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Hearing on "Examining FDA's Prescription Drug User Fee Program"

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Mr. Chairman, Ranking Member Green, and Members of the Subcommittee:

BIO appreciates the opportunity to speak with you today about the reauthorization of the Prescription Drug User Fee Act program (PDUFA). BIO strongly supports this fifth reauthorization of PDUFA and urges timely Congressional action.

I am Kay Holcombe, the Senior Vice President for Science Policy at BIO. BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. While our membership includes most of the large biopharmaceutical companies, the vast majority of our members are small biotechnology companies working on cutting-edge R&D. They have small staffs, no marketed products, and no profits, and they are heavily reliant on private capital to fund their work. They take enormous risks every day to develop the next generation of biomedical breakthroughs for the millions of patients suffering from diseases for which there are no effective cures or treatments today. BIO is proud of their innovative spirit and their dedication to alleviating human suffering.

All FDA stakeholders – the biopharmaceutical industry, patient and consumer advocates, health care providers, payers, and others in the healthcare system – recognize the importance of the PDUFA program. Many of them recall the time before enactment of PDFUA I in 1992, when FDA review times were lengthy and a high percentage of new drugs were on the market outside the United States before American patients had access to them. It was first at this Committee that FDA testified that review times could be reduced significantly if the agency could hire the additional staff, funded by user fees, needed to carry out the activities related to review of human drug applications more quickly.

PDUFA I proved this proposition. By the end of the five years of that first PDUFA program, review times had dropped by as much as three-fold. This significant improvement in review times has continued throughout the 24 years of PDUFA. Today, thanks to the resources PDUFA has provided FDA, U.S. patients are – in the vast majority of cases – the first in the world to have access to approved new drugs.

Formal FDA review time is, in fact, the shortest part of the process of moving a new therapy from its inception as a scientifically well-founded hypothesis to its use by patients. Today, it takes 10 to 12 to even 15 years and upwards of $2 billion to move a drug or biological product from a good idea to an approved product. During that lengthy period, unmet medical needs remain unmet and patients wait. Over the course of four previous PDUFA reauthorizations, the question has been raised as to whether and how the sorts of efficiencies that reduced review times also could reduce drug development times. How can FDA use PDUFA resources to address lengthy, expensive, risky drug development times?

PDUFA V, the program currently in place, was the first to include regulatory science initiatives – development of expertise in FDA to deal with cutting-edge technology and new ways of thinking about the studies and data associated with working toward approval of a new drug. PDUFA V provided funding for modest programs related to patient-focused drug development, the use of pharmacogenomics data, biomarkers as surrogate endpoints, patient-reported outcomes, and meta-analysis – some areas where additional expertise and resources could advance the science and the success rate. A key rationale for inclusion of those initiatives was that they are emerging areas in drug development that hold potential for reducing development times. Addressing drug development times would be a recurring theme entering this PDUFA reauthorization cycle.

Overall Goals for PDUFA VI

As BIO approached this reauthorization of PDUFA, we asked our member companies what they hoped to gain. We heard two themes: advance ways to reduce the time of drug development and ensure that PDUFA remains viable into the future. As to the former, our principal goals were to integrate the patient perspective in drug development; incorporate the use of innovative clinical trial designs, biomarkers as surrogate endpoints, and real-world evidence into acceptable approaches to drug development; and enhance some existing FDA processes, including the review of combination products that will be at the heart of personalized medicine. As to the viability of the PDUFA program, we sought to increase the transparency and accountability of PDUFA financial management and assure the long-term financial stability of the PDUFA program, including through a new time reporting system that would allow accurate capacity planning. Finally, but of primary importance, we sought to work with FDA to improve the agency's ability to attract, hire, and retain the numbers and kinds of employees it needs to do its job as efficiently and effectively as possible.

