



**STATEMENT**

**OF**

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**BEFORE THE**

**COMMITTEE ON ENERGY AND COMMERCE**  
**SUBCOMMITTEE ON HEALTH**  
**U.S. HOUSE OF REPRESENTATIVES**

**“FDA USER FEES 2012: HOW INNOVATION HELPS PATIENTS AND JOBS”**

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## INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA),<sup>1</sup> also referred to as PDUFA V, as well as the negotiated recommendations for a generic drug user fee program and a biosimilar user fee program. I will also discuss a number of other important issues facing FDA, including expediting access to new therapies, the renewal of legislation to promote pediatric drug testing, securing the supply chain for prescription drug products, the regulation of medical gases, efforts to facilitate the development of antibacterial drug products, as well as update you on actions the Agency is taking to address the ongoing problem of drug shortages.

### Background on PDUFA

FDA considers the timely review of the safety and effectiveness of New Drug Applications (NDA) and Biologics License Applications (BLA) 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

<sup>1</sup> PDUFA was enacted in 1992 and authorizes FDA to collect fees from companies that produce certain human drug and biological products. Industry agrees to pay fees to help fund a portion of FDA's drug review activities, while FDA agrees to overall performance goals, such as reviewing a certain percentage of applications within a particular

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 and orphan drugs.

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. In FY 2011, FDA approved 35 new, groundbreaking medicines, including two treatments for hepatitis C, a drug for late-stage prostate cancer, the first drug for Hodgkin's lymphoma in 30 years, and the first drug for lupus in 50 years. This was the second highest number of annual

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time frame. The current legislative authority for PDUFA expires on September 30, 2012. On January 13, 2012, HHS Secretary Kathleen Sebelius transmitted recommendations to Congress for the next reauthorization of PDUFA.

approvals in the past 10 years, surpassed only by 2009. Of the 35 innovative drugs approved in FY 2011, 34 met their PDUFA target dates for review.

### *Substantially Reduced Review Times*

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.

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 since the enactment of PDUFA in 1992, from an average of 2 years for the approval phase at the start of PDUFA to an average of 1.1 years more recently.<sup>2</sup>

FDA aims to review priority drugs more quickly, in six months vs. 10 months for standard drugs. Priority drugs are 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.

### *Reversal of the “Drug Lag”*

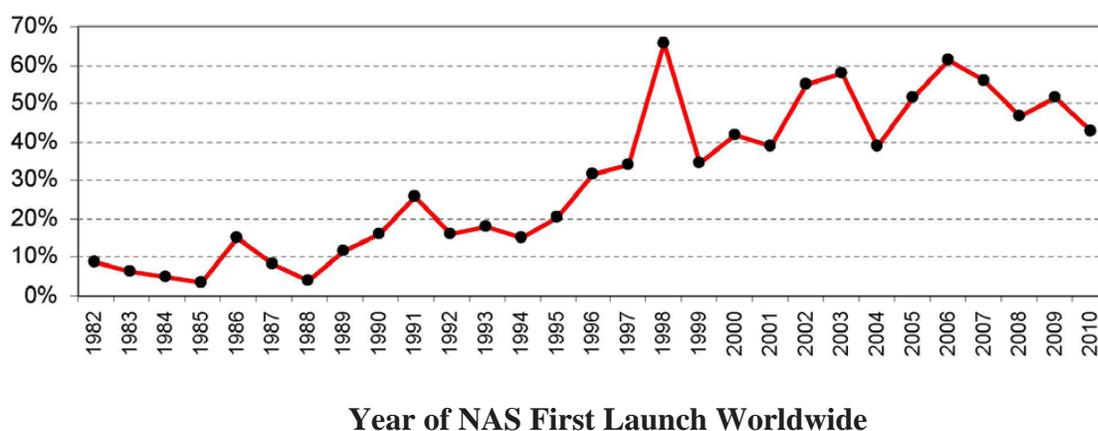
Importantly, PDUFA has led to the reversal of the drug lag that prompted its creation. Since the enactment of PDUFA, FDA has steadily increased the speed of Americans’ access to important new drugs compared to the European Union (EU) and the world as a whole. Of the 35 innovative drugs approved in FY 2011, 24 (almost 70 percent) were approved by FDA before any other regulatory agency in the world, including the European Medicines Agency. Of 57

<sup>2</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.

novel drugs approved by both FDA and the EU between 2006 and 2010, 43 (75 percent) were approved first in the United States.

Figure 1 below shows that since the late 1990s, the United States has regularly led the world in the first introduction of new active drug substances.<sup>3</sup> Preliminary data show that in 2011, over half of all new active drug substances were first launched in the United States.

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



In recent years, FDA’s drug review times also have been, on average, significantly faster than those in the EU. It is difficult to compare length of approvals for FY 2011, because many of the drugs approved in the United States have not yet been approved in the EU. A comparison of drugs approved in the United States and the EU between 2006 and 2010 is illustrative, however. For priority drugs approved between 2006 and 2010, FDA’s median time to approval was six months (183 days), more than twice as fast as the EU, which took a median time of 13.2 months (403 days). For standard drug reviews, FDA’s median time to approval was 13 months (396 days), 53 days faster than the EU time of 14.7 months (449 days).

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<sup>3</sup> Scrip NCE Review/Scrip Yearbook/Scrip Magazine (1982 -2005), PharmaProjects R&D Annual Review (2006-2010). New active substances include novel chemical or biological substances not previously approved to treat any disease. There is a close, but not complete overlap, between new active substances and new molecular entities: new active substances exclude radiopharmaceuticals.

