BIOTECHNOLOGY INDUSTRY ORGANIZATION

1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2011–N–0326: Biologics Price Competition and Innovation Act of 2009 (BPCIA); Options for a User Fee Program for Biosimilar and Interchangeable Biological Product Applications for Fiscal Years 2013 Through 2017

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments relating to the development of a user fee program for biosimilar and interchangeable biological product applications submitted under subsection 351(k) of the Public Health Service Act (PHSA). BIO supports the development of a well-constructed pathway for the approval of biosimilars, and acknowledges the Agency's request for comments on this matter as another important step in developing a transparent and effective regulatory framework for the review and approval of biosimilars.

BIO represents more than 1,100 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, sustainable agriculture, and a cleaner and safer environment.

As a general matter, BIO agrees with FDA's statements in the May 10, 2011, Federal Register Notice (Notice) that existing user fee programs can inform the Agency's development of a user fee program for 351(k) applications, and that the establishment of user fees for products subject to the 351(k) pathway also presents unique challenges compared to existing programs. Below, we address FDA's proposed principles for development of a biosimilars user fee program, as well as FDA's proposed structure for this program.

I. FDA'S PROPOSED PRINCIPLES FOR DEVELOPMENT OF A BIOSIMILARS USER FEE PROGRAM

As discussed in BIO's December 23, 2010, comments to FDA on the biosimilars regulatory pathway, BIO recognizes that 351(k) applications will raise novel and complex questions of science and law, requiring substantial time, expertise, and additional resources to ensure a thorough regulatory review. BIO believes that one of the principal goals of this new user fee program must be to ensure that workload associated with biosimilar applications does not harm the Agency's ability to efficiently review innovative drugs and biologics under subsection 351(a) of the PHSA, and that new treatments – many for currently untreatable and serious diseases – continue to have the highest review priority. Accordingly, we agree with FDA's principle that the Agency needs sufficient review capacity for 351(k) applications to assure that resources are not redirected from 351(a) reviews.

In the proposed 351(k) user fee principles, FDA states that the Agency's "services are most critical for continued and successful development of biosimilar and interchangeable biological products during the investigational stage prior to submission of a marketing application." Given that the expert scientific teams that review BLA applications will engage in reviews of biosimilar applications, it is unclear how FDA will ensure that critical resources will not be diverted from innovator product development support to biosimilar products. Further, given that there will be a time delay before user fees are collected and full-time-equivalents (FTEs) can be hired and trained, it is important that FDA address this interim resource issue. From a budgetary perspective, it also is critical that FDA establish mechanisms and processes to ensure that user fee resources, appropriations, and overall FTE headcounts are not diverted from innovator review programs, such as new drug and biologics review, to fund biosimilar activities in the event of a program funding shortfall.

In addition, to ensure that limited Agency resources are directed only to those applications that are in full compliance with the statutory requirements, we propose that FDA institute a compliance mechanism as part of the 351(k) marketing application acceptance process. As stated in our December 2010 comments, BIO members believe that FDA should require that the subsection (k) applicant formally certify that it has or will comply with the BPCIA provisions requiring the biosimilar applicant to timely share its BLA and manufacturing process information with the reference product's sponsor.[1] Specifically, we urge the Agency to require 351(k) applicants to certify that they will provide a copy of their application and manufacturing information to the reference product sponsor, as required by the BPCIA.[2] Such a mechanism will help to ensure that any patent disputes that may impact the marketing of a biosimilar can, consistent with Congressional intent, be resolved efficiently, while also facilitating the Agency's prerogative to devote its resources to those applicants that are complying with the statute in good faith, rather than using limited resources on those that might be subject to late-stage patent litigation because of a 351(k) applicant's refusal to comply with the statute's mandatory provisions.

More broadly, there are a number of advantages to drawing upon established precedents under the current FDA user fee programs when creating a new system for biosimilar applicants.

[1] http://bio.org/reg/20101223.pdf
[2] Subsection 351(l)(2) of the PHSA.

