



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

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

**“REVIEW OF THE PROPOSED GENERIC DRUG AND BIOSIMILARS
USER FEES AND FURTHER EXAMINATION OF DRUG
SHORTAGES”**

February 9, 2012

RELEASE ONLY UPON DELIVERY

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 negotiated recommendations for a generic drug user fee and a biosimilar user fee program, as well as to update you on actions the Agency is taking to address the ongoing problem of drug shortages.

The proposed user fee programs for generic drugs and biosimilars are modeled on the successful Prescription Drug User Fee Act (PDUFA) program which, over the past 20 years has ensured a more predictable, consistent, and streamlined premarket program for industry and helped speed access to new safe and effective prescription drugs for patients. Under a user fee program, 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. As a result of the continued investment of PDUFA resources, FDA has dramatically reduced the review time for new drugs, without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs prior to approval. New legislation is needed to allow FDA to establish similar programs for generic drugs and biosimilar drug products.

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.¹

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 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 Files² 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

¹ "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>.

² Drug Master Files are widely used to provide FDA with information about the drug substance, also known as the active pharmaceutical ingredient (API).

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)³ 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.

³ 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 API⁴ 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.

Program Funding and Metrics

If enacted as negotiated, as noted above, the program would provide FDA with additional funding for all aspects of the generic drug program in the amount of \$299 million per year, for five years, adjusted annually for inflation. With those additional user fee funds, FDA agrees to undertake a series of immediate program enhancements and performance

⁴ 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).

goals. Many performance metrics and efficiency enhancements are set forth in the negotiated documents. The proposed goals, which will, in most cases, be phased in, include:

1. New Applications: FDA will review and act on 90 percent of complete electronic ANDAs within 10 months after the date of submission;
2. Backlog: FDA will review and act on 90 percent of all ANDAs, ANDA amendments, and ANDA prior-approval supplements pending on October 1, 2012, by the end of FY 2017; and
3. Inspections: FDA will conduct risk-adjusted biennial Current Good Manufacturing Practice (CGMP) inspections of generic API and generic FDF manufacturers with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.

Under the program, fees would derive from two primary sources: generic drug-related submissions and generic drug-related facilities. In the first year of the program, there would also be a fee assessed for applications that are pending on October 1, 2012, the so-called “backlog.” Like PDUFA, individual fee amounts would be set annually, with the total annual user fee revenue target specified in statute. Overall, 70 percent of the user fee revenue would be generated by facility fees and 30 percent by application submission and Drug Master File fees. In the first year that ratio will be slightly different because of the one-time backlog fee. The revenue from facilities is split, with 80 percent provided by the FDF manufacturers and 20 percent by API manufacturers, a ratio determined and recommended by the generics industry.

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 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 biologics license application (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.

Proposed Fees

The proposed biosimilars user fee program includes biosimilar product development, marketing application, establishment, and product fees. The initial and annual biosimilar product development fees for biosimilar biological products in development would be equal to 10 percent of the fee established for a human drug application under PDUFA for that fiscal year. The sponsor would pay biosimilar product development fees each year until the sponsor submits a marketing application for the product that is accepted for filing, or discontinues participation in the biosimilar product development program for the product. The proposed marketing application fee for a biosimilar biological product is equal to the fee established for a human drug application under PDUFA, minus the cumulative amount of any biosimilar product development fees paid for the product that is the subject of the application.

Finally, the proposed establishment and product fees are equal to the establishment and product fees under PDUFA for any fiscal year because the level of effort required for FDA oversight of manufacturing and post-marketing safety activities is expected to be comparable for biosimilars and biological products under PDUFA. FDA anticipates a modest level of funding from these sources, initially because only biosimilar biological products that are approved for marketing would be subject to these fees.

Proposed Performance Goals and Procedures

The proposed performance goals include new types of development-phase meetings with associated time frames for timely review of data and feedback. In addition, the proposed performance goals include application review, first-cycle review, proprietary name review, major dispute resolution, clinical holds, and special protocol assessment performance goals. The proposed application performance goals for biosimilars are similar to the PDUFA performance goals and include the following:

1. Review and act on original biosimilar biological product application submissions within 10 months of receipt. Performance targets phase-in starting from 70 percent in FY 2013 to 90 percent in FY 2017.
2. Review and act on resubmitted original biosimilar biological product applications within 6 months of receipt. Performance targets phase-in starting from 70 percent in FY 2013 to 90 percent in FY 2017.
3. Review and act on 90 percent of original supplements with clinical data within 10 months of receipt.
4. Review and act on 90 percent of resubmitted supplements with clinical data within six months of receipt.
5. Review and act on 90 percent of manufacturing supplements within six months of receipt.

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.

Although our work has enabled the Agency to successfully prevent more than 250 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,⁵ 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

⁵ <http://www.whitehouse.gov/the-press-office/2011/10/31/we-can-t-wait-obama-administration-takes-action-reduce-prescription-drug>.

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 114 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, 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

Human drug user fees have revolutionized the drug review process in the United States since they were adopted 20 years ago, allowing FDA to speed the application review process without compromising the Agency's high standards. Final recommendations for generic drug user fees and biosimilars user fees offer a strong example of what can be achieved when FDA, industry and other stakeholders work together on the same goal. User fees provide a critical way for leveraging appropriated dollars, ensuring that FDA has the

resources needed to conduct reviews in a timely fashion. The passage of a generic drug user fee and a new biosimilars user fee would allow FDA to build upon the success of PDUFA.

Drug shortages present a challenge that we must work collaboratively to solve. FDA has taken a number of important steps and will continue to work with industry, health care professionals, and patients to address this issue. We welcome the opportunity to discuss this important topic with you both today and moving forward.

Thank you for your contributions to the mission of FDA. I am happy to answer questions you may have.