S. HRG. 109–850

BUILDING A 21ST CENTURY FDA: PROPOSALS TO IMPROVE DRUG SAFETY AND INNOVATION

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED NINTH CONGRESS

SECOND SESSION

ON

EXAMINING PROPOSALS TO IMPROVE DRUG SAFETY AND INNOVATION, AND S. 3807, TO AMEND THE PUBLIC HEALTH SERVICE ACT AND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT TO IMPROVE DRUG SAFETY AND OVERSIGHT

NOVEMBER 16, 2006

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BUILDING A 21ST CENTURY FDA: PROPOSALS TO IMPROVE DRUG SAFETY AND INNOVATION

THURSDAY, NOVEMBER 16, 2006

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

The committee met, pursuant to notice, at 10:02 a.m., in Room SD-426, Dirksen Senate Office Building, Hon. Michael B. Enzi, chairman of the committee, presiding.

Present: Senators Enzi, Isakson, DeWine, Hatch, Kennedy, Murray, Reed and Clinton.

OPENING STATEMENT OF SENATOR ENZI

The CHAIRMAN. Good morning and welcome to today's hearings on ideas and proposals for reforming our Nation's regulatory framework for reviewing and approving prescription drugs. For decades, the United States has been the standardbearer in bringing new drugs and medications to the world market. However, in the past few years there have been some concerns that caused the public to lose confidence in our drug safety system.

At the beginning of the 109th Congress last year, Senator Kennedy and I pledged to work together with the Food and Drug Administration and its policies and procedures for bringing new drugs to the marketplace. In fact, two of the very first HELP Committee hearings in this Congress were focused exclusively on drug safety. Overall we've had 10 hearings on issues involving the FDA. We incorporated the witnesses' recommendations and comments from a series of stakeholder meetings into the development of the Enhancing Drug Safety and Innovation Act, S. 3807.

We also took the extra step of posting the draft of the Enzi-Kennedy drug safety bill on the HELP Committee Website so the public could comment, and we received dozens of comments from consumer groups, from patient advocates, industry, and other members of the public, and we've incorporated as many as possible of those into the introduced bill.

Just like the bipartisan effort that led to the Prescription Drug User Fee Act and the Food and Drug Administration Modernization Act, now's the time for our bipartisan legislation to bring more consistency, transparency, and accountability to the drug approval process. This legislation would create a more structured framework, leverage advances in science and technology to build a more effective and efficient FDA. This is further evidenced by the fact that many of the recommendations made by the recent Institute of

Medicine report on drug safety were already part of the bill well before the release of the report.

Now, throughout our oversight process we heard repeatedly that all drugs have risks and the risks and benefits must be weighed together, not separately. We also learned that the FDA has considerable existing statutory authority. However, the application of that authority can often be too blunt an instrument for the situations currently faced by the agency. Perhaps that's because we do not have a confirmed commissioner.

Witness after witness recommended that the agency be granted a variety of intermediate authorities so that the agency can more finely calibrate its actions to match the problem and challenges presented to it. For example, granting FDA special authority for label changes, post-marketing studies, or delays in direct-to-consumer advertising.

However, rather than enact a series of solutions to accommodate each and every potential situation, we must look at a way to accommodate any needed change in the drug approval process and post-market monitoring. Under our legislation the FDA would begin to approve drugs and biologics and new uses for these products with risk evaluation and mitigation strategies, otherwise known as REMS. The REMS are designed to be an integrated, flexible mechanism to acquire and adapt to new safety information about a drug. The drug company sponsor and the FDA would assess and review an approved REMS at least annually for the first 3 years, as well as during review of applications for a new use for the drug, when the sponsor suggests changes, or when the FDA requests a review based on new safety information.

Another significant problem faced by the FDA is that the development of tools to evaluate medical products has not kept pace. New tools are needed to better predict safety and effectiveness of drugs, which in turn would increase the speed and efficiency of applied biomedical research. Our bill would spur innovation by establishing a new public-private partnership at the FDA to advance what's known as the Critical Path Initiative. This is the FDA's effort to improve the sciences of developing, manufacturing, and evaluating the safety and effectiveness of drugs, devices, biologics, and diagnostics. We can accelerate and assure its continued vitality by creating a permanent locus at the FDA, which we're calling the Reagan-Udall Institute for Applied Biomedical research.

Our bill also establishes a central clearinghouse for information about clinical trials and their results to help patients, providers, and researchers access these materials so they can make more informed healthcare decisions.

Finally, the act would make great improvements to the FDA's screening process for advisory committee members.

When we began our hearings early last year, the FDA asked the Institute of Medicine to conduct a study covering the agency and the U.S. drug safety system. That report was released in late September of this year. I've been struck by how closely the Institute of Medicine's exhaustive report recommendations parallel provisions in S. 3807. I look forward to hearing more today from Ms. Sheila Burke, Chair of the Institute of Medicine Committee on the Assessment of the U.S. Drug Safety System about those rec-

ommendations as well as the other findings and recommendations in the report. I'm also very interested to hear the reaction of our second panel to the recommendations raised in the IOM report and pending legislative proposals. I'm confident we can continue with the open process we've initiated to address the few areas of difference.

I want to thank the dozens of stakeholders, including the Food and Drug Administration, patient and consumer groups, industry associations, individuals, companies, and scientific experts, who have taken the time and effort to give us their comments and input on the bill. Their assistance has been invaluable.

I also look forward to working with my colleagues to advance this important piece of legislation. In the upcoming year we face an exceptionally full agenda with respect to the FDA. Besides updating the FDA's authorities—as proposed in S. 3807—we need to reauthorize both the drug and device user fee programs, as well as the Best Pharmaceuticals for Children and Pediatric Research Equity Acts. Also, we should move to confirm the nomination of Dr. Andrew von Eschenbach to be the Commissioner of Food and Drugs, and hopefully we'll do that before we leave this time. Dr. von Eschenbach has a strong record. He is an accomplished scientist, a proven manager, a man with vision. He's also a cancer survivor and has brought the perspective and compassion that goes with it to his government service. He gave up a job he loves directing the National Cancer Institute to offer his service in what I believe is a much more challenging and often thankless job of leading the FDA.

Dr. von Eschenbach has received significant support from the HELP Committee. I urge my colleagues who are not on the committee to give Dr. von Eschenbach the chance to effectively run the FDA with full statutory authority. The FDA needs a leader with the backing and the mandate that Senate confirmation provides. This Congress must take up Dr. von Eschenbach's nomination before we adjourn.

Before I invite Senator Kennedy to make his opening statement, I want to congratulate him as he prepares to take the gavel of this committee in the next Congress. I know that he has served as Chairman of this committee before and wields the gavel well.

Senator KENNEDY. Lightly, lightly.

The CHAIRMAN. After the first of the year, he will be my favorite chairman.

[Laughter.]

Senator KENNEDY. But until then——

The CHAIRMAN. It's a line I borrowed from him 2 years ago.

Senator KENNEDY. There you go. Thank you.

The CHAIRMAN. I'm proud that this committee has worked together to achieve a lot over the last 2 years. We approved 37 bills. Twenty-five of those bills passed the Senate and 15 bills were signed into law. Most of the bills passed with overwhelming bipartisan support and took up very little time on the floor. We still have more to do.

This committee has worked together to: strengthen our pension system, update our mine safety laws, create a national network of cord-blood stem cell banks, improve our career and technical edu-

cation programs, help the chronically ill navigate our healthcare system and afford health insurance, and allow doctors and nurses to work together in a protected legal environment toward reducing medical errors and improving patient safety.

Now, we have a lot on our plate for the next Congress—No Child Left Behind, Head Start, WIA, Higher Education, several pieces of food and drug legislation, and a reasonable solution for health insurance. If we work together in the same spirit we did in the last 2 years, I am confident we can get all of this done and more. So when this Congress comes to a close and the next one begins, I will be working with Senator Kennedy in every way possible to see that we can meet the challenges that are left over from the 109th and stand ready to work with him on important issues that come before us, just as he has worked with me.

And I thank you for that and I recognize you for your opening statement.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. Thank you. Well, thank you very much, Chairman Enzi, particularly for your kind and generous comments. You've arranged this extremely important hearing today with the same kind of consideration and courtesy that have been the hallmark of your chairmanship, and your bipartisanship is a major reason why this committee has worked so effectively over the past years on many, many, many problems that affect American families. And you've set a very high standard for reaching out and working with all the members of the committee to try and find common ground, and that is certainly a standard which I'll do the best I can to meet. It's been really a great honor and a pleasure to work with you.

This committee deals with some of the most important issues and questions that affect ordinary Americans in so many ways. Today is just one very extremely important aspect of it, but this committee works in so many different areas. So we have worked and I hope we will continue to work closely together as we address the unfinished business of our committee and of the Congress.

So I thank you for your kind words and congratulate you on really an extraordinary period of service to this committee and to the Senate and to Wyoming.

Millions of Americans rely on the drugs that FDA reviews to protect them from sickness and now the FDA itself urgently needs treatment. I join my colleague and friend. The agency needs to have a confirmed leader. We have been nearly 5 out of 6 years with acting directors. We need to make sure that we have a leader in the FDA, and I join the Chairman in hoping that the Senate will confirm Dr. von Eschenbach.

Science has too often had to take a back seat at the very agency which should be setting the standards for objectivity and integrity. There's growing evidence that the dedicated professionals at FDA have been pressured to trip the scientific views to prevailing patient winds. These are symptoms of a serious illness and we should act without delay to provide the cure.

The Institute of Medicine has done a valuable service for the Nation by diagnosing the problem and providing a prescription for

treatment, and it's up to us to see that the patient takes the right medicine and hopefully has a quick recovery.

The stakes are high. FDA oversees products accounting for a quarter of the U.S. economy. Every day it makes decisions that make the difference between life and death for American patients.

It's an honor to welcome Sheila Burke, who served the Senate with such distinction on the staff of former colleague Bob Dole. Sheila, who is now the Deputy Secretary of the Smithsonian, found the time to chair the panel on IOM and made these important recommendations on drug safety. As the IOM report makes clear, FDA has many needs that Congress must address, and we join in welcoming Sheila Burke.

The FDA budget is $1.8 billion a year. That may sound like a lot, but it works out to about $6 a year for every American. In Washington, DC., you can barely buy a sandwich for $6. Yet with that amount we expect the FDA to assure the safety of the food we eat, the drugs we take, the medical devices that save so many lives. Clearly we need to increase the FDA's budget so that it can do a better job of guaranteeing drug safety.

When I mention that, I see my friend and colleague from Utah, Senator Hatch, who's been the former chairman of this committee and also put the issue of the FDA as a high priority on his agenda in terms of the safety and making sure that it's going to have the kind of support here in Congress, along with my other colleagues Senator Murray and Jack Reed.

Additional authority is needed as well. The Institute of Medicine's report recommends the FDA have the power to require post-marketing risk assessment, risk management programs for new drugs, and require the industry to make the results of drug safety studies available to the public. The Enhancing Drug Safety and Innovation Act Chairman Enzi and I introduced earlier this year addresses these needs and, like the Institute of Medicine report, our bill emphasizes the need for a life cycle approach to drug regulation both before and after approval.

Mr. Chairman, I will include the rest of my statement, which is an analysis of the bill, which you've done very capably in your opening statement, in the record. I just wanted to mention how glad I am to see Senator Murray, who has been such a strong member of this committee and has been such a constructive and positive force in ensuring that we're going to have the best in terms of scientific integrity at the agency, and my colleague Jack Reed, who was a key figure at the time that we reauthorized the FDA. He was enormously involved in the details of this legislation, as he is in so many. So I welcome other members of our committee here and I thank you.

[The prepared statement of Senator Kennedy follows:]

PREPARED STATEMENT OF SENATOR EDWARD M. KENNEDY

Thank you Mr. Chairman. I commend you for calling this hearing on the role of the Food and Drug Administration in protecting the safety of the Nation's prescription drugs.

You've arranged today's hearing with the same consideration and courtesy that have been the hallmark of your chairmanship. Your bipartisanship is a major reason why the committee has worked so effectively over the past 2 years on many problems affecting America's families, and I'll do my best to see that the committee continues to do business in the same spirit in the next Congress.

Millions of Americans rely on the drugs that the FDA reviews to protect them from sickness. But now, the FDA itself urgently needs treatment.

For too long, the agency has been without a confirmed leader. Science has too often had to take a back seat at the very agency which should be setting the standard for objectivity and integrity. There is also growing evidence that the dedicated professionals at the FDA have been pressured to trim their scientific views to the prevailing political winds.

These are symptoms of a serious illness, and we should act without delay to provide the cure.

The Institute of Medicine has done a valuable service for the Nation by diagnosing the problem, and providing a prescription for treatment. It's up to us to see that the patient takes the right medicine, and hopefully has a quick recovery.

The stakes are high. The FDA oversees products accounting for a quarter of the U.S. economy. Every day, it makes decisions that mean the difference between life and death for American patients.

It is an honor to welcome, Sheila Burke, who served the Senate with such distinction on the staff of our former colleague Bob Dole. Sheila is now Deputy Secretary of the Smithsonian, but she found the time to chair the panel at the IOM that made these important recommendations on drug safety. As the IOM report makes clear, FDA has many needs that Congress must address.

Its budget is $1.8 billion a year. That may sound like a lot, but it works out to about $6 a year for every American. In Washington, DC, you can barely buy a sandwich for $6—yet for that amount, we expect the FDA to assure the safety of the food we eat, the drugs we take, and the medical devices that save so many lives. Clearly, we need to increase FDA's budget, so that it can do a better job of guaranteeing drug safety. But money alone won't meet all the challenges. Additional authority is needed as well.

The Institute of Medicine's report recommends that FDA have the power to require postmarketing risk assessment and risk management programs for new drugs, and to require the industry to make the results of drugs safety studies available to the public.

The Enhancing Drug Safety and Innovation Act, which Chairman Enzi and I introduced earlier this year, addresses these needs. Like the Institute of Medicine report, our bill emphasizes the need for a "life-cycle" approach to drug regulation, both before and after approval.

The bill would require every drug approved by the FDA to have an enforceable Risk Evaluation and Mitigation Strategy, tailored to fit the risk profile of each new drug. Where appropriate, the strategy could include special requirements for labeling, postmarket clinical studies, and limitations on marketing the drug directly to consumers. For drugs with the most dangerous side effects, the strategy might require that only doctors with specialized training be allowed to prescribe the drug. If a manufacturer fails to implement a precaution that it has agreed to, the FDA will have new authority to assess civil monetary penalties to enforce compliance.

By providing a legally enforceable yet flexible way for the FDA to oversee safety throughout the life cycle of a drug, the bill gives the agency the authority it now lacks to take effective action to ensure safety.

The legislation also creates a public-private partnership to improve the science of drug safety and drug development. It will help patients and physicians make more informed decisions by requiring the results of drug trials to be included in a public database. Our bill also takes stronger steps to avoid financial conflicts of interest by members of FDA advisory committees.

Again, Mr. Chairman, I commend you for calling this hearing. I look forward to working with you and our colleagues on both sides of the aisle to give the FDA the authority it needs to restore public trust in the safety of prescription drugs. I welcome our witnesses and look forward to their testimony.

The CHAIRMAN. Thank you, and I would mention that anyone on the committee that has a statement, we'll make it a part of the record without objection.

I'd like to welcome Ms. Sheila Burke, the Chair of the Institute of Medicine Committee on the Assessment of U.S. Drug Safety System and a member of the Institute of Medicine. She is also the Deputy Secretary and Chief Operating Officer of the Smithsonian Institution, Vice Chair of the Robert Wood Johnson Health Policy Fellowships Board, and a member of the Medicare Payment Advisory Commission.

Ms. Burke began her career as a staff nurse in Berkeley, California, and as Director of Program and Field Services for the National Student Nurses Association in New York. She earned a master's of public administration from Harvard University and a bachelor of science in nursing from the University of San Francisco. Ms. Burke will share the Institute of Medicine's perspective on what Congress can and should do to improve drug safety while preserving patient access to important pharmaceutical therapies.

STATEMENT OF SHEILA P. BURKE, CO-CHAIR, COMMITTEE ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYSTEM, INSTITUTE OF MEDICINE

Ms. BURKE. Good morning, Mr. Chairman, Senator Kennedy, members of the committee. I thank you very much for the opportunity to talk with you this morning.

The CHAIRMAN. I don't think the microphone's——

Ms. BURKE. On?

The CHAIRMAN. Is there a little light on there?

Ms. BURKE. It is.

The CHAIRMAN. Thank you.

Ms. BURKE. I am grateful for the opportunity to talk with you about the Institute of Medicine's report. The committee was convened in 2005 at the request of the Food and Drug Administration. In addition, we were supported by the Centers for Medicare and Medicaid Services, the Agency for Health Care Research and Quality, the National Institutes of Health, and the Department of Veterans Affairs.

One of the major areas of debate in the world of drug regulation is how one can monitor the safety profile of drugs once they are on the market. This, in fact, was our focus. As a result, while the committee considered a wide array of issues, there are several important topics that either fell outside of our charge or we were unable to consider.

For example, we did not undertake a systematic assessment of concerns related to the specific drugs that have captured the public's interest in recent years. Our report focuses on the post-approval process and period and therefore does not include a detailed examination of the pre-approval process, including the conduct of clinical trials.

The committee's attention was solely on prescription drugs and the drug safety system, in particular the functioning of the FDA's Center for Drug Evaluation and Research, or CDER, which is responsible for drug review, approval, and regulation. The report puts forth the vision of a transformed drug safety system that has at its core a life cycle approach to drug risk and benefit. Life cycle describes the level of attention to a drug's safety and efficacy that does not taper off after the time of approval, but is sustained from discovery and development to the end of useful product life. This is not a new concept, but it is one that we believe has been implemented at best in a limited and a fragmented manner.

The report contains 25 recommendations in 5 topic areas: CDER's organizational culture, science, scientific expertise, regulation, communication, and resources. There are 11 recommendations that may be of particular interest to the committee that are, in

fact, very similar to provisions that are contained in S. 3807, the bill introduced by the Chairman and Mr. Kennedy. The key areas covered by these recommendations include regulatory authority, agency leadership, resources, and credible science.

First, the FDA's regulatory authorities are derived from a statute that has been amended numerous times, yet requires in our view strengthening and clarification to allow the agency the flexibility to regulate increasingly complex drugs. The committee was cognizant of the fact that the outcomes of regulation are not simply paper documents, but, in fact, the health of living, breathing patients. Delaying approval until absolute complete certainty is reached or withdrawing a drug once safety problems arise are often not realistic options. Yet they reflect the largely all or nothing nature of FDA regulatory authorities.

Our committee recommended that FDA be given a tool kit of regulatory options that it can apply as appropriate and necessary at any time in the life cycle of a drug and clarified authority to enforce sponsor compliance with restrictions or limitations on marketing imposed at or after the time of approval.

Second, the committee found that, while CDER staff work with great dedication and professionalism, the center's organizational culture is in some ways and at some times dysfunctional. The report identified several factors that seem to shape organizational culture at CDER and offered solutions to strengthening collaborations, improving stability and the support of leadership's ability to affect organizational change.

We believe that the turnover and the instability in the commissioner's office leave the agency without effective leadership, and without stable leadership strongly and visibly committed to drug safety all other efforts to improve the effectiveness and the efforts to improve the agency or its position to effectively deal with safety for the truth and for the future will be seriously, if not fatally, compromised. To this end, the committee, among other things, has recommended that the commissioner be appointed for a 6-year fixed term.

Third, the commitment of public servants, the concern of Congress, the advocacy of consumer organizations, among others, is not enough to transform the drug safety system. A substantial and sustained financial investment is needed. An agency whose crucial mission it is to protect and advance the public's health should not have to go begging for resources to do its job.

We acknowledge that the user fee program in place has had many positive effects on the drug safety and drug approval process. However, we prefer that additional funding required to implement the recommendations in the report come entirely from appropriations. If securing this additional funding entirely from appropriations proves impossible, the committee urges that restrictions on the use of PDUFA funds be curtailed.

Fourth, the infusion of additional resources will also support the FDA's need for expertise in science and data. Research and the data that it produces is in many ways the lifeblood of the drug safety system. The committee believes that CDER needs to substantially increase the amount and quality of the data that accrue after a drug is on the market and to ensure systematic reviews of

what has been learned about a truly novel drug after its launch and its use in the real world.

We recognize that it is not enough to have strong science backing up regulatory decisions about safety. Safety science has to be credible. The committee has made several recommendations intended to expand expertise and research on drug safety at CDER. We have recommended measures to increase the credibility of the committee process as well, to increase opportunities for appropriate review of drug safety issues by advisory committees, provide greater transparency for patients and for providers of the information accumulated about a drug.

Our committee is grateful to have had the opportunity to be of assistance to the FDA and hopes that the agency and the Congress find that the report is useful in moving ahead to strengthen drug safety. Again my thanks for the opportunity to be with you today and I'm more than happy to answer any questions.

[The prepared statement of Ms. Burke follows:]

PREPARED STATEMENT OF SHEILA P. BURKE

Good morning, Mr. Chairman and members of the committee. Thank you for the opportunity to come speak to you this morning. My name is Sheila Burke. I am Chair of the Institute of Medicine (IOM) Committee on the Assessment of the U.S. Drug Safety System.

The Institute of Medicine of the National Academies is an independent, nongovernmental, nonprofit organization operating under the 1863 congressional charter to the National Academy of Sciences. The Institute of Medicine has provided advice to the Nation on matters of health and medicine for over 30 years. Early in 2005, the Food and Drug Administration (FDA) asked the Institute of Medicine to convene a committee of experts to conduct an independent assessment of the current system for evaluating and ensuring drug safety postmarketing and make recommendations to improve risk assessment, surveillance, and the safe use of drugs. In addition to FDA, the study was funded by the Centers for Medicare and Medicaid Services, the Agency for Healthcare Research and Quality, the National Institutes of Health, and the U.S. Department of Veterans' Affairs. The Committee on the Assessment of the U.S. Drug Safety System met for the first time in June 2005. The committee's areas of expertise include public policy, statistics, health informatics, pharmacy, clinical medicine, health plan management, pharmacoepidemiology, economics, drug regulation, consumer concerns, law and ethics, and academic research. The committee met six times, and held several information gathering sessions that were open to the public and included presentations from industry representatives and a variety of patient, consumer, and professional organizations. Some committee members also made two site visits to FDA, and engaged in confidential conversations with more than 30 former and current staff and leaders from FDA and especially its Center for Drug Evaluation and Research (CDER). The committee's report was released September 22, 2006.

First, let me speak briefly about what the report does and does not cover. The committee considered a wide array of issues, but there are several important topics that either fell outside the charge to the committee, or that the committee was unable to consider. For example, the committee did not undertake a systematic assessment of postmarketing safety concerns related to specific drugs that have captured the public's interest in recent years, such as the COX-2 inhibitors or the selective serotonin reuptake inhibitors. The report focuses on the postapproval period and therefore does not include a detailed examination of the preapproval process. The report also does not address over-the-counter drugs, or generics, nor does it treat at length the complex issues related to the conduct of clinical trials. The committee's focus was solely on prescription drugs and the drug safety system, in particular the functioning of FDA's Center for Drug Evaluation and Research, which is responsible for drug review, approval, and regulation.

The report recognized at the outset that it is impossible to think about safety independent of efficacy, and that the two must be considered together throughout the lifecycle of a drug. A drug's lifecycle begins at drug discovery and concludes at the end of useful product life. Drugs are approved after risk-benefit determinations made by FDA, but those determinations are made on the basis of clinical trials with

carefully selected participants and under controlled conditions. The real-life use of drugs is often quite different—a drug tested in a few hundred or thousand people is prescribed and used by millions often for longer periods and in conjunction with other drugs or supplements. That is why approval does not signify the end of uncertainty about a drug, and continued monitoring is necessary after approval. Most stakeholders in the drug safety system are aware of the need for continued attention to a drug's risk-benefit profile during the drug's lifecycle. However, the committee found an imbalance in the regulatory attention and resources available before and after a drug's approval. Staff and resources devoted to preapproval functions in CDER are substantially greater than those available for postapproval functions. The new drug review process involves sophisticated clinical trial design and execution; after approval, few high-quality studies are designed, conducted, and completed, and in general, the data available is quite limited. Before approval, regulatory authority is well-defined and robust; once a drug is marketed, FDA's ability to regulate and enforce becomes greatly diminished. Many of the committee's recommendations are intended to bring some of the strengths of the preapproval process to the postapproval process, to ensure ongoing attention to a drug's performance.

The committee made 25 recommendations in 5 topic areas: CDER organizational culture, science and scientific expertise, regulation, communication, and resources. A complete copy of the report is submitted for the record. Of the 25 recommendations, 11 are uniquely within Congressional purview or likely to be of interest to Congress. These include recommendations pertinent to expanding funding for the agency's mission, strengthening regulatory authority, stabilizing agency leadership, ensuring the credibility of regulatory science, and establishing a new advisory committee. More detailed discussion of key recommendations follows.

Research and the data it produces is in many ways the lifeblood of the drug safety system. The committee believes that CDER needs substantially increased resources to conduct and access better postmarketing safety research. The committee made a number of recommendations to increase the amount and quality of data that accrue after a drug is on the market. The committee recognized that it is not enough to have strong science backing up regulatory decisions about safety—safety science has to be credible. The committee made several recommendations intended to expand the expertise and research on drug safety at CDER. In addition, the committee recommended increased opportunities for appropriate review of drug safety issues by advisory committees, and transparency of the information accumulated about a drug (for example, the posting of structured field summaries and results of all efficacy and safety studies on a government Website, and the posting of all NDA and sNDA packages on the FDA Website). Other recommendations include: establishing a public-private partnership to prioritize, plan, and organize funding for confirmatory drug safety, efficacy, and effectiveness studies; demonstrating a commitment to research by appointing a Chief Scientist to oversee intramural and extramural research and by requesting and applying the necessary funding to support intramural research; and taking specific steps to increase the credibility of the advisory committee process.

FDA's regulatory authorities are derived from a statute that has been amended numerous times, yet requires some strengthening and clarification to allow the agency the flexibility to regulate increasingly complex drugs. In its discussion of FDA's ability to regulate, the committee was cognizant of the fact that the outcomes of regulation are not paper documents but the health of living, breathing patients. Delaying approval until complete certainty is reached, or withdrawing a drug once safety problems arise are often not realistic options, yet they reflect the largely all-or-nothing nature of FDA regulatory authorities. The committee recommended that FDA be given a tool kit of regulatory options it can apply as appropriate and necessary at any time in the lifecycle of a drug, and clarified authority to enforce sponsor compliance with restrictions or limitations on marketing imposed at or after the time of approval. The committee also recommended that CDER establish a milestone moment at 5 years after the approval of a new molecular entity (NME) (roughly 20–25 are approved yearly) to review all accumulated safety and efficacy data related to that NME. This will ensure that there is a systematic look back at everything that has been learned about a truly novel drug after its launch and use in the "real world." In another recommendation, the committee called for designating a special symbol to mark all new drugs, with the function of informing and educating the public that those products are placed under greater regulatory scrutiny and perhaps subject to stronger regulatory action (such as a moratorium on direct-to-consumer advertising during the period of time that the special symbol is in effect).

Anyone who has followed drug safety issues over the last several years has surely noticed that a theme that often surfaces is some type of management problem in

CDER. Information has emerged—both in the media and in government reports (e.g., from the DHHS Office of the Inspector General, and the Government Accountability Office)—about scientific disagreement poorly handled, a lack of collaboration among divisions, an appearance of interdisciplinary tension, a perception of inappropriate management expectations, and so on. On the basis of that information and discussions with present and former FDA staff and leaders, the committee has found that while CDER's staff work with great dedication and professionalism, the Center's organizational culture is, in some ways and at some times, dysfunctional. The report identified several factors that seem to shape organizational culture in CDER, and offered solutions to strengthening collaboration, improving stability and support of leadership's ability to effect organizational change, and addressing some of the challenges presented by a major force in FDA's external environment—the Prescription Drug User Fee Act. I'd like to draw your attention to two recommendations from the chapter on culture. The committee recommended that postmarketing safety staff have a formal role before approval and specific authority after approval. Although postmarketing staff, and specifically the staff of the Office of Drug Safety, now the Office of Surveillance and Epidemiology, are invited to some preapproval meetings, this does not occur consistently, it sometimes does not take place early enough in the preapproval process. Office of Surveillance and Epidemiology staff do not have a formal role before approval or authority after approval. This recommendation in the context of others in this report reflects the committee's view that keeping postmarketing safety activities closely linked with the drug approval process is crucial.

The committee also recommended a fixed-term for the FDA commissioner to stabilize the agency and promote a better integration of safety into the work of CDER. In the last 30 years, FDA has had eight commissioners and seven acting commissioners (including the current acting commissioner) or, when the post was vacant, an acting principal deputy commissioner. The eight commissioners have served an average of 2.5 years with a range of 2 months to 6.3 years. The committee believes that turnover and instability in the commissioner's office leave the agency without effective leadership or the potential to emphasize safety as having high priority in the work of the agency. Without stable leadership strongly and visibly committed to drug safety, all other efforts to improve the effectiveness of the agency or position it effectively for the future will be seriously, if not fatally, compromised.

In the area of communication, the committee referred to and endorsed the sentiment behind recommendations made in the recent report of the Committee on Preventing Medication Errors, released July 2006. (The summary of that report is found in Appendix E of the Future of Drug Safety report.) The committee also recommended a new mechanism—an advisory committee with the requisite expertise and representation—for improving FDA's communication to and with patients and the general public.

The commitment of public servants, the concern of Congress, the advocacy of consumer organizations, the interest of industry, among others, is not enough to transform the drug safety system in the ways outlined by the committee's suite of recommendations. A substantial and sustained financial investment is needed. The suite of recommendations put forward in this report—to improve the culture in CDER, attract and retain highly qualified staff, improve technological capacity, obtain and benefit from access to data and innovative scientific partnerships and so on—is dependent on adequate resources. An agency whose crucial mission is to protect and advance the public's health should not have to go begging for resources to do its job. The committee has acknowledged that the user fee program has had many positive effects on drug approval. However, the committee gave several reasons why it prefers that the additional funding required to implement the recommendations in the report for an improved drug safety system come entirely from appropriations. CDER's dependence on PDUFA funding with its associated restrictions may hurt FDA's credibility. If securing this additional funding entirely from appropriations proves impossible, the committee urges that restrictions on the use of PDUFA funds be curtailed.

The committee is grateful to have had the opportunity to be of assistance to FDA, and hopes that the agency and Congress find the report useful in moving ahead to strengthen drug safety.

Thank you for the opportunity to testify. I would be happy to address any questions the committee might have.

The CHAIRMAN. Thank you very much for chairing this very important committee and putting out this extremely helpful report. I do have, as many may have, some very detailed questions regard-

ing the report and I would submit some of those in writing. We definitely want to know what we've left out in the bill, and there are other people that have proposals and we'll have some evaluation of that, too.

But one of the big items is the benefit versus risk on prescription drugs, and I believe that they have to be considered together, not separately. Did the panel consider the idea of a separate office of drug safety, and if so what did the members of the panel think of that idea?

Ms. BURKE. Thank you, Mr. Chairman. We did, in fact, discuss that question and do not believe that breaking apart the agency and setting up a separate freestanding safety unit is in the interests of the kind of changes that we'd like to see go forward. We believe, in fact, it is inconsistent with the life cycle approach to drug safety and believe that for the regulatory staff to work more productively together, both pre- and post-marketing, that they are best kept together and have made a number of recommendations that would involve the post-marketing staff much earlier in the process, so, in fact, there is this attention to life cycle and they do develop the kind of collaboration we think is critical.

The CHAIRMAN. The report talks about life cycle of a product and how knowledge changes over time. Could you elaborate a little bit more on life cycle?

Ms. BURKE. Literally, Mr. Chairman, it is our view that the life cycle is from the point of the initial research until the end of a product life cycle. That is, its use in the market is really the timeframe in which we ought to really have in place a regulatory system that is adept at dealing with all aspects of that. That is in the gathering of the information on the pre-marketing and the review of that information and a linkage with the post-marketing tracking of data and analysis, and continue to be informed as new information becomes available.

One of the challenges I think that we face is in the course of clinical trials and the focus of those tends to be on a very narrow population, and one of the realities that we face in today's world is that once it goes into the market we are now in an instance where, in fact, there are patients perhaps that have different comorbidities, that may, in fact, be on different medications, that present a different picture than perhaps was looked at in the narrow range of a clinical trial, and that the gathering of that information and the continued information review and analysis is important to make sure that we fully are aware throughout that period of time of what takes place.

The CHAIRMAN. Thank you.

You also mentioned the cultural and administrative issues at the FDA and I appreciate that. Do you think it's possible for legislation to change an organization's culture?

Ms. BURKE. No, sir.

The CHAIRMAN. Would the pending legislative proposals on drug safety do so?

Ms. BURKE. You raise a very important question. In fact, there is nothing that we can do legislatively or, more appropriately, you could do legislatively that would, in fact, force a change in the culture. There are recommendations contained in the report that re-

late to essentially integrating the staffs differently, suggesting that, in fact, there be folks brought in from the outside to assist them and look at how one implements cultural change within the agency. We believe that there are in the normal course the kinds of relationships and challenges that occur in any environment where there are professionals that have different views, whether you have the folks that are managing the clinical trials who may approach it differently than the epidemiologists, for example.

But we leave the leadership, the stability of the leadership; the integration of those teams, the introduction of the safety decision-making earlier in the process that forces an integration, the placement of safety staff on that team, we hope, in fact, will begin to address some of those issues. But there is no question that it has to be done within the agency and it has to come from the top, which is why we think the stability and the leadership is so critical.

The CHAIRMAN. Thank you, and I really appreciate that the chairman of this very important committee is so able to speak in layman's terms so that even I can understand.

It's been very helpful, and I know that you have a plane to catch at 11 o'clock, so I'll relinquish the rest of my time and turn to Senator Kennedy.

Senator KENNEDY. Well, thank you and thank you, Sheila Burke, for a wide swath of service to the public interest. We're glad to have you here this morning.

Let me ask you, if we don't implement either the recommendations of IOM or some aspect of the Enzi legislation, what could you tell the public? I mean, how important is it that we do something, both in terms of innovation, and in terms of safety. How urgent is it? What's your sense and the sense of your committee, about the importance of moving this legislation forward? As you know from your own experience, we're going to be encumbered with a lot of different choices here in the Congress in prioritizing, and I'm just interested, based upon your own understanding of this institution and a very detailed study, how important is it in terms of the safety and innovation in a period I like to call the life science century? How important is it that we pass legislation, either what you've recommended or what we have recommended?

Ms. BURKE. I think, Senator Kennedy, it is enormously important, and I think you have—I mean, often you have circumstances where the stars align, where there are opportunities that arise. Certainly in the course of the review of PDUFA you have an opportunity. I think the timing is critical. I think passage of legislation is critical. I think the absence of that over the longterm would leave the agency starved for resources, I think with unclear authority in terms of being able to deal with the industry and to effect the kinds of changes that we believe are necessary.

We are an increasingly complex world with increasingly complex drugs dealing with increasingly complex problems. Drugs are now used far more consistently and prevalently than they ever have been in the course of caring for patients. So I think if there were ever a time when it is critical to address these issues, it is now.

Senator KENNEDY. I think just as you were mentioning, this is for me the life science century, with all of the possibilities that are

out there. The difference of getting drugs on stream earlier can offer incredible opportunities for people and yet we have, obviously, as we've seen in the recent times, serious kinds of safety issues and we have to bring the agency up to speed in terms of being able to do both.

