U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

BsUFA III Best Practices in Communication Summary Report

Biosimilar User Fee Act (BsUFA) Program

Office of Therapeutic Biologics and Biosimilars
Office of New Drugs
Center For Drug Evaluation and Research

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1. Background and Purpose

This report summarizes recommendations from industry stakeholders for best practices in communication following the Final BsUFA II Assessment and BsUFA Best Practices in Communication Workshop. The purpose of this report is to provide sponsors and applicants with FDA's conclusions following internal discussions and to summarize relevant FDA activities.

Under the second reauthorization of the Biosimilar User Fee Act (BsUFA) Program (i.e., BsUFA III), the U.S. Food and Drug Administration (FDA) is committed to advancing, improving, and updating its utilization of best practices when communicating with sponsors and applicants during application review. Under BsUFA III, FDA committed to updating relevant guidances, Manuals of Policies and Procedures (MAPPs), and Standard Operating Procedures and Policies (SOPPs) regarding best practices in communication on or before December 31, 2023, as appropriate.[1] To fulfill this commitment, FDA reviewed input from the "Assessment of the Program for Enhanced Review Transparency and Communication for 351(k) Biologics License Applications (BLAs) in BsUFA II" (herein referred to as the "Final BsUFA II Assessment").[2] In addition, FDA considered discussion and recommendations from the BsUFA Best Practices in Communication Workshop held on May 26, 2022.[3] This workshop brought together FDA and industry stakeholders to discuss best practices for communication during 351(k) BLA reviews that were identified within the Final BsUFA II Assessment and served as an opportunity to share ideas and perspectives to inform FDA's approach for enhancing communication with sponsors and applicants during biosimilar biological product (also referred to as "biosimilar" or "biosimilar product") application review. This report presents FDA's conclusions regarding suggested best practices from the Final BsUFA II Assessment and the BsUFA Best Practices in Communication Workshop and summarizes FDA activities toward fulfilling the BsUFA III commitment.

2. FDA Conclusions

The following section summarizes FDA's response and conclusions based on recommendations from the Final BsUFA II Assessment and BsUFA Best Practices in Communication Workshop.

FDA's Office of Therapeutic Biologics and Biosimilars (located within the Center for Drug Evaluation and Research's (CDER) Office of New Drugs (OND)) led internal discussions with the Office of Regulatory Operations (also located within CDER's OND), and the Office of Program and Regulatory Operations, the Office of Biotechnology Products and the Office of Pharmaceutical Manufacturing Assessment (all three of which are located within CDER's Office of Pharmaceutical Quality (OPQ)) regarding recommendations detailed in the Final BsUFA II Assessment and BsUFA Best Practices in Communication Workshop. This report is organized into five sections: Biosimilar Biological Product Development (BPD) Meetings, BLA Meetings, Inspections and Inspection Completion, Information Requests, and Other Topics of Discussion. Each section contains a summary of comments and suggestions from industry stakeholders collected from the Final BsUFA II Assessment and BsUFA Best Practices in Communication Workshop followed by FDA's assessment and conclusions.

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[1] See Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027 available at https://www.fda.gov/media/152279/download.

[2] Assessment of the Program for Enhanced Review Transparency and Communication for 351(k) BLAs in BsUFA II (https://www.fda.gov/media/156249/download?attachment)

[3] Unless explicitly specified, discussion in the current report refers to the BsUFA Best Practices in Communication Workshop.

Biosimilar Biological Product Development (BPD) Meetings

For certain circumstances, such as applications with complex study designs or under a new program, industry stakeholders expressed interest in the option to request longer meetings with FDA. However, since scheduling longer meetings with multiple disciplines can present challenges (e.g., competing schedules of reviewers and leadership), the approach described in the draft guidance *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products*[4] contemplates that applicants and sponsors can request multiple meetings. Such meetings could focus on gathering feedback from certain disciplines and allow for a more in-depth discussion of the topics presented. In instances where complex issues arise, FDA may respond to questions with post-meeting comments or in separate correspondence. However, industry stakeholders noted that the timeliness of FDA's response to questions in a meeting request can vary. Delays in post-meeting comments often relate to the Agency's internal discussions on the issue. For example, questions may raise novel issues that require assessment by multiple groups outside of the targeted review division, and FDA also coordinates internally to verify responses are consistently applied to similar scenarios and applications. Sponsors and applicants may contact FDA for a status update to confirm if internal discussions are still occurring.

