong bipartisan action on the part of the committee is a reflection of the hard work that you and your staffs—working with Senator Domenici—have put into this effort to end insurance discrimination. This is a strong bill that will make an enormous difference in the lives of people living with mental illnesses such as schizophrenia, bipolar disorder, major depression, severe anxiety disorders and other mental illnesses. NAMI is committed to working with you and your colleagues in the Senate and the House to make sure that this legislation reaches the President's desk this year.

NAMI has long placed the highest value on scientific advance and development of newer and more effective treatments for serious illnesses such as schizophrenia, bipolar disorder, major depression and severe anxiety disorders. Over the past two decades, we have seen a revolution in the development of new treatments for these disorders. While this advance has helped millions of individuals living with these illnesses move toward recovery, more is needed. NAMI feels strongly that both publicly funded research and the commercial market must move toward a new generation of medications that reach toward cures for severe mental illness.

NAMI is hopeful that the goals of PDUFA IV will help foster an environment in which this new generation of medications can be rapidly made available to millions of Americans living with these illnesses, and their families. As a patient advocacy and family organization, NAMI has a strong interest in PDUFA IV bringing the FDA forward as a stronger agency that is well resourced, develops modern information technology systems and is able to recruit and retain talented scientists.

In NAMI's view, PDUFA IV should help FDA progress toward being an agency that:

- Engages in effective pre-market review of products,
- Fosters expedited drug development,
- Moves toward rapid progress for fully automated drug reviews,
- Invests in full funding and staffing of the Critical Path Initiative (this agreement is a first step toward that goal), and
- Brings about a transformed post-market drug safety system at the agency.

It is on this final goal that NAMI believes PDUFA IV makes important progress. It is clear that additional resources are needed to address the increasing volume of adverse event reports. In NAMI's view, the FDA simply cannot keep pace with this increase in volume by relying solely on an expectation that Congress increase appropriated funds over the short term. Clearly, additional resources beyond appropriated funds are in order for the agency to engage in effective post-market safety beyond the current limited 3-year window. PDUFA IV moves us toward making sure that the agency has the resources to engage in these important safety review activities.

As this committee moves forward to enhance post-market safety review, NAMI urges that you not lose sight of what is the greatest risk for people living with severe mental illness and their families, not be able to access available treatments. NAMI strongly supports individuals living with mental illness being able to access the full array of available treatment options. They should be able to work with their physician to weigh efficacy, side effects, patient and family history and other factors to make an individualized treatment decision. NAMI's hope is that PDUFA IV will move toward an environment in which those treatment options are broadened.

In commenting on this PDUFA IV agreement, NAMI would make the following observations:

1. There is widespread agreement that the FDA has been hampered by a lack of resources, both in terms of financial resources and human capital. PDUFA IV is a significant step forward in terms of drug development, drug safety and information technology. NAMI also feels strongly that Congress must also step forward with additional appropriations for the agency.
2. Since the early 1990s, PDUFA has succeeded in expanding the drug review process, what was once a 3–4 year process has been reduced to less than a year in many instances.
3. People living with mental illness and their families—like other patients who live with significant chronic illness—understand that there are risks associated with any prescription medication. What patients and their families want most is to have a variety of treatment options and clear understanding of the risks and benefits of each treatment option and to make an informed decision in consultation with their doctor. PDUFA can, and should, help expand and illuminate these important treatment decisions.

NAMI would also like to go on record with concerns about the process for enactment of legislation in Congress that is needed to make this agreement a reality. Reauthorizing PDUFA this year presents the committee with an important opportunity to make improvements in the performance of the FDA, especially with respect to post-marketing safety monitoring. NAMI supports efforts to make these improvements to ensure that patients that rely on medications for daily living and functioning are protected from unsafe products.

At the same time, it should be recognized that the legal authority for the FDA to continue operating the PDUFA program and retain scientists and drug review staff at the agency depends on reauthorization of the law by October 1. Delaying action on PDUFA legislation would have enormous potential to derail drug reviews, hurt agency morale and in the long run, limit access to new medications. NAMI therefore urges the committee to move the reauthorization process forward expeditiously.

Finally Mr. Chairman NAMI would urge the committee to take a balanced approach to FDA reform. NAMI is especially concerned that some of the Agency's harshest critics may be using perceived problems with safety of medications commonly prescribed to treat mental illness as a proxy for a separate agenda that calls into question whether or not these serious disorders are genuine medical conditions. I want to be clear, NAMI supports giving the FDA all of the legal authority and financial resources it needs to ensure that all approved medications are safe and effective and prescribed consistent with recognized treatment guidelines and protocols.

At the same time, there are advocacy organizations that view the debate over PDUFA reauthorization and FDA reform as an opportunity to undermine public confidence both in the efficacy and safety of medications to treat mental illness—

specifically anti-depressants and anti-psychotics and the very existence of brain disorders such as schizophrenia, bipolar disorder, major depression and severe anxiety disorders. NAMI would urge the committee to be careful with respect to any effort to direct the FDA to impose a separate safety standard for psychotropic medications or separate threshold for safety warnings associated with these medications. Reform of the FDA should not result in barriers to treatment for people living with mental illness and their families.