One aspect of it is information technology. Using information technology, we can advance and bring on stream these newer prescription drugs and then monitor them more completely and get the telltale signals or potential dangers of it.

Isn't this an important area for us to give some focus and attention if we're interested in getting drugs on earlier and getting a better review of safety?

Ms. BURKE. You are absolutely correct, both in the nature of investment in the technology as well as the training of the staff in order to be able to use the information. The AIR system is a good example, where you are producing an enormous amount of information, in excess of 400,000 reports, but the ability to mine that information, the ability, for example, to partner with Medicare, the new information that will be produced in the course of the Part D benefit, we ought to be able to utilize that and FDA ought to have access to that and be able to utilize it to assist them in tracking what's occurring.

So investments both in human resources as well as technology I think are a very wise investment.

Senator KENNEDY. Finally, to underscore the importance of having administrative leadership out there in the FDA, if you could just underline that point. And finally, the safety issue is obviously front and center for many members of this committee, and other committees. We have a more elaborate description in your report about the administrative steps that can be taken, that you think will enhance drug safety in an effective way. If you could comment on both of those elements I'd appreciate it.

Ms. BURKE. I think the report does contain a number of recommendations both with respect to administrative changes, the integration of the staff, the placement of the safety staff earlier in the process, as well as the commitment on the part of the leadership at the agency to essentially instill safety as a critical component. Clearly the stability of the leadership of the agency is critical to that. The investment in human resources and technology resources allowing the staff to essentially do their jobs. They are a dedicated group of people who need the resources to do so.

There is currently an imbalance in the pre-approval and post-approval process in terms of resources. Clearly a great emphasis has been placed on pre-approval for good reasons in terms of the speed of drugs to the market. A similar emphasis needs to be placed on post-approval in terms of resources and I think that will help to address some of these issues.

Senator KENNEDY. Thank you very much.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Mr. Hatch.

OPENING STATEMENT OF SENATOR HATCH

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

Welcome to the committee, Sheila.

Ms. BURKE. Thank you.

Senator HATCH. We're glad to see you again.

I'm interested in your assessment of the next steps. I think the report is very interesting, but one of the questions I have is: do we really need legislation or can the recommendations in the report be implemented administratively?

Ms. BURKE. Mr. Hatch, we believe very firmly that there are areas that do, in fact, require legislation. In addition to those dealing with resources, that is obviously the appropriations process——

Senator HATCH. Well, that's obvious. But I'm talking about——

Ms. BURKE [continuing]. Clearly you need additional resources. But in terms of legislation otherwise, we clearly believe that the agency needs far greater clarity in terms of its authority, with respect to both the pre-approval and post-approval process, the ability essentially to do more than simply negotiate in good will with the agency—between the agency and the drug industry.

We believe the agency needs to have the authority to require that certain things occur, the ability for example to call unilaterally for changes in labels, the ability to essentially provide for followup to the kinds of studies. Intervening sanctions, for example, to encourage compliance we think need clear, clarified statutory authority on the part of the agency.

Senator HATCH. It still looks to me like a number of your suggestions can be implemented administratively.

Ms. BURKE. Yes, sir, many can, in fact, be implemented absent legislation. Some will, in fact, require statutory change.

Senator HATCH. Yes, I agree with you on that.

Could you please expand on your comments about PDUFA? Because you indicated—let's see; I've got your statement right here—that you felt like CDER's dependence on PDUFA funding with its associated restrictions may hurt FDA's credibility. Then you say: "If securing this additional funding entirely from appropriations proves impossible, the committee urges that restrictions on the use of PDUFA funds be curtailed."

Could you expand on that?

Ms. BURKE. Yes, sir. Our point in making that comment is that currently there are limitations in terms of the use of PDUFA funding. The bulk of the funding is clearly targeted towards the approval process and that is the time prior to marketing in terms of the staffing and the assets necessary for that process. It has made an enormous difference and a very positive one in speeding drugs to the market.

There have been restrictions on whether or not those funds can be used, for example, post-approval in terms of the additional safety staff, in terms of both the number of staff as well as their capacity, for example, to do research as well as contract with the drug companies themselves, but for the agency itself to do some of this analysis.

So again, our view is that, with additional funds necessary, our preference would be the appropriations process; should, in fact, that not be possible, if PDUFA funds, in fact, are the only source of funding that is available, that the limitations currently in place that limit largely its emphasis on the pre-approval process, be

broadened to allow for more use in the post-approval safety process as well.

Senator HATCH. I notice that some of the folks in the House, when they resume their leadership after the first of the year, have indicated that they would like to do a Hatch-Waxman or Waxman-Hatch approach to bio. Could you tell us what the IOM recommendations are there?

Ms. BURKE. We did not address that, sir.

Senator HATCH. I didn't think you did, but do you think we should weigh in and get IOM to address that?

Ms. BURKE. Senator, I frankly am not—I couldn't opine based on what the committee has done.

Senator HATCH. Well, it's a big problem because, of course, we had a time bringing about the Hatch-Waxman bill——

Ms. BURKE. Yes, sir.

Senator HATCH [continuing]. Because of the conflicts between the generics and the brand companies. And there's no question one of the big complaints is that the bio work is so expensive that it would be well if we could find some way of bringing some of those therapies into generic form. But then the next question is how do you do that since it's so difficult to duplicate large molecule individual therapy approaches.

I would like to have the IOM's viewpoint on that and how—Congressman Henry Waxman's talking about, using terms like "comparable" or "like." That is not as specific as the original Hatch-Waxman, which had an easier time being specific. These are areas that are really concerning me because I don't think they should be political areas. We ought to get these down so that they work well in the interests of the whole pharmaceutical industry, whether generic or brand name or whatever, in the interest of consumers, but also in the interest of propelling this type of really outstanding research forward.

So I would encourage you to get the folks there to spend a little time on this, because we could really screw this up. We're good at that. And I don't want to——

Ms. BURKE. I won't comment.

Senator HATCH. You're not going to comment? Here I give you a perfect opportunity and you won't do it.

Well, to make a long story short, I'd like to have some advice on that.

Ms. BURKE. All right, sir.

Senator HATCH. I think probably our chairmen would like to have advice. Certainly Congressman Waxman and Congressman Dingell would like advice. It's an area we just have to work on in the next Congress and hopefully we can come up with something that will function as well as the Hatch-Waxman bill did or has. It's still functioning well and saving over $10 billion a year in pharmaceutical costs. But we could use your help on it.

Ms. BURKE. All right, sir. Thank you.

Senator HATCH. Thank you.

Thanks, Mr. Chairman.

The CHAIRMAN. Thank you.

Senator Murray.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman. I really appreciate you and Senator Kennedy working together on this.

Ms. Burke, it's good to see you again and thank you for the incredible work your committee's done. I really appreciate the opportunity to have this hearing. I hope we have more of them as we really try and do this right in the coming Congress, because I think we have a real opportunity to restore some of the confidence the public needs to have in the health and safety mission of the FDA and a real chance to give the scientists at the FDA the tools and the authority they need to ensure greater safety for all Americans. I hope we really use this as an opportunity to restore the FDA to the gold standard of safety and efficacy that we all know is so important.

My colleagues and I have been very concerned about the political ideology that has undermined sound science at the FDA. I think we need to make sure that we address that and it is not a concern in the future. There are several other areas I'm concerned about. One of them is the critical balance between post-market safety and ensuring timely access to safe and effective drugs and devices. We have a system that relies heavily on user fees to ensure timely review process of our drug applications and I'm concerned the FDA's financial dependence on those fees may create a situation where user fees are having undue influence on approval decisions, and I want to make sure that user fees are providing timely reviews and not automatic approvals. It's a difficult balance, but I hope that we explore that as we move forward.

But let me take the short time—I know you need to leave—to just ask you a question. You touched on this briefly with Senator Hatch, but this committee held 2 days of hearings talking about drug safety in response to a number of the high profile cases involving Vioxx, and it was very troubling to hear that FDA spent almost 18 months negotiating with Merck for label changes and additional safety warnings. It's my understanding that FDA was prompted to propose those additional safety regulations because of a growing body of evidence. So a number of people were using those drugs while FDA was negotiating for 18 months and impeded the ability to get the information out there.

You have talked about this in your proposal of how we make sure that FDA has the authority to negotiate but still the companies have an ability to respond to that in a timely fashion. Can you talk about how you think we need to address that?

Ms. BURKE. Thank you, Senator. In fact, one of the provisions we believe does need clarity and does need statutory change is, in fact, to make it clear that the FDA does have the ability to act unilaterally. Clearly our goal here is not to prevent nor to discourage a relationship or a discussion between the industry and the FDA. But in cases where, in fact, evidence has arisen and time is of the essence, we believe, in fact, the FDA ought to be given the authority not simply to negotiate and depend on the good will of that relationship, but rather to intervene. So the report specifically calls for that authority to be given to the FDA.

Senator MURRAY. Thank you, and I really appreciate your attention to that as well. I think that's important.

The other question I wanted to ask you quickly, both the IOM and the Enzi-Kennedy bill place restrictions on direct-to-consumer advertising for new drugs and I think that is something we are all deeply concerned about addressing, and I agree with that approach. But I do know that sometimes getting information to consumers is just as important. If a parent hears about a new vaccine to protect their daughter against cervical cancer because of information that they heard, that can save lives, too.

So talk to me about how the IOM is looking at how we address that balance between not creating just a market situation, but we also assure that people get the information that is out there they may not hear otherwise?

Ms. BURKE. The point you raise is an extraordinarily important one. One of the questions of course is the balance of that information. Our concern obviously with the advertising in that period of time when a drug has just come onto the market is speeding up the use of the drug before we fully appreciate the risks that the drug might, in fact, present, that may well not have been fully understand in the pre-approval process.

Having said that, we also think it is incredibly important to provide a much better process for informing the consumer, and, in fact, there are a number of recommendations related to establishing a group to essentially assist the FDA in looking at exactly that question: What is the method by which you best communicate both with consumers as well as providers? The relationship between the provider, the physician who cares for the patient, and the patient is an enormously important one. That ought to be the source of the information that the patients seek out, rather than simply sitting at a Super Bowl and watching ads come up on TV.

So it is really both of those values that we're trying to balance. That is, informing the consumer, but in a way that is useful, that doesn't encourage use before perhaps it's best known what will happen. And how we deliver the information—some of the materials to date tend to be very complex, tend to be very lengthy, tend not to be very user friendly. We think a great deal of attention needs to be given to incorporating consumers into that review process and establishing a committee that essentially really pulls together the best information, frankly, from Madison Avenue and others about how you interact and how you inform.

So certainly, in no way do we intend for there not to be information, but the question is how is it delivered, by whom, and for what purpose. That we think has to be balanced and that's why we've suggested the creation of this committee and involving consumers in that process.

Senator MURRAY. Thank you very much. I really appreciate the opportunity to look at this.

I do have several more questions. I'll submit them for the record because of the timing, but thank you.

The CHAIRMAN. Senator Reed.

OPENING STATEMENT OF SENATOR REED

Senator Reed. Well, thank you very much, Mr. Chairman.

Welcome, Sheila Burke, and thank you, not only for your great public service, but for your service to the Kennedy School.

Ms. BURKE. Thank you, sir.

Senator REED. Good to see you again.

I have just two questions because I know your time is curtailed this morning. One of the recommendations in the IOM report was the introduction of specific safety-related performance goals as a means to restore the appropriate balance between the FDA's competing goals, speeding access as well as safety of the product. What kinds of safety and performance standards did you envision would be necessary to do this?

Ms. BURKE. Thank you, Senator Reed. One of the things that concerned the committee is, in fact, currently under the PDUFA structure there are very clearly established goals that are in place with respect to timing, that are, in fact, tracked and used to assist both the agency as well as the industry in understanding whether or not the agreements are being kept. There are no such similar requirements with respect to safety either in the course of the advisory committee process, the frequency with which they're used, when they're called together, the kind of followup in terms of safety information that's being gathered, the reports that have been required or requested by the agency prior to approval, then what occurs post-approval.

Our thought is that there ought to be a discussion and introduction of safety-related, whether it is about the advisory committee process, whether it is about the followup in terms of studies, that also ought to be tracked so that the Congress as well as the agency can fully understand whether, in fact, those requirements are being kept. So there really is—there are no specifics in terms of we've not listed specific goals, but rather suggested that conversation needs to occur. But those are the kinds of things that we're thinking about.

Senator REED. So it's more procedural than substantive recommendation?

Ms. BURKE. It is exactly that, yes, sir.

Senator REED. Let me follow on Senator Murray's questioning about advertising. I know the report recommends direct-to-consumer advertising on products be reviewed at least. A lot of the advertising, a lot of the promotion of these products, is done by representatives of the companies to physicians. Are you thinking about that as a way or an issue that you have to deal with?

Ms. BURKE. Senator, we only focused on the direct-to-consumer advertising. However, having said that, clearly there is also this issue of the information given to providers as well. One of the things we think needs great attention by the agency is the nature of the material that is given both to physicians as well as to consumers—its appearance, its content, its presentation, whether, in fact, it is easily understood, the frequency with which it is changed and updated, how one delivers it. So really both of those issues, but the specific moratorium issue relates specifically to direct-to-consumer.

Senator REED. With respect to the later issue, that is something, obviously, the agency can do. Are they interested and engaged in

that process? Is that something that we have to pay attention to, the company-to-physician relationship?

Ms. BURKE. I can't speak for the agency. Certainly it was of interest to the committee, because again we believed so firmly that the physician ought to be the source of information in many instances and the first contact for the patient, as to how one delivers that information, the timing by which it is delivered, the nature of the information. So while it is not something we spent a great deal of time on, it is certainly something that clearly the agency ought to be concerned about.

Senator REED. Thank you very much.

Ms. BURKE. You're welcome, sir.

The CHAIRMAN. Senator Isakson.

OPENING STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. Ms. Burke, I apologize. I missed your testimony and I wasn't going to ask a question, but Senator Reed piqued my interest when he talked about the advertising. I thought I heard him say you made a recommendation on the direct-to-consumer advertising; is that correct?

Ms. BURKE. Yes, sir, we do.

Senator ISAKSON. What is that recommendation?

Ms. BURKE. It relates specifically to new drugs coming on the market, that the FDA ought to have the authority to essentially curtail direct-to-consumer advertising during the startup period when the market is just new in terms of the drugs, that first 2 years or less, depending on what the agency decides makes sense. It will obviously relate to the risk issues with respect to the drug, to what extent they expect to have new information as a result of its broader use in the community.

So it's specifically to new drugs. It is specifically within that timeframe in which they are first introduced into the market.

Senator ISAKSON. In the case of mature—I don't know if "mature" is the right word, but drugs that have been on the marketplace——

Ms. BURKE. Yes, sir.

Senator ISAKSON [continuing]. For some time, more than 2 years, did you find any problems with direct-to-consumer advertising?

Ms. BURKE. We didn't examine that question, sir. Our focus was really on that new period when, in fact, we don't really yet have information about its use in a broader community.

Senator ISAKSON. Thank you very much.

Ms. BURKE. You're welcome.

The CHAIRMAN. Senator Clinton.

OPENING STATEMENT OF SENATOR CLINTON

Senator CLINTON. Thank you very much, Mr. Chairman, and it's wonderful to be here, and especially to see Sheila Burke. Welcome back to the Senate.

Ms. BURKE. Thank you.

Senator CLINTON. I want to thank you for really embarking upon this important effort. You know, from my perspective there couldn't be anything more critical that we turn our attention to. I was able

to get briefed on some of the questions and comments that were made before I arrived.

I want to ask the witness about something that I'm very concerned about. We're talking about post-approval, but I believe strongly in comparative effectiveness studies. I was able to get that through an amendment into the Medicare Modernization Act. One of the first studies to be carried out under that provision was a systematic review of the COX−2 drugs, and the results of the study, which were released in September, found no difference in the effectiveness of COX−2 painkillers compared with over-the-counter pain relieving drugs.

So I believe strongly that as we're looking at how to modernize the FDA, how to provide it additional resources, additional statutory authority where appropriate, that we really look at these comparative effectiveness studies, because they complement the drug approval work of the FDA. As we know, the agency's approval process focuses largely on ensuring that the drugs that come to market are safe for consumers. There is nothing more important than that, safe and efficacious.

But newer drugs are not always better drugs and they may not be the clinically appropriate choice for all patients with a given condition. Comparative effectiveness studies allow us to determine the benefits of a range of treatments for certain conditions and to make sure that providers and patients are making treatment choices that, frankly, are not unduly influenced by direct-to-consumer advertising or other marketing efforts.

So I would like to see us use the so far quite promising results of the comparative effectiveness studies through the Medicare Modernization Act amendment that I introduced and was approved, and I would like to ask our witness how she sees comparative effectiveness fitting into the pre-approval, post-approval, almost spectrum of concerns that we should be constantly addressing as we move forward.

Ms. BURKE. Thank you, Senator. We, in fact, didn't as a committee look specifically at that question. Having said that, there is clear attention in our recommendations to the value in the FDA both partnering with the private sector as well as seeking partnerships with the VA, with Medicare, with other Federal agencies that essentially have the ability to either sort out information, provide information, support studies either done with partnerships with either the industry or individually having the FDA seek out these kinds of studies to inform them farther along in the process.

Our particular attention, too, was that period largely just post-approval. Having said that, we know that the life cycle would produce lots of new information. The introduction of sort of new treatments, new opportunities, will inform us about drugs on the market as well as those coming on the market. Again, we believe the agency ought to have the resources to be able to test those questions, either again through partnerships in the private sector or individually with the companies or individually through the agency having the resources to conduct its own studies or call for those studies.

So clearly the life cycle, the point of that is, in fact, to inform us throughout that period of time where new information could well become available.

Senator CLINTON. Well, Mr. Chairman, I hope that as we move forward under your leadership and Chairman-to-be Kennedy's leadership that that will be part of our consideration. I would underscore the point that has been made by a number of my colleagues. You know, the FDA truly is the gold standard of drug approval for the entire world, and we've got to get back to absolute scientific impeccably independent judgments, so that no one can second-guess them. Scientists may be wrong. We all know that. Research may not be complete or it may be in some way inadequate for the purposes for which it was intended. But we shouldn't be engaged in any political debates about whether other agendas, ideological or other agendas, are driving the decisions made at the FDA.

Whatever we can do to guarantee the independence and the open scientific discourse that is needed as part of drug approval and review I am certainly going to support strongly, and I want to echo Senator Hatch's concern that we begin to look carefully at biologics, because this is an area of extraordinary complexity and we just don't have the range of infrastructure, intellectual capital, yet in the government to be a partner with the drug companies as they move forward.

The CHAIRMAN. I want to thank you for your time today in testifying, and your outstanding answers. Of course, we will be relying on you to give answers to any written questions that will be submitted. We'll keep the record open for 10 days.

But beyond that, we hope that you'll continue to work with us as we work through this very complicated piece of legislation to make sure that you and the members of your committee's ideas are properly represented as we do it.

So thank you very much——

Ms. BURKE. Thank you, Mr. Chairman.

The CHAIRMAN [continuing]. And we're getting you out before your plane deadline.

Ms. BURKE. You are. Thank you, sir.

The CHAIRMAN. Thank you very much.

As the next witnesses take their place at the table, I'll introduce the witnesses all at once and then they can give their statements and then we'll move to questions.

Ms. Diane Thompson is Vice President of Public Policy and Communications for the Elizabeth Glaser Pediatric AIDS Foundation, the worldwide leader in the fight against pediatric AIDS. Diane is a public policy manager with over 20 years experience in government and nonprofit organizations. She holds a bachelor's degree from Vassar College and a law degree from George Washington University's National Law Center.

The foundation is a founding member of the Alliance for Drug Safety and Access, which is comprised of 11 patient and provider organizations. ADSA members advocate on behalf of over 31 million patients, including those suffering from HIV-AIDS, spinal cord injuries, paralysis, multiple sclerosis, and over 6,000 known rare diseases.

She will share patient views on whether the IOM proposal and pending legislation would contribute to improving drug safety while preserving patient access to innovative pharmaceuticals.

Dr. Steven Nissen is the—did I get that right?

Dr. NISSEN. You got it right.

The CHAIRMAN [continuing]. Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic and President of the American College of Cardiology. From 2000 to 2005 he served on the FDA Cardio-Renal Advisory Panel, chairing this committee during the final year of his term. Dr. Nissen is actively involved in drug development and has served as principal investigator for several clinical trials designed to explore drug efficacy. He has also been an active proponent for improved drug safety.

Dr. Nissen is speaking on his own behalf today and not for any of the institutions he's affiliated with. He will discuss pending legislative proposals from his perspective as a physician who both treats patients and conducts large clinical trials to evaluate pharmaceutical benefits and risks.

Dr. Adrian Thomas is Vice President of Benefit-Risk Management at Johnson & Johnson Pharmaceuticals Group. Dr. Thomas is a visiting professor at Temple University and a research-trained clinical pharmacologist and vascular specialist. Dr. Thomas is an internationally recognized expert in drug safety and has 12 years experience in the pharmaceutical industry. His research experience includes clinical trials design and methodology, public health and preventive medicine.

Dr. Thomas has held academic and research appointments in epidemiology and preventive medicine at Monash University, Australia. Dr. Thomas will discuss current requirements for pre- and post-market safety evaluation by industry, as well as what Johnson & Johnson is doing beyond those requirements and how the IOM proposals and pending legislation would impact both drug safety and drug innovation.

Mr. Jim Guest is President and Chief Executive Officer of Consumers Union. Mr. Guest became President of Consumers Union in February 2001 after a long career in public service and the consumer interest, including 21 years as chair of Consumers Union's board of directors. Consumers Union is an independent nonprofit organization whose mission is to work for a fair, just and safe marketplace for all consumers. Consumers Union publishes Consumer Reports and consumerreports.org.

Mr. Guest's public service career has spanned more than 3 decades. He will share his perspective as President of a leading consumer organization on the challenge of ensuring drug safety without compromising patient access to important pharmaceutical advances.

Mr. Greg Simon joined as President of FasterCures in July 2003. FasterCures is an action tank committed to saving lives by saving time. The nonprofit, nonpartisan organization examines the medical research and development process to discover and promote ways to accelerate the discovery, development, and deployment of new medical treatment for today's deadly diseases.

Prior to joining FasterCures, Mr. Simon was a principal of Infotech Strategies, a Washington, DC., consuming firm, with spe-

cial expertise in health technology, biotech, education technology, and communication technology. Earlier he was the CEO of Simon Strategies-Mindbeam, a consulting firm specializing in biotechnology, healthcare technology, and information technology, among other issues.

Mr. Simon received his bachelor's degree from the University of Arkansas and his law degree from the University of Washington School of Law. He will share a somewhat different patient perspective on whether the IOM proposals and pending legislation would contribute to improving drug safety while preserving patient access to innovative pharmaceuticals.

Ms. Thompson, you may begin.

STATEMENTS OF DIANE E. THOMPSON, VICE PRESIDENT, PUBLIC POLICY AND COMMUNICATIONS, ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION; STEVEN E. NISSEN, M.D., CHAIRMAN, DEPARTMENT OF CARDIOVASCULAR MEDICINE, CLEVELAND CLINIC FOUNDATION; ADRIAN THOMAS, M.D., VICE PRESIDENT, BENEFIT-RISK MANAGEMENT, JOHNSON & JOHNSON PHARMACEUTICAL GROUP; JIM GUEST, PRESIDENT AND CHIEF EXECUTIVE OFFICER, CONSUMERS UNION; AND GREG SIMON, PRESIDENT, FASTERCURES

Ms. THOMPSON. Mr. Chairman, members of the committee, thank you very much for the opportunity to participate in today's hearing. I am Diane Thompson, Vice President for Public Policy and Communications at the Elizabeth Glaser Pediatric AIDS Foundation. I am testifying today on behalf of the Alliance for Drug Safety and Access, a coalition of 11 patient and provider organizations whose members advocate on behalf of over 30 million patients suffering from serious life-threatening illnesses and diseases, and also represent over 100,000 providers of care to children and individuals with mental illnesses.

As a representative of the Elizabeth Glaser Pediatric AIDS Foundation, I am proud to offer the perspective of an organization that has been focused on speeding patient access to safe medicine since its inception in 1988. The foundation's creation was sparked by Elizabeth Glaser's outrage over the lack of safe and effective options for treating her two HIV-infected children. Although Elizabeth's efforts were too late to save her daughter Ariel, who died from AIDS at the age of 7, her legacy includes her son Jake, now 22 years old, and the thousands of HIV-infected children around the world who now have the chance to grow up healthy thanks to the search for life-saving pediatric medicines that Elizabeth Glaser and the foundation have championed.

I would like to thank the committee for your leadership on this issue, for moving beyond the headlines to take on the difficult task of crafting bipartisan legislation to truly reform our Nation's drug safety system. We appreciate your efforts that you and your staff have made to work with patient advocates and your willingness to adopt so many of the recommendations of our coalition. We know you share our goal of ensuring that patients continue to have timely access to new therapies while strengthening and improving the drug safety system.

Simply put, we do not accept that patients should have to choose between safety and speedy access to new medications. The history of our foundation, of the broader HIV-AIDS community, and that of many of our coalition is the story of the power of patients' contributions to regulatory and scientific decisionmaking. One mom's determination to fight for her children's survival helped transform drug development for children in this country.

Given that no one stands to lose more than patients in drug safety decisions, we urge you to ensure that patient voices have an important place in the development of risk safety plans and particularly in the resolution of risk management disputes as provided for in the legislation.

We are pleased to see that both S. 3807 and the IOM report propose a fundamental paradigm shift in this country's approach to drug safety. There is agreement that attention to safety must be integrated throughout the life cycle of every drug and that continuous assessment of benefit and risk is every bit as important once a product is on the market and in the hands of patients as it is during the drug review phase.

Changing the paradigm will require leadership, determination, clarity, and resources. In addition to the important changes already included in S. 3807, we agree with the IOM's recommendation that FDA's safety staff must have a greater formal role in drug review and in development of risk management plans. We also strongly agree that safety-related performance goals must be added to PDUFA.

We applaud the focus of the legislation and the IOM report on strengthening FDA's ability to enforce requirements for continuing safety monitoring, on the importance of public dissemination of clinical trials data, and on the need for sufficient resources for the FDA to implement its new responsibilities. We need to make certain that we close the gaps that exist in each of those areas.

As the IOM report notes, a recent study found that 21 percent of prescriptions are written for off-label uses. Any effort to reform the drug safety system that fails to address one-fifth of the use of drugs in real world settings would create a significant safety gap, a safety gap particularly important to children because still far too few drugs are tested in children. The FDA's authority to require post-market safety studies must clearly extend to both on-label and off-label uses if we are to close that gap.

FDA needs enforcement mechanisms, including civil money penalties, that are substantial enough to be effective. By providing FDA the flexibility to impose fines for noncompliance, we can avoid the worst possible outcome for everyone, that FDA would have to resort to pulling a drug from the market that still holds some benefit for some group of patients because it has no other effective recourse.

In terms of clinical trials, we endorse the IOM recommendation that a mandatory clinical trials database incorporate phase two trials. In our view, however, that database should also include trials completed prior to enactment of this legislation and those for medical devices. From the point of view of a patient it is irrelevant whether a new therapy comes in the form of a drug or a device. The results of all such studies should be made publicly acceptable.

For FDA to succeed in implementing these reforms, it must have resources paired with its new responsibilities. A drug safety system that incorporates these core elements ultimately will benefit all stakeholders and we believe the changes outlined above, if adopted and resourced, will serve both timely review and safety.

Mr. Chairman, members of the committee, this committee has before it a historic opportunity to finally match our Nation's success in speeding new therapies to patients with a system that can better ensure the safety of those products once on the market. We very much appreciate your interest in the patient's perspective on these critical issues and we look forward to continuing to work with you over the next year to accomplish these goals. Thank you.

[The prepared statement of Ms. Thompson follows:]

PREPARED STATEMENT OF DIANE E. THOMPSON

Mr. Chairman, Senator Kennedy, and members of the committee, thank you for the opportunity to participate in today's hearing. I am Diane Thompson, Vice President for Public Policy and Communications at the Elizabeth Glaser Pediatric AIDS Foundation. Today, I will be testifying on behalf of the Alliance for Drug Safety and Access (ADSA), a coalition of 11 patient and provider organizations. Collectively, members of ADSA advocate on behalf of over 30 million patients, including those suffering from HIV/AIDS, Parkinson's disease, spinal cord injuries, paralysis, multiple sclerosis, leukodystrophies, Tourette Syndrome, and over 6,000 known rare diseases. In addition, our members represent over 100,000 providers of care to children and individuals with mental illnesses.

As a representative of the Elizabeth Glaser Pediatric AIDS Foundation, I am also proud to offer the perspective of an organization that has been focused on speeding patient access to safe medicines since its inception in 1988. This issue is at the heart of our mission—the Foundation's creation was sparked by Elizabeth Glaser's outrage over the lack of safe and effective options for treating her two HIV-infected children. Although Elizabeth's efforts were too late to save her daughter, Ariel, who died from AIDS at the age of 7, her legacy includes her son Jake, now 22 years old, and the thousands of HIV-infected children around the world who now have the chance to grow up healthy and even start families of their own, thanks to the search for lifesaving pediatric medicines that Elizabeth Glaser and the Foundation championed.

First, let me begin by thanking the Chairman, Senator Kennedy, Senator Dodd and other members of the committee for your leadership on this issue, for moving beyond the headlines to take on the difficult task of crafting bipartisan legislation to truly reform our Nation's drug safety system. We certainly appreciate the magnitude of the task and the historic nature of this undertaking.

We also appreciate the efforts you and your staff have made to incorporate the recommendations of our coalition. We know that you share our interest in both continuing the timely access of patients to new therapies and strengthening oversight of drugs already on the market. And, we believe that with sufficient resources both goals are achievable. Simply put, we do not accept that patients should have to choose between safety and speedy access to new medications.

Patients with serious illnesses understand that bringing drugs to market in a timely way means that not every risk can be identified in advance. However, what they also demand is sufficient information for them and their providers to continue to assess risks and benefits—which often means further testing of the drug after approval. Yet, as the report by the Institute of Medicine (IOM) so clearly illustrates, the Food and Drug Administration (FDA) has virtually no authority to compel drug manufacturers to continue to study the safety of products after they have been approved, to force changes to drug labels if dangerous side effects are uncovered, or to require that the results of critical studies be shared with patients and providers. In addition, at current funding levels, FDA lacks the resources to successfully accomplish many activities it is authorized to undertake, including effective collection and analysis of postmarket safety data.

Giving FDA these authorities and flexible tools to enforce them, as legislation pending before the committee would do, ultimately benefits both patients and drug manufacturers. Allowing FDA to require additional testing of drugs when there are clear signals of safety problems could actually allow the FDA to approve drugs more quickly, knowing it will have the ability to act if there are new safety concerns once

the drug is in the hands of patients. Also, by giving FDA the flexibility to impose fines for noncompliance, we can avoid the worst possible outcome for everyone: pulling a drug from the market that still holds some benefit for some group of patients.

We were pleased to see that S. 3807 essentially contains these critical elements. Perhaps most importantly, it frames them in a context of a risk-based approach. That model, rather than a one-size-fits-all approach to patient safety, will be key to the appropriate balancing of drug risks and benefits that is so critical to patients with life-threatening illnesses. Similarly, we welcome the IOM's vision of applying a "life-cycle" paradigm to drug risks and benefits, with its emphasis on the continuing pursuit of knowledge about a drug's safety profile and timely communication of that information to patients and providers. As recommended by the IOM, we hope that this will include the significant improvements to FDA's capacity to collect and analyze safety data through passive and active surveillance systems, as well as through prospective studies.

We are concerned however, that S. 3807 lacks sufficient mechanisms to elicit much needed patient and provider input. Some of the most critical patient safety decisions under the new structures proposed in the legislation will be those that relate to the development of risk evaluation and management strategies (REMS) plans. Yet, the bill currently assigns the responsibility for developing those plans and resolving related disputes solely to FDA and to an internal board composed entirely of Federal employees, with no opportunity for input from outside experts, patients, or providers.

The history of our Foundation and of the broader HIV/AIDS community is the story of the power of patients' contributions to scientific decisionmaking. Although they began as three mothers around a kitchen table with no formal training in science and medicine, Elizabeth Glaser and the other founders of the Foundation ultimately changed the accepted thinking of both the National Institutes of Health and FDA about the risks of *not* studying AIDS drugs in children—a success story that is repeated throughout the histories of patient organizations.

Given that no one stands to benefit or lose more than patients in drug safety decisions, we ask that you consider a greater role for patients in the development of REMS plans and resolution of REMS disputes. Specifically, we recommend that an existing or new advisory committee be utilized rather than the Drug Safety Oversight Board. Such a committee could draw on more diverse expertise, including the voices of patients and providers, and could make its deliberations public, which would be an important step in improving public trust in the process.

To further improve the depth and breadth of input into drug safety decisionmaking, we ask the committee to adopt the recommendation of the IOM that the Office of Surveillance and Epidemiology (OSE) be given a greater role in drug review and the development of safety plans. The lack of communication and cooperation between that office and the Office of New Drugs, highlighted in both the IOM report and a March 2006 report by the Government Accountability Office, is deeply troubling. At minimum, we urge the committee to formally assign OSE staff a role in the review of new drug applications and postapproval regulatory actions, as the IOM recommends.

We also urge the committee to clarify that the authority of FDA to require studies of postmarket safety concerns is not confined to on-label uses of the drug. In our efforts to improve the drug safety system, we need to pay particular attention to not only what happens inside the FDA, but also what goes on in the real world. As the IOM report notes, a recent study found that 21 percent of prescriptions written in 2001 were for off-label uses. Any effort to reform the drug safety system that fails to address ⅕ of the use of drugs in real-world settings would create a significant safety gap.

Children would be placed at particular risk by the failure to clarify this authority, since as much as ¾ of pediatric prescribing is off-label. Thanks to the efforts of Senators Dodd, Clinton, and DeWine, there are mechanisms available to both encourage and require manufacturers to study their products for children. However, there are gaps in those mechanisms. The existing pediatric study requirement does not apply to off-label uses. While the existing incentives can be applied to off-label studies, they are voluntary—and we are seeing that manufacturers are increasingly opting not to conduct the studies FDA requests. Unambiguous authority to require such studies when the off-label use is significant will help ensure that children too can reap the benefits of an improved drug safety system.

We applaud the significant focus placed by S. 3807 on the public dissemination of trial results through a clinical trials database. The establishment of such a database would be a significant step forward in providing patients and providers with additional information with which to assess benefits and risks. By linking the registration of new trials with final outcomes, this database could also help prevent selec-

tive reporting of positive results and further revelations about the withholding of negative trial results. And, not incidentally, given that clinical trials could not exist without patients' willingness to give of their time and health, such a mechanism could help restore patients' trust in the integrity of the clinical trials process.

However, in our view, a number of additions should be made to the database established by S. 3807 to ensure that it is as comprehensive and complete an accounting of trials as possible. We endorse the IOM recommendation that the database incorporate Phase II trials. We also believe that to satisfy the objective of providing patients and researchers with the full body of evidence on a drug or a class of drugs, there must be an element of retroactivity, perhaps beginning with trials of already approved products—both for the approved use and for any uses that were studied but not approved.

Following the recommendations of a previous report by the IOM in July 2005 on the postmarket safety of pediatric medical devices, we also ask that device clinical trials be added to the database. From the point of view of patients it is irrelevant whether a new therapy comes in the form of a drug or a device; the results of all such studies should be made publicly accessible. And, finally, while we endorse the concept of a single, comprehensive, national database that provides "one-stop-shopping" for patients and providers, until the concerns noted previously are remedied, we do not support pre-empting any efforts by States to also collect this information.

