BIOSIMILAR BIOLOGICAL PRODUCT REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2028 THROUGH 2032

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BIOSIMILAR BIOLOGICAL PRODUCT REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2028 THROUGH 2032

This document contains the performance goals and procedures for the Biosimilar User Fee Act (BsUFA) reauthorization for fiscal years (FYs) 2028-2032, known as BsUFA IV. It is commonly referred to as the "goals letter" or "commitment letter." The goals letter represents the product of FDA's discussions with the regulated industry and public stakeholders, as mandated by Congress. The performance and procedural goals and other commitments specified in this letter apply to aspects of the biosimilar biological product review program that are important for facilitating timely access to safe and effective biosimilar medicines for patients. FDA is committed to meeting the performance goals specified in this letter, enhancing management of BsUFA resources, and ensuring BsUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner.

Under BsUFA IV, FDA is committed to ensuring effective scientific coordination and review consistency, as well as efficient governance and operations across the biosimilar biological product review program.

FDA and the regulated industry will periodically and regularly assess the progress of the biosimilar biological product review program throughout BsUFA IV. This will allow FDA and the regulated industry to identify emerging challenges and develop strategies to address these challenges to ensure the efficiency and effectiveness of the biosimilar biological product review program.

I. ENSURING THE EFFECTIVENESS OF THE BIOSIMILAR BIOLOGICAL PRODUCT REVIEW PROGRAM

A. REVIEW PROCESSES AND PERFORMANCE GOALS

1. Original and Resubmitted Biosimilar Biological Product Applications

a. Review and act on 90 percent of original biosimilar biological product application submissions within 10 months of the 60 day filing date.

b. Review and act on 90 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

2. Original and Resubmitted Supplemental Biosimilar Biological Product Applications

a. Review and act on 90 percent of the following supplements within 4 months of receipt:

i. **Category 1**: Supplements seeking licensure for one or more of the following changes when the submission does not include new data from manufacturing, analytical, clinical, or human factors studies:

- Adding or modifying an indication
- Interchangeability

b. Review and act on 90 percent of the following supplements within 6 months of receipt:

i. **Category 2**: Supplements seeking licensure for one or more of the following changes when the submission includes new data from manufacturing, analytical, clinical pharmacology, or human factors studies:

- Adding or modifying an indication
- Interchangeability
- Adding a new strength, dosage form, or route of administration
- Adding a new delivery device or container closure system. (This excludes modifications to an approved delivery device or container closure system, unless such supplement includes new data from human factors studies.)

This category also includes any other supplements with new data from human factors studies.

c. FDA will issue a letter to the applicant for 90% of original Category 1 and Category 2 supplements within 60 calendar days of receipt. The letter will acknowledge receipt of the submission and provide the date for FDA to take action on the supplement.

i. Applicants may include in their cover letter a request that FDA not approve the supplement before a certain date, as long as that date is not later than the BsUFA goal date.

d. FDA will strive to issue a draft guidance and/or a MAPP and/or SOPP on post-approval submissions to 351(k) applications that seek to make labeling changes to conform to changes in reference product labeling by no later than September 30, 2028. If FDA issues a draft guidance, FDA will work toward the goal of publishing a revised draft or final guidance within 24 months after the close of the public comment period.

i. Prior to issuance of the above draft guidance and/or a MAPP and/or SOPP, if a supplement is submitted seeking to update the labeling for a licensed biosimilar or interchangeable product with regards to safety information that has been updated in the reference product labeling and is applicable to one or more indications for which the biosimilar or interchangeable product is licensed, and if FDA were to determine that such supplement should be classified as a Prior Approval Supplement, FDA will review and act on the supplement within 3 months of receipt. Once published, FDA will assess such labeling submissions as described in the related draft guidance and/or MAPP and/or SOPP.

e. FDA will strive to issue a draft guidance and/or a MAPP and/or SOPP on submissions for unbranded 351(k) labeling by no later than September 30, 2028. If FDA issues a draft guidance, FDA will work toward the goal of publishing a revised draft or final guidance within 24 months after the close of the public comment period.

3. Original Manufacturing Supplements

a. Review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

b. Review and act on 90 percent of all other manufacturing supplements within 6 months of receipt.