A BPD Type 4 meeting provides an applicant or sponsor with the opportunity to discuss format and content of a complete original application or supplement. Although the feedback provided in FDA's preliminary comments often resolves a sponsor's questions prior to the meeting, industry stakeholders suggested that FDA provide pre-submission advice and create templates for application content and organization. FDA notes that the content, structure and organization of applications are described in the International Council for Harmonisation *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*. In addition, the Agency has template language it uses when providing pre-submission advice regarding the content and organization of the BLA. This language is included in applicable BPD meeting correspondences to sponsors, and recommendations in that templated language regarding content and organization of applications is being used appropriately by sponsors (e.g., including information about microbial control and facilities in the BLA). Industry stakeholders also expressed that BPD Type 4 meetings are too broad and should be limited to the content and structure of an application. FDA agrees with this sentiment, and the Agency refers sponsors and applicants to the draft guidance *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products*[4] for information on discussion topics for such meetings.

BLA Meetings

A Late-Cycle Meeting (LCM) is held for 351(k) BLAs near the end of the review cycle and is designed to facilitate communication between FDA and sponsors and applicants, with an emphasis on significant issues. Industry stakeholders noted LCMs provide the most value when they include discussion of topics of interest (e.g., inspections, labeling). Industry stakeholders also suggested that FDA solicit discussion topics from industry, particularly when there are outstanding items related to information request (IR) responses, as this would help sponsors and applicants better focus and more effectively manage their resources to promote discussion with FDA on how to address issues. FDA emphasizes that this is already the purpose of the LCM and potential topics for discussion include IRs as well as any additional substantive application issues identified by FDA (e.g., product quality issues, inspectional findings).

Nearly all eligible BsUFA II applications conducted Mid-Cycle Communications (MCCs), with both sponsors and applicants and FDA expressing that MCCs helped to progress the review process. While discussions were held as part of the BsUFA II Final Assessment on MCCs, no issues were raised on the topic.

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Inspections and Inspection Completion

Generally, industry stakeholders noted that information on inspections was clear and direct, with most inspections occurring on time. For some applications, travel restrictions associated with the COVID-19 pandemic delayed inspection activities, causing unpredictability around when FDA would be able to complete facility inspections. Additional information on how FDA handled inspections impacted by the COVID-19 pandemic can be found in the Resiliency Roadmap for FDA Inspectional Oversight.[5] Industry stakeholders also expressed the desire for greater certainty about inspection methods (e.g., in-person, records review), additional dialogue during records review, and more predictability around when FDA will complete facility inspections for both backlogged activities and new submissions. FDA published a draft guidance on assessments of manufacturing facilities in September 2023 that addresses some of the previously mentioned concerns and is tied to a BsUFA III commitment (Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications[6]). Industry also expressed that more communication with FDA could improve the predictability of inspection timing and aid coordination with their batch manufacturing schedule, noting it can be expensive for industry to manufacture products that they must later discard. FDA recognizes this concern, but underscored that manufacturing site inspections must occur as the product is manufactured during the BLA review cycle. Therefore, the Agency noted it is the applicant's responsibility to work with the manufacturer and schedule production activities in such a way that allows FDA to conduct their inspection during the manufacturing process and complete their post-inspection activities reasonably ahead of the action date. FDA has observed that early communications about manufacturing plans facilitate scheduling inspections.

Information Requests (IRs)

Sponsors and applicants will commonly respond to IRs via email and subsequently submit a formal response through the electronic gateway. Industry stakeholders commented this is useful when FDA requests a short turnaround (e.g., labeling, IRs) and requested that FDA communicates when an IR is resolved. Industry stakeholders defined resolved as FDA deeming the response to have provided sufficient information to continue their review, while understanding FDA may still send other related or unrelated IRs during the review process. However, considering the volume of IRs from all relevant disciplines, it may not be realistic for FDA to communicate updates on all submitted IRs. Under the current process, FDA aims to acknowledge IR responses and, when possible, confirm whether the response is adequate when sponsors and applicants request this update. FDA also notes that MCCs and LCMs are appropriate venues to discuss the status of IRs.

