

# FDA USER FEES: ADVANCING PUBLIC HEALTH

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HEARING  
OF THE  
COMMITTEE ON HEALTH, EDUCATION,  
LABOR, AND PENSIONS  
UNITED STATES SENATE  
ONE HUNDRED TWELFTH CONGRESS  
FIRST SESSION  
ON  
EXAMINING FOOD AND DRUG ADMINISTRATION (FDA) USER FEES,  
FOCUSING ON ADVANCING PUBLIC HEALTH

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JULY 28, 2011  
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# **FDA USER FEES: ADVANCING PUBLIC HEALTH**

**THURSDAY, JULY 28, 2011**

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

The committee met, pursuant to notice, at 9:50 a.m. in Room 430, Dirksen Senate Office Building, Hon. Tom Harkin, chairman of the committee, presiding.

Present: Senators Harkin, Mikulski, Murray, Hagan, Merkley, Franken, Bennet, Enzi, Alexander, Burr, Isakson, and Hatch.

## **OPENING STATEMENT OF SENATOR HARKIN**

The CHAIRMAN. The Committee on Health, Education, Labor, and Pensions will come to order. We've convened this hearing today to kick off the FDA user fee reauthorization process. We will discuss the history and purpose of the user fee agreements between the FDA and the industries it regulates, and we will learn more about the importance of user fees to ensuring that new medical products get to the American patients as quickly and safely as possible.

Since 1992, the Prescription Drug User Fee Agreement has paved the way for quicker and more thorough reviews of applications for prescription drug products. Ten years later, beginning in 2002, the Medical Device User Fee Agreement has similarly facilitated getting medical devices onto the market. Currently, the drug and device user fees collectively make up 34 percent of FDA's overall budget. They are a significant source of the funds that FDA needs to get its job done.

Both the Prescription Drug User Fee Agreement and the Medical Device User Fee Agreement expire at the end of the next fiscal year. Failing to reauthorize them would have significant consequences for FDA, which would have to let staff go and substantially slow its approval process; and even more importantly, failing to pass the reauthorization legislation would have devastating consequences for the patients, whose health and lives depend on new medical treatments. We can't let that happen. For the health of the agency, the medical products industry and, most importantly, the patients who rely on new medical technologies, we need to reauthorize the user fee agreements before they expire.

I know that this legislation is likely to attract attention from everyone here who is interested in policy related to the FDA. I have policy priorities of my own, including helping to ensure the integrity of our global pharmaceutical supply chain at a time when our drug products and their ingredients are increasingly being brought to the United States from around the world.

This fall, we hope and expect to convene hearings to explore some of these policy issues. Today, however, we begin the process with a focus on user fees themselves.

We welcome Dr. Peggy Hamburg, the Commissioner of the FDA, and look forward to her description of the history and importance of the user fee program, and explanation of the impact user fees have on FDA's ability to get medical products to American consumers.

We look forward to hearing Commissioner Hamburg's views on this important subject, and I look forward to working with my colleague and Ranking Member, Senator Enzi, to continue the tradition of bipartisan cooperation on these user fee efforts.

Now I'll yield to Senator Enzi.

#### STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman, and thank you for having this hearing.

The Prescription Drug and Medical Device User Fee programs have been a success, originally decreasing product review times, stabilizing funding for FDA's Drug and Medical Device Centers, and decreasing the burden on taxpayers. I do believe, however, that the FDA can do better. On the metric most important for patients, the total time to market, FDA's performance regarding medical devices has declined sharply. According to a study by Boston Consulting Group, by the California Health Care Institute, overall 510(k) review times have increased 43 percent, and PMA review times have increased by 75 percent over the past 4 years. These findings have been widely corroborated. Numerous studies have identified serious problems with the Device Center's performance.

The Device Center's performance is not a partisan issue. Democrats and Republicans, patient and consumer groups, industry, academics, and nonprofits alike have all raised serious concerns about the Device Center's performance. FDA itself has engaged in extensive self-scrutiny, and the Institute of Medicine is expected to report on several controversial problems tomorrow.

In this Congress, I look forward to working with Chairman Harkin to reauthorize these user fee agreements. We have a couple of challenges as we try to move this legislation. First is timing. We plan to front-load as much of the work as possible to conclude the HELP Committee markup by the spring of 2012. Second, the Federal debt is about \$14 trillion and rising, and FDA is close to a tipping point. In the past few years, Congress has imposed several challenging new mandates on the agency. The Government Accountability Office has put FDA on its high-risk list because the FDA is overwhelmed by its many diverse public health responsibilities. We need to be practical and strategic about what FDA can and cannot do.

I do want to salute Commissioner Hamburg for recognizing and starting to address these strategic challenges, and I'll have some questions for the record concerning the agency's recent reorganization.

And last, we have a firm deadline. If we don't authorize new user fee programs before the old one expires, FDA will need to lay off approximately 20 percent of the Device Center and 60 percent of

the Drug Center's full-time employees. This would create a severe personnel shortage and disrupt important public health programs.

Having said all that, I'm an optimist, and I believe all of us, Congress and the outside stakeholders alike, can work together to enact a good user fee bill. The last time we did it in the 110th Congress, we got a good bill through the Senate unanimously and on time because we all worked together. I believe the way to do that is something called the 80 percent rule. I've learned over the years that for just about any given problem, reasonable people can agree on 80 percent of the solution. If we go ahead and get that done, the American people are very happy.

The problem is that the process of finding common ground is hard, slow work, and not always very exciting. The 20 percent where people strongly disagree is much more dramatic. The media love to cover the 20 percent and make it the story, but my hope is that we'll focus on the areas of broad agreement.

This committee has had great success on FDA legislation when we work together. In 2007 the New England Journal of Medicine said we passed the biggest drug bill in 50 years. We also gave FDA new authority to regulate tobacco and create new biosimilar pathways, and just last year Chairman Harkin and I and the many other members of the HELP Committee worked hard to give FDA new food safety authorities. We're going to need this kind of bipartisan inclusion and cooperation to get this done, and I hope today's hearing kicks off a constructive discussion on these serious problems.

The CHAIRMAN. Thank you very much, Senator Enzi.

And now we'll turn to our only witness today, Commissioner Hamburg. I'd like to welcome Dr. Hamburg back again to this committee. Commissioner Hamburg has an impressive background as a doctor, an NIH scientist, and significant administrative experience in protecting and promoting the public health from her previous post at New York's Department of Health and Mental Hygiene, and here in Washington at the Department of Health and Human Services.

Commissioner Hamburg is expertly positioned to lead the agency and to protect the public health as we work to reauthorize the user fee agreements in this Congress.

Thank you very much, Commissioner, for being here today. Your statement, which I tried to get through last night, is a long and very involved statement and very good statement, and it will be made a part of the record in its entirety, and I'd ask you to proceed as you so desire. You can ignore the 5-minute thing there, and if you need to take 10 minutes, please go ahead and take whatever time. If you start going over 10, I might start getting a little nervous about that time, but please proceed as you so desire.

**STATEMENT OF MARGARET HAMBURG, M.D., COMMISSIONER,  
FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES, SILVER SPRING, MD**

Commissioner HAMBURG. Thank you, Mr. Chairman and members of the committee. I promise that I will be shorter than the length of my written testimony.

I'm very, very pleased to have the opportunity to be here and to testify about the Prescription Drug User Fee Act, the PDUFA, and the Medical Device User Fee Act, or MDUFA.

The enactment of PDUFA back in 1992 was prompted by concerns that patients in the United States were waiting longer than patients in other countries for critical therapies, sometimes with tragic consequences. Through user fees paid by the drug industry, PDUFA provided FDA with a source of stable, consistent funding to hire additional reviewers, upgrade IT systems, and strengthen programs.

At the same time, FDA committed to complete reviews in a predictable timeframe, to meet more often with industry, and to provide more guidance.

These changes revolutionized the drug approval process in the United States and enabled FDA to speed its reviews without compromising the agency's high standards for safety and effectiveness, and our commitment to promote and protect the health of the public.

The time required for FDA approval has been cut by 60 percent since the enactment of PDUFA, and the United States now leads the world in the first introduction of new active drug substances. And so far this year, with the assistance of PDUFA user fees, FDA has approved 21 new ground-breaking medicines, including treatments for hepatitis C, late-stage prostate cancer, and lupus. In fact, this is the same number of novel drugs approved in all of 2010, and we're only in July. So that is very positive news.

But despite this positive news, we face a severe productivity problem worldwide in drug development in which an ever-increasing research and development investment is producing fewer new drugs. And at the same time, the scientific opportunities have never been greater due to new biomedical discoveries. And, of course, this is a complex ecosystem. FDA represents one important player in addressing this challenge, but the proposed PDUFA enhancements discussed in my written testimony include new steps to incorporate scientific advances into regulations so that we can modernize and streamline our processes to the benefit of both patients and industry.

The enactment of MDUFA in 2002 was prompted by similar concerns about the speed of the FDA review process for devices. User fees paid by the device industry under MDUFA have helped FDA expand available expertise and staffing, modernize IT systems, and provide additional guidance to industry. While FDA is meeting the vast majority of its goals under MDUFA, we know that the overall time to a decision, FDA time plus the time the manufacturer spends responding to FDA questions, has increased, as Senator Enzi noted. FDA and industry share responsibility for that increase, and FDA has been instituting management changes to address our role.

As a result, for 2010, total time for lower-risk devices appears to have stabilized, and preliminary data suggest that total time for higher-risk devices is improving. We appreciate that AdvaMed is also working to address the part that poor-quality applications play in delaying approval by offering training for its companies regarding FDA standards.



Beyond review times alone, we recognize that significant concerns have been raised about how well the device review program is meeting its two goals, ensuring that medical devices are safe and effective, and fostering medical device innovation.

In response to these concerns, the agency conducted an assessment of the 510(k) review program. What we found was that insufficient predictability in our premarket review programs was contributing to inconsistent decisions and longer times to market. The causes included unnecessary or inconsistent data requirements, insufficient guidance for industry, insufficient interactions with industry, high reviewer and manager turnover, insufficient reviewer training, insufficient managerial oversight, and a rapidly growing workload.

After soliciting public comment on these reports, we announced this past January 25 specific actions that we will take in 2011 to improve the predictability, consistency, and transparency of our pre-market review programs and have since announced additional actions.

For example, we've committed to developing updated and new guidances to clarify FDA requirements, and several have been released in recent days and weeks. We're enhancing the interactive review process and streamlining the review program for low to moderate-risk novel medical devices, called the "*de novo*" process.

We have established a new Center Science Council to help ensure consistency in our scientific decisionmaking and are developing a network of experts to help us to resolve complex scientific issues.

We're instituting a certification program and a pilot experiential learning program to provide review staff with necessary training and real-world experiences.

These and other efforts signify our commitment to improving our pre-market review programs to ensure that patients have timely access to safe and effective devices and that the U.S. device industry remains innovative and strong.

PDUFA IV and MDUFA II expire on September 30, 2012, and we're eager to work with you to achieve their timely reauthorization. These are critical programs and make possible the resources and tools that are so vitally needed if we are to provide the American people with the medical products they need and the safety and effectiveness they count on.

Thank you for your contributions to the continued success of PDUFA and MDUFA and to the mission of the Food and Drug Administration.

And I'm now happy to answer any questions that you may have.  
[The prepared statement of Commissioner Hamburg follows:]

PREPARED STATEMENT OF MARGARET A. HAMBURG, M.D.

#### INTRODUCTION

Mr. Chairman and members of the committee, I am Dr. Margaret Hamburg, Commissioner of Food and Drugs at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA), also referred to as "PDUFA V," and the third reauthorization of the Medical Device User Fee Act (MDUFA), also referred to as "MDUFA III." I will also talk about FDA's efforts to promote the science and innovation necessary to ensure that we are fully equipped to address the public

health issues of the 21st century and to address the continuing challenges of a global marketplace.

#### *Background on PDUFA*

FDA considers the timely review of the safety and effectiveness of New Drug Applications (NDAs) and Biologics License Applications (BLAs) to be central to the Agency's mission to protect and promote the public health. Prior to enactment of PDUFA in 1992, FDA's review process was understaffed, unpredictable, and slow. FDA lacked sufficient staff to perform timely reviews, or develop procedures and standards to make the process more rigorous, consistent and predictable. Access to new medicines for U.S. patients lagged behind other countries. As a result of concerns expressed by both industry and patients, Congress enacted PDUFA, which provided the added funds, through user fees, that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. At the same time, FDA committed to complete reviews in a predictable timeframe. These changes revolutionized the drug approval process in the United States and enabled FDA to speed the application review process for new drugs without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs prior to approval.

Three fees are collected under PDUFA: application fees, establishment fees, and product fees. An application fee must be submitted when certain NDAs or BLAs are submitted. Product and establishment fees are due annually. The total revenue amounts derived from each of the categories—application fees, establishment fees, and product fees—are set by the statute for each fiscal year. PDUFA permits waivers under certain circumstances, including a waiver of the application fee for small businesses.

Of the total \$931,845,581 obligated in support of the process for the review of human drug applications in fiscal year 2010, PDUFA fees funded 62 percent, with the remainder funded through appropriations.

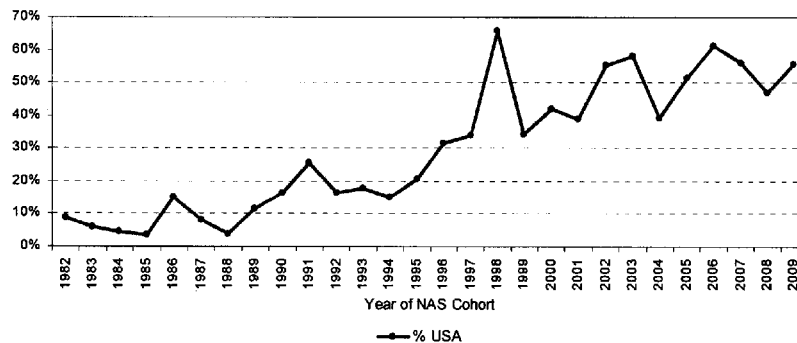
#### *PDUFA Achievements*

PDUFA has produced significant benefits for public health, providing patients faster access to over 1,500 new drugs and biologics, since enactment in 1992, including treatments for cancer, infectious diseases, neurological and psychiatric disorders, and cardiovascular diseases. Importantly, PDUFA has led to the reversal of the "drug lag" that prompted its creation. According to a study published in *Health Affairs* in June 2011, of the 35 cancer drugs approved over the last 7 years in either the United States or Europe, FDA approved 32, in an average time of 261 days. The European Medicines Agency (EMA) approved only 26 in an average time of 373 days. All 23 cancer drugs approved by both agencies during this period were marketed first in the United States.

As shown in Figure 1, the United States now leads the world in the first introduction of new active drug substances. According to researchers at the Tufts Center for the Study of Drug Development, the time required for the FDA approval phase of new drug development (i.e. time from submission until approval) has been cut by 60 percent since the enactment of PDUFA,<sup>1</sup> from an average of 2.0 years for the approval phase at the start of PDUFA to an average of 1.1 years today. So far this year, FDA has approved 21 new, groundbreaking medicines, including treatments for hepatitis C, late-stage prostate cancer, and lupus. This is the same number of novel drugs approved in *all* of 2010.

<sup>1</sup>Milne, Christopher-Paul (2010). *PDUFA and the Mission to Both Protect and Promote Public Health* [PowerPoint slides]. Presentation at the FDA PDUFA Public Meeting, Rockville, MD.

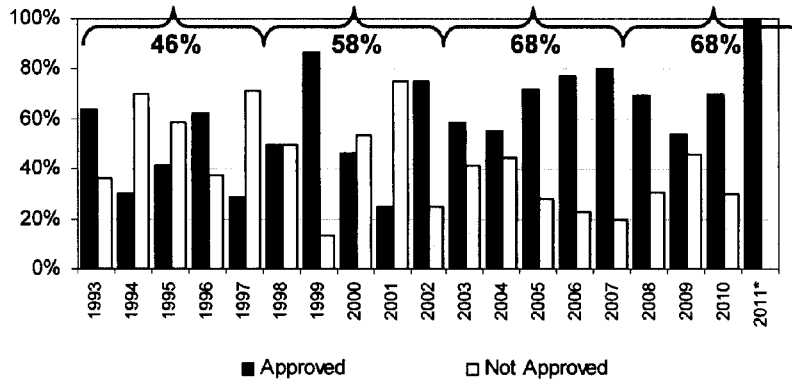
**Figure 1. US Share of New Active Substances (NAS) First Launched on the World Market**



Increased resources provided by user fees have enabled FDA to provide a large body of technical guidance to industry that clarified the drug development pathway for many diseases and meet with companies during drug development to provide critical advice on specific development programs. In the past 5 years alone, FDA has held over 7,000 meetings within a short time after a sponsor's request. Innovations in drug development are being advanced by many new companies as well as more established ones, and new sponsors may need, and often seek, more regulatory guidance during development. In fiscal year 2009, more than half of the meetings FDA held with companies at the early investigational stage and midway through the clinical trial process were with companies that had no approved product on the U.S. market.

PDUFA provides FDA with a source of stable, consistent funding that has made possible our efforts to focus on promoting innovative therapies and help bring to market critical products for patients. FDA aims to review priority new molecular entities (NME) more quickly—6 months vs. 10 months for standard drugs. Priority NMEs represent the truly innovative medicines generally targeted at severe illnesses with few or no available therapeutic options. FDA reviewers give these drugs priority attention throughout development, working with sponsors to determine the most efficient way to collect the data needed to provide evidence of safety and effectiveness.

Improvements in the efficiency of the drug review process and the quality of new drug applications is evident in the trends toward greater first-cycle approvals for priority NMEs. A first-cycle approval means that the product application is approved after the initial, complete FDA review, rather than entering another cycle of FDA questions. Importantly, first-cycle approvals bring innovative drugs with new benefits to patients sooner. When FDA is presented with high-quality applications that are based on strong science, we can approve these products quickly and efficiently. The average first-cycle approval rate for priority NMEs increased from 46 percent in PDUFA I to 68 percent to date in PDUFA IV, as shown in Figure 2. And I am pleased to report that we are on track for approving a historically high percentage of priority NMEs for 2011. First-cycle approval rates have also increased for standard NMEs from an average of 30 percent in PDUFA I to 38 percent to date in PDUFA IV.

**Figure 2. Priority NME First-Cycle Approval Actions**

\*CDER data as of 7/1/11.

It should be noted that FDA assesses the benefit-risk of new drugs on a case-by-case basis, considering the degree of unmet medical need and the severity and morbidity of the condition the drug is intended to treat. This approach has been critical to increasing patient access to new drugs for cancer and rare and other serious diseases, where existing therapies have been few and limited in their effectiveness. Some of these products have serious side effects but they were approved because the benefit outweighed the risk. For example, in March of this year, FDA approved Yervoy (ipilimumab) for the treatment of unresectable or metastatic melanoma. Yervoy also poses a risk of serious side effects, including severe to fatal autoimmune reactions, in 12.9 percent of patients treated with Yervoy. FDA decided that the benefits of Yervoy outweighed its risk, especially considering that no other melanoma treatment has been shown to prolong a patient's life.

PDUFA funds help support the use of existing mechanisms in place to expedite the approval of certain promising investigational drugs, and also to make them available to the very ill as early in the development process as possible, without unduly jeopardizing the patients' safety. One such program is accelerated approval. In 1992, FDA instituted the accelerated approval process, which allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need based on a surrogate endpoint that is reasonably likely to predict clinical benefit, but is not fully validated to do so. A surrogate endpoint is a marker—a laboratory measurement, or physical sign—that is used in clinical trials as an indirect or substitute measurement for a clinically meaningful outcome, such as survival or symptom improvement. The use of a surrogate endpoint can considerably shorten the time to approval. Approval of a drug based on an unvalidated surrogate endpoint is given on the condition that post-marketing clinical trials verify the anticipated clinical benefit. Over 60 critical products have been approved under accelerated approval since the program was established.

While the best means of providing access to useful medical treatments for all Americans is to approve drugs proven to be safe and effective, FDA also recognizes circumstances in which there is public health value in making products available prior to marketing approval. A promising but not yet fully evaluated treatment may sometimes represent the best choice for individuals with serious or life-threatening diseases who lack a satisfactory therapy.

FDA allows for access to investigational products through multiple mechanisms. Clinical trials are the best mechanism for a patient to receive an investigational drug, because they provide a range of patient protections and benefits and they maximize the gathering of useful information about the product, which benefits the entire patient population. However, there are times when an individual cannot enroll in a clinical trial. In these cases, the patient may gain access to an investigational therapy through one of the alternative mechanisms, and FDA's Office of Special Health Issues assists patients and their doctors in this endeavor.

### *Drug Safety Activities*

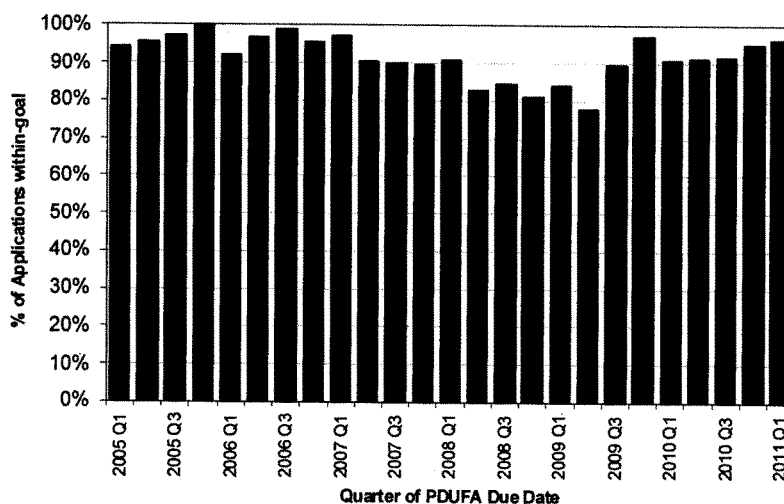
In parallel with improvements in the drug review process, FDA has increased its focus on safety, including implementing the Food and Drug Administration Amendments Act of 2007 (FDAAA). In FDAAA, Congress authorized additional user fees totaling \$225 million for the 5 years of PDUFA IV reauthorization to enhance drug safety activities. FDAAA also provided FDA with important post-market safety authorities. Under FDAAA, FDA was given the ability to require post-marketing studies and clinical trials to address important drug safety questions. Between the enactment of FDAAA on September 27, 2007, and June 1, 2011, FDA has required sponsors to conduct approximately 375 post-marketing studies or trials to address important drug safety questions that could not be addressed before the drug was approved. FDAAA also gave FDA the authority to require safety labeling changes based on new safety information identified after a drug is on the market. FDA has used its new authority to require sponsors to place important new safety information onto their drug labels quickly, in some cases using this authority to require changes to the labeling of all members of a class of drugs. FDAAA also provided FDA with authority to manage risks associated with marketed drug products through required Risk Evaluation and Mitigation Strategies (REMS). FDA has been using this new authority judiciously to ensure that drugs that could not otherwise be approved because the risks without a REMS would outweigh the benefits, are available to patients.

### *Challenges for the Current Drug Program*

Although we can report many important successes with the current program, new challenges have also emerged that offer an opportunity for further enhancement. While new FDAAA process requirements have strengthened drug safety, they have put strains on FDA's ability to meet pre-market review performance goals and address post-market review activities. In addition, there has been a significant increase in the number of foreign sites included in clinical trials to test drug safety and effectiveness, and an increase in the number of foreign facilities used in manufacturing new drugs for the U.S. market. While foreign sites can play an important role in enabling access to new drugs, the need to travel much farther to conduct pre-approval inspections for clinical trials and manufacturing sites overseas has created additional challenges for completion of FDA's review within the existing PDUFA review performance goals, while at the same time trying to communicate with sponsors to see if identified issues can be resolved before the review performance goal date.

Despite these challenges, FDA has maintained strong performance in meeting the PDUFA application review goals, with the exception of a dip in fiscal year 2008–9, when staff resources were shifted to ensure timely implementation of all the new FDAAA provisions that affected activities in the new drug review process. This is shown in Figure 3.

**Figure 3 CDER PDUFA Application Review Performance  
(NDAs, BLAs, Efficacy Supplements) 2005 - 2011**



However, FDA wants to meet not only the letter (i.e., PDUFA goal dates), but also the spirit of the PDUFA program—speeding patient access to drugs shown to be safe and effective for the indicated uses.

Although the NDA/BLA approval phase of drug development (the phase in which FDA plays the biggest role) is reported to have the highest success rate of any phase of drug development, it is critical to our public health mission that we work with industry and other stakeholders to take steps to reduce uncertainty and increase the success of all phases of drug development. We must leverage advances in science and technology to make sure that we have the knowledge and tools we need to rapidly and meaningfully evaluate medical products. The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products—known as “regulatory science”—is not exclusively about helping drug development to speed it along before it gets to FDA for review and approval. It also gives us the scientific tools to modernize and streamline our regulatory process. With so much at stake for public health, FDA has made advances in regulatory science a top priority. The Agency is both supporting mission-critical science at FDA and exploring a range of new partnerships with the National Institutes of Health and academic institutions to develop the science needed to maximize advances in biomedical research and bring the development and assessment of promising new therapies and devices into the 21st century. With this effort, FDA is poised to support a wave of innovation to transform medicine and save lives.

For example, FDA is working to improve the science behind certain clinical trial designs. Recent advances in two clinical trial designs—called non-inferiority and adaptive designs—have required FDA to conduct more complex reviews of clinical trial protocols and new marketing applications. Improving the scientific bases of these trial designs should add efficiency to the drug review process, encourage the development of novel products, and speed new therapies to patients.

FDA has also taken steps to facilitate the development and approval of safe and effective drugs for Americans with rare diseases. Therapies for rare diseases—those affecting fewer than 200,000 people in the United States—represent the most rapidly expanding area of drug development. Although each disease affects a relatively small population, collectively, rare diseases affect about 25 million Americans. Approximately one-third of the NMEs and new biological products approved in the last 5 years have been drugs for rare diseases. Because of the small numbers of patients who suffer from each disease, FDA often allows non-traditional approaches to establishing safety and effectiveness. For example, FDA recently approved Carbaglu (carglumic acid) for the treatment of N-acetylglutamate synthase (NAGS) deficiency,

a rare disorder of the urea cycle, caused by a genetic deficiency or absence of the NAGS enzyme that results in severe elevations in plasma ammonia levels and can rapidly result in injury to the brain or death. There have only been approximately 50 known cases reported in the literature worldwide to date. The disease can be diagnosed throughout life, but in infants, the disease can be rapidly fatal due to severe hyperammonemia that can result in cerebral edema, seizures, and death. FDA approved this drug in March 2010, based on the results of a single, non-concurrently controlled, retrospective review of the clinical course of 23 patients with NAGS deficiency treated with Carbaglu over a 21-year period.

#### BACKGROUND ON MDUFA

Similar to the PDUFA program, the enactment of the Medical Device User Fee and Modernization Act in 2002 (MDUFMA I) was prompted by growing concerns about the medical device review program's capacity and performance. MDUFMA I and the Medical Device User Fee Act of 2007 (MDUFA II) authorized user fees for the review of medical device pre-market applications, reports, supplements, and pre-market notification submissions. These additional resources enabled FDA to make its reviews more timely, predictable, and transparent to applicants. MDUFA fees and mandated appropriations for the medical device program helped FDA expand available expertise, modernize its information management systems, provide new review options, and provide more guidance to prospective applicants.

MDUFA authorizes FDA to collect user fees for certain medical device applications, the registration of certain medical device establishments, and certain other purposes. Small businesses may qualify for a waiver or a reduced fee on certain submissions to FDA.

Of the total \$292,707,540 obligated in support of the process for the review of medical device submissions in fiscal year 2010, MDUFA fees currently fund about 20 percent. The remainder of the funding is through appropriations.

#### MDUFA ACHIEVEMENTS

FDA has consistently met or exceeded goals agreed to by FDA and industry under MDUFA II for approximately 95 percent of the submissions we review each year. FDA consistently completes at least 90 percent of pre-market notification, or 510(k), reviews within 90 days or less, which meets the applicable goal. In the limited areas where FDA is not yet meeting its MDUFA II goals, the Agency's performance has been steadily improving, despite growing device complexity and an increased workload, and without a commensurate increase in user fees. And FDA is committed to continued improvements in the device approval process to address legitimate concerns raised by industry and other stakeholders, which I will discuss later in this testimony.

MDUFA II metrics reflect FDA time only; they do not reflect the time taken by industry to respond to requests from FDA for additional information. As Figure 4 and 5 illustrate, while the time FDA spends reviewing an application has improved for both low- and high-risk devices, overall time to decision—the time that FDA has the application, plus the time the manufacturer spends answering any questions FDA may have—has increased. FDA and industry share responsibility for the increase in overall time to final decision, and FDA has been instituting management changes to address this. As a result, in 2010, total time for 510(k)s appears to have stabilized and preliminary data suggest that the total time for pre-market approval (PMA) decisions is improving.

Figure 4.

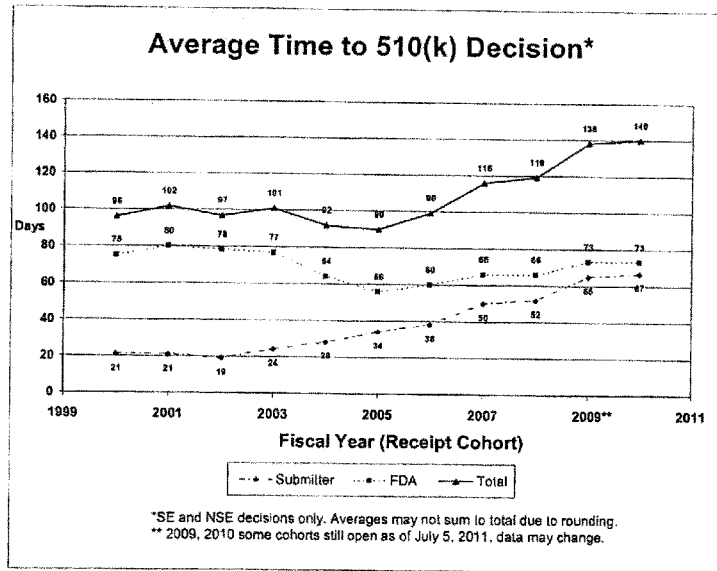
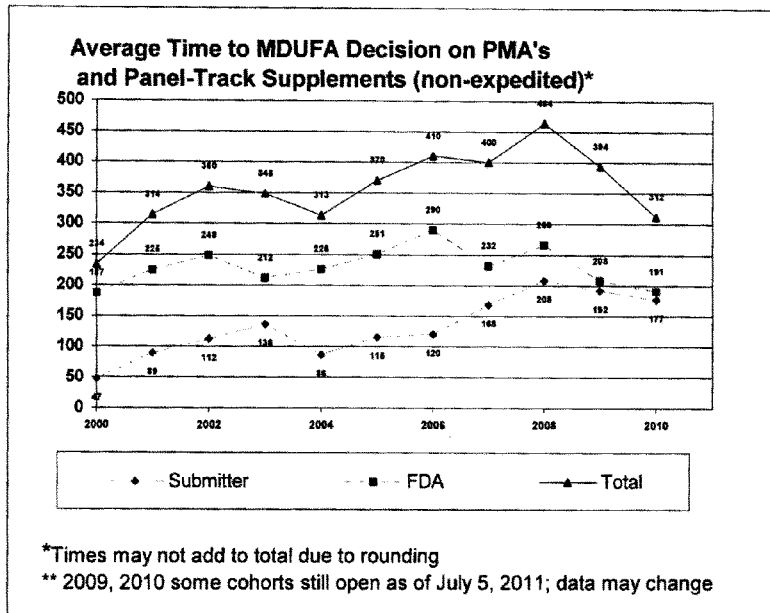




Figure 5.