Thank you for the opportunity to present NAMI's views on this important issue.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY AND SENATOR ENZI BY KIM WITCZAK

QUESTIONS OF SENATOR KENNEDY

Question 1. Some have said that Congress should not take action to improve drug safety. What would it do to your hopes and hopes of others who have experienced intense personal loss from drug side effects if Congress missed this opportunity to improve drug safety?

Answer 1. This year represents the greatest opportunity for Congress to help fix the broken drug safety system in our country. At the present time, the public has little faith in the FDA's ability to protect the American public. We are relying on Congress to step in and make meaningful change that brings back confidence to the phrase "FDA approved."

It's not only those who have been personally affected by FDA failures that are concerned with drug safety. The American public is taking prescription drugs more than ever. We rely on the FDA to make sure the drugs we take are "safe and effective." Every individual and family is potentially at risk. No one is immune from experiencing what our family and countless others have.

Drug safety is an extremely important part of the risk/benefit equation. It is simply good medicine practice. We need this information to be both accurate and timely.

While its seems like all the congressional pressure on the FDA has been a "good thing" with their recent warnings, policy changes, etc., it's when Congress isn't looking that the public needs to be concerned. The past behavior of the FDA and industry has shown that they can NOT be trusted to voluntarily manage drug safety system on their own without sweeping changes. The "sweep it under the rug" approach, explain it with "science" or manipulated statistics, or wait until it becomes a public relations issue before anything is done is not beneficial for anyone, including the drug companies.

PDUFA was originally created to help expedite the approval of lifesaving drugs at the FDA. While this goal has been accomplished, it has not been without consequences. Since the last PDUFA reauthorization, we have seen a plethora of drug safety scandals like Vioxx, antidepressants, Ketek and just last week with Pergolide and Zelnorm.

I have attached a copy of an internal FDA memo dated December 24, 1991 from Dr. Paul Leber to Dr. Robert Temple that serves as a good example of why we need a stronger post-market system in place at a time when the agency is expediting drug approvals. In the memo, Dr. Leber acknowledges that although several foreign national regulatory agencies were not willing to grant Zoloft approval due to "lack of robustness" in clinical evidence, the FDA felt pressured to quickly approve Zoloft.

In Dr. Leber's own words,

> . . . Many of these foreign regulatory initiatives have potential merit, but, given the perceived urgency we express as an institution for expediting the public's access to new, potentially promising, drugs, I do not believe we can successfully introduce similar, more demanding, requirements domestically, at least until there is a significant "sea change" in our society's collective attitude toward Federal regulation of new drug approvals.
>
> . . . Approval may, however, for the reasons enumerated above come under attack by constituencies that do not believe the agency is as demanding as it ought to be in regard to its standards for establishing the efficacy of antidepressant drug products.

This is heartbreaking to read when one's husband and many others unnecessarily died or were put at risk because the FDA did not do proper post-market surveillance or follow up in the subsequent years when there were thousands of serious adverse event reports including suicide. In addition, there was mounting scientific evidence from around the world of severe adverse reactions from this class of drugs. It seemed that the agency turned a blind eye and now is reeling to defend itself with manipulated "science."

By not adequately addressing the drug safety side of the equation, the FDA basically sends the message to the public that the status quo is good enough. How many

lives will be affected if Congress does nothing or just includes a few token safety changes? We need meaningful drug safety measures put in place that will help protect the public against the next Vioxx.

Things need to change and you have the ability and responsibility to help restore the FDA back to the gold standard it once was.

QUESTIONS OF SENATOR ENZI

Question 1. You have indicated that you would support preemption of State clinical trials databases if the Federal database created by our legislation contains the results of clinical trials conducted prior to enactment of the bill. I see your point, but I also see that there are thousands of drugs on the market, some approved many years ago. How might we limit the "look-back" provision so that we get the most beneficial clinical trials information for the least burden?

Answer 1. I would support Federal preemption of State clinical trial databases ONLY if S. 484 covered clinical trial data of drugs currently on the market. Right now, I am NOT comfortable with the current legislation as it only covers the Phase III and IV trials starting in 2008. It will be years before these drugs hit the market.

As you may be aware, we have been working hard in Minnesota to get a clinical trials disclosure bill passed that would require that all clinical trials (dating back to 1990) of drugs covered by the State's Medicaid program be posted on a publicly accessible Web site. Several other States have introduced similar legislation as well. Under the current language in S. 484, these sorts of State consumer protection laws would be preempted by S. 484. It's going to be hard to tell your constituents that the State law designed to protect them from potential drug safety scandals would be null and void by Federal preemption.

The plain and simple motivation behind the State-based clinical trial disclosure legislation is to protect the public where the Feds are not. As we have seen with the recent drug safety scandals, some of the serious side effects were first detected in the clinical trials and kept in drug company files, some without the FDA even knowing the trials existed. Ultimately, this sort of safety information does come out, usually through court proceedings after there has been serious harm or death caused by the drug.

PhRMA, in principal, has agreed this is a good idea and voluntarily agreed to post their clinical study results on their Web site from 2002 and on. Unfortunately, it is voluntary, doesn't go back far enough, and only provides the summary of the data. Most of the clinical trials of the recent drug safety scandals were conducted prior to 2002.

One compromise that I would be willing to support would be to amend S. 484 to require that the clinical trial data for drugs currently on the market that have known safety concerns (i.e. COX-2, NSAID/Celebrex, Antidepressants, Antipsychotics, sleep medications, etc.) or those that are most heavily advertised be covered in the legislation. As we all know, the advertising drives millions of people to take these drugs whether they truly need them or not and greatly increases the potential for serious side effects to emerge.