4. Goals Summary Tables

Table 1: Original and Resubmitted Applications & Category 1 and 2 Supplements

Original Biosimilar Biological Product Application Submissions	90% in 10 months of the 60 day filing date
Resubmitted Original Biosimilar Biological Product Applications	90% in 6 months of the receipt date

Category 1 Supplements **(original and resubmitted)**	90% in 4 months of the receipt date
Category 2 Supplements **(original and resubmitted)**	90% in 6 months of the receipt date

Table 2: Manufacturing Supplements

	PRIOR APPROVAL	**ALL OTHER**
Manufacturing Supplements	90% in 4 months of the receipt date	90% in 6 months of the receipt date

5. Review Performance Goal Extensions

a. Major Amendments

i. A major amendment to an original application, supplement with clinical efficacy data, or resubmission of any of these applications, submitted at any time during the review cycle, may extend the goal date by three months.

ii. A major amendment may include, for example, a major new clinical study report; major re-analysis of previously submitted study(ies); submission of a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) not included in the original application; or significant amendment to a previously submitted REMS with ETASU. Generally, changes to REMS that do not include ETASU and minor changes to REMS with ETASU will not be considered major amendments.

iii. A major amendment to a manufacturing supplement or Category 2 supplement submitted at any time during the review cycle may extend the goal date by two months.

iv. Only one extension can be given per review cycle.

v. Consistent with the underlying principles articulated in the Good Review Management Principles and Practices (GRMP) guidance, FDA's decision to extend the review clock should, except in rare circumstances, be limited to occasions where review of the new

information could address outstanding deficiencies in the application and lead to approval in the current review cycle.

vi. FDA will publish each FY on its website, using a consistent publicly disclosed methodology:

- the number and percentage of applications and supplements for which an amendment FDA deemed as major was submitted and resulted in a goal date extension.

b. Inspection of Facilities Not Adequately Identified in an Original Application or Supplement

i. All original applications and supplements are expected to include a comprehensive and readily located list of all manufacturing facilities included or referenced in the application or supplement. This list provides FDA with information needed to schedule inspections of manufacturing facilities that may be necessary before approval of the original application or supplement.

ii. If, during FDA's review of an original application or supplement, the Agency identifies a manufacturing facility that was not included in the comprehensive and readily located list, the goal date may be extended.

- If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in an original application or supplement with clinical data, the goal date may be extended by three months.

- If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in a manufacturing supplement, the goal date may be extended by two months.

c. Extensions Following a Post-PLI Meeting for Original 351(k) BLAs, Not Including Supplements

i. When a meeting request package containing substantive information related to a response to deficiencies observed on a Pre-License Inspection (PLI) is submitted prior to a post-PLI meeting (see section I.K.4.), or substantive information is provided to FDA following a post-PLI meeting, FDA may extend the goal date by 3 months.

ii. FDA's decision to extend the review clock should, except in rare circumstances, be limited to occasions when an extension would permit review of the new information provided, and there is a reasonable likelihood that review of the new information provided

could address outstanding facility deficiencies relevant to the application and lead to approval in the current review cycle.

iii. Only one extension will be afforded per review cycle, inclusive of extensions for Major Amendments and for Inspection of Facilities Not Adequately Identified in an Original Application or Supplement.

6. Provisional Determinations

FDA will issue a Provisional Determination Letter (PD) when it determines that a 351(k) BLA meets the applicable licensure standards, but FDA cannot make approval effective due to an unexpired period of exclusivity. Where approval of the entire application or supplement (referred to in this section as an application) is blocked, FDA will issue a PD for the entire application. Where exclusivity blocks only a part of the application, FDA will administratively split the application to issue an approval as well as a PD.

For purposes of this section, the earliest lawful approval date (ELAD) means the first date on which no applicable exclusivity prevents approval of the application.

An application is in PD status if FDA has issued a PD for that application. In certain situations, a product may be covered by both an approved application and an application in PD status, such as when FDA has administratively split an application.

The processes below are intended to enable FDA to complete any reviews and act on applications in PD status on their ELAD.

a. Changes to Applications in PD Status:

Applicants seeking to propose changes to a product covered by an application in PD status can submit those changes as follows:

i. When a product is covered by both an approved application and an application in PD status, applicants should submit any proposed change(s) in a supplement(s) to the approved application. This does not include a Request for Approval (RFA) described in paragraph 2 below, which is always submitted in an amendment.

ii. When a product is not covered by an approved application and only covered by an application in PD status, applicants should submit any proposed change(s) in an amendment(s) to the PD application (PD amendment).

PD Amendments Procedure: Upon receipt of a PD amendment (not including an RFA), FDA will convert the application's status from PD to Pending. FDA will review PD amendments using the same procedures and timelines that would apply if the proposed changes were submitted in a supplement. While BsUFA performance metrics will not apply to PD amendments, FDA will strive to take action within the assigned timeline. Upon completing review, FDA will reissue a PD, issue an Approval, or issue a Complete Response Letter, as appropriate.