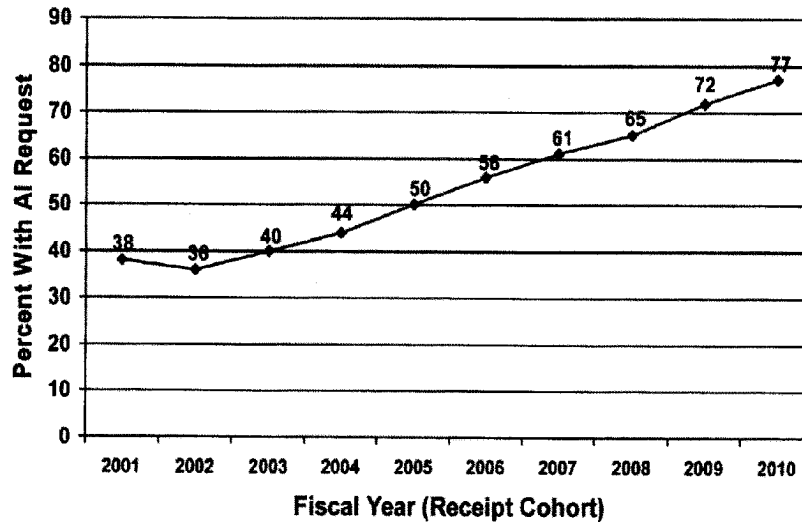


FDA is committed to working on ways to streamline the regulatory review process. Success will require that we continue to focus on our own internal process, but industry also bears responsibility for the increase in overall time to a decision. Poor-quality submissions that need to be addressed are significant contributors to delays in pre-market reviews. These include submissions that do not adhere to current guidance documents and existing standards that contain inadequate clinical data (e.g., missing data, or data that fail to meet endpoints), or that deviate from the study protocol agreed upon.

Figure 6 shows the steep and prolonged increase, since fiscal year 2002, in the percentage of 510(k) submissions requiring an Additional Information (AI) letter after the first review cycle. The increasing number of AI letters has contributed to the increasing total time from submission to decision. Over 80 percent of AI letters were sent because of problems with the quality of the submission. These submission quality problems waste FDA and sponsor time and resources and divert FDA resources from pending, higher-quality applications.

Figure 6.

**Percent of 510(k) Submissions with an AI Letter  
in First Review Cycle per Year**



We are pleased that, in response to FDA calls for improving the quality of pre-market submissions, AdvaMed has made available training courses for its companies to help them develop 510(k) and PMA submissions that meet FDA standards.

*Medical Device Safety*

The Food and Drug Administration Amendments Act of 2007 (FDAAA) authorized appropriations of \$39,231,982 in MDUFA user fees for fiscal year 2008–fiscal year 2012 for the collecting, developing, reviewing, and evaluating of post-market safety information on medical devices. This includes activities such as the Post-Approval Studies Program (Program) at the Agency’s Center for Devices and Radiological Health (CDRH), which encompasses the design, tracking, oversight, and review of studies mandated as a condition of approval of pre-market applications. This Program guides industry in the design of scientifically sound and feasible post-market studies that address relevant safety questions and ultimately provide valuable data for ongoing device evaluations. CDRH has also established a Center Electronic Submissions (CeSub) system that provides for electronic submission of adverse event reports and an efficient method for staff to perform analyses that bridge pre-market and post-market device safety data in support of the device review process. In addition, CDRH scientific investigations provide in-depth analyses of the underlying causes of post-market device safety issues, which increase reviewer understanding of issues that occur in marketed products. Findings from these scientific investigations are provided to industry to facilitate the redesign of existing devices and guide device development along paths that allow for the most efficient determination of device safety and effectiveness.

*Challenges for the Medical Device Program*

FDA recognizes that concerns have been raised about how well CDRH’s pre-market review program is meeting its two goals of ensuring that medical devices are safe and effective and fostering medical device innovation. Some stakeholders—particularly in industry—have argued that a lack of predictability, consistency, and transparency in the 510(k) program is stifling medical device innovation in the

United States and driving companies (and jobs) overseas. Other groups, including health care professional, patient, and third-party payer organizations, have argued that the 510(k) program allows devices to enter the market without sufficient evidence of safety and effectiveness, thereby putting patients at unnecessary risk and failing to provide practitioners with the necessary information to make well-informed treatment and diagnostic decisions.

In response to these concerns—and because FDA is continually looking for ways to improve its performance in helping to bring safe and effective devices to market—the Agency conducted an assessment of the 510(k) review program and an assessment of how it uses science in regulatory decisionmaking, which addressed aspects of its other pre-market review programs.

The two reports we released publicly in August 2010, with our analyses and recommendations, showed that we have not done as good a job managing our pre-market review programs as we should and that we needed to take several critical actions to improve the predictability, consistency, and transparency of these programs.

For example, we have new reviewers who need better training. We need to improve management oversight and standard operating procedures. We need to provide greater clarity for our staff and for industry through guidance about key parts of our pre-market review and clinical trial programs and how we make benefit-risk determinations. We need to provide greater clarity for industry through guidance and expanded interactions about what we need from them to facilitate more efficient, predictable reviews. We need to make greater use of outside experts who understand cutting-edge technologies. And we need to find the means to handle the ever-increasing workload and reduce staff and manager turnover, which is almost double that of the FDA's drugs and biologics centers. We are making progress in these areas.

The Agency solicited public comment on the recommendations identified in the studies and received a range of perspectives from stakeholders throughout the process at two public meetings and three town hall meetings, through three open public dockets and via many meetings with stakeholders. FDA received seventy-six (76) comments from medical device companies, industry representatives, venture capitalists, health care professional organizations, third-party payers, patient and consumer advocacy groups, foreign regulatory bodies, and others.

After considering the public input, in January 2011 FDA announced 25 specific actions that the Agency will take this year to improve the predictability, consistency, and transparency of our pre-market review programs. Since then, FDA has announced additional efforts, including actions to improve its program for clinical trials and the Investigational Device Exemptions (IDE) program. These are based on an analysis of this program that the Agency committed to as part of its January 2011 announcement.

These actions, many of which were supported by industry, include:

- Developing a range of updated and new guidances to clarify CDRH requirements for timely and consistent product review, including device-specific guidance in several areas such as mobile applications (released in July 2011) and artificial pancreas systems (to be completed by the end of 2011), and draft guidance that clarifies the kinds of changes that trigger the need for a new submission (released July 27, 2011);
- Revamping the guidance development process through a new tracking system and core staff to oversee the timely drafting and clearance of documents (to be completed by the end of 2011);
- Improving communication between FDA and industry through enhancements to interactive review (some of these enhancements will be in place by the end of 2011);
- Streamlining the *de novo* review process, to provide a more efficient pathway to market for novel devices that are low to moderate risk. This new structure will be described in draft guidance for industry that is expected to be available for public comment by September 30, 2011;
- Streamlining the clinical trial and IDE processes by providing industry with specific guidance on how to improve the quality and performance of clinical trials. (IDEs are required before device testing in humans may begin, and they ensure that the rights and welfare of human subjects are protected while gathering data on the safety and efficacy of medical products.) We are also developing guidance to clarify the criteria for approving clinical trials, and criteria for when a first-in-human study can be conducted earlier during device development (to be issued by October 31, 2011);
- Establishment of an internal Center Science Council to actively monitor the quality and performance of the Center's scientific programs and ensure consistency and predictability in CDRH scientific decisionmaking (already completed);

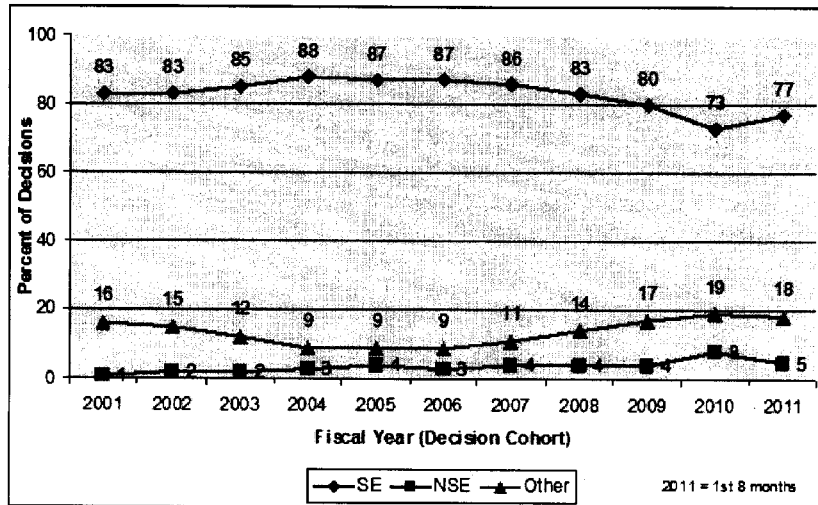
- Creating a network of experts to help the Center resolve complex scientific issues, which will ultimately result in more timely reviews. This network will be especially helpful as FDA confronts new technologies (expected in place by the end of 2011);
- Instituting a mandatory Reviewer Certification Program for new reviewers (to be completed by September 2011); and,
- Instituting a pilot Experiential Learning Program to provide review staff with real-world training experiences as they participate in visits to manufacturers, research and health care facilities, and academia (to begin in early 2012).

For manufacturers and FDA, “not substantially equivalent” (NSE) determinations often represent an inefficient use of time and resources. NSE determinations require significant Agency resources and time, yet fail to result in the marketing of a new product. The following chart shows a spike in the percentage of 510(k) decisions that were NSE in 2010. Among the reasons that 510(k) submissions result in NSE determinations are: lack of a suitable predicate device; intended use of the new device is not the same as the intended use of the predicate; technological characteristics are different from those of the predicate and raise new questions of safety and effectiveness; and/or performance data failed to demonstrate that the device is as safe and effective as the predicate. The vast majority of NSE decisions are due to the absence of adequate performance data, sometimes despite repeated FDA requests.

I’m pleased to report that, consistent with our many improvements to the 510(k) program, the recent increase in the NSE rate appears to be turning around. From a peak of 8 percent in 2010, the NSE rate has decreased to 5 percent through the first 8 months of 2011. Just as important, we also may be seeing a reversal in the trend of declining rate in Substantially Equivalent (SE) decisions that clear a 510(k) submission for marketing. After several years of declining percentages, reaching a low of 73 percent in 2010, we are seeing an increase of 4 percent through the first 8 months of 2011, as shown in Figure 7.

Figure 7.

**Percent of 510(k) Submissions with an NSE Decision per Year**



Facilitating medical device innovation is a top priority for FDA. As part of its 2010 and 2011 Strategic Plans, FDA’s medical device center has set goals to proactively facilitate innovation to address unmet public health needs. FDA’s Innovation Initiative seeks to accelerate the development and regulatory evaluation of innovative medical devices, strengthen the Nation’s research infrastructure for developing breakthrough technologies, and advance quality regulatory science. As part of this initiative, CDRH proposed additional actions to encourage innovation,

streamline regulatory and scientific device evaluation, and expedite the delivery of novel, important, safe and effective innovative medical devices to patients, including:

- Establishing the Innovation Pathway, a priority review program to expedite development, assessment, and review of important technologies;
- Advancing regulatory science through public-private partnerships;
- Facilitating the creation of a publicly available core curriculum for medical device development and testing to train the next generation of innovators; and
- Engaging in formal horizon scanning—the systematic monitoring of medical literature and scientific funding to predict where technology is heading, in order to prepare for and respond to transformative, innovative technologies and scientific breakthroughs.

A public docket has been set up to solicit public comment on the Innovation Initiative proposals, and a public meeting on the topic took place on March 15, 2011. In the near future, FDA will announce actions it plans to take under the Initiative.

#### *PDUFA/MDUFA Reauthorization*

With the reauthorization of PDUFA and MDUFA in 2007, Congress directed FDA to take additional steps to ensure that public stakeholders would have adequate opportunity to provide input to any program enhancements for PDUFA and MDUFA. In addition to receiving input from an initial public meeting, Congress directed the Agency to meet with public stakeholders every month while conducting negotiations with regulated industry, to hold discussions on their views on the reauthorization and hear their suggestions for changes to the PDUFA and MDUFA performance goals. After negotiations with regulated industry have concluded, PDUFA and MDUFA require that FDA present recommendations to congressional committees relating to reauthorization of those programs, publish such recommendations in the *Federal Register* for public comment, and hold a public meeting. Final PDUFA and MDUFA recommendations must be submitted to Congress no later than January 15, 2012. Below I will summarize the status of our PDUFA and MDUFA negotiations.

#### *PDUFA Negotiations*

Based on a public meeting held in April 2010, input from a public docket, and the Agency's own internal analyses of program challenge areas, FDA developed a set of potential proposed enhancements for PDUFA V. In July 2010, FDA began negotiations with industry and parallel discussions with public stakeholders. These discussions were concluded in May 2011, and the enhancements are under internal review.

We are very pleased to report that seven categories of enhancements for PDUFA V are under consideration. These enhancements address many of the top priorities identified by public stakeholders, the top concerns identified by industry, and the most important challenges identified within FDA. I will briefly summarize the enhancements under consideration.

- **Drug Review Process:** Increase the number of meetings between FDA and sponsors during FDA's review of NME NDAs and original BLAs, including pre-submission meetings, mid-cycle communications, and late-cycle meetings. To accommodate this increased interaction during regulatory review, FDA's review clock would begin after the 60-day administrative filing review period, rather than immediately upon filing. The impact of these modifications on the efficiency of drug review for this subset of applications would be assessed during PDUFA V.

- **Regulatory science:** Regulatory science is the science of developing and applying new tools, standards and approaches to assess the safety, effectiveness, quality and performance of FDA-regulated products. Under consideration for PDUFA V are:

- Promoting innovation by establishing a dedicated drug development communication and training staff. This staff will be responsible for identifying best practices for communication between the Agency and sponsors, training review staff, and disseminating best practices through published guidance.
- Developing a dedicated staff to evaluate best practices and limitations in meta-analysis methods. A meta-analysis typically attempts to combine the data or findings from multiple completed studies to explore drug benefits and risks and, in some cases, uncover what might be a potential safety signal in a pre-market or post-market context.
- Augmenting the Agency's clinical, clinical pharmacology, and statistical capacity to adequately address submissions that propose to utilize biomarkers or pharmacogenomic markers. Pharmacogenomics and the application of qualified biomarkers have the potential to decrease drug development time by

helping to demonstrate benefits, establish unmet medical needs, and identify patients who are pre-disposed to adverse events.

- Improving FDA's clinical and statistical capacity to address submissions involving patient-reported outcomes (PROs) and other endpoint assessment tools, including providing consultation during the early stages of drug development. PROs measure treatment benefit or risk in medical product clinical trials from the patients' points of view. They are critical in understanding the drug benefits and harm from the patients' perspectives.
- Facilitating rare disease drug development by issuing relevant guidance, increasing the Agency's outreach efforts to the rare disease patient community, and providing specialized training in rare disease drug development for sponsors and FDA staff.

- **Enhancing Benefit-Risk Assessment:** Part of FDA's decisionmaking lies in understanding the condition treated and the unmet medical need. Patients who live with a disease have a direct stake in the outcome of the drug review process. The FDA drug review process could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity and the potential gaps or limitations in available treatments in a therapeutic area. PDUFA V enhancements include expanded implementation of FDA's benefit-risk framework in the drug review process, including holding public workshops to discuss the application of frameworks for considering benefits and risks that are most appropriate for the regulatory setting. FDA will also conduct a series of public meetings between its review divisions and the relevant patient advocacy communities to review treatments available for specific indications or disease states.

- **Enhancement and Modernization of the FDA Drug Safety System:** Two post-market, safety-focused initiatives are being considered. First, PDUFA V enhancements would initiate a public process to standardize REMS with the goal of reducing burden on practitioners, patients, and others in the health care setting; additionally, FDA would conduct public workshops and develop guidance on methods for assessing the effectiveness of REMS and the impact on patient access and burden on the health care system. Second, FDA would use user fee funds to conduct a series of activities to determine the feasibility of using Sentinel, a long-term program designed to build and implement a national electronic system for monitoring the safety of FDA-approved medical products, to evaluate drug safety issues that may require regulatory action, e.g., labeling changes, post-marketing requirements, or post-marketing commitments. This may shorten the time it takes to better understand new or emerging drug safety issues, and may reduce the Agency's reliance on required post-marketing studies and clinical trials.

- **Required Electronic Submissions and Standardization of Electronic Application Data:** PDUFA V enhancements being considered include a phased-in requirement for standardized, fully electronic submissions for all marketing and investigational applications; this would facilitate a more timely and efficient rigorous review within PDUFA goal timeframes. The Agency would also conduct a public process to develop standardized terminology for clinical and nonclinical data submitted in marketing and investigational applications. Standardized data would translate into a more standardized approach to risk-benefit assessment and would be helpful in safety analyses that inform FDA decisions related to post-marketing requirements.

- **User Fee Increase for PDUFA V:** Implementing these PDUFA enhancements being considered would add \$40.4 million to the estimated PDUFA user fee revenue amount in fiscal year 2012. This translates to a modest 6 percent increase, and a total estimated base of \$712.8 million in fiscal year 2013.<sup>2</sup>

- **Modified Inflation Adjuster and Additional Evaluations of the Workload Adjuster:** PDUFA V enhancements being considered include a modification to the inflation adjuster to accurately account for changes in its costs related to payroll compensation and benefits as well as changes in non-payroll costs. FDA would continue evaluating the workload adjuster that was developed during the PDUFA IV negotiations to ensure that it continues to adequately capture changes in FDA's workload.

#### *PDUFA Negotiations*

In September 2010, prior to beginning negotiations with the regulated industry, FDA held a public meeting attended by a variety of stakeholders, including regulated industry, scientific and academic experts, health care professionals, and rep-

<sup>2</sup>The fiscal year 2012 estimated user fee amount is \$672.4 million. The exact amount will be determined when we have the final-year workload data for PDUFA IV. That number would be used to calculate the exact fee amounts for fiscal year 2013, the first year of PDUFA V.

representatives of patient and consumer advocacy groups. FDA heard stakeholders' views on medical device user fee reauthorization, including the public's assessment of the overall performance of the MDUFA program and opinions as to which aspects of the program should be retained, changed, or discontinued in order to further strengthen and improve the program.

Since January 2011, FDA has been holding discussions with regulated industry in an effort to develop a package of proposed recommendations for MDUFA reauthorization. Upon completion of these negotiations and discussions, FDA intends to develop a package of proposed recommendations for reauthorization of the MDUFA program. The public will have an opportunity to comment on these proposals prior to FDA's submission of MDUFA recommendations to Congress in January 2012.

#### *Biosimilar User Fees*

The Affordable Care Act directed FDA to develop a user fee program for review of biosimilar and interchangeable biological products. On May 9, 2011, FDA published a *Federal Register* notice to seek public comment on a proposed stakeholder meeting process and proposed principles for developing a user fee for biosimilar review. This summer, FDA is conducting a series of meetings and will develop a set of proposed recommendations. This fall, we plan to brief Congress on the recommendations, publishing them in the *Federal Register* for comment, and presenting them at a public meeting. After the public meeting, the proposed recommendations would be revised as necessary before transmittal to Congress by January 15, 2012. FDA expects to publish general guidance on biosimilar drug development by the end of 2011. FDA is currently actively meeting with sponsors interested in developing biosimilar drugs and providing advice specific to their individual development programs.

#### *Generic Drug User Fees*

The Administration supports legislation authorizing generic drug user fees. We have made significant progress in our current generic user fee negotiations and believe we can reach a final agreement with industry and submit recommendations to Congress as soon as possible. We expect such fees would reduce the currently pending application queue (the so-called "backlog") and permit FDA to process generic drug applications on a more timely basis.

#### *The Challenges Posed by Globalization*

In addition to reauthorizing PDUFA and MDUFA, FDA is also committed to meeting challenges posed by increased globalization. When President Franklin Delano Roosevelt established the modern FDA in 1938, the percentage of food and medical products imported into the United States was minimal. Today, approximately half of all medical devices used and 40 percent of the drugs Americans take are manufactured outside our borders, and up to 80 percent of the active pharmaceutical ingredients in those drugs comes from foreign sources. Last month, FDA published a special report, "Pathway to Global Product Safety and Quality," our global strategy and action plan that will allow us to more effectively oversee the safety of all products that reach U.S. consumers in the future. Over the next decade, FDA will transform itself from a domestic Agency, operating in a globalized world, to a truly global Agency fully prepared for a regulatory environment in which product safety and quality know no borders. To achieve this transformation, the Agency is developing a new, more international operating model that relies on strengthened collaboration, improved information sharing and gathering, data-driven risk analytics, and the smart allocation of resources through partnerships with counterpart regulatory agencies, other government entities, international organizations, and other key stakeholders, including industry.

Toward this goal, I recently created a directorate focused on grappling with the truly global nature of today's world—food and drug production and supply, as well as the science that undergirds the products we regulate—so that FDA can move from being a regulator of domestic products to one overseeing a worldwide enterprise. I have appointed a Deputy Commissioner for Global Regulatory Operations and Policy to provide broad direction and support to FDA's Office of Regulatory Affairs and Office of International Programs, with a mandate from me to make response to the challenges of globalization and import safety a top priority in the years to come and to ensure that we fully integrate our domestic and international programs to best promote and protect the health of the public.

New regulatory authorities may help ensure that we can hold industry accountable for the security and integrity of their supply chains and the quality control systems they use to produce medical products for the American people. In our increasingly complex and globalized world, additional authorities could be important tools

to help support FDA's efforts to protect the safety of imports and the health of our citizens.

#### CONCLUSION

PDUFA IV and MDUFA II expire on September 30, 2012, and FDA is ready to work with you to ensure timely reauthorization of these critical programs. If we are to sustain and build on our record of accomplishment, it is critical that these reauthorizations occur seamlessly, without any gap between the expiration of the old law and the enactment of PDUFA V and MDUFA III. Thank you for your contributions to the continued success of PDUFA and MDUFA and to the mission of FDA. I am happy to answer questions you may have.

The CHAIRMAN. Dr. Hamburg, thank you very much. We'll start a round of 5-minute questions.

First of all, let me compliment you and your leadership of the agency. It's not very often—I think it's very rare—that we get the administrator of any agency here before this committee or any other committee on which I serve. That, quite frankly, says that some of the things they were doing weren't quite right and they've taken action to correct them. I compliment you both for your investigation and your overview of that and for what you did in January to make the necessary changes. I think that is exemplary, so I really appreciate what you've done in that regard on the premarket approval and the 510(k).

Let me ask a general question. If we did not reauthorize user fees or didn't do so on time, what repercussions would that have for patients? Now, I know what it does to industry. I want to think about the patients. Can you give us some thought on that?

Commissioner HAMBURG. Of course, I worry that it would have enormous negative implications for patients because we would see significant delays in our ability to review and approve applications of promising medical products that could make a difference in treating, preventing, diagnosing and potentially curing medical conditions from which they suffer.

These user fee programs represent a very important component of our medical product review capabilities. They help to ensure, especially at a time of tightening budget constraints, a source of stable, reliable funding for our critical activities, for activities that, of course, involve our premarket review of candidate products, as well as our ability to provide management and oversight throughout the whole life cycle of a product and ensure the safety and effectiveness that Americans do so rely on.

The CHAIRMAN. Thank you, Dr. Hamburg. You mentioned in your testimony the importance of regulatory science. I never thought of it as being a science. But can you explain what that is and how it helps to facilitate innovation, and what are you doing to further this regulatory science?

Commissioner HAMBURG. Yes. This is an area of science that I have become deeply passionate about since becoming FDA commissioner, because as I've looked out over the landscape and looked inward in terms of our capacities, it is clear that we are not adequately harnessing advances in science and technology to really promote the development of new medical products and the knowledge and tools to enable their swift and meaningful review and approval.

When I talk about regulatory science from the perspective of FDA, it's the knowledge and tools that we need to effectively and



efficiently review for safety, efficacy, quality and performance, and it really is a gap in our overall scientific enterprise, and I think it's increasingly recognized within the scientific community as a critical gap.

And certainly academia, industry, and government, NIH, FDA, and other scientific agencies within government need to come together to really build this area of science to give us the ability, for example, to usher in the era of personalized medicine so that we can really identify the genetic traits and biomarkers that will enable us to target therapies in sub-populations of responders; to develop innovative new clinical trial models that will give us robust scientific answers, but in a more timely and cost-effective way; to enable us to really mine the available sources of data both to inform us about important aspects of the effectiveness of products, including this issue of sub-populations of responders, but also to enable us to look in the postapproval, postmarket period to really monitor for emerging safety signals.

There are a host of ways that targeted investments in the area of regulatory science can really enable us to bridge that gap between investments in biomedical research and the opportunities and discoveries that exist today, and the translation of those discoveries into real-world products, and that's what we're really focusing on, and in partnership with the other key stakeholders—patients, industry, academia, and particularly the National Institutes of Health, our sister scientific agency within HHS.

The CHAIRMAN. Thank you very much, Dr. Hamburg. My time has expired.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

A *Wall Street Journal* opinion piece yesterday talked about genomic sequencing and other new technologies that are going to usher in this era of personalized medicine. Last year the FDA approved 20 new drugs, but in the future it may be necessary to target hundreds or maybe thousands of drugs for specific patients. I know you've thought a lot about personalized medicine. How is the FDA's pre-market approval system preparing for that future?

Commissioner HAMBURG. I think, as I was just describing, this expansion of knowledge through investments in regulatory science and partnership is going to be very, very important. The models for drug development are certainly changing, and we are recognizing that the future, to really serve patients, is to try to better understand what therapies really work for what patients and why, and to better understand not just effectiveness but also safety, because we are increasingly realizing that there are subgroups of patients that may develop serious adverse events in response to a treatment, and others will not, and the more we can understand and target those therapies, the better we can serve patients and consumers.

So it is, on the part of industry and the part of FDA, a new world. We are trying to really clarify the regulatory expectations for these new kinds of products, often products that involve combining a device, a diagnostic with a therapeutic intervention, and so it requires more teamwork within FDA. It also requires new ways for companies to develop and present products to us. We are

trying to clarify our regulatory pathways, as well as to develop the underlying science to enable those pathways to be as modern and streamlined as possible.

And just within recent weeks, we did release a new guidance on combination—on companion diagnostics to help us move into this era of personalized medicine, and to help industry understand our expectations and standards.

Senator ENZI. I appreciate the thought that you've given it.

The Institute of Medicine is expected to make their recommendations tomorrow, I think, on how the FDA should change the 510(k) process. What process will the FDA use to evaluate and act on those recommendations, and will you have a notice and comment period?

Commissioner HAMBURG. We will welcome, of course, the IOM report and its recommendations, but they are just recommendations, and we will review them internally and engage with stakeholders to get their perspectives on the recommendations. Any actions that we would take in terms of program or policy change that would emerge from the recommendations of the IOM report would be done in an open and transparent process with lots of opportunity for discussion, for notice and comment and feedback as we go forward.

Senator ENZI. Thank you. And the last PDUFA reauthorization contained some new rules on conflicts of interest for the advisory committees. Are these rules making it harder for the FDA to get qualified experts on the advisory committees, especially for the rare diseases?

Commissioner HAMBURG. This is a very important question and, frankly, something that comes up in many contexts. Whatever groups I'm meeting with, whether it's patients and consumers, scientific societies and organizations, academic organizations, industry, we do hear the concern about are you able to get the experts that you need on your advisory committees.

We work very hard to get the appropriate experts, and in rare instances we can waive conflict of interest requirements in order to get the experts that we need. But I think it's something we need to—it's a dynamic process. We need to keep looking at it, especially, as you note, when you're talking about rare, unusual diseases, getting the people with true expertise is more challenging, and they're often ones that have been involved in some aspect of the development of new drugs or products for that disease condition.

And so we are certainly talking with our various stakeholders, happy to explore this issue further with you as well, because at the end of the day, we depend on the best possible science to make our decisions, and getting that external expertise is very, very critical.

Senator ENZI. Thank you. My time has expired.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Enzi.

In order of appearance, then, it would be the following. It would be Senator Franken, Senator Burr, Senator Hagan, Senator Isakson, Senator Bennet, Senator Alexander, Senator Murray, Senator Mikulski, and Senator Merkley.

And we'll recognize Senator Franken.

## STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman.

Dr. Hamburg, I think we can all agree that patient safety is a priority of Congress and a priority of the FDA, and it is my job and the job of the entire HELP Committee to help you to protect patient safety to the best of our ability.

When I talk to patients in Minnesota, they also tell me that they want to be able to access medical devices that have been developed, and their doctors want to provide them with the best devices for their conditions, but too often these devices haven't been approved by the FDA.

And when I talk to the medical device manufacturers in Minnesota, they tell me how frustrated they are that they're developing innovative and potentially life-saving devices, but they can't get them to their patients because the FDA is taking so long to approve the devices.

You and I both know that it takes time and effort for the FDA to thoroughly review devices for safety and effectiveness, but I believe that we can make the FDA processes more efficient, more predictable, and better support and reward biomedical innovation.

I really want to get into three areas here, and I just want to use my time wisely. But I just want to summarize them before I ask questions.

No. 1, is improving coordination between the FDA and the medical device industry and how we can do that.

No. 2, speaking to what Senator Enzi spoke to—dealing with FDA rules on conflict of interest, and so how you can avail yourself of expertise outside the agency when the review staff is confronted with novel technologies.

And I want to ask a bit about humanitarian use devices and how it has worked in banning profits or limiting profits on the sale of these devices.

Given those three areas, let me ask some questions and try to get through maybe three questions, if we can. And I apologize for taking half your time with the set-up here.

How can the FDA do a better job of working with the industry to answer questions, make the review process more predictable, and restore trust between the FDA and the industry, because we know that's been a problem?

Commissioner HAMBURG. It's so important, and it's something that we are very actively engaged in. And, of course, the MDUFA negotiations give us a chance to work with industry to lay out a set of critical issues and concerns and priorities for action.