A recent article in the journal *Health Affairs* also compared cancer drugs approved in the United States and EU from 2003 through 2010. Thirty-five cancer drugs were approved by the United States or the EU from October 2003 through December 2010. Of those, FDA approved 32—in an average time of 8.6 months (261 days). The EU approved only 26 of these products, and its average time was 12.2 months (373 days). This difference in approval times is not due to safety issues with these products. All 23 cancer drugs approved by both agencies during this period were approved first in the United States.<sup>4</sup>

### *Speeding Access to New Therapies*

PDUFA funds help support a number of existing FDA programs to expedite the approval of certain promising investigational drugs, and also to make them available to the very ill before they have been approved for marketing, without unduly jeopardizing patient safety.

The most important of these programs are Accelerated Approval, Fast Track, and Priority Review. In 1992, FDA instituted the Accelerated Approval process, which allows earlier approval of drugs that treat serious or life-threatening 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, or, in some cases, an effect on a clinical endpoint other than survival or irreversible morbidity. 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. For example, viral load is a surrogate endpoint for approval of drugs for the treatment of HIV/AIDS. The use of a surrogate endpoint can considerably shorten the time to approval, allowing more rapid patient access to promising new treatments for serious or life-threatening diseases. Accelerated Approval is given

<sup>4</sup> “Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe,” Samantha A. Roberts, Jeff D. Allen, and Ellen V. Sigal, *Health Affairs*, June 2011.

on the condition that sponsors conduct post-marketing clinical trials to verify the anticipated clinical benefit.

Over 80 new products have been approved under Accelerated Approval since the program was established, including 29 drugs to treat cancer, 32 to treat HIV, and 20 to treat other conditions such as pulmonary arterial hypertension, Fabry disease, and transfusion-dependent anemia. Three of the 30 new molecular entities (NMEs) and new BLAs approved in 2011 in CDER were approved under Accelerated Approval. Corifact, the first treatment approved for a rare blood-clotting disorder, also was approved under Accelerated Approval in FDA's Center for Biologics Evaluation and Research (CBER) on February 17, 2011.

Fast Track is a process designed to facilitate the development, and expedite the review, of drugs to treat serious or life-threatening diseases that will fill an unmet medical need. Once a drug receives Fast-Track designation, early and frequent communications between FDA and a drug company are encouraged throughout the entire drug development and review process. The frequency of communications ensures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients. For example, Zelboraf (vemurafenib) was given a Fast-Track designation because it had the potential to improve overall survival in patients with melanoma, the most dangerous type of skin cancer. Because of convincing early findings with this drug, FDA scientists worked proactively with the sponsor during drug testing to encourage early submission of the application. FDA approved Zelboraf in 2011 to treat patients with late-stage (metastatic) or unresectable (cannot be removed by surgery) melanoma.

In 1992, under PDUFA, FDA agreed to specific goals for improving drug review times and created a two-tiered system of review times—Priority Review and Standard Review. FDA aims to review priority drugs more quickly, in six months versus 10 months for standard drugs. Priority review designation is given to drugs that offer major advances in treatment, or provide a

treatment where no adequate therapy exists, while Standard Review is applied to drugs that offer at most only minor improvement over existing marketed therapies. FDA reviewers give Priority Review 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. For example, on January 31, 2012, FDA approved Kalydeco (ivacaftor) to treat patients age 6 or older with Cystic Fibrosis (CF) and who have a specific genetic defect (G551D mutation), after a Priority Review. CF occurs in approximately 30,000 children and adults in the United States. The G551D mutation occurs in approximately 4 percent of patients with CF, totaling approximately 1,200 patients in the United States. CF is a serious inherited disease that affects the lungs and other organs in the body, leading to breathing and digestive problems, trouble gaining weight, and other problems. There is no cure for CF, and despite progress in the treatment of the disease, most patients with CF have shortened life spans and do not live beyond their mid-30's. After the results of studies of ivacaftor showed a significant benefit to patients with CF with the G551D mutation, ivacaftor was reviewed and approved by FDA in approximately three months—half of the Priority Review period. Ivacaftor is the first medicine that targets the underlying cause of CF; to date, therapy has aimed at treating symptoms or complications of the disease.

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 some 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.

We are committed to using these programs to speed therapies to patients while upholding our high standards of safety and efficacy. Balancing these two objectives requires that we continue to evaluate our use of the tools available to us and consider whether additional tools would be helpful. We are eager to work with Congress in this area, and we note that several of the enhancements proposed for PDUFA V are aimed at expediting the availability of new therapies and providing FDA the scientific understanding necessary to modernize and streamline our regulatory process.

#### *Providing Guidance to Industry*

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 to 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 formal meetings with drug sponsors within a short time after a sponsor's request. Innovations in drug development are being advanced by many new emerging companies as well as more established ones, and new sponsors may need, and often seek, more regulatory guidance during development. In FY 2009 through FY 2011, more than half of the meetings FDA held during drug development were with companies that had no approved product on the U.S. market.

### *Weighing Benefit and Risk*

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 last year, FDA approved Yervoy (ipilimumab) for the treatment of unresectable or metastatic melanoma. Yervoy also poses a risk of serious side effects in 12.9 percent of patients treated, including severe to fatal autoimmune reactions. However, FDA decided that the benefits of Yervoy outweighed its risks, especially considering that no other melanoma treatment has been shown to prolong a patient's life.

As discussed in more detail below, PDUFA V will enable FDA to develop an enhanced, structured approach to benefit-risk assessments that accurately and concisely describes the benefit and risk considerations in the Agency's drug regulatory decision-making.

