BIO PDUFA V Public Statement

April 12, 2010

On behalf of the Biotechnology Industry Organization, I thank you for the opportunity to comment in support of the reauthorization of the Prescription Drug User Fee Act and discuss how we can ensure achievement of the goals envisioned under PDUFA, and make further refinements toward that end.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

Innovation in health care - including new therapies, vaccines and diagnostics - has been and will continue to be central to an improved health care system and a key driver of economic progress. Biotechnology has created more than 200 new therapies and vaccines, including products to treat cancer, diabetes, HIV/ AIDS and autoimmune disorders. There are more than 400 biotech drug products and vaccines currently in clinical trials targeting more than 200 diseases. Recognizing that a reliable, science-driven regulatory environment fosters innovation, promotes economic competitiveness, and maintains high patient confidence in the integrity of medicines, BIO member companies have supported a carefully structured user fee program to help fund FDA's human drug review activities.

I. PDUFA HAS BEEN A SUCCESS, BUT SHOULD BE CRITICALLY EVALUATED:

PDUFA has been widely credited as an innovative program that has strengthened FDA's capacity to evaluate expeditiously and efficiently the safety and effectiveness of new drugs and biologics, thereby making needed new safe and effective therapies available to patients in a timely and responsible fashion. Congress enacted PDUFA to provide FDA with multi-year resources, additive to its annual Congressional appropriations, to increase its review capacity, including new medical and scientific expertise, so the agency could become more efficient while continuing to employ the highest standards of empirically based product evaluation.

Since its inception in 1992, PDUFA has helped enable FDA to approve more than 1,200 new medicines and reduced review times for innovative drugs and biologics, providing patients and doctors with earlier access to breakthrough treatments. In fact, the median review time for Priority Review products – the greatest public health breakthroughs – has been cut from more than a year to 6 months; for Standard applications, review time has been reduced from almost two years to 15 months.[i,ii] While overall the PDUFA program has been successful, there have been recent slippages in FDA's performance which deeply trouble BIO's membership.

Through subsequent reauthorizations of PDUFA, the user fee program has been refined further to help achieve a full lifecycle approach to product evaluation. To help promote biomedical innovation, industry user fees are intended to provide FDA resources necessary to meet with Sponsors and provide scientific and regulatory advice during clinical development. Under PDUFA IV, industry reinforced its commitment to drug safety and strongly supported an increase in user fees and the application of user fees to enhance and modernize FDA's post-market safety and pharmacovigilance activities.

As we look ahead to the upcoming reauthorization of PDUFA, PDUFA V, we must critically evaluate the program. Have drug application reviews become more efficient? To what extent have the user fee program and user fees contributed to that? Have there been unintended consequences that may have undermined the original intent of the program? For example, are PDUFA review goals successfully speeding new medicines to patients or are the goals simply workload management tools? Why have significantly increased investments in the PDUFA program in recent years realized only marginal enhancements in the drug review program? The dramatic successes of the earlier years of PDUFA have not been seen in the recent past.

A. <u>The Appropriate Role of User Fees:</u>

Before considering changes to the PDUFA program as part of the reauthorization process, it is important to discuss the appropriate role and fundamental limitations of a user fee program and what can and cannot be addressed through the PDUFA commitment letter.

First, we must reinforce that PDUFA is about providing additive resources to hire staff for human drugs and biologics review to promote efficient performance management and application review processes. PDUFA is not about revisiting FDA policy or revising FDA's review standards.

Second, better managed human drug review processes, such as the use of performance metrics, have improved timely patient access to new therapies without compromising FDA's vigorous safety and efficacy standards. It is commonly said that you get what you measure and we believe that the continued utilizations of PDUFA performance metrics will track ongoing program progress and ensure accountability and transparency to the public. The user fee program supports FDA's ability to make a science-based, empirical judgment in an appropriate timeframe, and in no way pre-supposes the outcome of that product review - whether it be an approval or complete response letter.

Third, user fees by definition are fees paid by the user for the benefit of the user. The Office of Management and Budget defines a user charge as a fee "assessed against each identifiable recipient for special benefits derived from Federal activities beyond those received by the general public" that "enables the beneficiary to obtain more immediate or substantial gains or values (which may or may not be measurable in monetary terms) than those that accrue to the general public" including receiving "a license to carry on a specific activity or business."[iii] Biopharmaceutical companies pay application, establishment, and product fees because they benefit, as does the public, from more efficient reviews, timely scientific advice, and ongoing product evaluation. Newer medicines are increasingly more complex and FDA needs the appropriate level of scientific training and review quality to fully evaluate the benefit and risks of the product. This ultimately benefits U.S. patients by making decisions on applications earlier and allowing for safe and effective drugs to be made available to the American public in a timely manner. The larger mission responsibilities of FDA, to ensure and improve the public health for the benefit of all citizens, should be funded by the agency's appropriations, not by a specific part of the FDA-regulated industry.

