U.S. FOOD & DRUG ADMINISTRATION

SUMMARY OF PUBLIC VIEWS AND RECOMMENDATIONS FOR THE BIOSIMILAR USER FEE ACT II

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Contents

Executive Summary

The current legislative authority for BsUFA, authorized in 2012 by the Food and Drug Administration Safety and Innovation Act (FDASIA) will expire at the end of the 2017 fiscal year. The Federal Food, Drug, and Cosmetic Act (FD&C Act) includes a process for developing recommendations for the next BsUFA program (FY2018-2022) that involves holding two public meetings and conducting discussions with regulated industry. FDA has completed these steps and has solicited public comment on the proposed recommendations for BsUFA II. This document provides a summary of the findings from the submission of public comments in response to the proposed commitments for BsUFA II and provides recommendations for submission of the proposed enhancements for BsUFA II to Congress.

Public comments indicate overall support for the program enhancements proposed in the BsUFA II commitment letter. The comments received generally expressed the view that the provisions included in the BsUFA II package will enhance predictability, timeliness, and efficiency of the regulatory review of biosimilar biological products. Additionally, public input indicated that the proposed enhancements under BsUFA II were expected to increase patient access to biosimilars while ensuring the safety of approved products and manufacturing processes.

Many of the comments received expressed support for specific provisions included in the proposed BsUFA II package including enhancements to the review process, enhanced staff capacity for the program, proposed improvements to hiring and retention practices, and enhancements to the meeting management process. Additionally, commenters supported the proposed updates to the BsUFA fee structure, highlighting the importance of adequate fee funding so that sufficient resources are available for BsUFA II. Overall, comments indicated the proposals are supported and that the enhancements will lead to long-term stability of the BsUFA program and increase patient access to biosimilar biological products.

While public comments indicated support for the commitments proposed for BsUFA II, many of the commenters also indicated that they would like FDA to issue the proposed guidance documents earlier than the proposed goal date in the commitment letter. It should be noted that FDA is committed to delivering this guidance in a timely manner, and while the dates included in the provisions for guidance development do not preclude the possibility that these documents could be issued earlier, FDA is currently challenged by very limited staffing that limits the ability to meet these commitments in an earlier time frame. In addition, the timeline for guidelines to address scientifically and legally complex and novel issues such as those identified for biosimilars can be difficult to predict due to the technical uncertainty, and the range of public comments that may be received on draft guidance. Accordingly, the goal dates proposed in the enhancements for BsUFA II also try to factor in these considerations.

Following review of the public comments, FDA has made clarifying edits to the commitment letter and intends to send the recommendations to Congress in accordance with the procedures in section 744I(e)(2). The sections that follow provide a more detailed discussion of the process for preparing the proposed recommendations for BsUFA II, the comments received on each provision, additional comments and views that were received during the public consultation process, and ends with a summary of the findings from the comment analysis.

Introduction and Background

The Biosimilar User Fee Act (BsUFA) authorizes the Food and Drug Administration (FDA or Agency) to collect user fees for the review of biosimilar biological product applications. The authorization of BsUFA (BsUFA I) was part of the Food and Drug Administration Safety and Innovation Act of 2012 and will expire at the end of the 2017 fiscal year. Section 744I(e) of the Federal Food, Drug, and Cosmetic (FD&C) Act specifies the process for developing recommendations for the next BsUFA program (for FY2018-2022); this process includes negotiations with regulated industry and consultation with stakeholders. FDA began the reauthorization process in preparation for BsUFA II with a public meeting held on December 18, 2015. Following the meeting, a docket was open for 30 days for the public to submit written comments. In March 2016, FDA began negotiations with industry to determine the proposed recommendations for the next BsUFA program. These discussions concluded in May of 2016. Minutes of these meetings are posted on FDA's website at http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/ucm461774.htm.