Program Sustainability and Financial Transparency

Since PDUFA finances and personnel form the foundation that keeps the PDUFA program viable, it is important to look at the situation as it exists today and what needs to be addressed. Since 2002, the PDUFA program has grown at an average of 11% per year; this is unsustainable moving into the future. Changes are needed that address the fee collection structure to increase efficiency and reduce administrative burdens for both FDA and companies. These include reducing the volatility of fee collections, eliminating complicated collection and other financial mechanisms that are difficult to administer, improving predictability, and reducing variation of collections year over year. Together,

these changes will increase efficiency and reduce program growth rate substantially. Specifically, the PDUFA VI proposals would:

- limit the carryover balance levels, thus reducing possible over-collection of fees and the need for complicated administrative mechanisms to deal with such over-collections;

- eliminate supplement fees, which will further simplify fee collections;

- replace the current Product and Manufacturing fees with a new Program fee that will constitute 80% of the annual fee collections; and

- reduce the percentage that Application fees contribute to the total from the current 33% to 20%, thus mitigating the overall impact of this difficult-to-predict revenue source.

Increased financial transparency will provide a greater line of sight by Congress and the public into how PDUFA fees are collected and allocated and a more accurate picture of the costs associated with human drug review activities. This will be accomplished under PDUFA VI by improving resource management, thus allowing the public to know accurately how PDUFA fees are being used and to understand clearly the costs associated with human drug review related activities, and by providing a publicly available 5-year financial plan and annual updates of how the agency is executing against that plan. In both the development of the initial plan and throughout the remaining years of PDUFA VI, public input will be sought through public meetings and other mechanisms.

Transparency also will be increased as regards the calculation of the PDUFA workload. Until PDUFA VI, PDUFA fees have been adjusted annually by applying an inflation factor, which is straightforward and understandable, and a workload adjustor, which is neither. More than one outside consultant has stated that, while there is a clear need to apply an adjustment factor to account for differing workloads year over year, the particular adjustment factor was not a good one but was the only possibility unless there was systemic change in the way workload was measured. That systemic change is coming in PDUFA VI.

Beginning now, and through PDUFA VI, FDA will implement a new time reporting system, in which time and costs are measured on a continuous basis, rather than by sampling at pre-determined time periods throughout the year. This kind of system, used by multiple private sector organizations as well as in many government programs, provides significantly more accurate data than are now available on which to base workload calculations. FDA will be advised and assisted in establishing and executing the new system by an outside contractor with expertise in such systems. Progress toward this implementation and initiation of the new adjustment factor will be publicly available information, reported in the PDUFA annual Performance Report.

These more accurate time and cost data also will contribute to the ability to plan for future resource needs, contributing to the long-term sustainability of the PDUFA program. A capacity planning function will be established, which will allow FDA to assess in advance the number of staff that will be needed to assure a continuing efficient and effective human drug review program. Achievement of this goal is

under way, with a third-party expert already working with the agency on determining the best approach to development and use of capacity planning.

Personnel Management

Hiring and retaining the expert staff essential to carrying out user-fee-funded activities is critical for PDUFA VI to work. Without the necessary number and kinds of staff, FDA simply cannot meet the performance goals for which user fees are intended. Problems with FDA recruitment and hiring have existed for years, for a number of reasons, including cumbersome hiring processes and pay scales that generally are lower than for similar positions in the private sector. The 21st Century Cures Act, from this Committee, addressed some of the issues that have hindered FDA's ability to attract, hire, and bring on board the kinds of senior scientific and medical staff needed. Those provisions will make a significant positive impact. In addition, under PDUFA VI FDA has committed to make changes in its internal personnel operations, including implementing a dedicated senior scientist recruiting function, increasing staff capacity to recruit and to process personnel actions in a timely way, and engaging the services of independent contractors to assist in these functions, advise the agency in best human resources practices, and evaluate and report annually and publicly on hiring and retention progress.

For the first time, hiring goals are included in detail in the PDUFA VI Performance Goals Letter, and achievement of these goals will be detailed in the annual PDUFA Performance Reports. Many of these changes already are under way. For example, FDA has begun the process of hiring staff to replenish the long-under-staffed Office of New Drugs, responsible for the review of all new drug and biologics applications. This hiring in FY 2017 is funded from PDUFA V amounts in the carryover balance. The balance exists as a result of earlier sequestration and continuing resolutions, which prevented the allocation of some PDUFA V resources before now. This hiring will continue in the first several years of PDUFA VI, along with hiring of additional staff essential to carry out the new performance goals agreed to between FDA and industry, in collaboration with other stakeholders such as patient, consumer, and provider organizations.