The industry will say that this is proprietary company data. The clinical trial results are not proprietary when public safety is at risk. We are not asking for formulas or other true proprietary information to be disclosed. Only safety and efficacy data.

Ultimately, transparency of data is good for public health. It's good pharmacovigilance.

Question 2. Are there any changes to the Enzi-Kennedy drug safety legislation that you would suggest in addition to those in your testimony?

Answer 2. While, I am happy to see that the Enzi-Kennedy legislation brings much-needed attention to post-market safety, there are a couple of areas that could be strengthened to further enhance the bill.

• I would like to reiterate the need for a strong Office of Drug Safety that has separate but equal powers. Ideally, I support Grassley-Dodd's version of separate Office of Drug Safety. Barring that, I think there is a way to give the head of Drug Safety (currently the head of the Office of Surveillance and Epidemiology) the authority—and the responsibility—to say he believes there are enough safety questions about a drug, pre- or post-approval, that the drug should not be approved, or if approved, that REMS (as established by S. 484) should be adjusted, or request additional safety studies, or that it should be pulled from the market. If the head of the Office of New Drugs disagrees, the two Office heads present their cases to the Commissioner within a date certain, say a week, and he makes a decision within a day. This would not slow down the process, but it would make a career profes-

sional physician-scientist responsible for standing up for safety when they think the facts justify it. This process should, of course, be very public, with reports to Congress on the details of when such disagreements have arisen and how they were resolved. In addition, points of contention should be subject to Advisory Committee review and comment by national and international experts.

• The current legislation would require clinical trial results to be made public starting in 2008. It could be years before these drugs are on the market. I would like to see the results of drugs on the market today made public and not buried in drug company or FDA files. In the previous question, I offered a couple suggestions on how to get clinical study results made public for drugs currently on the market without being too burdensome for the drug companies.

• Require that simple, consumer-friendly or layperson language be used to describe a drug's risks and benefits. There has been talk about taking this provision out. The consumers should not be treated as too "dumb" to understand what these detailed warnings mean. We can make a decision for ourselves. It is often said, an informed consumer is the best consumer, especially when it comes to the drugs we put in our body.

• I fully support the use of the massive Medicare database to conduct epidemiological studies to detect more quickly safety problems in the use of a drug. This should serve as an additional tool, NOT a substitution for other new post-market safety measures in Enzi-Kennedy legislation to help proactively seek out potential safety issues.

• Finally, Title IV on the ethics of Advisory Committees has been rendered nearly moot by the FDA's recent announcements. At minimum, I hope you codify the FDA's proposed guidance policy of no participation on advisory board if conflict is over $50,000 and no voting rights if conflict is under $50,000. However, this is a perfect opportunity to strengthen the Advisory Committee policy by lowering the $50,000 to $10,000. If the FDA thinks that an individual who has more than $10,000 of conflicts is an expert in a particular field, they could be invited to testify as a "witness" but not as a panel member. A few other ideas include:

1. Ensure that each advisory committee has a full range of experts (i.e. epidemiology, pharmacovigilance, statistics, prescribing doctors, etc.). In the case of the recent antidepressant advisory board held in December 2006, the majority of members were psychiatrists discussing suicide blackbox issues. There were no General Practioners sitting on board when 70–80 percent of antidepressants are given by GPs.
2. Make all review materials available to the public at least 7 days ahead of advisory committee meetings so that public witnesses can have a chance to react to materials.
3. Require review papers to include room for additional scientific views, dissents, and remaining questions from FDA review staff. The public deserves to know if others within the FDA have dissenting views. This also could trigger the need for an advisory board meeting.
4. Impose monetary penalties for any drug company sponsor that withholds data or provides inaccurate or misleading information to the advisory committee. No more Keteks or Trasylol.
5. Hold semi-annual general drug safety and risk management advisory committees for the public.

RESPONSES TO QUESTIONS OF SENATOR KENNEDY AND SENATOR ENZI BY D. BRUCE BURLINGTON, M.D.

QUESTIONS OF SENATOR KENNEDY

Question 1. Please share with the committee your views on whether the additional money for drug safety in the user fee agreement provides enough for that function. If not, should Congress consider increasing the amount in the user fee program for drug safety, and by what amount?

Answer 1. Yes, the funds provided for in the user fee agreement are satisfactory to meet FDA's needs for the next 5 years. The funding will allow the FDA to enhance and modernize its drug safety operations by hiring additional staff for drug safety activities including experts in epidemiology; increasing access to and use of large medical databases to perform more active safety surveillance; and reducing the agency's reliance on spontaneous reports of adverse drug reactions. At the time these provisions were being developed, the Institute of Medicine (IOM) was completing its report on the U.S. drug safety system. The report was issued shortly after the PDUFA IV provisions were agreed to. Both FDA and industry examined the IOM recommendations to insure that those recommendations that could be ad-

dressed through PDUFA—recommendations pertaining to increased resources and the science of safety—were addressed. In separate analyses, both FDA and industry agreed that this was in fact the case.