We applaud the inclusion of civil money penalties in S. 3807 as a critical step in providing FDA with graduated, flexible enforcement authority. However, we are concerned that the current penalties are too low to have much impact, particularly for higher sales products, and ask that they be increased. To ensure compliance with the requirements of the clinical trials database, we ask that the authority for FDA to impose fines for other types of violations also be applied to this section.

Finally, we agree with the IOM recommendation that specific safety-related performance goals be added when the Prescription Drug User Fee Act (PDUFA) is reauthorized next year. Clearly the experience from PDUFA thus far is that deadlines generate attention and focus. Even with additional funding, if postmarket activities without performance goals have to compete with pre-market functions with performance goals, we would be concerned they would remain an afterthought.

Obviously, the drug safety reforms proposed by both S. 3807 and the IOM create considerable new responsibilities for the FDA. For FDA to succeed in implementing these reforms, it is essential that new and expanded safety activities be explicitly paired with increased resources. We would suggest a combination of an increase in user fees targeted to drug safety activities and an increase in appropriations. We also recognize that it may be necessary to prioritize the reforms that can be implemented in the short- and long-term depending on the availability of new resources and we look forward to working with the committee to do so.

Mr. Chairman, the committee has before it an historic opportunity to finally match our Nation's success in speeding new therapies to patients with a system that can better ensure the safety of those products once on the market. We appreciate your interest in patients' perspectives on these critical issues and look forward to working with you over the next year to accomplish these goals. Thank you again for the opportunity to share our views.

The CHAIRMAN. Thank you. I appreciate any summarizations that any of the presenters do. Your full testimony will be a part of the record, so if you hit on key points that'll give us more time for questions.

Dr. Nissen.

Dr. NISSEN. Thank you very much. My name is Stephen E. Nissen, M.D. I am Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic and President of the American College of Cardiology. My testimony does not reflect the views of either the Cleveland Clinic or the ACC. As an individual who has frequently served as the point on the end of the spear during the public debate on drug safety, I appreciate the opportunity to provide an independent perspective on the Enhancing Drug Safety and Innovation Act of 2006 introduced by Chairman Enzi and Ranking Member Kennedy.

We face a crisis in public confidence in the FDA following an unprecedented series of revelations about drug and device safety. The

American people no longer trust the FDA to protect their health. Unfortunately, patients are increasingly suspicious of new therapies and sometimes are reluctant to accept potentially life-saving medications or devices. Strong and decisive legislative action is now essential to improve the safety of drugs and medical devices and restore public confidence in this critically important regulatory agency.

The initiative now before you represents the best opportunity in many years to fix these chronic problems. We need new laws to strengthen the authority of the FDA. Currently the agency must negotiate with industry to make even simple changes in drug labels. I served on a 2001 advisory panel that recommended a warning label for Vioxx, but it took 14 months before the FDA could secure agreement from the company to accept a weakly written warning. Companies routinely make commitments to perform phase four studies, but never actually launch the promised clinical trials, and the agency is powerless to act.

When drug studies reveal toxicity or efficacy, the agency is not permitted to release the results and the findings are often not published, thereby denying patients and physicians access to vitally important safety information. The problem of negative publication bias, the practice of suppressing and never publishing unfavorable studies, has a catastrophic effect on the drug development system. 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 competitor's 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. In my view, when a patient volunteers to participate in a drug or device study there is an implicit moral obligation that patients' participations will benefit medical science. When studies are not published, we learn nothing from the experiment and make the same mistakes over and over again.

The post-marketing surveillance system for drugs and devices functions poorly. Adverse event reporting is voluntary and studies show that only 1 to 10 percent of serious adverse events are ever reported to the agency. Accordingly, the actual incidence of serious or life-threatening complications cannot be calculated accurately.

The current legislation proposed by Senators Enzi and Kennedy addresses many of these problems in a thoughtful fashion. The bill's authors have sought to simultaneously facilitate development of innovative therapies while aggressively protecting public safety. The proposed risk evaluation and mitigation strategy is a step toward a more robust post-marketing surveillance system. The system for dispute resolution is fair to the industry but makes certain that safety concerns are promptly addressed. The requirement to register clinical trials is essential and the establishment of a mandatory clinical trials results registry will guarantee that society reaps the benefits of knowledge whenever a study is conducted in human subjects. Finally, the improvements in the advisory committee process will help to ensure FDA consultants are less likely to be influenced by financial conflicts of interest.

Although this bill is a major step forward, I would like to see further legislative actions. The agency should be better funded. Virtually every American takes one or more medications, so drug safety affects every one of us. However, the annual expenditure for drug regulation approximates only about $500 million and is largely supported by user fees, creating a conflict in loyalty for FDA employees. We cannot expect outstanding performance from an agency operating on a poverty budget.

For high-risk drugs, another approach to drug approval should be considered: provisional approval, a limited term approval that would automatically expire unless certain criteria for efficacy and safety are met.

I believe that direct-to-consumer advertising requires legislative action. The standard for acceptable DTC advertising should require demonstration of a compelling public health benefit for this type of communication. Drugs with an addiction potential, such as sleeping medication, should be specifically prohibited from consumer advertising.

Finally, there is an important drug safety problem not addressed in this bill—the nutraceutical industry. I recognize that the HELP Committee has made progress by unanimously approving legislation requiring serious adverse event reporting for diet supplements. However, more needs to be done. These products are often worthless and occasionally harmful. It must be recognized that some patients take dietary supplements instead of effective medications, with negative implications for their health.

The current bill is an important step toward improving the safety of drugs and devices and restoring public confidence in the FDA. I strongly support its passage and commend the Senators for their bipartisan leadership. Let me add, if there was ever a bipartisan issue protecting the health and safety of the 300 million Americans who take drugs, this is a bipartisan issue and I really strongly support your efforts.

Thank you.

The CHAIRMAN. Thank you.

Dr. Thomas.

Dr. THOMAS. Thank you. Mr. Chairman and members of the committee: I'm pleased to be here today on behalf of Johnson & Johnson to discuss the important topics of drug safety and innovation. I am Dr. Adrian Thomas. I serve as Vice President of Benefit-Risk Management, which is drug safety for the J&J pharmaceutical companies.

J&J and this committee share a common goal of ensuring that doctors prescribe and patients use healthcare products safely. We commend you for the deliberative approach you've taken in crafting your bipartisan legislation, S. 3807, and we thank you for the opportunity to speak here today. J&J believes that patient needs are best served when benefits and risks are considered together in the context of how our medicine is actually being used. We know, for example, that patients and physicians often consider different levels of risks acceptable depending upon the disease being treated, the patient population, an individual's health status, and the availability of alternative therapies. The full benefits and risks of any medicine often emerge, however, over a significant period of time

after approval. Rare risks will only appear after a medicine has been used in many thousands of patients. Thus any legislative solution should balance established benefits for populations against potential risks for individuals.

As important as this bill is, it is no substitute for enhanced tools for monitoring patient safety or adequate appropriations to ensure a strong and science-based FDA.

I'll now provide some highlights of our analysis of S. 3807. With respect to the risk evaluation and mitigation strategies, recent concerns have rightly attracted attention on improving drug safety. Whilst we agree that safety issues must receive the attention they deserve, we cannot consider risks in isolation from product benefits or we risk denying patients access to valuable therapies.

Anti-cancer drugs are an obvious example of the complex relationship between risks and benefits. However, more common drugs such as statins and aspirin similarly provide a clear benefit, but are nonetheless accompanied by distinct and manageable risks. In fact, if aspirin were under review today one could speculate whether or not it would be improved.

This bill integrates risks and benefits through the REMS mechanism. We support this concept for products where the potential for risk is greatest, such as new products, novel mechanisms of action, or products that will be used in vulnerable populations, particularly the aged and children. That said, we have a number of concerns that I discussed in my written testimony. I would like to highlight three.

First, regarding potential requests for industry to conduct trials, we agree that—we recommend that such requests be limited to on-label indications under the context of an IND application.

Second, the committee may want to consider whether options such as restricted distribution should be authorized in the bill, as patient access could potentially be affected.

Third, the moratorium on DTC advertising has some problems. Appropriate DTC advertising can play a valuable role in education of patients about disease and treatments, although we acknowledge that there are many issues.

Regarding the dispute resolution process, it's important that drug safety oversight boards' considerations regarding product safety be integrated with the appropriate reviewing division to ensure a holistic view of the product.

I'd like to now comment on clinical trials. We are generally supportive of the legislation's clinical trial provisions. We would like to highlight one concern, the chief of which is the bill's requirement for registration and disclosure of results from exploratory clinical trials. These trials are designed to generate hypotheses about medicine, not confirm findings. As such, these results, either positive or negative, could be confusing or misleading and need to be placed in the appropriate scientific context.

With respect to the conflicts of interest, there is a general need—there's a genuine need for sufficient numbers of qualified experts for service on FDA committees. This is an issue of concern for FDA, for industry sponsors, patients, and providers. Greater transparency of the FDA decisionmaking process will enhance public confidence and reassure all these stakeholders. FDA should also be

mindful of non-financial biases, such as institutional affiliation, in the context of specific advisory committee meetings.

In conclusion, the bill reflects the desire that we all share, to enhance patient safety and access to new therapy, and J&J greatly appreciates the opportunity you have provided to discuss these issues with you today. However, it is important to note that your efforts to strengthen FDA could be undermined by increased reliance on user fees to fund FDA activities, as we've heard today. There is a perception that the agency is overreliant on user fees in a way that compromises the integrity of the decisionmaking process. To address this perception, Congress must increase FDA's appropriated funding to enable the agency to fulfill its mission and restore public confidence in its independence. Although we appreciate this committee is not responsible for appropriations for FDA, your status as the authorizing committee for FDA allows you to exercise considerable influence on your colleagues in the Senate.

On behalf of Johnson & Johnson, we look forward to working with you and your colleagues to address these important issues of patient safety and information. I want to thank you for the opportunity to speak with you today. I'm happy to answer any questions you may have.

[The prepared statement of Dr. Thomas follows:]

PREPARED STATEMENT OF ADRIAN THOMAS, M.D.

Mr. Chairman, Ranking Member and members of the committee, I am pleased to be here today on behalf of Johnson & Johnson to discuss the important topics of drug safety and innovation. I am Dr. Adrian Thomas, and I serve as Vice-President for Benefit-Risk Management for the pharmaceutical companies of Johnson & Johnson.

Let me start by saying that Johnson & Johnson and the Senate Health, Education, Labor, and Pensions Committee share a common goal of ensuring that doctors prescribe and patients use healthcare products safely. We commend you for the deliberative approach you have taken in crafting your bipartisan legislation, S. 3807, and we thank you for the opportunity to speak here today.

I will begin by setting forth the broad perspectives of my company on the topics of drug safety and innovation. Then I will provide some background on how companies such as Johnson & Johnson assess the safety of our products over their life cycles. Finally, I will comment on key provisions of S. 3807, Enhancing Drug Safety and Innovation Act of 2006, as well as recommendations of the Institute of Medicine's (IOM) Committee on the Assessment of the U.S. Drug Safety System regarding proposed changes to aspects of the system whereby the Food and Drug Administration (FDA) regulates medicines.

PERSPECTIVES

Since before Hippocrates first cautioned that physicians should "help, or at least, do no harm," treating disease has always involved balancing a therapy's benefits with its potential risks. At Johnson & Johnson, we believe that patient needs are best served when benefits and potential risks are assessed together, in an integrated, holistic way, and within the context of how a medicine is actually being used. We know, for example, that patients and physicians often consider different levels of risk acceptable, depending upon the disease being treated, the population being served, a patient's health status, the availability of alternative therapies, and other variables.

It is also important to note that as society addresses issues of drug safety, the full benefits and risks of any medicine often emerge over a significant period of time after approval. Many risks are exceedingly rare and may only emerge after a medicine has been used in many thousands of patients. So as Congress develops new legislative approaches, it should also continue to make it possible for patients to access a broad range of existing, and new, therapeutic options. This requires balancing protections for broad populations with access for appropriate patients.

I would like to make a few other broad comments: We support the use of Risk Evaluation and Mitigation Strategies proposed in S. 3807 to enhance safety, where these strategies are most needed. We believe the proposed Reagan-Udall Institute could be a valuable impetus to spur scientific innovation if consistent and adequate appropriations are provided. We support the provisions of S. 3807 and the IOM report regarding the registration and disclosure of results of confirmatory clinical trials. We support efforts to manage conflicts of interest in FDA Advisory Committees and to enhance transparency while retaining FDA's access to expertise. Finally, we believe that Congress should adequately fund the Food and Drug Administration in the interest of all Americans.

COMPANY SAFETY AND SURVEILLANCE ACTIVITIES

As I mentioned earlier, I serve as Vice-President for Benefit-Risk Management for Johnson & Johnson's pharmaceutical companies. In that capacity, my department and I work with the pharmaceutical research and development units and with the medical affairs organizations in our commercial operating companies to ensure that we appropriately consider safety, together with efficacy and outcomes data, throughout the life cycle of our products.

Like other pharmaceutical manufacturers, we evaluate the benefit-risk profiles of our products continuously, since important additional information is gained after approval of a medicine during real world use. At the time of submission, our knowledge of the risks and benefits of products, though quite detailed, is based typically on experience of the medicine in thousands of patients in a controlled clinical setting, whereas in the postmarketing life of the product additional data is gathered from many times more patients in settings that are less controlled. For example, in a study with 3,000 patients, one can identify adverse reactions that occur at a rate of 1 in 100 patients, but it is not possible in such a study to reliably identify an adverse reaction that occurs in fewer than 1 in 1,000 patients.

Monitoring the safety profile of products postapproval requires effective pharmacovigilance and postmarketing surveillance. Like others in our industry, we collect, assess, and evaluate safety reports from consumers, physicians, healthcare providers, regulatory agencies, clinical investigators, the literature and other sources globally. This requires numerous technical tools and substantial medical expertise, underpinned by a variety of specific processes to ensure diligence.

Not all products have the same level of risk. The degree of scrutiny for a given product depends on a number of variables, such as the stage of the product in its life cycle, known safety issues associated with the product or class, or specific requests from regulatory agencies. All products, however, are regularly reassessed as new knowledge routinely emerges about medical interventions; and science is not static. Companies such as ours continually invest in new technologies and methodologies to conduct pharmacovigilance and risk management. In the postapproval environment, we rely primarily on safety information from postmarketing reports, but we also conduct additional research, including epidemiologic studies and targeted trials, to evaluate potential safety concerns. In instances of serious unexpected safety issues, this integrated approach has proven to be successful in assuring patient safety while maintaining access for patients with significant medical needs.

Risk management cannot be undertaken in isolation by a pharmaceutical company, but requires interaction and cooperation between regulatory agencies and the company, as well as communication of benefit-risk information in a timely and transparent manner to healthcare professionals and ultimately to patients. The interaction between the company and regulatory agencies is a critical partnership from the time of early drug development throughout its marketed life, with the ultimate goal of providing and maintaining patient access to beneficial therapies. In this regard, it will be important for the committee to hear from FDA when its Study Groups report back early next year on any additional steps the agency may take to ensure the safe use of medicines.

ANALYSIS OF S. 3807

Title I—Risk Evaluation and Mitigation Strategies

Reports of unanticipated adverse effects associated with medicines taken by, in some cases, millions of Americans have undermined public confidence in the ability of the FDA to ensure the safe use of medicines. In that regard, today's hearing represents a step forward in defining specific activities that could make a real difference in safety margins, without unduly burdening the efficiency or speed of the FDA approval process. Access to novel treatments is of particular concern for patients suffering from serious or life-threatening diseases—especially in cases where previous therapies have failed.

Safety issues have attracted much attention, both in the Congress and among academicians. Some of the proposals (legislative and otherwise) have sought to elevate the profile of safety considerations by creating separate safety offices within FDA that would have equal or superior authority over drug approvals to that of the reviewing office, without having line of sight to the data on efficacy. This effective veto power over approval of new medicines fails to appropriately take into account the importance of benefit or efficacy considerations in achieving a balanced understanding about a medicine.

For example, many traditional cancer drugs are associated with substantial toxicities, but those toxicities are inseparable from the effectiveness of the drugs. Oncologists who administer those drugs are well aware of the toxicities and are capable of managing them for the benefit of their patients with cancer. Cancer patients also understand that the benefits of chemotherapy come with risks and those who elect to take these therapies accept the risks that are inherent in these drugs. If safety considerations had been permitted to trump drug efficacy or benefit, many of these life-extending drugs might never have been approved and might never have been available to cancer patients.

While anti-cancer drugs offer an obvious example of the complex relationship between risks and benefits, there are many other examples. Medicines known as TNF-inhibitors provide substantial relief to patients with rheumatoid arthritis, not only alleviating pain but actually affecting the progression of the disease. The drugs' mechanism, however, can interfere with normal immune system functioning, and use of TNF inhibitors requires careful management. Other more common drugs, ranging from statins to aspirin, similarly provide clear benefit but are nonetheless accompanied by distinct, though manageable, risks.

Your legislation, S. 3807, appropriately gives equal consideration to the inseparable elements of safety and benefits. It accomplishes this primarily through a mechanism called a Risk Evaluation and Mitigation Strategy, or REMS. At the core of REMS is a pharmacovigilance statement that creates a plan for managing the risks associated with a particular drug. The pharmacovigilance statement is based on an assessment of key variables, including estimated size of the treatment population, the seriousness of the disease or condition being treated, duration of treatment, availability of a comparable drug or other therapy, and the seriousness and incidence of the risk in the treatment population.

We support the concept of REMS for products where the potential for risks is greatest, such as new product classes, products with new mechanisms of action, or products that will be used in particularly vulnerable populations, such as the aged or children.

Through the REMS approach, S. 3807 takes into account both the benefits and risks of potential therapies, as is appropriate, to reach a balanced regulatory decision. S. 3807 is also commendable in providing a comprehensive menu of potential remedies that can be tailored to meet particular risks to be included in a REMS, ranging from a required medication guide or patient package insert and a communication plan for healthcare providers, through postapproval registries and clinical trials, to restrictions on advertising or on distribution and use.

We agree that these elements of the REMS should reflect the seriousness of the risks associated with a particular product and should be considered in a step-wise fashion. Regarding potential requests for industry to conduct clinical trials, we recommend that such requests be limited to on-label indications. The committee should consider whether an additional funding mechanism for off-label studies, as has been put forth in the context of pediatric drugs, would be appropriate. In addition, it would be reassuring to industry, practitioners and patients if it were clear that the most severe of these approaches—distribution restrictions, for example—would be limited to situations of very serious risk. Some of the more extreme elements that could be included in a REMS as set forth in the legislation, such as restrictions on distribution or direct-to-consumer advertising, have rarely been used to date and then only with the acquiescence of the sponsor.

Voluntary restrictions on distribution have occurred in a few situations in which there was a known serious risk to public health, with thalidomide being the signal example. A very different situation is created if the agency is authorized by statute to impose such restrictions, notwithstanding the negotiation and dispute resolution process. We recommend that the language of S. 3807 make clear that such newly authorized remedies should be utilized only in extreme and rare circumstances. The standard for restrictions on distribution should be no less than in the current Subpart H regulation on accelerated approval, 21 CFR 314.520, which permits restrictions ". . . if FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted" and ". . . the limitation imposed will be commensurate with the specific safety concerns presented by the drug product."

Certainly, restrictions on distribution will limit patient access. We believe access to new therapies should be assured.

Indeed, the committee may want to consider whether some of the remedies are ever appropriate or in fact have been proven to be useful in reducing risk. For example, the requirement that a patient must see a board-certified physician could present a real access problem for a sick patient who lives many miles from an appropriate doctor. The same could be said about potential restrictions on pharmacies. We urge the committee to very carefully weigh issues of patient access as it further considers this bill.

Another remedy that should be reconsidered is the proposed ability of FDA, under the legislation, to impose a moratorium on direct-to-consumer (DTC) advertising for up to 2 years. This restraint on advertising represents a troubling change. Many members of the industry, including Johnson & Johnson, have voluntarily agreed to exercise restraint with respect to DTC advertising, especially during the period of time after approval. But appropriate DTC advertising plays a valuable role in educating patients about diseases and treatments. The value of this education to patients, as well as the important first amendment issues that arise from banning truthful speech, even for a period of time, must be carefully considered before legislating in this area. At a minimum, the standard for imposing DTC advertising restraints should be much higher than is currently articulated in the legislation, to ensure appropriate application of this new authority.

Regarding the dispute resolution process, we have a concern about the elevation of the Drug Safety Oversight Board, an administrative creation with no previous statutory authority, to the role of primary final decisionmaker. As noted earlier, focusing solely on the risks of a medicine without the context of the medicine's benefits could result in limited access for patients. Given the enhanced status of the Drug Safety Oversight Board under this legislation, the committee should provide clearer definition of its composition and its place in the governance of FDA. In addition, in connection with dispute resolution, the Board should receive explicit statutory direction regarding the appropriate balance of safety and access and should be required, in resolving disputes, to apply a standard that balances safety concerns against benefits, particularly in the case of serious or life-threatening diseases.

S. 3807 provides a valuable platform for discussing how to address the concerns that have been raised about drug safety, without jeopardizing medical progress against serious and life-threatening diseases. We note that many of the recommendations of the Institute of Medicine (IOM) report on drug safety are consistent with the terms of the legislation, although they diverge in several significant respects. It is important to consider whether the IOM recommendation to assign joint authority for post-approval drug safety reviews to both the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) creates an unworkable situation with split accountabilities. We believe such authority should reside with OND, though with appropriate input from OSE. It is important to note that while OND reviews both benefit and safety information, OSE sees only safety data, potentially skewing the OSE's perspective on a particular medicine.

TITLE II—REAGAN-UDALL INSTITUTE FOR APPLIED BIOMEDICAL RESEARCH

While the drug safety reforms embodied in title I of the legislation are necessary to restore the confidence of legislators, regulators and the public in the safety use of marketed products, S. 3807 also makes a significant contribution to product innovation by operationalizing the FDA vision of a "critical path" to discovery. The industry knows that we lack the predictive tools to make drug discovery and development more efficient and cost-effective. This is particularly unfortunate, given the Nation's substantial investment in biomedical research, through both public and private funding. Recognizing this shortfall, FDA has fashioned what it terms a Critical Path Initiative to streamline the drug development and review process.

FDA has met with numerous stakeholders to explore options for developing its Critical Path Initiative, but lack of resources and coordination among public and private entities has resulted in relatively little progress in the development of biomarkers and other tools that will, in the words of the legislation, "modernize medical product development, accelerate innovation, and enhance product safety." The Reagan-Udall Institute for Applied Biomedical Research could fill an important role in bringing together the best of the public and private sectors to address this unmet need in a coordinated manner. The challenges of developing new drugs, biologics, devices and diagnostics may warrant the creation of a new entity utilizing the expertise and funding of both public and private entities.

In light of the proposed scope of this new entity's mission and its potential for advancing the science of drug development and life cycle management across many

disciplines, we question whether it is appropriate to lodge the Institute within FDA, as currently provided in S. 3807. Rather it would seem preferable that the Institute be placed within the Department of Health and Human Services (HHS), reporting directly to the HHS Secretary with liaison to FDA, the National Institutes of Health and other relevant agencies within HHS and perhaps even outside it.

Among the issues of potential concern for industry would be sources of funding for the work of the Institute. The contribution of Federal dollars is an important indicator of the Government's commitment to the process and may make it more likely that industry will choose to participate financially as well. Funding must be consistent and sustained for a research-related program of this sort to succeed, and the Federal contribution must not come from moneys currently allocated to operations at FDA. Even though this initiative may produce savings in administrative costs over the very longterm since the drug approval process may be shortened and simplified, new funds must be made available during the foreseeable future to avoid shortchanging FDA's current efforts.

Other issues that may emerge are those that are typical when there are collaborations among private entities or between private and public sector players. These include balancing transparency of operations against the need for confidentiality. Intellectual property issues may also pose obstacles that need to be addressed before the Institute can fulfill its mission. Early and frequent consultation with industry on these and other issues will be essential to the Institute's success.

TITLE III—CLINICAL TRIALS

Johnson & Johnson's pharmaceutical companies have a well-established policy for registering our clinical trials and publishing our clinical trial results, both positive and negative. Our policy is based on our conviction that ". . . well-informed risk-benefit assessments about our products rely upon the availability of product information that is accurate, comprehensive, fair-balanced and timely."

Thus, we now publicly register all confirmatory clinical trials of both marketed and investigational drugs regardless of location. For studies related to serious and life-threatening diseases, we register all that include efficacy endpoints, regardless of trial design or location. Registration is made to the National Library of Medicine's Website, *http://www.clinicaltrials.gov.* We believe that both patients and healthcare providers can benefit from knowledge of clinical trials that are open for enrollment, and our policy is intended to provide this information to consumers in a manner that is as clear and easy to access as possible. In the period from September 2005 to July 2006, more than 24,000 visitors browsed Johnson & Johnson sponsored studies on *http://www.clinicaltrials.gov.* Of these about 250 patients expressed interest in participating in one of our studies and were subsequently referred to investigators in their geographic region.

Our policy also addresses disclosure of trial results. For marketed medicines, we publish the results of all confirmatory clinical studies regardless of outcome. With respect to all other clinical studies of marketed medicines, we assess the medical importance of trial results and publish those results that are material and relevant to the clinical use of the medicine or to the care and safety of patients. These trial results appear either in peer-reviewed medical literature or in the form of a clinical study report synopsis in the ICH-E3 format. At present, our clinical study results are posted as links from the protocols we have registered on *http://www.clinicaltrials.gov.*

Clearly, there is industry support for organized clinical trial registries to inform patients and providers about the opportunities for enrollment in relevant clinical trials. Like our colleagues in industry, we also recognize the importance of sharing with regulators, with medical professionals, and with the general public the results of clinical trials, regardless of outcome.

S. 3807 establishes a comprehensive framework for both trial registration and reporting of trial results that should provide a clear roadmap for industry with respect to both activities. If properly implemented, the trial registry and results database will give industry clear guidance regarding which trials are covered, when, where, and what information must be posted, and last the consequences for failure to comply. Hopefully, the result will be convenient and understandable web-based destinations where patients and providers, as well as regulators, can readily access timely information about the availability of clinical trials and the results of trials, regardless of outcome.

While we are generally supportive of the legislation's clinical trial provisions, we are concerned about two matters: the requirement for registration and disclosure of results coming from exploratory clinical trials because they are not designed or powered to provide firm answers to questions regarding the safety and efficacy of medi-

cines. These trials are designed to generate hypotheses about medicine—not to confirm findings. As such, these results could be confusing or misleading to patients and to physicians.

We are also concerned that the requirement to register trials within 14 days of the first patient enrollment may be an unreasonably short timeline. We would recommend that the legislation provide for registration within 21 days of the first patient enrollment in order to be consistent with the terms of § 113 of the Food and Drug Administration Modernization Act, with which we and many other pharmaceutical companies currently comply.

S. 3807 is commendable in its specificity, but its provisions are not necessarily self-executing, and many questions will undoubtedly arise in the course of implementation. For this reason, consultation with industry as well as with patients, providers and other interested parties, is essential. In that connection, we note that the legislation contains several references to rulemaking or promulgation of regulations, as well as a requirement for a Guidance document to clarify what clinical trials are "applicable" for purposes of the trial registry. We believe that virtually *all* aspects of the systems for clinical trial registries and for a trial results database would benefit from the opportunity for public comment through rulemaking, and therefore we recommend prior publication in the Federal Register. While rulemaking might delay somewhat the implementation of these important policies, the trial registry and trial database are complex undertakings, and it is more important to get them right than to get them quickly.

TITLE IV—CONFLICTS OF INTEREST

FDA cannot possibly provide, solely from the ranks of its employees, the expertise necessary to evaluate the broad array of new medical interventions being brought to patients today. Therefore, advisory committees and other panels of outside experts are critical for the competent review of new drugs, biologics, devices and diagnostics. S. 3807 makes important changes to FDA's current practices to enhance the integrity of the advisory process through greater transparency in initial selection and in management of potential conflicts of interest for advisory committee members.

Public confidence in the FDA review process requires that members of advisory committees be as free as possible of financial entanglements or other possible conflicts such as positions of prestige or long-time investments in scientific positions or ideas. Such conflicts could theoretically influence a committee member's judgment. On the other hand, it is important that advisory committees include individuals with the highest qualifications and undoubted expertise to ensure that FDA decisions are guided by the best medical and scientific advice. Frequently, it is not feasible to exclude those with one or another type of conflict, as the resulting pool of expertise would be too small for a meaningful selection process. Thus, it is vital that restrictions on participation for reasons of conflicts be balanced and moderate, with sufficient flexibility to address the demand for expertise from what may be a limited supply of potential advisors.

It is important that S. 3807 seek an appropriate balance by measuring the magnitude of the potential advisor's financial involvement or other conflict against the necessity of access to his or her expertise. The legislation should also set forth a process, with applicable timelines, for identifying and assessing a range of potential conflicts, determining the appropriate remedy and communicating the agency's determination of approval for service, waiver, limited waiver or recusal. Greater transparency of the FDA decisionmaking process will enhance public confidence and reassure all stakeholders.

Unavailability of sufficient numbers of qualified experts to serve on advisory committees, however, could pose a serious obstacle to the efficiency as well as the competency of product review at FDA. It is therefore critical that conflict of interest provisions be applied in a fair and balanced manner so as not to unduly limit participation. While it is important that FDA have the tools to improve the current system for managing potential conflicts, attention must also be given to recruiting more qualified potential members of advisory committees. We support creation of a mechanism for nominating qualified academics and practitioners for potential advisory committee service and the publication of Guidance in the Federal Register establishing this mechanism. The need for sufficient numbers of qualified experts for service on FDA committees is an issue of concern for FDA, industry sponsors, patients and providers.

ANALYSIS OF IOM DRUG SAFETY REPORT

While we agree with many aspects of the IOM report, we disagree with the recommendation to incorporate specific safety-related performance goals in the standards for the 2007 version of the Prescription Drug User Fee Act (PDUFA). We accept that user fees may be applied to safety-related activities at FDA, but we question whether it would be appropriate to create new and untested safety-related performance goals as a measure of agency compliance with its user fee obligations.

As we discuss below, we are concerned that imbalances in financing of FDA activities, with increasing reliance on sponsor user fees as the core of agency funding accompanied by additional mandates for agency activities, are already a serious problem, which would only be exacerbated by this IOM proposal. Related to this, it is important to note that safety issues may also emerge in older products that are no longer marketed by research pharmaceutical companies. Additionally, we feel that the committee needs to consider what specific funding mechanism will be implemented for safety activities associated with the products of generic manufacturers.

CONCLUSION

S. 3807 reflects a desire that we all share, to enhance drug safety and access to new therapies, and Johnson & Johnson greatly appreciates the opportunity you have provided to discuss these issues with you today. An important consideration for the committee is the potential undermining of its efforts to strengthen FDA by increased reliance on user fees to fund FDA activities. User fees currently account for more than 50 percent of the agency's operating budget. At the same time, Congress and the Administration continue to burden FDA with additional unfunded responsibilities. We do not believe that FDA dependence on user fees creates institutional conflicts of interest. FDA's integrity is intact despite its receipt of user fees. Nevertheless, there is a perception, fostered by critics of FDA and of industry, that the agency is overly reliant on user fees in a way that compromises the integrity of its decisionmaking processes.

To address this inaccurate perception, Congress must increase FDA's appropriated funding, to restore balance to the agency's financing and to ensure public confidence in its independence. Although we appreciate that this committee is not responsible for appropriations for FDA, your status as the authorizing committee for FDA allows you to exercise considerable influence on your colleagues in the Senate.

On behalf of my colleagues at Johnson & Johnson, we look forward to working with you and your congressional colleagues to address this funding issue and to collaborate throughout the 110th Congress to refine the terms of this very important legislation on drug safety and innovation.

Thank you once again for the opportunity to speak with you today.

The CHAIRMAN. Thank you.

Mr. Guest.

Mr. GUEST. Mr. Chairman and members of the committee, I am Jim Guest, the President of Consumers Union, publisher of Consumer Reports, and I appreciate the opportunity to testify. For 70 years Consumers Union has provided consumers with independent unbiased information on vital public health issues. In the wake of the Vioxx and Paxil disasters, for example, where tens of thousands of Americans needlessly suffered, we have educated our more than 7 million subscribers, our more than 20 million readers, our many thousands, hundreds of thousands of citizen activists, on the need for stronger drug safety laws, and there is strong, compelling support for improvements in the FDA.

We applaud you, Mr. Chairman and Senator Kennedy, on S. 3807, which is a good first step towards meeting this need. It would bring greater balance to the process, save lives, help restore public trust in our Nation's drug safety system. Further, it does not impede another shared goal, which is rapid approval of safe, effective medications, particularly life-saving drugs.

In the interest of protecting consumer safety, we further urge that you strengthen the bill in several key areas. We endorse the bill's clinical trials registry requirements for phase two through

phase four trials and indeed we support and recommend even stronger provisions in S. 470. Publication of trials—however, should be within 1 year, not 2—would be our recommendation, and we urge that you require speedy publication of any other studies that indicate safety concerns. Too many Americans have died because pharmaceutical companies have suppressed clinical trials and other studies with crucial safety information.

We urge modifying the bill's GAO study requirements. It should be a given that all phase two trial results be public. That doesn't need a study. Rather, we urge a requirement that the GAO consider what useful phase one trial data might also be important to be made public, and we hope the registries, as you heard earlier, will be gradually expanded to include trials completed before the date of enactment.

The bill makes clear that once a drug is approved emphasis on safety does not end. We support the REMS provisions and urge that they be strengthened further, recognizing that the average drug adverse event does not show up until nearly 7 years after approval. To ensure that these risks are identified once a drug has been used by millions of people over time, we suggest the bill should approve—should provide for review on a 5-year basis and perhaps again on a 10- or 15-year basis as well.

In addition, advertising new drugs should be subject to limits for 3 years, not 2 as is in the bill. The FDA should require safety studies of those drugs most widely used off-label and civil monetary penalties should be strengthened, especially for repeat offenders.

Another area of great concern are the various reports about the severe morale and cultural problems at the FDA. These can be difficult to address, but we believe that legislation indeed can help set a higher ethical standard by requiring that all or at a minimum 90 percent of advisory committee members be free of conflict of interest.

Establish a climate of open and honest scientific debate and discussion at the FDA by institutionalizing a system of transparency, with staff dissenting or additional views on all new drug applications being public, along with whistleblower protections such as are contained in H.R. 5922.

Ensure more resources to the agency so it can do its job. One option would be to free the FDA from the detailed restrictions on how user fees are spent. Another option would be to increase user fees to deal with the huge backlog of safety issues. The appropriations process you have heard is ideal, but it's important one way or another that the FDA be sufficiently funded.

S. 3807 allows user fees to be used for post-market safety approval. We suggest it also set standards for the performance and safety of the computer modernization goals.

Finally, Consumers Union hopes that S. 3807 will be expanded to include reforming the laws on generic and biogeneric drugs and provide resources for the timely approval of safe, low-cost generics. Far too many families have suffered because the drug safety system is broken. Many victims and survivors are working tirelessly for reform so others won't have to endure their heartbreak.

I just want to note that two such extraordinary people are in the room today, Mr. Chairman, for this occasion: Eric Swann, whose

brother-in-law Woody Witzak was casually prescribed an antidepressant for insomnia and 5 weeks later killed himself; and Matthew Downing, whose daughter Candace was put on Zoloft because she was anxious taking tests at school and 10 months later she took her own life at the age of 21. Neither Eric nor Matthew knew about clinical trial results because they had been suppressed, that indicated increased risk of suicide for these types of anti-depressants.

