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Biotechnology Innovation Organization

United States Senate

Committee on Health, Education, Labor, and Pensions

Hearing on "FDA User Fee Agreements:

Improving Medical Product Regulation and Innovation for Patients Part II"

April 4, 2017

Chairman Alexander, Senator Murray, and Members of the Committee:

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

I am Kay Holcombe, 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 user fee programs. Many of them recall the time before enactment of PDUFA I – the grandfather of FDA user fee programs - 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. That situation was changed by the willingness of Congress to work with FDA, industry, and others to determine if, and how, review times could be reduced significantly through providing for user fees to support the additional FDA staff needed to carry out more quickly the activities related to review of human drug applications.

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PDUFA I proved this could be done. 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.

The successes of PDUFA gave rise to user fee programs to achieve greater efficiency in the review of medical devices, generic drugs and biosimilars. In the history of biosimilars user fees, this Committee features prominently. You developed and took the first Congressional action on legislation that became the Biologics Price Competition and Innovation Act (BPCIA), which established the FDA biosimilars program. And, recognizing the need for user fees to support that program, you began and executed the process that led to the Biosimilars User Fee Act (BsUFA). This young user fee program has been essential to ensuring that biosimilars would be developed and, although a small number of products has been approved, we believe the program is growing and will continue to grow.

Modifications of both the PDUFA and BsUFA programs, negotiated by FDA and the biopharmaceutical industry with support and input from patient, consumer, and healthcare provider organizations and other stakeholders, are designed principally to improve efficiency, reduce administrative burdens, enhance program long-term sustainability, and ensure that 21st century tools are used to the greatest advantage in the review of new drugs and biologics and of biosimilars – while maintaining the U.S. gold standard of safety and efficacy.

The vision of these user fee agreements is also the vision of 21st Century Cures – patients come first. Key components of both BsUFA and PDUFA are designed to achieve the goal of ensuring that patients have new drugs and biologics as quickly as possible; that timely and efficient processes allow patients access to biosimilars, which expand their choices for treatment; and that focus on good communication between FDA and sponsors results in reduced development times, so unmet needs can be met as soon as possible.

PDUFA VI

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

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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.

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

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. 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. Other changes also have been supported by user fees: enhancement in the efficiency and effectiveness of FDA's 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 8 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. Our U.S. economy has benefited from PDUFA, because drug and biologic applicants now have greater certainty of a reasonable timeline for completion of their applications, facilitating and encouraging investment in new biopharmaceutical R&D and increasing the number of good-paying jobs in the biopharmaceutical industry. Most importantly, though, patients have benefited. Before PDUFA, U.S. patients legitimately could say that their counterparts elsewhere in the world had new treatments available before they did. That largely is not the case anymore.

But FDA's application review time of fewer 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 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 regulatory processes have not kept up with the advancing science.

During the lengthy period of development, 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 might reduce drug development times. How can PDUFA resources be applied to address lengthy, expensive, and risky drug development times?

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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.

The question facing PDUFA VI stakeholders and FDA was the question that faced this Committee as it embarked on 21st Century Cures: What more can be done to change the course of drug development and to reduce the time it takes to get to the 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 Cures proposals and PDUFA VI commitments that would allow these tools to be used most effectively. In both cases, the goal was to ensure more timely availability of new drugs for patients by reducing the time and increasing the chance of success of drug development.

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 staff necessary to carry out the historic commitments of this agreement.

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 through a step-wise approach, with stakeholder input.

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The goal of this process can be described as converting largely qualitative information to quantitative information that can have clear application to determining evaluating the benefits and risks of a new drug. 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 revisit 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 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 possible 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 could receive timely responses to inquiries that might 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. A public meeting will allow stakeholders an opportunity for discussion and input into the evaluator's findings.

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Using Drug Development Tools, including Biomarkers

In PDUFA VI, FDA is committed to enhancing biomarker qualification processes. A number of the PDUFA VI goals are synergistic with those of the provisions of 21st Century Cures. One of those goals is implementation of a pilot program to seek and incorporate the input of external experts to assist in biomarker qualification, to verify if the use of such outside experts can make the processes more timely and efficient. FDA also 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 and additional opportunity for drug developers to discuss their development programs with FDA.

