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Submitted Electronically via www.regulations.gov

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Attention: Division of Dockets Management (HFA–305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Generic Drug User Fee, FDA Request for Comments
Docket No. FDA-2010-N-0381

Dear Commissioner Hamburg:

Mylan Inc. ("Mylan") appreciates the opportunity to submit additional written comments to the FDA as a follow-up to Mylan's statement made during the FDA's recent public meeting held to discuss generic drug User Fees on Sept. 17, 2010. With a 49-year history of working closely with the FDA, Mylan brings an important perspective to the user fee discussion. Mylan was founded in 1961 and is the largest global generics company headquartered in the U.S., providing products to customers in more than 140 countries and territories. Our company maintains one of the industry's broadest and highest quality product portfolios, which right now exceeds 900. In fact, one out of every 12 prescriptions dispensed in the U.S. is a Mylan product.

Provided in more detail below, Mylan is pleased to offer a comprehensive User Fee proposal that focuses on the FDA's global supply chain challenges by ensuring that all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard. Our proposal also aims to expedite the availability of low cost, high quality generic drugs by decreasing the median review time of applications and supplements. A Summary of this User Fee Proposal is attached.

I. KEY ISSUES FDA CURRENTLY FACES IN CARRYING OUT ITS CRITICAL MISSION FOR THE AMERICAN PUBLIC.

A. Challenges caused by global drug supply chain

With a mission to protect and promote the public health, the FDA has a critical responsibility to ensure the safety, efficacy and security of the U.S. drug supply and to address threats to public health. In fact, this mission is so critical it is no wonder the late Senator Kennedy once said the FDA is the most important health agency in America.

Since the enactment of the Food Drug and Cosmetic Act in 1938, the FDA's core public health mission remains today as it did back then. However, ensuring a safe and effective drug supply is much more challenging today than it was in 1938 due to the globalization of drug manufacturing, supply and testing and an increase in FDA-regulated drug products.

- Up to 40% of the drugs Americans take are imported, and up to 80% of the active pharmaceutical ingredients in those drugs come from foreign sources.[1]
- In 2010, nearly 20 million shipments of food, devices, drugs, and cosmetics are expected to arrive at U.S. ports of entry. Just a decade ago, that number was closer to 6 million, and a decade before only a fraction of that.[2]
- The number of FDA regulated products has grown substantially, too. Between 20 to 25 cents of every consumer dollar spent in the United States is spent on an FDA-regulated product.[3]

According to U.S. law, domestic drug establishments are required to be inspected at least once every two years, but the law is silent in this regard to foreign establishments. Given this mandate, and in light of CDER's risk-based site selection process, FDA inspects domestic facilities every two to three years.

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[1] Remarks of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs at the Center for Strategic and International Studies. Feb. 4, 2010.
[2] Id.
[3] Statement of Lester M. Crawford, Acting Commissioner, Food and Drug Administration, Committee on House Appropriations Subcommittee on Agriculture, Rural Development, FDA and Related Agencies (July 26, 2005).

However, due in part to the lack of a mandate for biennial inspections of establishments, only about 8% of foreign drug manufacturing establishments are inspected each year, which means it would take more than 13 years to inspect all registered foreign drug facilities at least once at the current rate.[4] All the while, both types of facilities are supplying drugs to U.S. consumers.

In 2007, the FDA conducted 1,119 GMP inspections of domestic facilities that resulted in 15 action items, including warning letters and product seizures.[5] During that same year, the FDA conducted 232 GMP inspections of foreign facilities that resulted in 3 warning letters.[6] The FDA estimates that there are about 3,250 foreign establishments. If you consider that approximately half of them would be inspected each year if they were held to the same standards as U.S. establishments, that means there are about 1,625 foreign establishments that should be inspected each year. That is almost 1,400 more inspections than were actually conducted in 2007. And, if we reason that foreign establishments would have about the same rate of action items resulting from inspection, we can conservatively estimate that a minimum of 15 action items - warning letters, import alerts, seizures - for foreign establishments were missed.

In addition, according to a 2008 GAO report, there are even some FDA registered establishments whose drugs are imported into the U.S. and have never had a GMP inspection. [7]

This is simply unacceptable. Safety is paramount and the American public deserves better.