The provisions of the 2012 reauthorization of BsUFA also include the following requirements:

> *(2) PUBLIC REVIEW OF RECOMMENDATIONS.—After negotiations with the regulated industry, the Secretary shall—*
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> *(A) present the recommendations developed under paragraph (A) to the Congressional committees specified in such paragraph;*
> *(B) publish such recommendations in the Federal Register;*
> *(C) provide for a period of 30 days for the public to provide written comments on such recommendations;*
> *(D) hold a meeting at which the public may present its views on such recommendations; and*
> *(E) after consideration of such public views and comments, revise such recommendations as necessary.*
>
> *(3)TRANSMITTAL OF RECOMMENDATIONS.—Not later than January 15, 2017, the Secretary shall transmit to the Congress the revised recommendations under paragraph (2), a summary of the views and comments received under such paragraph, and any changes made to the recommendations in response to such views and comments.*

FDA has followed the process described in paragraph (2) and the agency is publishing this summary in preparation for the transmittal of recommendations to Congress under paragraph (3). Following administration review and clearance, FDA posted the package of proposed recommendations for BsUFA II at http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/ucm461774.htm and published a Federal Register notice summarizing the proposed recommendations. FDA held a public meeting on October 20, 2016 to solicit public comment on the proposed package. The public docket subsequently closed on October 28, 2016. The transcript of the public meeting and the written comments submitted to the docket can be found on FDA's website at the same link provided earlier in this paragraph. This document provides a summary of 22 comments that were submitted in writing to the public docket before the close of the comment period as well as comments orally presented during the public meeting held on October 20th. In total, comments were provided by 4 patient organizations, 2 consumer organizations, 7 industry commenters, 2 policy organizations, and 7 healthcare professional organizations. Following review of the public comments, FDA has made clarifying edits , and intends to send the recommendations to Congress in accordance with the procedures in section 744I(e).

Summary of Public Comments

Many of the commenters expressed overall support for the recommendations for the reauthorization of the BsUFA program. In general, it was expressed that the commitments included in the BsUFA II package will enhance predictability, timeliness, and efficiency of the regulatory review of biosimilar biological products. Additionally, feedback was provided that the program will increase patient access to biosimilars while ensuring the safety of approved products and manufacturing processes. Furthermore, public comments indicated that the proposed recommendations would provide FDA will the support needed to enhance review processes and ensure sufficient resources to adequately staff the program. Two stakeholders explicitly mentioned their approval of submission of the proposed enhancements for BsUFA II to Congress and encouraged Congress to support the proposed commitments.

While several stakeholders provided general support for the BsUFA II recommendations, many comments were provided in support of specific provisions in the proposed package. Areas where significant support was specifically provided include the proposed enhancements to the review process to facilitate timely communication with a goal of minimizing the number of review cycles; enhancing capacity for biosimilar guidance development, reviewing training, and timely communications; enhancements to the meeting management process; and enhancements for improved hiring and retention practices. Additionally, commenters supported the proposed updates to the user fee structure highlighting the importance of the Agency to have adequate fee funding so that sufficient resources are available for BsUFA II. Overall, comments indicated the proposals were supported and that the enhancements will lead to long-term stability of the BsUFA program and increase patient access to biosimilar biological products.

While overall support was provided for the commitments proposed for BsUFA II, many of the commenters would like FDA to issue the proposed guidance documents earlier than the proposed goal date. These stakeholders are concerned with the potential policy implications due to the current lack of guidance on particular topics and consider that the proposed guidance documents will enhance patient safety and increase provider uptake of biosimilar biological products. FDA is committed to delivering guidance in a timely manner. The dates included in the provisions for guidance development do not preclude the possibility that some of these guidances could be issued at an earlier date as many of them are currently in development or FDA is currently in the process of reviewing comments received on previously issued draft guidance. Under FDA's good guidance practices regulation, FDA typically provides a period of time for the public to comment on draft guidance, after which FDA reviews any comments received. In some cases, the Agency may issue revised draft guidance prior to issuing final guidance depending on the comments received. In addition, the timeline for guidelines to address scientifically and legally complex and novel issues such as those that may be identified for biosimilars can be difficult to predict due to the uncertainty, including that related to the range of public comments received on draft guidance. Since the program is currently challenged by very limited staffing and it can be difficult to predict how much time this process will require dates for development of new guidance have been proposed in the enhancements for BsUFA II that will accommodate the process.