To minimize duplicative review, FDA may defer review of a PD amendment in limited circumstances, such as when the timing and content of an amendment suggests that the

Agency may need to review the same information again closer to the ELAD. If FDA defers review, it will communicate its intention to do so to the applicant, as well as the date on which it intends to commence review. If the sponsor believes that deferral or the date on which FDA intends to commence review is inappropriate, then the sponsor may provide a rationale explaining why review at the time of submission or commencing on a different date is warranted. For any deferred PD amendment, FDA will notify the applicant when FDA has commenced review.

b. Request for Approval (RFA)

i. RFA Procedure: An RFA is a type of PD amendment through which an applicant requests approval of an application in PD status. An RFA should not include new data or changes to the application (other than labeling). It should include a complete list of all changes, if any, since the time the PD was issued (including changes that may have been reviewed in a supplement as well as any pending changes under review), and the proposed final labeling.

- If an RFA is received between 4 and 6 months prior to the ELAD, FDA will review the RFA by such date, subject to the performance goal described below.

- If an RFA is received fewer than 4 months but more than 30 days before the ELAD, FDA will strive to review the RFA by such date.

- If an RFA is received 30 or fewer days before the ELAD, FDA will strive to review the RFA within 30 calendar days of receipt.

- If an RFA is received more than 6 months prior to the ELAD, FDA may request that the applicant withdraw the RFA and resubmit it between 4 to 6 months of the ELAD. Otherwise, FDA will strive to review the RFA by the ELAD.

ii. Performance goal: FDA will review and act on 90% of RFAs by the ELAD, provided that the RFA was received between 4 and 6 months before such date and that no other pending PD amendment for that application has a review date that falls after the ELAD.

If there are pending PD amendments for an application in PD status, and at least one PD amendment has been assigned a review date that falls after the ELAD, FDA will strive to take action on all PD amendments, including the RFA, on the latest assigned review date.

c. Guidance

FDA will strive to publish a draft guidance or MAPP and/or SOPP, and create or update relevant MAPPs and SOPPs, as appropriate, by September 30, 2030 to address considerations for the provisional determination process.

7. Imminent Action

Imminent Action is intended to promote efficient review by allowing FDA to work past a goal date to address discrete, late-arising, resolvable issues. This should help avoid otherwise unnecessary provisional determinations and complete response actions. Imminent action will not function as a routine mechanism to extend the review cycle.

Accordingly, FDA will continue assessing an original 351(k) BLA, resubmitted 351(k) BLA, or supplement through a BsUFA goal date when, in FDA's judgment, resolution would be reasonably likely and FDA could issue an approval or provisional determination within 60 days after the goal date under the following circumstances:

i. when an update(s) to reference product labeling late in the review cycle necessitates submission of additional information to the 351(k) BLA for FDA review;

ii. when a modification(s) to the reference product REMS or an approved single shared system REMS late in the review cycle necessitates submission of additional information to the 351(k) BLA for FDA review;

iii. when an original 351(k) BLA meets the requirements for approval but FDA cannot make approval effective due to exclusivity that will expire within 60 days of the applicable BsUFA goal date;

iv. when FDA, at its discretion, accepts an applicant's unsolicited amendment late in the review cycle that includes only limited additional (or no) data; or

v. when resolving one or more small issues (excluding facility-related issues) remaining from one or more disciplines that, in FDA's judgement, cannot be reasonably resolved during the remainder of the ongoing review cycle. A "small issue" means an issue that could not have reasonably been reviewed and resolved during the review cycle and can be resolved within 60 days of the goal date because resolution of the issue requires only: (1) a clarification of scientific information regarding data already submitted to the BLA, (2) submission of limited additional data (*e.g.*, an additional timepoint for stability testing), and/or (3) the submission of administrative information (e.g., completion of a form or a change in an address).[1]

If, after FDA invokes imminent action, an original 351(k) BLA, resubmission, or supplement is approved within 60 days after the goal date or FDA issues a Provisional Determination within such timeframe, the goal date will be considered to have been met.

[1] This provision does not apply to supplements.

FDA will strive to act prior to the 60-day period for an imminent action when the assessment is complete and there are no outstanding deficiencies.

FDA will promptly notify the applicant when it intends to exercise imminent action, including identification of the basis for its use and, if the basis is a small issue(s), identification of each small issue. Applicants may proactively request that FDA consider use of imminent action in advance of the goal date where the applicant believes the criteria described in this section are met.