Over the course of PDUFA VI, the negotiated and agreed-upon number of FTEs (full-time equivalents) necessary to carry out the goals of PDUFA VI is 230, hired over years of the user fee agreement, FY 2018 to 2022. These include medical reviewers, pharmacologists, pharmacists, chemists and other scientific experts, biostatisticians, financial managers, and other essential staff. In each year's performance report, beginning in FY 2018, FDA will report on its progress in achieving the hiring goals specified in the PDUFA VI Goals Letter.

To summarize our views on the financial and hiring enhancements of PDUFA VI: BIO believes they are on target and essential to ensure both the long-term viability of this crucially important use fee program and to ensure that FDA is able to hire, bring on board, and retain the expert staff who are crucial for the agency to meet its PDUFA VI goals and, in general, to carry out its public health mission. We all have the same goals – ensuring that FDA-approved safe and effective therapies are available to patients as soon as possible. This Committee addressed them in 21st Century Cures; we add to that work through the PDUFA VI goals.

Making a Difference for Drug Development = Making a Difference for Patients

PDUFA VI promises to transform drug development. We believe FDA can and will deliver on this promise, provided they continue to have the ability to hire the additional people needed to carry out the historic commitments of this agreement.

In the beginning, the intention of prescription drug user fees was to improve the efficiency of FDA's review and reduce its time. That goal has been achieved. Today, the vast majority of new drugs are available to U.S. patients before they are available to patients anywhere else. FDA is the fastest and most efficient drug regulator in the world. All those who supported the establishment of the PDUFA program have been proven right. In August 1992, then-FDA Commissioner David Kessler made his first appeal to Congress in his testimony before this Committee, that if the agency had access to greater resources through a user fee program, review times could be reduced significantly. Industry, though with some skepticism, agreed. The Committee reported the first user fee bill shortly thereafter, with strong bipartisan support, and PDUFA was signed into law on October 19, 1992, by President George H.W. Bush. The rest is history.

Over the course of the four reauthorizations of PDUFA and as a result of user fees, we have seen review times drop dramatically from what they were before 1992, and we have seen other changes as well, such as enhancement in FDA's efficient and effective communication with applicants; augmentation of the agency's ability to monitor and assure the safety of products both pre- and post-market, throughout product life cycles, including establishment and use of the Sentinel program; adoption of best practices for scientific review and communication across all the review divisions in the Centers for Drugs and Biologics; establishment and implementation of regulatory science programs to deal more effectively with emerging areas of product research and development, such as the use of biomarkers, pharmacogenomic data, and patient-reported outcomes; and multiple other goals to ensure timely, efficient review. While all of these goals were being achieved, review timelines were not negatively affected. FDA consistently has met or exceeded its established goals of completing the review of Priority applications in eight months (many such priority applications are completed in fewer than eight months) and of Standard applications in 12 months. These timelines are now the global gold standard for regulatory efficiency. In the U.S. our economy has benefited from PDUFA, because drug and biologic applicants now have greater certainty of a reasonable timeline for completion of their applications. Most importantly, though, patients have benefited. Before PDUFA, U.S. patients legitimately could say that their counterparts elsewhere in the world had treatments available before they did. That largely is not the case anymore.

For nearly its entire history, PDUFA has been focused principally on the timeliness and efficiency of the formal FDA review process after an application has been submitted for approval. Yet FDA's application review time of less than 12 months pales by comparison to the 10 to 12 years on average that it takes to develop a drug – time before an application even is submitted to the FDA. Development of new medicines is a long and rigorous process, and it has become more costly and complex over the past decade – partly because the science is harder, and partly because the regulatory review process has not kept up with the advancing science.

The question facing PDUFA VI stakeholders and FDA was the question that faced this Committee as it embarked on 21st Century Cures: What can be done to change the course of drug development and to reduce the time it takes to get to that goal of submitting an application to FDA?

To tackle these questions, it was important to identify what new tools are available today that aid in drug development. Advances in biology have made miracles such as gene therapy more than a pipe dream or science fiction. Are there other advances that, if used to greater advantage, can accomplish the miraculous with respect to drug development?