Question 2. As you know, the top trigger in the user fee program requires the total FDA appropriation to increase at the rate of inflation, but not at the higher rate at which FDA's costs actually increase. Should this trigger be changed so that the total FDA appropriation increases at the rate FDA's costs increase?

Answer 2. Yes, industry believes that the trigger should be changed to fairly adjust the appropriated portion of the budget for the real increases in personnel costs. It is our observation that the drug review program has suffered a loss in full time employees over the past 2 years because the current adjuster does not adequately cover these increases. At a minimum, appropriations should cover a fixed employee base within the agency. The PDUFA III agreement in 2002 assumed that there would be a fixed employee base of 1,277 FTEs. Unfortunately today, FDA is approximately 150 FTEs below this mark, a contributory factor to resource shortage.

Question 3. In your opinion, what would be the consequences if Congress failed to take action this year to improve the drug safety practices at FDA?

Answer 3. It is important to note that drug safety practices would be dramatically improved through several PDUFA IV provisions. As noted in the response to question 1, the agency would receive significant new funds ($150 million over 5 years) specifically allocated to the office that is engaged in studying post-market safety. This is in addition to funding that was agreed to in PDUFA III. The PDUFA IV agreement contains several other critical safety initiatives including:

- Modernizing the Adverse Event Reporting system (AERs) to enhance the collection, aggregation, and analysis of drug safety data,
- Development of a 5-year plan for the FDA to take advantage of new IT capabilities to conduct more active surveillance using electronic health records,
- Providing the FDA with the resources to examine which risk communication and risk management programs work and which don't, and
- Providing FDA with resources to improve trade name reviews so medication errors are reduced.

In addition, the Office of New Drugs, which is responsible for new drug reviews, would receive additional funding so that the Good Review Management Practices that were developed during PDUFA III can be fully implemented. One of the important parts of these practices is earlier discussions of drug labeling and post-market studies. Too often these discussions take place close to the action date, resulting in labeling that may not optimally convey information to health care providers or post-market studies that don't answer the most important questions. In fact, Dr. Bruce Psaty, a member of the IOM panel, noted in testimony before the House Energy and Commerce Committee that "many of the studies aren't well designed, and probably 20 percent don't deserve to be done." With the additional time coming from the PDUFA IV increases, studies will be designed to answer essential questions.

QUESTIONS OF SENATOR ENZI

Question 1. You indicate in your testimony that the REMS approach is similar to what your company is already complying with in Europe, and as such is not a bad idea. Yet you also suggest that REMS be limited in scope. Could you tell me more about what you had in mind, and how your proposed scope might differ from the European approach?

Answer 1. Harmonization of REMS with European risk management is desirable from our point of view. The European approach is comprehensive and should satisfy the goals of the REMS proposal without creating redundancy or conflict. We do not think that REMS should be limited as it relates to the EU approach but we believe that certain principles and elements of REMS should be limited in scope. First, this legislation should lay out principles and create a framework to guide the FDA in developing specific criteria for applying risk mitigation tools. Second, the controls mandated in the legislation should be applied when necessary (with well understood thresholds) so as to not unnecessarily restrict patient access to medicines and information. Any requirement applied in the interest of safety should impose the least possible burden to meet the intent of the restriction and to ensure it is commensurate to the risk it is aimed at addressing, including resulting in Medication Guides, communication plans, new studies, clinical trials, restrictions on advertising and promotion, or direct-to-consumer advertising bans. The threshold for imposing actions already described in current regulation or guidances should conform to the current standard. Third, the enforcement of these controls should not fall to the

sponsor because, in general, it is not feasible for a sponsor to control the individual physician/patient interaction.

Question 2. What is Wyeth doing regarding drug safety, beyond what is currently required in statute?

Answer 2. Wyeth strives to effectively manage and communicate the benefits and risks of our products to regulators, investigators, prescribers, and users of the Company's products. To that end, Wyeth is starting its formalized benefit risk assessments for development products early in the clinical development program. Currently Wyeth also submits a risk management plan with each NDA submission for a new chemical entity.

Question 3. In your testimony, you indicate that the potential costs of provisions in the Enzi-Kennedy bill (S. 484) are not included in the PDUFA agreement. That is true. How much more do you think our bill would cost?

Answer 3. It is very difficult to estimate how much the provisions in S. 484 will cost. During the PDUFA IV negotiations, participants had the benefit of significant data from FDA related to ongoing activities both with respect to their number and the FTE time allocations. In many cases there was 8–10 years of data. This made it possible to make informed estimates about how much new work arose from increased meetings, clinical protocol reviews, and IND workload. Even with such data, there was significant difference of opinion between the FDA and industry over the reliability of the new workload adjuster proposal. The industry agreed to an adjuster with the proviso that it would be examined in detail by an outside accountant following the first year of PDUFA IV. The REMS proposal in this legislation represents substantially new work for FDA. We do not know how FDA will implement or account for its REMS activities, the initial extent of FDA resources that will be required or how to compensate FDA for this increased work. In short, we do not have any historical data on which to base an accurate estimate. It is very possible, however, that the increased costs will be significant, pushing the proportion of the FDA's drug review budget funded by user fees even higher than it stands today.