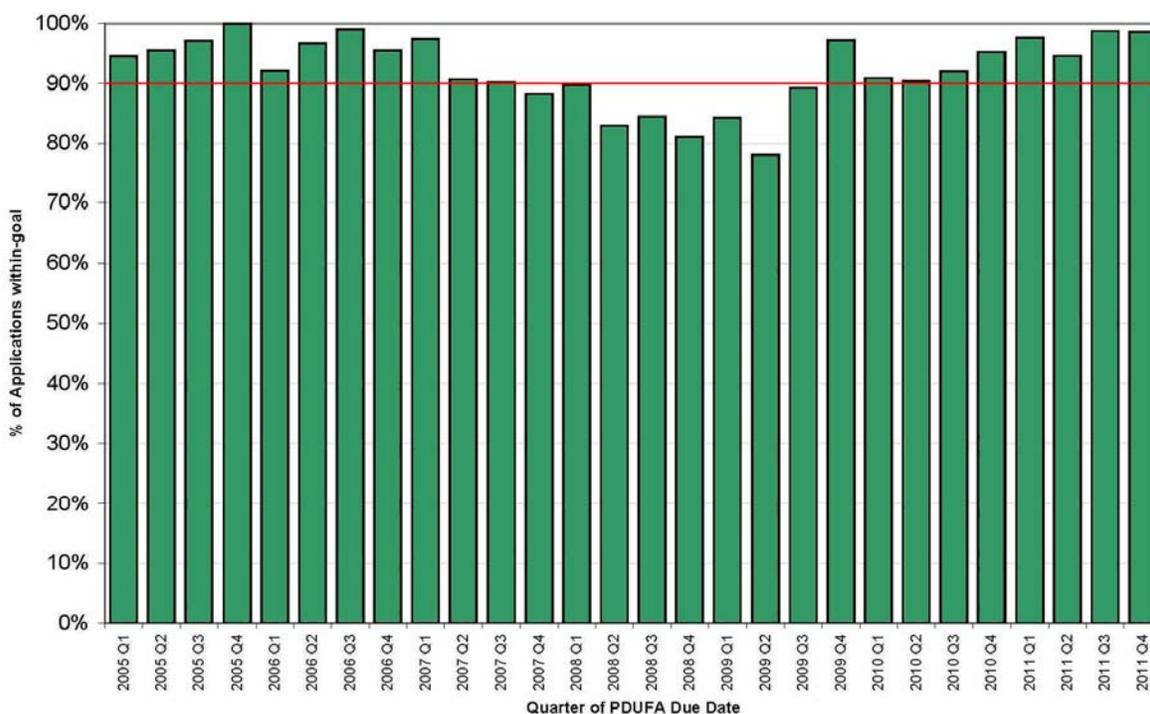
### Challenges for the Current Drug Program

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 authorities from the Food and Drug Administration Amendments Act of 2007 (FDAAA) 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 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 FY 2008-09, when staff resources were shifted within the discretion afforded FDA to ensure timely implementation of all the new FDAAA provisions that affected activities in the new drug review process. Recent performance data show that FDA has returned to meeting or exceeding goals for review of marketing applications under PDUFA. This is shown in Figure 3.

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



CDER data as of 12/31/2011. Figures reflect aggregate performance for all NDAs, BLAs, and Efficacy Supplements based on the month of the PDUFA review goal.

However, FDA wants to meet not only the letter, but also the spirit of the PDUFA program. That is, we want to speed patient access to drugs shown to be safe and effective for the indicated uses while also meeting our PDUFA goals.

The NDA/BLA approval phase of drug development is reported to have the highest success rate of any phase of drug development. That is, the percentage of drugs that fail after the sponsor submits an NDA/BLA to FDA is less than the percentages that fail in preclinical development and in each phase of clinical development. At the same time, 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 about more than just speeding drug development prior to the point at which FDA receives an application 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 (NIH) 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 21<sup>st</sup> 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 also has taken steps to help 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 approved Voraxaze

(glucarpidase) in January 2012 to treat patients with toxic methotrexate levels in their blood due to kidney failure, which affects a small population of patients each year. Methotrexate is a commonly used cancer chemotherapy drug normally eliminated from the body by the kidneys. Patients receiving high doses of methotrexate may develop kidney failure. Voraxaze was approved based on data in 22 patients from a single clinical trial, which showed decreased levels of methotrexate in the blood. Prior to the approval of Voraxaze, there were no effective therapies for the treatment of toxic methotrexate levels in patients with renal failure.

### PDUFA Reauthorization

In PDUFA IV, Congress directed FDA to take additional steps to ensure that public stakeholders, including consumer, patient, and health care professional organizations, would have adequate opportunity to provide input to the reauthorization and any program enhancements for PDUFA V. Congress directed the Agency to hold an initial public meeting and then to meet with public stakeholders periodically, while conducting negotiations with industry to hear their views on the reauthorization and their suggestions for changes to the PDUFA performance goals. PDUFA IV also required that minutes from negotiation sessions held with industry be made public.

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 and in July 2010, began negotiations with industry and parallel discussions with public stakeholders. These discussions concluded in May 2011 and we held a public meeting on October 24, 2011, where we solicited comments on the proposed recommendations. We also opened a public docket for comments. We considered these comments, and on January 13, 2012, we transmitted the final recommendations to Congress.

