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PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PhRMA)
HOUSE COMMITTEE ON ENERGY AND COMMERCE, SUBCOMMITTEE ON HEALTH
HEARING ON “REAUTHORIZATION OF PDUFA: WHAT IT MEANS FOR JOBS,
INNOVATION, AND PATIENTS”
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Chairman Pitts, Ranking Member Pallone, Members of the Subcommittee, good afternoon. I am David Wheadon, Senior Vice President, Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA appreciates the opportunity to testify today and share our views on the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) and the reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

Reauthorization of the Prescription Drug User Fee Act (PDUFA-V)

PDUFA has been a great success for patients – the tens of millions of Americans who rely on innovative drugs and biologics to treat disease and to extend and improve the quality of their lives. The PDUFA user fee program has provided the U.S. Food and Drug Administration (FDA) with additional staffing and resources needed to significantly reduce the timeframe for review of new medicines, while protecting public health by assuring the safety of these products. Furthermore, PDUFA has helped to improve America’s competitiveness around the world. Since the passage of the original PDUFA in 1992, the U.S. has become the word leader in bringing new medicines to patients first.

The PDUFA-V performance goals letter is the result of extensive negotiations between the FDA and the innovative biopharmaceutical industry and is intended to improve FDA's ability to conduct thorough and efficient reviews of new medicines for patients. FDA's process for negotiating these performance goals included unprecedented transparency and input from all stakeholders, including patient advocates, healthcare professionals, consumers and academia.

PhRMA and its members, the country's leading pharmaceutical research and biotechnology companies, strongly support the original goals of PDUFA, namely to provide patients with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the Agency's regulatory oversight.

PhRMA strongly endorses the recommendations of the PDUFA-V performance goals letter.

This agreement will provide FDA with the resources and tools required to further enhance the timeliness, completeness and efficiency of the drug review process.

The Role of PDUFA in Encouraging Innovation and Economic Growth

Ensuring that the U.S. maintains a policy and regulatory environment that encourages an efficient, consistent and predictable drug review process is key to keeping America competitive in today's global economy. A 2011 report by *Battelle*¹ found that the U.S. biopharmaceutical industry "is well recognized as a dynamic and innovative business sector generating high quality jobs and powering economic output and exports for the U.S. economy." According to the report, nationwide the sector supported a total of four million jobs in 2009, including 674,192 direct

¹ Battelle Technology Partnership Practice, The U.S. Biopharmaceuticals Sector: Economic Contribution of the Nation, July 2011, Battelle Memorial Institute, Prepared for the Pharmaceutical Research and Manufacturers of America.

jobs. The total economic output from the sector's direct, indirect and induced impacts was \$918 billion. Because PDUFA has injected greater consistency, transparency and predictability into the FDA's drug review process, its reauthorization is an important factor in ensuring that biopharmaceutical companies maintain this level of job creation and economic growth. Failure to reauthorize PDUFA in a timely manner would not only have an extraordinarily disruptive effect on the Agency and impede patients' access to new and innovative treatments, but such a failure would also endanger biopharmaceutical innovation.

There are a number of important new commitments in the carefully negotiated PDUFA-V performance goals letter, including provisions to make the regulatory review of new medicines more efficient and timely, to advance regulatory science and to modernize drug development, to improve benefit/risk decision-making, and to further strengthen FDA's focus on patient safety.

Below I will discuss these significant enhancements contained in the PDUFA-V performance goals letter.

Enhanced NME Review Program

PDUFA-V will improve the review process for new molecular entity (NME) drug and biologic applications which will be particularly significant for patients, because NMEs are novel compounds that have the potential to address unmet medical needs and advance patient care.

The enhanced NME review model addresses the increasing complexity of reviewing new drug applications (NDAs) and biologic license applications (BLAs), and provides for increased communication between FDA and drug sponsors prior to and during the drug review process. A

validation period will help FDA plan activities such as inspections and advisory committee meetings, and will accommodate iterative interactions between sponsors and the Agency. As a result, the NME review program is expected to improve the efficiency of the review process and reduce the overall time until new medicines become available to patients. Specifically, it is anticipated that earlier and more comprehensive communication between the Agency and drug sponsors will improve the rate of “on-time, first-cycle” successes – the number of new medicines that are fully reviewed and for which definitive regulatory action is taken within the target timeframe following initial submission. The success of the new review program and of the Agency’s ability to achieve its drug review goals will be independently assessed and publicly reported in 2015 and 2017.