For their sake, Mr. Chairman and members of the committee, and for others, thank you for the important work you're doing and thank you for your consideration of our recommendations. Again, we appreciate the chance to testify.

[The prepared statement of Mr. Guest follows:]

PREPARED STATEMENT OF JIM GUEST

Mr. Chairman and members of the committee, thank you for inviting Consumers Union, the nonprofit publisher of *Consumer Reports*, to testify. I request that our full statement appear in the Record.

For 70 years Consumers Union has provided consumers with independent, unbiased information on vital public health issues. In the wake of the Vioxx and Paxil disasters, for example, where tens of thousands of Americans needlessly suffered, we've educated our more than 7 million subscribers, our more than 20 million readers, many hundreds of thousands of our citizen activists, on the need for stronger State and Federal drug safety laws. They seek action.

We applaud you, Mr. Chairman and Senator Kennedy, on S. 3807, a good first step toward meeting this need. It would bring greater balance to the process, save countless lives, and help restore public trust in our Nation's drug safety system. Further, it does not impede another shared goal—rapid approval of safe, effective medications, particularly life-saving drugs.

We believe the committee would miss a great opportunity for protecting consumer safety, however, if you don't strengthen the bill in several key areas:

- assuring quicker publication of the results of more clinical drug trials;
- enhancing the FDA's power to protect public health;
- restoring the science-based culture and morale of the FDA;
- garnering more resources, especially for postapproval safety and information technology; and
- reforming the generic and biogeneric laws to bring lower-cost medicines to patients.

We will elaborate on each of these issues below, noting how the proposed bill addresses them, what the Institute of Medicine (IOM) and other research groups have concluded, and where Consumers Union recommends strengthening the bill.

1. DISCLOSURE OF CLINICAL TRIALS

Background

There are several major issues in the clinical trial area: the registration and disclosure of trials and studies, and the scientific integrity and reasonable patient safety of those trials.

Registration and Disclosure: The registration and public disclosure of clinical trials and other studies is key to determining the safety of drugs. Transparency of study results is necessary to understand the true safety and efficacy of drugs, to identify further research efforts and to ensure appropriate safety warnings. Too often, pharmaceutical companies distort, manipulate and conceal results from clinical studies in order to guarantee the approval of their drug. Today, there is an enormous bias toward reporting favorable results and the hiding or minimizing of lackluster and negative results. As one analyst has written:

> "Another problem with the existing system is that nonpublication of negative trials and nonreporting of negative outcomes, coupled with redundant publication of positive findings, has led to systematic publication bias, which can undermine the reliability of medical evidence." [1]

Two such examples are Vioxx and Paxil. Vioxx was removed from the market in 2004 after clinical trials revealed an increased risk of heart attack and stroke for those taking the drug.[2] According to testimony from Dr. Sandra Kweder, deputy di-

rector of the FDA's Office of New Drugs (OND), these trial results were not made available to the FDA prior to Merck's voluntary withdrawal of the drug.[3] Similarly, GlaxoSmithKline, maker of Paxil, concealed results from clinical trials linking the drug to an increased risk in suicidality among adolescents, as proven by New York Attorney General Eliot Spitzer's successful complaint against GlaxoSmithKline.[4] These trials also revealed that the drug was actually less effective than placebos among adolescents.[5]

These abuses have not ceased. As recently as September 29, 2006, the FDA released a Public Health Advisory that Bayer, maker of Trasylol, failed to inform the FDA Advisory Committee (which had convened 8 days earlier on September 21, 2006 to discuss Trasylol) of a new study that revealed an increased risk of death, serious kidney damage, congestive heart failure and stroke.[6] The FDA began conducting a review of Trasylol in January, 2006, after two published research articles reported serious risks associated with use of the drug.[7] [8] Such research misconduct has contributed to injuries and deaths by consumers who use these potentially dangerous drugs, and *USA Today* reports that the pharmaceutical industry faced more product liability lawsuits than any other industry last year.[9]

Abuses in the registration and reporting of clinical trial and study results highlight the need for increased transparency. Such transparency would enable the scientific community to better assess the true safety and efficacy of drugs. The World Health Organization (WHO) has taken steps to standardize trial registration and reporting through the International Clinical Trial Registry Platform (ICTRP), identifying a 20-item minimal dataset for all clinical trials, which includes target sample size and primary and secondary outcomes.[10] Many medical journals have formally supported these steps taken by the WHO and will now consider the publication of the results of a clinical trial only if it has been registered before the enrollment of the first patient.[11] The *Journal of the American Medical Association* is responding even more aggressively to ensure accuracy in data analysis by requiring all submissions of clinical trial results funded by industry to hire an independent statistician to analyze the data.[12] A coalition of over 100 healthcare stakeholders have signed the Ottawa Statement, making a moral case for full disclosure:

> "When members of the public agree to participate in trials, it is on the understanding that they are contributing to the global body of health-related knowledge. It is thus unethical to conduct human research without ensuring that valid descriptions of the study and its findings are publicly available." [13]

Lack of oversight and reasonable patient safety in clinical trials: The need for registration of clinical trials (at all phases) became even clearer after this spring's Phase 1 TGN1412 trial in which 6 healthy UK volunteers suffered catastrophic multiorgan failure after taking the drug. Many argue that these events could have been avoided had trial information been available for public review.[14] Although pharmaceutical companies argue that disclosing such sensitive information would allow competitors to conduct similar trials of their own, the WHO and many others in the field find that these concerns are not sufficient to delay disclosure.[15] Given the extraordinarily aggressive patenting of all aspects of a new drug, we do not believe that these public registrations will cause proprietary commercial losses. Disclosure of the TGN1412 trial would have allowed experts to determine if the trial was generally appropriate and if the procedures that were followed were sound.[16]

The research community must take more responsibility in protecting human volunteers, yet recent reports indicate that the FDA is about to loosen regulations in this area. Senator Charles Grassley, in a letter to the HHS Office of Inspector General (OIG), asserts that clinical trial subjects are not always adequately warned of potential risks, and are sometimes endangered and harmed as a direct result of participating in such trials.[17] *Bloomberg News* investigative reporting has found that safety oversight of clinical trials is often left in the hand of pharmaceutical companies and their contractors and that the quality of these experiments is often suspect and certainly dangerous to the participants.[18] The consequences are clear: the Center for Drug Evaluation and Research (CDER) recommended official action against 6 percent of the 319 clinical investigators it inspected in 2006 for noncompliance of regulations.[19] CDER requested voluntary corrections for an additional 42 percent of clinical investigators whose deviations from the regulations were considered to be "minor." Senator Grassley asserts that a fundamental concern regarding the participation of human subjects is the "lack of protections and respect for research participants who place their health and their lives in the hands of clinical investigators and the entities that are expected to monitor and oversee the studies." [20]

In addition to the lack of safety for individuals enrolled in some trials, there is the safety problem created by fraud in the falsification of data used to justify a drug's approval. In the recent case of Ketek, the FDA found multiple instances of

fraud in the company's clinical trial of about 24,000 patients, some cases of which the maker Sanofi already knew about yet failed to notify the agency.[21]

In light of the various abuses that may potentially occur while conducting clinical trials, the FDA must do more to ensure scientific integrity and patient safety in clinical trials. We comment on this problem further in the "Additional FDA Resources Needed" section.

Discussion of Solutions in S. 3807 and Further Recommendations

S. 3807 addresses the issues regarding transparency in research by establishing (1) a Clinical Trial *Registry* Database and (2) a Clinical Trial *Results* Database, both of which would be made public. These databases conform to the WHO ICTRP described in the previous section. If they are seeking journal publication, sponsors may take up to 2 years after they determine the trial is ended to report Phase 3 and Phase 4 trials to the public.

Consumers Union strongly supports the establishment of the Clinical Trial Registry Database and the Clinical Trial Results Database, but recommends that sponsors be required to report results, including the results of Phase 2 trials, within one (1) year, and that results from trials of drugs revealing safety concerns be reported publicly as soon as trials are completed. This recommendation follows that of the Institute of Medicine (IOM), which requests that trials be registered "in a timely manner."[22] Given the history of manipulation and concealment of results by pharmaceutical companies, a stricter deadline than 2 years for reporting results seems appropriate.

While the proposed legislation requires the registration of the results of Phase 3 and 4 trials, it does not require the registration of the results of Phase 2 trials unless the Government Accountability Office (GAO) specifically recommends registration, which would then be implemented through a further rulemaking process. The Institute of Medicine report recommends that, at a minimum, *all* Phase 2–4 trials be registered, including a posting of a "structured field summary of the efficacy and safety results of the studies.[23] Furthermore, trial registration will do nothing to diminish publication bias and misreporting if only trials that have been completed and reveal favorable results are reported and published.[24] In order to really address the problem of selective reporting—which is clearly an issue given recent history—all clinical trials should be registered.

In addition, some argue that even Phase 1 trials can gather data on efficacy in addition to safety, and therefore should also be subject to registration.[25] The data found in a Phase 1 trial can contribute to meta-analyses of adverse events and is used by successful safety projects such as RADAR.[26] Finally, there is a strong moral argument for such registration: fellow human beings have volunteered to serve basically as guinea pigs to test the basics of a new drug idea. If there is any adverse side effect from such tests, it seems immoral not to report such results and not to warn other companies who may stumble down the same research pathway. There may be little merit in the concern that a company will lose "proprietary" data. A company's proprietary and commercial interests are undoubtedly protected by the aggressive patenting that occurs in the drug industry. The safety of human test subjects should come first.

Consumers Union supports the public disclosure of as much scientific data as possible. S. 3807 should be amended to change the GAO study of whether Phase 2 trial results should be disclosed. We believe that Phase 2 disclosure should be a given. Instead, the GAO study should concentrate on whether all or some of Phase 1 trials should be disclosed at the point when a final decision is made on the drug subject to the trial (i.e., it is approved, or withdrawn).

Consumers Union also urges that the legislation extend the registry to gradually include all studies completed since at least 1996, and hopefully earlier. For example, each year over the next 5 years, 2 years of pre-enactment of S. 3807 trial results could be publicly posted. It would be a great service to the world's scientific community to have in one place an expanded, Internet available library of these past trials.

In order to address the potential of trial abuses and falsifications, the proposed bill calls for the FDA to "sample" clinical trials to ensure that the descriptions of results are "nonpromotional, and are not false or misleading in any particular. . ." **In light of past abuses, Consumers Union recommends that pharmaceutical companies that neglect to provide relevant results or falsify results should be subject to FDA Civil Monetary Penalties (CMPs). In the "Additional FDA Resources Needed" section, we urge that a higher percentage of trial and study papers be audited for scientific integrity and honesty.**

Finally, S. 3807 pre-empts State laws that require clinical trial registration. Because of lack of action at the Federal level, Consumers Union has been a driving force behind these State debates and laws. We accept the idea of pre-emption, but only if there is a strong Federal law. **If the type of changes we recommend above are not included, we oppose State pre-emption.** The States should be able to do more to protect the safety of their citizens.

2. FDA POWER TO ENSURE SAFETY

The IOM report highlights the fact that PDUFA has done a great deal to ensure speed in the drug approval process—perhaps at the neglect of safety. The report notes that although the PDUFA laws have established performance goals relating to review speed, there are no performance goals relating to safety.[27] Thus the FDA assigns priority to specific drug approval performance goals, and in turn (as the recent history of withdrawals suggests), lacks resources to act aggressively on safety issues which have no such performance goals.

S. 3807 provides exciting new powers, resources, and enforcement tools for the FDA to improve post-market approval safety. But in light of recent history, we urge even stronger actions. The following five (5) subsections offer recommendations on how to give the FDA clearer additional authority to ensure safety without in any way slowing the approval of life-saving medicines:

A. Effective use of adverse event reports
B. Postapproval management
C. Direct-To-Consumer (DTC) advertising
D. Off-label use
E. Enforcement

A. Effective use of Adverse Event Reports

Background

An estimated 700,000 people required emergency department attention due to Adverse Drug Reactions (ADRs) in 2004 and 2005.[28] ADRs are responsible for as many as 100,000 deaths annually.[29] Although these numbers indicate that ADRs are an enormous problem, no effective mechanisms for reporting and analyzing potentially serious ADRs exist today.[30] Spontaneous reporting systems such as MEDWATCH, while sometimes useful, are incapable of reliably or quickly detecting many long-range ADRs.[31]

Discussion of Solutions in S. 3807 and Further Recommendations

S. 3807 establishes a key principle: that drug safety issues do not stop with the approval of the drug. Instead a drug must be looked at over its "life cycle"—drugs need to be monitored and studied over many years. The bill establishes a system of Risk Evaluation and Mitigation Strategies (REMS). In addition, in title II it creates the Reagan-Udall Institute, in consultation with the National Institutes of Health (NIH) and other research programs, to explore ways to improve adverse event reporting and analysis and improve the science of drug development and safety.

The IOM report specifically calls for an improved Adverse Event Reporting System (AERS), and asks that the Center for Drug Evaluation and Research (CDER) conduct a scientific review of AERS to identify and implement improvements, and, "systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals."[32] While spontaneous reporting methods, such as MEDWATCH, may contribute to AERS, these methods are not the only tool to track and evaluate ADRs. **Consumers Union recommends the incorporation of a temporary demo whereby the FDA devotes resources (including user fees) to support NIH funding of a program like the Research on Adverse Drug Events and Reports (RADAR) project in which medical scientists proactively search ADRs for patterns.**[33] The RADAR project is funded entirely by peer-reviewed grants from the NIH, the Veterans Administration (VA), and the American Cancer Society (ACS). Summary safety information from the project is synthesized into reports for medical journals, revised package inserts, and "Dear Doctor" letters. The information is presented to physicians, the FDA and relevant sponsors. The RADAR project may provide important answers as to how more ADRs can be reported and evaluated in a meaningful way.

Today, it is estimated that only 1 to 10 percent of all adverse events are reported. But with the coming age of health information technology and personal health records (PHRs) where patients can be electronically warned of dangers and asked to report reactions to new drugs, we will soon have access to a huge amount of new data. The FDA is to be commended for contracting with a number of large patient

encounter databases. The use of these large databases can eventually permit the FDA to detect patterns of ADRs that are invisible when only smaller populations are examined. But it is not yet clear when and how they will be able to use the extraordinarily rich data that will be available from Medicare Parts A, B and D. **We urge the committee to lay the groundwork in S. 3807 for FDA to use the Medicare databases and PHR systems to establish a truly effective AERS that will be able to detect many more kinds of drug interactions.** Further, such a system will help us compare drug effectiveness to determine which medicines and courses of treatment are most effective in fighting life's diseases. Of course, using large databases to aggressively search out adverse drug events will take significant new resources (which we discuss below).

B. Postapproval Management

Background

As noted in the previous subsection, ADRs pose serious safety concerns. According to a study by the General Accounting Office (GAO), over 50 percent of all approved drugs had serious postapproval risks.[34] These ADRs are often detected years after the drug has been on the market. One study indicates that only 50 percent of ADRs are discovered within 7 years after approval.[35] This delay in detecting drugs with serious risks is apparent in the withdrawal process as well; one report documents the median time on the market, before a drug is withdrawn, to be 5.4 years.[36]

These figures highlight the importance of postmarketing surveillance, but in the current system the FDA focuses almost exclusively on pre-approval indicators. This strategy has proven to be inadequate and dangerous. Although pre-approval trials may assess efficacy, they cannot assess safety due to the fact that they are conducted in small, selected populations (often disproportionately males who are younger and healthier than the population which will actually use the drug) for very limited periods of time. In general, Phase 1 trials are conducted on several dozen healthy humans to determine safe dosages and generally evaluate safety. Phase 2 trials are conducted on a slightly larger population—perhaps several hundred people—to test effectiveness and further evaluate safety. Phase 3 trials are conducted on large populations of several thousand to confirm effectiveness, monitor side effects, and gather additional information that will allow the drug to be used safely. An abbreviated trial may be conducted for as little as 6 months. Finally, Phase 4 trials are conducted after a drug has been marketed to evaluate long-term safety. FDA regulations allow for the approval of a drug with evidence from a single clinical trial.[37] Clearly, clinical trials are simply incapable of portraying an accurate picture of how a drug will behave in the general population or the older patient population over many years. Thus, the need for reviewing drugs once they are on the market is essential.[38] [39]

Although the FDA has the authority to recommend Phase 4 postapproval studies, sponsors of drugs often fail to complete such studies. For example, Sanofi-Aventis failed to complete a postapproval study on the arthritis drug, Arava, after the FDA questioned its long-term safety at the time of its approval in 1998.[40] Arava has been on the market for 8 years and fatal liver complications have been reported in those using the drug.[41] *Bloomberg News* reports that 860 postapproval studies requested by the FDA have yet to be completed, 260 of which are on drugs that were approved at least 5 years ago.[42] It appears that many of these trials have not even been started and the commitments given to the FDA are often ignored.

Not only is there a problem with getting companies to fulfill their post-market study commitments, but lack of FDA resources has led to poor enforcement of this program. In June 2006 the HHS Inspector General reported that:

> FDA cannot readily identify whether or how timely post-marketing study commitments are progressing toward completion. About one-third of ASRs [Annual Status Reports on these studies] were missing or incomplete, . . . ASRs contain information of limited utility . . . FDA lacks an effective management information system for monitoring post-marketing study commitments. . . . Monitoring post-marketing study commitments is not a top priority at FDA. . . . Our analysis showed that FDA validated only 30 percent of ASRs submitted in fiscal year 2004. . . .

The OIG called on FDA to instruct companies to provide "additional, meaningful information in their ASRs, improve the management information system for monitoring post-marketing study commitments so that it provides timely, accurate, and useful information, and ensure that post-marketing study commitments are being monitored and that ASRs are being validated."[43]

Discussion of Solutions in S. 3807 and Further Recommendations

This year's GAO report on the FDA comments on the agency's inability to ensure the completion of postapproval studies, asserting that "FDA needs greater authority to require such studies."[44] The report goes on to further document cases where the FDA has been unable to negotiate with sponsors to ensure that postapproval studies are conducted. Since sponsors voluntarily agree to conduct such studies, the FDA has no authority to ensure their completion.

As part of REMS, S. 3807 gives the FDA authority to require safety trials and tools to enforce the requirement. Consumers Union strongly supports this provision: it is one of the most important in the bill.

In addition, required REMS call for 3 years of review, and additional review may be required "at a frequency determined by the Secretary for subsequent years." The IOM repeatedly highlights the need to perform postmarketing surveillance throughout the entire life cycle of a drug. In particular, the IOM recommends that the evaluation of a new drug's total safety profile occur after 5 years. **Consumers Union strongly supports the IOM's recommendation and asks that the review time cycle for a drug be increased from S. 3807's 3 years to 5 years. This review should be institutionalized, and not left to the total discretion of the Commissioner.** Given the history of ADRs and drug withdrawals that occur many years after a drug is first on the market, this kind of extended postmarketing surveillance is necessary. **Because of the history of problems detected many years and even decades after a drug's approval, we also support the institutionalization of another focused review of the literature, ADERs, etc., at some later interval, perhaps at the 10th or 15th year a drug has been on the market.**

With respect to industry conducted post-approval safety studies, HHS OIG recommended that the FDA instruct sponsors to provide "additional, meaningful information" in their annual status reports in order to determine how timely post-marketing study commitments are progressing toward completion.[45] According to the OIG, the FDA disagreed with this recommendation, stating that the implementation of such a recommendation would require additional regulations. The OIG concludes that the FDA cannot identify the progress of post-marketing study commitments, and that regulatory changes may need to be enacted in order to address these issues. Consumers Union supports the OIG's recommendation that sponsors include progress reports on post-approval safety issues in their annual status reports. S. 3807's annual REMS review process is a major step in this direction.

C. Direct-To-Consumer (DTC) Advertising

Background

Although full safety risks are often unknown for years after approval, pharmaceutical companies invest a great deal of money in the immediate promotion of approved drugs, including billions of dollars in Direct-To-Consumer (DTC) advertising. We have seen, too many times, the devastating effects of such DTC advertising. At least one study has commented on how DTC advertising contributed to the overuse and misuse of Vioxx by both consumers and physicians, which led to an unnecessary increase in the number of people at risk of heart attack and stroke.[46] In addition to the safety concerns, DTC advertising of Vioxx increased costs to consumers and health plans alike, which were paying significantly more for a new drug that added little or no benefit.[47]

Some defend the use of DTC advertising, asserting that it promotes patient-physician dialogue and increases awareness of diseases and treatments. One study shows, however, that these ads are rarely educational; while many advertisements gave the name of the drug and the condition being treated, very few provide any additional health information on alternative treatment of the condition.[48] The study reports that out of a possible 11 educational codes (specific educational points), the average number of codes present in advertisements was 3.2. Despite the lack of truly educational information in DTC advertising, consumers tend to believe the pharmaceutical industry's message that only the safest and most effective drugs appear in advertisements.[49] This is particularly dangerous given the fact that the goal of this advertising is to sell a costly product that can potentially have serious safety risks. Consumers Union believes that if we need to increase awareness or dialogue about certain medical problems, the industry could contribute to scientifically-based Public Service Announcements approved or managed by an impartial, expert group, such as the FDA, CDC, or NIH.[50]

Discussion of Solutions in S. 3807 and Further Recommendations

As a part of REMS, the proposed bill gives the FDA authority to require the preclearance of advertisement to ensure disclosure of a serious risk listed in the label-

ing of the drug. In light of the promotional nature of DTC advertising and the long history of abuses in DTC advertising, and given that such advertising strongly influences consumers, **Consumers Union recommends a requirement that ALL advertisements be pre-cleared by the FDA for accuracy and honesty, including the growing use of ads in the Internet and other nontraditional sites.**

In addition, the FDA may impose a 2-year moratorium on DTC advertising for drugs showing more serious safety concerns. Given the amount of influence this type of advertising has on consumers, and given the potential serious ADRs that may occur years after approval, **Consumers Union recommends a moratorium on DTC advertising of 3 or more years for all new drugs. The history of ADRs and withdrawals shows that drugs cannot be assumed safe after just 2 years. Adding a possible third year to the moratorium authorities in S. 3807 would be prudent and constitutional.**[51]

D. Off-Label Use

Background

The FDA currently approves drugs for specific indications based on scientific evidence and clinical trials. Off-label uses of these drugs (in which physicians prescribe medicines for indications other than the ones for which a drug is approved) lack the same kind of scientific scrutiny. In an analysis of 160 commonly prescribed drugs from 2001, off-label uses accounted for 21 percent of overall use, and most uses had little or no scientific support for such use.[52] In some classes of drugs, off-label use accounts for up to 75 percent of prescriptions.[53]

Often, drug companies inappropriately and illegally influence doctors to prescribe medications for off-label uses. In the case of gabapentin, pharmaceutical company Parke-Davis used teleconferences, consultant meetings, selective research, as well as other tactics to encourage doctors to use the drug for off-label uses.[54]

Despite the high occurrence of off-label uses, the scientific efficacy of such drugs for unapproved indications is not established.[55] [56] Many off-label uses are often helpful and probably have little adverse consequences, but since off-label uses are not subject to FDA approval, it is difficult to determine what scientific evidence exists to prove clinical effectiveness. Off-label use of prescription drugs also generally raises concerns regarding potential risks to patients as well as issues about the reimbursement and coverage of these drugs.[57] Adverse drug events may also occur more commonly in off-label settings than in on-label settings, since clinical trial information is often unavailable.[58] The *Wall Street Journal* recently reported on the off-label use of Actiq, a potent narcotic that is indicated for use in cancer patients who experience intense pain.[59] According to the article, Actiq is 80 times as potent as morphine and is in a group of drugs that has the highest risk of fatal overdose. In fact, 47 deaths due to overdose were associated with the use of Actiq. Despite the safety risks, data suggest that 80 percent of patients use the drug not for cancer pain, but for off-label uses such as headache and back pain.

Discussion of Solutions in S. 3807 and Further Recommendations

S. 3807 is silent on the issue of off-label use. Given the potential for off-label uses to create serious safety problems, **Consumers Union recommends that the FDA develop a program to scientifically study drugs widely used in off-label settings.** We are not advocating a ban on such use. We are simply asking that some scientific study be brought to this area, so that the labels on these drugs may be expanded and improved in the cases where the scientific evidence is supportive.

E. Enforcement

Background

As described above, the FDA has limited authority to effectively enforce post-approval safety. As this year's GAO report highlights, the "FDA has little leverage to ensure that these [commitments for post-approval safety studies are carried out . . . by imposing administrative penalties."[60] The IOM also reports that lack of clear regulatory authority is a serious problem at the FDA.

In addition to the lack of clear authority in some areas, there is the issue of failing to use existing authorities. Rep. Henry Waxman has reported that the level of enforcement actions has been declining and the recommendations of FDA field staff for corrective actions are often disregarded:

> "Internal agency documents show that in at least 138 cases over the last 5 years involving drugs and biological products, FDA failed to take enforcement actions despite receiving recommendations from agency field inspectors describing violations of FDA requirements."

The House Government Reform Committee report noted a 50-percent decline in warning letters in recent years.[61]

Discussion of Solutions in S. 3807 and Further Recommendations

In addition to existing authorities (some of which like drug withdrawals or seizures are so serious and disruptive they are not creditable and almost never used), the bill allows the FDA to issue Civil Monetary Penalties (CMPs) of between $15,000 to $250,000. CMPs may not add up to more than $1,000,000 for all violations "in a single proceeding." While this CMP authority is a major improvement, given the large profits that pharmaceutical companies can enjoy every day a drug is on the market, **Consumers Union recommends that CMP authority be increased to more than $1,000,000, especially when companies are repeated offenders.**

S. 3807 also gives the FDA more authority to order changes in drug labels and to control the dispensing of drugs so to ensure that particularly vulnerable populations (such as pregnant women) are better protected from unnecessarily dangerous forms of treatment. **Consumers Union strongly endorses these labeling and dispensing provisions in S. 3807.** As the Office of New Drugs Director Dr. John Jenkins said,

> "There's no doubt that there are situations where we internally feel frustrated that the discussions about label changes are taking longer than we would like. Remember that labeling is the primary way we have to communicate to practitioners and health providers about the safety and effectiveness of the drug. So everything keys off the labeling."[62]

The language in S. 3807 should prevent a recurrence of the 22 months of FDA-Merck "negotiating" on the Vioxx label while millions of patients continued to take an unnecessarily dangerous drug.

3. RESOURCES AT THE FDA

Background

The FDA needs more resources if it is to truly be the world's Gold Standard in prescription drug approval and safety.

We agree with the IOM report that the FDA suffers from serious resource limitations. The IOM notes that although user fees have greatly increased the resources for new drug review, FDA's other functions—such as post-approval drug safety monitoring—are seriously under funded. As the IOM notes, PDUFA not only sets performance goals, but also tightly restricts CDER's use of its funds: "each round of PDUFA negotiations has led to more demands on CDER and continued restrictions on CDER's flexibility."[63]

The lack of resources for safety is appalling. The public would be truly shocked if they realized how huge the FDA's jurisdiction is and how little the agency can really manage to do with its limited budget. Unfortunately, the public is periodically reminded of those limitations by outbursts of fatalities—such as the recent *E. coli* spinach deaths.

According to the 2006 GAO report on post-market drug safety, the FDA has currently allocated $1.1 million per year for its contracts with researchers outside of FDA to conduct postapproval studies. Yet the GAO also reports that just one clinical trial designed to study long-term drug safety could cost between $3 million and $7 million.[64] The IOM report also highlights the need for increased resources to support new staff devoted to post-market safety work. PDUFA funding has supported the surge of new drug review staff, whereas ODS has not experienced such a dramatic increase in staff: between 1996 and 2004, new drug review staff increased by 125 percent (from 600 to 1320) but ODS staff increased by only 75 percent (from 52 to 90).[65] While the drug companies flood the airwaves and Internet with ads, the FDA is only able to review about 24 percent of these for accuracy.[66] And while generic drugs can save consumers billions of dollars, this fall there is a backlog of 394 generic drugs awaiting approval because of FDA bottlenecks.[67]

The IOM highlights the need for resources to support Information Technology (IT) at the FDA, and concluded that CDER's IT systems are antiquated. Consumers Union staff has been told that half the FDA's computer systems are so old that they will no longer be served by vendors after this year. It is worth quoting at length Dr. Scott Gottlieb, writing before his appointment to the FDA:

> "Although it is impossible to calculate exactly how much the agency's review programs spend on IT-related infrastructure (because it is embedded in many different programs), consider that total spending on IT-related activities at the FDA was cut $29.1 million in 2004 from what the agency had requested so that the FDA could find savings to stay inside its congressional budget allocation.

That exceeds the entire $23.8 million budget of the FDA's Office of Drug Safety for 2004."

"All of this leaves little doubt that even the most basic IT improvements have been slow in coming, hobbled by a lack of budget and vision. As a result, information is made available to the FDA slowly and takes even longer to analyze by the FDA's trained personnel. Subtle side effects—especially medical problems that occur naturally in a large population or as a consequence of the condition that a drug aims to treat (the side effects at issue with Vioxx and the SSRIs met these criteria) could be easily dismissed as normal or "background" events as a result of inadequate sample sizes and the inability to easily aggregate and analyze population-based data on actual drug use."[68]

Yet IT resources are essential for making post-market surveillance work, improving AERS, and—in the long run—making comparative effectiveness analyses that will save the Nation tens of billions of dollars by identifying what courses of treatment work and don't work. In addition to modern systems, the FDA needs the resources to develop electronic data submission formats; today, all too many applications are submitted as expensive-to-process reams of paper, because the FDA says it doesn't have the resources to develop regulations for electronic submission formats.

Discussion of Solutions in S. 3807 and Further Recommendations

S. 3807 allows PDUFA user fees to be available for REMS work to improve post-approval safety. Many are concerned, however, that the FDA is too closely tied with the industries it regulates. User fees may contribute to the pharmaceutical industry's "capture" of the FDA.[69] The IOM recommends that Congress approve a substantial increase in both funds and personnel for FDA safety activities in order to counteract PDUFA's restrictions on how the FDA can use its funds. The IOM discusses the ideal option of general Treasury revenues to adequately fund the FDA. Importantly, however, the IOM notes that if user fees are required, Congress should greatly reduce current restrictions on how the FDA can use those funds.

Consumers Union strongly supports the IOM's recommendations for more resources with no "strings attached." This could be achieved, as Rep. Maurice Hinchey's bill (H.R. 2090) does, by depositing user fees into the Treasury, then entitling the FDA to an amount of money from the Treasury equal to the amount currently raised by user fees, but freeing the agency from detailed restrictions on how such moneys are spent. As noted in section 5 below, freeing the FDA from dependence on the industry is probably the single major thing we can do to improve the morale and culture within the FDA on behalf of consumers.

Another option would be to increase user fees to deal with a huge backlog of safety issues. Consumers Union echoes the IOM's words that regardless of the funding source, "the functioning of a drug safety system that assesses a drug's risks and benefits throughout its lifecycle is too important a public health need to continue to be under funded."[70]

If a user fee system is continued, we urge that **S. 3807's section 104 be strengthened to spell out adequate levels of resources and performance goals for safety. Just as the industry has goals for rapid drug approvals, consumers and patients should have goals for rapid resolution of safety concerns.**

Attachment #1 is a list of the kind of safety goals that should be funded, ideally by the general Treasury, but if the user fee program is continued, then by user fees. This list is illustrative. Of course, your committee would need to provide details on the exact performance levels and the realistic rate of increase in safety quality after consultation with the FDA, OMB, and after studying the President's fiscal year 2008 budget and the FDA's actual safety budget deficiencies in the middle of fiscal year 2007.

While all these safety standards are important, we particularly appreciate S. 3807's study of the FDA's IT needs. But another IT study, without funding, is meaningless. We urge you to give a priority to funding these crucial IT building blocks.

4. ADVISORY COMMITTEES (ACs) AT THE FDA

Background

Advisory committee meetings are a very important resource for the FDA. Such meetings are public and provide an opportunity for the agency's scientific experts, consumer advocates, and industry representatives to contribute to the regulatory process. Recently, however, there have been serious concerns about the process.

Although AC meetings provide a valuable contribution to the FDA's efforts to regulate drugs, the frequency with which they convene has been declining. The OIG reported that the number of AC meetings decreased from 40 in 1998 to 23 in 2001.[71] The OIG also reported that FDA managers believed that they had little time to hold these meetings. In addition, only 21 percent (5/24) of approved New Molecular Entities (NMEs) were preceded by an advisory committee meeting. NMEs are drugs that contain an active ingredient that has never before been approved, and may be more likely to carry safety risks.[72]

In addition to the recent reduction of meetings, important information regarding drug safety is sometimes purposefully excluded. For example, a senior epidemiologist at the FDA, Dr. Andrew Mosholder's concerns that Paxil increased suicidal behavior in children were dismissed by higher FDA authorities.[73] Dr. Mosholder was not allowed to present his analysis at the February 2004 joint meeting of the Psychopharmacologic Drugs Advisory and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee because it was believed to be too preliminary.[74] In later interviews with the GAO, the Directors of CDER and the Office of New Drugs (OND) said that in retrospect they felt it was a mistake for the FDA to have restricted Dr. Mosholder from presenting his safety information.[75]

The GAO report on post-market drug safety notes that the role of the Office of Drug Safety (ODS) in AC meetings is unclear. The report cites another case (in addition to the one above) in which ODS staff was not allowed to present their analysis: the OND did not allow the ODS to present their review of Arava at the Arthritis Advisory committee meeting in March 2003 because the OND division believed that ODS's review lacked scientific merit. ODS found the use of Arava to be associated with acute liver failure. GAO reports that after the meeting, ODS epidemiologists and safety evaluators requested clarification of ODS's role in advisory committee hearings, but that there was no written response to this request.

Although certain FDA experts have been refused permission to testify at AC meetings, many outside scientific experts are free to participate in such meetings despite having outstanding conflicts of interest. For example, at the February 2005 joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the safety of cyclooxygenase−2 (COX−2) inhibitors, 10 of the 32 voting panel members had financial associations with the manufacturers of these drugs (such as consulting fees or research support).[76] All 10 members were issued general waivers that allowed them to participate in the meeting. Twenty-eight out of the thirty votes cast by these 10 members favored marketing of Bextra, Celebrex and Vioxx, whereas only 37 out of the 66 votes cast by the remaining 22 members favored marketing of these drugs.[77] If the 10 panel members with conflicts of interest had not participated in the meeting, the committee would have voted to remove Bextra from the market, and to keep Vioxx from returning to the market (Merck voluntarily withdrew Vioxx from the market in 2004). Instead, due to the inclusion of the votes from the 10 conflicted panel members, the committee voted to keep these drugs on the market. The FDA consequently announced that it had asked Pfizer to voluntarily withdraw Bextra from the market, which it did in April 2005, 2 months after the advisory committee meeting.

Discussion of Solutions in S. 3807 and Further Recommendations

Frequency of Meetings: Title IV of S. 3807 recommends a series of clarifying efforts to reduce or disclose conflicts of interest. The IOM recommends that FDA advisory committees review all NMEs either prior to approval or soon after approval. The IOM notes that although it might be impossible to convene AC meetings for all NMEs prior to approval, the FDA should have the authority to require such meetings after approval. Since advisory committees provide valuable scientific expertise, it is important that the FDA capitalize on such a resource. **Consumers Union supports the IOM's recommendation that all NMEs be reviewed by FDA advisory committees and be part of the REMS process.**

ODS involvement in ACs: In addition to encouraging participation of outside scientific experts through AC meetings, it is important that FDA's own scientific experts also be heard. ODS staff has recommended that as a matter of policy, they present post-market safety data at these meetings.[78] **Consumers Union recommends that ODS always have the right to testify before ACs. If ODS chooses not to testify, Consumers Union strongly recommends that ACs be granted the authority to request such testimony or a statement from ODS that they have no safety concerns to raise.**

The IOM highlights the fact that the FDA must undergo cultural changes if post-approval safety is to be improved. Consumers Union encourages language in S. 3807 that would speak to this issue and assure the right of FDA scientists to dissent or

provide "additional views" to the majority view. The right to dissent must be especially acknowledged at AC meetings.