RESPONSE TO QUESTIONS OF SENATORS KENNEDY, ENZI, BURR, AND HATCH BY STEPHEN R. MASON, HHS ACTING ASSISTANT COMMISSIONER FOR LEGISLATION

QUESTIONS OF SENATOR KENNEDY

Question 1. The user fee program has allowed for significant resources to improve drug review and approval times at FDA. However, there are concerns that while user fees have strengthened drug reviews, resources for other functions such as drug safety have stagnated or fallen. What more, beyond money in the user fee agreement, does the agency need to ensure that safety can remain a top priority for the agency?

Answer 1. 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 rapid advances in science and technology that have resulted in increasingly complex medical products. We take very seriously our response to safety-related issues from all sources, including those raised by consumer advocates, health professionals, academic researchers, and Members of Congress. Some examples of what the Agency is doing to ensure the safety of drugs are described below.

Included in the fiscal year 2008 President's budget is a proposal for a significant additional investment in FDA to modernize the process for ensuring drug safety. With the funds requested, FDA expects to strengthen the science and tools that support the product safety system at all stages of the product life-cycle from pre-market testing and development through post-market surveillance and risk management. Also, FDA expects to improve communication and information flow among all stakeholders engaged in promoting the safe use of medical products. These additional appropriations, combined with PDUFA IV resources, will support FDA's ability to effectively detect, communicate, and act on important safety issues thereby improving patient safety.

On September 22, 2006, the Institute of Medicine (lOM) 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. The IOM report makes substantive recommendations about additional steps FDA can take to improve our drug safety program. The recommendations are consistent with the Agency's commitment to drug safety, including: (1) strengthening the science that supports our medical product safety system, (2) improving communication and information flow among key stakeholders, and (3) improving operations and man-

agement. Our Prescription Drug User Fee Act (PDUFA) proposal would, in part, support some of these initiatives.

We are working diligently on the actions we have committed to in our response to the IOM Report and have already made significant progress on several projects. For example, in March 2007, we issued final guidance that describes FDA's current approach to communicating drug safety information, including emerging safety information, to the public. The guidance affirms the Agency's commitment to communicate important drug safety information in a timely manner, including in some situations when the Agency is still evaluating whether to take any regulatory action. FDA's communication about drug safety information is available through FDA's Web site.

In addition, we are well on our way to implementing an electronic drug safety tracking system. This system, which replaces multiple office and division specific systems, is already helping the Center for Drug Evaluation and Research (CDER) reviewers and managers to prioritize their work on safety issues. In March 2007, FDA issued guidance designed to make the advisory committee process more rigorous and transparent so that the public has confidence in the integrity of the recommendations made by its advisory committees.

We have implemented an aggressive effort to strengthen our drug safety program, including developing new tools for communicating drug safety information to patients. Through our Critical Path initiative, we are working with our health care partners to improve the tools we use to more effectively evaluate products and processes.

Question 2. I think we agree Congress should increase the FDA's appropriation, and that it would be better for the FDA not to have to rely on user fees for its budget. But some have gone a step further, and have called on Congress to discontinue the user fee program. Can you describe for the committee what effect it would have on FDA and on medical innovation if Congress were to discontinue the user fee program?

Answer 2. In fiscal year 2008, FDA expects to collect approximately $438 million in PDUFA fees, after the workload adjustment is made. These fee revenues will provide the funds that will pay for about 60 percent of the staff that FDA will use for drug review in fiscal year 2008.

If PDUFA is not reauthorized, and if the $438 million anticipated from PDUFA fee revenue is not available in fiscal year 2008 through fees or made up by appropriations, then FDA could no longer employ the 60 percent of review staff paid for through the fees. FDA also would be responsible for severance pay and the payment of unused annual leave. The loss of 60 percent of the drug review staff would have a devastating impact on the drug review process in the United States. FDA would be unable to meet the 6- and 10-month review timelines that have existed under PDUFA. In the initial few years after such a reduction, the drug review process in America would most likely revert to review times that average 3 or more years, as was the case prior to the enactment of PDUFA. The United States would cease to be the first market of entry for most new pharmaceutical and biotechnology products that enter into world commerce, and "drug lag" would re-emerge—meaning that most new pharmaceutical and therapeutic biotechnology products would again only be available to U.S. citizens long after they were first approved and available in other countries.

Question 3. The Institute of Medicine report on drug safety raised concerns over the culture at the FDA. The report described the agency as "an organizational culture in crisis." We asked you about this issue at your confirmation hearing and you promised to address the problem. Please describe in detail what you have done.

Answer 3. Addressing the organizational culture issue is a top priority for FDA. Significant culture change is an evolving process that has already begun. As noted in FDA's written statement, FDA's Center for Drug Evaluation and Research (CDER or the Center) 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 already implemented process improvements recommended by CDER's Office of Surveillance and Epidemiology (OSE) and Office of New Drugs (OND) staff including 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.

Also, as noted in FDA's written statement, 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 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.

Question 4. I'm intrigued by the plan to review the available information about a drug, 18 months after approval. But this innovation suggests something very disturbing about the current drug safety system: FDA doesn't currently look proactively at the information about the safety of a drug. Instead, it only does so if something truly striking happens, like several liver failures, or the termination of a clinical trial for safety reasons. In the absence of something such as this, a drug simply isn't looked at now. Is that correct?

Answer 4. This is not correct. Staff in OSE and OND review post-marketing safety continuously. FDA reviews reports of serious and unexpected adverse experiences that drug companies are required to submit within 15 days, periodic safety reports that are submitted by drug companies quarterly for the first 3 years following approval and annually thereafter, and reports of serious problems sent directly by health care professionals and consumers, in addition to information from medical literature, clinical trials, other members of a class of drugs, and other sources.