Advancements in Regulatory Science

Several new provisions in the PDUFA-V performance goals letter will afford FDA with appropriate staffing and resources to develop, through public input, new tools and methods to integrate emerging scientific data and techniques into the drug development and review process. These advancements in regulatory science will rely on engagement with industry, academia and other stakeholders to identify best practices so the Agency can provide appropriate guidance to stakeholders involved in drug development.

Provisions to enhance FDA’s regulatory review capabilities include:

- The use of pharmacogenomics and biomarkers to decrease drug development time by helping demonstrate therapeutic benefits more rapidly, and identifying patients who are likely to benefit from treatment, as well as those at increased risk for serious adverse events;

- Avenues for accelerating drug development for rare and orphan diseases and provide FDA with the necessary regulatory flexibility to encourage and advance research into novel treatments for patients with significant unmet needs today;
- Standards for and validation of patient-reported outcomes and other assessment tools that may assist regulators in evaluating treatment benefits and potential risks from the patient's point of view; and
- The evaluation of the use of meta-analyses in regulatory review and decision-making, highlighting best practice and potential limitations.

Systematic Approach to Benefit-Risk Assessment

A key provision in the PDUFA-V performance goals letter recognizes that the drug review process could be improved by a more systematic and consistent approach to benefit-risk assessment that fairly considers disease severity and unmet medical needs. During PDUFA-V, the Agency will implement a structured benefit-risk framework, and hold public meetings to assess the application of such frameworks in the regulatory environment. In addition, over the course of PDUFA-V the Agency will hold a series of public meetings with the patient advocacy community to identify disease states that – from the patient perspective – have considerable unmet needs. Development and implementation of a patient-focused, structured framework for evaluating benefits and risks of new treatments will help inform the drug development process as well as ensure that regulatory decisions are consistent, appropriately balanced and based on best science.

Modernizing the U.S. Drug Safety System

Finally, further enhancement and modernization of the FDA drug safety system under PDUFA-V will ensure that patient safety remains paramount. The PDUFA-V performance goals letter provides for a public process to help standardize risk evaluation and mitigation strategies (REMS), with the intent to assess and reduce burden on healthcare providers and patients. Additionally, FDA will continue to evaluate the feasibility of using the Agency's Sentinel Initiative to actively evaluate post-marketing drug safety issues.

PDUFA has advanced public health by accelerating the availability of innovative medicines to patients while helping to ensure patient safety. The PDUFA program has strengthened the scientific basis of FDA's regulatory review process through the development and application of new tools, standards and approaches that facilitate assessment of the safety and efficacy of innovative drugs and biologics. PDUFA-V will continue to provide FDA with the resources and tools that are essential to support patient safety and promote medical innovation through enhanced timeliness, completeness and efficiency of the drug review process. PhRMA encourages Congress to reauthorize PDUFA in a timely manner based on the negotiated PDUFA-V performance goals and to minimize the inclusion of additional provisions that may have the unintended consequence of distracting from the Act's original intent - to provide patients with faster access to innovative medicines, to preserve and strengthen FDA's high standards for safety, efficacy and quality, and to advance the scientific basis for the Agency's regulatory oversight.

Reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research and Equity Act (PREA)

Prior to passage of the pediatric exclusivity provisions in the Food and Drug Modernization Act (FDAMA) of 1997, there were significant disincentives for biopharmaceutical companies to conduct clinical trials for pediatric use - generally speaking, in patients under the age of 18 - for medicines developed primarily for adults. At the same time, there were concerns that many FDA-approved drugs had not been clinically tested in children. For example, at that time about 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information.²

Growing recognition of the need for pediatric-specific information prompted action by Congress and the FDA. Congress responded by establishing BPCA to provide incentives to encourage manufacturers to conduct pediatric studies of medicines with the potential for use in children as part of FDAMA. The legislation included a provision that granted pharmaceutical companies an additional six-month period of exclusivity, known as pediatric exclusivity, upon the completion and submission of pediatric studies that meet the terms of a written request from FDA.