B. <u>There should be Greater Balance between Appropriations and User Fees:</u>

User fees were never intended to supplant a sound base of FDA appropriations. BIO continues to be concerned that the appropriated base of the human drug review program has not kept pace with FDA's needs and workload. In fact, in FY08 - the latest data available - two-thirds of the overall cost of human drug review was supported by industry user fees.[iv] This overreliance on funding collected from the industry FDA regulates undermines public confidence in the agency's objectivity and creates the misperception that FDA is beholden to the industry it regulates. In the long-term, this perception is not in the best interest of patients, biopharmaceutical innovators, or FDA.

The solution to this is to increase FDA appropriations for human drug review to meet the agency's program needs. We applaud Congress for recognizing the importance of the FDA and increasing the Agency's budget by nearly $1 billion over the last three budget cycles, but respectfully suggest that even with that increase, funding is still not adequate to assure FDA has sufficient resources to carry out effectively its continually increasing responsibilities. We look forward to working with Congress to ensure that FDA receives additional appropriated funding so that the agency can keep pace with the swift pace of biomedical scientific discovery, modernize its regulatory tools and scientific capacity, and respond to the challenges of regulating in a globalized economy. In part, our work to achieve that goal will be done in conjunction with and as a founding member of the *Alliance for a Stronger FDA*, a coalition of 180 organizations representing patient groups, consumer advocates, medical societies, and regulated industries.

While BIO continues to support increased FDA appropriations, we also believe that FDA should justify how increases in resources have contributed to advancing the Agency's public health mission. To demonstrate that FDA has been a responsible steward of both industry user fees and public appropriations, we urge that FDA transparently document how funds have been allocated internally and clearly explain the performance gains and public health improvements achieved through these increased funds. For example, between FY07 and the proposed FY11 budget,

PDUFA user fees have more than doubled from $320 million to $667 million and appropriated budget authority for the Human Drugs Program has increased by almost $170 million.[v] How have these increased resources been distributed within the Agency and the Office of New Drugs and what measurable increases in FDA performance have been achieved with this funding?

II. PDUFA V REAUTHORIZATION:

BIO supports reauthorization of PDUFA, but believes that future modifications to the program must be justified by robust data.

C. It is Premature to Evaluate Fully the Progress of PDUFA IV:

At this time, we are only halfway through PDUFA IV. It seems premature to evaluate the changes made in the last reauthorization since there are only limited data available on which to base an evaluation. Application cohorts have not yet fully matured, PDUFA Financial and Performance reports have not been publicly released, and the accelerated timing to begin consideration of PDUFA V means application review data and other performance metrics are available for only 2 years rather than the 3 years on which previous reauthorizations were based.

Although FDA's Performance reports have not yet been published, preliminary data that has been publicly released by FDA suggests that the Agency has been struggling to meet its PDUFA goals. In FY08 FDA fell far short of the 90% application review goals, even for products representing significant public health advances. For example, FDA acted on only 60% of Priority NMEs/New BLAs within 6 months and 71% of Priority NDA/BLAs.[vi]

This drop in performance may be due in part to a lag in recruitment that coincided with additional workload from FDAAA implementation. Over the last two years, PDUFA IV provided FDA with the resources to hire 760 new CDER staff, including 193 for OND.[vii] However, it takes 18-24 months to recruit, train, and integrate a new reviewer into the division. Before FDA could fully staff-up, the Agency was required to take on significant new responsibilities and mandates as part of FDAAA implementation.

Consequently, OND opted to triage their workload and granted reviewers permission to disregard certain PDUFA commitments. By the summer of 2009, an average of 25 applications per month was overdue, up from the low single digits in early 2007. While FY08 and FY09 data may not be representative of the full potential of a revitalized human drug review program with increased staff and resources, BIO is deeply troubled by the current trend lines and we note that this clearly illustrates the difficulty of evaluating the program with a limited data set. We recognize that as with any large organization, periods of significant growth and excessive workload can contribute to organizational disruption and decreases in efficiency and these factors be carefully considered when considering future regulatory changes. However, the dependability of FDA's good faith adherence to the established performance goals is one of the critical underpinnings to sustaining the PDUFA program.

D. BIO PDUFA Survey:

To generate additional information to inform the reauthorization process, BIO surveyed its membership to collect information about their experiences under PDUFA IV and identify areas for improvement or refinement under PDUFA V. 67 BIO member companies participated in the survey - a strong indication of the high level of importance attached to this topic - and represented an equal cross section of BIO's large, medium, and smaller companies. First, the bad news – when asked if the performance of the FDA human drug review program has increased, decreased, or remained the same since the start of PDUFA IV in 2007, 53% of respondents indicated that FDA's performance has decreased, while only 11% have seen improvements.

