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### Challenges and Opportunities for the Generic Drug Industry

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Remarks at the GPhA Annual Meeting as Delivered by Margaret A. Hamburg, M.D.

Commissioner of Food and Drugs

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Good morning—and thank you for that kind introduction and warm welcome. Being here this morning, I can tell that this is, as always, an engaged and energized group. Together in this room, you represent the extraordinary range—and reach—of the generics industry...and you know how to get things done.

Countless patients and their families are very grateful for your work. I'm also grateful to the GPhA, and its leadership—now enhanced with the vigor and vision and of your new President and CEO Ralph Neas. Thank you for your efforts on behalf of our vital generic drug industry...for your commitment to making safe, effective, quality drugs available to people who need them...and, of course, for partnering with the FDA as we strive to fulfill our mission of protecting and promoting the public health.

It's certainly a pleasure for me to join you again—and it seems extremely appropriate because 2012 marks a very special anniversary. It's true that the generic drug industry flourished after the passage of the Drug Price Competition and Patent Term Restoration Act of 1984—commonly known as Hatch-Waxman. Since then, this ground breaking pathway has provided for the approval of over 8,000 generic products. But the generic drug industry, as GPhA has noted, was actually born 50 years ago.

As many of you know, in 1962, the National Research Council of the National Academy of Sciences was instructed to evaluate all drugs that had been approved for use prior to that year. This resulted in a list of products considered effective for all of their claimed indications. And it enabled generic manufacturers to file premarket applications for quality products already ruled effective, allowing a number of pre-1962 medications to enter the market without additional study.

It was the birth of an industry...and the beginning of an era where more affordable medicines would get into the hands of patients who needed them.

Fifty years later, the generic drug industry has achieved remarkable success in getting affordable medicines to patients. Although I know that you are familiar with the statistics, it bears repeating that generic products typically cost 50 to 70 percent less than their brand-name counterparts—while meeting the very same standards for safety, quality, and effectiveness as innovator drugs. And today, some 80 percent of all retail prescriptions filled in the United States are filled with generic drugs. In the past decade alone, the American public collectively saved more than \$931 billion because of generic drugs. They have truly come to represent affordable access to treatment for many patients.

Of course, all of this depends on making sure that an ever-growing number of generic products make it into the marketplace. But, as we know, that seemingly simple solution does not come without challenges. It's no secret that there's a significant and growing backlog at FDA of applications for new generic drugs. Currently, it's about 2,500. And over the last several years, the time it takes to get a generic drug approved has nearly doubled...while the backlog is growing.

Applications have grown at an astounding rate, reflecting the success of the industry. But resources have not grown at the same rate. Chronic underfunding has left us without the necessary scientific and human resources to evaluate applications as quickly as we—and you—would like. We are seeing applications for more complex products. And applications frequently involve products manufactured outside of the U.S.

In fact, in our increasingly globalized economy, up to 40% of all drugs Americans take are imported...and up to 80% of the active pharmaceutical ingredients in those drugs come from foreign sources. This certainly complicates our inspection process.

A Government Accountability Office report released last September noted that the FDA was able to inspect just 11% of the foreign establishments in our database in 2009—compared to the 40% of domestic establishments we inspected that year. According to the GAO, in the absence of a paradigm shift—

including new resources and new ways of doing things—it would take FDA nine years to inspect all foreign facilities. Ensuring that all contributors to the U.S. drug system—both foreign and domestic—are held to the same quality standard is a critical issue for not just the FDA, but for the entire pharmaceutical industry...and for every patient.

As you're aware, to help reduce the critical backlog and the growing workload challenges—and after productive negotiations with GPhA and others—FDA proposed a generic drug user fee program based on our extremely successful prescription drug user fee program. That program has helped ensure a predictable, consistent, and streamlined premarket program for prescription drugs. And we're hopeful that GDUFA, which recognizes the unique challenges and features of the generic drug industry, will have the same result for generics.

Last year at this meeting, we talked about the importance of generic drug user fees—and I'm very glad that you all certainly stepped up to the plate to make them a reality. You agreed...we moved forward together quickly and productively...and GDUFA was transmitted to Congress in January of this year. This morning, I'd like to talk a little about GDUFA's provisions—most especially FDA responsibilities and how the Act will help ensure better medical treatments for all.