Specifically, BIO proposes that FDA incorporate the following elements from existing user fee programs:

- Transparent fee rates published in the Federal Register grounded by reasonable cost estimates of FDAs resource needs and workload.
- Annual fee adjustments for inflation and workload.
- Pre-determined definitions and triggers to ensure that fees are spent on biosimilar applications and not re-directed to unrelated FDA or other government activities.
- Transparent review management processes, publicly reported metrics and annual reports to track program performance and finances.
- Sunset of the program at specified intervals to provide an opportunity to make course corrections and other related improvements.
- Funding of post-market monitoring from user fees.

FDA proposes a basic principle unique to this biosimilars user fee program – that 351(k) user fees be used to support Agency activities that occur early in the biosimilar and interchangeable product development cycle. BIO agrees that these investigational stage activities are critical to support marketing applications and that early funding can enable sufficient Agency resources to focus on the scientific, technical and other regulatory activities associated with this stage. However, as discussed below in section II, BIO proposes an alternative to the Agency's proposal that this fee be paid at the time of submission of an investigational new drug application (IND).

FDA's Notice states that the same expert scientific teams that review 351(a) applications will typically be involved in the review of 351(k) applications. In BIO's January 10, 2011, letter to FDA, we noted in this regard that the development of a fair, efficient, and adequately resourced process for evaluation of biosimilars is of importance to both innovators and biosimilar manufacturers. Given the use of the same FDA Division, however, it is critical that FDA clearly define the process for review of 351(k) applications to assure protection against disclosure of trade secret/confidential information from a reference BLA, and that approval of a 351(k) application does not rely on any data or information from the reference BLA that is not publicly available. These are aspects of FDA's implementation of the 351(k) pathway that are critically necessary to maintain incentives for innovation and discovery of new biological medicines and to minimize legal challenges to the approval of biosimilars. As discussed in detail in BIO's December 23, 2010, comments, the following Agency actions are warranted:

- Technical correction of FDA's disclosure regulations to harmonize with the BPCIA, reflecting the current view that biologics application information is competitively sensitive.[3]
- Adoption of appropriate and transparent policies by FDA to protect against any direct or indirect disclosure of information contained in a reference product BLA to any third party. These policies should address meetings and other communications with 351(k)

[3] Currently, 21 C.F.R. Section 601.51(e) provides that information in a biologics application is available for public disclosure "unless extraordinary circumstances are shown." Despite FDA's current practice – which we understand is to *not* release biologics application information – it is important that FDA update this regulation, as it reflects FDA's view in the 1970s that it was not possible for an applicant to reference a previously-approved biologics application.

applicants or prospective applicants, as well as review mechanisms to prohibit indirect or inadvertent disclosures. For example, the asking of informed questions of biosimilar applicants by FDA reviewers that would reveal proprietary information from a reference BLA should not be permitted. FDA also should ensure that personnel discussing a proposed preclinical or clinical development program with a biosimilar applicant do not base their advice – even inadvertently – on protected information in the reference product sponsor's file.

- Adoption of appropriate and transparent policies by FDA to assure that approval of a biosimilar is based upon the information contained only in the 351(k) itself, and not on any information in the reference BLA. While the BPCIA provides for a biosimilar applicant's inclusion of publicly available information about a reference biologic to support its 351(k) application, it does not provide for reliance by Agency reviewers on any non-public information from the reference BLA, or allow BLA information to substitute in any way for the data and information required for approval of a 351(k) application. Instead, the Agency is limited to considering the "information submitted in the application (or the supplement)," which includes only publicly available information regarding FDA's prior finding that the reference product was safe, pure, and potent.[4] Considering confidential trade secret information in the reference product file, even inadvertently based upon a reviewer's past experience with the reference product molecule, would be inconsistent with decades of Agency policy,[5] would violate federal law,[6] and would raise serious constitutional questions under the Takings Clause.[7] Further, as BIO has urged previously, a 351(k) applicant should be required to formally certify to FDA that it has provided or will provide the 351(k) application and manufacturing information to the reference product sponsor as a condition for acceptance of the subsection 351(k) application for review. BIO urges FDA also to ensure that such a certification is required if an application is switched from a 351(a) application to a 351(k) application.