Many commenters provided their views on specific proposed enhancements for BsUFA II. These include comments of support, advice, and implementation considerations, as well as specific suggestions for enhancement proposals. FDA will further consider this input as it develops its implementation plans.

The discussion that follows provides a summary of comments organized by proposed enhancements included in the BsUFA II package.

Biosimilar Biological Product Review Program

For BsUFA II, it is proposed to establish a model for the review of biosimilar biological products similar to The Program for Enhanced Review Transparency and Communication for New Molecular Entity New Drug Applications and Original Biologics License Applications (the Program) that was established in the fifth authorization of the Prescription Drug User Fee Act (PDUFA). The Program is expected to enhance the ability of applicants and FDA reviewers to work toward application approval in the first cycle by allowing for additional communication between FDA review teams and the applicants of biosimilar biological products. Enhanced communication will be achieved through pre-submission meetings, mid-cycle communications, and late-cycle meetings, while adding 60 days to the review timeframe to accommodate this additional interaction.

Eleven commenters including one consumer organization, two healthcare professional organizations, seven industry commenters, and one patient organization provided support for the proposed changes to the review process and new timeline indicating that it will facilitate additional communication opportunities between FDA review teams and sponsors. Additionally, these commenters felt that the changes to the review process would increase the probability of a first cycle approval, shorten overall development timelines, and increase patient access to biosimilars.

One consumer organization noted a commitment to review and act upon 90% of the application review goals within the goal date, and indicated that this goal does not seem realistic. FDA notes that the proposed 90% metric in BsUFA II is consistent with the current goal under BsUFA I, which includes the commitment that by FY 2017 FDA would review and act on 90% of biosimilar biological product application submissions by the goal date[1]. In addition, FDA also considers that this goal could be met under BsUFA II since the agency has successfully met 100% of the review goal commitments during BsUFA I. Thus, for BsUFA II, a timeframe for the application review goals has been negotiated based on past review performance, and the expectation that FDA will secure additional resources as a result of improved hiring practices to address the anticipated growth in review work.

One industry organization raised a question around whether a 74 day letter would be provided for every application and expressed a desire that a 74 day letter should be issued for all applications. FDA notes that it is already standard practice for FDA to issue a Day 74 letter for all applications and efficacy supplements. The CDER 21st Century Review Desk Reference Guide[2] provides further explanation on how FDA handles filing communications.

Review Goal Extension for Missing Manufacturing Facilities

When manufacturing facilities are not adequately identified in a biosimilar marketing application, this may result in the need for FDA to conduct inspections late in the review process. This can adversely impact FDA's ability to complete application review within the performance goal timeframes. For BsUFA II, FDA has proposed to

[1] For BsUFA I Goals see:
http://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm281991.pdf

[2] For 21st Century Review Desk Reference Guide see:
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm

extend the goal date for an original application or a supplement when FDA identifies a need to inspect a facility that the sponsor had failed to include in a comprehensive and readily located list of manufacturing facilities in the submitted application.

No specific comments were provided on this proposed enhancement; however FDA notes that eight stakeholders including one healthcare professional organization, five industry commenters, and two patient organizations provided general support for the proposed recommendations for BsUFA II including this proposed enhancement.

Special Protocol Assessment and Agreement

For BsUFA II, it is proposed to provide further clarity regarding the types of clinical study protocols that may qualify for a Special Protocol Assessment and Agreement under BsUFA by adding Pharmacokinetic (PK) and Pharmacodynamic (PD) studies to the examples provided in the goals letter.

One industry commenter indicated that this provision will enhance the review process and make biosimilar development more predictable and affordable.

