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

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Docket No. FDA-2011-N-0426
Biologics Price Competition and Innovation Act (BPCIA) of 2009; Options for a User Fee Program for Biosimilar and Interchangeable Biological Product Applications for Fiscal Years 2013 Through 2017; Request for Comments[i] (hereafter "The Notice")

Dear Sir/Madam:

Thank you for the opportunity to provide the Generic Pharmaceutical Association's point of view on the user fee program being developed by the FDA to support the review of applications submitted using the new abbreviated pathway created in the Biologics Price Competition and Innovation Act of 2009.

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture the vast majority of all affordable pharmaceuticals dispensed in the United States, and have similarly paid long and sustained attention to the opportunities to manufacture cost effective and available biological medicines once patents and exclusivity on the originator moieties expire. Our products are already used in more than one billion prescriptions every year, and with our companies' sponsorship of biosimilars this will increase. While others have expressed an interest in biosimilars more recently, their history in this space does not have the credibility of those companies that have pursued a business model based on efficiencies in manufacturing and a focused attention on reducing the cost of goods while maintaining quality. We are advocates of biosimilars that are of the same quality, safety, purity and potency as their originator counterparts. GPhA's core purpose is to improve the lives of consumers by providing timely access to affordable medicines, and following the implementation of a viable regulatory pathway by FDA our members will be the lead sponsors of biosimilars with the FDA. A first step to this end is for the Agency to propose a user fee system for biosimilars that encourages sponsors to use the new 351(k) pathway, including policies now available for interchangeable biosimilars. Unfortunately the Notice, as currently drafted, does not encourage the use of the 351(k) pathway.

We have also had initial discussions with other members of industry in addition to GPhA's diverse membership, and we believe that we will be able to work together to assist the FDA in developing a viable user fee model for biosimilars that will have broad industry support.

GPhA is strongly supportive of the FDA having adequate reviewer-dedicated resources to review all applications for all medicinal products, biologic or drug, originator or generic, in a timely

manner. This is the only way to ensure patient access to originator products, as well as generic drugs and biosimilars. GPhA recognizes that current FDA appropriations are currently insufficient and we are already negotiating appropriate fees for generic drug applications, whose review times in the US are extremely long (31 months on average compared to 120 days in Europe). FDA does not face a similar backlog of biosimilar applications, and the right fee and review process can ensure that such a backlog never develops. GPhA has a clear position on both the user fee itself and the performance measures that are expected with that user fee. GPhA does not support a biosimilar user fee that matches that of an originator product because the dossier for a biosimilar will be abbreviated in a manner that both reduces FDA reviewer resources and sponsor data requirements.

First and foremost, it is GPhA's position that any meaningful user fee program should take a holistic user fee approach designed to help the FDA carry out its mission in this global age to perform its mission of ensuring all participants in the U.S. biologic system – whether U.S.-based or foreign – comply with all U.S. quality standards and to make certain Americans get timely access to low cost, high quality biosimilar products. With this in mind, GPhA proposes a comprehensive user fee structure focused on three key aims:

SAFETY- Ensuring all players, foreign or domestic, contributing to the U.S. biosimilar system are held to the same quality standard and, therefore, inspected by the FDA at least biennially;

ACCESS - Expediting the availability of low cost, high quality biosimilar products by creating a viable pathway that accelerates access and avoids unnecessary delays in the development and approval of these important products; and

TRANSPARENCY- Enhancing the FDA's ability to protect Americans in the complex global supply environment by identifying, tracking and requiring the registration of all contributors involved in each biosimilar product sold in the U.S.

To encompass a holistic user fee approach, GPhA supports a user fee structure as follows:

1. **Annual Establishment Registration Fee:** The annual establishment registration fee should act as a business license or registration tied simply to the act of participating in the U.S. biologic market. Registration will help the FDA identify and track all those contributing to each biosimilar product sold in the U.S and should be paid annually by each facility referenced or listed in the biologics license application. These fees would supplement existing FDA funds to assist the agency in carrying out its responsibility of ensuring the safety, efficacy and security of the U.S. pharmaceutical supply and provide additional resources necessary to support the increasingly complex global pharmaceutical supply. Importantly, these fees would also support FDA in carrying out biennial GMP inspections of all establishments – foreign or domestic and should be tiered depending on the type of facility involved.

2. **Product Development Fee:** GPhA will support a Product Development Fee if the fee facilitates meaningful, timely consultations with FDA with reliable feedback that submitting companies can incorporate into their product submissions. This feedback should be made

available both for applications based on biosimilarity and those seeking interchangeability. This fee would be paid upon submission of an investigational new drug application (IND) for a biosimilar product, and annually thereafter while the product remains in active development. When the 351(k) application is submitted, the sum of all Product Development Fees which have been paid with respect to that product will be deducted from the Application Fee.

3. Application Fees

GPhA supports a user fee for a biosimilar/interchangeable biosimilar (i.e., any 351(k) application) of between 50% and 65% that of a full BLA (351(a) application). Our rationale for this range is:

1. The Biosimilar application under 351(k) will represent a smaller data set than a full 351(a) application because it contains a reference to a previously-approved, specific biologic for which the safety, purity and potency is established, and with which there is at least 4 years of post-approval experience, and likely nearer 12 years (since the FDA cannot approve a 351(k) until a minimum of 12 years after the reference product was approved). A biosimilar will have a different, but smaller data set for review, and so the reviewer burden is less than for an originator application – **the user fee should be commensurately smaller**.