Also, a recent report by the National Resource Center for Women and Families[79] shows that while ACs often raise safety questions, they very seldom reject a drug. There appears to be a clear bias toward approval and a suppression of safety concerns (which is another reason to seek more conflict-free experts). The study also shows that even when an AC rejects a drug, the FDA frequently ignores the recommendation. We believe that if the FDA overrules an AC recommendation, it should provide a detailed public statement of why it disagrees and why it believes the science supports the FDA's disregard of the expert outside panel.

Ending Conflict of Interest: AC meetings must be conducted in such a way that scientific integrity is promoted. Recent history suggests that committee members are given voting rights despite significant financial associations with the pharmaceutical companies affected by the committee's review. The *New England Journal of Medicine* reports that, according to Dr. J. J. Wood, the chair of the joint meeting that reviewed the COX−2 inhibitors, the FDA made a "judgment error" when it decided to issue a general waiver and not to disclose specific information regarding the conflicts of interests of committee members.[80] The IOM recommends that a "substantial majority" (and suggests 60 percent) of the members of each advisory committee be "free of significant financial involvement" with the pharmaceutical companies that would be affected by the committee's review. In addition, the IOM recommends that the FDA issue waivers to committee members "very sparingly."

Consumers Unions recommends that no advisory committee meeting be convened unless a substantial majority of the committee is free of significant financial involvement. We think it is important for restoring public confidence in the agency and creating a culture of the highest public service that no less than 90 percent, and ideally 100 percent, of advisory committee members be free of conflict.

The public has lost confidence in the FDA. The *Wall Street Journal* reported on a May 24, 2006 WSJ Online/Harris Interactive poll that 58 percent of the public feels the FDA does a fair or poor job on ensuring the safety and efficacy of new drugs, and 80 percent said they are somewhat or very concerned about the agency's ability to make "independent" decisions. Clearly, this is a time to bend over backwards to ensure integrity and public interest in all aspects of the FDA, including the integrity of its Advisory Committees.

It is argued that the best experts in a field are those who have been working with drug companies on the research and development of specific drugs and that it would be impossible to staff conflict-of-interest-free committees with qualified experts. We argue that when one looks at the recent FDA's reports to the Congress on advisory committees, it is clear there is no one person at the FDA charged with coordinating the recruitment of advisors to all the various FDA Centers. **We urge the Congress to support a major outreach effort by the FDA to find nonconflicted advisory committee members.** Until one actively recruits, how can one know that AC's that would inspire public confidence cannot be created?

5. IMPROVING CULTURE AND MORALE AT FDA

Background

Some of the conflict of interest problems that plague FDA's advisory committees appear to affect other aspects of life at the FDA as well. The fact that many career FDA scientific staff members believe their voices are silenced speaks of larger, extremely serious troubles relating to culture and morale at the agency.

In August 2006, the Union of Concerned Scientists (UCS) and Public Employees for Environmental Responsibility (PPER) released their survey of FDA staff. The findings echoed those reported by the Office of Inspector General (OIG) in 2003.[81] For example, in response to the question: "Have you ever been pressured to approve or recommend approval for an NDA despite reservations about the safety, efficacy, or quality of the drug?" Forty-one respondents out of 217 Center for Drug Evaluation and Research (CDER) staff (nearly 19 percent) answered "yes."[82] These types of responses raise concerns regarding the extent to which these experts are capable of practicing their right to dissent on issues of drug safety.

These poll findings support the IOM report's finding that the organizational culture at the FDA is partially responsible for the marginalization of dissenting voices.[83] The IOM says that the polarization between the pre-marketing and post-marketing review staff contributes to a negative culture at the FDA. This polarization is evidenced in advisory committee meetings as described in the previous section, where the OND has prohibited the ODS from presenting pertinent safety information. In addition, the resource gap resulting from the introduction of user fees

has further divided the two offices and increased tension.[84] The IOM notes that ODS staff have been considered marginal players compared with OND staff, and that the ODS is perceived to have a lower status compared to the OND. According to the IOM, various concerns relating to culture at the FDA have resulted in a "persisting problem with retention, turnover, and morale in CDER."[85] Key relevant staff members are sometimes excluded from discussion and decisionmaking about the agency and the work they perform daily.

Discussion of Solutions in S. 3807 and Further Recommendations

In order to address the culture and morale challenges facing the FDA, it is imperative that the agency establish a climate of open scientific debate. **Consumers Union recommends institutionalizing a system of public staff dissent and additional views on all new drug applications, accompanied by "whistleblower" type staff protections.** Representative Ed Markey (D-MA) has a bill (H.R. 5922) with whistleblower language.

Just as Congress or the Courts have institutionalized a system where Members can and are expected to offer additional or dissenting views, we believe a similar, institutionalized system within the FDA would improve culture and morale, and contribute to a healthier scientific debate. Some say that this kind of dissent would confuse the public, make practitioners uncertain about whether a drug was good or not, and make people too cautious to use new, important new drugs. We believe that consumer empowerment is good, and that by making it clear where the scientific questions and uncertainty are, it will help researchers around the world concentrate on answering those questions as quickly as possible. The public would understand that while a majority of the FDA found a drug to be effective and safe, dangers were not swept under the rug as part of some pro-drug company conspiracy. The public will support dissent and debate—suppression of dissent will destroy confidence in the system.

6. SPEEDING APPROVAL OF GENERICS AND BIOGENERICS

Background

Healthcare costs continue to surge at double or triple the rate of general inflation, in part due to the high cost and rate of inflation of brand-name prescription drugs. Generic and biogeneric drugs, can dampen health inflation by providing equally safe and effective medicine at a far lower price—often prices only 70 percent or less of the brand name drug. Generics and biogenerics save consumers billions of dollars. For example, according to one study by the Pharmaceutical Care Management Association (PCMA), generic drugs could save consumers over $23 billion over the next 5 years if optimal use is made of the 14 generic drugs scheduled to enter the market during this time.[86] These savings could also significantly help reduce Medicare and Medicaid costs, since many of these 14 generic drugs are commonly used by senior citizens.

Despite the enormous savings available from generics, the FDA has been unable to ensure that these drugs are approved for the market in a timely manner. In a memo to Consumers Union this autumn, the FDA reported that an unduplicated count of pending generic applications showed a backlog of 394 drugs pending more than 180 days—drugs which could help lower costs to consumers if they were approved. An article in the *Washington Post*[87] explains that part of the problem is the lack of staff to review these applications: the Office of Generic Drugs only has 200 employees. This is in stark contrast with the OND, which has more than 2,500 employees to review about 150 (admittedly more complex) applications.

There is no clear law providing for the development of generic versions of more complex molecular biologic medicines. These new products are the most expensive medicines on the market—some costing as much as $100,000 to $250,000 for a course of treatment. Some criticize the notion that biogenerics could bring cost-saving benefits, saying that these drugs are far more complex than other drugs because they are made from living organisms, and therefore cannot be copied as easily, as inexpensively, or as safely as other drugs.[88] Nevertheless, the European Medicines Agency is creating a framework for biogenerics to be approved.[89] Consumers Union joins most other observers in believing that biogenerics could provide some savings and can be provided safely, thus helping some of our most severely ill patients.[90] The law should be clarified to allow us to do what the Europeans are doing: bringing some relief to consumers.

In addition to backlogs in the approval of generics and legal uncertainty and stalemate on the issue of biogenerics, there are a series of legal loopholes in the law that have allowed drug companies, often in collusion with generic companies themselves, to block the entry of lower-cost generics—sometimes for years. These loop-

holes range from abuse of the pediatric exclusivity provision to payment arrangements to keep a generic from entering the market. In recent years, the use of phony citizens petitions has cost consumers millions of dollars by delaying the entry of generics. According to the FDA, only 3 of 42 petitions answered between 2001 and 2005 raised issues that merited changes in the agency's policies about a drug. For example, Flonase, a commonly used prescription allergy medication, went off patent in May 2004. But GlaxoSmithKline stretched its monopoly window by almost 2 years with petitions and a legal challenge to the use of generics.[91]

Discussion of Solutions in S. 3807 and Further Recommendations

The current legislation is silent on issues surrounding generics and biogenerics. **Consumers Union urges that a major new title be added to S. 3807 to correct the full range of generic and biogeneric problems, or that the committee address these issues in separate legislation early in 2007.**

Specifically, Consumers Union asks that language be added to S. 3807 to:

• **increase funds and staff at the Office of Generic Drugs, and to set goals to ensure that application backlogs do not occur.** Given the significant savings that are associated with the marketing of generic drugs, this language will help moderate rising healthcare costs; and

• **establish a path for the approval of biogenerics. We strongly endorse H.R. 6257, a bill by Rep. Henry Waxman and others, that provides legal direction to the FDA to approve biogenerics.** Consumers Union hopes that Congress, learning from the European Union experience, will soon create a framework for biogenerics to enter the market.

We hope that the committee will hold hearings on the abuse of the citizen petition and patent and exclusivity laws to keep generics from the market. Senators Kohl and Leahy (S. 3981) and Stabenow and Lott (S. 2300) and Rep. Waxman and others (H.R. 6022) have bills to close these loopholes that are worth exploring in hearings and adopting as part of FDA reform legislation or as stand-alone proposals.

7. IMPROVING SCIENCE AT THE FDA: THE REAGAN-UDALL INSTITUTE

Background

The FDA's ability to make sound decisions and to regulate the pharmaceutical industry depends on the quality of scientific data that it receives. Recently, many experts have raised concerns regarding the quality of reports submitted to the FDA and the quality of the science used at the FDA. In particular, questions have been raised about noninferiority trials and the use of surrogate endpoints.

Often, drug company sponsors conducting clinical trials use "surrogate endpoints" rather than final outcomes. These endpoints are relatively easily and quickly obtainable physical markers that are used to reflect what is believed to be a clinically meaningful outcome. Clinically meaningful outcomes are often difficult and costly to obtain directly because they often require very large and long clinical trials. Although the use of surrogate endpoints is sometimes appropriate, this methodology is often abused and clinical trials which use surrogate endpoints often exaggerate the benefits. One recent article in *Health Affairs* reports that this methodology resulted in the overestimation of the benefits of Natrecor, a drug used to treat acute exacerbations of congestive heart failure.[92] The authors of the article note that higher rates of kidney impairment and mortality are found in those using the drug.

The use of the noninferiority design has also created a great deal of controversy. Non-inferiority trials are intended to show that the effect of a new treatment is not worse than that of a currently marketed treatment. But as FDA experts have pointed out, it is possible over time that the use of noninferiority trials could lead to the approval of drugs that are actually less effective and/or harmful compared to a placebo. A number of Members of Congress have requested that the GAO investigate the FDA's acceptance of noninferiority studies, and Rep. Markey's bill, H.R. 5922, calls for reports on the use of this method of approving drugs.[93] This congressional concern has been heightened by the FDA's approval of Ketek, which was based on noninferiority trials. Ketek, which is indicated for pneumonia, throat and sinus infections, and chronic bronchitis, has caused serious liver toxicity in some patients.[94]

Discussion of Solutions in S. 3807 and Further Recommendations

S. 3807 proposes the establishment of the Reagan-Udall Institute to "modernize medical product development, accelerate innovation, and enhance product safety by initiating, sponsoring, and organizing collaborative and multidisciplinary research." The Institute appears to be part of the Critical Path Initiative to increase the level of FDA's scientific research and to find faster, cheaper, and more effective ways to

develop drugs. It appears that the Institute's responsibilities are in line with some of the science recommendations of the IOM's report.

We strongly support increased high quality scientific work at the FDA, and research on how to solve problems like those that can occur with surrogate endpoints, noninferiority, and determining the comparative effectiveness of drugs and classes of drugs. Nevertheless, we hope the committee will hold further hearings on the idea of this Institute. It is not clear why these functions could not be placed within the FDA directly, rather than conducted through a quasi-private institute. It is important that any actions in this area are not just another industry-dominated effort to speed the development of drugs without adequate regard to their safety.[95] We commend you for including many references to drug safety in the Reagan-Udall Institute language. But the governing board of the Institute is tilted toward industry and lacks the guarantee of governance by nonconflicted public, consumer board members. The language calls for the acceptance of funds from private entities, which raises the same independence issues as we have seen in PDUFA fees. To repeat, we hope you will spend more time on this issue and refine some of the language to ensure that whatever is done serves the public in a balanced way.

We note that one way to improve science at the FDA is to reduce the level of staff turnover of experienced, trained personnel, which is higher at the FDA than many other Federal science agencies. Improving the FDA's culture and morale, as discussed earlier, and allowing FDA scientists more freedom to publish academically (as provided in Rep. Markey's bill H.R. 5922) are all keys to creating a better scientific climate.

CONCLUSION

Finally, I would be remiss not to acknowledge the countless families who have suffered because of our broken drug safety system. They are the reason we are here today. And many of them have worked tirelessly on this issue so others won't have to endure their heartbreak.

Two of these fine people are here today—Eric Swann, whose brother-in-law, Woody Witzak was casually prescribed an antidepressant for insomnia, and 5 weeks later killed himself. And Mathy Downing, whose daughter, Candace, was put on Zoloft because she was anxious taking tests at school. Ten months later, she took her own life at the age of 12. Neither Eric nor Mathy knew about clinical trial results that indicated increased risk of suicide from these types of antidepressants.

Senators, I deeply appreciate your time, and I thank you for your consideration of these ideas—and for the good work you have begun.

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ATTACHMENT #1

PROPOSAL FOR SAFETY RESOURCES AMENDMENT

Idea for amendment to S. 3807 to ensure adequate resources for needed FDA safety improvements and to set performance goals for the use of such resources. The percentage increases are just illustrative: the exact increases would have to be determined in consultation with the FDA and in light of the fiscal year 2007 appropriations and the President's budget proposals for fiscal year 2008.

On page 34, line 19, insert the following before the quotation mark:

"Such estimate shall provide enough increased revenue to achieve the following safety improvement goals on a phased-in basis between the date of enactment and the end of fiscal year 2012:

(A) ensure the pre-clearance of all electronic media (including Internet) advertisements and informationals[1];

(B) increase by 100 percent (that is, double) the percent of clinical trial data and investigational review board applications audited to ensure the ethical treatment of

[1] It would be good to define "advertisements" so as to pick up the many forms of promotions used to promote drugs and frequently to promote off-label use.

enrollees, and the experiments integrity and compliance with good scientific practice[2];

(C) ensure the electronic filing of all applications, amendments, petitions, adverse event reports, and other data required by FDCA laws relating to drugs;

(D) investigate all serious adverse event reports within 15 days, and conduct at least XX investigations per year into patterns or clusters of adverse event reports to determine if REMS action should be taken;

(E) increase by 100 percent the inspection of manufacturing (including compounding) facilities for compliance with FDCA laws;

(F) through active outreach and recruitment, develop and maintain a list of potential advisory committee specific experts who have no conflicts of interest and who have indicated a willingness to be appointed to future relevant advisory committee vacancies, and such advisory committee specific list shall equal 50 percent of the number of individuals serving on each such advisory committee;

(G) between the completion of the strategic plan for information technology provided for by subsection (c) of this section and the year 2012, collect and apply the resources described by subparagraph (4) of such subsection (c) to the implementation of the strategic plan;

(H) in addition to the clinical trial registry and results databases established by title III of this act for drug applications received after the enactment of this act, develop over a phased-in 4-year period ending in 2012 a similar registry of clinical trials and clinical trial results for those trials initiated or completed after 1997 and before the effective date of this act.

(I) take action, which may include the levying and collection of civil monetary penalties provided under section 502(f)(3) (as added by this Act) against at least 50 percent of the applicants who have failed to complete follow-up safety studies or trials as provided under section 505(o)(4)(D) and (E) (as added by this Act).

The CHAIRMAN. Thank you.

Mr. Simon.

Mr. SIMON. Thank you, Mr. Chairman. It's an honor to be at this hearing today and to serve on this panel with these distinguished witnesses. FasterCures is dedicated to saving lives by saving time in the way we research and discover new cures for diseases. We are independent and nonpartisan. We do not take funds from pharmaceutical companies, biotech companies, or medical device companies. We have one mission and that is to save patients' lives as quickly as possible, and we approach every problem from the patient's point of view.

This committee is asking a very important question, not just about the details of how the FDA should run, but how do we create an FDA for the 21st century? In the 20th century we saw the greatest extension of life expectancy in the history of humankind, 50 percent in the United States and a doubling of life expectancy globally. In the 21st century it is our challenge to make sure that those extra lives and extra years are quality years, free from debilitating pain and disease.

That raises the central question at this moment in our history as a Nation concerned about our people's safety and wellbeing: Do we believe that we can cure any of the diseases in this generation that are taking the lives of our friends and loved ones long before they otherwise would die? If you believe that we can do that and that we must do that, then creating an effective FDA for the 21st century is of the greatest importance.

But there is no defending the fact that the FDA budget for providing 300 million people and the global population confidence in

[2] It is reported that the FDA is revising regulations allowing drugs used in a Phase 1 trial to be exempt from quality control manufacturing requirements. If this is accurate, there should be some system of sampling a certain percentage of these drugs for purity and safety. See *Triangle Business Journal*, Nov. 3, 2006, "Triangle scientists reticent about FDA shift."

the food supply and the medicine supply is the same in real dollars as it was in 1996. The superintendent of the Montgomery County School Board has a budget equal to the commissioner of the FDA. Now, that's great for Montgomery County's children. It doesn't speak well of our commitment as a Nation to food and drug safety.

Many of the recommendations contained in the IOM report and the Enzi-Kennedy bill would go a long way toward building the proper FDA for the 21st century. FasterCures believes that the FDA needs to be able to assess a drug's impact post-approval, and to do that it needs stronger authority to regulate the way drugs enter the market, and to do that we have to have increased appropriations, not user fees that are restricted from being applied to post-market approval surveillance. To do any of this, we need strong leadership, and we support the confirmation of Dr. Andy von Eschenbach to be the commissioner of the FDA.

And the FDA, if it is trying to communicate risks to the public, has never hit the mark. We need to engage the patient community to help the FDA learn how to communicate risks and benefits to the patients. People with terminal diseases or debilitating diseases have a very different viewpoint about risks and benefits than those of us who are well. If the post-approval system is neglected, then the pre-approval system becomes too cautious because approval is the whole ballgame. That is why we support a strong approval system after a drug is marketed, so that we can move more expeditiously and quickly to get drugs to the market knowing that we're taking the life cycle approach, as was suggested by Sheila Burke.

Every one of us is touched every day by the FDA. Its mission in my opinion is the best example of the core function of government to protect the health and safety of people who could not do what the FDA does for themselves. We need to empower the FDA to do that for us and we need to show our commitment to the FDA by valuing its work at the same level that we value our health and the health of our families and our neighbors.

Thank you for having this hearing today.

[The prepared statement of Mr. Simon follows:]

PREPARED STATEMENT OF GREG SIMON

I. INTRODUCTION

I want to thank the committee for the opportunity to present testimony today. My name is Greg Simon, and I am the President of *FasterCures/The Center for Accelerating Medical Solutions*, based in Washington, DC.[1]

FasterCures is dedicated to saving lives by saving time in the discovery and development of new therapies for the treatment of deadly and debilitating diseases both in the United States and around the globe. The organization was founded in 2003 under the auspices of the Milken Institute to catalyze systemic change in cure research and to make the complex machinery that drives breakthroughs in medicine work for all of us faster and more efficiently. During our relatively brief history, *FasterCures* has worked with a broad range of individuals and organizations to

[1] Before joining *FasterCures*, I served as the Chief Domestic Policy Advisor to Vice President Al Gore from 1993 to 1997, specifically on economic, science and technology issues. In that role, I oversaw a number of initiatives, including the programs of the National Institutes of Health, the National Cancer Institute, the Food and Drug Administration (FDA), the Human Genome Project, and the development of the regulatory framework for biotechnology products. From 1991–1993, I served as Legislative Director for then-Senator Al Gore. From 1985 to 1991, I was Staff Director of the Investigations and Oversight Subcommittee of the House of Representatives Committee on Science, Space and Technology.

eliminate barriers to efficiency and effectiveness in our systems of disease prevention, treatment, research and development.

FasterCures is independent and nonpartisan. We do not accept funding from companies that develop pharmaceuticals, biotechnology drugs, or therapeutic medical devices. Our primary mission is to improve the lives of patients by improving the research environment, research resources, and research organizations.

I am honored to appear before this committee, which has a long history of spearheading efforts to protect and promote the health of the public by improving our Nation's process of drug discovery and evaluation. I want to commend Chairman Enzi, Senator Kennedy, and other members on this committee who have introduced and supported bipartisan legislation to strengthen the FDA's oversight of drug safety. I commend you for focusing this hearing on the broader issue of how to ensure that the FDA is truly prepared to meet the challenges and reap the benefits of 21st Century medicine.

Earlier this year, *FasterCures* provided detailed comments to Chairman Enzi and Senator Kennedy regarding the specific provisions of the "Enhancing Drug Safety and Innovation Act of 2006." I will touch on some of the major points covered in those comments that we believe deserve continued focus. However, I primarily want to discuss today the broader principles that *FasterCures* believes should guide any effort to strengthen the FDA so that the agency can continue to play a vital role in advancing 21st Century cures.

These principles are as follows:

1. The FDA needs to be able to assess a drug's impact postapproval, weigh both benefits and risks and take appropriate action to protect the public;
2. To do that the FDA needs much stronger authority to regulate and enforce how an approved drug enters the market, how it is advertised, what claims are made for it and how labels are updated to reflect growing knowledge of a product;
3. To do those things the FDA needs increased appropriations from Congress and should not be forced to rely on industry user fees which the FDA is largely restricted from using on postapproval activities;
4. To do any of this, the FDA needs a confirmed Commissioner to provide strong, effective and professional leadership with a long-term focus and vision; and
5. And for all of this to work, the FDA needs a better understanding of how to communicate its scientific findings to the public to make them better informed participants in our healthcare system.

II. THE FDA AT THE DAWN OF THE 21ST CENTURY

In the past 10 years, we have witnessed dramatic advances in science that impact the practice of medicine, including the mapping of the human genome, and advances in computational tools and broadband communications. Electronic health records and personalized medicine will likely change the practice of medicine and clinical research in the coming decade, and offer substantial benefits to monitoring adverse events.

Yet, while the personalized medicine era is leaping forward into the 21st Century, the FDA remains tethered to 20th Century technology, regulations and practices as if the Information Age had never happened. Worst of all, it remains mired there because we the people, and our elected government have deprived the FDA of the financial and human resources it needs to do the job we have asked it to do in the 90 laws Congress has passed since 1907 setting the FDA's goals and responsibilities.

There is simply no defending the fact that the FDA budget for providing 300 million Americans a safe food supply and safe and effective medical treatments is the same in real dollars as it was in 1996. The Superintendent of Schools for Montgomery County, Maryland has a budget equal to that of the FDA. This speaks well of Montgomery County's commitment to education but calls for questions of our national commitment to food and drug safety and the approval of new cures for diseases.

Each year, the FDA receives minimal new dollars and yet its costs increase, missions evolve, the scope of science expands, and inflation erodes the budget. In addition, innovative, future focused programs of the FDA such as the Critical Path Initiative that would bring the agency into the 21st century have not been given full financial support, and the impact of new technologies such as nanotechnology cannot be measured and evaluated. The budget is holding the FDA back and preventing the agency from maximizing the benefits of these historical advances in science for the American public. The staff of the FDA are dedicated public servants who are ready to tackle these problems.

The FDA plays a central role in American medicine. It has an incredibly challenging role to protect and promote the public's health. The agency must ensure

that products are safe, but also effective. It must help speed lifesaving drugs to patients, yet ensure that those same patients have the safest drugs possible. We expect the FDA to be committed to protecting our health and well-being. But we have not been committed to giving the agency the tools and resources it needs to meet our expectations.

So how do the Institute of Medicine (IOM) report *The Future of Drug Safety* and the Enzi-Kennedy bill address this gap between where we would like the agency to be and where it is?

The recommendations contained in the IOM report would go a long way toward helping the FDA meet the goal of speeding to patients innovative cures that are both safe and effective. Last month, shortly after the IOM report was released, *FasterCures* and the National Health Council hosted a forum for patients and medical research advocates to consider and debate the report's findings and recommendations. Sheila Burke, who chaired the IOM committee, as well as IOM Study Director Kathleen Stratton, participated in the meeting. The conference was our attempt to help focus involved members of the patient and research communities on the implications of the proposed policy changes. We believe the meeting was an important first step in ensuring that the perspectives of patients and researchers have a prominent place in any future debate on drug safety. A brief summary report on that meeting will be submitted for the hearing record later this week.

We urge the Congress to put the work of the IOM Committee front and center in its deliberations. As Ms. Burke stated at our meeting on the report,

> "We've revolutionized how we care and manage people with illness, but the FDA has not been able to keep up with that complexity. Delaying approval until certainty is reached is not always a good option. Patients depend on these drugs and yet there is an all or nothing environment."

We appreciated the opportunity to provide comments on your proposed legislation prior to introduction, and we look forward to continuing to draw on our experience to be a resource to the members of this committee as you consider any policy that will strengthen the FDA. Some specific comments are as follows:

- On the Risk Evaluation and Mitigation Strategies (REMS) process, we are concerned that this process has the potential to slow down product reviews if not constructed correctly and with precision. We believe scarce FDA resources should be concentrated on *activities* that actually mitigate safety risks for designated products rather than be focused on reviewing risk mitigation *plans* for all products and label changes.
- We welcome the draft bill's focus on using *www.clinicaltrials.gov* to support mandatory reporting of clinical trial data in a manner that is useful to both medical professionals and patients.
- The Reagan-Udall Institute for Applied Sciences concept for advancing the Critical Path Institute is an exciting development. We are pleased that the bill recognizes the importance of Federal funding and the importance of having representatives of the National Institutes of Health in this partnership.
- Finally, we believe strengthening the FDA Advisory Committee process is a very important goal, however we do not believe the bill goes far enough. Extricating all potentially perceived conflicts of interest will in fact "dumb down" these committees through overly broad definitions of conflict of interest. Conflicts can never be eliminated from panels of experts, but they can be disclosed and balanced.

III. FASTERCURES' PRESCRIPTION FOR CHANGE

I want to elaborate on our key principles that *FasterCures* believes are essential to strengthening the FDA and ensuring that our Federal drug approval and oversight processes are fully prepared to harness the promise of 21st century medical progress.

1. **The FDA needs to be able to assess a drug's impact postapproval and take appropriate action to protect the public.** The IOM report cited the need for a "lifecycle" approach to drug oversight. FDA's regulatory authority should not end with a drug's approval, because that is just the beginning of what we can learn about a medical treatment in the marketplace. Rather, we believe that FDA should have a greater role working with industry, doctors, and others to communicate what is learned about products once they have been introduced into real medical practice. As a drug moves from controlled trials in several hundreds or thousands of people to a potential market of millions, both its benefits and risks may be magnified. This will require more resources for the FDA. If the postapproval authority is exercised properly, we believe it will help speed the approval process because the agency, pol-

icymakers, and the public would have greater confidence that safety issues that are not apparent during the pre-approval phase—or that *cannot be detected* in pre-approval clinical trials—would be detected and addressed quickly postapproval. This knowledge should be captured and analyzed in a way that doctors can better communicate treatment benefits and risks to their patients so more informed decisions on options can be made.

2. **To do proper postmarket surveillance, the FDA needs much stronger authority to regulate and enforce how an approved drug enters the market, how it is advertised, what claims are made for it and how labels are updated to reflect growing knowledge of a product.** As the IOM report recognizes, safety and efficacy are the yin and yang of every drug and are best weighed together. We need a flexible system of approval and postapproval that helps consumers, physicians, and patients more appropriately weigh and respond to those risks and benefits. We specifically commend to the committee the important role highlighted by the IOM for nonprofit research organizations and the patient advocacy community in helping to bridge the gap between FDA and the public when discussing the benefits and risks of new medicines.

3. **To do any of this, the FDA needs a confirmed Commissioner to provide strong, effective and professional leadership with a long-term focus and vision.** *FasterCures* supports the confirmation of Dr. Andrew von Eschenbach to be the Commissioner of the FDA and urges he be confirmed as soon as possible.

4. **And for all of this to work, the FDA needs a better understanding of how to communicate its work to the public to make them better informed participants in our healthcare system.** Patients and consumers need timely information to help them make informed decisions. Toward this end, the FDA should take more aggressive steps to ensure that labeling information and supplemental safety and efficacy information are more patient-centered. Moreover, *FasterCures* supports proposals found in legislation before this committee and embraced by the IOM to give the FDA more authority to require sponsors to register data at a centralized independent Website, *www.clinicaltrials.gov*. We believe that posting appropriate information at a single, credible, widely available source will go a long way toward providing consumers, patients, providers, scientists and researchers with data they need to help analyze safety and efficacy information and make more informed decisions.

5. **To do all these things the FDA needs increased appropriations from Congress and should not be forced to rely on industry user fees which the FDA is largely restricted from using on postapproval activities.** The FDA needs greater resources to carry out its mission. Many of the improvements recommended by the IOM and included in several legislative proposals will simply not be possible without additional resources. The IOM recommended that Congress approve a substantial increase in both FDA funding and personnel. *FasterCures* strongly believes that any additional funding should come from appropriated funds, rather than user fees. Because *FasterCures* believes this is critical, we are actively participating in two coalitions that are aggressively advocating for additional funding for the agency: The FDA Alliance and the Coalition for a Stronger FDA.

IV. CONCLUSION

There is no agency or aspect of our government that touches more lives everyday than the FDA. Its mission is the highest and best example of the government's core mission—to protect the health and safety of the American people. Historically, the FDA has done its work so well that it represents the gold standard all other countries rely upon and seek to emulate. There can be no resting on our laurels. Either we provide the FDA the tools and resources it needs to thrive in the 21st Century or it will begin to atrophy and our Nations' health will begin to atrophy with it. Many of the proposals contained in both the IOM report and the Enzi-Kennedy legislation will help position the FDA to meet the medical challenges of the 21st Century. But those proposals will not succeed if we are not committed as a Nation to valuing the health of our people far greater than is now the case and to acting accordingly.

Thank you for the opportunity to testify. *FasterCures* looks forward to continuing to be a resource to the members of the HELP Committee and to Congress as you address these important issues.

The CHAIRMAN. Thank you very much, and I want to commend all of you for your ability to stay close to the time that was allotted. That's extremely helpful. And I've got to say your testimony, the written as well as what you've just presented, was outstanding and

extremely helpful. I do have a few questions. Actually, I've got a lot of questions. Some are of a fairly technical nature. Those I'll submit to you in writing so that I can get some fairly technical answers that won't put anybody to sleep, but will aid in the production of good legislation.

But in the line of some questions, Ms. Thompson, are you worried that asking the FDA to take on new responsibilities is going to result in a slowing down of drug approvals?

Ms. THOMPSON. We're obviously of the position that patients shouldn't have to choose between speed and safety, and that it is particularly important that as this committee looks to asking the FDA to take on new responsibilities or to improve the way that it performs existing responsibilities that that request, that mandate, be coupled with resources adequate to do the job. It can't be an either/or situation.

The CHAIRMAN. Thank you.

Dr. Nissen, as a practicing doctor doing these clinical trials, do you think that the restrictions on distribution and use interfere with the practice of medicine and prevent doctors from using their best judgment about how to treat patients?

Dr. NISSEN. I'm not sure I understand your question. What do you mean by "distribution and use?"

The CHAIRMAN. Well, I'll phrase it more broadly than that. The restrictions that are now being placed on drugs and the potential under this bill to place some requirements on it, do you think that will interfere with the practice of medicine and prevent the doctors from using their best judgment? Do you think it's open enough that we're not going to be constricting your practice?

Dr. NISSEN. I don't think that from the point of view of physicians that anything in this bill would restrict our ability to care for patients. It's important to understand that, in fact, physicians do retain a great deal of discretion in what we do and how we do it. But we can only make good decisions when we have access to all the information, and I would argue that you really are enhancing the ability of physicians to make good decisions, because you're providing for the disclosure of all the information on safety and efficacy that we need to make good choices, and that's why the increased transparency that's required in this bill, if anything, will enhance the ability of physicians to make good decisions.

The CHAIRMAN. Thank you.

Dr. Thomas, the legislation that we're proposing gives the FDA the authority to impose restrictions on drugs. Recently the iPLEDGE program for the acne drug Accutane has come under fire because, while it seems to be meeting the goal of reducing pregnancy exposures, it's also reducing the number of people who get the drug. We believe that we have taken steps in the pill to assure that patients get the drugs they need even if those drugs have restrictions on their use. Your comments?

Dr. THOMAS. Thank you, Chairman Enzi. I think the issue of restriction on distribution or supply is an interesting one and it's certainly true that there are many situations where the risk of inadvertent exposure may require agreements about how products are accessed. I come from a kind of large country with not many people and I have worked as a flying doctor, and I was probably one of

the only flying vascular surgeons or physicians around and patients' ability to get from isolated areas, to get to a specialist was difficult. So I can also foresee that one unintended outcome of distribution restrictions is, in fact, restrictions of access by a supplier.

So I think those things need to be carefully thought out. Without discounting the importance that one needs to place on the legitimate use of it, unintended consequences may follow.

The CHAIRMAN. Thank you.

Mr. Guest, in your testimony you recommended across the board restrictions on the direct-to-consumer advertising for 3 years as opposed to the 2 years that's in the bill. Banning all direct-to-consumer advertising is kind of a blunt authority. The bill that we've introduced tries to get away from that strict of an approach. Since every drug represents a unique profile of benefits and risks, would it make sense to give the FDA some discretion in this area?

Mr. GUEST. The bill does give the FDA restriction and that's okay. We would just say it should be for a longer period of time, because obviously a lot of the adverse consequences or events that can occur will occur after a pill is on the market, when there are then millions, hundreds of thousands and millions of people. That's the real clinical trial on a drug.

Our concern about direct-to-consumer advertising generally is that's not a good way for consumers or physicians or medical providers to be informed. At Consumer Reports our whole history is that consumers should be given full information, unbiased, independent, research-based information, about both the positive qualities and the negative qualities of products or services, whatever they may be.

The problem with direct-to-consumer advertising is that's a poor way to give comparative information to consumers so they can make informed choices. There was a conversation earlier with Sheila Burke that what's needed is a way for consumers to have full information about the range of choices that they have in a fashion that they can understand and not just a particular hype.

I mean, direct-to-consumer advertising is not a good way to convey really good information about pharmaceuticals. It's really—clinical trials should not be a marketing tool. They should be a tool for consumers to make informed choices and providers to make informed choices.

The CHAIRMAN. Thank you.

My time has expired.

Senator Reed.

Senator REED. Thank you very much, Mr. Chairman, and thank you, ladies and gentlemen, for your testimony.

I have just one major question. I think it's a threshold question for us. I'll start with Mr. Simon. Everyone understands that the FDA culture has to change and that's a function of funding, it's a function of other legislation we've created, PDUFA, the way we collaborate with the industry. But I presume, and I don't want to have it unstated, that you feel that the legislation that's being discussed today, both versions, are important; we have to do something legislatively, that we just can't rely upon a little more money and some spontaneous cultural change will happen at FDA. Mr.