Every consumer should have the peace of mind in knowing that every prescription purchased in the U.S. is held to the same standard of quality regardless of whether the product or its ingredients originated in the U.S. or outside its borders.

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[4] Remarks of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs at the Center for Strategic and International Studies. Feb. 4, 2010.
[5] CDER 2007 Update, Improving Public Health Through Human Drugs.
[6] Id.
[7] Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program, GAO. Sept. 2008.

We are pleased the FDA has recognized that the global drug supply chain requires the agency to address product safety at every point – from the onset of research and development to distribution to consumers. We are also pleased to see the recent increase in FDA enforcement action as the agency has increased inspections. The U.S. alone saw a 400% increase in recalls in 2009 compared to 2008 as a result of GMP problems.[8] Additionally, it has been reported that the FDA has doubled the number of GMP warning letters in the last year.[9] However, the agency needs additional resources to support its mission of ensuring all participants in the U.S. drug system – U.S. or foreign – are compliant with all U.S. quality standards.

B. User fees should help the FDA address global supply chain challenges and ensure all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard so that consumers can rely on the safety of the medications they consume.

To create an effective User Fee program that provides resources to be used in a meaningful way, we must shift the way we talk about User Fees to focus on the critical issues facing our government and the U.S. pharmaceutical consumer – access to needed drugs with the knowledge that those drugs are safe and effective regardless of where they are made, where the API is sourced, where clinical work is done, and where packaging and storage takes place.

We must also develop a user fee model that prohibits differences in application treatment based solely on the U.S. or non-U.S. location of an establishment.

Additionally the User Fee model should encourage the appropriate review and approval of ANDAs and not simply create a cookie cutter approach that treats all applications alike and fails to recognize legal distinctions between applications such as first to file ANDA v. subsequent ANDAs, and/or significance of a particular product, such as one that meets an unmet medical

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[8] Michael F. Bennet, United States Senator for Colorado, Press Release*, Following Record Recalls, Bennet Moves to Improve Safety of U.S. Drugs for Colorado Families* (Aug. 3, 2010), http://bennet.senate.gov/newsroom/press/release/?id=4e7472f1-cc15-4b76-9caa-c70be525ad08.

[9] *See generally, Enforcement on Steroids: FDA Delivers Twice the Drug GMP Warning Letters*, The Gold Sheet (Apr. 1, 2010).

need, a first generic, or an orphan drug. However, it is critical that the safety of our drug supply is never compromised for the sake of speed.

In short, a generic User Fees program should require a review tailored to each individual application while ensuring the good quality standing of each and every establishment - domestic and foreign - involved in the development and manufacture of each and every drug sold in the U.S., so that every American can have faith in the quality, safety and effectiveness of any pharmaceutical product they consume.

II. HOW TO HELP THE FDA BETTER ACHIEVE ITS MISSION IN RESPECT TO THE GLOBAL DRUG SUPPLY.

A. Typical User Fee thinking does not make sense for FDA and generic drug approval process given unique Hatch-Waxman generic drug approval system

Conversations about User Fees are typically focused solely on how to provide additional resources to the FDA so that the agency can expedite the application approval process and also eliminate the backlog of applications currently in place with the Office of Generic Drugs. This type of thinking simply makes no sense for the FDA and generics given the unique Hatch-Waxman generic drug approval system. However, the simple assertion that more money for faster and time specific reviews is the proper approach to improve our nation's supply chain of generic medications fails to take into account several critical realities of the U.S. generic pharmaceutical industry.

It also does not do enough to address the most critical point of any substantive User Fee discussion: making sure the FDA has the resources and processes to meet its mission of approving safe, effective, high-quality and bioequivalent generic drug products for the U.S. market.

Before considering Generic User Fees, it is critically important to recall the key underpinnings of our unique generic drug approval process. Hatch-Waxman created a unique approval system for generics that is different from brand drugs as well as any other drug approval system in the world.

The uniqueness stems from Congress' goal of balancing the need to bring low-cost generics to the public faster and the need for pharmaceutical innovation. This premise links the generic drug approval process and the patent dispute process and creates an automatic 30-month stay of approval when a brand patent is challenged.

Unlike a branded product, which can obtain approval and launch immediately following FDA's scientific review, the approval and launch of generic drugs is subject to months, sometimes years of additional delays following the FDA's review. Generics can also face a host of blocking factors that happen apart from FDA review that delay market entry. Most of these delays are caused by brands, the judicial system and the overall unique Hatch-Waxman framework itself.