Prior Approval Manufacturing Supplements

The review goal date for prior approval manufacturing supplements for biosimilar products is currently 6 months under BsUFA I, compared to 4 months for "stand-alone" biologics under PDUFA. To increase consistency among user fee programs, it is proposed that in BsUFA II there will be a phased-in performance goal that prior approval manufacturing supplements are reviewed in 4 months instead of 6 months.

One industry commenter indicated that this provision will enhance the review process and make biosimilar development more predictable and affordable.

Meeting Management

Three meeting management enhancements are proposed for BsUFA II to allow FDA to better manage meetings with sponsors of 351(k) applications. These enhancements include: the addition of a written response meeting format for Biosimilar Initial Advisory (BIA) and Biosimilar Program Development (BPD) Type 2 meetings; increasing the scheduling timeframe for BPD Type 2 meetings from the current 75-day timeframe to 90 days; and reducing the scheduling timeframe for Biosimilar Initial Advisory (BIA) meetings from the current 90-day timeframe to 75 calendar days. Six commenters (four industry commenters, one patient organization, and one consumer organization) provided comments in support of these proposed enhancements related to meeting management. They also indicated that these enhancements will help to ensure that review staff have information needed during review and will allow the Agency the flexibility needed in scheduling and determining the appropriate format of meetings. Additionally, commenters noted that the addition of a written response meeting format will accelerate the process of advice for applicants when a face to face meeting is unnecessary.

For BPD Type 2 meetings in BsUFA II, it has been proposed that the Agency will send preliminary responses to a sponsor's questions contained in the background package no later than five calendar days before the meeting date. One industry commenter indicated that this will allow sponsors to have more consistent expectations by requiring the provision for the Agency to provide this feedback within the specified timeframe.

Guidance Development

Several proposals related to guidance development have been included in the provisions for BsUFA II. This includes a proposal for FDA to revise its guidance entitled "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants". It also includes a proposal to update the draft guidance entitled "Best Practices for Communication Between IND Sponsors and FDA During Drug Development," as appropriate, to include communications between IND sponsors and FDA during biosimilar biological product development. Additionally, it is proposed that FDA publish draft or final guidance on several issues related to biosimilar biological product development. These include guidance on: considerations in demonstrating interchangeability of a biosimilar with a reference product; statistical considerations for analytical similarity for biosimilar biological products; processes and further considerations related to post-approval manufacturing changes for biosimilar biological products; clinical pharmacology data to support a demonstration of biosimilarity to a reference product; nonproprietary naming of biological products; and labeling for biosimilar biological products.

One industry commenter supported application of the guidance on best practices for communications for BsUFA II stating that this will help assure that development programs are well designed and that biosimilars and interchangeable biologics are subject to the same rigorous review and quality requirements.

One consumer organization, seven healthcare professional organizations, three industry commenters, three patient organizations, and one policy organization generally commented on the proposed enhancements related to guidance development. These stakeholders were generally pleased to see that FDA had committed to issuing guidance by a specific date citing that issuance of the proposed guidance documents will provide clarity to industry and other stakeholders on Agency expectations. However, nearly all of these stakeholders expressed concern around the length of time until these guidances would be issued and urged FDA to publish these guidance documents as soon as possible. Additionally, concern was expressed around the timeframe for which additional products will be approved and be brought to the market without final guidance in place.

As noted above, FDA is committed to delivering this guidance in a timely manner, and while the dates included in the provisions for guidance development do not preclude the possibility that these documents could be issued earlier, FDA is currently challenged by very limited staffing that limit the ability to meet these commitments in an earlier time frame. In addition, the timeline for guidelines to address scientifically and legally complex and novel issues such as those identified for biosimilars can be difficult to predict due to the technical uncertainty, and the range of public comments that may be received on draft guidance. Accordingly, the goal dates proposed in the enhancements for BsUFA II also try to factor in these considerations.

FDA received a number of comments on proposed content of guidances that are currently in development, such as labeling of biosimilar products, nonproprietary naming of biological products, and considerations in demonstrating interchangeability with a reference product. However, these comments on the content of the currently published draft guidances, regardless of merit, are outside the scope of the BsUFA reauthorization discussions—performance goals and procedures for the BsUFA program.