Using Real-World Evidence

The Sentinel system, established by FDA in response to Congressional direction, is the source of enormous amounts of 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 investigation 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 all 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 potential uses of such real-world data in regulatory decision-making. One possibility is that large databases might 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

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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 may not always be the most efficient or necessary approach. With new ways of thinking, and given new approaches to statistical analysis, are there better ways to conduct 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 begin answering 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 guidances based on its findings through the workshops and in the pilot program. Modeling

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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 human drug development.

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 to 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 successful and are reducing the time of drug development.

Program Sustainability and Financial Transparency

PDUFA finances and personnel form the foundation that keeps the PDUFA program viable. Since 2002, the PDUFA program has grown at an average of 11% per year; this is unsustainable moving into the future. Changes that address the fee collection structure to increase predictability and efficiency and to reduce administrative costs for both FDA and companies will lead to a lower and more sustainable growth rate. These include reducing the volatility of fee collections, eliminating complicated collection and other financial mechanisms that are difficult to administer, improving predictability of annual total revenue collection, and reducing variation of collections year over year. 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, changing the basis for calculating annual workload adjustments, and developing a 5-year financial plan and updating annually 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.

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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 ideal 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 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 will be a significant component of planning for future resource needs, which will contribute 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 resources that will be needed to assure a continuing efficient and effective human drug review program. This modernization of the time reporting system is under way, with a third-party expert already working with the agency to determine the best approach to development and use of capacity planning.

Personnel Management

Hiring and retaining the expert staff essential to carry out user-fee-funded activities is critical for PDUFA VI to succeed. 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 compared to similar positions in the private sector. The 21st Century Cures Act, in which this Committee played a significant role, 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 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.

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 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 timely allocation of some PDUFA V resources. The hiring of these staff will continue in the first several

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years of PDUFA VI, along with hiring of additional staff essential to carry out the new performance goals of PDUFA VI.

The negotiated number of FTEs (full-time equivalents) necessary to carry out the goals of PDUFA VI is 230, hired over the 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. For the first time, hiring goals are included in the PDUFA VI Performance Goals Letter, and FDA will report on its progress in meeting these hiring goals in each year's performance report, beginning in FY 2018.

BsUFA II

Overall Goals for BsUFA II

As we did to develop our approach for PDUFA VI, BIO worked with our members to define our over-arching goals. First, we want to ensure that FDA will have the resources, including human resources, over the next five years to accomplish the objectives of the BsUFA program, including timely and efficient review of biosimilars applications and further clarification and enhancement of the processes and tools the agency uses to regulate biosimilars. Second, as forPDUFA, we want to improve the transparency, financial accountability, and sustainability of the BsUFA program. We believe the BsUFA FDA-industry-stakeholder reauthorization proposal transmitted to Congress in December 2016 meets these two goals, and we strongly support its timely enactment.

What Has Been Accomplished during BsUFA I?

To inform our thinking, we looked at what FDA has accomplished in the first four years of the BsUFA program and reviewed the third-party assessment of the costs and workload associated with activities related to the review of biosimilar applications and the development of policies and procedures to implement the new biosimilars program.

During just the first 3 years of BsUFA I, the time period examined by the independent third party, FDA held 127 biosimilar product development meetings with sponsors. As of 2015, there were 57 biosimilars development programs under way – a number that has continued to increase.

FDA has issued five final Guidance documents to assist sponsors and other stakeholders to understand some of the agency's thinking about how the new biosimilars pathway would work and about the agency's expectations regarding the kinds of studies and data that would be required for biosimilars approval. FDA also issued final Guidance on naming for biosimilars and innovator biological products. This was a particularly important document, because FDA needed to take an approach to biosimilars names that would provide clarity for prescribers and patients and assist pharmacovigilance, but not suggest, by virtue of a naming convention, that some products may raise safety or efficacy issues that do not exist.

FDA also has issued an additional five Guidance documents that remain in draft, including the recent draft Guidance regarding FDA's views on determining interchangeability. BIO has urged FDA to lay out

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its thinking on interchangeability, so we are pleased that a draft is available for public comment. We hope the agency will finalize this draft as quickly as possible after the public comment period ends. Many stakeholders believe it is crucial for FDA to explicate its expectations for the data needed to determine that a biosimilar product is interchangeable with its reference biological product, which the statute defines as a biosimilar that can be substituted for, or switched with, the reference product with no adverse impact on any given patient's clinical outcome. Such a determination, many believe, may serve to encourage greater prescribing and use of biosimilars as the availability of biosimilar products increases, provided the determination is sufficiently rigorous.