Certainly, Dr. Jeff Shuren, who is with me and who is the director of the Center for Devices and Radiologic Health, and myself and other leaders of the FDA are trying very hard to reach out, to listen to, learn from and work with members of industry. In the last 10 days, I've actually been in Boston, California, and Cleveland meeting with leadership, CEOs of the device companies and entrepreneurs involved in the device industry. I haven't yet been to your State to do that, but I'll put that on my list.

Senator FRANKEN. We're the home of medical—

Commissioner HAMBURG. I know. But Dr. Shuren, I know, has spent a lot of time, and—

Senator FRANKEN. And I appreciate that, by the way.

Commissioner HAMBURG [continuing]. We've organized both formal and informal town hall meetings in order to facilitate these kinds of exchanges. And as we were developing, doing our internal review of the 510(k) process, also a lot of outreach to get feedback on our recommendations before we came out with our action steps.

There are some critical areas that will make a difference that we are working on and want to strengthen, communication in terms of both formal and informal mechanisms for sponsors to come in and meet with us, to ask questions, to get feedback in an ongoing way, because we know that early engagement, continuing engagement helps to smooth the process toward a successful outcome.

Being able to provide more guidance is really key, and it makes a difference, adding clarity to what our expectations are and giving industry the opportunity, as the guidances are being shaped, because we always start with draft guidances, to have input in the process as well.

I think that we have just recently put out some critical guidances in that regard.

The ability for us to really make sure also that our own staff are adequately trained and that we are as explicit as possible about our standards is another important aspect of what we're working on with new training, certification programs, and we're eager to work with AdvaMed and others representing the device industry, and companies on what is expected and how they can improve their ability to comply with our standards.

Senator FRANKEN. Submissions.

Commissioner HAMBURG. And we're really trying to reach out to small business as well, because we recognize that, especially in the device industry, so many of the companies are small. Many, many of the companies, a very high percentage, have never put forward an application to the FDA before, and we recognize that it's a complex landscape to navigate, and we're trying to build in some new points of contact and some new programs to make FDA more transparent in that regard.

Senator FRANKEN. Thank you. My time is up. I'll submit some questions for the record.

Mr. Chairman, going forward, I plan to work on the three policy issues that I touched on in my questions, communication between the FDA and the industry, unnecessarily restrictive conflict of interest rules, and the profit cap on humanitarian use devices, and I hope we can work together to address these issues.

The CHAIRMAN. I assure you, Senator Franken, I appreciate your leadership on these issues, and I'll be pleased to work with you to move this forward.

Senator FRANKEN. Thank you so much. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Senator Burr.

#### STATEMENT OF SENATOR BURR

Senator BURR. Dr. Hamburg, welcome.

Commissioner HAMBURG. Thank you.

Senator BURR. Thank you for what you do, and thank you for being here with us today.

Do you have any idea how many drugs and devices bypass the American market now and seek approvals in Europe, Asia, and South America because of time delays or the cost of approval in the United States?

Commissioner HAMBURG. Actually, on the drug side, we are—

Senator BURR. You're still the 800-pound gorilla in the room, but does it concern you that manufacturers make decisions not to seek approval in the United States for ground-breaking therapeutics?

Commissioner HAMBURG. I'm very concerned about the strength of the U.S. industry, the ability of American companies to deliver the products, drugs and devices that the American people need, and that we have a strong—

Senator BURR. Is it alarming to you that American companies would choose not to seek American approval for breakthroughs that they have?

Commissioner HAMBURG. It is important to step back and look at where we are and to strengthen the programs to make sure that we maintain our pre-eminence. On the drug side, as I said, we are the first to approve drugs in more than 50 percent of the cases. So Americans are getting those new products sooner.

Senator BURR. Tell me why we should reauthorize user fees for pharmaceuticals and devices when, in the case of devices, the length of time has gone up since we instituted user fees?

Commissioner HAMBURG. This chart, back on your other question, does speak to the success of the user fee program on drugs. And really the increase in terms of the new active substances first launched on the world market really came after the introduction of PDUFA, and it's very striking, and it's very, very important, and it matters to patients.

Senator BURR. Well, you had a very long—

Commissioner HAMBURG. But there's another chart I was going to show which gets to your question on medical devices. This is the average time to decision for the 510(k) process, and the blue line represents the FDA, and the red line represents the submitter, and the black line the overall time to decision.

Senator BURR. And charts have a tendency of flipping back and forth between real days and FDA days. That's something we've all got to get into to figure it out, but let me move, if I can, because you were talking about—

Commissioner HAMBURG. And I apologize. You were asking both questions in terms of our comparison with other countries and the times to review, and I was trying to answer both.

Senator BURR. And I think you've alluded to FDAMA as sort of the statutory guidelines. It's the blueprint out there right now. And FDAMA required FDA to eliminate unnecessary burdens that caused delays. The sections of the statute that capture that is the least burdensome language. For years, FDA included least burdensome in the guidance and the letters. Yet in 2009, least burdensome disappeared, no notification. Least burdensome just went away. An internal document from the FDA dated November 23,

2009 called for the removal of the least burdensome language to avoid confusion and inconsistency in its application.

Now, doesn't this memo basically say that the FDA applied these provisions in an unpredictable and inconsistent manner?

Commissioner HAMBURG. I think we are trying very hard on both the drug side and the device side to make our regulatory pathways as transparent, as predictable, and as consistent as possible. If you look at what we're trying to do on the device side, the 25 recommendations following our internal review of the 510(k) process—

Senator BURR. But is it the agency's policy to ignore the statute in the law?

Commissioner HAMBURG. Pardon me?

Senator BURR. Is it the agency's policy to ignore the statute in the law?

Commissioner HAMBURG. We are striving to be as least burdensome as possible and really trying to look hard at our business processes.

Senator BURR. But if it's in the law, why would you take it out of the process? Why would you take it out of the guidance?

Commissioner HAMBURG. You know, I'm not sure what document you're looking at.

Senator BURR. It's a document dated November 23d.

Commissioner HAMBURG. But we absolutely adhere to the least burdensome context for what we do, and as I said, we're trying very hard to—

Senator BURR. Let me read from the document, if I can.

"The approach the Center has followed in including least burdensome language in guidance documents is not consistent with either the 2002 guidance or the GGP Manual. To avoid further confusion and inconsistency, from the date of this memorandum forward, draft and final guidance should no longer include standard least burdensome paragraphs,"

which is the statute of the law that we follow least burdensome.

Commissioner HAMBURG. My sense is that it was a removal of certain boilerplate language, but that it is a fundamental concept and commitment that we have, and in the work that we're doing on both the device side and the drug side, we are striving to achieve that. We're trying to achieve it in both looking at our business processes and—

Senator BURR. But your own internal document states that there was inconsistency and confusion is the reason that the language is no longer there, yet least burdensome was put into the statute of the law to try to make sure that we didn't move the goalposts on applicants that were in the process for approval.

Now, my time has run out. Mr. Chairman, I'll stick around for as long as Dr. Hamburg will. Thank you.

The CHAIRMAN. Thank you, Senator Burr.

Now we go to Senator Hagan.

#### STATEMENT OF SENATOR HAGAN

Senator HAGAN. Dr. Hamburg, thank you for being here today and for your work at the FDA.

Just to follow up a little bit on the medical device, we are hearing that companies are taking research overseas, and taking jobs and closing down companies in North Carolina because of some of the unpredictability. And in particular, I'm hearing from medical device companies about the review of the 510(k) products. It's become particularly burdensome, causing product approval delays and the frustration for the manufacturers, providers, and obviously the patients. That's what we're most concerned about. And so anything that would delay the review process really concerns me at this time of economic job losses, of losing any jobs overseas, and then the inability to innovate.

The industry plays an important part in our economic recovery, and I want to support their growth. I also continue to hear from constituent companies that the FDA's medical device review process is pretty unpredictable.

How can we improve the situation? I think you talked about that in your opening remarks. And what I'm particularly interested in is that I've heard concerns that the FDA is stopping the clock. The clock stops when questions about more data are brought forward. And I certainly understand that the FDA is not responsible for how long it takes a company to respond, but I think the FDA does share responsibility in the delay when the agency requests additional data that warrants significant and additional financial and time burdens.

I know you can't speak about confidential negotiations, but can you discuss whether the agency has thought about providing early feedback to companies prior to application submissions or adjusting how the FDA measures time in relation to the user fee goals?

Commissioner HAMBURG. You have a lot of important questions embedded there. We are very committed to trying to streamline the review process and make it easier to navigate for companies, and importantly for patients, get products to them as quickly and efficiently as possible while, of course, safeguarding the important standards for safety and effectiveness.

I do think that in the MDUFA process we have an opportunity to really act in some key areas that will provide us with the necessary tools and resources to make significant strides forward in key areas, whether it's in terms of the review teams, their training, their management oversight, the ability to provide guidances in critical areas to industry, the ability to ensure consistency of decisionmaking with the creation and support of our Center Scientific Council, a number of things that I think we clearly agree with industry are very, very important to the effectiveness and performance of the program, and we're embarked on many of them. We need to strengthen and extend, and I think we have an opportunity if we can clarify some of the needs and priorities, and the sources of stable funding as well.

That said, I think it is important to look at that at the present time we are meeting most of the agreed-on goals with industry. Ninety percent of the 510(k) applications that come before us are reviewed within 90 days, 98 percent within 150 days. That was the agreed-on targets in terms of the FDA time with industry.

But what really matters, as you point out, is the time it takes to get that product to market, and that is longer. I had a chart that

I was showing earlier that shows an upward trend in terms of the time of the submitter as part of the contribution to the overall trend.

We're committed to working on our part. We're also committed to working with industry to reduce the time of their contribution to the overall time to decision. AdvaMed is moving forward in working with industry to train them to FDA standards so that some of the issues with poor quality submissions can be addressed. Earlier communication, more frequent communication can also help to bring that line down.

Senator HAGAN. When the clock stops, that's when we're hearing so much concern.

Commissioner HAMBURG. And I think the better the communication and the more clarity in terms of guidance and communication, the less frequently we'll have to stop the clock.

We also took a very serious look at whether or not our reviewers were asking for data that was appropriate to do the responsible review.

Senator HAGAN. That's what we're hearing a lot.

Commissioner HAMBURG. And we found that in some instances they were not. It wasn't a huge amount of the time, but more often than is acceptable, and that's why we're implementing these reviewer certification programs and training programs, and the oversight of the Center Scientific Council that will review and sign off on data requests and the scientific issues in terms of an application and its adequacy.

I think we are moving forward in some key ways that will make a difference, and I hope that as we move into the next stage of MDUFA we can really strengthen these programs and activities that will make a difference.

Senator HAGAN. My time is out. But just one thing—and I would like to submit some questions for the record.

And that is that I'm concerned that there's a proposal to regulate laboratory diagnostic tests as medical devices, and they're already regulated under CLIA, and I worry about the impact of the additional and duplicated requirements that the industry would have to meet under a second regulatory regime. So that's another huge concern out there, and maybe if we have time to come back around for a second round, we can go over that issue. Thank you.

The CHAIRMAN. Thank you, Senator Hagan.

Senator Bennet is gone.

Senator Murray.

#### STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman.

Dr. Hamburg, welcome. I appreciate you coming and all of the work that you and your agency are doing. It is always challenging to balance getting everything approved in a timely manner while making sure that the public is safe. I appreciate the job you do.

One issue that I wanted to raise this morning that is of concern to me is the safety and effectiveness of drugs used in children.

We have passed two laws, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, championed by Senator Dodd and Senator Clinton. They have both dramatically increased



the amount of information that we now have available on drugs for children. Studies conducted under those two laws have led to almost 400 pediatric label changes, and those two laws have historically been reauthorized along with the Prescription Drug User Fee Act. I hope we can further strengthen these laws in 2012.

Additionally, I wanted to direct you to a GAO report published in May which found that 130 additional products have been studied in children since these laws were last reauthorized in 2007, and as a result, all 130 products were revised with important pediatric information.

Can you just take a few minutes and tell us about the importance of these laws and whether you support reauthorization?

Commissioner HAMBURG. These laws, as you point out, have been very, very important and have really in many ways changed the landscape in terms of deepening our understanding about the appropriate use of products, drugs in pediatric populations and recognizing that children are not just small adults but there are differences in how they respond to various treatments, and we need to understand them, and we need to make it clear to patients and their health care providers about that appropriate use through labeling changes.

Senator MURRAY. So would you support their reauthorization?

Commissioner HAMBURG. We strongly support, we're very enthusiastic about what has been accomplished since these laws were enacted, want to work with you to make sure they are reauthorized and can remain vibrant and active going forward.

Senator MURRAY. OK, very good. I appreciate that response.

Mr. Chairman, I look forward to working with you to make sure those bills are reauthorized as we move forward, too. I think that's really important.

I do have several other questions I'm going to have to submit for the record.

I have to get to another hearing. But, Dr. Hamburg, thank you for your work. I appreciate it.

Commissioner HAMBURG. Thank you.

The CHAIRMAN. Thank you, Senator Murray.

Senator Mikulski.

#### STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Thank you very much, Mr. Chairman.

Good morning, Dr. Hamburg.

Commissioner HAMBURG. Good morning.

Senator MIKULSKI. I'm so glad to see you, and I welcome you with the same enthusiasm that I feel with pride that the FDA is located in my State, all the wonderful people, thousands, over 3,000 who get up every single day to think about how they can help with our drug and medical devices to make sure that we're saving lives, improving lives, and creating jobs.

I really would like to welcome the committee to go out to FDA, that we actually take a field walk-around where we go to see what FDA actually does and the wonderful people who work there, and the talent that we have that we have to keep, that we have to motivate, energize and so on. So often blaming the Federal employees

for the problems of Federal policy I think is a lesson we should learn.

I want to thank you for your self-evaluation of the agency that you presented here today. But I want our colleagues to realize who works at FDA—M.D.s, Ph.D.s. If you just take the word “bio,” bio-engineering, biostatisticians, computational biology, these are people who, if they left FDA, could go to Wall Street and make three to five times as much money managing money rather than managing this process.

We need to get real. We need to have the right policies, the right user fees, and the right way so that we can work, because for we in Maryland and we in America, life science is our jobs. It is our jobs, the medical devices we implement and the drugs that we do.

When I think of my own mother, who passed away in 1996 from the ravages of diabetes, she had the best that medicine, Medicare could offer. And now, what would she have now that she didn't have then? Better home testing medical devices to be able to provide her with the biofeedback to better monitor herself. She had three drugs to pick from. There are now 300 drugs to pick from. Her life would have been better, it would have been longer, and we would have created jobs to do that.

This is why I'm so passionate about FDA and what we need to do.

Having said that, let me go to your very meaty testimony. You raised the issues related to innovation. You have a series of recommendations. As you can see here today, there is an inherent tension between innovation and regulation, and we shouldn't have to pick one side or the other, regulation for safety first, efficacy as crucial for getting value for our dollar.

What can you see that we need to do in PDUFA to make sure we promote adequate regulation but we don't stifle innovation? So this is the underpinnings of some of the questions. Could you elaborate on that, and what do you need us to seriously think about?

Commissioner HAMBURG. I think you're absolutely right. We need to marry safety and innovation. We need to make sure that we are really capturing all the advances in science and technology today into real-world products for people. I think there are a number of things that are underway and a number of elements in the PDUFA V negotiation package that will help us to strengthen those activities.

One is critically building out some of these scientific capabilities so that we can really use science to target our therapies, to identify where are the critical opportunities in terms of the patterns of disease, how can we do clinical trials that are meaningful but shorter and more cost-effective, how can we look out across the whole life cycle of a drug to ensure safety and effectiveness by using data mining and monitoring available information in the real world.

Senator MIKULSKI. Dr. Hamburg, if you could withhold a minute. In your written testimony, you talk about how you want to streamline the regulatory process but make sure we ensure safety.

Commissioner HAMBURG. Right.

Senator MIKULSKI. It's an obsession with us and I think what separates Western democracies from those who just want to make products. You have several recommendations here. Were they sup-

ported by the private sector, and have you begun to implement them?

I'm talking about the innovation, pathway to public-private partnerships.

Commissioner HAMBURG. The innovation pathway—yes, very much so.

Senator MIKULSKI. Scanning.

Commissioner HAMBURG. I think one of the areas that's been very exciting is the opportunity through public-private partnerships to really address these critical issues in terms of the gaps in science and how to build on them to really spur innovation, and I met recently with R&D directors from some of the major pharmaceutical companies, and they really see this as a critical need from their perspective, and we see it as a critical need from our perspective in terms of having the tools to apply to the process.

I think that in terms of the device program, it's very, very important that we have a flexible regulatory process that recognizes that innovation is so dynamic in that area, and we need to be able to really support industry as it develops an idea and tests it and puts it into the marketplace, and continuing to monitor it.

As innovation occurs going forward, it requires that we have adequate support for science within FDA in terms of reviewers who understand the complexity of the products that are coming before us and have the access to external experts that they need to help enable the review process that will support these innovative products from—

Senator MIKULSKI. That's very helpful, and I don't mean to interrupt. My time is up because I wanted to get in my comments about FDA.

Also, you share with us the private sector's views and recommendations on just how to improve the process, from drug review to regulatory science to others, benefit/risk assessment. Have you incorporated these in the recommendations for the committee for reform and refreshing?

There's no doubt when we look at PDUFA, we've got to refresh it, reform it, re-energize it, but also keep on the right track for the balance between innovation and industry. So where are you on these private sector regs?

Commissioner HAMBURG. These are the elements, the seven categories of enhancements that were agreed to with industry as part of the PDUFA V negotiations. There was enormous enthusiasm and support for these activities. I would say that that negotiation process was very constructive and forward leaning, and we do think that these elements will really strengthen our programs and activities and our ability to deliver.

Senator MIKULSKI. Senator Harkin is giving me the tap. I got it.

Senator Harkin, I really am serious about my invitation to the committee to come out and really see FDA, because when you look at who is around the table, our economies in our State really rest on it, sir. Baltimore, our largest employer was Bethlehem Steel. Now our largest employer is Johns Hopkins. And one of which is because of NIH, but also the new products for FDA. Let's go out and actually see what they do, and let's work together. Our economy and our people depend on it.

Commissioner HAMBURG. We would welcome you, and we did host an event for congressional staff. I think it was very successful and useful, and I look forward to hosting all of you.

The CHAIRMAN. Senator Mikulski, I'll take you up on that sometime this fall if we can find a good day to do it on.

Senator Hatch.

#### STATEMENT OF SENATOR HATCH

Senator HATCH. Thank you, Mr. Chairman. I want to compliment my colleague from Maryland. We've worked together very strongly on these issues.

I think a great deal of her, and I also think a great deal of you, Dr. Hamburg.

Commissioner HAMBURG. Thank you.

Senator HATCH. In fact, I even like the people in the first row. [Laughter.]

I just wish you'd be a little less risk-averse, because I think I would like to see our medical device regulator start to match what Europe does. I think we're way behind as far as I can see. Now, I'd be happy to be convinced otherwise.

This is a great agency. It handles a tremendous amount of commerce in this country. In fact, it's almost impossible to handle all that you've been called upon to do, but you can do it. And I think you should call on us to help where we can.

It's clear that in the area of medical devices, we're losing ground to other countries, in part due to the increasing difficulty in getting new products approved by the FDA in a timely and efficient way. For complex and innovative devices, a whole series of studies have shown a device lag, and every device executive I talk to is saying that they are moving clinical trials for first product introductions overseas because of the challenges they face with FDA.

I've had some medical device manufacturers show me how the approvals in Europe are so much faster than here and, frankly, people have benefited from those approvals and those devices in ways that Americans have not, and I would like to see that change.

In fact, I read in a recent article in the Cleveland Plain Dealer that you acknowledge that FDA has played a role in the national decline in medical product innovation, adding that you felt much of the criticism of the agency was "deserved."

Let me just ask you this. What are you doing to get us at least back to where we were several years ago in terms of speed and consistency of review? And how are you attracting manufacturers to come to and remain in the United States? I think we're losing a number of them because of some of these difficulties that I've been raising.

Commissioner HAMBURG. Let me first thank you, Senator Hatch, for all your support over so many years and, of course, the great work that you and Senator Mikulski have done to support the White Oak facility and other important aspects of our work.

Let me then address the question about U.S. approvals versus Europe, because I think it is important to clarify.

A recent industry study that has been cited already did show that for lower-risk devices that don't require clinical data, which represents about 80 percent of the devices we review, that the

United States is, in fact, as fast or faster than Europe in bringing those products to market. For the higher-risk—and this chart does speak to that. For the higher-risk devices, we are slower than Europe, but it's important to recognize that we have a different standard, a different regulatory framework, and in Europe they don't require safety and effectiveness like we do. They require safety and performance.

And what that means in the real world is that, for example, for a condition like atrial fibrillation, which is an irregular beating of the heart that can be associated with serious medical complications, including stroke, that for a technique called ablation that tries to disrupt abnormal electrical pathways that cause the irregular beating, you can use a tool to basically cut or burn the tissue. And in the United States, we have to show that the device actually has a benefit for patients in terms of a positive impact on this underlying condition. In Europe they just have to show that it affects the heart tissue.

That is a different standard, and I think—

Senator HATCH. I understand that. Would it be better for us to switch to the European performance language?

Commissioner HAMBURG. I think it is very, very important. I think the American people really count on—

Senator HATCH. Let's get some answers.

Commissioner HAMBURG [continuing]. The fact that a medical device that they will use or a family member will use that may be implanted into them for a very long period of time, that not only will it be safe and effective, they count on that and that it will actually benefit them in terms of the intended use, and the European requirement is different.

I think it's a very different model where the sponsor pays a private entity, a so-called notified body, to review the product. These are not bodies that are under the oversight of any authority. They have different expertise and qualifications, and the information and data that goes into the decisionmaking is not made available to the public.

So, I think, the device industry leadership agrees that we should not change the standards for medical device approval in this country. AdvaMed recently put out a press release speaking to that. But I think what we can and must do is work together to make sure that we have the most streamlined and modern regulatory systems possible. At the end of the day, absolute speed is probably not the only and ultimate criteria to ensure safe and effective products.

Senator HATCH. I'd be the first to agree with that. Just the latter part of that question about attracting business to this country, could you elaborate on that for a minute?

Commissioner HAMBURG. That is a very, very important—

Senator HATCH. It really is.

Commissioner HAMBURG [continuing]. Issue, and we are—

Senator HATCH. I'm on your side.

Commissioner Hamburg [continuing]. Working very hard. No, and I think—

Senator HATCH. I'd like to help you. But I really think we're pretty slow. But go ahead, attracting—

Commissioner HAMBURG. I think we have a contribution to make in achieving that goal that's very, very real. It's also a more complex ecosystem with economic policies and issues around the costs of labor in other countries versus the United States.

But in terms of the FDA component, that is why we are so committed to making our regulatory pathways as clear, consistent, and predictable as possible, as streamlined and modern as possible, trying to develop guidances to address some of the key areas of concern for American manufacturers such as clinical trials, which are often cheaper and easier to do overseas. We're soon going to be putting out new guidance to encourage earlier in-human study of medical devices that will, I think, provide an important incentive to doing those studies here in the United States.

And I think that through the MDUFA process, we have the opportunity to really focus and act on some of the key areas that will help to make our medical device review systems as timely and efficient and responsive to the needs of patients and innovation as possible.

Senator HATCH. I want you to know I'm interested in all the UFA processes, not just MDUFA.

But I want to thank the Chairman for his leadership in these areas and, of course, the Ranking Member as well, both are terrific as far as I'm concerned. And I want to thank you, doctor.

Commissioner HAMBURG. Thank you.

Senator HATCH. Appreciate you.

The CHAIRMAN. Thank you very much, Senator Hatch.

Senator HATCH. I'll submit my questions, further questions.

The CHAIRMAN. OK. Thank you, Senator Hatch.

Senator Merkley.

#### STATEMENT OF SENATOR MERKLEY

Senator MERKLEY. Thank you very much, Mr. Chair.

It's a pleasure to have you here, Dr. Hamburg. I wanted to start with an article that came out yesterday regarding a report that's anticipated tomorrow. This is a report from the Institute of Medicine that was charged with analyzing regulatory proposals related to medical equipment like hip implants, hospital pumps and defibrillators.

And apparently, even before it's out, it's becoming quite a controversial study. Would you mind commenting on what are the issues here? Is there a problem with the balance of the panel? Is it already known what the report will say and people simply disagree with it, so on and so forth? What's going on here?

Commissioner HAMBURG. The Institute of Medicine is a branch of the National Academy of Sciences, and of course the National Academy of Sciences was actually begun by Abraham Lincoln many, many years ago to help provide scientific consultation and expertise to government as important decisions are made.

We actually asked the Institute of Medicine to put together a committee and do a study about important issues involving the 510(k) regulatory process, which is the largest component of our medical device review activities and so important.

They put together a committee, as they always do. We as the requesting agency have no input into the committee composition, but

they have standards and practices about diversity and conflict of interest on their committees. They will be putting out a report. That report, as I mentioned earlier, will provide us with recommendations, which will only be recommendations, and we will review them and we will get feedback in terms of if we want to pursue aspects of those recommendations.

Senator MERKLEY. But just cutting to the chase, is there something anticipated that is really quite controversial?

Commissioner HAMBURG. I think there was concern expressed by some components of the device industry about whether their perspective was adequately represented on the committee. I think that various lawyers have looked at that and feel that the composition of the committee is sufficiently diverse and containing—

Senator MERKLEY. My impression is that people are upset because they are disagreeing with what they think is going to be in the report tomorrow. I don't know if there was a pre-announcement or a draft announcement, but what is the heart of the actual policy issue that is being wrestled with here?

Commissioner HAMBURG. I think the heart of the policy issue is the adequacy and appropriateness of the 510(k) process, whether it achieves its dual goals of assuring safety and efficacy of products and the timely introduction of innovative products into the marketplace. I have been briefed but have not had a chance to actually read the report, which is embargoed until tomorrow.

But I think that it obviously will be speaking to very important issues, and I think that the concerns reflected in that newspaper article have to do with whether the committee was properly constituted.

Senator MERKLEY. OK. Let me switch gears here, then. Thank you.

Sometimes problems develop after a product is introduced that weren't caught in the clinical trials. Can you address how well the MedWatch system is publicized and being used by consumers? Is it providing valuable feedback? Could it be improved?

Commissioner HAMBURG. I think we need to strengthen many components of our postmarket surveillance activities, as you suggest. We often learn about safety concerns in much greater detail once the products are out in the marketplace being used, not just by a limited number of patients who are involved in the early clinical studies but by thousands, hundreds of thousands, millions of patients and individuals who may have other underlying medical conditions or are taking other drugs that may also affect the safety and safe use of those products.

So we do need to continue to strengthen the systems for adverse event reporting. We also, in large part due to efforts by Congress, through FDA in 2007, are strengthening our broader activities and programs in the postmarket period, including our ability to really target in on emerging safety concerns through changes in labeling, changes in data collection to further drill down and understand those problems, and in mining existing databases and creating new databases to inform our decisionmaking.

Senator MERKLEY. A last brief question, or at least I'll need a brief response.

Commissioner HAMBURG. Sorry.

Senator MERKLEY. And that is, given new forms of advertising, Internet and social media and so forth, and the types of cautions that are normally embedded in prescription drug and medical device advertising, are those presenting new issues that you're having to wrestle with?

Commissioner HAMBURG. Certainly the age of the Internet has created vast new challenges for us in terms of monitoring what information is out there about products in terms of advertising and its accuracy; and also products that are, in fact, being advertised for sale that are fraudulent or counterfeit. And we are working very hard—it's a domestic issue; it's also an international issue, because many of these Web sites are based overseas—to try to get a better handle on the scope of the problem and to identify solutions that will really work. But it's a huge, huge challenge.

Senator MERKLEY. Thank you very much.

Commissioner HAMBURG. Thank you.

The CHAIRMAN. Thank you, Senator Merkley.

Senator Bennet.

#### STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman. Thanks for letting me go and come back.

And, Dr. Hamburg, thank you so much for being here today.

Commissioner HAMBURG. Thank you.

Senator BENNET. I heard the questions at the beginning, the answers at the beginning, missed some in the middle. But I wanted to make one observation about the tension that I think exists around some of these issues.

The mission statement of the FDA is pretty clear that it's both about the public safety, public health, and also about driving innovation in our medical device industry, or supporting innovation maybe is a better way of saying it. The tension that the folks in my State feel that are in this, doing this work, this incredibly important work of developing medical devices, I think is rising as a reflection of the globalization of the industry, and the concern that a lot of us have is that we may not own this industry in the 21st century, or that we may lose it.

One thought that I have is whether we want to consider changing the mission statement to recognize the global economy that we're in and the importance to the United States of being able to drive this, or maybe that's not the right place to do it, maybe it's somewhere else. But I wonder whether just more broadly—your efforts are commendable, but are we moving at a rate of speed that's going to get us to a place where we're going to be able to compete in real time with the rest of the world, or not lose the advantage that we have?

Commissioner HAMBURG. I certainly share your concerns, and certainly in terms of my leadership at the FDA and the orientation of all the extraordinary staff that work with me at the FDA, we see our mission as doing our very, very best to assure the safety and effectiveness and quality of the products that we regulate, but also to help support and facilitate the translation of opportunities in biomedical research and science into products that people need, and also to try to provide some sort of recognition of the need to



match unmet public health needs with opportunities that exist in terms of available science and technology. And so we are committed to all of those things.

I have actually created within my office in recent months a special focus on innovation, trying to support all of the good ideas, programs and policies that are spread throughout FDA with a focus on advancing innovation. I've also been trying very hard to work with my colleagues in government and outside to really look at what can we, as a nation, do to strengthen our programs and policies to support innovation, because FDA plays a critical role, but it also has to do with patents and IP. It has to do with economic policies and taxes and incentives. It has to do with reimbursement issues, and it has to do with making sure that FDA takes a very hard, serious look, which we are doing, at how can we streamline and modernize our regulatory systems to make it easier for companies to work with us and to make sure that those exciting and promising candidate medical products actually make their way into the marketplace.

Senator BENNET. I think that's well said, and I think everything that you said is true. What concerns me when I have the people come in is because they're the life science manufacturers or the inventors or entrepreneurs, because their interaction with the Federal Government generally is the FDA, they're looking for the FDA to help solve this problem on competitiveness, or to at least not compromise their ability to be competitive and stay here in the United States and do the work, and I feel like I'm having the same conversation year after year, with respect, because I know you are doing a lot of this work, having the same conversation year after year, and it sometimes feels to me as though it's no one's day job, and you just said it is some people's day job, it's no one's day job to say how do we hold onto the competitive advantage that we have, or create more competitive advantage going forward.

And it's not just an FDA issue, as you said, patent issues, all kinds of things. Whose job is it to think about and to really implement policies that are going to drive innovation in the country?

I want you to know that I look forward to working with you on this to try to support these efforts on behalf of Colorado and on behalf of the country.