There are also other obstacles unique to the generics industry including delay tactics initiated by innovators that can impact the ability to market a generic product even when an application is otherwise approvable by the FDA. For example, all generic manufacturers have painfully experienced the abuse of the citizen petition process resulting in approval delays ranging from several months to several years. Additionally, matters such as last-minute label changes by the brand, last-minute patent filings, and last-minute brand product discontinuations can all impact the timing of generic approval despite the fact that the FDA would deem the application approvable. Even with the efforts of Congress and the FDA to mitigate these tactics, we can count on the fact that the brand companies will continue to find creative ways to delay generic competition. Again, under a solely application based User Fee structure, we would consistently be "paying to wait."

Because of these legal and regulatory variables, a User Fee system based on approval of all applications in accordance with a specific and arbitrary time-frame does not make for an efficient and effective process.

Perhaps it should come as no surprise that past discussions regarding Generic Drug User Fee programs have hit roadblocks when trying to develop reasonable and appropriate, one-size-fit-all application based performance metrics.

Timely access to life-saving medications is very important. However, a User Fee model that only looks at the timing of the approval process for an application misses a more critical point - SAFETY. Even without the variables commonly experienced by generic applicants, a User Fee system tied to the certainty of an artificial timeframe is still flawed because not all applications can or should be treated equally. While making sure the FDA has the resources to conduct timely and efficient reviews is important to all of us, it's also paramount that the agency have the flexibility to conduct more or less time-intensive reviews based upon the quality of the application filed.

The original brand application fee program, PDUFA, worked well for brand companies, largely because their industry lacks the legal complexities found in the generic industry. The success of PDUFA was in providing resources to help increase the number of drug reviewers and decrease median review times – two goals, among several others, that we should strive to achieve with the new Generic User Fees effort as well.

For this reason, we have adopted certain elements from PDUFA in the User Fees proposal described herein. The Establishment Registration Fee and Application Fee components of PDUFA are designed to generate financial resources for FDA and are tied simply to the act of participating in the U.S. brand pharmaceutical industry and to submitting applications for generic drug approval. Our proposal also contains an Inspection Fee, which directly addresses heightened awareness of the global nature of the pharmaceutical industry and the global complexity of meeting relevant safety and quality standards. These fees are described more fully below.

As you may recall from Mylan's proposal described during the FDA's Sept. 17, 2010 Generic User Fee Public Meeting, Mylan also proposed a "Product Fee" to be assessed against each application upon approval to help supplement costs associated with the FDA's post approval responsibilities. Following additional consideration, Mylan instead believes that this fee should not be back-end focused on post approval activity. Rather, Mylan agrees, as some others have suggested, that fees paid upfront at the time of application submission will better ensure that the FDA has the funds necessary for the application review staffing and resources to match demand on a prospective basis. These funds, which Mylan now refers to as an "**Application Fee**," will help provide the resources needed for the Agency to achieve an ultimate median substantive review time of 12 months for applications irrespective of whether the application is blocked from approval as a result of a patent, exclusivity, 30 month stay, or court order.

Mylan is also supplementing our initial Sept. 17th proposal from the Public Meeting to provide specific performance metrics to have measurement criteria for accountability and to evaluate the success of a User Fee program. To address the critical issues at which this User Fee program is aimed, in a general sense, appropriate metrics must include, among others identified further below, a decrease in median application review times to ultimately reach 12 months within three years, including pending applications; biennial inspections for all facilities, foreign and domestic, with prompt agency wrap-up or follow-up; improved reviewer to application ratio; an increase in staffing, including reviewers and inspectors and a requirement of prompt feedback to applicant requests as well as transparency regarding application status.

B. User fees should be paid by any company wanting to participate in the U.S. drug system

While it is widely recognized that Hatch-Waxman has successfully delivered significant savings to consumers, no one could have predicted in 1984 that the framework would over time tax the FDA system due to the complexity of the global marketplace. Today's reality means we must address the issue through a holistic approach: One that supports the mission and true intent of Hatch-Waxman, and at the same time, generates much needed funding for the FDA and assurance for product safety.