2. The reviewers, and certainly the FDA review division, will have prior experience reviewing and approving the reference biologic as stipulated by statute. They also will have overseen manufacturing changes to those reference products using comparability as the basis of the interchangeability of these products before and after implementation of manufacturing changes. **As a result of this previous experience with originator biologics, the learning curve for the reviewers of biosimilar applications is expected to be considerably shorter than that for reviewers of originator biologic applications.** This does not mean that FDA reviewers will revisit the files of the originator product – those remain trade secret, as will those of the biosimilar sponsor.

3. The BPCIA, as a statutory matter, uses the analytical standard of "highly similar," and this is the ICH Q5E product quality attributes standard for any biologic sponsor making a manufacturing change. **A supplement to a previously approved application requiring clinical data incurs a user fee that is 50% of that for a full application.** This is the reason for us proposing 50% as the minimum user fee to consider for a biosimilar application.

4. If the 351(k) application includes a request for an interchangeability designation, as long as it is filed as a single application at the time of initial submission, a single biosimilar user fee should apply. If an interchangeability request is filed AFTER the FDA has accepted and filed the initial biosimilar application (even if prior to its approval) then a supplementary fee can also apply.

5. In Europe, while all user fees are lower than in those in the United States, **the biosimilar fee is set at 65% of that of a full application**. The regulatory environment of the EU is similar to that of the US, and so the **relative difference of biosimilar and originator dossiers is**

likely comparable. This is the reason for us proposing 65% as the maximum user fee to consider for a biosimilar application.

GPhA supports a review time for a biosimilar application that is no more than that of a current full application, currently set at 10 months, including establishment inspection(s) as per 601.20(d)., and the performance goals must be on par with those for originator products. The performance goals proposed by FDA, starting with a 50% chance of a review action in 10 months for FY 2013 (2 years after the statute) and a 90% goal on par with originators in FY 2017 (7 years after the statute), is unreasonable and imposes a significant burden on the biosimilar industry because it lacks the predictability necessary to plan development, manufacturing and commercialization activities. For the FDA to impose this added burden of uncertainty to an approval pathway that is already troubled with ambiguity (e.g. intellectual property process) will significantly impact the viability of the pathway and is counter to the intent of the statute and importance of the pathway espoused by the FDA in its 2012 budget proposal.

Creating a viable abbreviated pathway for biosimilars that provides early dialogue and feedback into the development plan associated with a 351(k) application, must be a key principle of any biosimilar user fee program in order to ensure patients and payers are receiving access to low-cost, high-quality biosimilars as quickly as possible. Otherwise, the pathway will not be used at all. This includes identifying the current barriers in the pathway and the need for the user fee program to enable rather than dissuade submissions. Additionally, it is critical that FDA not only set review timeline targets but also targets for specific stages of submissions, and other efforts that will enable companies, payers and other stakeholders to understand and increasingly use and interchange biosimilars. GPhA looks forward to working with FDA to develop such measures as well as continuing conversations with FDA to address many of the concerns previously submitted by GPhA in other public forums and requests for comment associated with the implementation of the new abbreviated biosimilar pathway.

1. The biosimilar dossier will be smaller than that of a full BLA, and the FDA will have experience from previous review of a highly similar product, so no extra review time is necessary. Indeed, a compelling case could be made for a shorter review time for a biosimilar application compared to a full BLA (see discussion above).

2. While the originator user fee conditions may be changing, the reference products for biosimilars will be those reviewed under the current and previous PDUFA statutes where 10 months became the standard review period.

3. Even if the 351(k) application includes a request for an interchangeability designation, as long as it is filed as a single application at the time of initial submission, a 10 month review clock should apply.

4. EMA has generated guidelines, general and class-specific, and achieved a biosimilar performance of 100%. We believe that the FDA can match this standard given that they also have the benefit of learning from the European experience.

5. The payment of user fees shall offer biosimilar sponsors the same timing and performance goals as established by FDA CDER/CBER procedural guidance under PDUFA with regard to formal meeting scheduling, formal dispute resolution, special protocol assessments, review of complete responses to clinical holds, and the evaluation of proprietary names.[ii]

6. If the 351(k) application is just for a biosimilar, and the 351(k) interchangeability designation is received subsequently (even if pre-approved) then the clock would be extended by up to 3 months from the date of the submission for that interchangeability review.

GPhA looks forward to participating in the discussions with the FDA as the US trade association that will represent the greatest number of the most self-evidently capable and interested biosimilar sponsors – namely those that already have biosimilars approved in other highly regulated markets. We also have many members who have shared the long-term interests of biosimilar sponsors in helping access and affordability as a public health priority and they will be available to contribute ideas on what will facilitate a truly competitive marketplace for biosimilars in the US, such that Americans can benefit from high quality biosimilars similar to Europe and elsewhere. We want to thank the FDA for its time and interest in implementing the abbreviated biosimilar pathway created by BPCIA and facilitating greater access to these life-saving biological medicines through meaningful savings while ensuring that all biosimilars will be of the same quality, and as safe, pure and potent as their reference products. GPhA hopes that this public process on user fees to be assessed for biosimilars is part of a dialogue between FDA and stakeholders on these important issues, and a continuation of the public meeting held in November 2010.

Respectfully submitted,

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Endnotes:

[i] 76 Fed. Reg. 27062, 27063 (May 10, 2011) available at http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0326-0001 (accessed 11May11)

[ii] Formal Meeting Scheduling: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf, Formal Dispute Resolution: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079743.pdf, Special Protocol Assessments: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf, Review Of Complete Responses To Clinical Holds: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080581.pdf, and the Evaluation Of Proprietary Names: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.