Beyond issuing these Guidance documents, FDA has committed substantial time and resources to make the pathway to approval for biosimilars viable and credible. Because of both the complexity of the products and the novelty of this category of "highly similar" or "interchangeable" products, we recognize that these early years necessarily have been a time of learning and building within the agency. And although four new biosimilars approved since enactment of the BPCIA and the initiation of BsUFA may seem like a small number, we are confident that the program – and the availability of biosimilars – will grow as the agency builds expertise and capacity.

In fact, as FDA has reported in its annual BsUFA Performance reports, and as an independent contractor also has documented, the number of meetings between FDA and sponsors planning or executing biosimilars development programs has increased substantially since the program began. As of October 2016, based on meetings between FDA and sponsors, there are 66 biosimilar development programs under way, to develop biosimilars to 20 different reference biological products. Of course we do not know what percentage of those programs will result in applications, or which applications will be approved. But the numbers certainly demonstrate the upward trend for which supporters of biosimilars have hoped.

What Can Be Accomplished during BsUFA II?

BIO worked with FDA and other industry organizations representing biosimilars developers and innovators, with input from many other stakeholders such as patient organizations and healthcare providers, to develop detailed proposals for continued progress and enhancements during BsUFA II. These proposals are encapsulated both in the legislative language proposed to this Committee and in the Biosimilar Biological Product Authorization Performance Goals and Procedures for Fiscal Years 2018 through 2022. Among the commitments included in the BsUFA Goals Letter are the following.

<u>Review Timelines</u>

First, FDA agrees to meet defined timelines for its reviews and decisions regarding biosimilars applications. Specifically, for 90% of original applications, a decision will be made within 10 months of the date on which the application is officially accepted for review by the agency. How well FDA does in meeting this timeframe, like others for re-submitted applications and supplements, will be reported annually and publicly by the agency. These goals mirror those of the PDUFA program.

<u>Meeting Management</u>

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FDA-sponsor meetings before an application is submitted have been a key part of BsUFA and an essential component of a concerted effort to stand up this new program. These are formal opportunities for sponsors to discuss their development plans and approaches with the agency reviewers and receive technical assistance regarding ways to proceed that will give the development the highest chance of success. Under BsUFA I, there was agreement that user fees would be associated with these meetings; that will continue under BsUFA II. It is a long-term goal we share with FDA that these Biosimilar Product Development meeting fees eventually will be phased out, based on the agency's ability to meet its annual target revenue for the BsUFA program, and to meet its performance goals, with fees assessed on biosimilars applications and products – as is the case in the PDUFA program. This will require a more significant increase in the number of applications and products than is expected over the next five years.

Some enhancements to the formal meeting processes also are among the performance goals for BsUFA II. These have the purpose of ensuring that requirements for both FDA and sponsors, in terms of response times, meeting times, and documentation, are reasonable to allow for the best and most productive meetings and the most timely and useful advice for sponsors.

New Review Program

A new approach to the review of biosimilars applications will be implemented during BsUFA II, modeled after the "new NME" Program of PDUFA. The goal of this Program is an increase in the number of first-cycle approvals – saving time and money for sponsors and, importantly, making approved products available to patients as efficiently as possible. The Program provides applicants with new opportunities, during the course of the review, to receive updates and advice from FDA about how the review is proceeding and what additional information might be needed. If there are questions or concerns, the applicant will have a chance and the time to respond – avoiding last-minute problems that cannot be resolved adequately in the time remaining before the BsUFA deadline.

Based on an independent third-party review, the PDUFA new NME Program has been highly successful in the view of both the FDA and sponsors. Importantly, this approach has achieved its intent to increase the number of first-cycle approvals. In short, this means there is a higher chance that an application entering FDA in month one will exit, approved, in month 12. The chance that the 12-month timeline will be extended, or that the application will need to be submitted for a second review cycle, is greatly reduced.

The expectation for BsUFA II is that results will mirror those that have been seen for new drug and new biological license applications. In other words, more and more productive communication between FDA and sponsors will lead to less overall time to product approval.

Under the new Program, the applicant is encouraged to meet with the FDA review team to discuss the content of the planned application in advance of the submission. Once the complete application (as agreed at the pre-submission meeting) is accepted for review by the agency (60 days), a 10-month count-down begins. At approximately mid-cycle, FDA will arrange a mid-cycle meeting with the applicant – in most cases by telephone – during which appropriate review team members will update

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the status of the application and identify any concerns or questions, discuss the review team's thinking about possible post-market requirements, and provide the applicant with upcoming milestone dates such as advisory committee meetings. If an advisory committee is planned, it will be scheduled at least two months before the end of the 10-month review time.