We are very pleased to report that the enhancements for PDUFA V address many of the top priorities identified by public stakeholders, the top concerns identified by industry, and the most important challenges identified within FDA. PDUFA V enhancements include a review program for New Drug Applications, New Molecular Entities, and Original Biologics License Applications, regulatory science enhancements to expedite drug development, risk-benefit assessment enhancements, FDA drug safety system enhancement and modernization, requiring electronic submissions and standardization of electronic application data, a user fee increase, and enhancements for a modified inflation adjuster and additional evaluations of the workload adjuster.

### Generic Drug User Fees

As a result of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as Hatch-Waxman Amendments passed by Congress more than a quarter of a century ago, America's generic drug industry has been developing, manufacturing, and marketing—and FDA has been reviewing and approving—lower-cost versions of brand-name drugs. This legislation and the industry it fostered has been a true public health success. Last year, approximately 78 percent of the more than 3 billion new and refilled prescriptions dispensed in the United States were filled with generics. In the last decade alone, generic drugs have provided more than \$931 billion in savings to the nation's health care system.<sup>5</sup>

This success, however, also has come to represent a significant regulatory challenge, and delays in approvals of generic drugs have emerged as a major concern for the generics industry, FDA, consumers, and payers alike. Unlike the brand manufacturers who pay fees under PDUFA, the generic industry does not pay a user fee to support FDA activities related to its

<sup>5</sup> "An Economic Analysis of Generic Drug Usage in the U.S." Independent Analysis by IMS Health, Sept. 2011, <http://gphaonline.org/sites/default/files/GPhA%20IMS%20Study%20WEB%20Sep20%2011.pdf>.

applications. Over the last several years, the time it takes for FDA to approve a generic drug has nearly doubled as FDA's resources have not kept pace with an increasing number of Abbreviated New Drug Applications (ANDA) and other submissions related to generic drugs. The number of generic drug submissions sent annually to FDA has grown rapidly, reaching another record high this year, including nearly 1,000 ANDAs. Drug Master Files<sup>6</sup> have grown at a comparable pace and have reached similar heights. The current backlog of applications pending review is estimated to be over 2,500. The current median time to approval is approximately 31 months, though it should be noted that this includes time the application is back with the sponsor to answer any questions FDA may have about the application.

The regulatory challenge of ensuring safe, high-quality generic drugs includes inspecting manufacturing facilities, where the challenge is not just one of numbers but also of geography. To keep pace with the growth of the generic drug industry, FDA has had to conduct more inspections as the number of facilities supporting those applications has also increased, with the greatest increase coming from foreign facilities. Currently, the number of foreign Finished Dosage Form (FDF)<sup>7</sup> manufacturers exceeds the number found in the United States. The generic industry is also experiencing significant growth in India and China, a trend expected to continue. Foreign inspections represent a significant challenge and require significant resources.

The generic drug user fee agreement is designed to address the regulatory challenges mentioned above in an affordable manner. The annual fee total proposed represents approximately one half of 1 percent of generic drug sales. This modest cost should be offset by benefits received by the industry, as faster review times will bring products to market sooner.

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<sup>6</sup> Drug Master Files are widely used to provide FDA with information about the drug substance, also known as the active pharmaceutical ingredient (API).

<sup>7</sup> An FDF is the final drug product (e.g. tablet, capsule). An FDF is made up of both API(s) and any inactive excipients.

## *Overview of the Proposed Generic Drug User Fee Program*

To develop recommendations for a generic drug user fee effective beginning FY 2013, FDA conducted a process that involved the generic drug industry and public stakeholders. In addition to the negotiation sessions with industry trade associations, there were numerous public stakeholder meetings open to all, including industry, patient advocates, consumer advocates, health care professionals, and scientific and academic experts. The final agreement and the goals FDA and industry have agreed to were transmitted to Congress on January 13, 2012.

The Generic Drug User Fee Act (GDUFA) proposal, as negotiated, is aimed at putting FDA's generic drugs program on a firm financial footing and providing the additional resources necessary to ensure timely access to safe, high-quality, affordable generic drugs. The proposal focuses on quality, access, and transparency. Quality means ensuring that companies, foreign or domestic, that participate in the U.S. generic drug system are held to the same consistent high-quality standards and that their facilities are inspected biennially, using a risk-based approach, with foreign and domestic inspection frequency parity. Access means expediting the availability of low-cost, high-quality generic drugs by bringing greater predictability and timeliness to the review of ANDAs, amendments, and supplements. Transparency means requiring the identification of facilities involved in the manufacture of generic drugs and associated APIs, and improving FDA's communications and feedback with industry to expedite product access and enhance FDA's ability to protect Americans in our complex global supply environment.

The additional resources called for under the agreement will provide FDA with the ability to perform critical program functions that could not otherwise occur. With the adoption of user fees and the associated savings in development time, the overall expense of bringing a product to market is expected to decline. The program is expected to provide significant value to small companies and first-time entrants to the generic market. In particular, these companies will benefit significantly from the certainty associated with performance review metrics that offer the

potential to dramatically reduce the time needed to commercialize a generic drug, when compared to pre-GDUFA review times.

In addition, the variety of funding sources for the program will ensure that participants in the generic drug industry, whether FDF manufacturers or API<sup>8</sup> manufacturers, whether foreign or domestic, appropriately share the financial expense and benefits of the program. The broad range of funding sources, including and across facility and application types, as well as the large number of each, ensures that individual fees remain reasonable and significantly lower than associated branded drug fees.

As in all of FDA's other medical product user fee programs, under the proposed generic drug user fee program, user fee funding would supplement appropriated funding to ensure sufficient resources for the Agency's generic drug review program, and guarantees are in place to ensure that the user fees are supplemental to annual appropriations in the budget.