And before my time runs out, we're now at a point where, just to shift gears for a second, 80 percent of the active ingredients in our drug supply chain is coming to us from offshore, and you have acknowledged that as an issue and I think stated the need for us to work with international regulatory agencies to make sure that we can stay ahead of the problem of a compromised drug supply and other issues.

I wonder if you could talk a little bit about what that will look like and whether we are doing everything we can to try to inspire international cooperation around that issue.

It's a big surprise to people in Colorado when I tell them that 80 percent of the active ingredients in their drugs come from overseas and that we actually have very little in the way of inspection of those plants, especially in China and other places, and that we can't always be sure of what's in our pharmaceuticals.

Commissioner HAMBURG. It's such an important problem. Globalization has really changed the world, and it really requires that FDA changes the way that we do business. You're absolutely correct. Today, 80 percent of the active pharmaceutical ingredients in drugs taken here actually come from other countries. About 40 percent of the finished drugs taken here come from other countries. And we need to recognize that the supply chain for these products has gotten very complex and much more complicated, with many points along the way for potential unintentional or intentional contamination, adulteration, or impacts on quality.

And so we need to really transform. When our agency was first created, the world looked very different. We need to transform and we need to move beyond the borders in terms of how we inspect and ensure quality in products coming into this country. We need to work much more closely with sister regulatory authorities to share information, to try to harmonize standards and approaches, and to actually in some instances share the workload in terms of inspections. There are way too many facilities out there for any regulatory authority to get in and inspect them with the frequency that we would like. And so we're really developing those kinds of relationships.

We also have to work in much closer partnership with industry, who clearly needs to be accountable for the supply chain of their products, and at the end of the day, through working together, we need to be able to assure the integrity of the supply chain and the trust and confidence of the American people in these products.

We've also now set up offices in many countries around the world that provide a regional presence for inspections and activities, working with industry and other stakeholders and our counterpart regulatory authorities to ensure that our standards are understood and being met. We're also trying to work hard with many countries that have less sophisticated regulatory capabilities than we do to help raise their standards, which will serve us all.

There's an enormous amount to be done. I know that you've been taking a very serious look at this, and we welcome the opportunity to work with you as you examine what kinds of additional authorities might be needed.

Senator BENNET. I appreciate that, and my time is long expired. But I want to thank the Chairman and the Ranking Member for letting me go over for a second.

The authorizing statute for the FDA, as you know, was written I think in 1938. It was in the 1930s, sometime when the entire supply chain was domestic, and now I think it's high time for us to take a look at that.

I also want to let you know that I've asked the biotech and device guys in Colorado to give me the 9 or 10 pain points that they really have, and we will get those to you, in an effort to not have the same conversation next year that we had this year. And I hope it will be useful to you as you think about this.

Commissioner HAMBURG. Yes. I appreciate that. It is very useful to hear directly from people on the ground what are their critical issues and perceived barriers and concerns.

Senator BENNET. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Bennet.

Let's start a second round here.

I just want to say to Senator Bennet, looking at the supply chain, I had mentioned in my opening remarks that we wanted to focus today on PDUFA and MDUFA and the reauthorization in that area, and I said I'm going to have some hearings this fall on that very subject of the supply chain. I look forward to working with you.

Senator BENNET. Good. Thank you. I will as well. Thank you.

The CHAIRMAN. You know, we all want better devices. We all want innovation. We all want to know that if we have an injury or something like that, that there are devices out there that will permit us to live life to the fullest, and we've made great strides in that area in this country, in innovation in devices. I've followed them for years with my work on disability issues, for example.

But, you know, let's face it, there's a lot of money to be made in devices. People have gotten immensely rich in this country because they've innovated, they've invented, they made a device and got out there, and people have gotten immensely wealthy in this area. I don't deny that. That's fine. That's part of the American dream.

But I do want to make sure that we have an agency that is independent and that is able to withstand the tremendous fire power of an industry that has a lot of money and obviously wants the least amount of regulatory oversight. I understand that. I mean, that is, again, part of the give and take of our society.

I think it is a gross disservice to many of us who have been supportive of the industry, as I have been in the past, as I said, through my work with disability issues over most of my adult lifetime. I've seen the tremendous help that devices have provided for people so that they could have a better life. It does a great disservice to us when an article like this appears in the *New York Times* this morning outlining how—I'll just read the first sentence.

"Allies of the medical device industry are waging an extraordinary campaign in Washington to discredit a coming report by one of the country's pre-eminent scientific groups that examines possible new regulations on the industry. The scientific group being"—of course—"the Institute of Medicine, is scheduled to release a report on Friday that could,"—that could, I don't know, I haven't seen the report yet—"that could propose a tougher approval process for a wide range of devices like hip implants, hospital pumps external heart defibrillators."

"The report, commissioned by the Food and Drug Administration, comes after several well-publicized recalls in recent years of devices that have failed in thousands of patients, causing numerous injuries. But a business group and others have taken the highly unusual step of making a pre-emptive strike, arguing that the report is biased. That attack began even before the study panel finished its review and has intensified in recent weeks."

"The challenge to the panel has been led by a Ralph F. Hall,"—who I don't know—"a professor of law at the University of Minnesota and a device industry lawyer. . . . 'I could have waited until the report came out,' Mr. Hall said in an interview. 'That seems intellectually less than satisfactory with me.'"

Say again? I attack something before it comes out rather than waiting until it comes out to read it, to analyze it, to see what the input was? But I attack it before that, and that's more intellectually satisfactory?

I'm going to ask that this article be made a part of the record here, since I quoted from it.

[The article referred to may be found in Additional Material.]

The CHAIRMAN. Look, there have been times in the past when I've seen studies from the Institute of Medicine that I didn't like because it went against my preconceived beliefs. Well, then it made me really question my preconceived beliefs.

I say to the device industry, the kind of story that appeared in the *New York Times* this morning, and the statements by Mr. Hall and others do a disservice to your industry, because the FDA is charged, as you said, Dr. Hamburg, quite frankly, not only with making sure that products are safe, but that they are effective, different than what they do in Europe. I want the FDA to continue that, and I want it to continue to be an independent agency.

From my standpoint and having been here for so many years, on both this committee and the Appropriations Committee, perhaps one of the most unbiased scientifically oriented groups in this country is the Institute of Medicine. I hope you will continue to rely upon them, and don't let this kind of stuff that's coming out here today and other days dissuade you from that.

I want you to continue to be independent, use the best science. I know you're going to get pulled from one way and pulled from the other way. I understand that. This industry is so important to our country. We don't want it to go overseas. We want it to stay here. But to take this kind of attitude that they will not even listen to a report from the IOM and engage in a reasonable conversation about it but they just attack it before it comes out, as I said again, not only it does a disservice to the industry, it does a disservice I think to the patients and our country.

So having said that, I've used up my time. I didn't even get to ask a question. But I just wanted to respond on that issue with the difference between here and Europe. I'll just take a couple of more seconds.

In Europe, you're right, they just want to know if it performs as they say, without deciding whether it is effective. But that's covered later on in their reimbursement systems in Europe, which is quite different than ours. And since we are not really changing our form of reimbursement system to be like Europe's, then we rely upon the FDA to make that decision, is it effective, does it really lead to good clinical outcomes.

As I said, that's not part of the European system. It's part of their system later on in the reimbursement side of it. So that's why our system is different than Europe's.

Thank you very much, Dr. Hamburg, and I'll yield to Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman. I'll follow up a little bit on what you said and ask a question.

The last PDUFA law authorized the risk evaluation and mitigation strategies to speed access to drugs with risk concerns, but in many cases REMS just ended up slowing down the review process.

Can you fix that process administratively, or could small statutory fixes help you to effectuate legislative intent?

Commissioner HAMBURG. As you know, REMS, the authority to pursue that strategy, was given to us in 2007 in FDAA, and we had to put in place new systems and really sort of develop strategies that would enable us to better monitor and assess safety in the postmarket period, which is so important, as we've talked about.

As we have implemented it, I think it has put new burdens on FDA and on industry, and we are looking now at ways that we can really sort of systematize how we do it and look not at a product-by-product way of implementing some components of it, but really having guidelines for classes of products. It's an area where, obviously, the feedback and the exchange with industry and their experience is helping us to shape how we organize this program.

And I think that working in that manner, we can move forward and improve and strengthen REMS. It does give us a set of important tools that actually give us more confidence on the front end as we improve promising candidates that may have safety concerns, that we can continue to monitor and address those as they go into the marketplace and we learn more about them.

So I think we can continue to strengthen and streamline the program. At the moment I, at least, am not aware that there is any particular need for a legislative fix, but I think we recognize that the program has been somewhat cumbersome, and it certainly has put a lot of additional demands on us as we develop and implement it, and we want to see it really achieve the goals but not be as complex in its administration and the workload on both companies and on FDA.

Senator ENZI. Thank you. A June 2011 report from the Government Accountability Office found that the Device Center is not overseeing recalls effectively. FDA already has a clear statutory authority to mandate device recalls, but the average time it took for FDA to effectuate a Class I recall, which is the highest risk type of recall, was 516 days. There have been incidents where individuals were seriously injured or died due to continued use of defective devices that were supposed to have been recalled. In one instance, a supposedly recalled device was re-introduced to the market and patients needed surgery to remove them. In addition, GAO found that the FDA does not use recall data to identify systemic safety risks.

What steps are being taken to address those problems?

Commissioner HAMBURG. Very, very crucial concern, and we do need to strengthen our programs and reduce our response times. There are a number of important activities that are underway, including the creation of a unique device identifier that will enable us to more effectively track devices, that health care providers and the FDA can have much better information about who has what products, and working with industry when there is a problem, we can move more swiftly to actually address the immediate patient needs.

In addition to that kind of activity that will make a difference from a safety perspective, we have to look at our systems to make sure that we are responding to emerging concerns in as timely a

way as possible, both in terms of collecting the safety information, analyzing it, responding to it and, importantly, acting on it.

Senator ENZI. Thank you. Also referring to the Government Accountability Office, in 1998 they called for FDA to implement a series of recommendations to respond to challenges posed by the globalization of drug manufacturing.

What progress has the agency made on the GAO's longstanding recommendations on that globalization of drug manufacturing?

Commissioner HAMBURG. As I was discussing with Senator Bennet, this is a huge and growing area of focus, concern, and activity. We are trying to extend our capabilities in terms of our foreign inspections, working with counterpart regulatory authorities to try to share information as well about the inspections that they are doing and information about supply chain integrity and the quality of products.

Really, working with industry also because, of course, at the end of the day their knowledge and accountability around the supply chains and the manufacturing practices in these overseas sites is critically important and fundamental to our shared goal of achieving integrity and safety of the supply chain.

So we are very, very much focused on this as a priority. You mentioned I think some interest in the reorganization that I recently did, and one of the areas was really to try to bring greater integration of our Office of Regulatory Affairs activities, which is out in the field doing inspections and compliance activities, with our Office of International Programs so that we can really use our resources in the most coordinated way possible and really focus on strategies that take into account risk, risk of certain types of products, risk in terms of past history of certain products or manufacturers, and really within the realm of possibility enables us to engage all of the important partners and really use all the best possible information, wherever it comes from, to inform our activities.

Senator ENZI. Thank you. My time is up, but I'll have a followup question. I'll send that in writing.

Commissioner Hamburg. Thank you.

The CHAIRMAN. Thank you, Senator Enzi.

Senator Burr.

Senator BURR. Dr. Hamburg, on the question of the IOM report, if the IOM report on 510(k)s triggers a change in process, do you commit to make sure that that process is a notice and comment rulemaking process?

Commissioner HAMBURG. Oh, absolutely. We would view their recommendations as just that, recommendations, and we would review them internally and seek the perspective of key stakeholders on those recommendations, and anything that we would do that would be a permanent action coming out of that report and those recommendations would be done in an open and transparent way in notice and comment.

Senator BURR. Let me stay on 510(k)s, if I can. I heard you say to Senator Merkley that the 510(k) process looks at safety and effectiveness. Did I hear that correctly?

Commissioner HAMBURG. Through the 510(k) process we are trying to assess safety and effectiveness, yes.

Senator BURR. In reality, the process for 510(k) is substantially equivalent. Now, if FDA has made a shift to an assessment of safety and efficacy on 510(k)s, this would be an earth-changing move.

Commissioner HAMBURG. It's clearly a different process than when you talk about the drug evaluation process and the way that we look at data and require information to demonstrate safety and effectiveness.

We're looking at predicates, and we're looking at a different model. But at the end of the day, the goal is to support the assessment of safety and effectiveness of that product.

Senator BURR. Let me just say the statute that's applicable here is substantially equivalent. That is the process for 510(k) approval. Are you telling me that's not the threshold?

Commissioner HAMBURG. That is the criteria. What I'm saying is that the goal is to make sure that devices that are reviewed—

Senator BURR. So if you determine that it's substantially equivalent but you feel that it doesn't meet safety and efficacy, you're not going to approve the 510(k)s?

Commissioner HAMBURG. It's a different model of regulation, as I said, from the drugs, and it does build on track records of prior products.

Senator BURR. I'll certainly follow-up on this with additional questions.

But I would question whether you've got the authority without a change in rules to do exactly what you've stated. And if it does, then it may explain a lot as to why there has been an increase in the time that it takes for device approval.

Has the increase in fees resulted in fewer review cycles per submission compared to previous user fee agreements on devices?

Commissioner HAMBURG. On devices, unfortunately, the review cycle has increased somewhat over time, and it's something that we're focused on and we want to bring down, and we think that by working together with industry to try to both address the issues within FDA that we've talked about and the issues around the quality of applications and response to information requests from FDA, that we can continue to move in the direction of bringing those review cycles down.

Senator BURR. Industry says the FDA is moving the goal posts. The FDA says that this whole process is the result of poor quality 510(k) applications. Do you want to comment on it?

Commissioner HAMBURG. I think that's a very stark view of what is the conversation. I think that we recognize that it's a combination of factors. FDA has a role to play, and that's why we have undertaken this fairly self-critical internal review and made recommendations for problems that have been identified that we can act on.

But it is the case that the delays in the time of getting a new product to market do also reflect the time taken by the submitter, whether it's because the quality of the application wasn't adequate and we've had to have a lot of back and forth to get the information that we need, or because in some instances we have asked for information that, in fact, wasn't necessary.

We need to make the overall time as short as it needs to be to achieve the goals of the review, which is to make sure that we un-

derstand the nature of the product and its risks and benefits in terms of its use for a given medical condition.

Senator BURR. You're in the middle of negotiating the device user fees. Would you consider a new structure with the device user fees where the industry would pay at different intervals based upon FDA performance?

Commissioner HAMBURG. Right now the model does really focus on FDA review time. I think what you're saying is would we look at it in terms of the overall performance of the system.

Senator BURR. If the FDA doesn't perform, they don't pay. I mean, the whole user fee foundation was built on if you supply us this money, we will become more efficient at what we do, which one would assume that from all the conversations I heard today—increased communication, less confusion, clearer guidelines—that that would all be incorporated so that the FDA would actually meet and exceed what the expectations were of the companies and the industries that were paying the fees.

Now, were I in the industry, I would be very reluctant to come to the table and talk about even reauthorizing the fees because of the performance that I've seen. Dr. Coburn and I have asked the GAO to examine the performance goals so that Congress can fully be informed when we consider the user fee reauthorizations, and I look forward to reviewing those GAO recommendations because it's an independent assessment of how well the industry is meeting the performance goals and the data on these numbers. The industry says one thing, the FDA says another. GAO can now sort this out so that whether it's Senator Harkin or Senator Hagan or Senator Enzi or Senator Burr, that we can look at it and determine did you meet the performance goals or didn't you.

Commissioner HAMBURG. I can assure you that we track our performance on the existing MDUFA goals, and in fact those goals were negotiated with industry, as you know. And at the present time, we are meeting, in the 510(k) process, 95 percent of the goals.

I think the larger concern, which is one that we share, is are we doing an adequate job getting products to market as quickly as possible, and that involves both the time taken by the submitter during the process and the time taken by FDA.

The MDUFA goals that were negotiated with industry only do focus on that FDA component. I think we have a commitment to working with industry, whether it's part of the MDUFA negotiations or it's part of our overall work as the regulator of medical devices, to doing everything that we can to bring down that overall time so that we can deliver important products to patients in as timely a way as possible, but with adherence to the standards that we all agree really matter.

Senator BURR. The Chairman has been gracious to me, and I will have one more round, Mr. Chairman, just to put you on notice. But I want to ask this because it's applicable to the conversation we were just on.

Of the applications counted toward meeting the performance goals in your chart, what percentage are either approval or denial letters?

Commissioner HAMBURG. Which chart are you referring to?



Senator BURR. I think it's the one on page 10 of your testimony. I think that's one that your staff has diligently put up every time we've gotten on devices, but I can't read it from here because of the light.

But of those applications counted toward performance goals in the chart, what percentage are actually approval or denial letters versus—

Commissioner HAMBURG. First of all, I have to confess, I'm not sure what chart you're referring to. But I also think that in terms of the level of detail of your question, it would be best if we could get back to you.

Senator BURR. Would you answer that for the record for me?

Commissioner HAMBURG. I absolutely will, sir.

Senator BURR. Mr. Chairman, you've been gracious, but please come back to me.

The CHAIRMAN. But you have very good questions, Senator Burr. Senator Hagan.

Senator HAGAN. Thank you, Mr. Chairman.

Once again, Dr. Hamburg, thank you for all of your work and service in this job. I really do appreciate all the efforts that you're putting forward.

I did mention about the laboratory diagnostic tests, that I would like to go back to that question, and I've heard concerns about the FDA's proposal to regulate these tests as medical devices.

As you know, LDTs are already regulated under the CLIA, and a lot of the industry is worried about the additional impact of duplicating requirements that they would have to meet under a second regulatory regime, and I'm concerned once again that this added regulatory process would definitely slow innovation, which is what we're really looking for here, impeding the improvements to patient care, as well as job growth that has come with innovation across this industry.

It is my understanding that the FDA is in the process of developing guidance to regulate laboratory-developed tests as medical devices. Where is the FDA in the development of this guidance?

Commissioner HAMBURG. Laboratory-developed tests clearly are devices. They are diagnostic tests that are often used to guide clinical treatment of very serious, often life-threatening diseases. FDA does have the authority to regulate them historically because of the nature of how these tests were developed and used, which was all in-house. FDA exercised enforcement discretion.

But I think given the realities of the world that we're in today and that these laboratory developed tests are being done in commercial laboratories and treating patients in facilities that are widespread, that it is important that there be a common standard of review and approval for those tests, along with other comparable diagnostics. We shouldn't have different standards depending on where the test was developed. We are going to be putting out several guidances to help the laboratory-developed test industry understand what will be expected of them in terms of regulatory oversight. I think it actually will create for industry a level playing field in terms of the companies that are involved in LDTs per se, or diagnostics more broadly.

We are very mindful of the fact that the LDTs are subject to CLIA regulation. That, of course, looks at very different things. They don't look at the actual clinical validity of the laboratory-developed test. They're looking at aspects of the laboratory and the credentials of the people that work there, etc. But we are going to provide guidance to companies about how they can use the materials that they have to do under the CLIA regulatory program to support what they need to provide to FDA so that we don't—so we try to minimize any duplication of effort under that circumstance.

Senator HAGAN. When are these guidance—when will these be put forward?

Commissioner HAMBURG. I think I can tell you quite soon. They are at somewhat different stages of development and review, but they will all be moving forward in a timely way.

Senator HAGAN. With the effective dates being—I mean, once you put your guidance forward in the regulatory process, then they would have to take effect? Is there a timeframe?

Commissioner HAMBURG. Draft guidance. It would be draft guidance. So we'd have the opportunity for—

Senator HAGAN. Public comment.

Commissioner HAMBURG [continuing]. Public comment and engagement around the issues as perceived by the various stakeholders, and we would obviously take that into consideration as we move toward final guidance.

Senator HAGAN. I know we've talked a lot today about the drugs and the process there. But in North Carolina, we have about 19,000 biopharmaceutical jobs in our State, and it is such an important part of our economy, and I want to make sure we do all we can to invest in this sector and protect and attract even more jobs.

I've heard from companies that they've experienced, obviously, what we've been talking about, the delays in their approvals. But the main concern has been the FDA's issuance of a complete response letter and the fact that once the FDA issues this complete response letter, the agency is no longer bound by any deadline to make the decision on the product. And the crux of the problem seems to stem from inadequate communication between the agency and the company at all stages of the process. So I would just urge you to help improve upon the efforts to provide frequent, transparent communication with the companies.

Can you tell me, is the FDA providing early feedback to companies to ensure that their application submission contains all the necessary data? And what is the FDA doing to provide companies with feedback when the agency issues this complete response letter or doesn't approve the application?

Commissioner HAMBURG. I think one piece of good news is that, as this chart shows, we actually are approving more things in the first cycle rather than using the complete response. So you can see that from the early days of PDUFA, we've gone from 46 percent approval in the first cycle to now 68 percent. And so that is good news, and it means timely review and approval, and that's for priority MMEs, but similar trends, not quite as marked, for the non-priority review drugs that come before us.

In the PDUFA V categories of activity, we do include a focus on strengthening communication at various stages in the cycle because that really does matter to sponsors, and we do know that it makes a real difference, but it of course does stretch our resources further. So we're very, very happy that that is a part of the PDUFA V strategy, and we think that if we can move forward on that, in fact, it will make a real difference in terms of opportunities to provide more feedback and to address questions early and in a continuing way.

Senator HAGAN. My time has run out. Once again, thank you very much for your service.

Commissioner HAMBURG. Thank you.

The CHAIRMAN. Thanks, Senator Hagan.

I have no more questions.

Senator Enzi.

Senator ENZI. I appreciate all the time that Dr. Hamburg has spent with us. I'll submit some questions in writing and relinquish my time to Senator Burr.

Senator BURR. Thank you. Thank you, Mr. Chairman. I'll try to be brief.

Dr. Hamburg, getting back to a conversation you had with Senator Hatch, in PDUFA we created the opportunity for the FDA to use outside review for predominantly Class I devices with accredited institutions that the FDA could exercise who to accreditate, what the accreditation requirements would be, and whether it extended out of Class I into some Class II. But the objective was to try to move things out of the FDA so that we could stay focused within the FDA with the limited number of reviewers on the most sensitive and potentially difficult devices.

In addition to that, part of PDUFA gave the authority for the FDA to include foreign clinical data in submissions of applicants. Now, the first one with the devices was never fully fleshed. The second one has never been used. Do you see an appropriate use of either one of those options that are current authorities given to the FDA?

Commissioner HAMBURG. We do use data from foreign clinical trials in our drug review and approval.

Senator BURR. But not to substitute for the U.S. trials you require. You use it to supplement. Is that correct?

Commissioner HAMBURG. We can use them. We often do see a situation where there's a U.S.-based trial and an international trial, but we can use foreign clinical trials data.

Senator BURR. I'd love for your staff to highlight any of that that is appropriate that they can share with me.

Commissioner HAMBURG. OK. And we do seek outside expertise in our device review programs as well, and it's actually one of the areas that Dr. Shuren has identified as a priority for strengthening as well, because it is so critical. And as the world of devices gets so much more complex and scientifically and technologically advanced, it is, of course, very hard for FDA to have all of the expertise in-house that's needed to review products.

Senator BURR. One has to question whether you can have an accredited institution approve a band-aid versus the FDA have to be the one to review it and go through it.

Commissioner HAMBURG. We don't spend a lot of time reviewing band-aids.

Senator BURR. Much of your testimony today highlights certain data points and performance goals reports. However, the time to market is probably the most important metric for patients waiting for life-saving products. How would moving from FDA days to calendar days help to ensure that the review clock is not skewed and the performance goals truly reflect the time that it really takes for life-saving products to reach patients?

Commissioner HAMBURG. At the end of the day, I think we all agree that what really matters, the outcome measure that makes the difference, is what American consumers can access in the marketplace. That is our overall goal in terms of the mission of the agency and what we're trying to accomplish.

I think that there are different strategies in terms of identifying the performance goals and the metrics to get there that can be discussed as part of the MDUFA negotiations, and I think that we want to see a program where industry and FDA are working together with clearly defined, achievable goals, and that it has to be a partnership, and that we have to be held accountable for what we can do, and I think industry also has a critical role to play whether it's in terms of the quality of the submissions or the time that they take to respond to our questions.

We are working very hard to make sure that we have the proper oversight, the proper review teams, the proper scientific management structures, that we're asking only for the data that's appropriate and necessary, that we are reviewing what comes before us in as timely a way as possible, that we are seeking the external expertise that we need to be able to make the right decisions in as timely a way as possible.

But we also want to work with industry so that that lag in time in terms of the submitter also declines, and I think that's very, very important. I think we're committed to doing that with industry. I think we agree that there are a set of issues that we need to work on together, that there is a blueprint for action. We need to really clarify that, and then we need to make sure that we have the resources and tools to build on it and make that real.

Senator BURR. Would you be supportive of eliminating FDA days and going to calendar days?

Commissioner HAMBURG. You know, I don't think it's appropriate for me to step up to the negotiating table. I think that that's important—

Senator BURR. I'm not asking you to negotiate. I'm asking you would you be supportive if an initiative, if a legislative initiative went to eliminate FDA days and switch to calendar days.

Commissioner Hamburg. I think it is hard for us to be held completely accountable. If you're talking about trying to achieve a program that really works, we have to have—

Senator BURR. My intent is not necessarily to hold you accountable. My intent is that Members of Congress, policymakers understand how dang long it takes to approve something, and your charts are all based upon FDA days, and I'd be willing to bet that less than 10 percent of the Members up here even understand what FDA days are.

Commissioner HAMBURG. But that is what was negotiated with industry around our performance goals. So that's why we're speaking to that.

Senator BURR. In defense of my colleagues, we all know what calendar days are. So do the American people. And you start talking about FDA days to somebody who's got cancer and waiting for a therapy to be approved, and this is a very difficult thing.

I'm increasingly concerned that the agency is not striking an appropriate risk/benefit balance for patients. The California Health Care Institute recently reported that FDA is focused, "less on the benefits of new products than on potential risk, and to try to mitigate the risk by demanding larger, more expensive, and more costly clinical trials."

In 2007, Congress gave the agency postmarketing risk-evaluation mitigation strategy, REMS, authority to address theoretical risk and empower doctors to prescribe the best medicine for their patients in an attempt to help the agency strike the risk/benefit balance. I'm concerned that this authority is not being used appropriately.

We all want safe and effective drugs. But what are you doing to ensure that there's a balanced approach that does not create a barrier to new drugs such as drugs to treat diabetes or obesity, and has the agency considered the possibility that patients and physicians would be willing to tolerate some level of risk in order to obtain new alternatives to treat costly conditions?

Commissioner HAMBURG. We always do look at the risk/benefit balance, and we recognize that patients are willing to take very significant risks when they face a very serious life-threatening or debilitating disease. We certainly approve drugs all the time that have known associated risks. We do look at what is the risk/benefit balance.

We recently approved a new drug for malignant melanoma, I believe, that has a very high risk, almost 13 percent risk of serious autoimmune disorder associated with it, which can, in fact, even be life-threatening. But the demonstration of benefit in treating a disease that otherwise has so very limited treatment options made that risk/benefit equation make sense.

Another drug that was approved a while back for migraine headaches comes with a significant set of risks, including potential cardiovascular problems. But it is because of the migraine sufferer—it's different than cancer, those headaches can be so severe and debilitating—that that risk/benefit equation was taken.

I do think that in the PDUFA V plan that's going to come before you, we have an opportunity to address risk/benefit in a more systematic way. Industry and FDA agreed that this is a very important area, and that as we really build out a framework for how to systematically look at risk/benefit, we also need to make sure that the patient perspective is very much engaged.

One of the categories of focus in PDUFA V is really going to strengthen our activities in that area and build out a new program. And on the device side, we're going to be putting out very soon guidance about how we think about the risk/benefit equation and recognizing the complexity of the problem and its importance in terms of making sure that we get products to people. And you're

right that our postmarket surveillance authorities also give us different tools as we think about risk and benefit across the life cycle of a product.

Senator BURR. Doctor, let me thank you for being here today, allowing me to go through three sessions. I know to answer any question in FDA is difficult, especially when we're spanning such a timeframe. But I'd like to make one thing abundantly clear to you and to the chairman.

This committee, as well as one in the House, has the policy responsibilities for the Food and Drug Administration. No matter what you negotiate with an industry on user fees, it's got to pass through Congress under a reauthorization. I've raised issues today about measurement tools. If in those agreements there's not something that addresses to my satisfaction the ability to measure, whether it's devices or pharmaceuticals, this will be a very slow and laborious process.

I'm somewhat bewildered that both industries even sat down and talked about reauthorization given what I looked at and my judgments of what they have gotten for the money. It's a disturbing day when I think that the argument is, provide us more money and we'll do a better job. I don't think that's the case.

I think in many cases, follow the statutes and the law, and there's a pathway to either approval or denial. As you know, I'm intimately familiar with FDAMA. In 1997, I was one of the authors. And it amazes me, Mr. Chairman, how far we have strayed from what is the statutory language of the law. I don't think that's something I'd suggest the committee undertake, but if we don't have measurement tools to determine whether a fee system produces a better outcome, then I'm not sure why we would sign off on it as policymakers, and I wanted to be very candid with you today, as I did with the chairman.

If we meet the threshold of satisfaction, I'll be the biggest fan of the agreement. If not, I will do everything to try to change it to make sure that we've got the measures in place that are sufficient for me and for others to agree to sign off on it.

I thank the Chair.

The CHAIRMAN. I thank the Senator from North Carolina.

Commissioner HAMBURG. Can I briefly respond?

The CHAIRMAN. Please.

Commissioner HAMBURG. I do feel obliged to respond. I think that if you look at the PDUFA program, you can really see dramatic changes in our drug review programs that have been fostered, enabled by that important legislation and have really changed review times and have really enabled us to address what was an early concern about Americans not getting access to drugs and therapies as early as people in Europe and elsewhere.

We've seen the dramatic shifts as a result of PDUFA. I think industry would agree that it has made a real difference having that source of stable and predictable funding and the ability to identify together key areas of priority for action. We're at an earlier stage with the MDUFA process, but I think that we have the opportunity to really transform that review process as well and to support the industry in its critical goals.

And so I'm very, very optimistic about what we can achieve through this reauthorization process, very, very eager to work with you and others to provide all of the information that we can.

I think that it is going to be a very productive and meaningful process, and I welcome the opportunity to be here today to begin those discussions and to continue to work with you to achieve the goals that we share of making sure that the American people have access to safe and effective products that can make a difference in their lives, in the lives of their families, and improving the health of our Nation.

The CHAIRMAN. Thank you, Dr. Hamburg. And I thank the Senator from North Carolina.

I have just three or four statements.

Time to market I do not believe is the most important metric, I say to my friend from North Carolina, who is my friend and who is very diligent in his efforts. I don't think time to market is the most important metric. I think safety and effectiveness is the most important metric, first.