The authors of 21st Century Cures and the PDUFA VI agreement independently recognized some of the same new tools and developed proposals and PDUFA VI commitments that would allow these tools to be used most effectively, with the goal of ensuring more timely availability of new drugs for patients by reducing the time and increasing the chance of success of drug development.

Key Drug Development Goals of PDUFA VI

Integrating the Patient Voice in Drug Development and Regulatory Decision-Making

One of the most important goals of PDUFA VI was building on the success of the PDUFA V Voice of the Patient program, in which public meetings brought FDA and patient representatives together so the agency and other stakeholders could hear how these patients perceived their condition, what they hoped for in terms of a "benefit" from a therapy, and how they viewed "risk." Those meetings, and the reports produced from them, were a positive step forward in terms of bringing these patient perceptions into the FDA determination of the benefit-risk calculus. Patients augmented that deliberation by adding the crucial patient perception dimension to an often largely mathematical and statistical evaluation. They also helped drug developers to understand better what patients viewed as their needs, so this could be taken into account when planning and executing a development program.

The next step in this approach is to engage patients and other stakeholders in another public process that will result in guidance, developed by FDA with stakeholder input, in a step-wise fashion. First, guidance will be developed regarding how to collect evidence-based and representative patient information. Next will be guidance on processes and approaches to determine what is most important to patients in terms of the impacts of their disease and potential impact of new treatments. This will be followed by guidance on how to measure impacts in a way that will facilitate meaningful patient input into the design of clinical trials. This is particularly important in light of the cost and length of clinical trials, the difficulty of enrolling sufficient numbers of patients, and the risk of patient drop-out, which can compromise or even negate the trial results. Finally, FDA will re-visit its existing guidance on patient-reported outcomes and address incorporating clinical outcome assessments into endpoints.

To accomplish these objectives, FDA will strengthen its staff capacity, including bringing on board experts in psychometrics and health outcomes research. These staff will be integrated into the review teams to ensure the engagement of patients and to consult with drug developers during their development programs.

Ultimately, the goal of good data collection, representative sampling, and appropriate use of data is to be able to include information on the drug label that can be used by prescribers, patients, and caregivers. The drug label is the trusted source of information about the best and safest ways to use a drug. Reliable patient input into belongs in that label, and this PDUFA VI agreement will help make that happen.

Enhancing Benefit-Risk Assessment

FDA established a structured benefit-risk approach under PDUFA V. In PDUFA VI, implementation of this approach will be enhanced through one or more public meetings with and for stakeholders, and through development and publication of guidance on the use of the benefit-risk framework throughout the drug life cycle. The incorporation of patient perspectives will be a key part of these activities. An independent third party will evaluate the implementation of the benefit-risk framework and whether it is being implemented consistently across the review divisions. The importance of this goal is three-fold: first, it solidifies and evaluates the use of the benefit-risk framework, which allows greater transparency for all stakeholders into FDA's thinking about how to measure the potential benefits of a potential new drug against its known risks; second, it emphasizes the importance of patient input into this crucial decision; and, third, it helps drug developers use the benefit-risk assessment as a marker and a tool in the course of the development of a drug and throughout its lifecycle.

Enhancing Communication between FDA and Drug Sponsors

PDUFA VI builds on the enhanced communications program established under PDUFA V, which was intended to assure that sponsors were able to receive timely responses to inquiries that could be dealt with outside of the formal FDA-sponsor meeting process. Under PDUFA VI, a third party will evaluate how this program is proceeding, how such informal communications are handled across review divisions, and what best practices may be adopted across the board. A public meeting will allow stakeholders an opportunity for discussion and input into the evaluator's findings.

Using Drug Development Tools, including Biomarkers

In PDUFA VI, FDA is committed to enhancing biomarker qualification processes. In addition, the agency will implement a pilot program to seek and incorporate the input of external experts to assist in the qualification, to verify if the use of such outside experts can make the processes more timely and efficient. In addition, the agency will augment its staff capacity to conduct qualification of drug development tools, hold a public workshop particularly aimed at discussing nomenclature, standards, and elements of a biomarker qualification plan; publish guidance; and publish and update lists of qualified biomarkers and of pending applications. Significantly, FDA will establish a process for holding dedicated meetings with sponsors to discuss the use of biomarkers as surrogate endpoints. This will be a new meeting, additional to those meetings that all drug developers are entitled to have with FDA during their development programs.