### Biosimilars User Fees

A successful biosimilars review program within FDA will spark the development of a new segment of the biotechnology industry in the United States. The Biologics Price Competition and Innovation Act (BPCI Act) of 2009, which was enacted as part of the Affordable Care Act of 2010, established a new abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological product. With this new abbreviated approval pathway, a biosimilar biologic can be approved by demonstrating, among other things, that it is highly similar to a reference biological product already licensed by FDA. Development of biosimilars is expected to be less risky, less costly, and take less time; therefore, approved biosimilars are expected to be less expensive than the

<sup>8</sup> An API is the drug substance responsible for the therapeutic effect (e.g. the chemical aspirin that is combined with excipients to produce the FDF aspirin tablet).

reference product. This program will provide significant benefits for patients, making available more affordable treatments that clinicians will know are biosimilar or interchangeable. The development of this new market segment will expand the opportunities for technical innovation and job growth.

### *Background*

A biosimilar is a biological product that is highly similar to a U.S.-licensed reference product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar product and the reference product in terms of the safety, purity, and potency of the product.

Under the transition provisions in the BPCI Act, user fees for a biosimilar biological product are assessed under PDUFA. Accordingly, currently, user fees for biological products are the same, regardless of whether the BLA is submitted under the new, abbreviated biosimilar pathway or under the previously existing approval pathway for biological products. However, PDUFA IV expires on September 30, 2012, and the BPCI Act directs FDA to develop recommendations for a biosimilars user fee program for fiscal years 2013 through 2017. To develop these recommendations, FDA consulted with industry and public stakeholders, including patient advocates, consumer advocates, health care professionals, and scientific and academic experts, as directed by Congress. The final recommendations were transmitted to Congress on January 13, 2012.

### *Program Funding and Metrics*

The proposed biosimilars user fee program for FY 2013 to 2017 addresses many of the top priorities identified by public and industry stakeholders and the most important

challenges identified by FDA. The proposed biosimilars user fee program is similar to the PDUFA program in that it includes fees for marketing applications, manufacturing establishments, and products. However, there are some differences because of the nascent state of the biosimilars industry in the United States. For example, there are no currently marketed biosimilar biological products; accordingly, the recommended biosimilars user fee program includes fees for products in the development phase to generate fee revenue in the near-term and to enable sponsors to have meetings with FDA early in the development of biosimilar biological product candidates.

As in all of FDA's medical product user fee programs, the proposed biosimilars user fee program supplements appropriated funding to ensure sufficient resources for the Agency's review programs. Under the proposed biosimilars user fee program, FDA would be authorized to spend biosimilars user fees on Agency activities related to the review of submissions in connection with biosimilar biological product development, biosimilar biological product applications, and supplements. This would include activities related to biosimilar biological product development meetings and investigational new drug applications (INDs). It would also include development of the scientific, regulatory, and policy infrastructure necessary for review of biosimilar biological product applications, such as regulation and policy development, related to the review of biosimilar biological product applications, and development of standards for biological products subject to review and evaluation.

The biosimilars user fee program would support FDA activities at the application stage, such as review of advertising and labeling prior to approval of a biosimilar biological product application or supplement; review of required post-marketing studies and post-marketing studies that have been agreed to by sponsors as a condition of approval; the issuance of action letters that communicate decisions on biosimilar biological product applications; and inspection of biosimilar biological product establishments and other facilities undertaken as part of FDA's

review of pending biosimilar biological product applications and supplements (but not inspections unrelated to the review of biosimilar biological product applications and supplements). Finally, it would support some activities at the post-approval stage, such as post-marketing safety activities, with respect to biologics approved under biosimilar biological product applications or supplements.

### Best Pharmaceuticals for Children Act /Pediatric Research Equity Act

#### *Background*

The Best Pharmaceuticals for Children Act (BPCA), enacted in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA) and reauthorized in 2002 and 2007, provides incentives to manufacturers who voluntarily conduct studies of drugs in children. This law provides six months of additional exclusivity for a drug (active moiety), in return for conducting pediatric studies in response to a written request (WR) issued by FDA. To qualify for pediatric exclusivity, the pediatric studies must “fairly respond” to a WR issued by FDA that describes the needed pediatric studies (including, for example, indications to be studied or number of patients). The Patient Protection and Affordable Care Act (Affordable Care Act) extended availability of pediatric exclusivity to biological products but, due to the recent nature of this change, no biological product has received pediatric exclusivity to date.

The Pediatric Research Equity Act (PREA), enacted in 2003, works in concert with BPCA. PREA provides FDA the authority to require pediatric studies under certain conditions. PREA requires pediatric assessments of drugs and biological products for the same indications previously approved or pending approval, when the sponsor submits an application or supplemental application to FDA for a new indication, new dosing regimen, new active ingredient, new dosage form, or new route of administration.

Both BPCA and PREA expire September 30, 2012, if not reauthorized.

### *Need for Pediatric Information*

Before enactment of BPCA in 1997, approximately 80 percent of medication labels in the Physician's Desk Reference did not have pediatric-use information—data to establish the correct dose for pediatric patients or confirm safety or efficacy in the pediatric population. All too often health care professionals were forced to rely on imprecise and ineffective methods to provide medications for children, such as adjusting dosing based on weight or crushing pills and mixing them in food. Pediatric patients are subject to many of the same diseases as adults and are, by necessity, often treated with the same drugs and biological products as adults. Inadequate dosing information may expose pediatric patients to overdosing or underdosing. Overdosing may increase the risk of adverse reactions that could be avoided with an appropriate pediatric dose; underdosing may lead to ineffective treatment. The lack of pediatric-specific safety information in product labeling also means caretakers and health care professionals are unable to monitor for and manage pediatric-specific adverse events. In situations where younger pediatric populations cannot take the adult formulation of a product, the failure to develop a pediatric formulation that can be used by young children (e.g., a liquid or chewable tablet) also can deny children access to important medications.

