PhRMA

June 9, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-N-0326: Biologics Price Competition and Innovation Act of 2009; Options for a User Fee Program for Biosimilar and Interchangeable Biological Product Applications for Fiscal Years 2013 Through 2017; 76 Fed. Reg. 27,062 (May 10, 2011)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to FDA's request for comments entitled "Biologics Price Competition and Innovation Act of 2009; Options for a User Fee Program for Biosimilar and Interchangeable Biological Product Applications for Fiscal Years 2013 Through 2017."[1] PhRMA is a voluntary, nonprofit association of the country's leading pharmaceutical research and biotechnology companies, which are dedicated to inventing medicines that allow patients to live longer, healthier, and more productive lives. In 2010 alone, the pharmaceutical industry invested more than $67 billion in developing new medicines. PhRMA's membership includes research-based biopharmaceutical companies and companies that have publicly stated that they intend to develop biosimilar medicines.

PhRMA supported enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) and supports FDA's ongoing implementation efforts. We believe the statute appropriately balances encouraging investment in innovative treatments, on the one hand, with promoting timely market entry of biosimilar products, on the other hand. We were pleased to participate in the November 2010 Part 15 hearing regarding biosimilars, and we submitted written comments to the accompanying docket, including brief comments on the user fee aspects of the new scheme.[2]

The design of the agency's user fee program for biosimilars will be critical to maintaining the balance struck by Congress in the BPCIA. We are pleased to offer our general comments on FDA's proposal for the user fee program and our responses to the specific questions raised by FDA in its *Federal Register* notice. PhRMA generally supports the outlined user fee proposal -- but only for the first five years of the biosimilar user fee program, and FDA should not avoid its statutory obligation to negotiate the user fee terms with the regulated

[1] 76 Fed. Reg. 27,062 (May 10, 2011).

[2] 75 Fed. Reg. 61,497 (Oct. 5, 2010).

industry. In addition, the user fee proposal contains numerous assumptions about biosimilar applications and FDA review of those applications that must be studied by the agency in the coming years.

Background

In the *Federal Register* notice, FDA proposes to require a fee associated with the submission of an application under section 351(k) of the Public Health Service Act, a manufacturing establishment fee, and a product fee for marketed biosimilar and interchangeable products. In addition, under FDA's proposal, a 351(k) applicant would be required to pay an annual product development fee starting at the time an investigational new drug application (IND) was submitted. The total amount of product development fees would ultimately be deducted from the subsequent 351(k) application fee.

I. General Comments

- **FDA should initiate negotiations with the regulated industry soon consistent with BPCIA.**

PhRMA supports FDA's decision to seek comment on the appropriate approach to biosimilar user fees and its plan to hold meetings with public stakeholders and industry stakeholders.[3] We note that the statute requires that the agency conduct "negotiations" with the "regulated industry" when developing its user fee recommendations for Congress.[4] The requirement to conduct negotiations is separate from, and in addition to, the requirement to hold public meetings for review of any resulting recommendations, and we assume that FDA will initiate negotiations soon using PDUFA negotiations as a model.[5]

The agency states that it is unclear which companies comprise the regulated industry for purposes of the required negotiations. PhRMA and other stakeholders have already identified their readiness to engage in the required negotiations, and we request that FDA initiate the negotiations required by Congress with PhRMA and the leading trade associations consistent with many years of precedent set by the PDUFA negotiations.

- **PhRMA generally supports FDA's four proposed principles for development of a biosimilar user fee program.**

FDA proposes four principles to guide its recommendations for a biosimilar user fee program. PhRMA generally supports these principles, although we suggest some refinements below. First, we agree that adequate review capacity is necessary to prevent

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[3] *See* 76 Fed. Reg. at 27,067.

[4] Pub. L. No. 111-148 § 7002(f)(1)(B).

[5] *Id*. § 7002(f)(1)(B).