A second, late-cycle meeting will be held no later than 12 days before any planned advisory committee meeting. At this meeting – usually a face-to-face meeting – FDA and the applicant will discuss any major deficiencies in the application, the agency's views on the submitted data and any additional data that may be needed, manufacturing issues, inspectional findings, any proposed post-market requirements, and any issues FDA plans to raise with the advisory committee. This timeframe will provide the applicant more than two months before the BsUFA goal date to work with FDA to resolve outstanding issues – a meaningfully longer time than frequently was the case previously. If there is no advisory committee planned, the late-cycle meeting will occur no later than three months before the BsUFA goal date.

The establishment of this new review approach is significant for several reasons. First, it provides clear, guaranteed, important opportunities for applicants to know what is happening with their reviews – in a timely way that allows them to have meaningful input and an opportunity to address problems and concerns. Second, it provides timeframes for various steps in the review process that are publicly reportable through FDA's BsUFA annual Performance Reports. While we expect that this Program will be as relevant and helpful as it has been in PDUFA, it is critical that, given the inherent differences between the development and approval processes for new biological products and biosimilars, an independent third-party evaluation of this new biosimilars review program be undertaken. The Goals Letter lays out specific components of the evaluation. The evaluator will look not only at how the program is working and whether it is achieving its aim of more first-cycle approvals, but also at the question of whether and to what extent the earlier Biosimilar Product Development meetings, for which applicants also pay user fees, could have or should have identified issues that subsequently may be raised at a mid-cycle or late-cycle meeting during the review. The third-party evaluator will submit both an interim and a final assessment of the program, by the end of 2020 and by June 2022 respectively. These reports will be published for public comment, and public meetings will be held on each.

Guidance

Stakeholders across the spectrum agree that timely and substantive guidance, particularly in this new program area and for this new approval pathway, is essential to the success of the program. The lack of Guidance leads to uncertainty and missteps that limit or delay the availability of new safe and effective products for patients. Guidance that remains in draft for lengthy periods of time has the same effect. Thus, it is important that goals be set under BsUFA II not only for the issuance of new Guidance that explains FDA's perspectives in general, as well as with respect to specific biosimilars products or types of products, but also for the finalization of Guidance already issued in draft. Those goals are laid out clearly in the Goals Letter. While meeting these goals – a key publicly reportable user fee commitment – FDA also needs to ensure that the public has ample opportunity to comment on draft Guidance and that such public comment is taken into account in the finalization of any Guidance.

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In addition, the Goals Letter provides FDA's commitment to revise and update the Good Review Management Practices Guidance and general guidance relating to processes, procedures, and timelines for meetings between FDA and sponsors, both of which apply to NDAs and BLAs, to include and specifically reference biosimilars.

Finally, the Goals Letter includes FDA's commitment to continuing to clarify the biosimilars review pathway and provide information important to sponsors of both biosimilars and innovator biological products. This includes, for example, revision or re-issuance of Guidance relating to the so-called "transition" products; harmonization of varying definitions of "biological product;" and updating of the "Purple Book" with information including the date of first licensure of potential reference biological products.

Program sustainability and Financial Transparency

BsUFA will benefit from the modernized time reporting and new capacity planning efforts that are also part of the PDUFA VI goals, as these changes are being implemented across the Centers for Biologics (CBER) and Drugs (CDER). By statute, FDA staff who conduct the activities related to the review of biosimilars applications are the same as those who review applications for approval of new drugs and new biological products. Therefore, modernized time reporting will be as useful for determining resource needs for BsUFA as for PDUFA. Modernized time reporting will provide data that are much more accurate than currently available about the time and resources required to complete the various tasks associated with application review. In addition, the modernized system will ensure accurate allocation of time and resources to BsUFA activities and to PDUFA activities.

Having this information also will allow FDA, for the BsUFA as for the PDUFA program, to plan for the capacity necessary to meet the needs of future years.