In addition to BPCA, PREA gave FDA the authority to require manufacturers to conduct pediatric studies for certain new drugs and biologics approved for use in adults where the indication for use in children would be comparable to that for adults and produce formulations appropriate for children, *e.g.* liquid or chewable tablets.

² U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

Although FDAMA included a sunset provision effective January 1, 2002, Congress subsequently reauthorized these provisions in BPCA and PREA in 2002, and again in 2007 as part of the Food and Drug Administration Amendments Act (FDAAA). Similarly, there are provisions in the Biologics Price Competition and Innovation Act of 2009 (BPCIA) to provide pediatric exclusivity for biologics if the sponsor submits pediatric studies in accordance with a written request from FDA. BPCA and PREA both sunset on September 30, 2012, unless reauthorized or made permanent.

BPCA and PREA have been extraordinarily successful in improving medical care for children by driving research to create innovative medicines for use in pediatric patients. According to the FDA, the current pediatric exclusivity program has done more to spur research and generate critical information about the use of medicines in pediatric patients than any other government initiative.³ As of 2008, an estimated 50 to 60 percent of prescription drugs used to treat children have been studied in some part of the pediatric population.⁴ Since 1998, BPCA and PREA have resulted in 426 pediatric labeling changes,⁵ and a GAO report released in May 2011 states that pediatric studies conducted in the past five years represent 16 different therapeutic areas including oncology, endocrinology, hematology, cardiovascular disease, infectious disease and neurology.

A recent issue of *NIH MedlinePlus* magazine notes the importance of pediatric clinical trials and cites several examples of how clinical trial knowledge has improved the lives of children. The

³ Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.

⁴ FDA, "Giving Medication to Children: Q&A With Dianne Murphy, MD," June 2009.

⁵ FDA, <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf>

article states that, among other examples of great progress in innovative pediatric drug development, “as a result of repeated clinical trials in children with cancer, most children who develop leukemia survive” compared to 50 years ago when “acute leukemia was almost universally fatal in young children”. Additionally, clinical trials in young children “showed that surfactant - a substance that keeps air sacs in the lungs inflated - helps premature infants breathe” and with this knowledge “the lives of thousands of babies who would otherwise die of respiratory failure are saved each year”.⁶

Permanent Reauthorization of BPCA and PREA is Key to Ensuring Innovation in Pediatric Research

Ensuring that the pediatric exclusivity incentive is preserved is key to continued innovation and improvement in pediatric medical care in the face of rising research costs. Since their initial enactment and subsequent reauthorizations, the pediatric exclusivity incentive and PREA have been subject to a “sunset clause” under which their provisions expire after five years unless reauthorized by Congress. To build upon the tremendous success of BPCA and PREA in improving medical care for children over the past fifteen years, Congress should permanently reauthorize BPCA and PREA.

Permanent reauthorization of these provisions would provide greater certainty to companies by allowing a more predictable regulatory path and would help spur increased pediatric research. Pediatric product development would also benefit from updated regulatory guidance to assist both industry and FDA review staff in achieving a common understanding of the requirements

⁶ NIH Medline Plus, “Developing Safe and Effective Medicines for Children,” Winter 2012, <http://www.nlm.nih.gov/Program_MLP/MLP_intro.html>

under the Federal Food, Drug, and Cosmetic Act (FDCA). Because of the five-year BPCA/PREA sunset and reauthorization cycle, no such current guidance exists, since every reauthorization has brought new changes to the law. The lack of current FDA guidance creates additional challenges for sponsors involved in pediatric product development to incorporate any differences into its plans due to changes in statutory requirements. If Congress were to reauthorize BPCA and PREA permanently, it would enable the FDA to publish and maintain up-to-date regulatory guidance for companies that seek to develop pediatric treatments.

Further, making BPCA and PREA permanent would allow sponsors to build upon the existing pediatric research infrastructure and expand their capacity to conduct clinical studies.

Uncertainty about whether incentives will continue could deter this vital investment. A similar pediatric incentive was successfully introduced in the European Union (EU) in 2007, and while the regulation is subject to review, the EU's pediatric incentive is permanent. The permanent incentive in the EU has enabled the European Medicines Agency (EMA) to publish clear guidelines for industry and regulators making the process more efficient, transparent and predictable.

Given the undisputed success of BPCA and PREA, we urge Congress to permanently reauthorize BPCA and PREA in their current forms to allow pediatric research to thrive and create more options for our most vulnerable population: children.