"unnecessary delays in the development and approval" of biosimilars.[6] This is crucial, but equally important is the need to ensure that approved biosimilars are as safe and effective as innovative biological products. The agency must at all times balance the twin goals of "taking appropriate action on the marketing of regulated products in a timely manner," on the one hand, and "ensuring" that drugs are "safe and effective," on the other hand.[7] Thus, we agree with the principle that review of 351(k) applications must not divert resources from review of innovative 351(a) applications. Moreover, as explained below, FDA must take steps to ensure that confidential commercial information and trade secrets in a 351(a) application are not referenced or used during review of corresponding biosimilar applications. Second, we agree that at least for the initial five-year authorization period, biosimilar application user fees should remain comparable to user fees for 351(a) applications. This decision is necessarily based on untested assumptions about the size, scope, and complexity of biosimilar applications. The statute requires FDA to audit the costs of reviewing biosimilar applications, however, in order to determine whether an adjustment to the fee is required.[8] Such an FDA review of the *actual costs* of FDA's review of biosimilar and interchangability applications will be critical for setting appropriate fees going forward. Third, FDA assumes that agency consultation will be most needed early in a biosimilar product's development cycle. While PhRMA believes that this is a reasonable *initial* approach, we urge the agency to reevaluate the focus of the third principle on early activities based on data acquired during the initial five-year authorization period such that it incorporates appropriate pharmacovigilance activities for biosimilar and interchangeable products. Furthermore, to ensure that adequate funding is available during the initial five-year period and that resources are not diverted from review of 351(a) applications, we urge the agency to differentiate between the section 351 approval pathways at all times based on actual FDA and sponsor activities.

- **FDA's proposal is grounded in assumptions about the nature of biosimilar applications which may be appropriate for the first five years of the user fee program, however these premises must be scrutinized as part of the statutorily mandated auditing process and for future reauthorization of the program.**

Many aspects of FDA's proposal are grounded in assumptions about the biosimilar program. For example, FDA assumes that its expertise will be most needed early in the biosimilar development cycle. The agency also assumes that review of a biosimilar application is likely to be as "complex, technically demanding, and resource-intensive" as review of a section 351(a) application.[9] Although assumptions of this sort may be necessary in order to create a user fee program for fiscal years 2013 to 2017, concrete data about the complexity of applications and the burden of administering section 351(k) will become available during that

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[6] *See* 76 Fed. Reg. at 27,063.

[7] FDCA § 1003.

[8] Pub. L. No. 111-148 § 7002(f)(3)(C).

[9] 76 Fed. Reg. at 27,063.

time period. The biosimilar user fee program reauthorized in 2017 must be informed by these data rather than the current assumptions.

As noted, the statute requires FDA to conduct annual and biennial audits of the actual costs of reviewing biosimilar applications.[10] These audits should be used not only for the narrow task of making potential user fee adjustments (as the statute requires), but also to more generally examine whether these assumptions are warranted and to explore how the user fee program can be improved in future reauthorizations. FDA should also promote transparency with regard to the resources involved in reviewing biosimilar applications by publishing all nonconfidential information from the audits and by inviting public comment regarding the methodology and conclusions of the audits.

- **Pre-payment of a portion of the application fee at the time of IND submission should be understood as a stop-gap measure, applicable for a <u>maximum</u> of five years to biosimilar INDs, until other fees are sufficient to fund the relevant FDA activities.**

PhRMA understands that the initial user fee program for 351(k) products must be structured differently from user fee programs for other FDA-regulated products because there are no marketed biosimilar products in the United States and therefore no product fees to support initial agency review –related activities. PhRMA therefore supports the agency's proposal to collect a portion of the application fee at the time of IND submission (and in annual payments thereafter) for a maximum of the initial five years of the biosimilar user fee program. PhRMA also agrees that any such payments made should be deducted from the final application fee that is owed when the biosimilar application is filed. Because FDA will be collecting user fees at the submission of an IND and annually thereafter, we recommend that the agency and biopharmaceutical companies develop a method for taking into account inflation and the time value of money when deducting such fees from the 351(k) application fee, which could be several years after submission of an IND.

FDA's proposed novel structural approach to user fees must, however, be understood as a stop-gap measure. Over time the agency will approve biosimilars and begin to receive product fees. In addition, over time the agency's annual activities in the IND phase for biosimilars — which it suggests may be "greater than" activities in the IND phase for new biological products[11] — may taper down. As soon as fees from marketed products (in combination with application and establishment fees) provide sufficient support for the agency's IND phase activities, and at the very latest upon reauthorization in 2017, this temporary measure will no longer be justified and should be eliminated. PhRMA does not support the general idea of user fees during the IND phase for drugs or biologics.