Second, when we talk about FDA days, I'm quite familiar with that I say again to my friend from North Carolina, who just had to leave. But why should the clock continue to tick if FDA asks for additional information from the industry, and they don't give the information, they drag it out? Why should the clock continue to run? So again, I understand why we stop the clock until we get that information in.

Third, on the more money and better job, I think if we look at the staffing of FDA 20 years ago—well, I'll go before PDUFA—if you look at the staffing of FDA and the amount and the number of items that they were involved in approving and compare to today, when we have MDUFA and PDUFA, and not only that, we've asked you to do other things, like how about food safety. We just dumped a lot on you 2 years ago on food safety, and I can tell you, I want you to do that. I want the FDA to be more active in inspecting the food that comes from other countries into this country.

So if you look at all of the things that we've asked FDA to do in the last 20 years, and the staffing, I think you will see that if we had kept the staffing at that level, we are understaffed at FDA right now, quite frankly. We are understaffed and underfunded.

So again, more money, better job, that's true. You need more staff to do all the myriad things that we've asked FDA to do.

Last, I'd just say, as we're reauthorizing this, and the user fees that came in, which were meant to help FDA do its job, and it has. I said that in my opening statement. It helped provide a lot of funding to FDA to help speed up the process to provide additional personnel. It has done that. I just hope that there isn't this mistaken idea somewhere out there that somehow that if you provide the money, you get to buy the outcome. I don't want the money buying the outcome. I want the agency to be as independent as possible. I want it to be scientifically based. I want it to use resources that are also scientifically independently based.

Balance? Yes, there should be balance in the input that's coming in. But I don't want anyone to get any mistaken idea that somehow the money is going to buy the outcome.

With that, I request to keep the record open for 10 days for Senators to submit statements and questions for the record, and the hearing will stand adjourned.

Thank you again very much, Commissioner Hamburg.

Commissioner HAMBURG. Thank you.

[Additional material follows.]



## ADDITIONAL MATERIAL

[The New York Times, July 27, 2011]

### STUDY OF MEDICAL DEVICE RULES IS ATTACKED SIGHT UNSEEN

(By Barry Meier)

Allies of the medical device industry are waging an extraordinary campaign in Washington to discredit a coming report by one of the country's pre-eminent scientific groups that examines possible new regulations on the industry.

The scientific group, the Institute of Medicine, is scheduled to release a report on Friday that could propose a tougher approval process for a wide range of devices like hip implants, hospital pumps and external heart defibrillators. The report, commissioned by the Food and Drug Administration, comes after several well-publicized recalls in recent years of devices that have failed in thousands of patients, causing numerous injuries.

But a business group and others have taken the highly unusual step of making a pre-emptive strike, arguing that the report is biased. That attack began even before the study panel finished its review, and has intensified in recent weeks.

Device producers have also released a series of their own reports that say more regulation would slow innovation, harm patients and cost jobs. An official of a group that represents surgeons who implant hips and other artificial joints has also voiced support for a recent filing by a pro-business organization that challenged the scientific report's credibility and argued that the F.D.A. was statutorily required to ignore it.

Christine Stencel, a spokeswoman for the Institute of Medicine, which is part of the National Academy of Sciences, said the group was unaware of a previous instance in which one of its reports, sight unseen, was the target of a similar effort to invalidate it.

Dr. Sheldon Greenfield of the University of California, Irvine, who has served on several Institute of Medicine panels, said he was surprised by the campaign's intensity. "It is pretty audacious," he said.

The challenge to the panel has been led by Ralph F. Hall, a professor of law at the University of Minnesota and a device industry lawyer, who said the criticism was not an attempt to front-run the report's conclusions but rather to air legitimate concerns about how the review had been conducted.

"I could have waited until the report came out," Mr. Hall said in an interview. "That seems intellectually less than satisfactory with me."

Medical experts said the institute's study, regardless of how it falls, was likely to have a significant impact on patient safety, device effectiveness and the speed at which new products reached the market.

With millions of dollars of product sales at stake, the experts said, it is not surprising that the device industry and others would want to avert what they see as potentially restrictive new rules. Still, the lobbying has taken on a tone akin to Washington infighting over an issue like bank regulation, rather than patient health, they said.

"We are trying to get to good policies, and the spin game doesn't help us," said Dr. Harlan M. Krumholz, a professor of medicine at Yale who has served on a different Institute of Medicine panel.

The Institute of Medicine is a widely respected organization that assembles experts to study a range of health-related issues, often at the request of government agencies. In 2009, the F.D.A. contracted with the group to review the adequacy of one of the two regulatory pathways through which it approves medical devices, a process known as 510K.

Some devices, like implanted heart defibrillators, undergo clinical trials in patients before they can be sold. But most medical devices, including implanted hips, go through the 510K route. Under that pathway, a producer need show only that a new product is "substantially equivalent" to one already sold to gain approval.

For example, so-called metal-on-metal artificial hips, which are currently the subject of scrutiny and lawsuits, appeared to work well when tested only on mechanical simulators but then failed disastrously when implanted in patients.

The 12-member review panel assembled by the Institute of Medicine included physicians, academics and two lawyers who had worked for device makers on regulatory issues. Another lawyer on the panel, Brian Wolfman, who once worked for Public Citizen, a consumer advocacy group, has come under particular attack by business-affiliated groups.

Mr. Wolfman and several other panel members declined to be interviewed for this article or did not respond to telephone calls or e-mails.

Last month, the Washington Legal Foundation, a pro-business group, filed a petition with the F.D.A. arguing that the agency was statutorily barred from adopting any of the report's recommendations because of what it claimed was the panel's bias. The legal foundation argued that the Institute of Medicine had failed to balance the panel by including officials from industry, the investment community or patients who had benefited from devices.

"We wanted to let F.D.A. know that there are significant concerns with the composition of the committee," said Richard A. Samp, a lawyer for the legal foundation.

Mr. Samp said his organization took action after the issue was brought to its attention by a lawyer who works at a firm that represents device makers. Shortly after filing its petition, the legal foundation was contacted by an official of the American Academy of Orthopaedic Surgeons, which represents doctors who perform joint replacements, who congratulated it for "taking the bull by the horns," Mr. Samp said.

A spokeswoman for the doctors' group confirmed that one of its officials had called Mr. Samp, adding that it was concerned that the Institute of Medicine panel did not include a practicing surgeon.

William Skane, a spokesman for the National Academy of Sciences, said the group worked hard to balance its committees and barred people from serving on a panel if they had a financial conflict of interest or a clear bias on an issue.

Dr. William Maisel, the chief scientist of the F.D.A. division that oversees medical devices, said the agency was satisfied with the panel's makeup.

"I think it would be difficult to find a more reputable scientific organization than the Institute of Medicine," Dr. Maisel said. He added that the F.D.A. was not bound to accept the report's recommendations.

Over the last year, the panel charged with reviewing device approvals has also held hearings to gather feedback and data from all interested parties, including device producers and investors.

Earlier this year, Mr. Hall, the lawyer and Minnesota professor, wrote an article with a colleague, arguing that the Institute of Medicine, in selecting its panel, had violated a little-known rule, the Federal Advisory Committee Act, which requires balance on such committees.

In the interview, Mr. Hall acknowledged that he had worked either directly or in the same law firm with the two lawyers on the panel who had advised device makers on F.D.A. matters.

At a Congressional hearing this month, the editors of two medical journals—The Journal of the American Medical Association, The New England Journal of Medicine and the Archives of Internal Medicine—questioned the value of two industry-backed studies that claimed that new regulations would create hardships for patients and producers, describing them as methodologically flawed.

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DEPARTMENT OF HEALTH & HUMAN SERVICES,  
FOOD AND DRUG ADMINISTRATION,  
SILVER SPRING, MD 20993,  
*November 10, 2011.*

Hon. TOM HARKIN, *Chairman,*  
*Committee on Health, Education, Labor, and Pensions,*  
*U.S. Senate,*  
*Washington, DC 20510.*

DEAR MR. CHAIRMAN: Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the July 28, 2011 hearing, before the Committee on Health, Education, Labor, and Pensions, entitled "FDA User Fees: Advancing Public Health." This letter provides responses for the record to questions posed by certain members of the committee, which we received on August 12, 2011.

We have addressed our responses to each member. We have re-stated each question below in bold type, followed by FDA's responses.

Thank you, again, for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,

KAREN MEISTER FOR JEANNE IRELAND,  
*Assistant Commissioner for Legislation.*

RESPONSE BY THE FOOD AND DRUG ADMINISTRATION (FDA) TO QUESTIONS OF  
SENATOR ENZI, SENATOR ALEXANDER, SENATOR BURR, AND SENATOR HATCH

SENATOR ENZI

*Question 1.* Beginning in 1998, the Government Accountability Office has called for FDA to implement a series of recommendations to respond to the challenges posed by the globalization of drug manufacturing. What progress has the agency made on GAO's longstanding recommendations? How will your recent reorganization help you make additional progress? Please be as specific as you can in answering these two questions.

*Answer 1.* FDA takes recommendations from the Government Accountability Office (GAO) very seriously. Below are several specific GAO recommendations related to responding to the challenges posed by the globalization of drug manufacturing, followed by the Agency's activities in response to these recommendations.

GAO RECOMMENDATION

FDA should, "[c]onduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics."<sup>1</sup>

AGENCY RESPONSE

In recent years, FDA has taken measures that have resulted in an increased number of foreign inspections, a more sophisticated approach to identifying facilities for inspection, and a more streamlined approach to conducting inspections. For example, we have implemented collaborative efforts with our foreign counterparts, and we have issued a new compliance program within the Compliance Program Guidance Manual (CPGM) for pre-approval inspections that strengthens the criteria for determining when a pre-approval inspection is necessary. We also have established a cadre of dedicated foreign investigators, managed from headquarters with employees located in FDA districts whose work is dedicated to conducting foreign inspection assignments. It is important to note, however, that inspections are necessary but not sufficient to ensure quality.

In large part as a result of these initiatives, FDA has increased the frequency of its foreign Current Good Manufacturing Practice (CGMP) surveillance inspections from 347 in Fiscal Year 2007 to 443 in fiscal year 2010 and the Agency is better positioned to conduct enforcement followup after the issuance of a Warning Letter (WL). The number of WLs issued to foreign facilities also has increased significantly. For example, in calendar year 2008 the Agency issued four WLs to foreign facilities (two to sites in China and two to sites in India), and in 2010, the Agency issued 19 WLs to foreign facilities, also including sites in China and India.

GAO RECOMMENDATION

FDA should "[c]onduct timely inspections of foreign establishments that have received warning letters to determine continued compliance."<sup>2</sup>

During 2010, FDA issued 19 WLs to foreign establishments. Of the 19 establishments that received WLs during 2010, six have been re-inspected. Of the 13 foreign firms to which the Agency issued WLs in 2009, the Agency has already re-inspected 11. The remaining firms are either implementing corrective action plans or will be re-inspected in the near future. Once re-inspected, FDA will determine if they are in compliance with GMPs and evaluate whether or not they can be removed from import alert status.

GAO RECOMMENDATION

FDA should "enforce the requirements that establishments manufacturing drugs for the U.S. market update their registration annually."<sup>3</sup>

AGENCY RESPONSE

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) most foreign drug establishments shipping drugs to the United States must register with FDA electronically. Registration is completed through FDA's electronic drug registration and listing system (eDRLS) and must be resubmitted on or before Decem-

<sup>1</sup> GAO, *Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program*, GAO-08-970, September 2008, p. 8.

<sup>2</sup> *Ibid.* page 43.

<sup>3</sup> *Ibid.* page 43.

ber 31 of each calendar year. The implementation of eDRLS helps FDA to identify foreign establishments that have not satisfied their statutory registration obligations and helps the Agency to assemble more reliable information about drug establishments.

Revising FDA's statutory provisions to modernize drug registration and listing may improve the timeliness, completeness, and accuracy of FDA's current database, making sure that FDA has accurate and up-to-date information about foreign and domestic parties involved in medical product manufacture.

#### GAO RECOMMENDATION

FDA should "[e]stablish mechanisms for verifying information provided by the establishment at the time of registration."<sup>4</sup>

#### AGENCY RESPONSE

FDA recently hired a contractor to verify registrations of foreign firms. A total of 373 site visits were conducted over a 3-year period. Of the 373 visits, 142 sites were drug firms. Two-hundred and thirty sites were food firms, and one site was a medical device firm. The contract ended in August 2011 and FDA is also continuing to explore additional avenues for verifying the registration information submitted by foreign facilities.

FDA, working with Dun and Bradstreet (D&B), has established a pilot project to verify foreign establishments in the drug GMP inventory for whom FDA's records are incomplete or dated. The U.S. Customs and Border Protection identified for the pilot nearly 160 establishments who have shipped drugs to the United States from these countries in recent years. D&B employees located in India and China are using phone calls, email, site visits or a combination of these methods to engage to attempt to acquire complete and accurate registration information. About two-thirds of the verifications are complete.

FDA is also working towards use of a unique facility identifier, such as the D&B DUNS number, which would allow the Agency to verify the accuracy of registration information using robust, established databases. Section 510(e) of the FD&C Act states that the Secretary may assign a registration number to any establishment registered in accordance with section 510. However, FDA does not currently have explicit statutory authority to require the submission of a unique identifier, such as a DUNS number, as a condition of drug establishment registration and drug import. Current FDA guidance states that DUNS numbers serve as the registration numbers for drug establishments in the electronic system, and thus recommends, but does not require, that industry provide DUNS numbers during the registration and listing process.

#### GAO RECOMMENDATION

FDA should "[e]nsure that information on the classification of inspections with serious deficiencies is accurate in all FDA databases."<sup>5</sup>

#### AGENCY RESPONSE

In 2008, GAO identified discrepancies between the Office of Regulatory Affairs' (ORA's) Field Accomplishments and Compliance Tracking System (FACTS) database and the Center for Drug Evaluation and Research's (CDER's) Office of Compliance Foreign Inspection Tracking System (OCFITS) database, with regard to the types of action indicated in following a foreign inspection. Since GAO's report, FDA has identified the cause of these discrepancies and has implemented measures to prevent them in the future.

CDER's Office of Compliance has now replaced OCFITS with a new information management system referred to as Compliance Management Services. The new system links directly to FACTS for some critical information and the information about sites and inspection events is more accurate than the earlier system, OCFITS.

#### GAO RECOMMENDATION

FDA should [c]onduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics."<sup>6</sup>

<sup>4</sup> Ibid, page 43.

<sup>5</sup> Ibid, page 43.

<sup>6</sup> Ibid, page 43.

## AGENCY RESPONSE

FDA has committed to conducting more foreign inspections to achieve the Agency's goal of addressing the risks posed by the global supply chain. The Agency increased foreign inspections by 27 percent from 2007 to 2010 as stated above and it continues to identify opportunities for increasing our surveillance and knowledge about foreign drug manufacturers whose drugs are consumed in the United States.

The statute directs FDA to inspect domestic manufacturers every 2 years. However, an overall risk-based approach to foreign and domestic inspections would be a far better approach than a mandatory inspection frequency. There are a number of obstacles that make conducting foreign inspections challenging, including:

- Cost of conducting foreign inspections—it is exponentially more expensive to conduct a foreign inspection than a domestic inspection.
- Sovereignty issues—FDA must obtain a visa to enter a foreign country in order to conduct an inspection, and a firm does not have to let FDA in, although the product would not be approved if a pre-approval inspection is necessary.
- Cooperation with the foreign firm—FDA must notify foreign firms of the Agency's intent to conduct an inspection and rely upon foreign firms to facilitate the inspection. While foreign firms that refuse to permit FDA inspection present a challenge to achieving a 2-year inspection frequency, it does not impede FDA's ability to protect the safety of the drug supply. FDA may refuse entry of goods from foreign firms that refuse to permit FDA inspection and may withhold approval of pending new drug applications submitted by firms that refuse to permit an FDA inspection.

Given the challenges in achieving a 2-year inspection frequency abroad, FDA has supplemented its use of foreign inspections with other reliable sources of compliance information and has instituted risk analytics to make best use of this information, including:

- Using the PREDICT import information technology system to target the highest-risk entries for further scrutiny, field examinations, and/or sample collection analyses.
- Establishing dedicated foreign cadres: FDA has established dedicated cadres of foreign investigators for pharmaceutical, device, and foreign food inspections.
- Increasing leveraging: FDA continues to increase its collaborative efforts with foreign counterparts.

## GAO RECOMMENDATION

FDA should “take steps to enhance strategic planning to ensure coordination between overseas and domestic activities and develop a workforce plan to help recruit and retain overseas staff.”<sup>7</sup>

## AGENCY RESPONSE

We now have permanent FDA overseas posts in Beijing, Shanghai, and Guangzhou, China; New Delhi and Mumbai, India; San Jose, Costa Rica; Mexico City, Mexico; Santiago, Chile; Brussels, Belgium; London, England; and Parma, Italy. This year, we have opened posts in Amman, Jordan and Pretoria, South Africa. These offices enable us to have a regional presence around the world and serve as important hubs for improved coordination with regulatory authorities and industry in other nations. FDA personnel assigned to these posts can also conduct and facilitate inspections.

The Agency is doing strategic and operational planning for its foreign offices and has initiated a workforce planning process. As noted in the GAO report, FDA recognizes that this process will be ongoing and informed by the experience of several cycles of overseas staff appointments (deployment and return), and that the Agency will benefit from the process.

We are also supporting our strategic planning efforts by employing the FDA-TRACK performance management initiative to identify and track performance indicators and milestones for key program activities. The transparency of this management process contributes to the coordination of our overseas and domestic activities. For more information, please visit: <http://www.fda.gov/AboutFDA/Transparency/track/default.htm>.

<sup>7</sup> GAO, *Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-term Planning is Needed*, GAO-10-960, Highlights.

## AGENCY REORGANIZATION

You also asked how our recent reorganization will help us make additional progress. On July 13, 2011, we announced that the Office of the Commissioner (OC) would be restructured to more accurately reflect the Agency's responsibilities, subject matter expertise, and mandates in an ever-increasing complex world, where products and services do not fit into a single category. OC has been divided into "directorates" that reflect the core functions and responsibilities of the Agency. This new management structure will enable OC to better support the Agency's core scientific and regulatory functions, and help tie together programs that share regulatory and scientific foundations.

As part of this reorganization, the Agency created a new position, Deputy Commissioner for Global Regulatory Operations and Policy, to provide broad direction and support to ORA and to the Office of International Programs. The Deputy Commissioner is charged with ensuring that FDA responds to the challenges of globalization and import safety and ensures that globalization issues are a top priority for the Agency in the years to come.

*Question 2.* FDA has committed to provide a guidance on the artificial pancreas by December of this year. Publication of a draft guidance is a very important first step, but it is just that, a first step. Can you assure me that the final guidance will reflect the input of clinical experts and that FDA will finalize it in a timely way so products can be timely tested and moved to market?

FDA is committed to facilitating and expediting development of the artificial pancreas and continues to work diligently with stakeholders. The low-glucose suspend system draft guidance, issued on June 22, 2011, was developed with considerable input from industry, researchers, and the clinical community. The Agency requested additional feedback through a 90-day public comment period. FDA is now reviewing and addressing the comments received and will finalize that guidance document as expeditiously as possible.

As part of the outreach for the low-glucose suspend draft guidance, FDA specifically targeted health care professionals, alerting them to the availability of the draft guidance and asking for their comment. Provider groups targeted include the Diabetes Technology Society, the American Association of Clinical Endocrinologists, the American Diabetes Association, the Endocrine Society, the Juvenile Diabetes Research Foundation, the National Institutes of Health, the Endocrine Nurses Society, and the American Association of Diabetes Educators.

FDA will continue to collaborate with the medical community and other stakeholders and will continue our efforts to prioritize and expedite clinical research in this area.

A critical aspect of a second draft guidance, which is currently under development, for the more sophisticated treat-to-target or treat-to-range systems<sup>8</sup> is addressing their safety in real-world scenarios, i.e., outside of the protection of the clinical or hospital setting. That guidance is projected for publication in December 2011.

## SENATOR ALEXANDER

*Question 1.* I have heard from a start-up device company in my home State of Tennessee that, "Whenever people call us looking for employment we tell them we can't hire them, because the Federal Government won't let us." They went on to cite some of the several studies published in recent months that make comparisons between the EU and U.S. systems of medical device regulation, which they feel indicate that the FDA is over-regulating the U.S. medical device industry, which has a negative effect on the industry's ability to raise capital and create jobs and doesn't make medical devices safer in the United States than they are in Europe.

My question is, why if a product is available in Europe would that product need to go through more pre-clinical testing before beginning a U.S. clinical trial? Why isn't an EU CE Mark approval ("European Conformity" meaning it conforms to all required safety and health standards) to use in humans enough to allow access for Americans via a clinical trial?

<sup>8</sup>A treat-to-range system reduces the likelihood of a hypoglycemic event or a hyperglycemic event (when blood glucose is dangerously high) by adjusting insulin dosing only if a person's glucose level approaches the low or high glucose thresholds. Patients using this system will still need to check blood glucose levels with a glucose meter and give themselves insulin to maintain control of glucose levels. A treat-to-target system sets target glucose levels and tries to achieve these levels at all times. It would be fully automated and require no interaction from the user, except for calibration of the continuous glucose monitoring system.

Answer 1. The FD&C Act requires that a Class III medical device (i.e., those with the highest risk) be approved on the basis of clinical data demonstrating reasonable safety and effectiveness for its intended uses. The fact that a device has received the European Union (EU) CE mark of approval tells us nothing about the clinical data underlying that decision. However, FDA does not require studies to support device approvals to be conducted in the United States. We accept trials or data from outside the United States as long as the studies meet regulatory standards and are applicable to U.S. populations.

Data collected from other countries can be used to support a product's safety and effectiveness. Foreign studies performed under an Investigational New Drug (IND) application or Investigational Device Exemption (IDE) must meet the same requirements of 21 CFR part 312 or 21 CFR part 812, respectively, that apply to U.S. studies conducted under an IND or IDE. The acceptance of foreign clinical studies not conducted under an IND or IDE, as support for a marketing application, is generally governed by 21 CFR 312.120 and 21 CFR 814.15.

A marketing application that is based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if:

- the foreign data are applicable to the U.S. population and medical practice;
- the studies have been performed by clinical investigators of recognized competence; and
- the data may be considered valid without the need for an on-site inspection by FDA or if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means.

*Question 2.* Is there something about the U.S. device review system that is inherently slower than that of the EU? Yes there are different standards, but is there something unique about our system that leads to delays in patient access?

Answer 2. A recent industry-sponsored study<sup>9</sup> compared time to market between the United States and the EU. Although the study is flawed in some regards, it does show that devices subject to a 510(k) without clinical data tend to come on the market first, as often or more often in the United States as in the EU. That's approximately 90 percent of devices marketed in the United States. Higher risk medical devices are typically approved faster in the EU than in the United States because, unlike the United States, the EU does not require the manufacturer to demonstrate that the device actually benefits patients.

*Question 3.* Could you please define "reasonable assurance?" Does this term also include some risk?

Answer 3. Although a manufacturer may submit any form of evidence to FDA in an attempt to substantiate the safety and effectiveness of a device, by statute the Agency must rely upon valid scientific evidence to determine whether there is "reasonable assurance" that the device is safe and effective. After considering the nature of the device and the rules in 21 CFR 860.7, FDA determines whether the evidence submitted or otherwise available to FDA is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device, and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.

There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

In order for industry and others to better understand how FDA makes these decisions, we recently published for public comment a "Draft Guidance for Industry and Food and Drug Administration Staff—Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Review," which may be viewed at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm>.

*Question 4a.* I hear from device manufacturers that they are looking for more consistency and predictability, which you state in your testimony that you have heard for yourself, and the standard in the United States is safety and effective while in the EU the standard is safety and performance. Is there something about the U.S.

<sup>9</sup>California Healthcare Institute and The Boston Consulting Group. "Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry" (Feb. 2011), available at <http://www.bdg.com/documents/file72060.pdf>.

standard that prevents FDA from providing consistency and predictability in the review process? (YES OR NO)

Answer 4a. No. There is nothing inherent in the U.S. standard that prevents consistency and predictability in the review process. However, safety and effectiveness is a higher standard than safety and performance. For example, in the EU, to clear a laser to cut heart tissue to treat heart arrhythmia, it must only be demonstrated that the device cuts tissue. In the United States, it must be demonstrated that the patient actually benefits from the cutting of the tissue, i.e., that the laser treats the arrhythmia.

Comparisons between the United States and EU systems are not easy to make, as the European device review process is less transparent than FDA's. There are significant differences between the EU and U.S. device review systems. In the EU:

- Manufacturers do not have to demonstrate that their products are effective at treating the disease or condition for which they are approved;
- Private entities chosen and paid by manufacturers review and approve medical devices by giving them a CE mark; these decisions are kept confidential and not released to the public or to EU regulatory bodies;
- There is not one, centralized regulatory body for review of medical devices: instead, each member State has its own system for determining reimbursement of medical devices and it is impossible to track approvals, adverse events, or recalls; and
- There is little to no publicly accessible, centralized system for collecting and monitoring information about device approvals or safety problems.

These differences have recently been highlighted by several prestigious European medical journals. Both the *British Medical Journal*<sup>10</sup> and the *European Society of Cardiology*<sup>11</sup> have published reports noting that the lack of transparency and clinical data requirements in the EU system have led to patient harm.

For more information about steps FDA is taking to improve consistency and predictability in its review processes, see the answer to the following question.

*Question 4b.* Why are we seeing this lag? Is it because your reviewers are not properly trained? Is it because you are not using resources at your disposal such as interactive review? Is it because FDA guidance is lacking?

Answer 4b. As noted in answer to question #2, a recent industry-sponsored study<sup>12</sup> compared time to market between the United States and the EU. Although the study is flawed in some regards, it does show that devices subject to a 510(k) without clinical data tend to come on the market first, as often or more often in the United States as in the EU. That's approximately 90 percent of devices marketed in the United States. Higher-risk medical devices are typically approved faster in the EU than in the United States because, unlike the United States, the EU does not require the manufacturer to demonstrate that the device actually benefits patients.

Although FDA is meeting its 510(k) performance goals under MDUFA, overall time to decision (i.e., FDA review time plus industry response time) for 510(k) submissions has increased over the past 10 years, due primarily to an increase in the number of review cycles and in the amount of time companies take to respond to requests for additional information.

We recognize our role in this and are taking steps to address it. The two reports we released publicly in August 2010, with our analyses and recommendations, showed that we have not done as good a job managing our premarket review programs as we should and that we need to take several critical actions to improve the predictability, consistency, and transparency of these programs.

For example, we have new reviewers who need better training. We need to improve management oversight and standard operating procedures. We need to provide greater clarity for our staff and for industry through guidance about key parts of our premarket review and clinical trial programs and how we make benefit-risk determinations. We need to provide greater clarity for industry through guidance

<sup>10</sup>Deborah Cohen, "Europeans Are Left to Their Own Devices," *British Medical Journal* 342:d2748 (2011), available at <http://www.bmj.com/content/342/bmj.d2748.full.pdf>.

<sup>11</sup>Alan G. Fraser, et al., "Clinical Evaluation of Cardiovascular Devices: Principles, Problems, and Proposals for European Regulatory Reform: Report of a Policy Conference of the European Society of Cardiology," *European Heart Journal* 32 (13): 1673–86, available at <http://eurheartj.oxfordjournals.org/content/32/13/1673.full.pdf+htm>; See also Jacqui Wise, "Cardiologists Call for a Single European System to Oversee Medical Devices," *British Medical Journal* 342:d3144 (2011), available at <http://www.bmj.com/content/342/bmj.d3144.full.pdf>.

<sup>12</sup>California Healthcare Institute and The Boston Consulting Group, "Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry" (Feb. 2011), available at: <http://www.bdg.com/documents/file72060.pdf>.



and greater interactions about what we need from them to facilitate more efficient, predictable reviews. We need to make greater use of outside experts who understand cutting-edge technologies. And we need to find the means to handle the ever-increasing workload and reduce staff and manager turnover, which is almost double that of FDA's drugs and biologics centers.

In January 2011, FDA announced a Plan of Action that included 25 specific actions that we would take this year to improve the predictability, consistency, and transparency of our premarket programs. The following month, we announced our Innovation Initiative, which included several proposals to help maintain the position of the United States as the world's leader in medical device innovation, including the creation of a new approach for important, new technologies called the Innovation Pathway.

Since then, we have announced additional efforts to improve our premarket programs, including actions to improve our program for clinical trials and the Investigational Device Exemption (IDE) program. The actions we are taking can be grouped into three main areas of emphasis:

- Create a culture change toward greater transparency, interaction, collaboration, and the appropriate balancing of benefits and risks;
- Ensure predictable and consistent recommendations, decisionmaking, and application of the least-burdensome principle; and
- Implement efficient processes and use of resources.

Specific steps that we are taking, many of which are supported by industry, include:

- Issuing guidance clarifying the criteria used to make benefit-risk determinations a part of device premarket decisions to provide greater predictability and consistency and apply a more patient-centric approach by considering patients' tolerance for risk in appropriate cases (draft guidance issued August 15, 2011);
- Creating standard operating procedures for when a reviewer can request additional information regarding a premarket submission and at what management level the decision must be made to provide greater predictability, consistency, and the appropriate application of the least-burdensome principle by reducing the number of inappropriate information requests (Standard Operating Procedures issued November 2011);
- Developing a range of updated and new guidances to clarify CDRH requirements for predictable, timely, and consistent product review, including device-specific guidance in several areas such as mobile applications (draft guidance released July 19, 2011) and artificial pancreas systems (to be completed by the end of 2011);
- Revamping the guidance development process through a new tracking system and, to the extent resources permit, core staff to oversee the timely drafting and clearance of documents (to be completed by the end of 2011);
- Improving communication between FDA and industry through enhancements to interactive review (some of these enhancements will be in place by the end of 2011);
- Streamlining the clinical trial and IDE processes by providing industry with guidance to clarify the criteria for approving clinical trials, and criteria for when a first-in-human study can be conducted earlier during device development to create incentives to bring new technologies to the United States first (guidance to be issued November 2011) (IDEs are required before device testing in humans that involve significant risks may begin, and they ensure that the rights of human subjects are protected while gathering data on the safety and efficacy of medical devices);
- Implementing internal business process improvements to ensure that decisions are made by the appropriate level of management, that decisions are made consistently and efficiently, and that we appropriately apply the least-burdensome principle. For example, CDRH created the internal Center Science Council (Council) to actively monitor the quality and performance of the Center's scientific programs and ensure consistency and predictability in CDRH scientific decisionmaking (Council established March 31, 2011);
- Creating a network of experts to help CDRH resolve complex scientific issues, which will ultimately result in more timely reviews. This network will be especially helpful as FDA confronts new technologies (Standard Operating Procedures issued September 30, 2011);
- Instituting a mandatory Reviewer Certification Program for new reviewers (program launched September 2011);
- Instituting a pilot Experiential Learning Program to provide review staff with real-world training experiences as they participate in visits to manufacturers, research, and health care facilities, and academia (to begin in early 2012);
- Providing industry with specific guidance on how to ensure the quality and performance of clinical trials while applying the least-burdensome principle, and there-

by conduct studies that are more likely to support the approval of their products (guidance released August 15, 2011); and

- Streamlining the *de novo* review process, the pathway by which novel, lower-risk devices without a predicate can come to market (draft guidance released September 30, 2011).