Maintaining Pharmaceutical Supply Chain Integrity

In addition to the Subcommittee's focus on the reauthorization of PDUFA, BPCA, and PREA, PhRMA shares the Subcommittee's longstanding interest in helping to assure the safety of the U.S. pharmaceutical supply.

The U.S. ensures drug safety in part by maintaining a closed system for the distribution of prescription medicines. In addition to the existing standards that require an NDA or a BLA and maintenance of current Good Manufacturing Practice (cGMP), the U.S. closed prescription distribution system helps provide assurance regarding the quality, safety and integrity of the products lawfully sold in the U.S., and helps minimize the possibility that a consumer receives a counterfeit medicine. Even with FDA's comprehensive regulatory system, increasing globalization of pharmaceutical supply chains presents challenges that require biopharmaceutical companies and the FDA to be more adaptive and flexible in the review and oversight of entities located around the world. Relying on risk-based approaches will help achieve these goals.

Supply chain security is the responsibility of all parties involved in the distribution of medicines to patients in the U.S. We appreciate the Subcommittee's long-standing commitment to these issues and Congressman Dingell's particular focus on these topics. As you know, PhRMA has constructively engaged with this Subcommittee, with the full Committee and other stakeholders on all aspects of supply chain security, and appreciates the opportunity to continue to be part of this important dialogue.

As part of this discussion, we are pleased to provide the following preliminary comments, and look forward to an ongoing dialogue on these important issues.

Enhancements to FDA’s Inspection Regime – Adoption of Risk-Based Inspection Intervals

PhRMA supports granting FDA discretion to set routine inspection intervals for foreign and domestic facilities according to risk. The use of risk-based approaches to regulation, and in particular, to cGMP inspections is not a new concept.⁷ We support providing FDA with the flexibility to prioritize inspections of foreign establishments based on the risks they present, and believe relying on set criteria such as compliance history, time since last inspection, and volume and type of products produced, will enhance the FDA’s ability to target its inspection resources efficiently and effectively.

Leverage FDA’s Inspection Resources by Allowing Use of Foreign Inspection Reports or Accredited Third Parties as Appropriate

In recognition of the fact that the Agency does not have unlimited resources and in order to help ensure that foreign inspections occur on a more regular basis, Congress should consider allowing FDA to rely on the inspection results of other foreign regulatory bodies with similarly robust drug regulatory oversight systems, or to use accredited third parties to conduct certain foreign inspections, such as inspections of facilities considered moderate to low risk based on appropriate criteria. These inspections would not take the place of FDA inspections, which are a necessary and important part of the Agency’s mandate; however, they would provide FDA with the flexibility to leverage the work of foreign regulatory bodies of similar standing and maximize

⁷ See e.g., “FDA Guidance: Risk-Based Method for Prioritizing GMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model,” (Sept. 2004).

its resources, all without foreclosing its ability to inspect any facility. FDA recently acknowledged and embraced the concept of relying on “public and private third parties to conduct audits and other oversight activities on behalf of FDA.”⁸

A risk-based approach to inspections and reliance on third parties inherently contemplate that limited sharing of inspection-related information may be a necessary component of these proposals. In those circumstances, we must also protect confidential commercial and trade secret information, including information related to manufacturing methods and processes. It will be critical for FDA to have in place written agreements with relevant foreign governments setting out the scope of information that can be shared and obtaining assurances from those foreign governments that the pharmaceutical sector’s innovation and ingenuity will be protected from public disclosure. Continued innovation of developing and manufacturing tomorrow’s new medicines depends on this information being adequately protected.

When considering the issues of supply chain security, another enhancement that could be considered would include requiring all foreign facilities manufacturing prescription drug products or components destined for import into the U.S. to register with FDA and list their products, to the extent they are not already required to do so under current law. By requiring such facilities to register, the FDA will be able to establish a single database that will contain information on all facilities that manufacture products or components of products that are sold in the U.S.

⁸ “Pathway to Global Product Safety and Quality: Special Report,” Food and Drug Administration, (July 7, 2011), available at: <<http://www.fda.gov/AboutFDA/CentersOffices/OC/GlobalProductPathway/default.htm>>.