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[10] Pub. L. No. 111-148 § 7002(f)(3)(C).

[11] 76 Fed. Reg. at 27,064.

In order to align with FDA's stated principle of ensuring fairness to all industry sponsors and the patients we serve, PhRMA recommends FDA consideration of mechanisms to ensure that both innovator and biosimilar sponsors have equal opportunity for transparency and access to FDA review staff from filing of an IND through the application submission phase.

- **FDA should not use clinical holds to enforce the annual product development fee.**

The agency suggests that failure to pay the biosimilar product development fee on initial IND submission or annually thereafter should result in the IND being placed on full clinical hold. We agree that an IND should not be reviewed or go into effect — and clinical trials should not begin — if the initial product development fee has not been paid, because the sponsor would not have complied with the requirements of the user fee program and biosimilar IND filing requirements. But PhRMA does not support use of the clinical hold mechanism where a biosimilar applicant fails to pay the annual fee that follows. The clinical hold mechanism is designed to ensure the safety of clinical trial participants.[12] The agency's use of clinical holds to enforce user fee requirements would be inconsistent with this safety function, and this critical patient protection function should not be confused with a failure to pay a user fee.

The agency should therefore use an alternative means of enforcing the annual product development fee. We recommend that FDA require that IND sponsor certify in the initial IND submission and IND annual reports under 21 C.F.R. § 312.33 that it has paid the product development fee as required. This approach would be similar to the certification required by PHSA section 402(j), which requires sponsors to certify in various IND and NDA submissions that they are in compliance with 402(j).[13]

- **Although it may be appropriate in rare cases for a sponsor to switch from one approval pathway to another, Congress intended two distinct approval pathways, and FDA must clearly differentiate between them.**

Section 351 describes two mutually exclusive and fundamentally different pathways to market. The agency suggests that in some cases a sponsor might "change[]" its approval pathway from section 351(k) to section 351(a) (or vice versa).[14] We agree that permitting an applicant to switch pathways may be scientifically justified or required by the

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[12] *See* 21 C.F.R. § 312.42.

[13] *See* Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff - Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007 (January 2009).

[14] The agency states that the sponsor might change the pathway from section 351(k) to "another, *such as* the 351(a) approval pathway." 76 Fed. Reg. at 27,064 (emphasis added). PhRMA requests that the agency clarify what *other* pathways, apart from section 351(a), might be appropriate.

statutory scheme in certain situations. For example, if a product that was originally considered for a 351(k) application does not meet the biosimilarity standard, it must be the subject of a full application under section 351(a). We agree that sponsors and the agency must have the flexibility to adjust product development programs and application strategies in view of the analytical, preclinical, and clinical data that emerge while a product is under investigation. At the same time, and particularly in view of the possibility that applicants will switch pathways, PhRMA believes FDA should take steps to articulate and maintain the clear distinction between applications to be filed under section 351(a) and applications to be filed under section 351(k) and should ensure that applications are at all times properly categorized by their sponsors and the agency.

We support the agency's proposal to require sponsors to "declare" that a development program is intended to support a biosimilar application.[15] This will help to maintain the distinction between the two pathways. FDA should require this declaration to take the form of a written submission to the agency (*e.g.,* through one of FDA's IND submission forms). The agency should also be especially cautious about the possibility for miscategorization where an applicant changes pathway after development has begun. It may be appropriate to establish a formal internal process for agency review and designation of the appropriate pathway in those cases. We also continue to urge a refusal-to-file policy that requires the use of the biosimilar pathway for any application that relies, implicitly or explicitly, without consent, on previously submitted data or the fact of a prior approval. FDA lacks authority to approve such an application under section 351(a). The agency has long and consistently taken the position that applications submitted under section 351(a) may not rely on data and findings relevant to another product — that the section requires original and comprehensive applications demonstrating product safety, purity, and potency. It would upset the careful balance struck by Congress between biosimilar market entry and competition, on the one hand, and incentives for biological product innovation, on the other hand, if FDA allowed section 351(a) applications to rely on prior findings, prior approvals, or previously submitted data. This would give the biosimilar applicant the benefits of an abbreviated pathway without imposing the associated burdens (for example, waiting for the expiration of the exclusivity period and confidentially sharing its application with the reference product sponsor for purposes of the patent litigation procedures). Such an approach would also raise grave issues under the takings clause of the U.S. Constitution, the Administrative Procedure Act, and U.S. treaty obligations.