As many of you know—at its core—GDUFA calls for the generic drug industry to pay \$299 million annually in user fees for the next five years, beginning October 1, 2012—and with an annual adjustment for inflation. To properly assess individual fee amounts—which will be set annually to generate a statutorily mandated user fee revenue amount—we will need you to help identify your facilities: how many you have; the type; whether they are foreign or domestic, whether they make APIs or finished doses, or both. This is vital for all of us, because to collect the agreed amount of user fee revenue—as negotiated with industry—FDA needs to be able to accurately predict the number of fee paying facilities and the number of applications. Otherwise, we risk over or under collecting. If we undercollect, GDUFA will not be as effective in achieving its goals.

And I want to note that if we overcollect, it doesn't do any of us any good. You pay too much, and anything above the agreed and appropriated statutory cap doesn't stay with the FDA—but goes to the General Fund.

One of the primary goals of GDUFA is to bring the median review time of generic applications from the current average of approximately 30 months—down to a primary review goal of 10 months for unamended applications. And to help attain this goal, FDA will need streamlined hiring authority for all GDUFA-related positions prior to the implementation date of the program. This is in the legislative proposal sent to Congress, and is critical for the success of the program.

Under GDUFA, FDA will also ensure that manufacturers—foreign or domestic—who participate in the U.S. generic drug market are held to the same, consistent, high quality standards. We will conduct risk-adjusted biennial surveillance inspections of all generic API and finished form manufacturers—with the goal of achieving parity of inspection frequency between foreign and domestic firms by year five. Having the resources to undertake these regular inspections will level the playing field for foreign and domestic manufacturers...and help to protect the extraordinary reputation of our drug industry around the world.

As we move forward with GDUFA, we pledge to use the resources that GDUFA will provide to improve predictability and timeliness in the FDA application process. And we will work to enhance FDA's guidance, communications and feedback with industry. We want to be able to give you the kind of clear, understandable and accessible information that you need. One way in which we plan to improve communication is by utilizing a complete review standard—noting any first cycle deficiencies in a single, complete response letter...instead of issuing various letters for various deficiencies.

Additionally, very soon we will be announcing our new director of the Office of Generic Drugs to help ensure strong, effective, scientifically sound generic drug regulatory decision-making. Once the selection is finalized, we will make sure that you will all be among the first to know.

One of the most important public health benefits is how GDUFA will support regulatory science. **If we are to develop new tools, new standards, and new approaches that will enable us to efficiently and consistently assess the safety, efficacy, quality, and performance of products, we must build and maintain a robust and evolving infrastructure for state-of-the art regulatory science.**

Advancing regulatory science has always been one of my personal mantras, so it's great to see the emphasis on regulatory science in the GDUFA proposal. The agreement calls for FDA to convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER's Center Director.

The plan for FY 2012 already includes 13 distinct topics ranging from bioequivalence of orally inhaled drugs...quality by design of generic drug products...modeling and simulation...and postmarketing surveillance of generic drug usage patterns and adverse events—just to name a few.

GDUFA is truly landmark—and it illustrates what we can accomplish when we come together and work together. Today, I'd like to discuss with you three other areas that require our continued cooperation and partnership: biosimilars, drug shortages, and the issue of quality.

As we've been working to address the backlog in applications for new generic drugs, we're also working on creating an abbreviated approval pathway for biosimilar biologics. This was authorized as part of the Patient Protection and Affordable Care Act of 2010.

Since President Obama signed that act into law in March 2010, we've been basically open for business, encouraging companies to come in and talk to us early—and often—before they start development. The new user fee program for biosimilars is intended to support these important development phase meetings. So far, we've received 35 pre-IND meeting requests...have held 21 pre-IND meetings...and have had 9 INDs in house. However, we have yet to receive a product application.