### *Success of BPCA and PREA*

Together, BPCA and PREA have generated pediatric studies on many drugs and helped to provide important new safety, effectiveness, and dosing information for drugs used in

children. Both statutes continue to foster an environment that promotes pediatric studies and to build an infrastructure for pediatric trials that was previously non-existent.

Over the past 15 years, approximately 400 drugs have been studied and labeled for pediatric use under these two laws. Since 1997, BPCA, the exclusivity incentive program, has generated labeling changes for 250 products. The labeling for 120 products has been updated to include new information, expanding use of the product to a broader pediatric population; the labeling of 29 products had specific dosing adjustments; the labeling of 69 products was changed to show that the products were found not to be safe and effective for children; and 55 products had new or enhanced pediatric safety information added to the labeling.<sup>9</sup>

Since PREA was enacted, FDA has approved approximately 1,450 NDAs and supplemental NDAs that fell within the scope of PREA (i.e., applications for new active ingredients, new dosage forms, new indications, new routes of administration, or new dosing regimens). These approvals have resulted in approximately 231 labeling changes involving pediatric studies linked to PREA assessments. In addition, FDA has approved approximately 105 BLAs and supplemental BLAs that fell within the scope of PREA.

#### *Examples of New Pediatric Information Generated by BPCA and PREA*

- Migraine headaches – Axert (almotriptan) was studied and labeled for age 12 years and older. Before enactment of BPCA and PREA, no medications were studied and labeled for migraines in children.

<sup>9</sup> These numbers add up to a number greater than 205 because some products had more than one change to the labeling.

- Diabetes – Apidra (insulin glulisine recombinant) has been studied and labeled down to age 4 for Type 1 diabetes.
- Arthritis – Actemra (tocilizumab) has been studied and labeled down to age 2 for Active Systemic Juvenile Idiopathic Arthritis (SJIA).
- Pain – Ofirmev/acetaminophen injection has been studied and labeled down to age 2 for mild-to-moderate pain/moderate-to-severe pain with adjunctive opioid analgesics and reduction of fever.
- Brain Tumors – Afinitor (everolimus) has been studied and labeled down to age 3 for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

BPCA and PREA require review of adverse event reports on a regular basis. To date, adverse event reviews have been presented to the Pediatric Advisory Committee (PAC) for 129 products. In addition, as directed by BPCA, FDA has worked with NIH and the Foundation for the National Institutes of Health (FNIH) to facilitate the study of off-patent drugs not eligible for exclusivity under BPCA.

Despite the successes of these two programs, there is more work to be done. There is still a large number of drug and biological products that are inadequately labeled for children. More broadly, long-term safety and effects on growth, learning, and behavior are critically important to the safe use of certain medications and continue to be understudied. Due to technical challenges and the need for sequential studies, slow but deliberate progress is being made studying the safety and efficacy of approved therapies used to treat neonates (age birth to one month). These issues are still of concern, as it is this youngest population that is undergoing marked physiologic and developmental changes, which are affected by drug therapies.

FDA welcomes the opportunity to work with Congress to ensure that the benefits of an incentive program can continue, in conjunction with FDA's authority to require mandatory studies, as Congress considers the reauthorization of the BPCA and PREA programs.

### Securing the Supply Chain for Prescription Drugs

As FDA has previously testified before this Committee, the increasingly complex drug supply chain, from raw source materials to finished products for consumers, presents multiple opportunities for the product to be contaminated, diverted, counterfeited, or otherwise adulterated. Our efforts to secure the supply chain both in the United States and abroad include minimizing risks that arise anywhere along the supply chain continuum, from sourcing a product's ingredients through the product's manufacture, storage, transit, sale, and distribution. A breach at any point in this continuum could lead to dangerous and even deadly outcomes for consumers. Supply chain safety threats also affect manufacturers' bottom lines due to costs associated with both recalls and decreased public confidence.

Counterfeit drugs also raise significant public health concerns, because their safety and effectiveness is unknown. A counterfeit drug could be made up of a substance that is toxic to patients. But even a non-toxic counterfeit drug with a substitute or no active ingredient could prove harmful to patients who take it, thinking that they are taking a lifesaving or life-sustaining medication. In 2003, over \$20 million in illegally imported and counterfeit Lipitor (atorvastatin calcium), a popular cholesterol-lowering drug, was distributed throughout the United States. The source and manufacturing methods of the product were unknown and had the potential to endanger patients. Just last month, FDA alerted 19 medical practices in three states that they had purchased unapproved drugs, which may have included a counterfeit version of a widely used cancer drug, from a foreign supplier and distributed through a wholesaler in the United States.

While labeled as Avastin (bevacizumab), the imported injectable vials contained none of the medicine's active ingredient. This fake product presents a major public health issue, because some patients may not have received needed therapy.

Implementation of a system to fully track and trace prescription drugs throughout the supply chain would help in combating incidents like the counterfeit Avastin example. Currently there is no complete record of all parties who have been involved with the distribution of a product after it leaves the manufacturer until it reaches the hands of the patient. This leaves multiple opportunities for counterfeit, adulterated, stolen, or otherwise violative products to be introduced into the supply chain.