A recent FDA analysis<sup>13</sup> shows that poor submission quality is a major contributor to the increase in total review times. The most common deficiencies included:

- Inadequate device descriptions;
- Discrepancies throughout the submission;
- Failure to address necessary information as outlined in guidance documents;
- Problems with the proposed indications for use;
- Completely missing performance testing; and
- Completely missing clinical data.

In addition, sponsors' failure to address deficiencies identified in first-round Additional Information (AI) Letters is a major contributor to the increase in total review times. For example, 65 percent of the time, FDA sent a second-round AI Letter because the sponsor failed to submit information requested in the first AI Letter.

FDA has already taken steps to address some of the issues identified in this analysis. We are working to provide greater predictability for industry by communicating justified changes in data requirements more quickly and transparently. We recently issued draft Standard Operating Procedures for Notice to Industry Letters,<sup>14</sup> which provides a format for communicating changes more quickly within the existing Good Guidance Practices framework. FDA is also enhancing training for staff and industry, which is aimed at reducing inappropriate requests for additional information and helping sponsors understand when they are required to submit data. We will continue to work with industry to identify additional actions to reduce the average number of review cycles and the percent of 510(k) submissions for which an AI Letter is sent.

Through these and other steps we are taking to address weaknesses in the 510(k) program, FDA aims to reduce the total time to clearance for 510(k) devices, while assuring that we maintain the same levels of safety and effectiveness. It is our hope that taking actions to increase submission quality and avoid inappropriate requests for additional information will prevent avoidable delays and reduce total time to decision, which will, in turn, get safe and effective devices to market faster.

With regard to PMA applications, FDA's internal analysis found that, for those PMAs that were not reviewed within the performance goals, the main reasons for the longer review times were:

- Poor quality clinical studies, such as clinical trial execution issues and problematic data analyses;
- Reviewer turnover, especially changing medical officers and branch chiefs; and
- Taking a PMA to an FDA advisory committee. (In general, all PMAs for the first-of-a-kind device are taken before the appropriate advisory panel for review and recommendations. The preparation for an FDA advisory committee involves significant calendar time and review team resources.)

*Question 4c.* While I appreciate that you have taken steps to address some of these issues, what else are you doing right now in the short term to manage and increase consistency and predictability in the review process?

*Answer 4c.* Our most recent activities aimed at increasing consistency and predictability in the medical device review process include the following:

- On September 6, 2011, CDRH announced that our new Reviewer Certification Program, which began as a pilot in April 2010 with participants from CDRH's Division of Anesthesia, General Hospital, and Infection Control and Dental Devices, would launch that month and is intended to include all new device reviewers. The program includes up to 18 months of training, aimed at complementing the skills and knowledge that new reviewers bring to CDRH from fields such as biomedical engineering and health care. Reviewers in the program will complete online training modules and instructor-led courses, and obtain practical experience in the medical device review process.<sup>15</sup>

<sup>13</sup> CDRH, "Analysis of Premarket Review Times Under the 510(k) Program" (July 2011), available at <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm263385.htm#5>.

<sup>14</sup> CDRH, "Standard Operating Procedure for 'Notice to Industry' Letters" (August 2011), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259172.pdf>.

<sup>15</sup> CDRH also announced that it is developing a pilot Experiential Learning Program for pre-market reviewers, which will include visits to academic institutions, manufacturers, research or-

- On August 15, CDRH issued draft guidance (with a request for public comment) to help researchers and manufacturers design better quality clinical studies in support of PMA applications for medical devices. Manufacturers submit PMA applications for high-risk (Class III) medical devices. These applications undergo the most stringent type of FDA device review. PMA submissions include data from pivotal clinical studies, which FDA uses, along with other information, in determining approval.
- Also on August 15, CDRH published draft guidance (with a request for public comment) clarifying how benefit-risk determinations are made during premarket review of certain medical devices. The guidance focuses on PMAs—the regulatory pathway for high-risk medical devices. The recommendations made in the guidance are intended to improve the predictability, consistency and transparency of the premarket review process for applicable devices, and should help manufacturers navigate the approval process more easily.

*Question 5.* I have another question relating to the consistent application of regulatory standards and maintaining a level playing field for all manufacturers. Again, I have heard from manufacturers in Tennessee who feel that the current criteria demanded by CDRH to evaluate new medical devices in a specific product class can seem arbitrary. They feel the criteria often are inconsistent with FDA precedent for similar devices, and changes in the criteria are not scientifically justified by CDRH. They say it has become a noticeable trend during the last 2 years, and is exacerbated by staffing changes at the agency and lack of reviewer training. More specifically, CDRH appears to be applying clinical trial success requirements that are significantly different with respect to primary and secondary endpoints from those that have been used to evaluate and approve other products, even those approved within the past 18 months. The application of new standards for approvability of similar products that exceed the standards applied to contemporary approvals negatively impact both patients and jobs while also increasing healthcare costs by limiting competition. Please comment on the regulatory process and statutory standards at CDRH that allow review teams to arbitrarily (no scientific or regulatory standard basis) apply different criteria to the new products of a given class that are far above those criteria used to approve similar device types that have been recently (within the past 18 months) reviewed by an FDA Advisory Panel and approved by the FDA.

*Answer 5.* Consistent with the requirements for 510(k) submissions, FDA may require clinical data when a firm seeks a new indication for use or where there are differences in the technological characteristics between the firm's device and its predicate that could affect safety or effectiveness. FDA asks for clinical studies in only 8 to 10 percent of 510(k) submissions, and often the requested studies are simple and small. For example, FDA recommends that for pulse oximeters—medical devices that indirectly monitor the oxygen saturation of a patient's blood—clinical data be collected from as few as 10 patients. In addition, for establishing clinical data in support of a 510(k) application, the Agency recognizes a standard set by the Association for the Advancement of Medical Instrumentation, which requires a validation study consisting of as few as 35 subjects for which clinical data are required. Consistent with statutory requirements, all PMAs contain clinical data.

The Agency has no data to suggest that, as a general matter, FDA has demanded larger, more extensive clinical trials in the past 5 years for 510(k)s or PMAs. Clinical studies are tailored to the type of device and the specific questions that need to be addressed. That is not to say that FDA demands full knowledge and understanding of long-term risks and performance before it will approve a device for marketing. For PMA devices, the Agency increasingly uses its authority to require post-approval studies to answer important, specific questions regarding device performance after the device has been approved for marketing. For example, if there are questions about long-term durability of an implanted device, the Agency may allow the device to be marketed while further data collection continues to address that issue.

Whenever possible, FDA seeks to minimize clinical trial or preclinical requirements when scientific knowledge suggests that this is appropriate. For example, establishing the safety and effectiveness of a first-generation drug eluting stent (DES) required extensive preclinical testing programs and clinical studies. However, the fundamental work performed to gain initial approval of first-generation DES devices has been successfully leveraged by several DES manufacturers to decrease clinical

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ganizations, and health care facilities and is intended to give reviewers a better understanding of how medical devices are designed, manufactured and used. The Experiential Learning Program is in the design stage and scheduled to begin as a pilot program in 2012.

trial requirements for next-generation stents, which typically incorporate modest changes to the first-generation design.

More specifically, FDA reviewers concluded that a single-arm clinical trial (rather than a randomized controlled study) would be an acceptable design for the pivotal IDE trials of the Boston Scientific TAXUS® Liberte™, Abbott XIENCE Prime™, and Medtronic Resolute® next-generation DES. The reason CDRH permitted this approach is that these devices represent iterations of prior DES, in which a component of the combination product has been modified (e.g., a polymer coating or stent platform). This was acceptable based on our analysis of the comprehensive pre-clinical and clinical data generated from the prior generation DES, and demonstrates the Agency's flexibility and willingness to tailor data requirements when appropriate.

Another example is the total artificial hip. CeramTec purchased the rights to the Wright Medical TRANSCEND® ceramic-on-ceramic total artificial hip clinical data set and approved PMA. Because the articulating surfaces of the components are all manufactured by CeramTec, FDA allowed manufacturers to use preclinical testing to leverage the Wright Medical TRANSCEND® data set. Five manufacturers had their PMAs approved referencing the TRANSCEND® clinical data set with a condition of approval to conduct a post-approval study in a new cohort of patients.

This sometimes works in the other direction, too, in that information gleaned from competitor application reviews and post-market studies may bring to light information that changes the risk-benefit analysis and causes the Agency to look more critically at the next submission in a product category. This is appropriate. The reasons for it cannot always be shared with applicants due to statutory confidentiality requirements, possibly causing the Agency to appear arbitrary.

Under the 510(k) Action Plan, we have established an internal Center Science Council (Council) to actively monitor the quality and performance of the Center's scientific programs and ensure consistency and predictability in CDRH scientific decisionmaking. The Council, which is comprised of experienced managers and employees, operates under the direction of the Deputy Center Director for Science and is responsible for overseeing science-based decisionmaking across CDRH, including premarket review; periodically auditing decisions and assessing program performance; and acting as a resource for staff on scientific questions, to support greater consistency in decisionmaking and the treatment of cross-cutting issues. We are also creating a network of experts to help CDRH resolve complex scientific issues. This network will be especially helpful as FDA confronts new technologies. And we are instituting a mandatory Reviewer Certification Program for new reviewers, as detailed in our answer to question #4.

*Question 6.* Last week, the FDA released a report called the "Analysis of Premarket Review Times under the 510(k) Program." In reviewing this report, I am curious about the FDA's conclusion that in the Premarket Review Time analysis that poor quality submissions are the major cause of the increased review times for 510(k) submissions. Is the FDA implying that the medical device industry has universally forgotten how to submit a good, quality application? Could another explanation be that application process has become less predictable, more risk averse, and therefore, is requiring more data and information in 510(k) submissions than it has in the past?

Answer 6. FDA's standards for the review of medical devices are specified in statute and our application of those standards has not changed.

Application quality has always varied and the Agency has consistently strived to help device manufacturers, many of which are small companies, through a sometimes unfamiliar process, rather than refuse deficient applications. Since the advent of MDUFA, the time cost associated with that extra assistance has taken on added significance.

The study cited in your question—which is available on FDA's Web site at: <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm263385.htm>—showed that poor submission quality and sponsors' failure to address deficiencies identified in first-round AI Letters are major contributors to the increase in total review times. We are pleased that, in response to FDA calls for improving the quality of premarket submissions, the medical device trade association, AdvaMed, has improved and made available more training courses for its companies to help them develop 510(k) and PMA submissions that meet FDA standards.

We also recognize our role in this and are taking steps to address it. The two reports we released publicly in August 2010, with our analyses and recommendations, showed that we had not done as good a job managing our premarket review programs as we should and that we need to take several critical actions to improve the predictability, consistency, and transparency of these programs.

In January 2011, FDA announced a Plan of Action that included 25 specific actions that we would take this year to improve the predictability, consistency, and transparency of our premarket programs. The following month, we announced our Innovation Initiative, which included several proposals to help maintain the position of the United States as the world's leader in medical device innovation, including the creation of a new approach for important, new technologies called the Innovation Pathway. For details on specific activities, please see our response to question #4.

*Question 7.* The Analysis of Premarket Review Times under the 510(k) Program, released last week, states that,

“FDA develops guidance documents and recognizes standards established by national and international standards development organizations to provide greater predictability, consistency and transparency in our premarket review programs.”

Yet, I along with my colleagues keep hearing from companies in our States that just the opposite is occurring specifically, we hear that the goal posts keep being moved. Additional Information (AI) letters are issued requiring submitters to provide data that are above and beyond what is stated in the guidance documents, as well as other deviations from published guidance and standards. What is FDA doing to ensure that all guidance available to the public is up-to-date, and if not, that all data requirements not addressed in, or changed from, current guidance are consistently conveyed to industry prior to submission of a 510(k)?

Answer 7. Developing and updating guidance documents is a resource-intensive task, currently performed by the same professionals who review device applications. Additional resources devoted to guidance development are necessary to optimize this function. Nevertheless, we are taking steps to improve the guidance development process through the 510(k) Action Plan<sup>16</sup> and have stepped up development of specific guidance documents that will make the review process more predictable, consistent, and transparent. Examples include streamlining *de novo* classification, clarifying when changes to a device require a 510(k),<sup>17</sup> and improving the quality of clinical trials.<sup>18</sup>

The study that you reference<sup>19</sup> showed that reviewers do not often ask for data inappropriately. Results of first round AI Letters in Cohort 1 showed that reviewers asked for data that had not previously been requested for particular device types only 12 percent of the time. Of those requests, 8 percent were inappropriate. Results of second round AI Letters in Cohort 2 showed that reviewers asked for data that had not been previously requested 4 percent of the time. Of those requests, 2 percent were inappropriate.

This analysis shows that poor submission quality and sponsors' failure to address deficiencies identified in first-round AI Letters are major contributors to the increase in total review times. For example, 65 percent of the time FDA sent a second-round AI Letter because the sponsor failed to submit information requested in the first AI Letter. However, FDA has also contributed to the increase by making inappropriate requests for additional information in limited instances.

FDA will continue to work with industry to identify additional actions to reduce the average number of review cycles and the percent of 510(k) submissions for which an AI Letter is sent. FDA has already taken steps to address some of the issues identified in this analysis. We are working to provide greater predictability for industry by communicating justified changes in data requirements more quickly and transparently. We recently issued a draft Standard Operating Procedure for

<sup>16</sup>CDRH, “Plan of Action for Implementation of 510(k) and Science Recommendations” (January 2011), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM239450.pdf>.

<sup>17</sup>CDRH, “Draft Guidance for Industry and FDA Staff—510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device” (July 2011), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265274.htm>.

<sup>18</sup>CDRH, Draft Guidance for Industry, Clinical Investigators, and Food and Drug Administration Staff—Design Considerations for Pivotal Clinical Investigations for Medical Devices” (August 2011), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm>.

<sup>19</sup>CDRH, “Analysis of Premarket Review Times Under the 510(k) Program” (July 2011), available at <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm263385.htm>.

“Notice to Industry” Letters,<sup>20</sup> which provides a format for communicating changes expeditiously within the existing Good Guidance Practices framework. FDA is also enhancing training for FDA staff and industry, which is aimed at reducing inappropriate requests for additional information and helping sponsors understand when they are required to submit data.

Through these and other steps we are taking to address weaknesses in the 510(k) program, FDA aims to reduce the amount of time to clearance for 510(k) devices, while ensuring that we maintain the same standards of safety and effectiveness. It is our hope that taking actions to increase submission quality and avoid inappropriate requests for additional information will prevent avoidable delays and reduce review times, which will, in turn, get safe and effective devices to market faster.

*Question 8.* I’m concerned about what appears to be a lack of urgency on the part of FDA with respect to newer, better therapies to treat diabetes and obesity. These are diseases that increasingly threaten our Nation’s health care system—diabetes alone accounts for one-third of Medicare costs and almost 80 million Americans have pre-diabetes (on top of the 25.8 million Americans already living with the disease).

My home State of Tennessee has one of the highest obesity rates at being over 30 percent, and obesity is nearing epidemic proportions across the country. We are at a time in our history where reports by distinguished journals of medicine and health experts say today’s children are likely to be the first generation to live shorter, less healthy lives than their parents. This is a health care crisis. One of the biggest reasons for this is the growing childhood obesity problem, and the increasing rates of diseases normally associated with adults such as Type 2 diabetes, heart disease, and other chronic illnesses.

What are you doing to encourage the development of new therapies to treat these diseases? Are you considering using the authority given to the FDA under REMS to follow the drugs closely after approval?

It’s essential that we take strong steps to prevent the spread of diabetes through better nutrition and physical fitness, but we must also encourage innovation of better therapies to treat diabetes and obesity. What are you doing to support that needed innovation?

*Answer 8.* FDA recognizes the rising incidence of diabetes in the United States and the need for innovative therapies to treat this chronic condition. We currently have 11 different drug classes to treat Type 2 diabetes, and many of these newer therapies became available within the past 5 to 7 years, despite the withdrawal of troglitazone in 1999 for liver toxicity and the cardiovascular safety concerns of rosiglitazone presented at two public meetings in 2007 and 2010.

These safety concerns serve as a reminder that while the goal is to ensure effective treatments for diabetes to the American public, these therapies must be carefully studied to ensure that side effects do not outweigh the benefits of blood sugar control, especially when physicians and patients have many classes of drugs from which to choose. For this reason, FDA held a 2-day public advisory committee meeting in July 2008 to seek scientific advice on the design of diabetes drug development programs to evaluate the cardiovascular safety of these drugs. In December 2008, a Guidance for Industry was published, outlining FDA’s requirements for new anti-diabetic therapies: “Diabetes Mellitus—Evaluating Cardiovascular Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes.”

The Guidance calls for more extensive evaluation of new anti-diabetic therapies to help to ensure that these therapies are safe and effective. However, to avoid delay in approving innovative therapies, FDA has employed new authorities under the FDA Amendments Act of 2007 FDAAA and required companies to collect such data through post-marketing studies. Since December 2008, FDA has approved four new drugs for the treatment of Type 2 diabetes.

Similarly, we recognize that obesity poses a serious public health problem to this country. In 2007, FDA issued a draft guidance document for industry entitled “Developing Products for Weight Management.” FDA is committed to working with pharmaceutical companies to bring new obesity drugs with favorable benefit-risk profiles to the market, but obesity has been a difficult area in which to develop drugs with favorable benefit-to-risk profiles. Two obesity drugs and one dietary supplement have been withdrawn from the market because they increased blood pressure and, in the case of the two obesity drugs, were documented to increase the incidence of stroke and/or heart attacks. FDA took another class of obesity drugs off the market because they increased the risk for heart valve disease, in some cases,

<sup>20</sup>CDRH, “Standard Operating Procedure for ‘Notice to Industry’ Letters” (August 2011), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259172.pdf>.

requiring patients to have open heart surgery to replace their damaged valve. An additional drug to treat obesity that was recently approved by the European Medicines Agency (EMA), but not by FDA, was later withdrawn from the European market due to an increased risk of suicide. We must make sure that any new products to treat obesity are safe, while taking into account the public health impact of obesity.

FDA is planning a scientific meeting to discuss obesity drugs and cardiovascular safety, and we are also planning to attend stakeholder meetings involving pharmaceutical companies, patient advocacy groups, and obesity experts to discuss development of obesity drugs. We expect these meetings to be very helpful to industry in developing drug products to treat obesity.

As FDA evaluates new drugs for the treatment of obesity, we will carefully consider the role of Risk Evaluation and Mitigation Strategies (REMS) and required post-marketing studies to ensure that the benefits of the drug outweigh its risks.

*Question 9.* In the last PDUFA bill (FDAAA), the critical path partnerships were authorized and FDA has awarded collaborative agreements to several entities. It is my understanding that one of these collaborations has made it possible for the industry to share their data from clinical trials for Alzheimer's disease. From FDA's perspective, what has been learned and will other disease databases result from this work?

*Answer 9.* One of the greatest challenges facing biomedical sciences in the 21st century is the development of better treatments for neurodegenerative diseases. The two most prevalent of these, Alzheimer's disease and Parkinson's disease, exert a heavy and growing burden on our society. Our lack of knowledge about the specific cause or causes of either disease is a major obstacle to the development of new treatments that have the potential to cure or prevent these devastating and tragic diseases.

The Coalition Against Major Diseases (CAMD) was formed by the non-profit Critical Path Institute, in cooperation with FDA, patient organizations, the medical products industry, and the Engelberg Center for Health Care Reform at the Brookings Institution. CAMD's focus is to develop new tools and methods that can be applied during the development of new treatments for neurodegenerative diseases, focusing on Alzheimer's and Parkinson's first. In CAMD, data integration and sharing are planned to create a quantitative disease-progression model that includes biomarkers that potentially identify discrete patient subsets of the disease. CAMD, working with the Clinical Data Interchange Standards Consortium, has developed and published data standards for Alzheimer's clinical trials. CAMD has been able to pool data from 11 clinical trials conducted by seven pharmaceutical companies into an Alzheimer's disease database that describes the natural history of the disease in over 4,000 patients. This database, along with the mathematical models of the disease available to researchers in the field, will allow clinical investigators to more accurately predict the outcome for a given clinical trial, the length of time needed for the trial, how many patients should be enrolled in the trial, and how genetic subsets of the population might respond. Hopefully, CAMD efforts will help reduce the failures in development of new drugs for Alzheimer's and will be a model for the establishment of other disease databases.

*Question 10.* The EU has made a significant long-term commitment to advancing the science that supports drug development with the goal of increasing investment and productivity for the biotech industry in Europe. I understand that they committed 1 billion euros and the industry is matching it with in kind contributions. They proclaim that this is the largest public private partnership in the world. What can the United States do to protect its investment in biotechnology? In this country, is the industry actively participating in the critical path public-private partnerships? Can we do more to encourage their participation?

*Answer 10.* Yes. Industry is participating in Critical Path and other public-private partnerships, but there is much more we can do. Government investment in regulatory science, combined with FDA-driven policy approaches to promote medical product innovation, are critical to maintain U.S. competitiveness in an increasingly globalized market.

The closest counterpart to the European IMI is the Critical Path Initiative, which is currently funded at a level of \$18 million annually. FDA's new Regulatory Science Initiative seeks to build on the Critical Path program by expanding awareness and laying out a strategy for making investments in key applied scientific areas that will facilitate increasing innovation and safer and more efficacious medical products. In addition, the Regulatory Science Initiative addresses the entire product lifespan,

from preclinical through post-market, including assessment of real-world performance of drugs, patient utilization and communication, and outcomes.

On October 5, 2011, FDA released a blueprint to lay out key policy suggestions that, in conjunction with regulatory science investments, will drive medical product innovation. The goal is to enhance both the health of the American people and the health of the medical product industry, a key component of our technology sector, and an area where the United States still leads in innovation and creativity.

Public-private partnerships between FDA, other government agencies, industry, and academia are a central component of both our innovation and regulatory science strategies. But government investments in the form of dollars and sound cross-agency collaborations and policies must be made to maintain U.S. leadership in the biotechnology sector. In our extensive discussions with business leaders from both large and small medical product development companies, it is clear that companies want to collaborate and will invest in these important areas, both in dollars and through partnering—if they see a significant and sustained commitment from the U.S. government to support the infrastructure, science, and policies that create an environment poised for innovation and global competitiveness.

In 2007, Congress created the Reagan-Udall Foundation as a vehicle for public-private partnerships in regulatory science. The Foundation has been able to initiate a few regulatory science partnerships, but absent the funding support initially contemplated has not been able to build a robust scientific program.

*Question 11.* One area of focus in the PDUFA V proposal is on advancing Regulatory science, specifically, as stated by the Agency, Enhancing Regulatory Science and Expediting Drug Development. What process will you use to set priorities for how to enhance regulatory science? Will the industry and patients have voices in setting these priorities?

Answer 11. FDA is recommending a set of specific review program enhancements that will strengthen the science and expedite drug development as part of the PDUFA V recommendations. Under PDUFA V FDA would commit to accomplish all of these enhancements and not prioritize among them. These PDUFA V recommendations are the product of FDA's extensive negotiations with industry and parallel consultations with patients and other stakeholders from April 2010 through May 2011 and reflect the priorities identified by these groups. The initiatives included in these recommendations are directly related to areas where specific near-term advances can be made to reduce the scientific uncertainty, business risk, and in some cases reduce the time and other resources required for new drug development.

These enhancements include:

1. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development;
2. Methods for meta-analysis;
3. Biomarkers and pharmacogenomics;
4. Use of patient-reported outcomes (PROs); and
5. Development of drugs for rare diseases.

As stated below, each of these addresses specific challenges with the current drug development and review processes.

1. Promoting innovation through enhanced communication between FDA and sponsors during drug development:

- **Problem:** New drug innovators operate at the cutting edge of science but may have less experience with FDA regulatory requirements to ensure substantial evidence of safety and efficacy. Timely communication between FDA and sponsors during development helps to ensure efficient and effective drug development, and also helps achieve FDA's mission by making safe and effective new drugs available in a timely manner.

- **Proposed Recommendation:** FDA will develop a dedicated drug development communication and training staff in CDER and CBER, focused on enhancing communication between FDA and sponsors during development. The liaison staff will conduct a range of tasks including identification and dissemination of best practices for enhanced communication and development of training programs for review staff. FDA will publish a guidance describing its philosophy on timely interactive communications and the scope of appropriate interactions with sponsors during drug development.

Methods for meta-analysis:

- **Problem:** Currently, there is no consensus on best practices in conducting a meta-analysis. FDA is often forced to evaluate meta-analyses of published or unpublished clinical trials, usually addressing a high visibility safety problem for an ap-



proved product. Review and evaluation of a meta-analysis, sometimes conducting the Agency's own meta-analysis, can exceed FDA's current scientific and computational capacity.

- Proposed Recommendations: FDA will develop a dedicated review team to evaluate scientific methods, limitations in the methods, and potential best practices for the conduct of meta-analyses. FDA will also hold a public meeting on the current and emerging approaches to meta-analyses, and develop guidance on FDA's intended approach to meta-analysis in the regulatory review process and in regulatory decisionmaking.

### 3. Biomarkers and pharmacogenomics:

- Problem: Pharmacogenomics and the application of qualified biomarkers have the potential to decrease drug development time. Qualified biomarkers can enrich clinical trials by demonstrating benefits, establishing unmet medical needs, and identifying patients with a predisposition to adverse events, and regulatory submissions of this type have increased recently, outstripping FDA capacity for review.

- Proposed Recommendations: FDA will increase clinical, clinical pharmacology, and statistical capacity to adequately address submissions that propose to utilize biomarkers or pharmacogenomic markers in development programs. FDA will hold a public meeting to discuss potential strategies to facilitate scientific exchanges in regulatory and non-regulatory contexts.

### 4. Use of patient-reported outcomes (PROs):

- Problem: Study endpoint assessments are increasingly an important part of successful drug development, requiring rigorous evaluation and statistical design and analysis. However, there is a high study-failure rate for PRO endpoints not qualified in advance of phase 3 trials. Early consultation could ensure that endpoints are well-defined and reliable.

- Proposed Recommendations: FDA will enhance clinical and statistical capacity to address submissions involving PROs and other endpoint assessment tools, including providing IND consultation, and will convene a public meeting to discuss PRO qualification standards, new endpoint measurement theory, and implications for multinational trials.

### Development of drugs for rare diseases:

- Problem: Regulatory oversight of rare disease drug development is complex and resource intensive. Recent trends in orphan designations may indicate an expected future increase in investigational activity and marketing applications for orphan products.

- Proposed Recommendations: FDA will develop guidance related to advancing and facilitating development of drugs for rare diseases, increase outreach to patient representatives and industry regarding development of these drugs, convene a public meeting to discuss complex issues in clinical trials for studying drugs for rare diseases, and develop and implement training for all review staff on development and review of drugs for rare diseases as part of the core reviewer curriculum.

In August 2011, FDA released its Strategic Plan for Regulatory Science. The strategic plan describes the Agency's intent to collaboratively enhance the process for developing and evaluating promising new products and defines the Agency's highest cross-cutting priorities linking to several themes contained in a report from CDER as well as other reports across the Agency.

CDER released its draft report entitled "Identifying CDER's Science and Research Needs" in July 2011. This report is an essential first step to formulating regulatory science priorities, which will guide development of a CDER regulatory science and research agenda. Release of the Science and Research Needs Report is the culmination of an exhaustive process that started with interviews of over 200 reviewers and scientists from across CDER—those who are closest to the regulatory processes and the regulatory science needed to support those processes. The comprehensive report on regulatory science and research needs was compiled from these discussions.

We have opened a docket to solicit critical input from our external stakeholders in industry, academia, and patient organizations, and our governmental partners, on CDER's draft report "Identifying CDER's Science and Research Needs," and to solicit input on additional critical science needs, ongoing efforts to address them, and creative mechanisms for collaboration. Further, we will be continuing to ask our reviewers for input and are making the identification of critical regulatory science challenges an ongoing process. We have provided our reviewers and scientists a direct route to comment on our science needs document and to add new challenges. This mechanism for horizon scanning will provide an ongoing system to identify emerging regulatory science issues. While we compile external and internal comments, we will be examining our current regulatory science and research portfolio

to identify areas where progress is being made and to identify critical gaps that are not being adequately addressed.

*Question 12.* Patient response and satisfaction with treatment is an area that often is left out of our discussions yet new medicines should keep patient benefit front and center. I understand that the Critical Path Institute is the Agency's partner working with the industry to develop standardized, validated questionnaires and electronic diaries to be used in testing new drugs and devices. How many Agency scientists are working with them and would more resources and FTE speed up this important work?

Answer 12. Study endpoint assessments, known as patient-reported outcomes (PROs), are an important part of successful drug development. PROs are critical in understanding the drug benefits and harm from the patients' perspectives. However, PROs, like other outcome assessments, require rigorous development to ensure validity and reliability to support claims of clinical benefit.

Early consultation between FDA and outcome assessment developers can ensure that endpoints are well-defined and reliable. In addition to the Critical Path Institute, FDA is working with several other public and private partners, including the Foundation for the National Institutes of Health and individual NIH institutes to develop standardized questionnaires, clinician assessments, and electronic diaries under the qualification pathway. Qualification is the regulatory conclusion that within the stated context of use, the results of assessment with a particular tool can be relied upon to have a specific interpretation and application in drug development and regulatory decisionmaking and labeling. Outcome assessments that undergo qualification will be publicly available, eliminating the need for multiple drug sponsors to repeat this critical work. Therefore, these activities promise to make medical product development and clinical trials more informative and efficient.

A dedicated FDA staff provides review for PRO measures, not only under the qualification pathway (e.g., with the Critical Path Initiative), but also in the context of specific investigational drugs. Therefore, the number of full-time employees (FTEs) currently dedicated to this work is difficult to calculate. It is clear, however, that the Agency does not have the capacity to meet the current demand for both of these review processes. In CDER, the primary review team for PRO measures and other clinical assessment tools includes a total of seven individuals, including the director and a temporary fellow. The team reviews the tools in conjunction with the clinical reviewers in the Office of New Drugs (OND) and also provides consultation and advice to the submitters.

FDA recently announced its proposed recommendations for PDUFA V. We propose several measures to enhance regulatory science and expedite drug development, including a proposal to increase clinical and statistical staff capacity to more efficiently and effectively respond to submissions that involve PROs and other outcome assessment tools. We also propose a public meeting to discuss FDA's qualification standards for development tools, new measurement theory, and implications for multi-national trials.

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*Question 1.* For each of the FDAAA review performance goals, what was the average length of response time for the Agency? What was the average length of response times that did not fall within the performance goals?