FDA has and will continue to engage with public stakeholders on topics of interest, including the comments mentioned above. FDA typically provides a public comment period and docket for receipt of comments for each draft guidance that is published and considers any comments provided to that docket when publishing a revised draft or final guidance.

Improving Hiring and Retention of Review Staff

In order to provide sufficient resources for the review of 351(k) applications during BsUFA II, a provision has been included to implement a full time equivalent staff-based position management system capability and an online position classification system. In addition, BsUFA II includes provisions for FDA to complete implementation of corporate recruiting practices, augment hiring capacity with expert contractor support, establish a dedicated function for staffing of the human drug review program, establish clear goals for biosimilar review program hiring, and conduct comprehensive and continuous assessments of hiring and retention performance. These activities are intended to speed and improve development of safe and effective biosimilar biological products for patients by allowing FDA to hire and retain sufficient numbers and types of technical and scientific experts to efficiently conduct reviews of 351(k) applications.

Four public commenters including one industry commenter, one patient organization, one consumer organization, and one healthcare professionals organization, expressed support for improving hiring and retention practices to ensure timely review of biosimilar products. FDA was urged to adopt human resource processes that allow for appropriate staffing. Additionally the importance of third party evaluation of hiring and retention activities was highlighted. One stakeholder stated that FDA must be able to hire and retain staff to carry out its mission in support for the enhancements to the hiring process.

Enhancing Capacity for Biosimilar Guidance Development, Reviewer Training, and Timely Communication

BsUFA II proposes to strengthen FDA's staff capacity to develop new regulations and guidance, to develop or revise processes as appropriate, to develop and deliver training to review staff involved in the review of 351(k) BLAs, to deliver timely information to the public to improve public understanding of biosimilarity and interchangeability, and to deliver information concerning the date of first licensure and the reference product exclusivity expiry date, to be included in the Purple Book .

Several commenters (one consumer organization, three healthcare professionals organizations, six industry commenters, one patient organization, and one policy organization) provided comments in support of this provision. These stakeholders felt that enhanced staff capacity is critical to achieving the proposed commitments related to guidance development, training, and communication. One policy organization stated that FDA should not have any unnecessary delays in the process and that it is important for FDA to have adequate resources to conduct review activities.

Two commenters including one consumer organization and one patient organization provided comments highlighting the importance for FDA to conduct outreach and to provide unbiased education to healthcare professionals and consumers to enhance the understanding and acceptance of biosimilars in the treatment of disease. Additionally, support was also expressed by one consumer organization and one healthcare professional organization for the updates to the Purple Book to include the date of first licensure and reference product exclusivity expiry date as well as other comprehensive information about biologics.

One consumer organization, one healthcare professional organization, and one industry commenter expressed support for the extra staff capacity to develop and deliver training to review staff.

Enhance Management of User Fee Resources – Modernized Time Reporting, Enhance Financial Transparency

For BsUFA II, it is proposed to establish a resource capacity planning function to improve the ability to analyze current resource needs and project future resource needs, to modernize the time reporting approach, to conduct an evaluation of BsUFA program resource management, to publish a 5-year BsUFA financial plan with annual updates, and to convene an annual public meeting, beginning in FY 2019, to discuss the financial plan and progress towards the financial management enhancements. FDA also proposes to reduce the carryover balance to no greater than 21 weeks of the FY 2022 target revenue by the end of FY 2022.

One industry commenter stated that modernization of time reporting system will yield more precise data and a better understanding of the resource needs for biosimilar program activities. Another industry commenter provided support for the establishment of a resource capacity planning function.

