DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
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STATEMENT

OF

MARGARET A. HAMBURG, M.D.

COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON HEALTH, EDUCATION, LABOR AND PENSIONS

U.S. SENATE

FDA USER FEES: ADVANCING PUBLIC HEALTH

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RELEASE ONLY UPON DELIVERY

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 time frame. 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 (FY). PDUFA permits waivers under certain circumstances, including a waiver of the application fee for small businesses.

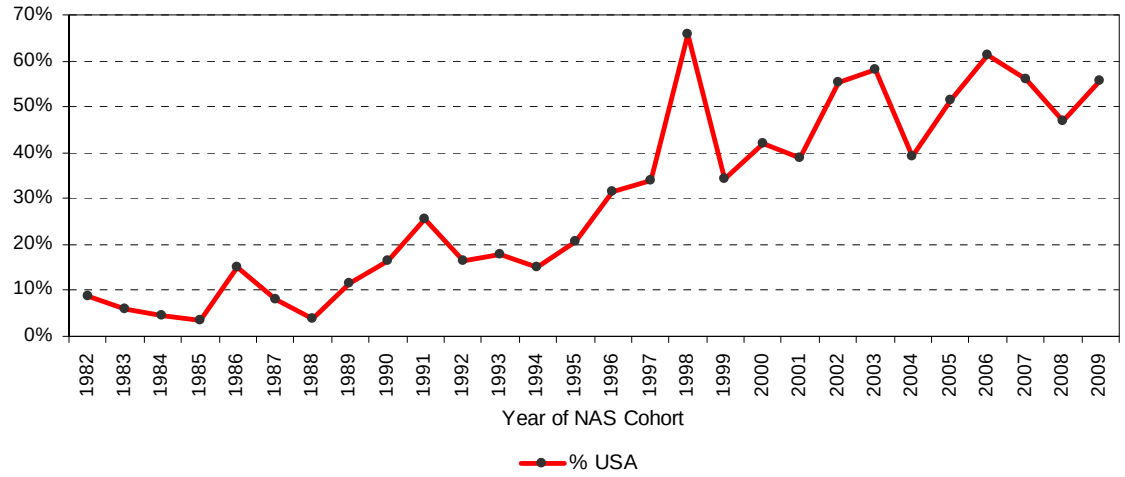
Of the total $931,845,581 obligated in support of the process for the review of human drug applications in FY 2010, PDUFA fees funded 62 percent, with the remainder funded through appropriations.

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 seven 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,[1] 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.

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



[1] 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.

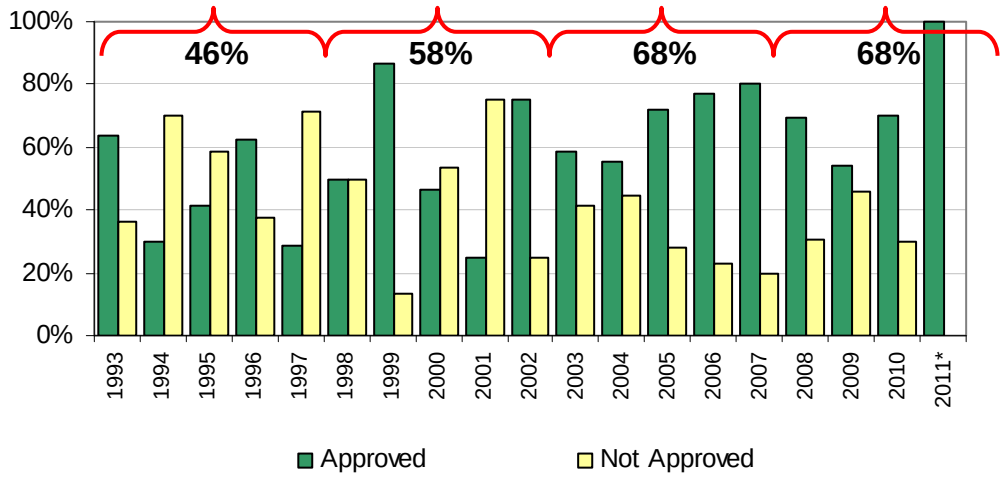
Increased resources provided by user fees have enabled FDA to provide a large body of technical guidance to industry that clarified the drug development pathway for many diseases and meet with companies during drug development to provide critical advice on specific development programs. In the past five 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 FY 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 five 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