While the Food and Drug Administration Amendments Act of 2007 (FDAAA) gives FDA authority to set standards for identification, validation, authentication, and tracking and tracing of prescription drugs, explicit authority to require and enforce the implementation of a national track-and- trace system throughout the supply chain is lacking. In March 2010, FDA issued a final guidance for industry, which describes the Agency's current thinking for standardized numerical identification (also known as serialization) for prescription drug packages. This guidance was the first of several steps that FDA intends to take to implement these provisions of FDAAA. FDA continues to work on developing these standards and held a Track and Trace Public Workshop in February 2011 to obtain public input on the necessary elements to achieve effective authentication and the desirable attributes of a track-and-trace system. Providing the Agency authority to require a cost-effective track-and-trace system for all drug products throughout the supply chain would improve the security and integrity of the drug supply and ensure transparency and accountability of product manufacturing and distribution, whether the product is manufactured domestically or internationally.

## FDA Regulation of Medical Gases

Medical gases are among the most widely prescribed drugs in the United States, and some have been in use since before the enactment of the Federal Food, Drug, and Cosmetic Act of 1938. Medical gases are typically used to treat vulnerable patient populations, including the elderly and the seriously ill, in a range of health-care settings such as emergency rooms, intensive care units, neonatal care units, ambulance transport, and home/ambulatory use. They are often used in combination with other medical products, such as medical devices.

Medical gases, including those that have been in widespread use for decades, may under some circumstances pose safety and efficacy concerns similar to other new drugs. These gases have been associated with adverse events, and in some cases have been implicated in mislabeling and contamination incidents that have resulted in deaths or serious injuries. Accordingly, as with other drugs, it is critical that the benefit associated with any given medical gas outweighs its risks when used in a particular patient population for a specific purpose, dose, and duration.

## Facilitating the Development of New Antibacterial Products

Antimicrobial agents have been used in human and veterinary medicine for more than 70 years, with tremendous benefits to both human and animal health. However, because bacteria are so adept at becoming resistant to antibacterial drugs, it is essential that such drugs be used judiciously to delay the development of resistance. Preserving the effectiveness of current antimicrobials and encouraging the continued development of new ones is vital to protecting human and animal health against infectious microbes.

The field of antibacterial drug development is currently facing challenges because of the complexities in designing informative, ethical, scientifically sound, and feasible, clinical trials

for studying antibacterial drugs. In addition, there are challenges because of the lack of standardized data on the effect of treatment with antibacterial drugs in certain infections.

FDA cannot overcome these scientific challenges alone, so we have been working to address these issues through guidance development, public workshops, and Advisory Committee meetings. We are working to provide scientifically sound guidance to industry on demonstrating the safety and effectiveness of new antibacterial drugs, particularly on indication-specific trial designs used to study a new drug.

Although the development of new antibacterial drugs is not the entire solution to the important public health problem of antimicrobial resistance, it is a very important part. We are at a critical juncture in this field. We are in urgent need of new therapeutic options to treat the resistant bacteria that we currently face, and we will need new therapeutic options in the future. FDA will continue to work with patients, health care providers, academia, industry, and others within the federal government to modernize the paradigm of antibacterial drug development through guidance and clinical trial designs, and to seek additional solutions to the challenging scientific issues facing the field of antibacterial drug development.

### Drug Shortages

In September of last year, Dr. Howard Koh, Assistant Secretary for Health at HHS, testified before this Subcommittee to discuss the growing problem of drug shortages. FDA and the Administration at large share your concern about the rising incidence of drug shortages in the United States and the significant and even life-threatening impact of these shortages on patients, and I am pleased to have the opportunity to update you on what FDA has been doing to help alleviate this problem. Although many of the root causes of drug shortages are beyond our

control, we are committed to addressing this important issue and look forward to working with this Subcommittee on this issue.

Manufacturers can play a critical role in avoiding shortages by taking appropriate measures to reduce the risk of unplanned disruptions in supply. For example, manufacturers who maintain their facilities and equipment in good working order, develop contingency plans to minimize the effects of unanticipated problems, and work closely with FDA to resolve potential problems are less likely to face shortage situations. Manufacturers can also help to minimize drug shortages and decrease the impact of shortages by notifying FDA as early as possible of situations that might lead to a drug shortage.

When FDA learns of a potential shortage situation, we work directly with the affected manufacturer to help prevent the shortage or to minimize its effect on patients. This may include developing temporary workaround solutions to manufacturing or quality issues; consulting with the manufacturer to resolve the underlying problem; or helping the manufacturer find additional sources of raw materials. We also expedite the review of submissions by the manufacturer that may alleviate the drug shortage while continuing to meet safety standards, which may include requests to extend the expiration date of products, make manufacturing changes to increase capacity, use a new raw material source, or change product specifications. FDA can also use our regulatory discretion for a manufacturer to continue marketing a medically necessary drug, if the manufacturer can develop a method to resolve a quality issue prior to the drug's administration. A recent example was potassium phosphate, which is a medically necessary injectable drug needed for intravenous nutrition in critically ill patients. The firm found glass particles in the vials, posing a significant safety concern. The manufacturer was able to provide data to FDA showing the particles could successfully be removed with a filter. FDA then exercised enforcement discretion for the drug to be shipped with a letter to notify health care professionals

that the filter needed to be used with the drug. This resulted in the drug being available for patients in a safe manner while the firm addressed the particulate issue for future production.