It also must not delegate FDA inspectional responsibilities to third parties, tie fees (including application specific fees) to an artificial timeframe for application review because not all applications or supplements can or should be treated equally; and because generic applicants uniquely experience various Hatch-Waxman delays that prevent launch even after the application review is complete. In addition, it must not encourage different application treatment or different safety standards based solely on the U.S. or non-U.S. location of an establishment.

Therefore, to help the FDA obtain the resources it needs to perform its mission in this global age, Mylan proposes the following comprehensive User Fee structure focused on three key aims:

- SAFETY - Ensuring all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard and inspected by the FDA on an biennial basis;
- ACCESS - Expediting the availability of low cost, high quality generic drugs by decreasing the median review time of applications and supplements; and
- TRANSPARENCY - Enhancing the FDA's ability to protect Americans in the complex global supply environment by identifying, tracking and requiring the registration of all contributors involved in each drug product sold in the U.S.

1. ESTABLISHMENT REGISTRATION FEE

A. Purpose

The Establishment Registration Fee acts like a business license or registration tied simply to the act of participating in and benefiting from the U.S. pharmaceutical market, which is regulated by the FDA. The creation of such a fee will supplement existing FDA funds to assist FDA in carrying out its responsibility of ensuring the safety, efficacy and security of the U.S. drug supply and provide additional resources necessary to support the increasing complex global drug supply environment.

Requiring all participants in the U.S. pharmaceutical market to register with FDA will also give the Agency the ability to identify and track all contributors involved with each drug product, and provide information to create an accurate database of sites around the world that play a part in making the pharmaceuticals that U.S. consumers purchase.

Funds derived from the annual Establishment Registration Fee will also allow the FDA to increase the number of agency staff, including inspectors and application reviewers, among others and would also allow the agency to invest in continual improvement measures (i.e. a system to track and monitor the time an application spends in the review queue in active and inactive status, as well as review times by division, by individual, by application, and by applicant).

B. Scope

An Establishment Registration Fee will be required for any facility that seeks to participate in the process of researching, developing, manufacturing, supplying active ingredients for or performing clinical or other laboratory work in support of a pharmaceutical product to be sold in the U.S.

C. Mechanics

An Establishment Registration Fee would be paid annually by any facility that wants to participate in the research, development, clinical, packaging, and supply of ingredients for and/or manufacturing of a product to be sold in the U.S. A facility that performs more than one function identified above at the same site will not be charged twice. The following participants would be required to register and pay an Establishment Registration Fee: finished dose manufacturers, API suppliers, bio-analytical labs, clinical labs, contract analytical labs, contract research organizations, packagers/re-packagers.

As a self policing mechanism, an establishment may not submit a DMF or an application unless the applicant and/or all of the facilities the applicant is utilizing to support the application has paid the annual Establishment Registration Fee. The FDA will maintain a publicly accessible database to allow others to verify registration status and license number.

To ensure unreasonable delays of product do not occur, foreign registered establishments will not experience import delays except for good cause shown. If an import hold or delay is imposed at the border involving an FDA registered establishment's product, FDA must provide notice of the concern(s) within 24 hours of imposing an import delay or hold, and then take action to resolve or request further information within 48 hours of receipt of any additional information. In addition, foreign registered establishments must be permitted to import more than one shipment at a time to receive the forecasted quantities needed prior to approval under FDA's Pre-Launch Activities Import Request Program.

D. Metrics

For additional performance metrics associated with the Establishment Registration Fee, please see the attached *Performance Metrics Summary Chart*.

E. Potential Funding Estimate

So let's look at what a tiered "Establishment Registration Fee" structure could potentially generate. Hypothetically, let's say that all FDF manufacturers paid a $100,000 annual Establishment Registration Fee, and the system then adjusted accordingly from there with API manufacturers potentially paying $50,000, Packagers and Re-packagers $25,000, Bio-Clinical Sites and Bio-Analytical Laboratories $12,500, etc. If we also say conservatively that there are 3,000 FDF and API establishments that would be registered in the U.S. under our proposal, and they paid on average a fee of $75,000, the annual revenue under this scenario alone would generate 225 million dollars.