Simon, do you want to comment? And you can use this as a broader springboard to discuss, and I'll go down the line.

Mr. Simon.

Mr. SIMON. Thank you. First, Senator, with regard to resources, there is no amount of leadership or organizational change that can trump a lack of resources. So you have to have a balance.

Secondly, the greatest asset of the FDA is its people and they have too few assets. They need far more people to do this. We spend as a Nation $100 billion a year researching new drugs and treatments for diseases as a government, as industry, and as nonprofits, and then we ask the FDA on a budget of $1 billion on the drug side to review the product of this enormous pipeline, and then we wonder why they don't do it fast enough and well enough. So they need more people.

But they also need organizational change. You can't have people wait until the end to start asking safety questions. You need people to see all the information through the entire process. I totally agree with Sheila Burke that we should not separate these functions. They need to be integrated. And when you have the money and you have the leadership and you have the organizational structure, then you need political independence to be able to take the science where the science goes and be able to tell the American people, this is where the science is and now you as the patient with your provider can make a decision about how to treat your condition.

Senator REED. Please.

Mr. GUEST. Just briefly, I think this legislation, and hopefully with the changes we recommend, will help restore trust in the FDA and help the FDA actually earn that trust, because there's a real skepticism right now among the American public, are our drugs safe and is this agency that's supposed to be protecting our safety really doing it in an independent scientific, unbiased way.

That's why, among other things, we think it's really important that the other scientists who do the research at the FDA, that their information also be public, because these decisions are not all black or all white. There are subtleties and the public and consumers and members of the medical community ought to know where there are reservations or concerns so they can take that into effect when they're making their decisions.

Senator REED. Dr. Nissen.

Dr. NISSEN. Yes. I must tell you that the staff at the FDA are demoralized. I know them very well and I've worked with them 5 years on their advisory panel. Some of the best people have left the agency. There's a flight going on now. It will take us years to recover from what's happened already. That flight has occurred because of underfunding. There is a lot of concern expressed, not publicly but privately, about the politicization of the agency. It's very discouraging when you want to do the right thing and you feel like you're not free to do so, and I have heard this from staffers at the FDA.

I believe that also, that the entire PDUFA principle has undermined the FDA. It's created dual loyalty, and we need to have one loyalty and the loyalty is to the American public. That's what we've got to get back to. We're not asking for the Congress to fund this agency with tens of billions of dollars, just somewhat modest in-

creases, and we could get away from the user fee principle and we could go to recruiting back into the agency the kind of quality people that we need to get the job done.

Senator REED. Thank you, doctor.

Ms. Thompson, do you have a comment?

Ms. THOMPSON. Yes. I would certainly like to echo the comments made about the importance and professionalism of the FDA and its staff. Clearly the people at that agency are its most precious resource and in order for them to do the best that they can they must have effective leadership, they must have the resources they need to do the job, and there must be a transparent system that will enable all of us to participate in rebuilding the sort of support for the FDA that traditionally has existed.

You know, the ability of a mom and two of her friends sitting around the table to engage in the drug review process, as Elizabeth Glaser and her friends in the foundation were able to do, is enormously important to the public credibility for this agency. So clearly leadership, resources, and transparency are key components to re-establishing that credibility.

Senator REED. Before I call on Dr. Thomas, I think we all agree with that, but I don't want to assume that people would be suggesting that we don't need to do this legislation. I think this legislation's an important part of the ingredients for that accountability, resources, and structural changes within the organization, and we have your advice on changes to that and there's two very good models that have been proposed by my colleagues. But simply to sit back and maybe put a little more money into the till is not going to fix the problem.

Ms. THOMPSON. Well, Senator, if I may.

Senator REED. Yes, ma'am.

Ms. THOMPSON. Thank you for that. That's absolutely right. In resources I would include the tools that the agency needs, the enforcement tools, informatics infrastructure. There's a whole range of elements that come under resources, but of course the ability to keep those key staff as well.

But this legislation and many of the recommendations that have been made will be key elements to providing—will provide those key elements in terms of authority, structure, emphasis, priorities, that will be critical to moving this drug safety system forward.

Senator REED. Dr. Thomas, I'd appreciate your comments very much.

Dr. THOMAS. Thank you, Senator Reed. Broadly speaking, this piece of legislation, this bill, is a very important piece of work towards enhancing patient safety, and I want to say that up front. However, I agree with the rest of the panel, you need to have both the resources and leadership to enable the agency to meet what is fundamentally a very important and very significant role within this country, not just this country, but as someone who works broadly around the world, the U.S. FDA is today a very respected and strong provider of scientific leadership in regulatory matters.

So we should not diminish the role they play today. But without the appropriate leadership, without the appropriate resources—and industry is not averse to increases in PDUFA fees. But when the increases lead to industry funding more than 50 percent of the

agency's activities, that's a legitimate matter for public concern. So I think the agency needs all the things the panel has discussed and we in the industry agree fully that the first responsibility of the agency and its accountability is to the American public.

Senator REED. Thank you very much. Thank you, gentlemen. Thank you, Ms. Thompson.

Thank you.

The CHAIRMAN. Senator Clinton.

Senator CLINTON. Thank you, Mr. Chairman.

I want to really thank and compliment this panel. I'm sorry that I had to step out to tend to some other business, but I am very grateful to each of you. Dr. Thomas, thank you for your last comments. I think that that's very helpful. Ms. Thompson, Elizabeth Glaser was a friend of mine and I'm very pleased that you're here representing the foundation and that the foundation continues to play such an important role in public policy. Dr. Nissen, thank you not only for your testimony but for your courage. I appreciate you being on the end of the spear, as you say in your testimony, because we need you there and your stepping forward and lending your expertise to this debate is absolutely essential. I also want to thank my friend Greg Simon for his continuing public service, and this FasterCures approach is one that I hope we can really see as a tremendous partner as we move forward in this.

I particularly want to thank Jim Guest for being here. I'm proud that Consumers Union is based in Yonkers, New York, and I was delighted to go to their facilities and see all of the great work that is being done there. Jim, it's terrific that you're here. I want to also thank the families that you mentioned in your testimony for joining us today.

As Jim noted, the problems of our drug safety system are not just abstract questions of studies and trials. Really, the failure to place concerns about safety above ideological or economic concerns has had an impact on the lives of Americans. As we continue to work on drug safety and broader FDA legislation next year, I think it will be important to give those impacted, such as the families you reference, a voice in this debate, because we need to put a human face on it. We often get caught up in the statistics and the dollars and all of the complexity of legislative language, but this comes down to people's lives, to their well-being.

Jim, in your written testimony you talk about the need for legislation that would establish a path for the approval of biogeneric drugs. I think we have to look both at what we do with respect to biologics from pharma as well as biogeneric. We're not doing a very good job on the former yet. We don't have a good partnership. I visited a plant in my State that is one of the great leaders in biologics right in Syracuse, New York, Bristol-Myers-Squibb, and they have concerns about where the expertise is going to come from inside the FDA to help them work on biologics. So we've got to simultaneously work on biologics and biogenerics and try to understand what we have to do going forward.

I've introduced along with Senator Schumer and Congressman Waxman the Access to Life-Saving Medicine Act, a bill that would improve the FDA's ability to quickly bring safe biogeneric products

to the market. But I just want to say a word of caution. I don't think we've done a very good job on biologics yet.

But would you elaborate on the ways in which you think increasing access to biogenerics could improve access to safe and appropriate treatments for patients?

Mr. GUEST. Well, let me first say I agree with you, it's both biologics and biogenerics which are really complicated, and to break through a process for responsible and timely review on both counts I think is important. I certainly hope that there'll be hearings and really serious consideration of your proposals on it. That's a whole new hearing almost and a whole new set of things to do it.

But I mean, clearly the future of people's health is going to be significantly affected by biologics and biogenerics. Again, as an organization that's interested in consumer safety and consumer opportunity, I think that it's—I think the emphasis that you're giving it is absolutely well placed and would hope that the Congress would move forward on that front as well.

Senator CLINTON. I thank you for that, and I think that in addition to what is clearly a complicated area, there are very few of us—there are some, but I think there are few of us in the Congress who really have the background in this complex, fast-moving area. We need quite a bit of discussion. I would throw on the table another issue which I am increasingly having questions about and that's the whole area of nanotechnology and the creation of these nanodevices and nanoelements. They are clearly part of the whole biologics effort. We don't really understand the impact on our health or our environment of them.

We are truly on a new frontier, Mr. Chairman. I hope that as we go forward we will take the time to educate ourselves thoughtfully about this range of issues. But the bottom line is we need, as Dr. Thomas said, to make sure that the FDA remains the gold standard. We've got to give it the resources, the morale, and the authority it needs, because we're on the brink of extraordinary, breathtaking changes and we're not even particularly well equipped for what's already on the table.

So I thank you, Mr. Chairman, for holding this important hearing.

The CHAIRMAN. Thank you very much.

I want to thank the witnesses for their time that it took to prepare the testimony, the time to give it, the time to answer the questions that we've had here. And of course I am hoping that obligates you to also answer the questions that we'll provide in writing. Around here there are a lot of things going on at the same time, so there are a lot of conflicts with different committees. So members of our committee will have to educate themselves on what has been said and they'll do that through staff that's been attending, and we'll undoubtedly have some questions for you, too. But that will all play a vital role in us getting it right, which is what we want to do. This has been a fantastic panel because it's a wide spectrum of stakeholders and it's been very helpful.

The record will stay open for 10 days and members of the committee can submit their questions. I would also mention that I do have a number of comments from other colleagues, some of whom are not on the committee, and I would ask unanimous consent that

the number of outside groups as well as colleagues' comments be entered in the record. Without objection.

Thank you very much. This hearing is adjourned.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF THE ADVANCED MEDICAL TECHNOLOGY ASSOCIATION (ADVAMED)

AdvaMed and its member companies thank the committee for holding this hearing on improving drug safety and innovation. Although the bill under review is not specifically intended to affect medical devices, there are two provisions in the bill pertaining to FDA advisory panels and critical path which could affect our industry. We respectfully submit our comments for your review.

AdvaMed member companies produce the medical devices, diagnostic products and health information systems that are transforming healthcare through earlier disease detection, less invasive procedures and more effective treatments. Our members produce nearly 90 percent of the healthcare technology purchased annually in the United States and more than 50 percent of the healthcare technology purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies.

FDA ADVISORY PANELS

A rational conflict of interest policy for panel members is critically important to the effective functioning of panels. It is equally important, however, to ensure that highly capable, expert physicians and researchers continue to be willing to serve on FDA advisory panels, and we are concerned that the current bill language may discourage such experts from participating in the FDA panel process.

The pool of experts in the device arena is limited due to the fast-advancing product developments and diverse product areas where only a handful of national experts may exist within literally thousands of different product areas. It is important that physicians and researchers at the top of their fields be able to provide their expertise, insights and perspective to FDA on emerging technologies to advance patient care and ensure safe and effective technologies.

Workable conflict of interest rules and/or guidance can strike a healthy balance between ensuring the participation of knowledgeable panel members and avoiding bias attributable to self-interest. A more measured approach to addressing potential conflicts for panel members should include a broad requirement for the FDA to review its guidance and rules related to panel member conflicts and to update them to be more precise and understandable. Any legislation in this area should avoid impinging on the privacy of persons who are performing a public service.

AdvaMed is concerned about provisions to standardize how panel members are evaluated and require FDA to publicly disclose the financial status of potential panel members over the Internet and via guidance documents. Under current law, waivers are published on the Internet and financial and other personal information about panel members is redacted. The legislation would discourage individuals with needed expertise from participating in FDA panels by broadly publicizing the details of determinations about advisory panel members over the Internet, and by requiring the issuance of guidance that is aimed at revealing the financial status, including possibly the net worth of individual panel members. For example, the legislation would publicly release detailed financial information and "involvements"—requirements that will clearly discourage needed panel participation. AdvaMed recommends changing the legislation to allow the FDA to individually evaluate each panel member for conflict of interest status.

We are also concerned about provisions in the legislation to require the HHS Inspector General (OIG) to "on an ongoing basis" conduct reviews "of the financial interests of a representative sample of individuals who have served on a[n] [FDA] panel . . . ". As part of a semi-annual report, the OIG would also be required to include the results of the OIG's review of the financial interests of panel members. These measures would discourage the foremost device experts as well as experts with no conflicts at all from serving on FDA panels.

CRITICAL PATH

AdvaMed strongly supports the objectives of FDA's Critical Path Initiative and the intentions of the proposed Reagan-Udall Institute envisioned in S. 3807, particularly regarding the Institute's potential role in focusing resources on the unique challenges of medical device development and evaluation. Our member companies and the academic research community are pioneering new research methods that can speed medical product development and more quickly identify and assess emerging safety issues.

AdvaMed urges the Administration and Congress to allocate new funds to the FDA device program to ensure that device-related aspects of the Critical Path Initiative are able to develop fully. The additive nature of user fee programs should not be violated by diverting these funds to activities far removed from the product application review function.

AdvaMed also recommends that programs undertaken through both the Critical Path Initiative and the proposed Reagan-Udall Institute be implemented to clearly reflect the important differences between drugs and devices. We recommend the specific inclusion of device expertise in the leadership structure of both programs at all levels.

The mission of both programs should be adjusted to reflect the fundamental differences between the medical device development and drug discovery processes; while new drugs stem from discovered molecules, new devices are developed through a design and engineering process with specific, intended functions in mind. AdvaMed and its member companies are committed to working with FDA and the leadership of the Reagan-Udall Institute to broaden understanding of the unique nature of medical device technology development and to working to maximize the contributions of the medical device community to the Critical Path Initiative.

CONCLUSION

Again, we thank the committee for holding this hearing today. As the committee works to create a 21st Century FDA, AdvaMed looks forward to working with you to create a balanced approach to expert panels at FDA, increase the attention to devices within the Critical Path Initiative and Reagan-Udall Institute efforts, and enhance patient access to lifesaving and life-enhancing medical technologies.

PREPARED STATEMENT OF THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHAMACISTS (ASHP)

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 "Building a 21st Century FDA: Proposals to Improve Drug Safety and Innovation."

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.

ASHP applauds Chairman Enzi and Senator Kennedy for their efforts to try and address the difficult challenge of establishing a system of drug approval and monitoring that maintains a balance between the benefits of an innovative, potentially life-saving drug and the risks associated with its widespread use in the population. The current drug safety system can be improved through increased regulation, but it is important to realize that no system will succeed without the commitment and proper training of healthcare professionals and the understanding of patients of medication risks and benefits.

As you move forward with legislation to address drug safety, we would urge you to continue to evaluate the essential role that healthcare professionals and especially pharmacists play in ongoing post-marketing surveillance and in managing known risks. As medication-use experts and frontline providers of medication management services, pharmacists are necessary and fundamental to the drug safety system, with a responsibility to assist patients, physicians, and other healthcare professionals.

As the committee pursues its legislative strategy, we would ask that you consider several points in key areas:

POST-MARKETING SURVEILLANCE STRATEGY & RESTRICTED DRUG DISTRIBUTION SYSTEMS

The "Enhancing Drug Safety and Innovation Act" (S. 3807) does permit the establishment of new Restricted Drug Distribution Systems (RDDS) in some limited circumstances. While ASHP values and acknowledges the critical role that an RDDS plays in managing drug safety, the use of such systems should not compromise timely and appropriate patient care and should not be overly burdensome to healthcare practitioners who are attempting to meet patient needs. This is especially of concern in hospital settings where pharmacists are trying to deliver medications and manage the therapy for high-risk patients.

While we understand that new RDDS programs will only occur in limited circumstances, they do have a cumulative effect on health-system pharmacy practice and patients directly. Many ASHP members have reported that RDDS programs are burdensome and confusing for practitioners and that they at times result in delayed care and inconvenience for patients and disrupt the continuity of care.

In order to simplify these programs while maintaining their intent, we urge the committee to work with ASHP and other stakeholders to develop legislation that would standardize RDDS programs, require pharmacist input into each program's development, and improve access to information for clinicians and patients about the types of restricted distribution systems.

DIRECT-TO-CONSUMER ADVERTISING

ASHP policy supports direct-to-consumer advertising of drug products only when the following requirements are met: (1) such advertising is delayed until post-marketing surveillance data are collected and assessed, (2) the benefits and risks of therapy are presented in an understandable format at an accepted literacy level for the intended population, (3) that such advertising promotes medication safety and allows informed decisions, and (4) that a clear relationship between the medication and the disease state is presented.

While ASHP is pleased to see that S. 3807 permits FDA to place certain requirements on manufacturers' drug advertising efforts, we would recommend that the committee permit the FDA to extend any moratorium period over 2 years should additional delays be required to collect and assess essential post-marketing surveillance data.

CLINICAL TRIALS REGISTRY AND CLINICAL TRIALS RESULTS DATABASE

ASHP policy supports the disclosure of the most complete information possible on the safety and efficacy of drug products and has recommended the establishment of a mandatory results registry for all Phase II, III and IV clinical trials that are conducted on drugs intended for use in the United States. All clinical trials undertaken, but not yet completed, should be added to the registry and, upon completion, the results should be posted electronically with unrestricted access as quickly as possible after FDA approval but before marketing commences. Strong enforcement mechanisms are necessary to ensure compliance.

ADDITIONAL FDA FUNDING NEEDED FOR POST-MARKETING SURVEILLANCE

While we acknowledge funding is not in the jurisdiction of this committee, we cannot discuss enhancing FDA's ability to meet its public health mission without expressing support for increased resources for the agency. It is startling that the resources designated for all food and drug regulatory activities in the United States are equivalent to the budget of the Montgomery County, Maryland, public school system ($1.85 billion for 2007), which is the county where the agency is located. ASHP is a member of the FDA Alliance and supports funding increases for the agency for the 2008 fiscal year.

BETTER UTILIZATION OF PHARMACISTS SHOULD BE FOSTERED

Increased Federal regulations of drug approval and marketing alone will not result in an improved drug safety system. We urge the committee to look carefully at methods to better prepare healthcare professionals for playing a larger role in post-marketing surveillance and in managing known risks. ASHP believes pharmacists have a crucial role in fostering improved medication-use safety. Postgraduate pharmacy residency training is especially designed to prepare pharmacists for this role. Unfortunately, there are an insufficient number of such accredited programs to meet the Nation's needs. Additional Federal support for pharmacy residency training would have a major effect on improving the outcomes from medication use, especially in high-risk patients.

As medication-use experts and frontline providers of medication management services, pharmacists are necessary and fundamental to the drug safety system. All medications have associated risks, and pharmacists have a responsibility to assist patients, physicians, and other healthcare professionals in managing medicines with risk profiles that require careful patient selection and monitoring. Products that are safe and effective only in certain patients, but not in others, have been withdrawn from the market due to inappropriate management of well-known risks and a lack of ability to differentiate appropriately among patients. If a pharmacist, as part of the healthcare team, had monitored and adjusted the therapy to minimize or eliminate risks, a subset of patients could have continued to receive benefits from the withdrawn medications.

CONCLUSION

We appreciate the opportunity to share our views on how to improve the drug safety system in this country. 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.

PREPARED STATEMENT OF THE NATIONAL ASSOCIATION OF CHAIN DRUG STORES (NACDS)

Chairman Enzi, Ranking Member Kennedy, and Members of the Health, Education, Labor, and Pensions Committee. The National Association of Chain Drug Stores (NACDS) appreciates this opportunity to provide the committee with a statement for your hearing, "Building a 21st Century FDA: Proposals to Improve Drug Safety and Innovation."

NACDS represents the Nation's leading retail chain pharmacies and suppliers, helping them to better meet the changing needs of their patients and customers. Chain pharmacies operate more than 37,000 pharmacies, employ 114,000 pharmacists, fill more than 2.3 billion prescriptions yearly, and have annual sales of nearly $700 billion.

The chain pharmacy industry agrees with the need to enhance the safety of medication use in the United States, and shares the committee's goal of improving public safety and helping patients and healthcare providers make informed decisions about healthcare. Because the methods in which community pharmacies protect the safety of their patients would be directly impacted by drug safety legislative changes, we are providing comments to you on two specific elements of drug safety proposals: Medication Guides and restricted distribution systems.

MEDICATION GUIDES

Over the past 2 years, the Food and Drug Administration (FDA) has significantly increased the number of pharmaceutical products which require a Medication Guide ("MedGuide") to be dispensed with each new and refilled prescription. Currently, there are over 1,500 individually-manufactured products with different National Drug Codes (NDCs) that require the dispensing of a MedGuide.

With over 1,500 individual products needing to be dispensed with MedGuides, we are concerned about proposals that could lead to the unnecessary approval of MedGuides outside the scope of the FDA's original intention to require them only for a few products which pose a "serious or significant concern." Requiring the use of a MedGuide as part of all Risk Evaluation and Mitigation Strategies (REMS) may result in overuse of MedGuides.

All pharmacies already provide patients with comprehensive written information on their medications. This information, which is updated continuously, is provided to pharmacies electronically by database companies and then printed by pharmacies. To enhance the distribution of MedGuides, we suggest a similar procedure be developed for MedGuides, in which pharmacies are permitted to print MedGuides through their computer systems. This will enhance the percentage of patients that receive Medguides that are consumer friendly and easy to read.

NACDS supports educating patients on their medications. However, the use of MedGuides may not be the most effective way to educate patients for all medications. MedGuides should remain a resource only for medications which pose a serious or significant concern. It is important to note that while the FDA has significantly increased the number of MedGuides recently, there is no evidence which demonstrates that MedGuides enhance patients' understanding of medication risks.

Although manufacturers are required to provide MedGuides in "sufficient quantities" to pharmacies, there is no standard method of distribution used throughout the industry. Instead, each manufacturer of a product with a required MedGuide can choose from an unlimited number of methods. Most commonly, manufacturers provide pharmacies with small MedGuide documents which are difficult to handle for pharmacists and even more difficult to read for patients. In most cases, this results in a MedGuide which does not achieve its intended goal of educating patients on their medications.

We suggest that drug safety proposals enhance the process by which MedGuides are provided by manufacturers and dispensed to patients. FDA should use its authority to require manufacturers to use identical procedures for producing MedGuides and distributing them to pharmacies.

In order to determine whether or not MedGuides are meeting the goals of educating patients on their medications, we suggest that the FDA assess the benefits of different types of written information, including MedGuides. This information will be very helpful in determining how to best educate patients on their medications so they can use them safely and effectively.

RESTRICTED DISTRIBUTION PROGRAMS

NACDS and the community pharmacy industry believe there is a need for significant changes to the manner in which restricted distribution programs are developed, approved, and monitored. We support proposals to provide the FDA with more authority over the development of these programs so that they are effectively and efficiently implemented by healthcare providers.

Community pharmacies have extensive experience with many restricted distribution programs, including one of the largest programs, the iPledge program for isotretinoin (Accutane). As a result, we have several recommendations for drug safety legislation as it relates to restricted distribution programs.

As evidenced through the challenges with the recently implemented iPledge risk management program for isotretinoin, if restricted distribution programs are not developed properly, patient access can be hindered significantly. As a result, a delay in patient access to medications in restricted distribution programs can have negative consequences on health outcomes.

To help limit burdens on patients, NACDS suggests that drug manufacturers and the FDA obtain the input of stakeholders, including patients, pharmacies, and physicians that will ultimately implement the restricted distribution program. This will result in a more effective program which builds upon the risk management strategies already put into place in the private sector. Programs developed using industry capabilities will also result in enhanced compliance by all participants with fewer interruptions in patient care.

Although NACDS recognizes the necessity of training practitioners, pharmacists, and other healthcare providers as part of restricted distribution programs, it is important to note that there are already rigorous requirements on pharmacists and pharmacies in order to be licensed by States to dispense medications. We believe pharmacists and pharmacies should not be subject to certification requirements to participate in restricted distribution programs.

NACDS also urges restricted distribution programs to provide all dispensing locations, including community pharmacies, with the opportunity to participate. There are some medications that are only appropriately dispensed in the institutional setting because of specific monitoring necessities, but these prescription drugs are the exception. Many patients prefer to use their local community pharmacy for their prescription needs. Also, having patients fill all of their prescriptions at one location helps assure that their pharmacy is able to identify and prevent any potential adverse drug reactions (ADRs) or complications between the restricted distribution medication and the other medications the patient is taking. Participation by pharmacies or other healthcare providers in a restricted distribution program should only be limited if a dispensing location cannot meet the program requirements.

CONCLUSION

Thank you for the opportunity to provide this statement to the hearing record. We look forward to working with the committee on advancing legislation that improves drug safety and public health.

Response to Questions of Senators Enzi, Kennedy, Murray, and Clinton by Sheila Burke

QUESTIONS OF SENATOR ENZI

Question 1. Do you believe that comparative effectiveness studies for drugs should be done by the FDA or by payers?

Answer 1. Such studies can be done by FDA, by payers, or by both working collaboratively on some or all aspects of study design and execution.

Question 2. Do you think that user fees affect product approval decisions by FDA?

Answer 2. The committee did not attempt to conduct a systematic analysis of the impact of user fees on product approval decisions by FDA. However, the committee recognizes that a perception exists that user fees influence approval decisions. Also, in its information gathering, the committee has learned that the time pressures associated with the user fees program requirements may contribute to an inability to examine pre-approval safety issues as closely or thoroughly as a reviewer may believe is necessary. The committee also noted that the attention and resources devoted to the pre-approval (review) process are substantially greater than those available to monitor and effectively react to a drug's post-approval performance.

Question 3. The IOM report addresses some communication issues within FDA and their impacts on drug safety. Are communications between FDA and other agencies on drug safety issues effective? If not, how might they be improved?

Answer 3. The committee was not asked specifically to consider interagency communication on drug issues, but the committee did comment on the existing and increasing data available from publicly funded healthcare programs (those of CMS and VA), and the need for better communication and especially greater resources to support collaborative efforts among FDA and other agencies. For example, collecting and analyzing relevant Medicare part D data for FDA drug safety surveillance purposes requires funds for staff, information technology, etc.

Question 4. I agree with you and with some of the other witnesses that, absent increased appropriations, we should expand what activities may be covered by user fees. However, approximately half of CDER's budget is currently derived from user fees. If we increase this figure, do we run the risk of undermining the perceived independence of the agency?

Answer 4. That is a legitimate concern. In acknowledgement of the high likelihood of PDUFA reauthorization, the committee has called for removing the restrictions on how user fee funds are used, in the belief that these not only create hardships for certain CDER programs important to drug safety, but also reinforce the perception that the sponsors unduly influence the process. It is also incumbent on the Commissioner and center director to clearly explain the science based behind the decisions that are made in order to dispel any inaccurate assumptions or interpretations of what motivated certain regulatory decisions. In other words, it is important that agency leadership "go the extra mile" in the area of transparency.

QUESTION OF SENATOR KENNEDY

Question. There has been a lot of debate on whether to establish a safety center at FDA that is separate from the office that approves new drugs, but your report rejected this idea. Why did you conclude that this was not the right approach?

Answer. There are two reasons for the committee's discomfort with the idea of a separate safety center. *First*, the committee believes strongly that safety and efficacy must be considered together during a drug's lifecycle by professionals who can work collaboratively to piece together a complex and evolving puzzle—what was known before approval, and what is learned about a drug's risks and benefits after it has been on the market for some time. Staff in the Office of New Drugs and those in the Office of Surveillance and Epidemiology (formerly Office of Drug Safety) each possess information and skills that are important to the process. For example, reviewers of new drugs know a lot about (classes of) drugs that never make it to market. Separating post-marketing safety staff from review staff would break down and complicate the lines of communication and it could compromise the institutional memory about drugs reviewed in the past and those that were actually approved. *Second*, the reasons that have been given for creating a separate safety center have included the claim that the staff who were responsible for approving a drug have a built-in bias against overturning their previous decision once safety problems arise. There have not been in-depth studies to support this theory, but the committee in its information gathering activities found no reason to suspect this would be the case. In fact, the committee found that drug reviewers are deeply aware of

and sensitive to the reality that the risk-benefit analysis that leads to a drug approval is frequently based on limited information, and that only more extensive and prolonged experience with a drug in a real-life setting will either solidify the earlier position on a drug, or lead to identifying and then confirming serious safety problems with the drug.

QUESTION OF SENATOR MURRAY

Question. I know that the IOM did not look at the over-the-counter application and review process. However, we know that the recent experience on the Plan B OTC application did impact morale and that reviewers who supported this application were silenced. Dr. Susan Wood is probably the most visible casualty of this process and I truly hope that no one else ever feels that they must resign in protest at the FDA. How can we legislate a better culture and improve morale at FDA as is proposed by the IOM? How can we create a structure to allow for scientific disagreement without undermining the agency?

Answer. This is an enormously difficult question to answer. Unfortunately, it seems difficult if not impossible to legislate a better culture. However, the committee believes that it is possible to put in place some of the elements management literature has shown may help support organizational change and lead to good morale and a healthy organization. The committee believes that stability at the top may help contribute to this, as well as a group of experienced leadership advisors to help support agency and center leadership, systematic management efforts to facilitate communication and collaboration, and addressing some of the imbalances that may exacerbate polarization among offices and disciplines. The committee is aware of the recent efforts at CDER to establish mechanisms for dispute resolution, but it believes that management must make such issues a priority and consistently demonstrate that they are not simply empty words on paper, but evidence of support for a true spirit of open-minded scientific inquiry. Finally, and most importantly, the Commissioner and the center director need to make it clear to all staff that a healthy organizational culture is a high priority, and that specific actions will be implemented to facilitate and maintain an atmosphere of transparency, inclusion, optimal communication, and mutual trust.

QUESTIONS OF SENATOR CLINTON

Question 1. The IOM report recommends giving the FDA increased authority to revise labels, require conditions on distribution, and changes in promotional materials. It also recommends increasing the range of tools available to ensure that this new authority can be effectively enforced. Yet we know that the agency relies heavily upon drug agency user fees, and have seen examples of when scientists were pressured to lessen their criticism of products. How can we change the culture at FDA to ensure that new enforcement authority is used? What kinds of enforcement mechanisms would be most effective in combating these cultural issues and helping to improve consumer safety?

Answer 1. It is difficult to make a direct link between culture and authority. However, the committee believes that agency leadership can play an absolutely essential role in organizational culture change. The Commissioner and center director must send a clear message that agency leadership expects (and will support) staff in exercising authorities available to them when the scientific evidence calls for certain regulatory decisions. However, in order to be able to base decisions on the best science, staff require the funding, skills, information technology, and institutional relationships to access and analyze the necessary data which then justifies use of specific authorities. Adequate resources (preferably from appropriations) are key. The committee believes that the heavy workloads and tight review timelines (linked to user fees) of drug reviewers make it difficult for them to thoroughly attend to safety issues, and their counterparts in the Office of Surveillance and Epidemiology are so few in number and so severely underfunded that safety concerns may slip through the cracks.

Question 2. In recent years, the agency's employees have been suffering a crisis of morale. Career scientists report being pressured to change their findings by senior level officials. Ideological concerns, not scientific data, delayed the decision on the over-the-counter application for Plan B. We have seen multiple examples where political and commercial interests were given higher priority than consumer safety.

The IOM report recommends establishing a fixed 6-year term for the Commissioner, to isolate him or her from political pressures. Could you comment on the ways in which this fixed term will help address the concerns over the current FDA

culture? What other reforms might be necessary to address the concerns expressed about senior-level management, in addition to the Commissioner's post?

Answer 2. The fixed-term appointment of a thoroughly qualified individual may help to set the tone for the organizational culture. A commissioner who is "here to stay" for several years would have the opportunity to support center directors and other agency leaders and to ensure that his or her leadership philosophy and priorities are implemented.

Some of the management literature cited in the report refers to past leaders of government agencies who were effective in bringing about profound cultural changes through their vision and their leadership style (participatory, encouraging of transparent and frequent communication among all levels of the agency, respectful of the diversity of disciplines and viewpoints in the organization, etc.). The report states,

> "Assessments of government agency performance and examples from the management literature have shown repeatedly that organizational cultures that stifle dissent, exclude staff from decisions about the organization's vision, and allow cultural problems to linger unaddressed are not healthy cultures, and those problems interfere with their ability to achieve their goals (Weick and Sutcliffe, 2001; O'Leary R, 2006; Return to Flight Task Group, 2005; Heifetz and Laurie, 1998; Khademian, 2002; Kotter, 2005)."

Question 3. The Drug Safety Oversight Board (DSOB) currently has no patient or provider representatives. Patient input into this process could help to improve public oversight on issues that will have significant impact on patients and to restore public trust in the drug safety system. What recommendations does the IOM have for improving public input into the FDA's drug safety oversight process?

Answer 3. The committee believes that FDA did not communicate clearly about the nature of the DSOB and its role. Although the board seemed to be "offered" as a solution to the drug safety problems of the several years, one of its functions is to provide internal oversight of how safety issues are handled within the agency (tracking of issues, resolution, etc.)—a function that needs to be performed by an internal group. Obviously, this is not the type of group that could be expected to address public concerns and tackle the difficult issues of external communication (although the DSOB's job description does include the latter, the committee finds this to be inappropriate—see Chapter 3).

The Drug Safety and Risk Management Advisory Committee is the external body that could (and already does to some extent) advise CDER on drug safety issues. DSaRM, not the DSOB, may be the type of group that could demonstrate agency commitment to receiving and acting on public input. Furthermore, in Chapter 6 of its report, the committee recommended the creation of a new advisory committee to focus on patient and consumer communication issues. Such a group, representing patient and consumer views and relevant professional expertise, could play a dramatic role in improving the quantity, quality, and timeliness of agency communication to and with the public.

Question 4. The IOM report recommends that civil monetary penalties be available to FDA as an enforcement tool for various forms of non-compliance. The report also recommends that industry sponsors be required to register and submit clinical trial data. What kind of enforcement mechanisms would the IOM consider appropriate to ensure that industry sponsors comply with such submission and registry requirements?

Answer 4. The committee did not describe the enforcement mechanisms that could be used, other than civil monetary penalties (and offered no specifics in this regard). However, such mechanisms are clearly needed—the agency's enforcement authorities are extremely limited.

RESPONSE TO QUESTIONS OF SENATORS ENZI, KENNEDY, MURRAY, AND CLINTON BY DIANE E. THOMPSON

QUESTIONS OF SENATOR ENZI

Question 1. Some have suggested that the drug safety system is broken. Do you agree? Are we seeing drugs being approved that truly shouldn't have been?

Answer 1. Several recent high profile drug safety incidents have highlighted the need for a stronger drug safety system. However, as Institute of Medicine (IOM) has pointed out, the fact that these instances uncovered safety risks after a drug was already on the market doesn't mean FDA shouldn't have approved it. Most new drugs are studied in fewer than 3,000 patients. And, most often those patients are far from a representative sample of the U.S. population. Consequently, adverse events that occur even as often as 1 in 10,000 patients are not likely to be discov-

ered until the product is on the market. The answer to improving drug safety is not to return to the days of significant delays in access to new therapies for life-threatening illnesses. Instead, we need to continue to study drugs in real life situations in larger groups of people in phase IV trails and after FDA approval. It is clear that our current drug safety paradigm poses considerable, avoidable danger, where the flow of risk-benefit information between drug manufacturers and the FDA occurs pre-approval and is extremely limited post-approval. This is one of the unintended consequences of the Prescription Drug User Fee Act (PDUFA). As the IOM report notes, continuing formal evaluations after a drug is approved is necessary. We have a historic opportunity to correct the current imbalance in our Nation's drug safety system. A reformed drug safety system that, as the IOM suggests, takes a life-cycle approach to assessing drug risks and benefits is in the best interest of all stakeholders.