BIO encourages FDA to propose such policies for public review and comment as soon as practicable, so the Agency's implementation of a biosimilars pathway and review of 351(k) applications can proceed in a fair, transparent, and consistent manner.

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[4] Subsections 351(k)(3)(A) and (k)(2)(A)(iii) of the PHSA.

[5] *See* Letter of Steven K. Galson, M.D., M.P.H., Director, CDER, to BIO, Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP, Stephan E. Lawton, Esq., and Stephen G. Juelsgaard, Esq., at 37 (May 30, 2006) (stating that review and approval of the Omnitrope 505(b)(2) application "did not require use or disclosure of trade secret or confidential commercial information, and therefore is consistent both with the appropriate use of section 505(b)(2) of the Act and with the protection of trade secret and confidential commercial information").

[6] *See* 18 U.S.C. §1905; *Tri-Bio Laboratories, Inc. v. United States*, 836 F.2d 135, 141 n.7 (3d Cir. 1987) (stating that the Federal Trade Secrets Act prohibits FDA disclosure of "application data"); Letter from Mark Raza, Associate Chief Counsel, FDA, to William C. Brashares, Esq. & Kate C. Beardsley, Esq., Counsel to Biogen, Inc., at 1 (Sept. 11, 1996) (stating that the "Trade Secrets Act, 18 U.S.C. 1905, prohibits FDA from publicly disclosing any trade secrets or confidential commercial information in the [BLA] file").

[7] U.S. CONST. Amendment V (". . . nor shall private property be taken for public use, without just compensation."). While the statute permits FDA to rely on its public finding of safety and effectiveness 12 years after first licensure of the innovative product, this was balanced by new protections for the innovator, including the pre-market patent litigation process. Deviation from the statutory compromise would raise legal issues under *Ruckelshaus v. Monsanto*, 467 U.S. 986 (1984) and *Nollan v. California Coastal Commission*, 483 U.S. 825 (1987), among other cases.

II. FDA'S PROPOSED STRUCTURE AND FEES

FDA's Notice proposes that the biosimilar user fee program be composed of four distinct fees, the first of which would be a product development fee, to be paid upon submission of an IND. While, as stated above, BIO supports the proposal to collect fees in the product development phase as a transitional program, we believe a fee collected upon FDA's review of the analytical and other pre-clinical data – prior to IND submission – would better serve to support FDA's activities relating to early-stage development of biosimilars.

- PRODUCT DEVELOPMENT FEE

Under FDA's proposal, a "product development fee" would be paid initially upon submission of an IND and annually thereafter until the filing of a 351(k) application. A "marketing application fee" equal to that associated with a 351(a) BLA then would be assessed, reduced by the total amount already paid during the product development stage. However, FDA's proposal acknowledges that key activities would occur during early product development, including "characterizing biological products for the purpose of determining biosimilarity …," and that the 351(k) user fee program should provide funding to support such activities. It is BIO's understanding that a considerable portion of such activities would occur in the pre-clinical stage, prior to the filing of an IND.

Activities such as characterization and evaluation of analytical data to support biosimilarity more often than not would be undertaken prior to the submission of an IND. Indeed, if analytical data would not support a finding by FDA of "highly similar," the standard in the law, it seems unlikely that a sponsor would proceed to clinical development. In such cases, no IND would be submitted. FDA itself has recognized that the Agency undoubtedly would be involved in substantial interaction with potential biosimilars sponsors and in significant analytical work early in development, almost certainly prior to submission of an IND. If, however, no fees are paid until IND submission, what funding will support FDA's activities in this arena? We suggest considering other options to enable collection of fees prior to the clinical trial stage, rather than waiting for IND submission to collect fees. For example, FDA could assess the Development Fee at the time of the Agency's first meeting with a potential biosimilars sponsor at which the sponsor is discussing, and the Agency is providing consultation on, pre-IND information and analyses. Such discussions may lead to Agency review of data and analyses related, for example, to characterization, which may then be a precursor to filing an IND, or, if they do not show high similarity, could lead to a decision not to pursue the development program further or to delay an IND filing. In such a situation, however, the Agency nevertheless has expended substantial resources in advance of IND filing, or in the event that an IND is not pursued.