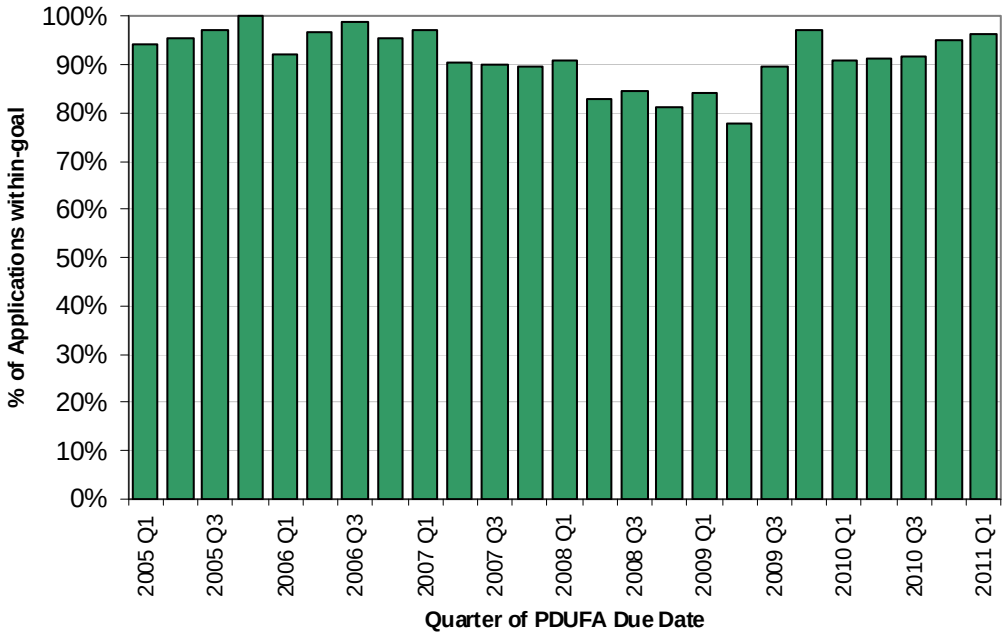
on new safety information identified after a drug is on the market. FDA has used its new authority to require sponsors to place important new safety information onto their drug labels quickly, in some cases using this authority to require changes to the labeling of all members of a class of drugs. FDAAA 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 premarket 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 preapproval 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 FY 2008-09, 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 five 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 premarket applications, reports, supplements, and premarket 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 FY2010, 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 premarket 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 below 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 premarket approval (PMA) decisions is improving.

Figure 4.