Question 2. Your testimony calls for giving FDA the authority to require studies of "significant" off-label uses. I expect these post-market trials of off-label uses would be rather expensive. I worry about the impact on patients if companies start discouraging off-label uses to avoid having to conduct a set of new and expensive trials. You also noted that there are existing incentives to encourage pediatric studies of off-label uses. These incentives were created through the Best Pharmaceuticals for Children Act, which is due to be reauthorized next year. Have you considered ways we could amend that law to create better incentives for conducting studies of off-label uses in children?

Answer 2. Since off-label prescriptions are such a large proportion of medicines being prescribed by doctors, granting FDA authority to require studies of off-label uses is a necessary safety requirement. It is especially critical to children, who already are being placed at considerable risk because ¾ of pediatric prescribing is off-label. The expense of such studies needs to be balanced against the expense of treating patients with medicines that have not been proved to be safe or effective for the prescribed use.

Currently, companies cannot advertise or encourage off-label use, since these uses are not included on the label nor included during label negotiations between FDA and drug companies. It may actually be of significant benefit for companies to conduct off-label studies, because if studies confirm safety and efficacy for the off-label use, companies could then have an opportunity to advertise and market the drug for the new use once it is negotiated onto the label. Overall, patients stand to benefit greatly from new safety and efficacy information, where the public health impact of the off-label use was unknown before.

The reauthorizations of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), both of which expire next year, are extremely important to children's health. Although BPCA creates incentives to encourage manufacturers to study their products for children, these incentives are voluntary. We're seeing that manufacturers are increasingly opting not to conduct the studies FDA requests. Unambiguous authority to require such studies when the off-label use is significant will help ensure that children too can reap the benefits of an improved drug safety system. In both BPCA and PREA, the balance between incentive and mandate needs careful review to ensure that we accomplish the objective of the statute and fairly compensate the company for their investment. We look forward to working with the committee to further explore this.

Question 3. Do you think the timeframes for FDA action proposed in S. 3807 are reasonable?

Answer 3. It is very important that when new safety issues arise, there be quick and decisive action to address these concerns. Patients should not have to choose between safety and access. Safety assessments must be incorporated into the approval process so as not to slow the process down. This can only happen if FDA has adequate resources to address safety issues. Through the Risk Evaluation and Mitigation Strategy (REMS) plan, S. 3807 proposes that when new safety information demonstrates significant risk, FDA reassess REMS and enter into discussions with the manufacturer. We support the requirement that action on new safety information be completed in a timely way.

S. 3807 also establishes a dispute resolution process for resolving disagreements between FDA and drug companies related to REMS, referring such disputes to the closed-door Drug Safety Oversight Board (DSOB), which would review cases swiftly. In our view, transparency and patient input into this process is critical, both to ensure that there is public oversight on issues that will have significant impact on patients and to restore public trust in the drug safety system. We recommend that patient and consumer representatives be included on any such boards.

Question 4. Do you believe mandatory reporting of clinical trial results would compromise proprietary company information?

Answer 4. The release of proprietary information is not required in order to establish a clinical trials and results database. It's important to note that while drug manufacturers invest their resources and expertise into the clinical trial process, patients make an investment of their own, of their health and their lives. In that sense, they also "own" the data. Understanding the results of clinical trails is of critical importance to participants who, in some cases, have heard about trial results via the media rather than the trial sponsor. In addition, community members who may not have been eligible for a trial but might benefit from the therapy in development are also invested in trial outcomes. A clinical trial results registry would provide a central, credible source for information, much of which currently is widely shared within patient communities. These informal communication mechanisms that have developed out of necessity must be replaced with a credible, comprehensive, and reliable registry. Access to reliable information about drug trials should not be dependent on whether a patient has the right contacts.

To the extent a manufacturer can make the case that the release of some piece of data would severely compromise their research efforts, the release of such information could be examined on a case-by-case basis. If the information is provided to each study patient on the trial it should be considered in the public domain for all intents and purposes. We should start from the premise that all parties benefit if we can restore trust in the clinical trials system, which will only come from more transparency in the process. Moreover, the availability of clinical trials information will serve to accrue more patients into studies more quickly, resulting in faster trial results and FDA approval forthcoming sooner. This provides a clear benefit to both sponsors and patients.

QUESTION OF SENATOR KENNEDY

Question. Outcomes of studies that are negative or that suggest toxicity in patients are often not published. The legislation I introduced with Senator Enzi requires publishing clinical trial results, both positive and negative, in a public database. What impact do you think this would have for patients, healthcare providers, and the research community?

Answer. Several events over the past few years involving selective reporting of clinical trials data and more specifically, the suppression of negative research have generated concern over whether enough is being done to ensure that important information about ongoing and completed scientific studies of drugs and devices is easily accessible to patients, healthcare providers, and researchers. While the NIH currently operates a clinical trials database, it was designed solely to help patients find ongoing trials and does not contain trial results.

Creating a mandatory and publicly accessible registry of clinical trials and their results is important, to not only provide the public with access to critical information affecting their health, but also for improving patients' trust in the clinical trial process. As IOM notes, the results of trials of not yet approved products is also of value to patients and researchers. For example, a drug may be a new member of a class of products already on the market and safety signals from the trial can help to highlight potential concerns with the already approved products. Information from trials on new uses of existing products can also be valuable, particularly if the new use is one that is already in practice. Furthermore, in our view, for the database to be of greatest use to patients, researchers, and healthcare providers, it will be critical that it be as comprehensive as possible, and that it include trials completed prior to enactment of the proposed S. 3807 legislation as well as medical device trials.

QUESTIONS OF SENATOR MURRAY

Question 1. One of my goals for FDA has always been trying to find the right balance between getting new drugs to patients without delay while ensuring safety and effectiveness. I know it's a tough balance and we always have to be concerned about unintended consequences for any actions we take legislatively. I also think we need to be concerned about making sure that patients get good information—not conflicting information or even information that simply focuses on risks and not benefits. We have to be sure not to scare patients away from potentially beneficial treatments. There are risks with any drug or device, and we could raise safety flags on any new treatment, but this could also deter access. How can we achieve this balance and do you have concerns about the impact of the IOM recommendations or the Enzi/Kennedy bill as it relates to access?

Answer 1. In our view, patients should not have to choose between safety and access. There should be equal focus on speedy access to new lifesaving drugs and safer, more effective medicines. As the AIDS epidemic has shown, patients are thirsty for greater access to information that affects their health and are both very capable of absorbing this information and better informed to make decisions regarding their health because of it. For example, access to information in a clinical trials and results database goes a long way toward ensuring that patients have access to unbiased information and to a full body of trial results for a condition or drug—a vast improvement over the fragmented, promotional sources too frequently relied on now. In addition, patients aren't alone in the decisionmaking process. As always when the decision involves the prescribing of a new course of treatment, providers will have a role in navigating new information.

Question 2. As the IOM report noted, 21 percent of prescriptions in 2001 were for off-label uses, meaning of course that these uses were never reviewed or approved by FDA. Many patients often are not even aware of off-label use. However, as you pointed out, off-label use is extremely important for pediatric patients as well as patients with rare diseases. I agree that additional safety data is warranted for off-label use, but are you concerned about efforts to discourage off-label use? Once again is there a way we can encourage greater safety data on off-label use without jeopardizing access or impeding the practice of medicine?

Answer 2. As you mentioned above, a substantial number of prescriptions are written for off-label uses. Any effort to reform the drug safety system that fails to address ⅕ of the use of drugs in real-world settings would create a significant safety gap. Requiring that companies conduct clinical trials of off-label uses would not jeopardize or impede access or the practice of medicine. Instead, it would inform medical practice by providing the necessary safety and efficacy information to better assess the impact on public health in an area where both efficacy and safety have heretofore been unaddressed.

Question 3. It has become very clear that we need a more uniform mechanism for collecting safety data. Currently the process for reporting adverse events is fragmented and there is little role for the patient. In fact, FDA does not even have a database of reported adverse events.

As an early champion, with Senator DeWine, of 1-800 Mr. Yuck, a national poison control center hotline that provides real time, accurate information to parents and providers in response to accidental poison exposure, I know how difficult it is to create a national database of real time information. But, we did succeed. We now have a national poison control database that can provide information to any caller across the country regarding accidental exposure to poisons. Using the data mined from this database we can also find information on increases in exposure to certain poisons and even local trends that could indicate widespread problems.

I think we need to consider a national reporting structure for adverse events associated to all medications. Many patients don't even know what an adverse event is and when a side effect may or may not be a concern. This kind of database could provide a great early warning system as well.

What steps can we take to improve the collection of adverse events and how can we be sure that patients are included in this process?

Answer 3. S. 3807 creates a Risk Evaluations and Management Strategy (REMS) system that would allow FDA and manufacturers to develop a plan to adapt and integrate new safety information about a drug, including regular review of adverse events reports by FDA. Because adverse events are not likely to be discovered until the product is on the market, it is critical that they be addressed post-approval. IOM recommends improving the current adverse event reporting system, through systemic review, to increase its usefulness in post-market surveillance, which we support. This approach is in-line with the idea of taking an overall "life-cycle" approach to drug safety, allowing for periodic reassessment of the risk-benefit of a drug over time. We also recommend that the process be amended to include patient representation in the dispute resolution process.

QUESTION OF SENATOR CLINTON

Question. Ms. Thompson, in your testimony, you discuss the ways in which the protections in Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act have resulted in safer drugs for our children.

With these protections, we can ensure that drugs that are labeled for use by children have first been tested to determine effects in pediatric populations.

However, you note that there is significant off-label use of medications among pediatric populations, meaning that many children are still exposed to unknown risks at the very moments when we are trying to improve their health.

Could you please elaborate on the ways in which giving FDA the authority to require studies for off-label utilization of drugs would improve children's health? What impact would this authority have on adult health outcomes?

Answer. As the IOM report notes, a recent study found that 21 percent of prescriptions written in 2001 were for off-label uses. Children are placed at particular risk, since as much as ¾ of pediatric prescribing is off-label and children are prescribed drugs for uses different than the adult use. Any safety and efficacy information for off-label uses would be extremely useful for children's health. Thanks to your efforts and those of Senators Dodd and DeWine, there are incentives available to encourage manufacturers to study their products for children. However, they are voluntary—and we're seeing that manufacturers are increasingly opting not to conduct the studies FDA requests. Unambiguous authority to require such studies when the off-label use is significant will help ensure that children too can reap the benefits of an improved drug safety system. Whether focusing on children or adults, the effect of off-label studies is the same. Health outcomes are improved when prescribing is guided by safety and efficacy for any use of a drug. There would also be an added benefit for adult populations who would know with much more certainty the benefits and risks of medicine they may be now taking without such vital information.

As valuable as comprehensive drug safety reform improvements would be in improving FDA's ability to monitor and act on safety signal once drugs are on the market, they don't obviate the need for renewal of BPCA and PREA—both of which expire next year. Most importantly, PREA creates the presumption that drugs to treat conditions that occur in children will be tested in children before approval or soon thereafter. This critical authority is not addressed by the proposed general drug safety reforms and should not be allowed to expire. In addition, both BPCA and PREA extend beyond simply a focus on safety data. Because children are not small adults and their bodies can respond very differently to a drug than adults, FDA can use the carrot and stick combination of PREA and BPCA to also generate critical data on dosing and efficacy.

RESPONSES TO QUESTIONS OF SENATORS ENZI, KENNEDY, MURRAY, AND CLINTON BY STEVE E. NISSEN, M.D.

QUESTIONS OF SENATOR ENZI

Question 1. Can you comment on the feasibility of the Enhancing Drug Safety and Innovation Act (S. 3807) to simultaneously shorten the time to bring new medications to patients, while improving the safety of drugs?

Answer 1. I remain strongly convinced that the Enhancing Drug Safety and Innovation Act (S. 3807) can simultaneously shorten the time to develop new medications, while improving drug safety. Because the current regulatory environment does not facilitate robust post-marketing surveillance, the FDA and its Advisory Committees must necessarily be cautious in approving new medications. This caution is warranted because we lack confidence that emerging drug safety problems will be promptly identified and addressed. The Enzi-Kennedy bill strengthens the post-marketing risk mitigation, which will increase confidence that the Agency can rapidly identify any unforeseen drug safety problems. This enhanced confidence will allow more rapid approval of innovative new therapies, while protecting against unexpected post-marketing risks.

In addition, the requirement for transparency in reporting the results of late stage clinical trials can also help to speed new drug development. Currently, enormous resources are expended in the development of agents that are often similar to failed compounds. Because companies developing these therapies are unaware of the problems that led to failure of similar agents, enormous resources are wasted exploring failed or nonproductive pathways. The increased transparency afforded by S. 3807 will help companies to focus their development efforts on truly innovative approaches, while avoiding pathways likely to lead to failure. This concentration of resources on the most promising therapies should serve to speed drug development.

Question 2. You suggest a new type of new drug approval that you describe as "provisional." Some have suggested that a provisional or conditional approval could have very negative market effects, but you suggest that it might in fact improve innovation and drug safety. Could you elaborate?

Answer 2. Making provisional approval work in the current market environment is possible with creative regulatory strategies. Provisional approval would be appro-

priate for important potentially life-saving therapies for which there is inadequate data, particularly with respect to long-term benefits vs. risks. For lethal disorders such as AIDS or cancer, permitting more rapid access to potentially breakthrough medications makes good sense, even if there are remaining safety and efficacy concerns. It would be necessary to provide legislative support empowering the FDA to mandate that certain Phase IV trials must be completed by the end of the provisional approval period. If the studies were not performed, approval would automatically be rescinded.

To compensate companies for the shortened period of exclusivity that would likely result from provisional approval, legislation could adjust the exclusivity period to provide an economic incentive to seek provisional approval. This would be similar to the additional 6 months of exclusivity that is provided for companies that study therapies in pediatric populations. With the proper incentives, new therapies could be made available to the public without compromising safety or resulting in economic disincentives for industry to seek provisional approval.

Question 3. Do you believe mandatory reporting of clinical trial results would compromise proprietary company information?

Answer 3. In my view, when patients are asked to participate in randomized clinical trials, there is a moral and ethical obligation to translate their participation into the advancement of scientific knowledge. We owe this obligation to our patients who selflessly consent to participate in clinical trials. Therefore, I strongly disagree with the contention that mandatory reporting of clinical trial results would compromise proprietary company information. Most of the studies that go unreported are clinical trials in which the agent either failed to show benefit or exhibited unacceptable toxicity. In either case, there is little or no proprietary information involved. The results of clinical trials affect the health and even the survival of many of our citizens. It is just simply unacceptable to withhold such knowledge under the guise of proprietary interest.

If a drug fails during Phase II or Phase III due to toxicity, it is essential that the scientific community be informed of the nature of that toxicity, so that patients treated with related agents can be appropriately protected. Similarly, if toxicity is experienced in Phase IV trials, physicians must be provided with such information to optimally protect their patients from the hazards of such therapies. Interestingly, there is dissociation between release of information for studies that are reviewed by FDA Advisory Panels and those that are not. Currently, the FDA posts the briefing documents for advisory panels on the "worldwide web" the night before advisory committee meetings. But if studies never come to an advisory committee, the information is withheld. Since both types of trials contribute to knowledge and release of the results always serves the public interest.

Question 4. Can professional medical societies play a greater role in communicating the benefits and risks of drugs to their physician members and to the general public? If so, how?

Answer 4. I believe that professional societies have been under-utilized as a contributing source for information on the benefits and risks of drugs. Professional societies can serve as impartial sources of information independent of both the FDA and the pharmaceutical industry. Members and leaders of these professional societies include individuals with great expertise on the clinical application of pharmacotherapy. They provide a source for objective information and balanced recommendations for practitioners and the public at large.

In addition, many professional societies operate databases that include unique information about outcomes for patients treated with pharmacological agents. I am currently President of the American College of Cardiology, an organization with 33,000 members that includes more than 90 percent of the cardiovascular practitioners in the United States. We operate a database known as the National Cardiovascular Database Registry (NCDR) that has information on several million patients who have undergone various interventional procedures, including cardiac catheterization, intervention, carotid stenting and implantation of cardioverter-defibrillators (ICDs). This information provides vital opportunities for post-marketing surveillance of safety, but is currently not generally utilized by regulatory agencies as a source for unbiased information. Rather than have the Federal Government recreate such databases through the FDA, partnership opportunities with professional societies can enable access to this information to enhance quality and patient safety.

Question 5. You conduct large safety trials. Could you give us a sense of what is involved in tracking down a safety issue that occurs in, say, 1 in 10,000 people who take a drug?

Answer 5. Evaluating serious or potentially lethal risks that have a low frequency of occurrence represents the single greatest challenge in post-marketing surveillance. Such risks can virtually never be determined prior to drug approval, since most approval packages involve treatment of substantially less than 10,000 patients.

Several strategies have been employed in the past to assess these low frequency risks. For example, in the case of rare liver failure events, certain biochemical markers can be used to predict which drugs will likely have a risk and can estimate with reasonable precision the likely rates of occurrence of fatal outcomes. However, for many idiosyncratic drug reactions, there exist no predictive biochemical markers.

Ultimately, detection of these low frequency events requires a very robust post-marketing surveillance system. The best sources of information are patient databases that record clinical outcomes and adverse events for larger populations. Several health maintenance organizations such as Kaiser Permanente maintain such large databases, which have been used successfully in the past to detect low frequency risks. I also believe that partnership with professional societies can be very helpful since many of these societies maintain ongoing databases for monitoring quality and health outcomes.

Other innovations, available in the near future, may be helpful. For example, electronic medical records (EMR's) allow rapid and reliable assessment of patient outcomes. EMR's are much easier and less expensive to evaluate than abstraction of outcomes information from paper records. Current legislative initiatives designed to enhance the electronic medical record have the potential to greatly enhance drug safety. EMR's make possible nearly automated reporting of outcomes, a potentially powerful approach to identification of unanticipated risks.

Finally, the current Adverse Event Reporting System (AERS) has proven inadequate for assessing low frequency events even when they are serious or fatal. There are considerable burdens upon the practicing physicians to report these rare events. Currently, there exists no incentive for voluntary reporting. Perhaps there is an opportunity to create incentives for physicians to take the time to report unusual events to the FDA. Perhaps, a provision of Continuing Medical Education (CME) credits might encourage reporting.

QUESTION OF SENATOR KENNEDY

Question. Outcomes of studies that are negative or that suggest toxicity in patients are often not published. The legislation I introduced with Senator Enzi requires publishing clinical trial results, both positive and negative, in a public database. What impact do you think this would have for patients, healthcare providers, and the research community?

Answer. The requirement in S. 3807 for mandatory registration reporting of clinical trial results represents one of the most important and valuable provisions of this bill. During the past several decades, there has been an enormous proliferation of clinical trials throughout most medical disciplines. Increasingly, these trials are directed by pharmaceutical companies, often working in conjunction with independent operators known as contract research organizations (CRO's). It is also becoming increasingly clear that such trials are promptly published when they show benefits for a pharmacological therapy, but are often never published if the study shows no benefits or serious toxicity. This practice, known as negative publication bias, has a catastrophic effect on the practice of medicine. For example, if 10 clinical trials are conducted to study a class of medications and 9 of the 10 studies show either lack of efficacy or toxicity, it is highly likely that the therapy is not beneficial. Yet, if a 10th study is conducted and it shows a marginal, but statistically significant evidence of benefit, this may be the only study of the therapy that is ever published. Physicians unaware of the 9 failed studies may prescribe this ineffective or potentially risky therapy because they have no knowledge of the studies that failed to show benefit or showed toxicity.

Negative publication bias also has major negative effects on drug development. Many companies are unaware that a competitor has studied a drug and found it ineffective or showed unacceptable toxicity. As a result, they may proceed with clinical trials of a very similar compound. This exposes patients to risky drugs, when such exposure could have been avoided had the company developing the drug been aware of poor outcomes for similar drugs in the class. I strongly believe that when we ask patients to consent to participate in a clinical trial, there is a moral and ethical obligation to ensure that their participation results in the advancement of science. Science cannot advance if the results of this study are never published. Accordingly, I strongly support the provision of bill S. 3807 requiring registration and publication of all late stage clinical trials. This provision is essential to restoring an adequate balance between safety and efficacy in drug development.

QUESTIONS OF SENATOR MURRAY

Question 1. One of my goals for FDA has always been trying to find the right balance between getting new drugs to patients without delay while ensuring safety and effectiveness. I know it's a tough balance and we always have to be concerned about unintended consequences for any actions we take legislatively. I also think we need to be concerned about making sure that patients get good information—not conflicting information or even information that simply focuses on risks and not benefits. We have to be sure not to scare patients away from potentially beneficial treatments. There are risks with any drug or device, and we could raise safety flags on any new treatment, but this could also deter access. How can we achieve this balance and do you have concerns about the impact of the IOM recommendations or the Enzi/Kennedy bill as it relates to access?

Answer 1. I understand and share your concerns about achieving the right balance between bringing new medicines forward and ensuring public safety. I am very comfortable that S. 3807 will achieve both goals in a balanced fashion. There is nothing in the bill that directly affects patients' perception about the safety of beneficial therapies. We have seen a series of drugs withdrawn from the market or come under serious scrutiny because of drug safety problems. This has seriously undermined public confidence in the safety of medications. As a consequence of this series of safety revelations, many patients are reluctant to accept life saving therapies. Improving drug safety has the potential to improve public confidence and access to innovative therapies. If we can improve the approval process and post-marketing surveillance, we will avoid the kind of public attention that has undermined confidence in drug safety.

In addition, I believe the FDA has a great opportunity to do a better job of communicating the issues of benefit versus risk. In several recent FDA advisory panels, I recommended the development of "Patient Guides." These are mandatory brochures provided to patients at the time of dispensing certain risky medications. These Guides explain to patients both the benefits and risks of these drugs. The Guides are written in language easily understood by the general public and carefully explain to patients what side effects to look for and how to report these adverse effects to their physicians. I believe that an informed public is much more likely to accept the benefits of therapies. A public that is suspicious about the relative benefits and risks may not comply with therapy. The enhanced transparency of the Enzi-Kennedy bill in making certain that we have all the information necessary within the public domain can help to improve, rather than undermine public confidence.

Question 2. As the IOM report noted, 21 percent of prescriptions in 2001 were for off-label uses, meaning of course that these uses were never reviewed or approved by FDA. Many patients often are not even aware of off-label use. However, as Diane Thompson pointed out, off-label use is extremely important for pediatric patients as well as patients with rare diseases. I agree that additional safety data is warranted for off-label use, but are you concerned about efforts to discourage off-label use? Once again is there a way we can encourage greater safety data on off-label use without jeopardizing access or impeding the practice of medicine?

Answer 2. Off label use of medications is an important issue and must be addressed in a thoughtful fashion. Nothing in the Enzi-Kennedy bill restricts the rights of physicians to make individual choices about which therapies would be beneficial for their patients. I strongly support the notion of physician and patient choice. There are many examples where so called "off label" therapies have become the treatments of choice for important medical conditions. Examples include the use of β-blocking agents for angina and clopidigrel to prevent thromboses following coronary stent placement.

However, it is important to distinguish between physician choice and active commercial promotion of off-label treatments. Therefore, I strongly support the current approach that precludes marketing drugs for off-label indications. If a medical therapy is effective, it should be demonstrated in an appropriate clinical trial.

With respect to rare diseases, I also favor "lowering the bar" for development of therapies for these indications. I served on the FDA Advisory Board that approved a drug therapy for a rare fatal disease known as pulmonary arterial hypertension. I and other members of this panel strongly supported approval of this drug despite a clinical trial that provided less statistically robust demonstration of efficacy than would ordinarily be required. This adjustment to the standards for approval represents good regulatory policy and should be encouraged in selected circumstances. This is particularly advisable when the disease is potentially lethal and there are few, if any, accepted therapies.

Question 3. It has become very clear that we need a more uniform mechanism for collecting safety data. Currently the process for reporting adverse events is fragmented and there is little role for the patient. In fact, FDA does not even have a database of reported adverse events.

As an early champion, with Senator DeWine, of 1-800 Mr. Yuck, a national poison control center hotline that provides real time, accurate information to parents and providers in response to accidental poison exposure, I know how difficult it is to create a national database of real time information. But, we did succeed. We now have a national poison control database that can provide information to any caller across the country regarding accidental exposure to poisons. Using the data mined from this database we can also find information on increases in exposure to certain poisons and even local trends that could indicate widespread problems.

I think we need to consider a national reporting structure for adverse events associated to all medications. Many patients don't even know what an adverse event is and when a side effect may or may not be a concern. This kind of database could provide a great early warning system as well.

What steps can we take to improve the collection of adverse events and how can we be sure that patients are included in this process?

Answer 3. The current AERS is ineffective. Reporting of adverse events is voluntary which limits effective analysis. We need to find creative approaches to the collection and evaluation of adverse event data. I am convinced that the electronic medical record can help substantially. If patient outcomes are recorded electronically, it becomes much easier to collect and report outcomes data, including adverse effects for a wide range of therapies. My own institution, the Cleveland Clinic, has very effectively used our EMR in this way. Similarly, many professional medical societies maintain large prospective databases that record outcomes for quality initiatives. Providing support for the FDA to partner with medical societies represents a truly innovative opportunity. Similar opportunities exist for large health maintenance organizations, such as Kaiser Permanente, which has played an important role providing independent data during several recent drug safety discussions.

Finally, I support your concept of involving the patient in adverse event reporting. We must recognize that such reporting may not have the scientific quality of physician reporting, but it is very useful nonetheless. There may be an opportunity to provide a vehicle for patients to express their observations and have the opportunity for the FDA to evaluate such reports.

QUESTION OF SENATOR CLINTON

Question. The IOM report notes that direct-to-consumer (DTC) advertising has been shown to have an impact on physician prescribing practices, and you stated in your testimony that such advertising should be more heavily regulated, with companies required to demonstrate a compelling public health benefit for this communication.

However, we also face challenges from advertising targeted to physicians, such as conferences or lunches, at which favorable studies and journal articles can be highlighted.

As a doctor yourself, what are your recommendations for addressing pharmaceutical marketing efforts that target physicians? How do we ensure that such efforts do not also result in the over-prescription of therapies that may be more expensive without being more effective?

Answer. I share your concerns about the effect of very aggressive advertising directed at physicians and other healthcare providers by the pharmaceutical industry. Through voluntary restrictions, there has been some improvement in these practices in recent years. However, in my opinion, these reforms have not gone far enough. Pharmaceutical companies now dominate medical education. For example, in smaller hospitals "Grand Rounds" is typically a weekly conference in which emerging educational topics are discussed. In most cases, pharmaceutical companies sponsor such Grand Rounds and provide the speakers. Often such lecturers are scientifically unbalanced, presenting highly promotional material under the guise of medical education.

In addition, there has been a proliferation of so-called "medical education companies." Although these entities are loosely regulated by the Accreditation Council for Continuing Medical Education, such voluntary regulation is largely ineffective. "Scientific" symposia sponsored by most medical education companies often consist of promotional material in which speakers favorable to a particular therapy dominate the activity.

In many hospitals with post-graduate training programs, pharmaceutical companies provide lunches and other perquisites for the physicians in training, along with

a variety of "educational materials" that are largely promotional. As a consequence of these practices, newer and expensive therapies are often favored over older, generically available treatments. In some cases, the earlier treatments are actually better, but in most cases they are simply more cost-effective.

Determining how to regulate physician-targeted advertising is a challenging problem. Obviously, we must respect the principles of the first amendment in which "commercial speech" is traditionally considered privileged. Nonetheless, I think we will need to consider creative strategies for curtailing inappropriate physician targeted advertising. Drugs are not "widgets" and the manner in which they are marketed affects the health of all 300 million Americans. The standards for promotion of drugs should be higher than any other industry. Currently, they are not.

RESPONSE TO QUESTIONS OF SENATORS ENZI, KENNEDY, AND MURRAY BY ADRIAN THOMAS, M.D.

QUESTIONS OF SENATOR ENZI

Question 1a. I would like to ask you some questions about clinical trials, particularly clinical trial registries and results databases. What is an "adequately designed and well-controlled clinical trial?"

Answer 1a. An adequately designed and well-controlled clinical trial is a clinical study that has the following characteristics:

- Clear objectives and a measurable hypothesis;
- Study design that distinguishes treatment effects from other influences;
- Enrolls patients that have evidence of the disease under study or of susceptibility;
- Uses methods for assessing patient outcomes that are reproducible and valid;
- Has an appropriate control;
- Is adequately powered to achieve the objective of the study;
- Has adequate measures to minimize bias such as blinding of patients, investigators and data analysts;
- Has random assignment to the test therapy or control group; and
- Produces an analysis of the results of the study that is adequate to assess the effects of the drug.

Adequately designed and well-controlled clinical trials are the primary basis upon which the FDA determines whether there is substantial evidence of effectiveness for a new drug. (Reference: 21 CFR 314.126 adequate and well-controlled studies)

Question 1b. What clinical studies does Johnson & Johnson register with ClinicalTrials.gov?

Answer 1b. We publicly register all adequate and well-controlled studies of both marketed and investigational drugs regardless of location. For studies related to serious and life threatening diseases, we register all that include efficacy endpoints, regardless of trial design or location. Registration is made to the National Library of Medicine's Website, *http://www.clinicaltrials.gov.*

We believe that both patients and healthcare providers can benefit from knowledge of clinical trials that are open for enrollment, and our policy is intended to provide this information to consumers in a manner that is as clear and easy to access as possible.

Question 1c. What clinical study results does Johnson & Johnson currently disclose?

Answer 1c. For marketed medicines, we publish the results of all adequate and well-controlled studies regardless of outcome. We also publish results of any other clinical studies of our marketed medicines that are material and relevant to the clinical use of the medicine or to the care and safety of patients.

Question 1d. How are these results disclosed?

Answer 1d. These trial results appear either in peer-reviewed medical literature or in the form of a clinical study report synopsis in the ICH-E3 format, which is designed to present data for a standardized scientific regulatory review. At present, our clinical study results are posted as links from the protocols we have registered on *http://www.clinicaltrials.gov.*

Question 2. Do you think the timeframes for FDA action proposed in S. 3807 are reasonable?

Answer 2. Yes, as long as we understand that these are minimum timelines and companies should engage with FDA and relevant stakeholders earlier if possible.

Question 3. S. 3807 requires generic drugs to have REMS that are identical to the REMS for the innovator product. However, some very stringent RiskMAPS are based on patents. I would hope that in such cases the patent holder would be amenable to licensing, but that may not always be possible. How might this requirement be filled for generic versions of these products, without compulsory licensure of the patent?

Answer 3. This is a difficult situation that may not be able to be addressed simply. Innovation necessary to address safety concerns should not be undervalued, and incentives for this innovation must be maintained. There are elements of RiskMAPS such as the "STEPS" program for thalidomide, which has been patented, and thus a product or molecule patent may not be what is at issue, but rather the risk management plan itself. It may not even be the company marketing the drug that owns a REMS-related patent, but a contract research organization, commercial vendor or other third party. This issue is complex and we recommend that the committee engage other interested stakeholders in this debate.

Question 4. In your testimony you suggest that the Reagan-Udall Institute should not be associated with the FDA and should report directly to the HHS Secretary and that intense interaction with the pharmaceutical industry is needed for success. Finding the right place for the Institute has been a challenge. Could you discuss the benefits of placing the Institute outside of the FDA, and if it were placed outside the FDA, how would you ensure that what is learned at the Institute is integrated into FDA safety reviews?

Answer 4. The Reagan-Udall Institute could contribute much more broadly than to FDA and its output should be optimized by placing it at the correct level within the framework of HHS. This would allow it to pursue valuable areas of research, for example into effectiveness and outcomes areas that are not directly the focus of FDA. In addition, one potentially exciting output of this institute could be research into methodologies for improving the approval processes. Such research could be conflicted if the Institute were placed within the FDA as the current process reflects the regulatory tools now used by the agency in its activities. Placing this institute at the level of reporting to the Secretary of HHS would give this organization appropriate independence from FDA, visibility and stature and does not undermine the agency's ability to implement output from the institute. Also, industry funding partners would be able to distance themselves from the regulatory approval process and potential for criticisms that would result if the organization were placed within the FDA.

QUESTION OF SENATOR KENNEDY

Question. Outcomes of studies that are negative or that suggest toxicity in patients are often not published. The legislation I introduced with Senator Enzi requires publishing clinical trial results, both positive and negative, in a public database. What impact do you think this would have for patients, healthcare providers, and the research community?

Answer. We believe that physicians, patients and the research community have a legitimate interest in clinical trial results regardless of whether the results show an advantage for an intervention or not.

In recent months, the traffic to clinicaltrials.gov has grown illustrating an interest in the availability of trial information, but not necessarily reflecting the utility of the information. A patient or treating physician needs to know how to interpret the information (either positive or negative) in order for it to be useful.

- During the period from May until October 2005 there was a 73 percent increase in the number of trials registered to *www.clinicaltrials.gov*—from 13,153 to 22,714 (see graph).
- During the period from September 2005 until November 2006 there was a more than a hundred-fold increase in the number of browsers to Johnson & Johnson's postings on *www.clinicaltrials.gov* from 37 to more than 4,000 in November of this year (see graph).

In order for *patients* and *physicians* to effectively use the information they learn from clinicaltrials.gov, it is important to understand the strength of the clinical evidence. The strength of the clinical evidence is related to the scientific method that was used to produce the results. In the case of a consumer encountering postings of negative information, there could be unintended consequences in terms of misinterpretation, or cessation of use of a needed medicine. A consumer must know how to interpret the information they read and this should be through the assistance of a learned intermediary who can evaluate the relevance of the information to a specific situation and guide the decisions on the course of treatment. The importance

of the contribution of the learned intermediary in this context should not be underestimated.

When apparently similar studies, with similar populations and ostensibly the same intervention, give apparently conflicting results, physicians and even other researchers may not be in a position to reconcile and integrate the findings in such a way that meaningful conclusions can be drawn.

There is genuine scientific benefit in having results from all studies available to members of the scientific research community, who can bring sophisticated skill to evaluating complex and often preliminary and exploratory data from early clinical trials. These experts often specialize within specific therapeutics areas, use sophisticated statistical methods, and apply experience and judgment of the principles of evidence-based medicine to weigh the strengths and weaknesses of various types of trials and their resulting data. This skill is needed to be able to assess varying and sometimes conflicting data into an interpretable body of evidence.

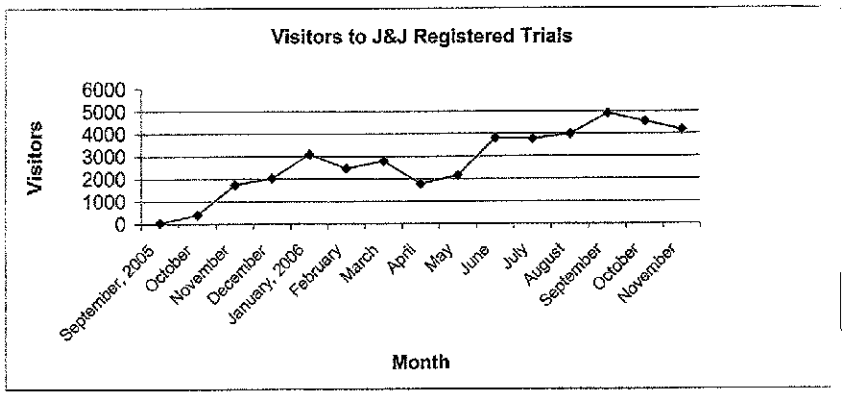
For experts who synthesize research findings, particularly when they calculate a quantitative summary of results, the unavailability of unpublished results may produce misleading summary evaluations. This would be the case if the publication of certain types of results (e.g., those not favoring the intervention of interest, or those showing harm resulting from an intervention), were systematically suppressed from the scientific literature, either through the researchers' failure to submit the papers for publication or through the failure of journals to publish what editors might view as "uninteresting" results (e.g., results showing no difference between two treatments).