With the rapidly increasing number of adverse event reports that the Agency receives (under 200,000 in 1996 and over 470,000 in 2006), we are focusing on making our post-marketing drug safety review processes more effective and efficient. We embarked on the New Molecular Entity Pilot Evaluations to examine whether we can more rapidly and predictably detect problems in newly approved drugs. In the pilot program, we are closely examining all available safety data of a few drugs selected for the pilot after they have been on the market for a period of time, such as 18 months or 2 years. We are examining the analyses needed, the most efficient approaches to communicating and discussing the data, the timeframes in which it can be accomplished, and how this systematic look compares to the review processes already in place. We will also be measuring the resources needed to conduct these scheduled reviews. At least four drugs will be studied initially. Then, FDA will assess the pilot program for possible wider implementation.

Question 5. I am concerned about antibiotics used for human treatment and how use of these antibiotics in animals may contribute to the development of drug-resistance in bacteria. I have several questions related to the use of antibiotics in animals. Do you think Congress should give the FDA the authority to collect data on how much of an antibiotic is used for treatment of animals and on which animals it is used in a way that protects legitimate confidential business information? What programs does the FDA's Center for Veterinary Medicine now have in place to collect and compile information on post-approval antibiotic use?

Answer 5. FDA currently requires that drug sponsors provide information on the distribution of each approved new animal drug product. Title 21, *Code of Federal Regulations* (CFR) 514.80(b)(4)(i). This requirement applies to all approved new animal drugs and does not include any provisions specific to antimicrobial new animal drugs. The required information must include the total number of distributed units of each size, strength, or potency. However, the current requirements are limited to drug distribution (sales) data. Furthermore, depending on whether a given product is approved for multiple animal species or indications, the current requirements do not necessarily provide information for each intended use or type of animal for which the drug is approved.

Question 6. FDA Guidance Document #152 focuses on the impact of animal drugs on food-borne infections in people. The World Health Organization has issued a report examining the impact on all human infections. Do you think the FDA, when considering approval of medically important antibiotics for use in animals, should follow WHO's approach and consider the impact of such use on all human infections?

Answer 6. FDA recognizes that food-borne human exposure to antimicrobial resistant bacteria is complex and often involves the contributions from other sources of exposure; for example, direct contact between animals and humans and the introduction of resistant bacteria and resistance determinants into the environment. However, FDA believes that evaluating antimicrobial new animal drug safety relative to the most significant exposure pathway, i.e., food-borne pathway, is the best

way to qualitatively assess the risk of antimicrobial drug use in food-producing animals. Nonetheless, as stated in Guidance 152, non-food-borne bacteria may be considered when deemed necessary; for example, uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies.

In developing criteria for ranking antimicrobial drugs with regard to their importance in human medicine, FDA considered broad issues associated with the efficacy of drugs in human medicine and factors influencing the development of antimicrobial resistance. Specific factors include the usefulness of the drug in food-borne infections, the types of infections treated, the availability of alternative therapies, the uniqueness of the mechanism of action, and the ease with which resistance develops and is transferred between organisms.

The World Health Organization (WHO) has also developed a system for ranking antimicrobial drugs with regard to their importance to human medicine. However, the WHO approach differs somewhat from the approach adopted by FDA. WHO determines the critical nature of an antimicrobial drug based on its use as the sole therapy or one of few alternatives to treat serious human disease and on its use to treat diseases caused by organisms that may be transmitted via non-human sources or diseases caused by organisms that may acquire resistance genes from non-human sources. WHO is looking broadly at diseases worldwide that may not be present in the United States.

As mentioned previously, FDA believes that human consumption of animal-derived foods represents the most significant pathway for human exposure to antimicrobial resistant bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals.

Question 7. Does the FDA have legal authority to place extra-label use restrictions on an animal drug prior to the drugs' being marketed when either a drug sponsor's own risk assessment or an internal FDA risk assessment finds that a potential drug approval presents a high risk of resistance adversely affecting human health? Does the FDA have the legal authority to act pro-actively to put in place an extra-label prohibition on an antimicrobial drug in cases where research shows that the drug is likely to select for resistance that would harm human health, but because the drug has not yet been marketed there is no evidence that extra-label use has caused a problem?

Answer 7. FDA has the legal authority to prohibit the extra-label use of an approved new animal drug or human drug if it has evidence to support the conclusion that the extra-label use in question presents a risk to public health. Such evidence could be based on a risk assessment, published literature, surveillance data, or any other available information. FDA issued an order in May 1997 (62 FR 27944) to prohibit the extra-label use of fluoroquinolone and glycopeptide drugs in food-producing animals. At the time of issuance of that order, fluoroquinolone drugs were approved and marketed for use in certain animal species. Although certain glycopeptide drugs were approved for use in humans at that time, no glycopeptide drugs were approved or marketed for use in animals nor are any drugs in the glycopeptide class approved for use in animals today. To date, FDA has not issued an order to prohibit the extra-label use of a drug concurrently with the approval of that drug in animals. However, FDA believes it has the authority to do so if evidence supports a finding that extralabel use of the drug presents a risk to public health.