Earlier this month, as some of you likely know, we released our first guidance documents on biosimilars. One addresses scientific issues in determining biosimilarity... another addresses quality related issues...and a third deals with a variety of your logistical questions. The guidances are intended to provide a transparent, clear and predictable pathway to market for this important new product category. This will not be a one size fits all program – our requirements will depend upon the product...and we need your continuing partnership, your input and feedback, as we advance this new initiative. To help support FDA's work with biosimilars we negotiated BsUFA, a new user fee program for biosimilars. However, we also will pledge to commit \$20 million of the Agency's appropriated funding to biosimilar approvals before triggering BsUFA monies.

Together, GDUFA and BsUFA represent truly historic advances...and opportunities for our health care system to deliver on the promise of science to treat, cure and prevent disease. They are great steps—but, as I noted, there are other areas that require our ongoing cooperation and partnership. First, we're all acutely aware of the critical challenge of drug shortages. Between 2005 and 2010, the number of drug shortages per year nearly tripled from 61 to 178. In 2011, the number was up to some 250. We simply must turn this dangerous trend around...now.

We do recognize that the problem of drug shortages is complex—and stems from an interconnected series of factors. These include demand outpacing supply; complex supply chains; cost and other economic issues; legal and regulatory issues; manufacturing equipment and practices; and, most important, quality.

It's a problem we share and must work on together. And one on which we're also making real progress together. Let me take a few minutes to talk a little about some of what we are doing at the FDA and beyond.

On October 31, 2011, President Obama issued an Executive Order directing the FDA to use all available administrative tools to expand efforts already underway to combat drug shortages. At that time, we issued a letter to all pharmaceutical manufacturers reminding them of their legal responsibility to report the discontinuation of certain drugs to the FDA and to encourage voluntary disclosure of shortages and disruptions—even when not required by law.

In December, we issued an interim final rule that requires manufacturers that are the only producer of certain critical drugs to report to the FDA interruptions in manufacturing that could lead to a potential disruption of supply.

We've also increased the number of full-time drug shortage staff to 11—which does not include the many FDA employees who mobilize to work on aspects of shortages across the agency.

And we've been actively and aggressively working with industry and other stakeholders—including GPhA, along with PhRMA, and BIO—as well as with drug wholesalers, to discuss the development of strategies to prevent and reduce shortages.

Thanks to the efforts of so many—including many in this room—we've taken some huge steps forward. There were 195 drug shortages prevented in 2011—114 prevented since the Executive Order, thanks to early notification. And we've seen a six-fold increase in voluntary reports of potential drug shortages.

Building on our efforts, we've just released draft guidance on mandatory and voluntary notification related to drug shortages. The draft guidance attempts to clearly describe for industry how, what, when and why they should notify FDA of an issue that could lead to a product shortage or disruption in supply. This is

critical, because the data is clear that early notification has a significant and meaningful impact on drug shortages.

This week, we also took critical measures to increase supplies of two vital oncology drugs: Methotrexate and Doxil. As you may know, Methotrexate is a chemotherapy drug used to treat children with acute lymphocytic leukemia and osteosarcoma. Our Drug Shortages team began working with various drug companies—specifically Hospira, Sandoz and Mylan, to encourage them to ramp up production when the predominant manufacturer of preservative-free Methotrexate experienced quality and other problems. And we began working with them months before that manufacturer voluntarily shutdown the plant where they were making that drug. We also reached out to another company who had previously made the product to see if they could get back into production. Our efforts, together with these companies, helped to prevent a crisis. On Tuesday, we were able to announce the approval of APP Pharmaceuticals' preservative-free Methotrexate generic application—which we had prioritized. We were also pleased to announce that Hospira received an earlier than expected supply of Methotrexate that started to arrive in hospitals and clinics that very day. And the ramp up by the other manufacturers will be contributing additional products to the market...and to patients. Today, I think we can feel confident that we have an adequate and sustainable supply of Methotrexate for those in need.

Doxil, a chemotherapy drug that is used in the treatment of some types of ovarian cancers, in addition to AIDS-related Kaposi sarcoma, and other cancer regimens, has been in short supply for several months. We also announced on Tuesday that there will be temporary overseas importation of a substitute liposomal doxorubicin into the country, under the agency's exercise of enforcement discretion. When a critical drug is unavailable, and a substitute available elsewhere can produce a comparable outcome—and has been evaluated by us for quality and safety—we will use our enforcement discretion to allow for its temporary and limited use. It's one of the many ways we're working to prevent and alleviate drug shortages.