In addition to working with the affected manufacturer, FDA also works with third parties to determine whether they can help avoid or minimize the shortage. For example, our Drug Shortage Staff frequently reaches out to alternate manufacturers who may be able to initiate or ramp-up production of the product at issue. We also expedite reviews of generic applications for products facing potential shortages. In certain situations, when a shortage cannot be resolved immediately, we will use our regulatory discretion for the temporary import of non-FDA-approved versions of critical drugs after ensuring there are no significant safety or efficacy risks for U.S. patients.

For example, FDA announced on February 21, 2012, that in response to the critical shortage of the cancer drug Doxil (doxorubicin hydrochloride liposome injection) and rapidly declining supplies of methotrexate, FDA took proactive steps needed to increase available supply for patients in the United States. For Doxil, FDA exercised enforcement discretion to allow temporary importation of a replacement drug, Lipodox (doxorubicin hydrochloride liposome injection). With regard to methotrexate, FDA successfully engaged many firms to assist in maintaining supplies to meet all patient needs, in addition to approving a preservative-free methotrexate generic application, which we prioritized.

Although our work has enabled the Agency to successfully prevent 255 potential shortages since the beginning of 2010, drug shortages are on the rise. In response to this growing problem, the Administration has taken several actions to better understand and respond to drug shortages. On September 26, 2011, FDA hosted a public meeting to gain additional insight into the causes and impacts of drug shortages and possible strategies for preventing or mitigating drug shortages. Interested parties who attended included professional societies,

patient advocates, industry, researchers, pharmacists, and other health care professionals. A docket has been opened in relation to the public workshop, where comments can be received from the public.

On October 31, 2011, the President issued an Executive Order,<sup>10</sup> which directed FDA, as well as the Department of Justice, to take action to help further reduce and prevent drug shortages, protect consumers, and prevent inappropriate stockpiling and exorbitant pricing of prescription drugs in shortage situations. In an effort to encourage broader reporting of manufacturing discontinuances, the President's order directs FDA to use all appropriate administrative tools to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life-supporting or life-sustaining, or that prevent debilitating disease. The Executive Order also requires FDA to expand its current efforts to expedite review of new manufacturing sites, drug suppliers, and manufacturing changes to help prevent shortages. Under the President's Order, FDA is also directed to report to the Department of Justice situations in which secondary wholesalers or other market participants have responded to potential drug shortages by stockpiling medications or pricing drugs exorbitantly, so that the Department of Justice can determine whether these actions are consistent with applicable law. Since the issuance of the Executive Order, FDA has successfully prevented 118 drug shortages.

On the same day the President signed the Executive Order, the Administration announced its support for bipartisan bills (S. 296 and H.R. 2245) that would require all prescription drug shortages to be reported to FDA and would give FDA new authority to enforce these requirements. The Administration also announced that FDA would provide additional staffing resources to enhance the Agency's ability to prevent and mitigate drug shortages. Additionally,

<sup>10</sup> <http://www.whitehouse.gov/the-press-office/2011/10/31/we-can-t-wait-obama-administration-takes-action-reduce-prescription-drug>.

FDA released a report entitled “A Review of FDA’s Approach to Medical Product Shortages” on its role in monitoring, preventing, and mitigating drug shortages, which included recommendations to further reduce the impact of these shortages.

In addition, FDA sent a letter to pharmaceutical manufacturers, reminding them of their current legal obligations to report certain discontinuances to the Agency, and urging them to voluntarily notify FDA of all potential disruptions of the prescription drug supply to the U.S. market, even where disclosure is not currently required by law. The letters to manufacturers and the Executive Order have produced a significant increase in the number of potential shortages reported to FDA. In the 10 months preceding the Administration’s actions (January through October 2011), the Agency received an average of approximately 10 notifications per month. In the four weeks following the letters to the manufacturers and issuance of the Executive Order, we received 61 notifications, a six-fold increase. This increased level of reporting by manufacturers of potential supply problems has continued into 2012.

Also, on December 19, 2011, FDA issued an Interim Final Rule (IFR) amending regulations relating to provisions of the Federal Food, Drug, and Cosmetic Act requiring manufacturers who are the sole source of certain drug products to notify FDA at least six months before discontinuance of manufacture of the products. The IFR modifies the term “discontinuance” to include both permanent and temporary disruptions in the manufacturing of a drug product and clarifies the term “sole manufacturer” to mean the only manufacturer currently supplying the U.S. market with the drug product. The broader reporting resulting from these changes will enable FDA to improve its collection and distribution of drug shortage information to physician and patient organizations and to work with manufacturers and other stakeholders to respond to potential drug shortages. We requested comments on the IFR to be submitted by February 17, 2012.

Since the Executive Order was issued, FDA has continued its work to help prevent or mitigate drug shortages in a number of ways, including:

- Doubling the number of staff in the Center to assist in coordination and response activities, as well as expediting actions (e.g., inspections) that would help to alleviate drug shortages;
- Meeting with various stakeholders to discuss shared opportunities to prevent and mitigate shortages, including the Generic Pharmaceutical Association, the Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization, manufacturers, and wholesalers;
- Exploring options for improving our drug shortage database for the tracking of shortages, as well as utilizing the database to develop prediction models for drug shortages;
- Working with the Department of Justice, as directed in the Executive Order, regarding issues related to stockpiling and exorbitant pricing, including reports from pharmacists and other health care professionals in connection with drug shortages; and
- Continuing to prioritize review applications for products that are in shortage situations.

FDA is committed to doing everything in our authority to prevent and address drug shortages and looks forward to working with the Subcommittee on this important issue.

## **CONCLUSION**

Thank you for your interest in the important work we do at FDA. We look forward to working with you to continuously improve our processes to enable new products to reach patients faster while maintaining the safety of our drug supply. I am happy to answer questions you may have.