Using Real-World Evidence

The Sentinel system, established by FDA in response to Congressional direction, is the source of enormous data regarding the health care and health outcomes of tens of millions of patients covered by several private insurance plans. FDA uses the system to search for safety signals that may lead to further investigations regarding the safety of marketed drug products. The system is supported by a number of sources, including user fees. Under PDUFA VI, prescription drug user fees will provide $50 million to continue to support the operation and use of Sentinel. FDA will work, during the course of PDUFA VI, to ensure that stakeholders, including industry, are well informed about how the agency is using the system and to seek additional ways to help others, beyond FDA, access this treasure trove of data while protecting any patient and drug sponsor confidential information.

In addition to the data available through Sentinel, there are multiple other sources of "real-world evidence" that currently are seen primarily as a potential source of drug safety information. Under PDUFA VI, FDA will hold a public meeting and, based on that input, develop pilot studies or related activities to determine other uses of such real-world data in regulatory decision-making. One possibility is that large data bases could be used as a source of information that could augment other sponsor-developed data in applications for approval of a new indication for an already approved drug. Another possible use is for the fulfillment of post-marketing requirements associated with newly marketed drugs.

Data are everywhere. The question PDUFA VI will begin to answer is how such data can be harnessed and used effectively to advance, enhance, and reduce the time of drug development.

Improving the Review of Combination Products

Combination products – which join two drugs, a drug and a biologic, or a drug or biologic and a medical device, commonly a diagnostic test – pose some unique challenges to developers. Streamlining and better assignment of roles and responsibilities at FDA could help address these challenges and advance these products, which many see as a wave of the future. For example, personalized medicine is highly dependent on identifying, often through a diagnostic test, patients who will benefit from a particular drug and those who are likely not to benefit, or who may be subject to greater risk. Such advancements will not only benefit patients, but also facilitate the broader move toward a more cost-effective healthcare system.

The challenges that have been identified as slowing the review of such products include the decision as to which FDA Center has primary or lead responsibility, which Center has decision-making authority, and how to speed the work of the "other" Center that may not have a user fee goal impetus to make a particular application a priority. PDUFA VI will address these challenges in several ways. First, staff capacity and training will be increased in all three medical product Centers, the Centers for Drugs, Biologics, and Devices. PDUFA funds will be used for bringing staff on board in all three Centers. Second, performance goals will be established specific to combination products and will be phased in over the course of the 5 years of PDUFA VI. Submission procedures and guidance related to unique features of combination products will be developed and published.

Using Innovative Clinical Trial Designs

Clinical trials are the most costly and difficult parts of drug development, and their design, enrollment, and execution can add extraordinarily to the time of drug development. Many experts in trial design have argued that the "traditional" randomized, double-blind, controlled trial is not always the most efficient or necessary approach. With new ways of thinking, and given new approaches to statistical analysis, are there better ways to do trials without losing their validity, their amenability to appropriate data analysis, and, thus, their contribution to the most appropriate regulatory decision?

In PDUFA VI, FDA is committed to beginning to answer that question. First, additional FDA staff, particularly additional biostatisticians, and especially those with training and expertise in "non-traditional" statistical analysis, will be added. FDA will hold a public workshop on innovative trial design and will publish guidance on adaptive trials. Finally, and of particular significance for moving this idea forward, FDA will conduct a pilot program focused on innovative trial designs. This program will be voluntary – i.e., companies may opt in to the program and, in exchange for their participation, will be given two meetings with FDA to discuss the proposed trial design and its execution, to enhance the likelihood of success of the development program. Companies in the program will agree to allow FDA to discuss the trial design as a case study at a subsequent public workshop or in guidance (protecting all company-specific confidential information). Participation in the pilot program is voluntary, but the hope is that there will be strong participation, so the ability for others to learn from case studies will "raise all boats," expand the use of innovative trials, and contribute to reducing the time and cost of clinical trials.