- **FDA must take steps to ensure that its review of biosimilar applications does not rely on the underlying data and information in a reference product application.**

In its *Federal Register* notice, FDA states that the "same expert scientific teams that conduct FDA's review of 351(a) applications will typically be involved in the review of 351(k) applications."[16] The agency should clarify how it will handle the assignment of

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[15] *See* 76 Fed. Reg. at 27,064.

[16] *Id*. at 27,063.

biosimilar applications to individual reviewers. Section 351(k)(5)(B) states that a biosimilar application must be reviewed by the same *division* that is responsible for review of the reference product application. The statute does not require review by the same individuals that reviewed the reference product. Moreover, the agency is limited in its review and approval of a biosimilar application to information in that application and to publicly available information about the reference product.[17] Thus, FDA may not look at the data or manufacturing information in the reference product application when reviewing a biosimilar application The agency should develop specific procedures to avoid any inadvertent transfer or utilization of knowledge regarding the underlying data and information.

- **FDA should clarify that each establishment is subject to only one establishment fee.**

PhRMA supports the agency's decision to collect establishment fees for facilities manufacturing biosimilar products. The agency should clarify, however, that if a facility manufactures both innovative products and biosimilar products, it will be subject to only one establishment fee.

- **FDA should use the date the application is received as the trigger for the performance goal window and should commit to reviewing 70 percent of applications on time for FY 2013.**

FDA has selected the 60-day application filing date as the starting point for its performance goals. For fiscal year 2013, for example, the agency proposes to review 50 percent of original 351(k) applications within 10 months from the 60-day filing date. The addition of the 60 days for the filing decision presumably reflects the negotiations between PhRMA, BIO, and FDA regarding prescription drug user fees for PDUFA V. This additional two month window has been proposed exclusively for new molecular entities (NMEs), however, and it is unclear why it should be extended to biosimilars. FDA should therefore commit to reviewing applications within 10 months of the date of receipt of the application.

In addition, FDA has committed to reviewing only 50 percent of applications within the performance goals for fiscal year 2013. The agency has offered no explanation for setting such a low goal for the early years of the biosimilar program. As FDA recognized in its principles, timely market access to biosimilars is expected to help support the public health. We suggest the agency commit to reviewing at least 70 percent of all 351(k) applications and resubmissions within the allotted time periods for fiscal year 2013 (and 80 percent for fiscal 2014 and 90 percent for fiscal years 2015, 2016, and 2017).

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[17] *See, e.g.*, PHSA § 351(k)(2)(A)(iii) (stating that a biosimilar application must include "publicly-available information regarding" FDA's previous determination that the reference product is safe, pure, and potent); § 351(k)(3) (limiting FDA in its approval decision to "the information submitted in the application (or the supplement)").

II. Response to Specific Questions

IV.1: What factors should the Agency consider in determining appropriate performance goals for 351(k) applications that are filed earlier than 2 years prior to the date on which a 351(k) application would be eligible for approval?

The agency proposes separate sets of performance goals for 351(k) applications: one set for applications filed more than 2 years before they are eligible for final approval and one set for applications filed after this date. The statute does not differentiate among applications in this manner, but PhRMA shares the agency's concern about commitment of resources to meeting performance goals with respect to applications that might later be significantly amended due to any manufacturing or other changes in the proposed biosimilar or reference products.

We recommend that the agency use the abbreviated new drug application (ANDA) minor amendment model. These amendments are submitted before the generic applicant believes it is entitled to final approval, and they contain, among other things, updated manufacturing information. For biosimilar products for which all applicable initial reviews are completed more than one year before they are eligible for final approval, FDA should require a similar 180-day amendment for submission of further information.[18] This amendment should contain adequate data to establish that any manufacturing or other changes in the biosimilar or reference product since the product was initially reviewed would not affect the biosimilarity, in terms of safety, purity, and potency, of the biosimilar to its FDA-approved reference product. The agency should consider requiring an additional user fee in connection with any 180-day amendments that contain substantial data. FDA will also need to consider the possibility that major amendments supported by substantial (particularly clinical) data may not be approvable within the 180-day window.