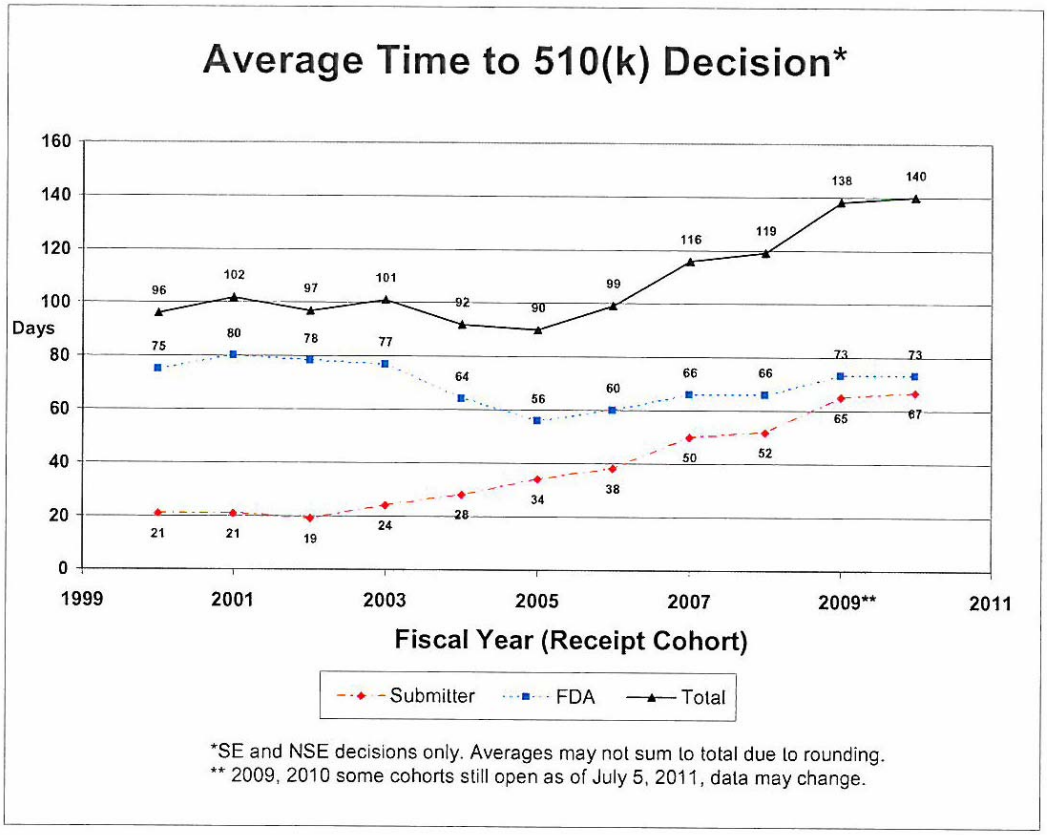
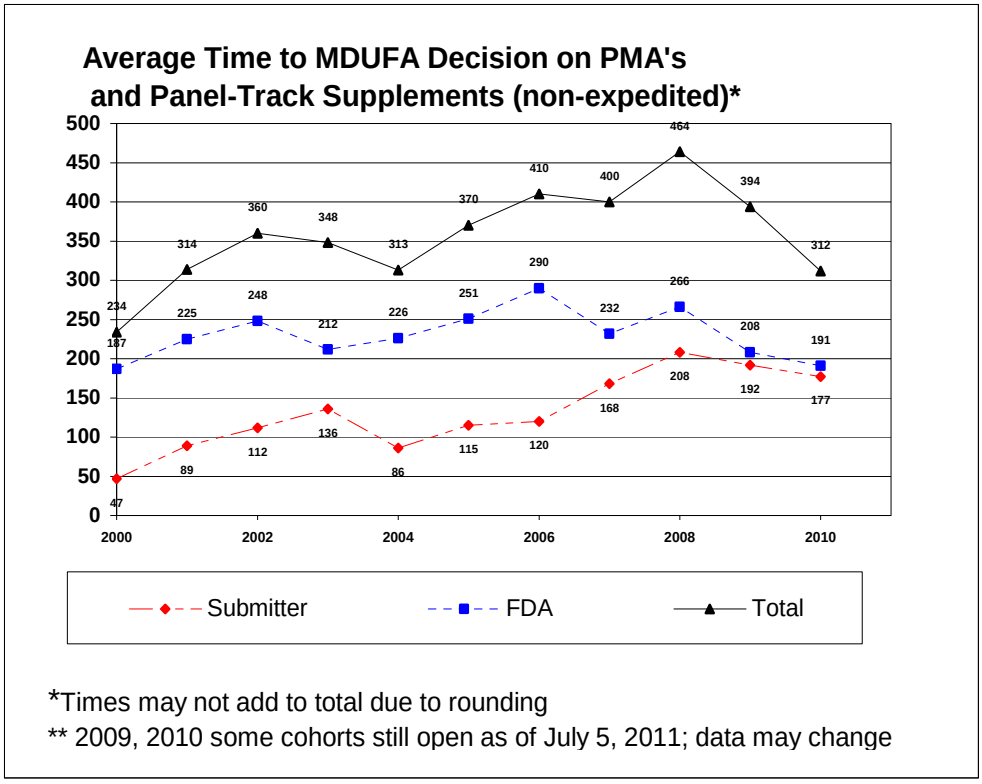

Average Time to 510(k) Decision*
Days
160
140
120
100
80
60
40
20
0
1999
2001
2003
2005
2007
2009**
2011
Fiscal Year (Receipt Cohort)
Submitter
FDA
Total
96
102
97
101
92
90
99
116
119
138
140
75
80
78
77
64
56
60
66
66
73
73
21
21
19
24
28
34
38
50
52
65
67
*SE and NSE decisions only. Averages may not sum to total due to rounding.
** 2009, 2010 some cohorts still open as of July 5, 2011, data may change.

Figure 5.