FDA's extra-label use regulation defines *presents a risk to public health* to mean FDA has evidence that demonstrates that the use of the drug has caused or likely will cause an adverse event. (21 CFR 530.3(e)) The most recent example of FDA exercising its authority to prohibit extra-label use was the order issued on March 22, 2006, to prohibit the extra-label use by veterinarians of anti-influenza adamantane and neuraminidase inhibitor drugs in chickens, turkeys, and ducks. Although these anti-influenza drugs are approved for use in humans, these drugs are not approved or marketed for use in animals. Nevertheless, FDA compiled sufficient evidence to meet the statutory standard that such extra-label use presents a risk to public health.

Question 8. Section 17 of the Best Pharmaceuticals for Children Act required the Food and Drug Administration to issue within a year a final rule to require that FDA-approved drugs be dispensed with the toll-free MedWatch number, so patients can report adverse events. FDA issued a proposed rule on April 22, 2004, more than 2 years after the date of enactment of the BPCA. FDA has yet to issue the final rule, more than 5 years after enactment. When will FDA issue the final rule required by BPCA?

Answer 8. The proposed rule on Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products published on April 22, 2004, with the comment period ending July 21, 2004. In the proposed rule FDA solicited comments on the wording of the proposed labeling statements. We received a number of comments suggesting changes to the specific wording of the proposed statements. We have been conducting studies designed to resolve issues raised by the comments and to optimize consumer understanding of the labeling statements. We plan to finalize the rule upon completion of these studies.

QUESTIONS OF SENATOR ENZI

Question 1. Some PDUFA IV resources are focused on giving FDA more ability to use some of the large patient databases to conduct drug safety studies. How many new information sources would the PDUFA IV funds allow access to? How many studies of the user fees might these increased fees support?

Answer 1. PDUFA IV proposes to increase funding directed to purchasing access to databases for post-marketing research to about five times the current funding level (from about $1,000,000 to $5,000,000). The funding will support formal epidemiologic drug safety studies and active surveillance. We cannot determine how many databases or studies we will be able to support with these funds because the cost depends on a number of factors such as size of the database, type of study, i.e., epidemiological or active surveillance research, and other study design elements. One study alone could cost as much as $500,000 to $1,000,000, or even more.

Question 2. Right now, if a safety issue arises after a drug is marketed, can the agency require a study or clinical trial to follow up on the issue? My understanding is that you can request it, but not require it. Is that correct?

Answer 2. Yes, that is correct, but post-marketing studies may occur in the following circumstances:

- A post-marketing study might be conducted because an applicant and FDA agree, in writing, that one or more such study should be conducted. These agreements can be made at the time of approval or after FDA grants marketing approval.
- In addition, an applicant may be required to conduct a post-marketing study under certain circumstances. FDA can require an applicant to conduct studies to verify and describe clinical benefit for a drug or biological product approved in accordance with the accelerated approval provisions at 21 U.S.C. 356(b)(2)(A); 21 CFR 314.510 and 601.41.
- For a drug or biological product approved on the basis of animal efficacy data because human efficacy studies are not ethical or feasible, an applicant must conduct studies when ethical and feasible to verify and describe clinical benefit and to assess the product's safety.
- The Pediatric Research Equity Act of 2003 authorized FDA to require pediatric studies of marketed drugs that are not adequately labeled for children.

Question 3. I think there's a lot to like in the PDUFA IV proposal for drug safety. However, I believe FDA needs new authorities to really do its job. Do you agree? If not, why not?

Answer 3. We believe it is important that FDA have appropriate resources and the capacity to develop better scientific tools and approaches to drug review and safety. We have provided technical assistance on drug safety bills and FDA and the Administration are currently evaluating whether new authorities are necessary or appropriate. FDA will use our current authority to the best of our ability.

QUESTIONS OF SENATOR BURR

Question 1. I know that this is off-subject, but last week we held a hearing on follow-on biologics, I like to call them biosimilars. Do you think that the Clinton-Schumer bill sets up a good pathway for the FDA to approve biosimilars?

Answer 1. Given the complex scientific and legal considerations addressed in this legislation, we are still looking at this and other bills in relation to our developing thoughts on this issue. We would be happy to speak with you or appropriate staff about this legislation.

Please let us know if you have further questions.

QUESTIONS OF SENATOR HATCH

Question 1. On January 11, 2007, FDA announced that "serious questions remain about the validity of bioequivalence data" of 140 marketed generic drugs. As FDA has previously said, "bioequivalence is critical for drawing the conclusion that both the original and generic drugs will produce similar therapeutic results." If FDA has

"serious questions" about whether 140 generic drugs actually work like the brand drugs for which they are substituted, how can FDA allow those questionable drugs to stay on the market?

Answer 1. FDA had serious questions about the conduct of bioequivalence studies done by MDS Pharma Services (MDS Pharma) that were submitted to the Agency in support of various abbreviated new drug applications (ANDAs). MDS Pharma is a contract company that performs bioequivalence studies for a number of pharmaceutical companies.

FDA conducted a series of lengthy inspections of MDS Pharma bioequivalence studies covering laboratory analyses and analytical results, and found significant deficiencies with several studies that were conducted by MDS Pharma from 2001 to 2005. As a result of these deficiencies, FDA was unable to verify the results reported from these studies. The bioequivalence studies for these particular products in question were either re-analyzed or repeated by the ANDA sponsors, and this additional work by the sponsors confirmed the accuracy of the bioequivalence findings from the initial studies. It is important to note that FDA inspected many other MDS Pharma bioequivalence studies conducted during the 2001 to 2005 time period and found those studies acceptable.