The survey further identified several areas where there may be room for future improvement and opportunities to fully integrate new FDAAA statutory requirements into the drug and biologics review and evaluation process. For example:

- Risk Evaluation and Mitigation Strategies (REMS): One of the most significant changes under FDAAA was the codification of Risk Evaluation and Mitigation Strategies (REMS). Best practices have demonstrated that it is critical that FDA and Sponsors have a common understanding of when and how Sponsors should communicate with FDA regarding a potential REMS and how that discussion should be integrated into the review process. However, 81% of respondents with a REMS reported that FDA did not initiate risk management discussions early enough in the review cycle and 77% reported that the REMS discussion contributed to a review extension. BIO believes it is important to update the Good Review Management Principles and Practices (GRMP) documents so that REMs, Post-market Requirements (PMR), and other FDAAA-related discussions occur earlier in the review process.

- OND/OSE Interaction: Multiple review cycles caused by REMS may be in part symptomatic of sub-optimal internal communication at FDA. For example, 61% of survey respondents reported inadequate coordination between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) during product reviews. FDA needs to utilize a clear and efficient escalation and decision making process with a well articulated and transparent method for individuals who have differing opinions to voice their concerns so that FDA managers can make a decision based on the available scientific data. We would also like to better understand the interactions between OND and the OSE and how differing safety interpretations are resolved both internally and with external stakeholders. For example, prior to a public communication, FDA should share confirmatory analyses and study methodologies with the Sponsor so that the company can fully understand the scientific context of the safety signal, and further evaluate it, if necessary.

- Meetings and Scientific Dialogue: Meetings and communications between FDA and companies early in the development/review process is crucial to the advancement of new cures. In fact, a 2008 independent analysis by Booz Allen Hamilton found that early and frequent FDA-Sponsor communication contributes to higher first cycle approval rates,

which can reduce FDA's overall resubmission workload.[viii] BIO members value the opportunity to meet with FDA staff to engage in technical expert-to-expert scientific dialogue, yet more than half of survey respondents (52%) indicated that requested meetings are not being granted on a consistent basis. Of those reporting difficulty with meetings, 71% reported being denied an entitled Type B meeting and 74% were denied a Type C meeting. We hope to work with FDA, during PDUFA V discussions and elsewhere, to identify and minimize barriers to granting formal meeting requests and to also encourage opportunities for informal scientific and technical dialogue.

- Good Review Management Principles and Practices: FDA drug and biologics review processes can be inconsistent across different review divisions. For example, review divisions appear to have differing informal criteria for meeting with Sponsors, requesting clinical data, and interacting with Sponsors during the review process. This can lead to difficulty anticipating FDA regulatory expectations and uncertainty for Sponsors. We are pleased to see FDA managers implementing the Agency's Good Review Management Principles and Practices through the *21st Century Review Program* and establishing timelines and milestones for certain Sponsor-FDA interactions. Although only a handful of applications have been reviewed under the *21st Century Review Program*, survey respondents reported that FDA provided a timeline of review milestones 57% of the time, but managed to successfully meet those milestones only 40% of the time. We encourage FDA to continue to fully implement and adhere to the *21st Century Review Program*, which will encourage greater consistency and predictability in the review process as part of a clear and transparent regulatory decision making process.

- Advisory Committees: BIO supports FDA's efforts to recruit the best available external scientific expertise to serve on FDA Advisory Committees. However, we are concerned that under new conflict of interest policies and the FDAAA waiver cap, FDA has not been able consistently to recruit advisors who have the requisite breadth and depth of expertise that is necessary to provide the best possible advice. In fact, 56% of survey respondents indicated that FDA was unable to recruit highly qualified experts to provide scientific advice on advisory committees. This is particularly troubling for the biotech industry because the available pool of qualified experts can be small in certain high-tech areas or rare diseases.

CONCLUSION:

Thank you again for the opportunity to present BIO's views on the state of the PDUFA program. BIO looks forward to working with FDA and other stakeholders to achieve full realization of the goals of PDUFA.

REFERENCES:

[i] FDA, "FY2008 PDUFA Performance Report", http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm *(web post pending)*

[ii] FDA, "White Paper Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications", http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119253.htm

[iii] Office of Management and Budget (OMB), "Circular A-25 Revised", http://www.whitehouse.gov/omb/circulars_a025/

[iv] FDA, "FY2008 PDUFA Financial Report", http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/PDUFA/default.htm *(web post pending)*

[v] FDA, "FY11 Congressional Budget Justification", P. 41, P.110, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM199447.pdf

[vi] FDA, "FY2008 PDUFA Performance Report", http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm *(web post pending)*

[vii] John Jenkins, M.D., Director, Office of New Drugs, FDA, "New Drug Review: 2009 Update", FDA/CMS Summit, December 3, 2009.

[viii] Booz Allen Hamilton, "Independent Evaluation of FDA's First Cycle Review Performance – Final Report", July 16, 2008, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127117.htm