Using Model-Informed Drug Development (MIDD)

Biological and statistical modeling can contribute greatly to a knowledge base that can advance drug development, reduce the time of development, and allow development to proceed even in cases where clinical data may be limited. FDA will explore the use of MIDD through both increasing its staff capabilities and establishing a voluntary pilot program similar to that for innovative clinical trial design. In addition, the agency will hold workshops to identify best practices for various types of modeling and publish guidance based on its findings through the workshops and in the pilot program. Modeling informs development, and is not intended as a complete substitute for clinical data. Part of the importance of this program is that it can determine how modeling can assist in moving forward a significant development program where clinical data are limited. Modeling or simulation would not be the only source of data in any program of developing a human drug.

Continuing and Enhancing Successful Programs

PDUFA VI will continue and enhance its efforts related to the highly successful Breakthrough Therapy program, which has shown the power of enhanced communication between FDA and sponsors to speed drug development for exciting new products; augment its capacity and enhance its processes for reviewing applications for rare disease therapies, to continue its record of success in prioritizing these applications based on the high unmet medical need of patients with rare diseases; and continue and build on the successful New Molecular Entity (NME) review program, which has accomplished its goal of

increasing the number of products approved after only one cycle of review. All of these programs are resulting in reducing the time of drug development. All of them are verified and verifiable successes.

PDUFA VI and 21st Century Cures: Great Minds Think Alike

When this Committee embarked in a bipartisan effort to learn how to advance science and regulation in ways that would lead to better, healthier lives for patients, it identified – through consultation with experts around the country, including patients, caregivers, regulators and former regulators, industry, and many others – it achieved the near-impossible. It found suggestions common to many disparate stakeholders for improving the processes of basic research that are fundamental to understanding disease and treating it and for improving the processes of translating that research into real products that are safe and effective and can be made available to patients. In the latter category were suggestions that focused on improving drug development timelines through applying new tools and new ideas and encouraging and directing FDA to incorporate those into its thinking when reviewing applications.

Perhaps not surprisingly, some of these tools and ideas also came into the discussions between FDA and stakeholders in developing the PDUFA VI agreement. The skeptical might worry that such an overlap of ideas in two separate and very different contexts is a recipe for disaster. Not so. In fact, there is the best sort of overlap between the provisions of 21st Century Cures and PDUFA VI – the kind that results in each enhancing the other. A few examples, not an exhaustive list, are illustrative.

Biomarkers – a word that has, over the last two years, come into the lexicon of people who never thought of a biomarker before – are a focus both of PDUFA VI and of 21st Century Cures. The Act and PDUFA VI are complementary, in terms of ensuring that FDA has and uses effectively an efficient process for qualifying biomarkers; publishes guidance to help applicants for biomarker qualification understand the taxonomy and data standards; makes public a list of qualified biomarkers and pending applications; and engages external experts in biomarker qualification.

Patient-focused drug development – in this area as well, it is clear that there is near-universal agreement on the need to do more, and in a more systematic way, to incorporate the patient perspective into drug development and regulatory decision-making. Guidance development, public meetings, development of methods and standards for collecting information and data, and use of patient perception and experience information in the FDA regulatory decision about the benefits and risks of a drug are all elements of both 21st Century Cures and the PDUFA VI agreement.

Real-World Evidence – there is considerable overlap between the provisions of 21st Century Cures and PDUFA VI. 21st Century Cures provides helpful context for the work under PDUFA VI, and provisions of the two that differ are easily harmonized.

Innovative Trial Design – while 21st Century Cures focuses on adaptive trials and Bayesian approaches, PDUFA VI takes a broader approach, opening its pilot program to other trial designs while also highlighting adaptive trials and Bayesian approaches. Public processes, including workshops, and guidance development are parts of both.

In short, it surely is the case, looking at PDUFA VI and 21st Century Cures together, that there is broad agreement about what is needed to reduce the time of drug development.

BIO strongly supported and applauds the enactment of 21st Century Cures, as we strongly support the PDUFA VI negotiated agreement. We believe that, together, these two efforts will make a difference for patients.

BIO urges Congress to act swiftly to move the PDUFA VI reauthorization forward. This agreement, negotiated between FDA and the biopharmaceutical industry with input and support from multiple other stakeholders, positively advances our shared goal of making safe and effective treatments available to patients as efficiently and quickly as possible.

Thank you for the opportunity to present our views today. I am happy to answer any questions you may have.