Of course, when discussing drug shortages, we do have to acknowledge some important—though sometimes difficult truths. First, the majority of problems are related to compliance issues that affect the safety and quality of finished products. Manufacturers of medically necessary drugs—whether innovators or generics—must invest in their manufacturing facilities to ensure the availability of these drugs to the patients who need them. This means quality manufacturing. It's also important to have back-up plans—and to manage and mitigate the risks of facilities being compromised by unforeseen events... or by more routine, but still unwelcome problems. Having safety nets in place to ensure availability is sound business practice—and can only yield positive outcomes. To that end, we're still evaluating GPhA's Accelerated Recovery Initiative for drug shortages, and meeting with your staff to better understand the concept. But we appreciate the leadership, commitment and problem-solving spirit that GPhA is bringing to the table.

I do think that drug shortages raise special challenges for the generic industry. There's a growing perception that drug shortages predominantly involve generics. In fact, of the 111 drugs in current shortage, 60--or 54%--are generic or unapproved, with 11 of the 60 being unapproved drugs; 28--or 25%--are innovator drugs; and 23--or 21%-- have both categories in shortage. Nonetheless, perceptions are not always fair but they still matter.

I know that we all understand the overriding importance of quality manufacturing. Quality is crucial for a products—whether innovator or generic—but if there are frequent, visible shortages involving generic drugs, there's a danger that the public may start to equate generics with quality concerns. That's something we all want to avoid. To accomplish this, we need to place renewed focus on therapeutic equivalence and quality products.

On the therapeutic equivalence front, we all know that the differences between generic and innovator drugs are usually no greater than differences between batches of innovator drugs. However, much of the public does not understand this. So continued efforts to educate the public about generic products is essential, and we will work with you on this. And we need to have members of your industry supporting studies on generic drugs that address key patient concerns or medical issues.

Second, it's also in everyone's interest for you to invest in consumer confidence by making high-quality products. Quality manufacturing is obviously key. But it's also important to take rapid, decisive action when problems arise...and to conduct recalls when they are necessary. And studies have shown that companies benefit financially if they build in a culture of quality.

Of course, the ultimate goal is to avoid quality problems in the first place. Generic manufacturers need to be doing even more to ensure the quality of their products—for example, sharing best practices. And you have a particular responsibility to step forward when a product you are producing is medically necessary.



We have many shared interests and responsibilities—but earning and sustaining the trust of the American people in the entire lifecycle of products you make and we approve is among the most important of all.

There's still so much we need to do together...on biosimilars...on drug shortages...on ensuring that we can deliver the best possible products to people who need them, and depend on them, and must have confidence in them.

We even still have work to do, together, on GDUFA. We all need to do our part to make GDUFA a reality. We will need the active support of GPhA, and all of its members, to help ensure that the final version passed by Congress is one that expedites access to low-cost, high-quality generic drugs...while further enhancing the quality of our nation's drug supply.

Additionally, we need to lay the groundwork at the FDA to implement all the provisions of GDUFA—to ensure that we can push off the starting block as soon as Congress gives the signal. Databases of facilities must be built...and existing review systems will need to be expanded. This isn't an endpoint...it's really just the beginning of our work.

Last year, you promised to invite me back—and I agreed to come—if we accomplished user fees. Well, here I am—and the journey we took...the distance we traveled together over the past year has been nothing short of remarkable. And for that, I want to again thank the leadership of GPhA—and so many of you in this room today.

GDUFA is an extraordinary—and exciting—accomplishment that couldn't have been achieved without the hard work and support of all the stakeholders.

This extraordinary agreement—which is a wonderful way to mark the 50th anniversary of the generic drug industry— will greatly benefit both industry and patients.

It will be good for the bottom lines of private industry...and the needs of public health.

And—most important—this extraordinary agreement underlines our shared goals...our commitment to cooperate...and our public-private partnership. It's a partnership that can serve as a model—a blueprint—as we tackle the public health challenges I've discussed today...and whatever new ones we will face, together, tomorrow.

For that, I am very grateful.

Thank you—and you have my best wishes for a very successful annual meeting.

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