



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

**STATEMENT
OF
JANET WOODCOCK, M.D.
DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
BEFORE THE
SUBCOMMITTEE ON HEALTH
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U.S. HOUSE OF REPRESENTATIVES
“FDA User Fees 2012: Hearing on Issues Related to Accelerated Approval,
Medical Gas, Antibiotic Development, and Downstream Pharmaceutical
Supply Chain”**

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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 a number of important issues facing FDA, including expediting access to new therapies, efforts to facilitate the development of antibacterial drug products, securing the supply chain for prescription drug products, and the regulation of medical gases.

The Availability of New Therapies

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. In the past 20 years, American patients have been provided access to over 1,500 new drugs and biologics, 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 approvals in the past 10 years, surpassed only by 2009. Of the 35

innovative drugs approved in FY 2011, 34 met the target dates for review as agreed to in the Prescription Drug User Fee Act (PDUFA).¹

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 2.0 years for the approval phase at the start of PDUFA to an average of 1.1 years more recently.²

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

A recent article in the journal *Health Affairs* also compared cancer drugs approved in the United States and the 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

¹ 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 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 (known as PDUFA V).

² 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.

only 26 of these products, and its average time was 12.2 months (373 days). All 23 cancer drugs approved by both agencies during this period were approved first in the United States.³

Speeding Access to New Therapies

FDA administers a number of existing 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 provide meaningful therapeutic benefit over existing treatments 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 on the condition that sponsors conduct post-marketing clinical trials to verify the anticipated clinical benefit.

³ “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.

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) approved in 2011 were approved under Accelerated Approval. For example, FDA approved Corifact, the first treatment approved for a rare blood-clotting disorder, under Accelerated Approval 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. The purpose is to get important new drugs to the patient earlier. Once a drug receives Fast-Track designation, early and frequent communication between FDA and a drug company are encouraged throughout the entire drug development and review process. The frequency of communication 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 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 will be the first medicine that targets the underlying cause of CF; currently, therapy is 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.

Therapies for Rare Diseases

Speeding the development and approval of safe and effective drugs for Americans with rare diseases is particularly important. 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.

We look forward to working with Congress on this issue and note that another PDUFA V enhancement includes FDA facilitation of 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.

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.

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.

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.