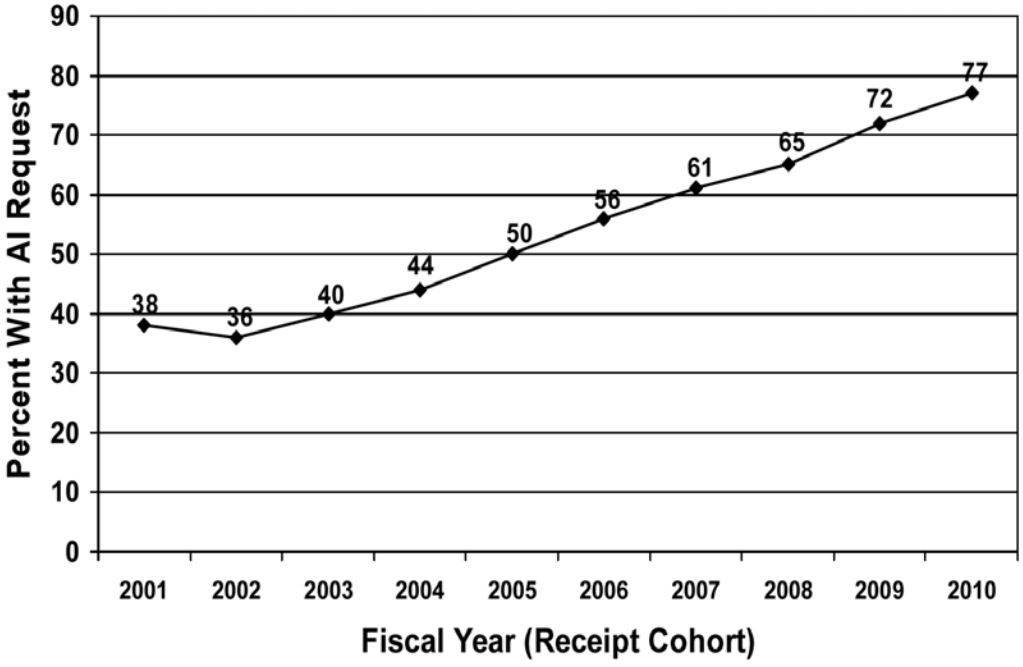


FDA is committed to working on ways to streamline the regulatory review process. Success will require that we continue to focus on our own internal process, but industry also bears responsibility for the increase in overall time to a decision. Poor-quality submissions that need to be addressed are significant contributors to delays in premarket 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 below shows the steep and prolonged increase, since FY 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 premarket 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 FY 2008–FY 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 premarket 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 premarket 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 premarket 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 decision-making, which addressed aspects of its other premarket 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 premarket 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 premarket 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 premarket 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:

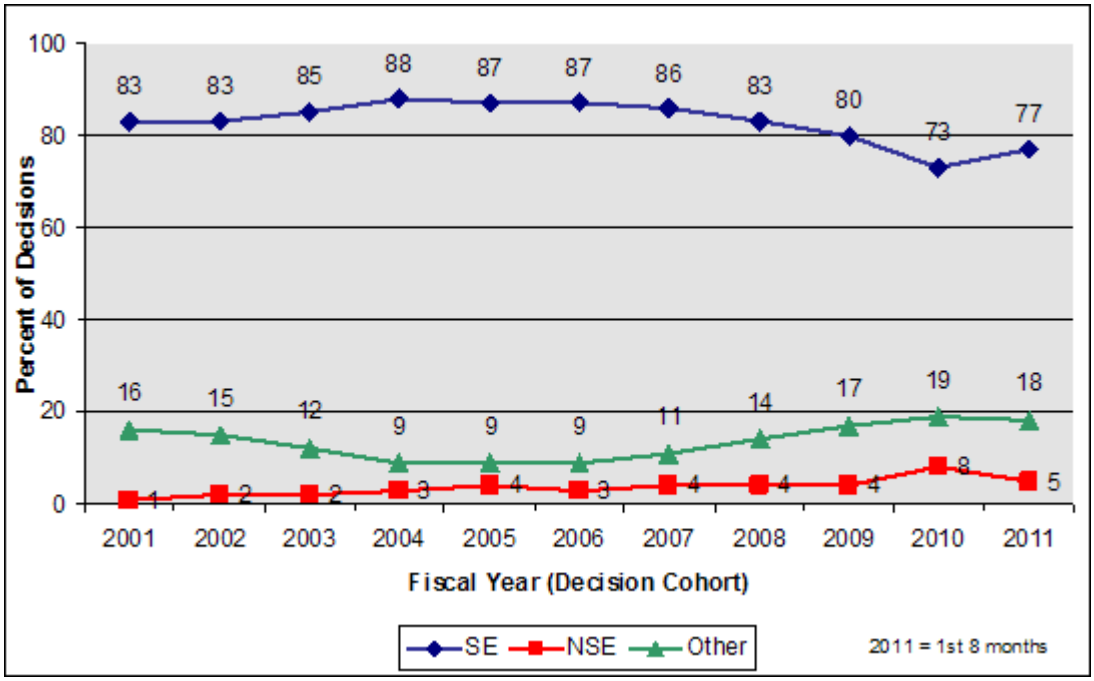
- Developing a range of updated and new guidances to clarify CDRH requirements for timely and consistent product review, including device-specific guidance in several areas such as mobile applications (released in July 2011) and artificial pancreas systems (to be completed by the end of 2011), and draft 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 decision-making (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 eight 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 eight months of 2011, as shown below 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 premarket 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 predisposed 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 decision-making 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 time frames. 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 FY 2012. This translates to a modest 6 percent increase, and a total estimated base of $712.8 million in FY 2013.[2]

- **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.

MDUFA 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 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

[2]The FY 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 FY 2013, the first year of PDUFA V.

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.