In regard to FDA's proposal to assess a fee upon submission of an IND, *per se*, we suggest that, if the IND-associated fee is determined to be the appropriate approach, two points are essential. First, it must be clear that the collection of a user fee with IND submission is unique to this particular situation – namely, where there is no established industry, no facility base, and no product base to form a stable funding source for activities that occur before submission of applications. The assessment of a fee with the submission of an IND, and annually thereafter based on that submission, would be unique to this situation and should not establish any precedent for IND fees under the Prescription Drug User Fee Act (PDUFA) program. Second,

any IND-associated fee should sunset permanently in FY 2018 – when both PDUFA and this new user fee program would sunset – or sooner if an adequate base funding pool has been established.

- CHANGE OF APPROVAL PATHWAY

In FDA's discussion of the proposed product development fee, the Notice recognizes that a sponsor may need to switch from the 351(a) pathway to the 351(k) pathway (or vice versa) while developing a biologic.[8] Subsection 351(a) provides for submission of a full analytical, pre-clinical, and clinical package to independently establish the safety, purity, and potency of a biological. In contrast, subsection 351(k) presumably permits an applicant to submit an abbreviated and comparative application that relies on a prior Agency finding that a highly similar, cited reference product was safe, pure, and potent. Although changing pathways after development has begun may be justifiable in certain cases, FDA must ensure that such a change is based on bona fide scientific developments and that all applications are properly categorized at the end of the day, in view of the clear differences between the pathways. In addition, FDA must ensure that, if a switch is made, the application is in full compliance with each provision of the applicable pathway.

In particular, FDA must be careful not to accept applications under subsection 351(a) that should be filed under subsection 351(k) – meaning applications that seek to rely (explicitly or implicitly) on prior Agency approvals. Accepting such an application – sometimes described as a "skinny BLA" – would be inconsistent with the statute and with Congressional intent. The BPCIA reflects a carefully negotiated compromise, pursuant to which a biosimilar applicant may obtain approval based, in part, on FDA's prior public finding that the reference product is safe and effective. In return, however, the applicant is subject to the constraints of subsections 351(k) and 351(l), which include time limits on filings and approvals and a mandatory application notice and patent dispute resolution process. A "skinny BLA" applicant, therefore, would receive the benefit of FDA's prior finding without being subject to the balance of the statutory bargain. Further, FDA acceptance of a "skinny BLA" under subsection 351(a) would essentially enable approval of a BLA that does not, in and of itself, demonstrate safety, purity, and potency. As stated in our December 2010 comments to the Agency, FDA has consistently interpreted subsection 351(a) to require a full complement of original data to support BLA approval. FDA should remain firm in this policy and refuse to accept for filing under subsection 351(a) any application for which the sponsor seeks to abbreviate its testing program through reliance on FDA's prior findings of safety and effectiveness for a highly similar approved biologic for which the sponsor does not have a right of reference. As previously noted, to do otherwise would raise serious legal questions, including constitutional ones under the Takings Clause.[9]

[8] 76 Fed. Reg. at 27,064.
[9] *See supra* note 7.

CONCLUSION

BIO appreciates this opportunity to comment on the development of a user fee program for biosimilar and interchangeable biological product applications. As requested previously, we look forward to participating in FDA's consultation process on this topic. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sandra J.P. Dennis
Deputy General Counsel for Healthcare
Biotechnology Industry Organization

/S/

Kelly Lai
Director, Science & Regulatory Affairs
Biotechnology Industry Organization