Finally, as we consider whether new authorities are needed to help strengthen our existing prescription drug supply chain, we must also consider the appropriateness of including new burdens on the import of materials for use in preclinical and clinical investigations. The continued, uninterrupted access to preclinical research and clinical trial materials, including active pharmaceutical ingredients (APIs), is essential to ensure that vital research into innovative, life-saving and life-enhancing new treatments is not hindered in any way. Materials and articles used in preclinical research activities are not used in the treatment of patients, but instead are used in laboratory testing as scientists try to understand the pharmaceutical properties and initial safety profile of the test article. Thus, we strongly encourage the inclusion of an exemption for APIs, investigational drugs and other materials intended for use in preclinical testing and clinical trials that comply with FDA's stringent requirements relating to the proper use of investigational material, including labeling and import of investigational products and materials for use in clinical trials under an Investigational New Drug application (IND), into any new provisions related to securing our pharmaceutical supply chain.

We commend the Subcommittee for its focus on and commitment to the issue of securing the pharmaceutical supply chain. The U.S. system of prescription drug supply chain security today is of a very high standard, but even good systems can be improved upon. We look forward to continuing to work with the Committee, FDA and other stakeholders on these important issues.

Thank you for the opportunity to testify today and I welcome any questions you may have.

“Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients”

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Summary of Testimony

- **The Prescription Drug User Fee Act (PDUFA).** PDUFA has been a great success for patients since its initial passage in 1992. The PDUFA user fee program has provided FDA with the additional staffing and resources it needed to significantly reduce the timeframe for the review of new medicines, while protecting public health by assuring the safety of these products.
- The PDUFA-V performance goals letter is the result of extensive negotiations between the FDA and the innovative biopharmaceutical industry. FDA’s process for negotiating these performance goals included unprecedented transparency and input from all stakeholders, including patient advocates, healthcare professionals, consumers and academia.
- A number of important new commitments are detailed in the PDUFA-V performance goals letter, including provisions to make the regulatory review of new medicines more efficient and timely, to advance regulatory science and to modernize drug development, to improve benefit/risk decision-making, and to further strengthen FDA’s focus on patient safety. PhRMA strongly endorses the recommendations of the PDUFA-V performance goals letter.
- Since the passage of PDUFA-I in 1992, the U.S. has become the world leader in bringing new medicines to patients first and PDUFA has helped to improve America’s competitiveness around the world. The reauthorization of PDUFA is an important factor in ensuring that biopharmaceutical companies maintain this level of job creation and economic growth.
- Failure to reauthorize PDUFA in a timely manner would not only have an extraordinarily disruptive effect on the FDA and impede patients’ access to new and innovative treatments, but such a failure would also endanger biopharmaceutical innovation.
- **Advancing Pediatric Drug Development.** The Best Pharmaceuticals for Children Act (BPCA). BPCA was established in 1997 as part of FDAMA to provide incentives to encourage manufacturers to conduct pediatric studies of medicines with the potential for use in children. The legislation grants pharmaceutical companies an additional six-month period of pediatric exclusivity upon the completion and submission of pediatric studies that meet the terms of a written request from FDA.
- The Pediatric Research and Equity Act (PREA) gave FDA the authority to require manufacturers to conduct pediatric studies for certain new drugs and biologics approved for use in adults where the indication for use in children would be comparable to that for adults and to produce formulations appropriate for children, *e.g.* liquid or chewable tablets.
- BPCA and PREA have been extraordinarily successful in improving medical care for children by driving research to create innovative medicines for use in pediatric patients.
- Ensuring that the pediatric exclusivity incentive is preserved is key to continued innovation and improvement in pediatric medical care. Since their initial enactment and subsequent reauthorizations, BPCA and PREA have been subject to a “sunset clause” under which their provisions expire after five years unless reauthorized by Congress. To build upon the tremendous success of BPCA and PREA in improving medical care for children, Congress should permanently reauthorize BPCA and PREA.
- **Supply Chain Security.** The U.S. ensures drug safety in part by maintaining a closed system for the distribution of prescription medicines. Supply chain security is the responsibility of all parties involved in the distribution of medicines to patients in the U.S.
- PhRMA supports granting FDA discretion to set routine inspection intervals for foreign and domestic facilities according to risk by providing FDA with the flexibility to prioritize inspections of foreign establishments based on the risks they present.