2. INSPECTION FEE

A. Purpose

The purpose of an Inspection Fee is to provide the FDA with additional resources to ensure that all establishments, regardless of whether they are located in the U.S. or outside the country, comply with U.S. quality standards. An Inspection Fee would be charged on an inspection-by-inspection basis to help cover expenses associated with carrying out an onsite agency inspection of a FDA facility. This Inspection Fee would supplement FDA funding in order to ensure that all facilities, foreign ***and*** domestic, are inspected at least once every two years. Biennial inspections should be legally required for foreign establishments, not just domestic, as provided under current law.

In addition, the Inspection Fee will provide additional resources to ensure timely administrative follow-up after an inspection occurs.

B. Scope

An Inspection Fee should be required of any facility that seeks to participate in the process of researching, developing, manufacturing, supplying active ingredients for or performing clinical or other laboratory work in support of a pharmaceutical product to be sold in the U.S. An Inspection Fee should be assessed for all inspections (including, for example, pre-approval product inspections, new site inspections, GMP inspections, for cause inspections, 483 related follow-up inspections, etc).

C. Mechanics

An Inspection Fee would be paid at the time of inspection. The Inspection Fee would be based, at least in part, on the type of establishment inspected. It must also be designed to promote the effective use of FDA resources including travel costs as well as scope and length of an inspection.

The Inspection Fee will be charged to the site being inspected with the understanding that the inspected site has discretion to pass through costs as appropriate. The Inspection Fee would also account for the estimated amount of time and related expenses any particular inspection takes, and account for the additional staffing, additional travel and interpreter related expenses involved in conducting foreign inspections.

D. Metrics

For additional performance metrics associated with the Inspection Fee, please see the attached *Performance Metrics Summary Chart*.

E. Potential Funding Estimate

So let's look back at our conservative estimate of 3,000 FDF and API establishments. Under our proposal, foreign establishments would pay a $30,000 Inspection Fee and domestic establishments would pay $15,000 for inspections. If half of these establishments, roughly 1,500, have a biennial inspection each year, and with the mix of foreign and domestic establishments, an average inspection fee of $20,000 would generate 30 million dollars annually.

3. APPLICATION FEE

A. Purpose

An Application Fee is a payment intended to supplement FDA's costs associated with conducting review of abbreviated new drug applications (ANDA) and provide the Agency with additional resources necessary to hire and train an appropriate number of reviewers to achieve the median review times outlined below. The same Application Fee shall be applied regardless of the product type. Because the fee will be assessed on each application submitted, the fees generated will ensure that the FDA has continuous supplemental resources to match review demand. The fees will also supplement post-approval associated resources needed to make sure all approved applications are maintained and reviewed annually. These fees will also be

used for monitoring adverse events, annual report reviews, promotional materials review, and other post approval commitments made by application holders.

B. Scope

This fee will be paid by each ANDA applicant at the time the application is submitted to the FDA for review. The fee would be assessed on all ANDAs that are pending approval at the time of the effective date and on all ANDAs submitted after the effective date going forward.

D. Metrics

For additional performance metrics associated with the Application Fee, please see the attached *Performance Metrics Summary Chart*.

III. CONCLUSION

Mylan appreciates the opportunity to provide comments and offer a comprehensive User Fee proposal that:

- Takes into account the unique generic drug approval process under the Hatch-Waxman system;
- Addresses global supply chain challenges and ensures that all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard;
- Expedites the availability of low cost, high quality generic drugs by decreasing the median review time of applications and supplements; and
- Enhances FDA's ability to protect Americans in the complex global supply environment by identifying, tracking and requiring the registration of all contributors involved in each drug product sold in the U.S.

We believe Mylan's proposal would provide significant financial resources to the FDA to achieve these goals. These resources, coupled with the additional funds appropriated by Congress, would ensure the FDA can perform its duties more efficiently and effectively, increase the

number of foreign inspections, decrease median application review times and address its current backlog.

It also establishes one quality standard for every entity doing business in the U.S. and a better record-keeping system so that there is certainty about where products sold in the U.S. are developed or manufactured. In addition, this proposal will result in all stakeholders who do or want to do business in the U.S. market having a vested interest in ensuring the quality of drugs sold in the U.S. The proposal also allows US consumers to have the same confidence in the safety, purity and effectiveness of their drugs no matter where they are made.

Thank you for considering this proposal. Mylan looks forward to a productive dialogue with FDA on this important topic.

Respectfully Submitted,

Heather Bresch
President