To assist in the development of a capacity planning function, an independent third party will evaluate various options and make recommendations regarding the best ways for FDA to assess its resource needs on an ongoing and forward-looking basis, for all CDER and CBER review-related activities. The specific tasks associated with the review of biosimilars applications will be built into this assessment. As with all other BsUFA and PDUFA reports and assessments by FDA or by independent contractors, this evaluation will be public, and public comment will be invited and taken into account.

By the second quarter of 2018, FDA will publish an implementation plan for establishing and utilizing a capacity planning function and modernized time reporting, which will include biosimilars review activities specifically.

These activities provide confidence to fee payers and other stakeholders that there is a sound basis on which target revenues and fee amounts are calculated. It has been especially difficult to predict the amount of funding needed for BsUFA, because this is a new-to-the-U.S. industry without a history of development times or application submissions. This will change with time, but until then, the perspectives of experienced independent experts will be essential.

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FDA also will include BsUFA resource management in the scope of work for the contractor that will evaluate PDUFA resource management. This evaluation will include an assessment of how the BsUFA program is administered, how the user fee funds are allocated and used, and what changes might be made to improve the governance of the program.

These activities, including the more accurate resource assessments that will be possible from modernized time reporting, will allow FDA to establish an independent BsUFA user fee structure. While elements of the PDUFA structure that enhance financial management will apply, BsUFA will have its own fees not necessarily based on PDUFA fees.

Personnel Management

FDA's well documented hiring difficulties are problems for BsUFA as for PDUFA. Neither of these programs can work without a strong, capable, and skilled FDA that can make timely and science-based decisions in the interest of patients and the public health. We appreciate this Committee's efforts, working with the House Energy and Commerce Committee and many other Members of the House and Senate, to include changes in the 21st Century Cures Act that will greatly benefit FDA's hiring capabilities. These changes will provide FDA with some key authorities that it needs to attract the highly educated, experienced, and talented individuals we all want to see working on our applications for approval.

Process improvements are under way already at FDA. Both the BsUFA II and the PDUFA VI agreements include a commitment that FDA will contract with third parties to help implement new processes and to evaluate on an ongoing basis the progress the agency is making. Because all the reviewers in the BsUFA program also are PDUFA reviewers, it is crucially important to the success of the biosimilars program for FDA to meet the significant hiring goals under PDUFA. Even more important is for the agency to put in place sustainable and durable processes and procedures, so this hiring is not merely a five-year surge, but is a lasting approach that keeps FDA staffed at the level it requires to do its job.

Importantly, all of the activities that will be and already are being undertaken to improve the hiring situation will be public. We all will be able to see the assessment of the third-party evaluator, consider any recommendations, and provide comments to FDA. We also will be able to see the numbers. We do not want FDA to fall behind its hiring goals, because we know that the user fee commitments we rely on cannot be met unless the people are there to meet them. Annual hiring goals are included in the BsUFA agreement as they are in the PDUFA agreement~~,~~ and the public will be able to see in the annual Performance Reports whether these goals are being met. We want to see what is happening so we can work with this Committee and FDA to help stop any downward trend. We believe we share this goal with stakeholders across the spectrum.

In discussing FDA hiring, I also want to reiterate BIO's longstanding views on the potential negative consequences that arise from the sequester of user fee funds or hiring freezes that can result in FDA's inability to fill vacancies and make new hires that are necessary for meeting its commitments under PDUFA and BsUFA – or, in general, for carrying out its crucial public health responsibilities. User fees paid by biosimilars applicants and by applicants for new drug and new biological product approvals support a significant number of FDA personnel. In particular, they support the staff identified to carry

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out the program performance goals. If FDA is unable to make these hires, user fees cannot be spent. This is a situation that is not good for fee payers, for FDA, or for patients who are waiting for approved therapies.

To summarize our views on the financial and hiring enhancements of PDUFA VI and BsUFA: BIO believes they are on target and essential to ensure both the long-term viability of these important user fee programs 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 user fee goals and carry out its public health mission.

BIO strongly supported and applauds the enactment of 21st Century Cures, as we strongly support the PDUFA VI and BsUFA II negotiated agreements. These efforts will make a difference for patients.

BIO urges Congress to act swiftly to move the PDUFA VI and BsUFA II authorizations forward. These agreements, negotiated between FDA and the biopharmaceutical industry with input and support from multiple other stakeholders, positively advance our shared goal of making safe and effective treatments available to patients as efficiently and quickly as possible. We shortly will provide a letter expressing our strong support for timely enactment of the PDUFA and BsUFA reauthorizations.

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

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