The Agency then focused on those remaining bioequivalence studies conducted by MDS Pharma during the 2001 to 2005 time period that had not been inspected by FDA and that were submitted in support of 140 approved ANDAs. Although the Agency had serious concerns about the conduct of some of the bioequivalence studies by MDS Pharma based on its previous inspection findings, the Agency did not have any adverse inspection findings for these specific studies that would undermine the Agency's bioequivalence conclusions regarding these products. In addition, these products had satisfied the Agency's rigorous chemistry and manufacturing standards for approved drugs.

Nevertheless, FDA took additional steps to assure that the bioequivalence data for these 140 products were reliable. To obtain these necessary assurances, on January 11, 2007, FDA sent written requests asking that the ANDA sponsors do one of the following, in order of FDA preference, within 6 months:

a. Repeat the bioequivalence studies;

b. Re-assay the samples at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period; and

c. Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of bioequivalence studies and bioanalytical data, selected by the manufacturer rather than by MDS, to verify the results obtained by MDS.

Confirmatory data received from sponsors thus far have supported the bioequivalence determinations that were made. At the end of the 6-month period, FDA will reassess whether any additional steps will need to be taken.

Question 2. Why did FDA announce it had "serious questions" about these 140 marketed drugs, but not disclose their identities to the American public, so they could decide for themselves whether they wanted to take these questionable products?

Answer 2. FDA took these actions described in response to Question 1 as a precautionary measure to ensure that data submitted to the Agency and used to support approval decisions were accurate. FDA's routine adverse event surveillance monitoring program has not detected any signals or evidence that any of the drugs involved pose a safety risk or that there has been any impact on efficacy. FDA does not have any evidence that there are problems with the quality, purity, or potency of the affected drug products. Moreover, the studies at issue were conducted by MDS Pharma, a contract research organization with which the ANDA holders had a contractual arrangement, and the information was considered to be confidential commercial information and not releasable to the public.

Question 3. Absence of evidence is not evidence of absence. FDA says it has no evidence that the 140 drugs pose a safety risk or have impaired efficacy. I question how you can be sure. You stated, "FDA's routine adverse event surveillance monitoring program" has not detected any problems. This is the same monitoring that the recent IOM Report found inadequate for new drug adverse event reporting, and which current drug safety legislative proposals seek to improve. If FDA's current monitoring system is inadequate, how can you be sure none of the 140 drugs have problems?

Answer 3. Approval of a generic product depends on meeting standards for purity and potency of the drug substance as well as bioequivalence. These products have all met the usual chemistry and manufacturing standards for approved drugs. As

noted in the answer to Question 1, FDA has asked all sponsors of the 140 relevant products to follow one of the three options within 6 months to confirm that bioequivalence standards have been met.

While FDA generally relies on AERS and MedWatch and post-marketing safety reporting as the sources for surveillance monitoring, the Office of Generic Drugs (OGD) also receives reports of potential bioequivalence problems from many other sources, and follows up on these reports from sources including individual patients, and problems reported in the literature.

Question 4. Please explain how FDA's adverse event monitoring system tracks generic drugs. Do you track adverse events by manufacturer?

Answer 4. The Adverse Event Reporting System (AERS) is a computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products (including both brand and generic products). The goal of this system is to improve the public health by providing the best available tools for storing and analyzing safety reports.

FDA receives adverse drug reaction reports from manufacturers as required by regulation. Health care professionals and consumers send reports voluntarily through the MedWatch program. These reports become part of a database. The structure of this database is in compliance with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization.

The reports in AERS are evaluated by clinical reviewers in the Office of Surveillance and Epidemiology in CDER to detect safety signals and to monitor drug safety. Reports about generic drugs are tracked in the same manner as reports about new drug products. The analyses of reports are usually done to assess the potential adverse effects of the molecule, and not the drug product of an individual manufacturer.

Question 5. Does FDA have any monitoring system capable of detecting bioequivalence problems? If so, what data are incorporated into the monitoring program that would provide a signal of a bioequivalence problem? If not, on what scientific basis can FDA confer a judgment that the absence of evidence of safety and efficacy problems is a sufficient validation that ANDA sponsors have submitted information showing bioequivalence?

Answer 5. Although bioequivalence problems are difficult to detect because of the large amount of variability between individuals, and from time to time within the same individual, regarding the therapeutic response to a drug, the AERS database and MedWatch post-marketing safety reporting are capable of detecting bioequivalence problems. It is acknowledged that the voluntary reporting on which the systems are based is a limiting factor. However, OGD also receives reports of potential bioequivalence problems from many other sources, and follows up on these reports from other sources including individual patients, and problems reported in the literature. See the response to Question 1 for a description of the steps FDA has taken with respect to the 140 products at issue in the MDS Pharma case.

Question 6. Please provide the committee with a list of the 140 generic drugs subject to the January 11 announcement.

Answer 6. We are unable to provide the list of products because information about companies that have contractual arrangements with MDS Pharma is confidential commercial information.

[Whereupon, at 12:42 p.m., the hearing was adjourned.]

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