Answer 1. Under performance timelines associated with PDUFA IV, which was enacted as part of the FDA Amendments Act of 2007 (FDAAA), FDA has committed to review and act on 90 percent of original New Drug Applications (NDAs) and Biologics License Applications (BLAs)<sup>21</sup> within 10 months of receipt for standard applications and 6 months for priority-designated applications.<sup>22</sup> The performance level of 90 percent was chosen in acknowledgement of the fact that in some cases it is appropriate that FDA continue its review of an application past the goal date to address important outstanding issues. In fact, in some cases FDA continues its review past the PDUFA goal date to address remaining issues so that the application can be approved on that review cycle and thus avoid the need for a second review cycle that would be triggered by issuance of a complete response letter by the PDUFA

<sup>21</sup>Note that FDA relied on data captured by PDUFA and MDUFA reporting requirements to provide these responses. Therefore, they do not include data on applications reviewed by the Agency that are not subject to user fees.

<sup>22</sup>It should be noted that a review action does not imply application approval. NDAs and BLAs submitted for FDA review may receive a complete response that does not allow marketing approval, but identifies the application deficiencies that would need to be addressed in order to obtain marketing approval.

goal date. This can allow a drug to be available to patients in a more timely manner while allowing the Agency to still meet its 90 percent goal for actions.

As of March 31, 2011, FDA's average review time for priority NDAs and BLAs filed in fiscal year 2010 and reaching a regulatory action is approximately 6.6 months,<sup>23</sup> compared with 5.8 months for priority applications filed in fiscal year 2006. As of March 31, 2010, the average review time to regulatory action for standard original NDAs and BLAs filed in fiscal year 2010 is 10.3 months,<sup>24</sup> compared with 10.6 months for standard applications filed in fiscal year 2006.

We are pleased to report that as of March 31, 2011, for applications received in fiscal year 2010, FDA has met its PDUFA review goals 100 percent of the time for priority applications and 97 percent of the time for standard applications, with 5 percent of priority applications and 25 percent of standard applications still pending FDA review, all within their PDUFA goal.<sup>25</sup>

It is important to note that the PDUFA goal for an application may be extended by up to 3 months if the sponsor submits a major amendment (e.g., a new clinical study report) during the last 3 months of review. If FDA completes its review and issues its action on or before the extended goal date, this is counted as having met the PDUFA goal even though the overall time required for the review may be 9 months (priority) or 13 months (standard). This provision is included in the PDUFA performance goals to avoid an unnecessary second cycle of review in cases where the clock extension can allow FDA to complete its review of the major amendment and approve the application in that review cycle. This explains why the average review time for a cohort of applications can be greater than 6 (priority) or 10 (standard) months, even if all the applications in the cohort are acted on or before their PDUFA goal date.

*Question 2.* Since 1993, among all regulatory actions that count as meeting PDUFA performance goals, what percentage were:

- a. Approvals?
- b. Not approved?
- c. "Complete Response" letters?

*Answer 2.* For all original applications<sup>26</sup> filed and action taken within PDUFA performance goals by FDA from fiscal year 1993 through fiscal year 2011, as of July 2011, 74 percent of the products have received Approval actions,<sup>27</sup> which include Approval and Tentative Approval, and 26 percent of the products have only received Non Approval actions, which include Not Approvable, Approvable, Withdrawn after filing, and Complete Response.

It should be noted that as of August 2008, FDA replaced the "Approvable" regulatory action and the "Not Approvable" regulatory action with the "Complete Response" regulatory action. We cannot distinguish between "Not Approved" and "Complete Response" as questioned and so we compared products that have received Approval actions compared to products that have not received Approval actions. Since every review cycle requires a regulatory action, any application that has not received an Approval action has received a Non Approval action.

*Question 3.* If the Agency did not count "complete response" letters, or "approvable" or "not approvable" responses towards the performance goals, how would the reported performance goals since 1993 be adjusted? In short, what percentage of the time does FDA complete its review of an application—approve or not approve—during the first review cycle?

*Answer 3.* Each review cycle requires a regulatory action. Approval actions include Approval and Tentative Approval, and Non Approval actions include Not Ap-

<sup>23</sup>FDA was able to meet its PDUFA goals 100 percent of the time, even though the review time on average is 6.6 months, because the Agency may extend goal dates by 3 months when the sponsor submits a major application amendment within 3 months of the goal due date. Therefore, some priority goals may be extended to 9 months, resulting in the higher average,

<sup>24</sup>This number reflects the average review time for standard applications as of March 31, 2011, and final performance can be expected to change slightly, given that 25 percent of fiscal year 2010 standard implications were still pending within goal as of this date.

<sup>25</sup>For more information on PDUFA performance, see the 2010 report to Congress: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf>. Please note that the data as of March 31, 2011, may differ from the figures in the Performance Report, which reflect more current data as of September 30, 2010.

<sup>26</sup>This response assumes that the term "original applications" is defined as original Filed NDAs and BLAs as well as resubmissions. This does not include supplements.

<sup>27</sup>We define the Approval-Non Approval determination on the current status, as applications currently with a Non Approval action can still be approved in the future.

provable, Approvable, Withdrawn after filing, and Complete Response.<sup>28</sup> Thus, the answer to this question is the same as above.

*Question 4.* With respect to pre-market applications, of the device PMAs acted upon by the FDA and counted towards the reported user fee performance goals, what percentage of the reported performance goals were:

- a. Approvals?
- b. Approvables?
- c. Not Approvables?
- d. Denials?
- e. Withdrawn applications?

Answer 4. [Note: Numbers were rounded; therefore percentages don't always equal 100.]

|   | Fiscal year<br>2008<br>[in percent] | Fiscal year<br>2009<br>[in percent] | Fiscal year<br>2010<br>[in percent] | Fiscal year<br>2011<br>[in percent] |
|---|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| <b>PMA Orig. &amp; Panel (non-expedited):</b> |                                     |                                     |                                     |                                     |
| Approvals .....                               | 36                                  | 16                                  | 36                                  | 56                                  |
| Approvables .....                             | 18                                  | 27                                  | 28                                  | 22                                  |
| Not Approvables .....                         | 27                                  | 30                                  | 33                                  | 22                                  |
| Denials .....                                 | 0                                   | 0                                   | 0                                   | 0                                   |
| Withdrawn .....                               | 18                                  | 27                                  | 3                                   | 0                                   |
| <b>PMA Orig. &amp; Panel (expedited):</b>     |                                     |                                     |                                     |                                     |
| Approvals .....                               | 25                                  | 25                                  | 75                                  | 100                                 |
| Approvables .....                             | 0                                   | 25                                  | 0                                   | 0                                   |
| Not Approvables .....                         | 75                                  | 25                                  | 25                                  | 0                                   |
| Denials .....                                 | 0                                   | 0                                   | 0                                   | 0                                   |
| Withdrawn .....                               | 0                                   | 25                                  | 0                                   | 0                                   |
| <b>180-day Supplements:</b>                   |                                     |                                     |                                     |                                     |
| Approvals .....                               | 71                                  | 71                                  | 54                                  | 75                                  |
| Approvables .....                             | 13                                  | 12                                  | 12                                  | 3                                   |
| Not Approvables .....                         | 16                                  | 15                                  | 30                                  | 12                                  |
| Denials .....                                 | 0                                   | 0                                   | 0                                   | 0                                   |
| Withdrawn .....                               | 1                                   | 2                                   | 4                                   | 10                                  |
| <b>Real-Time Supplements:</b>                 |                                     |                                     |                                     |                                     |
| Approvals .....                               | 89                                  | 88                                  | 75                                  | 84                                  |
| Approvables .....                             | 1                                   | 1                                   | 13                                  | 5                                   |
| Not Approvables .....                         | 10                                  | 11                                  | 12                                  | 11                                  |
| Denials .....                                 | 0                                   | 0                                   | 0                                   | 0                                   |
| Withdrawn .....                               | 0                                   | 0                                   | 0                                   | 0                                   |

*Question 5a, b, and c.* With respect to 510(k) submissions, of the submissions acted upon by the FDA and counted towards the reported user fee performance goals, what percentage of the reported performance goals were:

- a. Substantially Equivalent determinations (clearance)?
- b. Not Substantially Equivalent determinations (denial of clearance)?
- c. Not Approvables?

Answer 5a, b, and c. The following table shows the percentage of 510(k) MDUFA decisions in each fiscal year that were substantially equivalent (SE) or not substantially equivalent (NSE). Only SE and NSE decisions are counted in the user fee performance goals.

| Decision cohort        | Total # MDUFA<br>510(k) decisions | SE<br>[in percent] | NSE<br>[in percent] |
|------------------------|-----------------------------------|--------------------|---------------------|
| Fiscal year 2008 ..... | 3,669                             | 83                 | 4                   |
| Fiscal year 2009 ..... | 3,829                             | 80                 | 4                   |
| Fiscal year 2010 ..... | 3,786                             | 73                 | 8                   |

<sup>28</sup> As stated above, in August 2008, FDA replaced the "Approvable" regulatory action and the "Not Approvable" regulatory action with the "Complete Response" regulatory action.

| Decision cohort        | Total # MDUFA 510(k) decisions | SE [in percent] | NSE [in percent] |
|------------------------|--------------------------------|-----------------|------------------|
| Fiscal year 2011 ..... | 3,929                          | 78              | 5                |

[Note: Decision cohort was used in order to provide data as close to real-time as possible.]

**Question 6.** For questions 4, and 5 above, how many approvals or clearances occurred on a first-cycle review?

| 1st Cycle PMA approval decisions       | Fiscal year 2008 | Fiscal year 2009 | Fiscal year 2010 | Fiscal year 2011 |
|--|------------------|------------------|------------------|------------------|
| PMA Orig & Panel (non-expedited) ..... | 12 (36%)         | 6 (16%)          | 13 (33%)         | 5 (56%)          |
| PMA Orig & Panel (expedited) .....     | 1 (25%)          | 1 (25%)          | 3 (75%)          | 1 (25%)          |
| 180-Day Supplements .....              | 114 (71%)        | 115 (71%)        | 71 (54%)         | 45 (75%)         |
| Real-Time Supplements .....            | 215 (89%)        | 246 (88%)        | 192 (75%)        | 134 (84%)        |

| 1st Cycle PMA SE decisions | Fiscal year 2008 | Fiscal year 2009 | Fiscal year 2010 | Fiscal year 2011 |
|----------------------------|------------------|------------------|------------------|------------------|
| 510(k) .....               | 1,276 (41%)      | 1,076 (34%)      | 769 (27%)        | 674 (42%)        |

[Note: All receipt cohorts are still open—data will change; all data are as of 8/31/2011.]

**Question 7.** Beginning in 1992 and for every year thereafter to present, please report on the average time for the review of a human drug application (NDAs, BLAs, and supplements). For the same time period, please report on the percentage of human drug applications approved on a first cycle review.

Answer 7. Please see the chart attached as Appendix 1. PDUFA was first enacted in 1992, and 1993 represents the first year we reported data. Thus, we have provided data from 1993 to present.

**Question 8.** Has the increase in user fees in MDUFA II translated into more timely or faster review periods? Has the increase in user fees in MDUFA II resulted in an increase in the number of FDA-approved or cleared products for patients? Has the increase in fees resulted in fewer review cycles per submission compared to previous user fee agreements?

Before addressing the performance issues raised in this question, it is important to note the context for the increase in user fees that took place as a result of the enactment of MDUFA II in 2007. Those user fee increases were intended to cover the anticipated increase in the cost of maintaining FDA device review staffing levels that were achieved at the end of MDUFA I, which FDA believed would be sufficient to meet the performance goals regarding timely decisionmaking. The increases were not intended to achieve any particular outcomes of those decisions, such as product approvals or clearances.

The average review time for original PMAs and Panel Track Supplements (supplements for a new indication, which contain new clinical data) has improved from 11 months in fiscal year 2005 to 8 months in fiscal year 2009 (Tier 1 goal: 60 percent of original PMAs and Panel Track Supplements in 180 days). This is a 42 percent decrease in days from 2005 to 2009.

With respect to the Tier 2 goal for PMAs and Panel Track Supplements (90 percent in 295 days), there has been a 48 percent decrease in days from 2005 to 2009. These improvements are the result of more efficient submission management due to additional resources provided through MDUFA and process improvements implemented by FDA.

Although FDA is meeting its 510(k) performance goals under MDUFA, overall time to decision (i.e., FDA review time plus industry response time) for 510(k) submissions has increased over the past 10 years, due primarily to an increase in the number of review cycles and in the amount of time companies take to respond to requests for additional information.

We recognize our role in this and are taking steps to address it. The two reports we released publicly in August 2010, with our analyses and recommendations, showed that we have not done as good a job managing our pre-market review programs as we should and that we need to take several critical actions to improve the predictability, consistency, and transparency of these programs.

For example, we have new reviewers who need better training. We need to improve management oversight and standard operating procedures. We need to provide greater clarity for our staff and for industry through guidance about key parts of our premarket review and clinical trial programs and how we make benefit-risk determinations. We need to provide greater clarity for industry through guidance and greater interactions about what we need from them to facilitate more efficient, predictable reviews. We need to make greater use of outside experts who understand cutting-edge technologies. And we need to find the means to handle the ever-increasing workload and reduce staff and manager turnover, which is almost double that of FDA's drugs and biologics centers.

In January 2011, FDA announced a Plan of Action that included 25 specific actions that we would take this year to improve the predictability, consistency, and transparency of our premarket programs. The following month, we announced our Innovation Initiative, which included several proposals to help maintain the position of the United States as the world's leader in medical device innovation, including the creation of a new approach for important, new technologies called the Innovation Pathway.

Since then, we have announced additional efforts to improve our premarket programs, including actions to improve our program for clinical trials and the Investigational Device Exemption (IDE) program. The actions we are taking can be grouped into three main areas of emphasis:

- Create a culture change toward greater transparency, interaction, collaboration, and the appropriate balancing of benefits and risks;
- Ensure predictable and consistent recommendations, decisionmaking, and application of the least-burdensome principle; and
- Implement efficient processes and use of resources.

Specific steps that we are taking, many of which are supported by industry, include:

- Issuing guidance clarifying the criteria used to make benefit-risk determinations a part of device premarket decisions to provide greater predictability and consistency and apply a more patient-centric approach by considering patients' tolerance for risk in appropriate cases (draft guidance issued August 15, 2011);
- Creating standard operating procedures for when a reviewer can request additional information regarding a premarket submission and at what management level the decision must be made to provide greater predictability, consistency, and the appropriate application of the least-burdensome principle by reducing the number of inappropriate information requests (Standard Operating Procedures issued November 2011).
- Developing a range of updated and new guidances to clarify CDRH requirements for predictable, timely, and consistent product review, including device-specific guidance in several areas such as mobile applications (draft guidance released July 19, 2011) and artificial pancreas systems (to be completed by the end of 2011);
- Revamping the guidance development process through a new tracking system and, to the extent resources permit, core staff to oversee the timely drafting and clearance of documents (to be completed by the end of 2011);
- Improving communication between FDA and industry through enhancements to interactive review (some of these enhancements will be in place by the end of 2011);
- Streamlining the clinical trial and IDE processes by providing industry with guidance to clarify the criteria for approving clinical trials, and criteria for when a first-in-human study can be conducted earlier during device development to create incentives to bring new technologies to the United States first (guidance to be issued November 2011) (IDEs are required before device testing in humans that involve significant risks may begin, and they ensure that the rights of human subjects are protected while gathering data on the safety and efficacy of medical devices);
- Implementing internal business process improvements to ensure that decisions are made by the appropriate level of management, that decisions are made consistently and efficiently, and that we appropriately apply the least-burdensome principle. For example,

CDRH created the internal Center Science Council to actively monitor the quality and performance of the Center's scientific programs and ensure consistency and predictability in CDRH scientific decisionmaking (Center Science Council established March 31, 2011);

- Creating a network of experts to help CDRH resolve complex scientific issues, which will ultimately result in more timely reviews. This network will be especially helpful as FDA confronts new technologies (Standard Operating Procedures issued September 30, 2011);
- Instituting a mandatory Reviewer Certification Program for new reviewers (program launched September 2011);
- Instituting a pilot Experiential Learning Program to provide review staff with real-world training experiences as they participate in visits to manufacturers, research, and health care facilities, and academia (to begin in early 2012);
- Providing industry with specific guidance on how to ensure the quality and performance of clinical trials while applying the least-burdensome principle, and thereby conduct studies that are more likely to support the approval of their products (guidance released August 15, 2011); and
- Streamlining the *de novo* review process, the pathway by which novel, lower-risk devices without a predicate can come to market (draft guidance released September 30, 2011).

A recent FDA analysis<sup>29</sup> shows that poor submission quality is a major contributor to the increase in total review times. The most common deficiencies included:

- Inadequate device descriptions;
- Discrepancies throughout the submission;
- Failure to address necessary information as outlined in guidance documents;
- Problems with the proposed indications for use;
- Completely missing performance testing; and
- Completely missing clinical data.

In addition, sponsors' failure to address deficiencies identified in first-round AI Letters is a major contributor to the increase in total review times. For example, 65 percent of the time, FDA sent a second-round AI Letter because the sponsor failed to submit information requested in the first AI Letter.

FDA has already taken steps to address some of the issues identified in this analysis. We are working to provide greater predictability for industry by communicating justified changes in data requirements more quickly and transparently. We recently issued draft Standard Operating Procedures for Notice to Industry Letters,<sup>30</sup> which provides a format for communicating changes more quickly within the existing Good Guidance Practices framework. FDA is also enhancing training for staff and industry, which is aimed at reducing inappropriate requests for additional information and helping sponsors understand when they are required to submit data. We will continue to work with industry to identify additional actions to reduce the average number of review cycles and the percent of 510(k) submissions for which an AI Letter is sent.

Through these and other steps we are taking to address weaknesses in the 510(k) program, FDA aims to reduce the total time to clearance for 510(k) devices, while assuring that we maintain the same levels of safety and effectiveness. It is our hope that taking actions to increase submission quality and avoid inappropriate requests for additional information will prevent avoidable delays and reduce total time to decision, which will, in turn, get safe and effective devices to market faster.

With regard to PMA applications, FDA's internal analysis found that, for those PMAs that were not reviewed within the performance goals, the main reasons for the longer review times were:

- Poor quality clinical studies, such as clinical trial execution issues and problematic data analyses;
- Reviewer turnover, especially changing medical officers and branch chiefs; and
- Taking a PMA to an FDA advisory committee. (In general, all PMAs for the first-of-a-kind device are taken before the appropriate advisory panel for review and recommendations. The preparation for an FDA advisory committee involves significant calendar time and review team resources.)

*Question 9.* Beginning in 2007, and for every year thereafter, what percentage of products seeking to rely solely on foreign clinical trial data for approval have been approved without requiring any further clinical requirements, such as domestic clin-

<sup>29</sup> CDRH, "Analysis of Premarket Review Times Under the 510(k) Program" (July 2011), available at <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm263385.htm#5>.

<sup>30</sup> CDRH, "Standard Operating Procedure for 'Notice to Industry' Letters" (August 2011), available at <http://www.fda.gov/downloads/MedicalDevicesRegulationandGuidance/GuidanceDocuments/UCM259172.pdf>.

ical trials? Since enactment of FDAMA in 1997, how many products have been approved based just on foreign clinical trial data?

Answer 9. We are unable to provide statistics in response to this question, as FDA does not track applications on the basis of the source of the clinical data.

FDA does not require studies to support drug or device approvals to be conducted in the United States. Data collected from other countries can be used to support a product's safety and effectiveness. Foreign studies performed under an IND or IDE must meet the same requirements of 21 CFR part 312 or 21 CFR part 812, respectively, that apply to U.S. studies conducted under an IND or IDE. The acceptance of foreign clinical studies not conducted under an IND or IDE, as support for a marketing application, is generally governed by 21 CFR 312.120 and 21 CFR 814.15.

A marketing application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if:

- the foreign data are applicable to the U.S. population and U.S. medical practice;
- the studies have been performed by clinical investigators of recognized competence; and
- the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, the Agency can validate the data through an on-site inspection or other appropriate means.

The following are examples of drugs approved on the basis of foreign data:

- Eloxatin (oxaliplatin) for injection—was approved under FDA's accelerated approval regulations, based exclusively on foreign clinical data from trials conducted in Israel, Singapore, Australia, and 17 European countries.
- Aggrenox (aspirin/extended-release dipyridamole)—Capsules were approved based exclusively on foreign clinical data from trials conducted in 13 European countries.

The following are examples of devices approved on the basis of foreign data:

- The FC2 Female Condom® was approved using clinical data from investigations conducted in South Africa.
- The Boston Scientific Corp. Express® LD Iliac Premounted Stent System was approved using clinical data generated from trials in the Netherlands, Belgium, the Czech Republic, Poland, and Canada. In an effort to ensure that FDA was open to the OUS (outside the United States) clinical data being used to support PMA approval, the sponsor had several pre-IDE, interactions with FDA. In these pre-submission interactions, agreement was reached on the retrospective performance goal that would be applied to the study data. In addition, the review team worked interactively with the sponsor through a number of minor pre-clinical and clinical issues prior to submission of the PMA.

*Question 10.* The Commissioner's testimony states that, "FDA aims to review priority new molecular entities more quickly—6 months vs. 10 months for standard drugs" and that "Priority NMEs represent truly innovative medicines generally targeted at severe illnesses with few or no available therapeutic options." Is the Agency meeting the 6-month and 10-month review targets for priority and standard NMEs? The testimony also states that the Agency is "on track for approving a historically high percentage of priority NMEs for 2011." What is the percentage the Agency is on track to approve with respect to both priority and standard NMEs for 2011?

Answer 10. As of March 31, 2011, for applications received in fiscal year 2010, FDA has met its PDUFA goals 100 percent of the time for priority applications and 97 percent of the time for standard applications, with 5 percent of priority applications and 25 percent of standard applications of these applications still pending FDA review, all within their PDUFA goal.<sup>31</sup> This performance exceeds our goal to review and act on 90 percent of original NDAs and BLAs<sup>32</sup> within 10 months of receipt for standard applications and 6 months for priority-designated applications.<sup>33</sup>

<sup>31</sup>For more information on PDUFA performance, see the 2010 report to Congress: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM243358.pdf>. Please note that the data as of March 31, 2011 may differ from the figures in the Performance Report, which reflect more current data as of September 30, 2010.

<sup>32</sup>Note that FDA relied on data captured by PDUFA and MDUFA reporting requirements to provide these responses. Therefore, they do not include data on applications reviewed by the Agency that are not subject to user fees.

<sup>33</sup>It should be noted that a review action does not imply application approval. NDAs and BLAs submitted for FDA review may receive a Complete Response that does not allow marketing approval, but identifies the application deficiencies that would need to be addressed in order to obtain marketing approval.



As of July 2011, of the six priority applications received and acted upon in fiscal year 2011, four of which were NMEs, all were approved. This number could increase as current pending priority NME applications mature to their review performance goal dates. It is premature to report on performance for fiscal year 2011 standard NME applications.

*Question 11.* The Commissioner's testimony states that "so far this year, FDA has approved 21 new, groundbreaking medicines . . ." What percentage do these 21 medicines represent of the total applications submitted for review? What percentage do these 21 medicines represent of the total approvals for 2011?

Answer 11. Approval figures in the response to this question are for calendar year (CY) 2011. As of July, there were 63 total Approvals, of which 21 were for NMEs/new BLAs. These NMEs/new BLAs represent 33 percent of the total Approvals. These figures will change as additional applications are approved during the remaining months of CY 2011.

FDA generally reports PDUFA performance in terms of cohorts of applications received in a given fiscal year. Because FDA is still receiving applications in CY 2011 and since there are still pending applications in the fiscal year 2011 cohort that are within their PDUFA goal date, it would be premature to otherwise assess program performance based on CY or fiscal year 2011 information. The most recent measure of program performance is contained in FDA's response to Question 12 below.

*Question 12.* Please report on the total number of human drug applications (NDAs, BLAs, and supplements) received by FDA each year beginning in 2000 to present. Please report on the total number of applications approved on first cycle review and what percentage of total applications and total approvals they represent for each year.

Answer 12. Please refer to the data in the tables below. Because the fiscal year 2011 cohort of applications has not yet matured (i.e., applications in this cohort are still pending and within their PDUFA goal date), FDA is reporting on the receipt cohorts from fiscal year 2000 through fiscal year 2010. We have also provided the data by priority and standard applications as this is typically how FDA reports data on the performance of the drug review program.

You had also requested the percentage of total approved applications in each year that were approved on the first cycle. We could not provide a valid statistic in response to this request. Total approvals in a given year include approvals of resubmitted applications. As requested, this statistic could never be 100 percent since the denominator of total approvals contains approvals of resubmitted applications that could never be counted in the numerator of first cycle approvals.

**Number of NDAs, CDER BLAs, Supplements, and Resubmissions Filed, Approved First Cycle and Total Approved for Fiscal Years 2000 to 2011**

**NDA and BLA Original Submissions**

| Fiscal year  | 2000    | 2001    | 2002    | 2003    | 2004    | 2005    | 2006    | 2007    | 2008    | 2009    | 2010    |
|--|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Number of Filed Submissions (Priority/Standard) .....  | 30/90   | 11/82   | 12/84   | 19/83   | 28/94   | 29/73   | 31/87   | 22/81   | 31/103  | 20/116  | 18/83   |
| Approved First Cycle (Applications Received, Filed, and Approved in First Cycle) (Priority/Standard) ..... | 15/31   | 2/16    | 7/31    | 9/29    | 16/45   | 19/28   | 21/40   | 15/32   | 18/44   | 11/50   | 9/42    |
| Percentage of Filed Submissions that were Approved First Cycle (Priority/Standard) .....                   | 50%/34% | 18%/20% | 58%/37% | 47%/35% | 57%/48% | 66%/38% | 68%/46% | 68%/40% | 58%/43% | 55%/43% | 44%/52% |

**NDA and BLA Efficacy Supplements**

| Fiscal year  | 2000    | 2001    | 2002    | 2003    | 2004    | 2005    | 2006    | 2007    | 2008    | 2009    | 2010    |
|--|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Number of Filed Submissions (P/S) .....  | 19/155  | 8/150   | 34/124  | 35/99   | 50/149  | 42/106  | 45/139  | 45/138  | 36/104  | 42/102  | 19/100  |
| Approved First Cycle (Applications Received, Filed, and Approved in First Cycle) (Priority/Standard) ..... | 15/65   | 4/79    | 15/66   | 24/52   | 36/83   | 27/80   | 35/82   | 26/99   | 23/72   | 27/65   | 11/68   |
| Percentage of Filed Submissions that were Approved First Cycle (Priority/Standard) .....                   | 36%/71% | 14%/76% | 35%/70% | 36%/55% | 46%/66% | 48%/73% | 63%/81% | 50%/79% | 48%/74% | 60%/78% | 37%/78% |

**NDA and BLA Manufacturing Supplements**

| Fiscal year   | 2000    | 2001    | 2002     | 2003     | 2004     | 2005     | 2006     | 2007     | 2008     | 2009     | 2010     |
|---|---------|---------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Number of Filed Submissions (Prior Approval (PA)/ Changes Being Effected (CBE)) .....           | 672/745 | 542/896 | 598/1142 | 608/1072 | 596/1239 | 699/1206 | 638/1305 | 674/1365 | 628/1180 | 712/1199 | 721/1078 |
| Approved First Cycle (Applications Received, Filed, and Approved in First Cycle) (PA/CBE) ..... | 519/681 | 411/838 | 446/1029 | 440/999  | 468/1172 | 573/1144 | 515/1247 | 529/1301 | 460/1083 | 517/1093 | 510/944  |
| Percentage of Filed Submissions that were Approved First Cycle (PA/CBE) .....                   | 77%/91% | 76%/94% | 75%/90%  | 72%/93%  | 79%/95%  | 82%/95%  | 81%/96%  | 78%/95%  | 73%/92%  | 73%/91%  | 71%/88%  |

Resubmissions of NDA and BLA Original Submissions, Efficacy Supplements, and Manufacturing Supplements

| Fiscal year   | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
|---|------|------|------|------|------|------|------|------|------|------|------|
| Number of Original NDA and BLA Resubmissions .....              | 78   | 62   | 62   | 62   | 81   | 51   | 60   | 66   | 52   | 62   | 51   |
| Number of Original NDA and BLA Resubmissions Approved .....     | 45   | 42   | 42   | 44   | 55   | 37   | 41   | 37   | 36   | 39   | 34   |
| Number of Efficacy Supplement Resubmissions .....               | 35   | 36   | 36   | 56   | 58   | 46   | 30   | 41   | 42   | 33   | 28   |
| Number of Efficacy Supplement Resubmissions Approved .....      | 27   | 25   | 28   | 43   | 43   | 29   | 21   | 26   | 25   | 18   | 19   |
| Number of Manufacturing Supplement Resubmissions .....          | 145  | 178  | 177  | 250  | 219  | 175  | 186  | 152  | 170  | 209  | 262  |
| Number of Manufacturing Supplement Resubmissions Approved ..... | 124  | 122  | 137  | 199  | 183  | 153  | 164  | 133  | 129  | 184  | 211  |

*Question 13.* Many concerns have arisen regarding the regulatory certainty of the FDA's review process for drugs and devices. How could FDA better articulate requirements and develop more predictable approaches so that sponsor applications have a higher likelihood of first cycle approvals? How can FDA provide more timely and transparent guidance to sponsors regarding expectations with regard to compliance with the Agency's regulations?

Answer 13. FDA has been taking action for some time to help drive innovation in new drug development. In 2004, FDA launched its Critical Path Initiative, FDA's national strategy to help advance pharmaceutical innovation. Our long-term efforts are showing positive signs, and FDA will continue to support the scientific community to advance new drug development.

The key challenges facing scientific progress and innovation in drug development are cost and uncertainty. Stakeholders in all areas of industry repeatedly tell FDA that their biggest obstacle to successful drug development is uncertainty. FDA has taken an approach to supporting new drug innovations by generating initiatives to drive down development costs and reduce uncertainty in all phases of drug development.

FDA is spearheading several initiatives to directly reduce the cost of drug development. For example, we are making great progress in the area of Adaptive Trial Design. Clinical trials do not always go as planned and Adaptive Trial Design allows the drug sponsor to change a clinical trial after patients are enrolled without compromising researchers' ability to assess the effectiveness of the drug being studied. This helps researchers make important changes to studies that otherwise may be delayed or discontinued and helps bring down the costs of clinical trials, which are often extremely expensive. We have also co-founded the Clinical Trials Transformation Initiative with Duke University to modernize the entire clinical trial system.

FDA is also working to reduce the scientific uncertainty in drug development. For example, we have collaborated with the European Medicines Agency (EMA) to found the Predictive Safety Testing Consortium (PSTC). The PSTC has brought together scientists from 17 drug companies, who collaborate to share and validate each other's safety methods. Such collaboration advances scientific knowledge and helps the industry to develop safer drugs faster and less expensively.