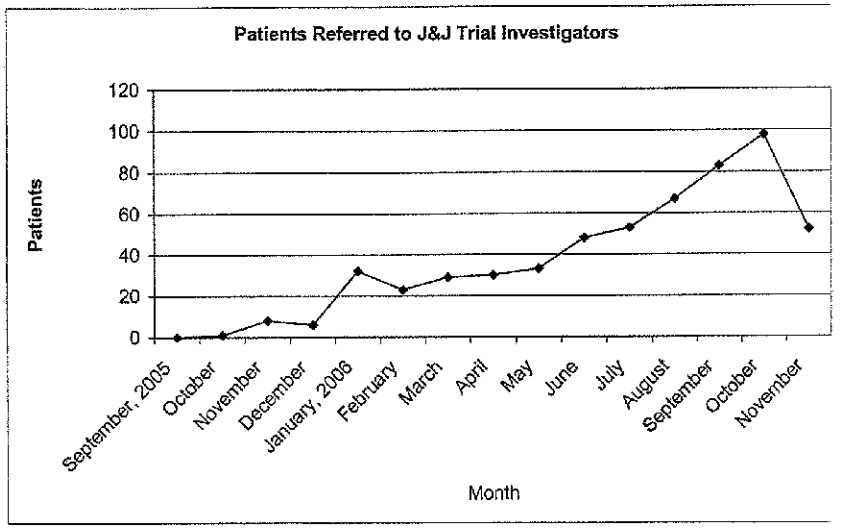
At the same time, information from clinical trials may well be difficult for patients, and indeed, some healthcare professionals, to assess accurately. Significant patient education will be necessary in order to avoid unintended and potentially harmful effects to patients. Congress should consider how best to ensure patients are educated before raw results are made broadly available. Laypersons, as well as many healthcare professionals who are not experts in clinical trial analysis may misinterpret data in two ways:

- First, by interpreting data from early stages of human research as if it were from later stages of research. The research methodology of early trials is not robust enough to formally test for benefits, but rather is designed to evaluate adverse experiences or assess maximum tolerated doses. A related issue is interpreting data from a study in one indication as if it is in a different indication. It would be unfortunate for patients who are receiving potentially life saving treatment for one indication to cease therapy because they become aware of toxicity data in another newly tested indication or population.
- Second, promising but preliminary data from dose ranging studies, or hypotheses-generating studies may be misinterpreted as implying benefits that cannot be proved by the study design. Benefit cannot be formally evaluated in other than definitive studies, such as, for example, mortality studies in cardiovascular disease. By assuming benefit that has not been proven, patients could be exposed to potentially harmful untested therapies.

Organizations conducting new drug development studies invest significant research time and resources in exploring potentially beneficial uses of novel therapies. Typically this involves the exploration of multiple indications, populations, dose ranges over increasing numbers of patients treated in clinical trials. Much negative trial data is to be expected from such research and this should be well understood. If early clinical trial data is made broadly available, it will be necessary to educate patients so that they can better communicate with their physicians about these data.

One final caution is that there is a major investment in innovation associated with investigating novel therapies. This investment could be compromised through early release of commercially sensitive data from clinical trials. Sufficient protections to support these investments must be considered.





QUESTIONS OF SENATOR MURRAY

Question 1. One of my goals for FDA has always been trying to find the right balance between getting new drugs to patients without delay while ensuring safety and effectiveness. I know it's a tough balance and we always have to be concerned about unintended consequences for any actions we take legislatively. I also think we need to be concerned about making sure that patients get good information—not conflicting information or even information that simply focuses on risks and not benefits. We have to be sure not to scare patients away from potentially beneficial treatments. There are risks with any drug or device, and we could raise safety flags on any new treatment, but this could also deter access. How can we achieve this balance and do you have concerns about the impact of the IOM recommendations or the Enzi-Kennedy bill as it relates to access?

Answer 1. Senator Murray raises very real issues about the loss of balance potentially resulting from a singular focus on safety, and not benefit/risk. The issues at hand are especially pertinent to the inherent tension between early approval and availability of products for unmet medical needs and the fact that we will always know less about risks than is ideal in this situation. The balance needs to be achieved through avoiding legislation that may result in inadvertently denying access to therapies (i.e., distribution restrictions) but focusing more on ensuring the agency has administrative mechanisms for evaluating potential risks and negotiating with companies on the product and population-specific methods of minimizing those risks. Overall, the IOM report and the Enzi-Kennedy bill recognize the need

for this balance, but Congress should consider carefully before legislating periods of restrictions such as fixed moratoriums on DTC, distribution restrictions, or REMS that are template in nature. A preferable alternative would be for Congress to direct FDA to consider these matters through administrative procedures that ensure an appropriate risk-based scientific evaluation guides such restrictions.

Question 2. As the IOM report noted, 21 percent of prescriptions in 2001 were for off-label uses, meaning of course that these uses were never reviewed or approved by FDA. Many patients often are not even aware of off-label use. However, as Diane Thompson pointed out, off-label use is extremely important for pediatric patients as well as patients with rare diseases. I agree that additional safety data is warranted for off-label use, but are you concerned about efforts to discourage off-label use? Once again is there a way we can encourage greater safety data on off-label use without jeopardizing access or impeding the practice of medicine?

Answer 2. In the opinion of treating physicians the use of products in unapproved, or off-label, indications may be in the best interest of the patient because it is consistent with the best science at the time. That said, it may not be a priority for an innovator company focusing its limited research resources on areas of larger medical need and where more safety data exist to support development programs. The FDA can always discuss with companies, as can any scientific organization, the potential for areas of research in unapproved indications, and these need to be balanced against other research opportunities and priorities of the company. With respect to pediatric indications, encouraging specific research through offering data exclusivity and other programs has been a very useful path forward, and is now also being followed in the EU as a way of generating these data. We should be very careful not to inadvertently expose patients to unethical or unsafe exposure to products in unapproved indications outside the protections provided under an IND. The matter of unapproved uses is an important area for continued discussion.

Question 3. It has become very clear that we need a more uniform mechanism for collecting safety data. Currently the process for reporting adverse events is fragmented and there is little role for the patient. In fact, FDA does not even have a database of reported adverse events.

As an early champion, with Senator DeWine, of 1-800 Mr. Yuck, a national poison control center hotline that provides real time, accurate information to parents and providers in response to accidental poison exposure, I know how difficult it is to create a national database of real time information. But, we did succeed. We now have a national poison control database that can provide information to any caller across the country regarding accidental exposure to poisons. Using the data mined from this database we can also find information on increases in exposure to certain poisons and even local trends that could indicate widespread problems.

I think we need to consider a national reporting structure for adverse events associated to all medications. Many patients don't even know what an adverse event is and when a side effect may or may not be a concern. This kind of database could provide a great early warning system as well.

What steps can we take to improve the collection of adverse events and how can we be sure that patients are included in this process?

Answer 3. There are a number of very important steps that can be taken to improve the collection and analysis of adverse events. A key issue is to collect high quality information and ensure appropriate followup. This balance can be achieved, although with the following potential considerations:

- The current FDA Adverse Event Reporting System (AERS) database needs to be updated and maintained. One option would be to streamline this by private/public partnerships to ensure that cutting edge technologies, validated and maintained current with dictionary and database oversight, are implemented to allow consistent reproducible searching of data.
- Physicians and healthcare professionals need to be encouraged to report adverse events, perhaps through incentives linked to performance measures specifically in this area. Considerations such as how to streamline this activity are critical as disruption to clinical workflow will need to be avoided.
- Opportunities to gather rich clinical data and safety information from claims and clinical databases should be accelerated, once again through public/private initiatives while protecting patient privacy. We need to move away from passive, spontaneous reporting to automated systems of surveillance.

Thank you for the opportunity to provide input on these important issues before the Senate HELP Committee. Please let me know if I can provide any further information.

RESPONSE TO QUESTIONS OF SENATORS ENZI, KENNEDY, MURRAY, AND CLINTON BY JIM GUEST

QUESTIONS OF SENATOR ENZI

Question 1. You suggest increasing the opportunity for and transparency of scientific dissent within FDA. One of the recommendations you make is that dissenters be offered whistleblower protections. However, dissent and discussion are an inherent part of the scientific enterprise. Rarely is there complete certainty based on the data. Do you really think it helps the FDA scientists to equate dissent with whistleblowing?

Answer 1. Of course dissent and debate should be part of the scientific process. However, there is a distinction between an honest, competent scientific discussion—including disagreement—and a whistleblower who reports on an illegal or improper action which threatens the public interest. In a very real sense, in a scientific agency like the FDA, allowing and encouraging public scientific dissent (and making such dissent public in a timely manner) will eliminate many or even most of the need for public servants to become whistleblowers.

What I am suggesting in the way of additional views and dissent is elaborated on in my response to Senator Kennedy's question. Our concern is that, for example, a junior staffer might feel that a dissent from the opinion held by, say, a section head would destroy future promotion opportunities. Assuming that the dissent (or additional views) were based on reasonable science, what guarantees can we give to younger civil servants that raising red flags is acceptable within the FDA? There should be a civil service appeals process in which staffers who believe their career path is harmed by speaking out can seek review and redress. To ensure objectivity in that appeals system, the office of review should have some independence—like a whistleblower/ombudsmen office would have. As you indicate, names are important, and perhaps it should be called something like "Office of Scientific Integrity."

It is worth noting the December 1, 2006, *Wall Street Journal* article "Virulent Strain: Inside FDA, a Battle Over Drug to Treat 'Darth Vader' Bacteria." The report describes the issues over the approval of the anti-heart valve infection drug Cubicin. It concludes with the following paragraph:

> "An internal e-mail sent out to staffers who worked on the Cubicin application by an FDA administrator said, 'this has been a very difficult application,' and promised that dissenting reviewers could note their disagreement for the record, with no retribution. . . ."

In short, there is precedent for this idea of dissent, but it should go without saying that there is "no retribution," and a system should be institutionalized *to make that promise a guarantee*.

There is language in the FDA regulations that seems ignored, but which, if codified and made prominent in the agency's culture, could address many of the morale and scientific problems that have plagued the FDA in recent years. We urge you to codify and put some teeth into compliance with 21 CFR 10.70, which currently reads as follows:

(1) Appropriate documentation of the basis for the decision, including relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents; and

(2) The recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter.

> *(i) The recommendations and decisions are to reveal significant controversies or differences of opinion and their resolution.*
>
> *(ii) An agency employee working on a matter and, consistent with the prompt completion of other assignments, an agency employee who has worked on a matter may record individual views on that matter in a written memorandum, which is to be placed in the file.*

The type of serious concerns identified by the Union of Concerned Scientists (and by the HHS OIG) in their poll of FDA scientists could also be addressed by institutionalizing respect for science. S. 1358 (Senators Durbin and Lautenberg), the "Restore Scientific Integrity to Federal Research and Policymaking Act," has language we urge you to consider which would prevent political interference with science and punish managers who violate such non-interference provisions. One of the reasons for the culture/morale problems in the FDA is the widespread belief that senior managers regularly have *ex parte* contacts with industry applicants and then use these undocumented contacts to overrule line staff. We hope that you could also codify the idea that *ex parte* contacts are prohibited, or if they occur, must be documented.

Question 2. You suggest that the clinical trial results disclosure provisions in the Enzi-Kennedy drug safety proposal allow too much time for study sponsors to seek publication of their results. But don't we want to encourage publication in peer-reviewed medical journals?

Answer 2. We must find a way to move this science into the public domain sooner. Certainly, if there are findings of danger, or warnings of danger that call for additional research, the findings should be posted immediately or within a set period of time, such as 2 working days.

We urge your consideration of an exciting article in *www.plosclinicaltrials.org*, October 2006 e31, by Elizabeth Wager and entitled "Publishing Clinical Trial Results: The Future Beckons." The article makes a moral case for publication of trial results, points to the many problems with the current journal system, and basically concludes:

> "A new model might therefore be for investigators or sponsors to make results available on publicly accessible Websites using standard templates and for journals to add value by publishing peer-reviewed commentary and synthesis."

Wager notes that "it is ironic that medical journals, for so long the bastion of publishing research findings, may now prevent or delay other, possibly better, forms of publication."

A 1-year limit in your bill on the publication of results should help force changes in this sector that we believe would be in the public interest.

Question 3. Where is the line between the FDA limiting the marketing and use of a new drug and the FDA interfering in the practice of medicine?

Answer 3. Your bill encourages the practice of *good* medicine. There have been repeated studies showing that despite black box warnings and other strong guidance to the medical community, very potent drugs are repeatedly prescribed inappropriately. Physicians are busy and errors happen. For drugs that can be dangerous (e.g., accutane in a pregnant woman), your bill systemizes safeguards that will reduce mortality and morbidity in the future. We see nothing in your bill that interferes with the good practice of medicine, though it does interfere with the bad practice of medicine. Physicians should thank you for reducing the chance for errors that may harm their patients.

Question 4. Without advertisements, how would consumers learn about drugs that might help them?

Answer 4. Just as most of us don't need ads to tell us when to eat, most of us go to a doctor when we feel sick or something doesn't feel right—and that's the best way to get an appropriate prescription. Studies have shown that DTC ads prompt people to ask for medicines that are often inappropriate, and to keep customers happy, doctors all too often comply with the request.

We are seeing the over-medication of America because of the enormous profits that flow from direct-to-consumer advertising. I was nervous testifying before the committee—but I don't think that means I needed to take a pill, like the television ads keep pushing. In short, Americans were doing fine before DTC ads, and we will do fine without them. And remember, the proposal is simply to limit for a few years ads for drugs which have shown warning signs of trouble.

In cases where there may be a problem that is hard to talk about, or a new vaccine, such as the one for young women to help prevent cervical cancer, Public Service Announcements could be run. The PSAs could be cleared for objectivity and scientific validity by a group within the FDA or NIH and funded through an industry user fee system.

QUESTIONS OF SENATOR KENNEDY

Question 1. The IOM report discusses the need to encourage a culture of safety at FDA. Some commentators have argued that FDA needs better ways to recognize diverse scientific interpretations of data in its review panels, and to create a climate where scientific debate is encouraged. What actions need to be taken legislatively to bring about this cultural change?

Answer 1. I would like to offer two different ideas, either of which could be legislated and, I believe, would greatly increase the morale and culture of scientific vigor at the FDA.

Proposal #1: Recently Acting Commissioner Dr. von Eschenbach responded to a question by Senator Grassley about the need for an independent office of safety by describing, in detail, all the ways that the Office of Surveillance and Epidemiology (OSE) works with the Office of New Drugs (OND), and indicating it would be duplicative and wasteful to separate the two offices. But we believe that the FDA's mo-

rale and culture of scientific vigor could be improved by a variation of the separation of offices proposal, and avoid all the problems raised by Dr. von Eschenbach. Legislation could state:

• CDER consists of an OND and an OSE, and such other offices as the Commissioner may determine necessary.
• The Director of the OSE may, at any time, order a REMS process or an amendment to any REMS process (consistent with some timeframe for notice to the company, etc.), or order the suspension or withdrawal of a drug, and shall provide a written brief as to his/her reasons.
• If the Director of the OND disagrees, in whole or part, and provides a written brief as to his/her reasons within x days, the Commissioner shall decide the issue(s) within y days, and provide a written explanation for the decision.
• After the decision has been made, the briefs and final decision explanation shall be public documents.

Nothing else that the OSE does, which Dr. von Eschenbach defends in his letter to Senator Grassley as coordinating and working with OND, would change. This proposal would not disrupt anything. What it would do is make the Director of OSE more responsible for raising questions, and forcing an FDA-wide debate and decision within a tight timeframe. It would give him/her co-authority with OND to force a decision at the Commissioner level. Basically, it would focus more responsibility on three people, rather than the very diffuse Drug Safety Oversight Board.

Proposal #2: (See also our response to Senator Enzi question #1 relating to codification of current FDA regulations.)

• For every NDA (and other significant approval action) the FDA shall develop a memorandum (to be made public at the point of final decision) explaining the decision to approve, adjust, or reject an application, signed by the members of the team working on the NDA.
• The memorandum shall include a provision for additional views, in which any staff member may raise questions, and urge further studies and clarifications.
• It shall also include a provision for dissenting views in the case of any staff person who believes unresolved questions and issues outweigh potential benefits.
• In determining what level of REMS to establish, the Commissioner shall give "weight" to the additional and/or dissenting views.
• There would be Office of Scientific Integrity language (see response to Chairman Enzi's first question) to protect those who participate in additional or dissenting views.
• Title IV would be amended to provide that any advisory committee member can request the presence and participation of any FDA staffer who signed a NDA memorandum, either in the majority, additional views, or dissenting views. Any FDA staff that conceals relevant information from an Advisory Committee should be subject to discipline.

(In the meantime, we have seen press reports (*Inside Health Policy*, November 14, 2006, "HHS Seeks to do Away with Incentives, Protections for Scientists"), that in on-going labor negotiations between FDA management and union representatives, that the Administration is trying to weaken protections for workers who dissent. If these press reports are true, they take the agency in absolutely the wrong direction, and we urge you to contact the FDA as soon as possible in opposition to such a negotiating position.)

There has to be science for there to be scientific dissent, and the IOM report makes clear that the FDA needs to do more to promote and advance science. We urge you to do more to encourage original scientific work within the FDA. The IOM report makes many recommendations for increasing the level of science within the agency, both for the public good, and as a way to increase morale and build a more stable FDA workforce. In addition to resources for continuing medical education and participation in scientific conferences, more should be done to encourage scientific publication: pre-clearances and restrictions on publishing should be dropped (anyone intelligent enough to be published in a Journal is smart enough to know what is and is not the policy on proprietary information), and managers and staff should be measured by and rewarded for the quantity and quality of scientific publication that comes out of their Office and Center. We urge you to consider the language in H.R. 5922 which provides encouragement for scientific publication.

Question 2. Outcomes of studies that are negative or that suggest toxicity in patients are often not published. The legislation I introduced with Senator Enzi requires publishing clinical trial results, both positive and negative, in a public database. What impact do you think this would have for patients, healthcare providers, and the research community?

Answer 2. This is a very important provision that will truly save lives, reduce illness, and speed the rate of scientific research and knowledge through the world medical community. It is one of the key improvements in S. 3807.

We hope it can be strengthened even more by covering all Phase 2 results. We hope that you will ask the GAO, or some other appropriate body, to report on whether some or all Phase 1 results should be made public at the time the drug involved is either approved or withdrawn from development. People should not be treated as guinea pigs and then have the scientific knowledge gained from their participation in sometimes dangerous trials hidden from the world scientific community.

We urge that the bill also provide for the quicker publication of results (especially negative results showing dangers). Finally, we think this data is so important, we hope that you will phase in the publication in the database of the last 10 years of trial results.

QUESTIONS OF SENATOR MURRAY

Question 1. One of my goals for FDA has always been trying to find the right balance between getting new drugs to patients without delay while ensuring safety and effectiveness. I know it's a tough balance and we always have to be concerned about unintended consequences for any actions we take legislatively. I also think we need to be concerned about making sure that patients get good information—not conflicting information or even information that simply focuses on risks and not benefits. We have to be sure not to scare patients away from potentially beneficial treatments. There are risks with any drug or device, and we could raise safety flags on any new treatment, but this could also deter access. How can we achieve this balance and do you have concerns about the impact of the IOM recommendations or the Enzi/Kennedy bill as it relates to access?

Answer 1. I do not see any way that the IOM recommendations or the Enzi/Kennedy bill denies access.

I understand your concern that too much negative information may deter some from trying a drug. But in general, we always support the right of consumers to full information about products—whether it is the safety of cars or of prescription drugs. A consumer should have the right to decide whether a drug's possible side effects, even though unlikely, might not be worth the risk for the condition in question. Or, if the consumer has information identifying possible problems with one drug, it can help them ask whether there are other drugs in the class or in another class that can work without the risk.

The right of consumers to have full information is particularly important in this age where so much is spent on slick direct-to-consumer ads, and so many researchers, journals, and even physicians have become financially conflicted.

Question 2. As the IOM report noted, 21 percent of prescriptions in 2001 were for off-label uses, meaning of course that these uses were never reviewed or approved by FDA. Many patients often are not even aware of off-label use. However, as Diane Thompson pointed out, off-label use is extremely important for pediatric patients as well as patients with rare diseases. I agree that additional safety data is warranted for off-label use, but are you concerned about efforts to discourage off-label use? Once again is there a way we can encourage greater safety data on off-label use without jeopardizing access or impeding the practice of medicine?

Answer 2. We in no way want to discourage responsible off-label use. We are simply asking for the FDA to obtain studies on the most commonly prescribed off-label uses to ensure that the science supports the safe use of these drugs. Ideally, the studies will lead to label amendments so that the drugs are used "on-label" and the science of pharmaceuticals is expanded and improved. The requirement for studies is an obligation on the companies (or the FDA/NIH if their budgets permit) and not on the individual physician or pharmacist. The proposal does not in any way interfere with the doctor/patient relationship.

As you know, one recent medical journal article found that of the 21 percent prescribed off-label, in 73 percent of those cases there was no science to support such use. A little more science would be a good thing. Also, since the hearing, there are major new reports about the safety of drug-coated stents. These stents have been used extensively off-label on older, less healthy patients than the FDA approved. The result is a high level of heart incidents and deaths—and reminds us once again about the importance of applying more science before drugs or devices are used widely off-label.

Question 3. It has become very clear that we need a more uniform mechanism for collecting safety data. Currently the process for reporting adverse events is frag-

mented and there is little role for the patient. In fact, FDA does not even have a database of reported adverse events.

As an early champion, with Senator DeWine, of 1-800 Mr. Yuck, a national poison control center hotline that provides real time, accurate information to parents and providers in response to accidental poison exposure, I know how difficult it is to create a national database of real time information. But, we did succeed. We now have a national poison control database that can provide information to any caller across the country regarding accidental exposure to poisons. Using the data mined from this database we can also find information on increases in exposure to certain poisons and even local trends that could indicate widespread problems.

I think we need to consider a national reporting structure for adverse events associated to all medications. Many patients don't even know what an adverse event is and when a side effect may or may not be a concern. This kind of database could provide a great early warning system as well.

What steps can we take to improve the collection of adverse events and how can we be sure that patients are included in this process?

Answer 3. This is an exciting proposal. I believe that within a few years, there will be widespread use of electronic Personal Health Records (PHR), and we hope that there are strong patient privacy and security built-in. We urge you to include a new section in the bill which will establish a system that enables a patient (with their consent) who gets a prescription (especially a new molecular entity or other new, breakthrough drug) to be queried electronically at, say, 2 weeks, 1 month, 2 months, and at some later dates. The query would ask for any adverse events and any major medical events in the patient's life, etc., with responses collected in certain electronic fields. The electronic response would go to a secure FDA database in a format that would allow systematic analysis and the search for short- and long-term problems.

Such a system would be an enormous improvement over today's systems which we estimate collect only 1 to 10 percent of all ADRs, and which often miss major problems that are buried in the "background noise" of the medical incidents of an aging society.

QUESTIONS OF SENATOR CLINTON

Question 1. In your written testimony, you talk about the need for legislation that would establish a path for the approval of biogeneric drugs. Could you elaborate on the ways in which increasing access to biogenerics could improve access to safe and appropriate treatments for patients?

Answer 1. Biologics hold much promise for the future, but come with awesome price tags. Without generics available at the end of the biologics patent/exclusivity life, there will be little or no price competition, and some consumers might never be able to afford such medicines.

We know that the development of safe biogenerics will not be easy, and it will take time. We hope you will start the process of developing a biogeneric pathway in this bill, so that there is hope for financial relief in the future.

Question 2. Consumers Union has been a strong advocate of comparative effectiveness studies, which allow us to determine the benefits of a range of treatments for a certain disease and ensure that providers and patients are making treatment choices that are evidence-based, and not unduly influenced by direct-to-consumer advertising or other marketing efforts.

These comparative effectiveness studies complement the drug approval work of the FDA. The agency's approval process focuses largely on ensuring that the drugs that come to market are safe for consumers. But newer drugs are not always better drugs, and may not be the clinically appropriate choice for all patients with a given condition.

Comparative effectiveness studies are not a substitute for thorough and unbiased safety reviews at the FDA. But the studies completed so far highlight the shortcomings that we have faced at the agency and the need for reforms in our drug safety system.

One of the first studies to be carried out under the comparative effectiveness studies provision of the Medicare Modernization Act was a systematic review of COX−2 drugs, the class of drugs that includes Vioxx.

The results of this study, which were released in September, found no difference in the effectiveness of COX−2 painkillers compared with over-the-counter pain relieving drugs.

How can comparative effectiveness studies help us to weigh the risks and benefits of the drugs used by consumers?

Answer 2. We believe one of the long-term hopes for slowing the unsustainable inflation in American healthcare is through comparative effectiveness research and trials—not just of pharmaceuticals, but of medical processes, devices, surgeries, etc. We deeply appreciate your leadership in the passage of Section 1013 of the Medicare Modernization Act, which establishes a program of comparative effectiveness research within the Agency for Healthcare Research and Quality.

The example you provided on COX−2 Inhibitors is an excellent example of the usefulness of comparative effectiveness studies. Another example that emerged within weeks of the hearing where I testified was the report showing that the expensive new generation of anti-psychotic drugs offers little or no advantage over the older drugs in this field. For newly diagnosed patients or patients having trouble with one of the new generation anti-psychotics, this comparative effectiveness analysis shows that other, much lower cost medicines are available that may be equally helpful. A third example was illustrated on December 6, 2006, at a hearing before the Ways and Means Committee, which identified serious danger to the Nation's hundreds of thousands of end stage renal disease patients, and hundreds of millions of dollars in excessive payments for a drug used in kidney dialysis. There had been warnings for years about the over-use of this drug, but no research had been undertaken until very lately to determine whether the warnings were valid, despite the lives at stake and the enormous cost of the drug.

For Americans to receive the safest, most effective, and in the long run lowest cost medicines (because they work safely), we need to greatly increase the funding of section 1013 and use the Medicare Part A, B, and D databases to link various drug and treatment options with actual successful outcomes. We hope that you will include resources (if necessary, through user fees) in S. 3807 to fund an aggressive FDA use of the huge new patient de-identified databases now available to us. In addition to increased appropriations for section 1013, we hope Congress will explore through hearings other ways to provide greatly expanded, reliable sources of funding comparative effectiveness trials. For example, such funding could be through a very small medical drugs and devices profit surtax or "user free" at the company level, or a penny fee per prescription and device at the customer level. Even at the level of a penny per prescription, millions would be raised for section 1013 research which could quickly save billions of dollars in future healthcare costs.

RESPONSE TO QUESTIONS OF SENATORS ENZI, KENNEDY, AND MURRAY BY GREG SIMON

Thank you for the opportunity to answer questions based on my testimony before the HELP Committee on November 16.

QUESTIONS OF SENATOR ENZI

Question 1. How can we design and enforce post-approval studies that would be early indicators of safety issues to enable earlier approval of treatments with proven benefits?

Answer 1. The actual design of a safety study is intricately tied to the nature of the therapy, the intended use, foreseeable off-label uses and sectors of the population expected to use the drug or device. The FDA needs access to more reviewers and experts who can give careful thought to these issues during the pre-approval NDA submissions so that in the case FDA approves a product, thoughtful post-approval studies are designed based on the most up to date, available science.

The FDA's authority to enforce post-approval studies needs to be strengthened and its budget increased to permit improved continuous safety monitoring and enable the FDA to balance its obligation to bring new therapies to the public and to monitor adverse effects that are inevitable for any therapy in some segment of the population.

As stated in our testimony,

- 1. The FDA needs to be able to assess a drug's impact post-approval, weigh both benefits and risks and take appropriate action to protect the public;
- 2. To do that the FDA needs much stronger authority to regulate and enforce how an approved drug enters the market, how it is advertised, what claims are made for it and how labels are updated to reflect growing knowledge of a product;
- 3. To do those things the FDA needs increased appropriations from Congress and should not be forced to rely on industry user fees which the FDA is largely restricted from using on post-approval activities.

Question 2. Can you comment on the balance between increasing transparency and commercially sensitive information in the context of clinical trial results disclosure?

Answer 2. It is well established that commercial speech is less protected under the Constitution than is non-commercial speech. When there is a conflict between the public's right to know what happened in a clinical trial affecting human health and safety and a company's interest in protecting commercial interests, the public should win every time barring extraordinary circumstances. *FasterCures* as an organization advocates for positions that save lives by saving time. We believe that it is very important to consider and protect patients' interests at each step of the process of scientific discovery.

We believe that patients should be armed with information that will help them and their health providers make good treatment decisions for the individual. Part of this is making available meaningful information during and after the clinical trial process.

We believe that disclosure of both positive and negative outcomes is vital to the progress of medical research and to patient safety. While there is a case to be made to disclose all clinical trials data starting with Phase 1 trials, *FasterCures* supports the Enzi-Kennedy bill requirement of disclosure of aggregated clinical trial data starting with Phase 2 data. We want companies to be able to compete adequately in the market place of ideas and to retain proprietary information that will motivate them to innovate and improve safety profiles of treatments, but we also want this information to inform treatment decisionmaking.

We believe one area of this debate that has not had enough thought and energy is finding policies that will help avoid exposing people to potential harms that have been shown to have no benefit or to unnecessarily repeating trials that worked and that need to move forward into therapies.

Question 3a. I noted in your testimony you expressed support for the creation of the Reagan-Udall (RU) Institute. Do you have any thoughts about the placement of the Institute and how to maximize its chances of it being successful and minimization of conflicts of interest?

Answer 3a. To keep FDA moving forward and preparing for the science of tomorrow, we must continue to invest in the infrastructure of regulatory science. The RU Institute should be located at the FDA and serve as the FDA's research arm to examine the FDA's extensive accumulated data of the history of drug development and to identify best practices and new promising approaches to therapy development.

Question 3b. Do you think the timeframes for FDA action proposed in S. 3807 are reasonable?

Answer 3b. *FasterCures* believes the timeframes are reasonable generally but that the committee should be flexible in this area and focus more on provisions to strengthen the FDA's authority and budget.

Question 4. Does our current system of approval and post-approval review take into account the very different perspectives people with life threatening diseases have about "risk," as compared to the concerns of the "well" population?

Answer 4. Finding a way to adequately balance risk tolerance and benefit for individual patients is very challenging. Each person assesses benefit differently based on his or her life experience. We believe the agency should redouble its effort to communicate its benefit and risk determinations in the approval process. *FasterCures* believes patients should have access to new and innovative medicines even when they have known risks. The challenge is to inform these patients and their healthcare providers properly so that they have a clear understanding of a product's benefit and risk profile and can make good decisions for that individual patient.

FasterCures believes that properly addressing post-approval safety issues should allow the FDA to move more expeditiously to approve therapies for terminal illnesses and conditions, knowing that the chance of a benefit can outweigh the known threats from the disease or condition.

We believe properly addressing post-approval safety issues will help agency reviewers avoid being overly cautious in the pre-approval stage out of fear that they have few good options to monitor or affect use of the product post-approval.

QUESTION OF SENATOR KENNEDY

Question. Outcomes of studies that are negative or that suggest toxicity in patients are often not published. The legislation I introduced with Senator Enzi requires publishing clinical trial results, both positive and negative, in a public database. What impact do you think this would have for patients, healthcare providers, and the research community?

Answer. At *FasterCures*, we often talk about the need for a *Journal of Failure*. We believe a public database to capture the results of both positive and negative clinical trials is vital to pursuing cures. Although this will mean culture change in the research community, it is the most efficient antidote to the lack of awareness that can exist when information is not available about who has done what and what has and has not worked.

QUESTIONS OF SENATOR MURRAY

Question 1. One of my goals for FDA has always been trying to find the right balance between getting new drugs to patients without delay while ensuring safety and effectiveness. I know it's a tough balance and we always have to be concerned about unintended consequences for any actions we take legislatively. I also think we need to be concerned about making sure that patients get good information—not conflicting information or even information that simply focuses on risks and not benefits. We have to be sure not to scare patients away from potentially beneficial treatments. There are risks with any drug or device, and we could raise safety flags on any new treatment, but this could also deter access. How can we achieve this balance and do you have concerns about the impact of the IOM recommendations or the Enzi/Kennedy bill as it relates to access?

Answer 1. Both the Institute of Medicine (IOM) report and S. 3807 will improve access by focusing resources on post-approval safety studies, thereby improving the FDA's ability to approve needed drugs knowing they are being well monitored for safety post-approval.

The IOM focus on better labels to communicate with the public is vital to increasing the public's understanding of the risks and benefits of new therapies.

Disclosure of clinical trial results is also critical to communicating to the public, the medical research community, and physicians the risks and benefits of new proposed therapies.

Question 2. As the IOM report noted, 21 percent of prescriptions in 2001 were for off-label uses, meaning of course that these uses were never reviewed or approved by FDA. Many patients often are not even aware of off-label use. However, as Diane Thompson pointed out, off-label use is extremely important for pediatric patients as well as patients with rare diseases. I agree that additional safety data is warranted for off-label use, but are you concerned about efforts to discourage off-label use? Once again is there a way we can encourage greater safety data on off-label use without jeopardizing access or impeding the practice of medicine?

Answer 2. At *FasterCures*, we believe that off-label use of medication remains an important option for health providers and their patients. Those patients with the most intractable and serious diseases that often have no identified cures need to be able to work with their healthcare providers to find the best treatment options. Thus, we are concerned with efforts to discourage off-label use.

With that said, we believe that medical professional societies should, and can, do more to ensure that doctors are aware of the latest, unbiased treatment options. Physicians should be encouraged to share voluntarily their knowledge and experience from off-label usage of a drug so that we learn how medications are succeeding and failing in various populations.

Question 3. It has become very clear that we need a more uniform mechanism for collecting safety data. Currently the process for reporting adverse events is fragmented and there is little role for the patient. In fact, FDA does not even have a database of reported adverse events.

As an early champion, with Senator DeWine, of 1-800 Mr. Yuk, a national poison control center hotline that provides real time, accurate information to parents and providers in response to accidental poison exposure, I know how difficult it is to create a national database of real time information. However, we did succeed. We now have a national poison control database that can provide information to any caller across the country regarding accidental exposure to poisons. Using the data mined from this database we can also find information on increases in exposure to certain poisons and even local trends that could indicate widespread problems.

I think we need to consider a national reporting structure for adverse events associated to all medications. Many patients don't even know what an adverse event is and when a side effect may or may not be a concern. This kind of database could provide a great early warning system as well.

What steps can we take to improve the collection of adverse events and how can we be sure that patients are included in this process?

Answer 3. *FasterCures* supports improving the adverse event reporting system from both the reporting side and the monitoring and evaluation side by dedicating significant financial and staff resources to overhauling the current system.

Currently the United States has a voluntary reporting system for health professionals. Constraints on physicians' time and a reluctance to seek out and report adverse events, have contributed to the system's lack of effectiveness.

We need to identify ways to make reporting more consistent so that better data is captured. We also need to invest in an electronic real-time system that allows computer analysis to spot trends and patterns that might elude a human reviewer. We believe an analysis of the pros and cons of the "yellow card" system in England need to be explored and examined.

Again, thank you for the opportunity to provide answers to these questions. Please contact Margaret Anderson at *manderson@fastercures.org* if you have questions before January 8th, as I will be out of the country. Thank you.

[Whereupon, at 11:53 a.m., the hearing was adjourned.]

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