Industry stakeholders offered several suggestions regarding IRs, particularly on their timing and response processes. For most IRs, sponsors and applicants provide responses by the date specified by FDA unless they request an extension. Industry stakeholders conveyed that it may not be feasible for international sponsors and applicants to respond to certain IRs within a requested two-day window due to the need for data analysis or data generation as well as the potential time difference between the Agency and the applicant location. In these cases, FDA notes sponsors and applicants can request an extension, and the Agency's review teams will consider the applicant's request and, if acceptable, provide an updated response date for the IR. FDA sends IRs to gather information and data necessary to continue their application review and encourages sponsors and applicants to meet the requested response dates when possible. For IRs requiring specific data, industry stakeholders suggested that FDA provide a template table and specific instructions to assist sponsors and applicants to respond in a complete and correct manner. FDA notes that IRs greatly vary depending on the discipline and the type of data and information requested, therefore a specific template for IR responses is generally not practical.

[5] https://www.fda.gov/media/148197/download.

[6] When final, this guidance will represent the FDA's current thinking on this topic.

Another recommendation from industry stakeholders was that FDA Regulatory Project Managers discuss and consider applicant preferences for issuing IRs (i.e., bundling IRs versus issuing as available) and other response time issues or constraints. For example, some industry stakeholders suggested that FDA could prioritize the review of specific types of deficiencies the Agency deems to be significant (e.g., Chemistry, Manufacturing, and Controls (CMC), other clinical issues). FDA notes that CMC issues and other clinical questions are identified throughout the review cycle, and the Agency sends IRs once they identify an issue. In addition, bundling requests may lead to difficulties in tracking or be impractical if a specific IR requires more immediate attention. As noted above, FDA sends IRs to gather information and data necessary to continue review of the application. Delaying an IR response to bundle responses together may lead to unnecessary delays in review. Therefore, FDA generally has requested that sponsors and applicants respond to IRs once the data and information is available to facilitate timely reviews.

Industry stakeholders also suggested that FDA consider holding ad hoc meetings to help clarify complex issues and reduce the number of back-and-forth communications needed to address any major concerns raised by FDA. FDA recommends that current practices remain in place, where ad hoc meetings are held as needed depending on the workload capacity of the appropriate divisions. FDA also notes there are preestablished avenues of communication under the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs ("The Program") to discuss and clarify IRs and complex issues. FDA continues to uphold the fundamental values of clear and effective communication and related concepts described in the draft guidance for industry and review staff *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications.*[7]

Other Topics of Discussion

Industry stakeholders expressed concern that divisions that traditionally review originator biological products (i.e., those developed under the 351(a) regulatory pathway) and individual reviewers who are new to biosimilars may be unfamiliar with biosimilar review and policies. As a result, FDA reviewers may default to practices specific to originator biological products during the review process, which could affect biosimilar development and approval. To address this, FDA has provided, and continues to provide, internal education on biosimilars to relevant FDA staff, utilizing information from various sources (e.g., laws, regulations, guidances). This internal education supplements the numerous additional public-facing FDA educational trainings and materials on biosimilars.[8]

While industry stakeholders generally found that Good Review Management Principles (GRMPs) provide clear operational principles, they expressed uncertainty regarding labeling negotiations. Sponsors and applicants expressed belief that inconsistencies in labeling negotiation timelines result from different labeling reviews occurring over the review period. While FDA acknowledges that timelines for labeling review can vary among applications, labeling negotiations commence once all required FDA staff finalizes their initial review of the draft labeling. In addition, FDA notes that labeling review timelines are described in the *21st Century Review Process Desk Reference Guide*[9] and are communicated in the Day 74 letter. FDA acknowledges that some labeling negotiations may be delayed if novel issues arise during review that require input from other FDA staff during the review cycle. FDA issued Day-74 letters for all applications in the BsUFA II Program, with one-third of baseline applications and one-quarter of these applications having potential review issues identified. While discussions were held regarding Day 74 letters as part of the BsUFA II Final Assessment, no concerns were voiced by industry stakeholders.

[7] When final, this guidance will represent the FDA's current thinking on this topic.

[8] Biosimilars (https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars)

[9] 21st Century Review Process Desk Reference Guide (https://www.fda.gov/media/78941/download)

3. Appendix

This section includes a definition for all acronyms used in this document.

Acronym	Definition
BLA	Biologics License Application
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Act
CMC	Chemistry, Manufacturing, and Controls
CDER	Center for Drug Evaluation and Research
GRMPs	Good Review Management Principles
FDA	U.S. Food and Drug Administration
IR	Information Request
LCM	Late-Cycle Meeting
MAPP	Manual of Policies and Procedures
MCC	Mid-Cycle Communication
SOPP	Standard Operating Procedures and Policies