FDA's recommendations for PDUFA V include proposals aimed at promoting innovation through enhanced communication between FDA and sponsors during drug development. Enhanced communication should help sponsors better understand how to best test their products for safety and effectiveness and ultimately bring new treatments to the U.S. market.

One proposal will establish a new review model for the more innovative products (New Molecular Entity New Drug Applications and original Biologics License Applications) aimed specifically at decreasing the number of review cycles needed for approval. This model should provide greater transparency and improve communication by increasing the level of interaction between FDA and sponsors during the FDA review process. Similarly, FDA's PDUFA V recommendations also include a proposal to improve communication with sponsors during drug development. This proposal will establish a dedicated drug development communication and training staff that will conduct a range of tasks associated with enhancing communication between the review team and sponsors.

Furthermore, FDA is committed to continuing to improve the surveillance of products after they have reached the market. Our PDUFA V recommendations include funds to continue implementing FDA's Sentinel Initiative. This is FDA's evolving electronic "active surveillance" system, which will augment FDA's current safety monitoring program. The new system will transform FDA's ability to track the safety of drugs, biologics, and medical devices after they reach the market and will help to answer key safety questions about medical products in near real-time.

Our efforts to improve the predictability of the device review process are described in our response to question #8 submitted by Senator Burr.

*Question 14.* The possibility of first cycle approval or clearance appears to vary by review division. What steps is FDA taking to ensure a consistent risk-benefit approach across divisions? Please describe the application of the FDA's new risk-benefit matrix that was recently made operational.

Answer 14. In both CDRH and CDER, the review divisions evaluate applications from different therapeutic areas, and each therapeutic area has different benefit-risk considerations. For example, FDA will accept more risk with a drug to treat a potentially fatal and previously untreatable form of cancer than we would for a chronic but non-serious condition such as mild eczema. However, FDA has identified

the need to establish a formal, systematic benefit-risk assessment within disease areas.

CDER is currently developing an enhanced structured approach to considering benefits and risks in the Agency's drug regulatory decisionmaking. We have gathered input from senior CDER leadership and reviewers to ensure the development of a tool that can serve as a template for the full range of benefit-risk decisions. In addition, CDER has piloted the use of the benefit-risk framework for pharmaceuticals in 10 case studies across review divisions in OND. In the PDUFA V recommendations, the Agency has committed to expanding implementation of CDER's benefit-risk assessment framework in the drug review process, including workshops on patient-focused drug development. FDA will also conduct a series of public meetings with the relevant patient advocacy communities to review the medical products available for use in specific therapeutic areas. The therapeutic areas to be discussed will be chosen through a public process. We will begin execution of the plan to implement that framework by the end of the fourth quarter of fiscal year 2013.

With respect to medical devices, CDRH recently issued, with request for public comment, a new draft guidance<sup>34</sup> describing factors to consider in making benefit-risk determinations in device premarket review. This draft guidance explains in detail the many factors for FDA to consider when weighing the probable benefit of a device versus its probable risk, and also gives examples of how the factors interrelate and how they may affect FDA's decisions. These factors include, among others, whether the device is a first-of-a-kind treatment or diagnostic, whether the device provides significant improvement in diagnosis and patient management of a serious disease, how known risks of the device can be mitigated, reliability of the study, whether there are multiple studies and the strength of those studies, what amount of risk the target population will tolerate in light of the condition being treated or diagnosed and the probable benefit of the device, and whether there are alternate treatments or diagnostic techniques available.

By clarifying FDA's decisionmaking process for medical devices in this way, we hope to improve the predictability, consistency, and transparency of the review process for applicable devices. The draft guidance includes (also for public comment) a draft worksheet that reviewers may use in making benefit-risk determinations; we believe that this level of documentation will be very helpful in maintaining the consistency of review across the different review divisions and it will provide further assurance that an appropriate decision is reached. The draft guidance is not in final form or in effect at this time, but CDRH has requested that interested persons provide their comments on the guidance by November 14, so that those comments can be considered before we begin work on the final version.

*Question 15a.* In 1997, Congress passed the FDA Modernization Act, which gave amongst other things, new authority to review and subsequently approve drugs based on limited clinical data and that demonstrated efficacy based on a validated surrogate endpoint.

How many oncology drug applications (NDAs, BLAs, and supplements) approved by FDA were granted accelerated approval since 2001?

*Answer 15a.* Between January 1, 2001, and August 30, 2011, there have been 39 oncology drug applications (NDAs, BLAs and supplements) approved by FDA under Accelerated Approval.

Between January 1, 2001, to December 31, 2010 (time period referenced in questions below), there have been 36 oncology drug applications (NDAs, BLAs and supplements) approved by FDA under Accelerated Approval.

*Question 15b.* For each year, from 2001 through 2010, how many of these accelerated applications did FDA: (i) Successfully complete in the first cycle?

*Answer 15b(i).* Between the years 2001 and 2010 (denominator of 36 oncology drug applications), 32 of these accelerated approvals were completed within the first cycle.

*Question 15b(ii) Approve on the basis of two on-going confirmatory studies?*

*Answer 15b(ii).* Between the years 2001 and 2010, 30 of these applications had at least one ongoing confirmatory trial at the time of accelerated approval. A minority of applications have more than one post-approval clinical trial required to demonstrate clinical benefit for the specific indication approved under Subpart H.

<sup>34</sup>CDRH, "Draft Guidance for Industry and Food and Drug Administration Staff—Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Review" (Aug. 15, 2011), available at <http://www.fda.gov/MedicalDeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm>.

*Question 15b(iii).* Approve on the basis of a single-arm study or on the basis of a more lenient statistical orthodoxy?

Answer 15b(iii). Between the years 2001 and 2010, 23 oncology drug applications (NDAs, BLAs and supplements) have been granted Accelerated Approval based on single-arm trials.

*Question 16.* What is the FDA doing to identify and limit redundancies within the Agency, including high numbers of FTEs who do not review applications, to improve its productivity and efficiency?

Answer 16. It is important to recognize that both CDER and CDRH are responsible for a variety of complex functions that are not directly associated with the review of new drug and medical device applications. Examples of these functions include ensuring industry's sustained compliance with manufacturing requirements, performing post-market drug and device safety surveillance and risk communication, developing guidance for the pharmaceutical, biologics, and medical device industries, conducting post-approval inspections of domestic and foreign facilities, and analyzing and responding to Citizen Petitions. CDRH also is responsible for implementation of the Radiation Control for Health and Safety Act and the Mammography Quality Standards Act. In addition, there are essential cross-cutting activities that must be performed by CDER and CDRH personnel to support premarket regulatory review, including management, planning, policy, information management, and science-related activities. These non-review functions are critical to successful regulation of pharmaceuticals and medical devices and to the overall health and safety of the American public.

To promote productivity and efficiency, CDER is designing a quality systems framework to enhance regulatory review and its supporting cross-cutting business processes, to ensure consistent, scientifically sound, high-quality work product. CDER has also been focusing on the "Lean" methodology for managing work, focusing on the key principles of maximizing value while also eliminating redundancies or other waste in business processes. In addition, CDER recently published its Data Standards Plan, which includes several cost-cutting initiatives, such as transitioning from paper submissions to an electronic data submission system.

Likewise, CDRH is actively working to enhance its efficiency and productivity. For example, starting next month, the Office of Device Evaluation (ODE) will pilot an internal corrective and preventive action (CAPA) system—a database in which office-level issues, such as inconsistency in application of policies or failure to follow policies or SOPs, will be entered and assigned to a staff member for followup and resolution. The CAPA system will formalize existing continuous improvement efforts and help to ensure that identified issues are tracked to resolution and appropriate corrective and preventive actions are taken. Office-level management will periodically review the information contained in the CAPA system to ensure adequate resourcing and timely resolution of issues. CDRH is also working to modernize the tracking system that the Center uses to manage and track premarket submissions that are under review and to provide review performance reports. Advanced features are being added to the system to allow for better management reports used by review branch chiefs for everyday work and to provide reports for past performance to identify areas in need of improvement. This project will modernize the premarket database systems to enable the Center to identify, collect, search, and report on medical devices in a consistent, reliable, and efficient manner. These efforts are vital to support and enhance the Center's premarket, post-market, and compliance-related activities.

*Question 17a.* There appears to be a lack of transparency and timeline consistency in the development and submission of FDA's scheduling recommendations through HHS and DEA. Unnecessary delays in process result in delayed patient access to new medicines.

Is there a documented, formal procedure for completing the scheduling recommendation made by CDER Controlled Substance staff and the submission of FDA's recommendation to DEA?

Answer 17a. FDA's role in scheduling drug substances under the Controlled Substance Act (CSA) is to perform a scientific and medical evaluation of drugs and to provide, through the Secretary of Health and Human Services, a recommendation to the Attorney General as to whether a drug should be controlled. Under the CSA, the Attorney General is required to request from the Secretary of Health and Human Services (Secretary) an evaluation of certain medical and scientific factors for a drug or other substance, a recommendation as to whether the substance should be controlled or not controlled under the CSA, and, if controlled, the appropriate

level of control or “schedule” under the CSA. The CSA establishes the factors and findings determinative for control.

The CSA requires the Secretary of the Department of Health and Human Services (HHS) to notify the Attorney General, through the Drug Enforcement Administration (DEA), at the time an NDA is submitted for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system and it appears that the drug has an abuse potential. HHS has delegated this function to FDA. FDA’s CDER, and the Controlled Substance Staff (CSS), perform this role for the Agency. In addition, proceedings to add, delete or change the schedule of a drug or other substance may be initiated by petition to DEA from any interested party such as a drug manufacturer, medical society, pharmacy association, public interest group, State and local government, or an individual citizen.

Throughout the drug development process, CSS evaluates preclinical, clinical, and epidemiological data to determine whether a drug under review requires abuse liability studies or scheduling under the CSA and recommends additional measures, such as those related to risk management, if needed, directed to reducing abuse, misuse and overdose. In addition, international drug control treaties to which the United States is a signatory may affect the regulation of new drugs with abuse liability. CSS also contributes to this area and works with the appropriate government agencies, including DEA, the National Institute on Drug Abuse (NIDA), HHS, and the U.S. Department of State.

The procedure for completion of the scheduling request and submission to DEA involves CSS analyzing the factors and findings determinative for control and preparing the scheduling recommendation (if appropriate); consulting with NIDA, FDA Office of Chief Counsel, the CDER Center Director, and the FDA Commissioner; reviewing the scheduling recommendation; and forwarding to the Assistant Secretary for Health, who makes the HHS recommendation for scheduling that is transmitted to DEA. This procedure is described in the FDA/CDER draft guidance entitled, *Guidance for Industry: Assessment of the Abuse Potential of Drugs*.

*Question 17b.* During FDA’s human drug review process, when does work related to a potential scheduling recommendation start? Are there timeline requirements for each step? How is the Agency performance relative to this process measured?

*Answer 17b.* The Agency’s evaluation of the abuse potential of a drug, whether under IND or NDA review, is subject to review timelines established under CDER’s OND for all of the review divisions relative to CDER’s Good Review Practices and PDUFA. Drug scheduling under the Controlled Substances Act (CSA) is a separate process that is largely carried out in parallel with the PDUFA timeline. The Agency’s goal for completing the assessment of abuse potential of a drug is the timeline for approval of the drug within the PDUFA timeline.

Typically, FDA does not begin its medical and scientific evaluation to support a scheduling recommendation until it receives a formal request from DEA. FDA may also initiate such an evaluation during the drug development process. Such an evaluation typically begins during the investigational stages of drug development or when an application to market a new drug is received by FDA and the Agency determines that the substance may be a candidate for scheduling under the CSA.

*Question 17c.* What steps, if any, is FDA taking to improve transparency and consistency of the Agency’s work on scheduling recommendations that are ultimately submitted to DEA?

*Answer 17c.* It is important to understand that NDA review and drug scheduling are two independent review processes regulated by two different laws. NDA review and approval is under the FD&C Act and timelines for review are established by PDUFA, while the process for drug scheduling is under the CSA. Even though these two processes are independent from a regulatory perspective, FDA strives to coordinate the CSA scheduling of a drug as closely as possible with that drug’s approval for marketing.

There are many factors influencing the time it takes for HHS to develop a final scheduling recommendation. The steps necessary to develop a scheduling recommendation need to be performed in a certain order. A delay in any step of the process can adversely affect the timeliness of scheduling relative to the NDA action date.

Some of the factors that can potentially affect the timeliness of the drug scheduling process are:

1. Timeliness, quality and completeness of data submitted by the drug company (Commercial Sponsor) to support drug scheduling determination by FDA.
2. Completion of all primary reviews for the new drug product (medical/pharmacology, clinical pharmacology, chemistry, and scientific issues).

3. Review and clearances by multiple Federal agencies (legal/regulatory issues).
4. New or precedent-setting medical and legal issues requiring regulatory policy development.

In order to expedite the scheduling process and to guide Sponsors on the type of studies needed to characterize the abuse potential of a drug, FDA/CDER published in January 2010, draft guidance entitled, *Guidance for Industry: Assessment of the Abuse Potential of Drugs* link: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>. In addition, FDA communicates to Sponsors the importance of an early interaction and high-quality submissions to support scheduling.

If sufficient information exists to make and support a drug scheduling recommendation, the FDA procedure, though complex, is not excessively long or delayed and closely parallels the PDUFA timeline.

Once the HHS recommendation is with DEA, FDA is removed from the process and not involved in scheduling other than to respond to DEA questions on issues that may need to be clarified.

SENATOR HATCH

*Question 1.* As we briefly discussed at the hearing, I hear from companies on a weekly basis about their plans to move their development efforts and manufacturing overseas to places like Europe because the regulatory pathway that is more predictable and reasonable when it comes to assessing safety and effectiveness. This move overseas results in the United States quickly losing its innovation edge over the rest of the world, not to mention the thousands of jobs being lost. What specific actions have you taken, to encourage manufacturers to remain in the United States? How does an increase in user fees compliment these efforts?

Answer 1. FDA's mission includes promoting the public health and that includes facilitating medical product innovation with respect to drugs, biologics, and devices. Global production of FDA-regulated goods has exploded over the past 10 years, but increased globalization has been seen across nearly all business sectors in the United States. Both the pharmaceutical and medical device industries are moving business overseas, mostly because of decreased costs in manufacturing and in conducting clinical trials. However, they are still submitting their products to FDA so that they can have access to the U.S. market.

The key challenges facing scientific progress and innovation in drug and device development are cost and uncertainty. Stakeholders in all areas of these industries repeatedly tell FDA that their biggest obstacle to successful product development is uncertainty. FDA has taken an approach to supporting new medical product innovations by generating initiatives to drive down development costs and reduce uncertainty in all phases of product development. FDA is spearheading several initiatives to directly reduce the cost of drug and device development.

FDA is also making great progress in the area of Adaptive Trial Design. Clinical trials do not always go as planned and Adaptive Trial Design allows the drug sponsor to change a clinical trial after patients are enrolled without compromising researchers' ability to assess the effectiveness of the drug being studied. This helps researchers make important changes to studies that otherwise may be delayed or discontinued and helps bring down the costs of clinical trials, which are often extremely expensive. We have also co-founded the Clinical Trials Transformation Initiative with Duke University to modernize the clinical trial system.

In addition, FDA is working to reduce the scientific uncertainty in drug development. For example, FDA has collaborated with the European Medicines Agency (EMA) to found the Predictive Safety Testing Consortium (PSTC). The PSTC has brought together scientists from 17 drug companies who collaborate to share and test new methods that are more reliable predictors of human safety. Such collaboration advances scientific knowledge and helps the industry to develop safer drugs faster and less expensively.

We are committed to continuing to improve the surveillance of products after they have reached the market. Our PDUFA V recommendations include funds to continue implementing FDA's Sentinel Initiative. This is FDA's evolving electronic "active surveillance" system—which will augment FDA's current safety monitoring program. The new system will transform FDA's ability to track the safety of drugs, biologics, and medical devices after they reach the market and will help to answer key safety questions about medical products in near real-time.

In 2004, FDA launched its Critical Path Initiative, FDA's national strategy to help advance pharmaceutical innovation. Our long-term efforts are showing positive signs and FDA will continue to support the scientific community to advance new drug development. Many of the concepts and initiatives set in motion by FDA's Crit-



ical Path Initiative may be beginning to show signs of benefit. For instance, as of July 23, 2011, FDA has approved 21 novel new drugs, equaling the total approved during all of 2010. The list of novel new drugs includes the first drug to treat lupus in over 56 years, a completely new treatment for chronic obstructive pulmonary disease (COPD), the first skin cancer therapy for metastatic melanoma (skin cancer) that demonstrates an improvement in overall patient survival, the only drug shown to be effective against medullary thyroid cancer, a new agent that can help diagnose Parkinson's disease, and two new and highly effective treatments for hepatitis C. Additionally, the 2011 NME list includes drugs intended for post-surgical use: one to decrease the likelihood of rejection after a kidney transplant and another to prevent deep vein thrombosis and pulmonary embolism after knee and/or hip replacement surgery.

In the device area, most of the proposed actions under CDRH's Innovation Initiative would foster innovation for all types of devices. For example, the new Innovation Pathway, if adequately resourced, could be applied to all or most devices for which a clinical study has to be conducted. In addition, the 25 actions the Agency announced it would take in 2011 to improve the 510(k) review process are intended to facilitate innovation for all types of devices by improving the predictability, consistency, and transparency of our pre-market review program.

Periodic reauthorization of MDUFA ensures that the device review program continues to operate on a sound financial footing, to the benefit of patients, health professionals, and industry. In part this is related to both existing workload and inflation that FDA experiences in operating the program.

*Question 2.* With a medical device tax about to hit the industry across the board in 2013, shouldn't the Federal Government be looking for ways to unburden industry instead of making their burden greater by adding more user fees on top of an already onerous medical device excise tax?

*Answer 2.* FDA has no jurisdiction or policy role with respect to the medical device excise tax.

Medical device user fees consist of congressionally authorized private money, which is paid by medical device companies to FDA in return for FDA's commitment to meet specific performance goals. Congress first authorized FDA to collect user fees from device manufacturers in 2002, with the passage of the Medical Device User Fee and Modernization Act (MDUFMA);<sup>35</sup> in 2007, MDUFMA's user fee authorities were reauthorized by Congress for another 5-year period.<sup>36</sup>

The authority to collect user fees is subject to two statutory triggers: if either trigger is not satisfied for a given fiscal year, FDA loses authority to collect user fees. The first trigger prohibits FDA from collecting fees if direct congressional appropriations to FDA for salaries and expenses related to devices and radiological health fall below a certain threshold. The second trigger requires that fees only be collected and available to defray increases in the cost of the resources allocated for the process for the review of device applications.

FDA has the authority to collect three types of medical device user fees: application fees (paid each time an application is submitted), establishment fees (paid annually by all non-exempt establishments), and product fees (paid annually for each qualifying Class III device). The amount of each type of user fee is determined by Congress. Application and product fees are set as a percentage of the PMA fee (also called the "base fee"). The law prescribes both the base fee amount for each fiscal year, and also the percentage of the base fee that constitutes most other fees; the law raises the base fee annually by a certain percentage. The amount of the establishment fee (unlike the other user fees) is set in its own section of the medical device user fee law.

Because medical device user fees consist solely of congressionally authorized private money, FDA may only collect fees as authorized by Congress (and in the amounts set forth by Congress) in the user fee law.

The current medical device user fee law is set to expire on September 30, 2012. As required by the 2007 user fee law, FDA is currently engaged in the process of working with various stakeholders—including the regulated industry, as well as consumer and patient groups—to prepare for user fee reauthorization in 2012. As part of that process, FDA will publish its recommendations for the reauthorization in the *Federal Register*, provide a public comment period, hold a public meeting, and then revise its recommendations upon consideration of the public comments. FDA

<sup>35</sup> P.L. 107-250 (2002).

<sup>36</sup> Medical Device User Fee Amendments of 2007 (MDUFA 2007), enacted as Title II of the Food and Drug Administration Amendments Act of 2007 (FDAAA: H.R. 3580; P.L. 110-85).

is required to transmit its recommendations for reauthorization of the user fee program to Congress no later than January 15, 2012.

*Question 3.* Is the current draft guidance that the FDA issued in 2007 still consistent with FDA's current policies and views of what sponsors need to demonstrate in order for an obesity drug to obtain approval?

*Answer 3.* Yes. The current draft guidance is consistent with FDA's current policies and views for what sponsors need to demonstrate for effectiveness of an obesity drug. The 2007 draft guidance states:

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- The difference in mean weight loss between active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant.
- The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

To fully evaluate an obesity drug for approval, it is important to consider the weight-loss efficacy or benefit of a drug in the context of the drug's potential risks or harms, thereby determining whether the drug's benefits outweigh its risks and is therefore appropriate for approval.

FDA is planning a scientific meeting to discuss obesity and cardiovascular safety, and we are also planning to hold a series of stakeholder meetings where we bring in pharmaceutical and patient groups, FDA, and other experts to talk about how obesity drugs should be developed. We expect these meetings to be very helpful to industry.

*Question 4.* I was pleased to see the President's Executive order directing agencies to examine both their existing and new regulations to make sure they are not unnecessarily burdensome for industry and that they support innovation. What actions and initiatives have you done or are you currently doing or plan to do in response to the Order. In addition, while the Order, as I understand it, only formally extends to actual regulations, much of the work the FDA does is by guidance or other sub-regulatory activities which have a huge impact on industry. What other activities beyond re-evaluating the regulations are you doing in the spirit of the Executive order. Will you be evaluating the actions you are taking to implement the 510(k) reform plans in the spirit of the President's order—in particular by looking at whether any additional burdens on industry are truly necessary and how your actions will support innovation?

*Answer 4.* The President has directed Agencies to review regulations and other procedures to see if they can withdraw or modify regulations, or otherwise improve procedures, to reduce regulatory burden and improve competitiveness, innovation, economic growth, and jobs, while assuring safety. As a first step in the regulatory review, the Secretary of HHS asked each component Agency to do an inventory of its existing significant regulations to provide information that will assist HHS in constructing an ongoing retrospective review process. FDA sought comment on how the Agency could revise its existing review framework to meet the objectives of Executive Order 13563, regarding the development of a plan with a defined method and schedule for identifying certain significant rules that may be obsolete, unnecessary, unjustified, excessively burdensome, or counterproductive. FDA focuses its retrospective review effort on regulations that have a significant public health impact and regulations that impose a significant burden on the Agency and/or industry. FDA has under review, or has identified, over 40 rules as candidates for regulatory review.

FDA already estimates the effects of its regulations on industry when we initially promulgate the regulation and has been doing so for over 30 years. The laws and Executive orders that the Agency follows require FDA to measure the effect of regulations on employment, innovation, and economic growth. For example, the Unfunded Mandates Reform Act of 1995 requires that major rules include estimated effects on employment, competitiveness, and growth. Another example is Executive Order 12866, which requires all Federal agencies to consider effects on innovation, when writing regulations.

On April 27, 2011, FDA published a notice in the *Federal Register*, requesting comment and supporting data on which, if any of our existing rules are outmoded, ineffective, insufficient, or excessively burdensome and thus may be candidates for review. This docket closed on June 27, 2011. FDA is now reviewing the comments received and will be using the comments to inform its future regulatory review activities.

Relating to medical devices, FDA has already identified improvements to regulatory science as well as other initiatives—such as its medical device innovation initiative, the 510(k) Plan of Action, and the FDA/CMS voluntary pilot for parallel review of medical devices—that will help it and the industries it regulates innovate and remain competitive.

With respect to initiatives under the 510(k) action plan, those implemented by guidance or regulation will be subject to public comment periods. Those requiring legislation are for Congress to determine. The rest were well-vetted through the numerous opportunities afforded industry and the public to comment on the proposals.

We are also converting the device registration and listing process to a paperless system, allowing for the utilization of the latest technology in the collection of information, while maintaining an avenue for companies for which paper applications are more convenient. This will speed reporting and analysis of adverse events and identification of emerging public health problems, as well as lower costs for manufacturers.

We are also revising device pre-market approval regulations (Special PMA Supplement Changes Being Effected) to remove duplicative requirements and streamline and clarify regulatory requirements. And we will be proposing to allow the use of validated symbol in device labeling, without the need for accompanying English text, thereby reducing the burden of labeling requirements by permitting harmonization with labeling for international markets.

Relating to drugs, FDA has reviewed its regulations and guidance documents to identify areas in which the Agency can reduce burden on industry and support innovation. FDA has identified several areas where activities are already in progress to achieve these objectives. For example, through regulations and guidance, FDA is clarifying and streamlining safety reporting requirements for drug manufacturers to improve the overall quality of safety reporting, to harmonize certain reporting requirements with international standards, and to ensure timely reporting of safety signals with critical public health implications. In addition, FDA is revising existing regulations and guidance documents, as well as developing new regulations and guidance, to facilitate the electronic filing of various types of information that drug manufacturers are required to submit to the Agency. Our initiatives on this front include drug registration and listing information, manufacturing site information, drug safety reports, and clinical study data for new applications and supplements. These changes are expected to reduce the administrative burden on applicants and allow for more efficient and comprehensive data review by the Agency. FDA is committed to continuous review of its regulatory framework to improve procedures, streamline the process for compliance with regulatory requirements, and balance innovation strategies with our obligation to ensure the safety and efficacy of human pharmaceuticals.

*Question 5.* Last month the FDA issued, “Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues.” As you know, this document is voluminous and takes some time to properly evaluate and analyze. Considering the potential impact the guidance may have on industry will you extend the comment period to provide stakeholders with enough time to review and to submit well thought out comments on the draft guidance?

*Answer 5.* Yes. FDA announced in the September 9, 2011, *Federal Register* (76 FR 55927) that we are extending the comment period on the New Dietary Ingredient guidance by 60 days. until December 2, 2011.

**Appendix I  
NDA and BLA Original Submissions**

| Fiscal year  | 1993       | 1994       | 1995      | 1996      | 1997      | 1998      | 1999      | 2000      | 2001      | 2002      | 2003      | 2004      | 2005      | 2006      | 2007      | 2008      | 2009      | 2010      |
|--|------------|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Percentage of Filed Submissions that were Approved First Cycle (Priority/Standard) ... | 57%/ 21%   | 28%/ 22%   | 47%/ 29%  | 68%/ 41%  | 44%/ 45%  | 53%/ 31%  | 63%/ 42%  | 50%/ 34%  | 18%/ 20%  | 58%/ 37%  | 47%/ 35%  | 57%/ 48%  | 66%/ 38%  | 68%/ 46%  | 68%/ 40%  | 58%/ 43%  | 55%/ 43%  | 44%/ 52%  |
| Median FDA Time to First Action (in Months)  | 10.9/ 12.8 | 12.0/ 12.0 | 9.0/ 12.0 | 6.0/ 12.0 | 6.0/ 12.0 | 6.0/ 11.9 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.1/ 8.3/ | 6.1/ 7.2/ | 6.0/ 10.0 |
| Mean FDA Time to First Action (in Months) ...  | 15.4       | 12.8       | 11.9      | 12.0      | 11.6      | 11.5      | 11.2      | 10.2      | 10.5      | 10.2      | 10.2      | 10.2      | 10.6      | 10.6      | 11.3      | 10.8      | 10.5      | 10.3      |

**NDA and BLA Efficacy Supplements**

| Fiscal year  | 1993      | 1994      | 1995      | 1996      | 1997      | 1998      | 1999      | 2000     | 2001     | 2002     | 2003      | 2004      | 2005     | 2006      | 2007      | 2008      | 2009      | 2010      |
|--|-----------|-----------|-----------|-----------|-----------|-----------|-----------|----------|----------|----------|-----------|-----------|----------|-----------|-----------|-----------|-----------|-----------|
| Percentage of Filed Submissions that were Approved First Cycle (P/S) ..... | 0%/ 96%   | 26%/ 48%  | 15%/ 47%  | 12%/ 51%  | 17%/ 76%  | 24%/ 78%  | 32%/ 80%  | 36%/ 71% | 14%/ 76% | 35%/ 70% | 36%/ 55%  | 46%/ 66%  | 48%/ 73% | 63%/ 81%  | 50%/ 79%  | 48%/ 74%  | 60%/ 78%  | 37%/ 71   |
| Median FDA Time to First Action (in Months)                                | 9.3/ 17.4 | 5.7/ 12.0 | 6.0/ 11.8 | 6.0/ 11.7 | 4.4/ 11.2 | 6.0/ 11.4 | 6.0/ 10.0 | 6.0/ 9.9 | 6.0/ 9.9 | 5.9/ 9.9 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 9.9 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 | 6.0/ 10.0 |
| Mean FDA Time to First Action (in Months) ...                              | 9.0/ 18.6 | 7.1/ 13.3 | 8.2/ 10.6 | 6.6/ 10.1 | 4.5/ 9.6  | 6.8/ 10.3 | 6.0/ 9.6  | 5.7/ 9.4 | 6.7/ 9.5 | 5.9/ 9.3 | 6.0/ 9.3  | 6.0/ 9.6  | 5.9/ 9.3 | 6.1/ 9.9  | 6.3/ 10.2 | 6.4/ 10.4 | 6.8/ 10.2 | 6.3/ 10.0 |

**NDA and BLA Manufacturing Supplements**

| Fiscal year   | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999     | 2000     | 2001     | 2002     | 2003     | 2004     | 2005     | 2006     | 2007     | 2008     | 2009     | 2010     |
|---|------|------|------|------|------|------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Percentage of Filed Submissions that were Approved First Cycle (PA/CBE) ..... | 71%  | 74%  | 67%  | 85%  | 83%  | 86%  | 78%/ 90% | 77%/ 91% | 76%/ 94% | 75%/ 90% | 72%/ 93% | 79%/ 95% | 82%/ 95% | 81%/ 96% | 78%/ 95% | 73%/ 92% | 73%/ 91% | 71%/ 88% |
| Median FDA Time to First Action (in Months)                                   | 5.9  | 5.3  | 4.7  | 4.8  | 5.1  | 5.2  | 3.9/ 4.4 | 3.9/ 4.9 | 3.9/ 5.5 | 3.9/ 5.8 | 3.9/ 5.8 | 3.9/ 5.8 | 3.9/ 5.7 | 3.9/ 5.8 | 3.9/ 5.9 | 4.0/ 6.0 | 3.9/ 5.9 | 3.9/ 5.9 |
| Mean FDA Time to First Action (in Months) ...                                 | 7.1  | 6.4  | 4.5  | 4.3  | 4.5  | 4.5  | 4.0/ 4.3 | 3.8/ 4.1 | 3.7/ 4.5 | 3.6/ 4.9 | 3.6/ 5.0 | 3.7/ 5.1 | 3.7/ 5.1 | 3.9/ 5.5 | 3.9/ 5.6 | 4.5/ 5.8 | 4.3/ 5.6 | 4.2/ 5.7 |

[Whereupon, at 12:00 p.m., the hearing was adjourned.]

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