FDA should ensure that the approach it takes with respect to early filed biosimilar applications does not undermine the legislative compromise in the BPCIA. Congress amended the Patent Act in addition to the PHSA so that biosimilar applicants and reference product sponsors could litigate potential patent infringement issues prior to biosimilar market entry. The ability to obtain certainty without any need for damages benefits both biosimilar applicants and reference product sponsors. Moreover, a special statutory injunction is available to reference product sponsors who prevail in a subset of the patent litigation before the end of the 12-year period.[19] Reference product sponsors will be able to obtain the benefit of the injunction only if

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[18] This 180-day amendment could coincide with the 180-day marketing notice that the biosimilar applicant must provide to the reference product sponsor pursuant to section 351(l)(8) of the PHSA. To ensure that biosimilar applicants continue to comply with their obligations under the statute, FDA should require that the applicant include with its 180-day amendment a certification that it has sent the reference product sponsor notice of marketing pursuant to section 351(l)(8).

[19] 35 U.S.C. § 271(e)(4).

there is adequate time between the filing of the biosimilar application and the end of the exclusivity term. FDA must keep in mind the possibility that a differential approach to performance goals and user fees based on when (in the exclusivity term) applications are filed will undermine the incentive to file early applications and decisively litigate the patents prior to market entry.

FDA should distinguish between major amendments, which should extend the performance goal review date by at least three months, and minor amendments, which should not affect the goal date. Significant changes or additions to the analytical, preclinical, or clinical data package should be considered major amendments, and in certain circumstances, may require an application to be resubmitted in its entirety, in which case FDA's proposed six-month performance goal should apply.[20]

IV.2. How should the performance goals take into account readiness for inspection?

FDA has asked how an applicant's readiness for preapproval inspection should affect the agency's performance goals. For example, the agency asks whether performance goals and user fees should take into account the fact that the biosimilar is already in commercial production for sale in another country.

For a biosimilar application to be complete, it must contain information about a manufacturing facility that is ready for manufacture and inspection. PhRMA agrees that it may be helpful to the agency to observe the actual commercial manufacturing process for a biosimilar approved by a foreign regulator that is also proposed for approval in the United States, but we do not believe the ability to do so should affect either the performance goals or the user fees payable. Each biosimilar product should be the subject of a preapproval inspections, conducted shortly before final approval of the 351(k) application.

IV.3: What other factors relating to the unique characteristics of the 351(k) approval pathway should the Agency consider when setting performance goals for 351(k) applications?

Finally, the performance goals and user fees for interchangeability supplements should reflect the fact that these applications may require substantially more agency resources

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[20] If a 351(k) application is resubmitted, the patent exchange process outlined in section 351(l) will need to be completed anew. Thus, a biosimilar applicant will need to provide its resubmitted application and manufacturing information to the reference product sponsor. As we stated in our biosimilar docket comments, PhRMA believes that FDA should require biosimilar applicants to certify, when submitting their applications, that they will comply with the provisions of section 351(l) and provide the reference product sponsor with a copy of the application and information describing the processes used to manufacture the biosimilar product within 20 days after notification has been received that the application was accepted for review. FDA should also require that the applicant amend the pending application on the 20th day with a certification that it has done so, and the agency should refuse to further process any application that fails to include the second certification.

than other supplements. When setting the performance goals for 351(k) applications, the agency should consider the fact that it may eventually receive supplements seeking interchangeability designations and that these supplements will be extensive and will require substantial agency resources for review. The statutory standard for demonstrating interchangeability is appropriately high to protect patient safety. The standard requires a showing beyond that which is necessary to establish biosimilarity, and cannot be currently met in view of the current state of the science.

The statutory standard for interchangeability is justifiably extremely high to protect patients, and a determination of interchangeability would likely require specialized "switching" studies designed to show that switching between the reference product and the biosimilar does not increase the risk to patients. Such submissions would be expected to contain a great deal of clinical study data, including clinical data for each indication for which the reference product has approval. All of these factors suggest the need for FDA to consider the need for a different user fee and performance goal for interchangeability applications compared to 351(k) applications that are not seeking an interchangeability determination.

III. Conclusion

PhRMA appreciates the opportunity for continued involvement in FDA's implementation of the BPCIA. We look forward to engaging with the agency during the negotiations with regulated industry.

If you have any questions, please do not hesitate to contact us.

Respectfully submitted,

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