Financial Enhancements

For BsUFA II, several modifications are proposed to the user fee structure including: (1) to discontinue the reduction of the biosimilar biological product application fee by the cumulative BPD fees paid by sponsors, (2) to discontinue the establishment and supplement fees, (3) to rename the product fee as the BsUFA Program fee, (4) to modify the Program fee billing date to minimize the need for multiple billing cycles, and (5) to add a limitation that a sponsor shall not be assessed more than five BsUFA Program fees for a fiscal year for products identified in each distinct approved biosimilar biological product application held by that sponsor. Additionally, the current BsUFA fee structure references PDUFA fees each fiscal year and calculates biosimilar biological product development program (BPD) fees based on the PDUFA application fee. For BsUFA II, it is proposed that the user fee revenue amounts and fee amounts are independent of PDUFA and based on BsUFA program costs.

Two consumer organizations, one healthcare professionals organization, six industry commenters, and one patient organization provided support for the proposed modifications to the user fee structure highlighting the importance for FDA to have adequate fee funding and that the proposed changes will provide more predictability. One industry commenter provided specific comments in support of an independent user fee structure. Additionally, one industry commenter mentioned that the proposed adjustments will account for the unpredictability in the number of applications received by collecting a smaller portion of fees from applications and a larger percentage from a program fee based on the number of products.

FDA was urged to ensure that the fee amounts will be sufficient to offset increased workload required under BsUFA II. One industry commenter expressed concern with discontinuation of the deduction of the biosimilar marketing application fee by the total of the annual biosimilar biological product develop program fees paid prior to submitting a biosimilar application.

In addition, one healthcare professional organization indicated support for increased Congressional appropriation of non-fee funds specifically for the biosimilar user fee program.

Other Comments

This section provides a discussion of the comments that were provided on additional topics, many of which are not explicitly covered in the commitment letter and relate to broader program operations or regulatory policy issues. These include, for example, a recommendation that FDA address abuses of the citizen petition process that seek to prevent biosimilar review and approval, a recommendation that FDA address interference by

originator companies of access to reference products for biosimilar testing, a recommendation that FDA assist the Center for Medicare and Medicaid Services' in developing its policy on interchangeable biologics, and support for further efforts by FDA to clarify the definition of a "biologic."

One consumer organization and three healthcare professional organizations provided recommendations on post-market surveillance and one consumer organization expressed concern that post-market surveillance activities are not included under BsUFA II. We note that FDA has addressed post-marketing safety monitoring considerations in the guidance for industry: "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product." Additionally, FDA maintains a system of active post-marketing surveillance and risk assessment programs for all approved drugs and therapeutic biologic products, including biosimilars, to identify adverse events that did not appear during the approval process.

A number of stakeholders commented on a need for FDA to develop a process to include patients during drug development similar to the model used under PDUFA. Although the patient focused drug development meetings are a commitment completed under the PDUFA program, this does not limit the applicability of the findings from these meetings to PDUFA products. FDA appreciates the thoughtful input provided by these stakeholders and will consider this input for future patient engagement activities.

One consumer organization also commented that in general it is critical for the Agency to act independently of industry influence and to uphold its high standards for safety, efficacy, and quality of biological products.

In addition, one consumer organization expressed concern around backlog, the pace of the process, and a lack of cost savings. FDA notes that there is no backlog of applications for biosimilar biological products.[3] In addition, since the authorization of 351(k) products was only established in 2010 and the industry is still early in development, with relatively few marketing application submissions and approved products to date, it may be too early to observe the cost savings that are expected for biosimilars over time as this market matures and expands.

Conclusion

FDA has worked to follow the procedures specified in the statute for developing proposed recommendations on the reauthorization of BsUFA, and has benefited significantly from opportunities for stakeholders to provide input into those recommendations. FDA greatly appreciates the significant and thoughtful input provided by stakeholders at the two public meetings, in addition to the docket comments described above. This input has helped FDA better understand and incorporate stakeholder perspectives and priorities and this has ultimately contributed to a stronger set of proposed recommendations. FDA will continue to consider the input provided when developing plans for implementation.

Following review of the public comments, FDA has made clarifying edits to the commitment letter , and intends to send the recommendations to Congress in accordance with the procedures in section 744I(e).

[3] See FY2015 BsUFA performance report for information on program accomplishments: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM493870.pdf.