FDA will publish each FY on its website, using a consistent publicly disclosed methodology:

- the number and percentage of applications and supplements for which imminent action was exercised
- the number and percentage of applications and supplements for which imminent action was exercised that were approved or resulted in a provisional determination within 60 days of the goal date

8. New Target Action Dates

By the goal date, if the goal date will be missed and FDA has not informed the applicant of its intent to exercise imminent action per section I.A.7., FDA will notify the applicant that FDA will miss the BLA or supplement goal date. In that communication, FDA will include a new internal target action date ("target date") 6 months from the goal date and identify the issue(s) causing delay (consistent with confidentiality obligations). FDA will also strive to issue any Information Requests (IRs) by the goal date and continue reviewing the application to resolve any outstanding issues unrelated to the issue causing the delay. FDA will strive to take action on the BLA or supplement as soon as possible. If the target date is not met, no subsequent target date will be assigned to the submission. FDA will contact the applicant to inform them that the target date will not be met and communicate an update on the issue causing delay (consistent with confidentiality obligations) and the estimated timeline for action, when possible.

FDA will publish each FY on its website, using a consistent, publicly disclosed reporting methodology:

- the number of applications and supplements for which a new target action date was issued
- the percentage of those new target action dates that were met

B. PROGRAM FOR ENHANCED REVIEW TRANSPARENCY AND COMMUNICATION FOR ORIGINAL 351(K) BLAS

To promote transparency and communication between the FDA review team and the applicant, FDA will apply the following model ("the Program") to the review of all original Biologics License Applications (BLAs) submitted under section 351(k) of the Public Health Service Act ("351(k) BLAs"), including applications that are resubmitted following a Refuse-to-File

decision, received from October 1, 2027, through September 30, 2032.[2] The goal of the Program is to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality biosimilar and interchangeable biological products.

The standard approach for the review of original 351(k) BLAs is described in this section. However, the FDA review team and the applicant may discuss and reach mutual agreement on an alternative approach to the timing and nature of interactions and information exchange between the applicant and FDA, i.e., a Formal Communication Plan for the review of the original 351(k) BLA. The Formal Communication Plan may include elements of the standard approach (e.g., a mid-cycle communication or a late-cycle meeting) as well as other interactions that sometimes occur during the review process (e.g., a meeting during the filing period to discuss the application, i.e., an "application orientation meeting"). If appropriate, the Formal Communication Plan should specify those elements of the Program that FDA and the sponsor agree are unnecessary for the application under review. If the review team and the applicant anticipate developing a Formal Communication Plan, the elements of the plan should be discussed and agreed to at the pre-submission meeting (see section I.B.1.) and reflected in the meeting minutes. The Formal Communication Plan may be reviewed and amended at any time based on the progress of the review and the mutual agreement of the review team and the applicant. For example, the review team and the applicant may mutually agree at any time to cancel future specified interactions in the Program (e.g., the late-cycle meeting) that become unnecessary (e.g., because previous communications between the review team and the applicant are sufficient). Any amendments made to the Formal Communication Plan should be consistent with the goal of an efficient and timely first cycle review process and not impede the review team's ability to conduct its review.

The remainder of this section I.B. describes the parameters that will apply to FDA's review of applications in the Program.

1. **Pre-submission meeting:** The applicant is strongly encouraged to discuss the planned content of the application with the appropriate FDA review division at a biosimilar biological product development (BPD) Type 4 (pre-351(k) BLA) meeting. This meeting will be attended by the FDA review team, including appropriate senior FDA staff.

    a. The BPD Type 4 (pre-351(k) BLA) meeting should be held sufficiently in advance of the planned submission of the application to allow for meaningful response to FDA feedback and should generally occur not less than 2 months prior to the planned submission of the application.

    b. In addition to FDA's preliminary responses to the applicant's questions, other potential discussion topics include preliminary discussions regarding the approach to developing the content for REMS, where applicable, patient labeling (e.g.,

[2] The "Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs" (referred to as "the Program" and described in this goals letter) is distinct from the statutory term, "biosimilar biological product development program," which is defined in section 744G of the Federal Food, Drug, and Cosmetic (FD&C Act) as "the program under [the statutory BsUFA fee provisions] for expediting the process for the review of submissions in connection with biosimilar biological product development." Section 744G(6) of the FD&C Act.

Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. These discussions will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

The FDA and the applicant will agree on the content of a complete application for the proposed indication(s) at the pre-submission meeting. The FDA and the applicant may also reach agreement on submission of a limited number of application components not later than 30 calendar days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. These agreements will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

i. Examples of application components that may be appropriate for delayed submission include updated stability data (e.g., 15-month data to update 12-month data submitted with the original submission).

ii. Major components of the application (e.g., the complete comparative analytical assessment, the complete study report of a comparative clinical study or the full study report of necessary immunogenicity data) are expected to be submitted with the original application and are not subject to agreement for late submission.

2. **Original application submission:** Applications are expected to be complete, as agreed between the FDA review team and the applicant at the BPD Type 4 (pre-351(k) BLA) meeting, at the time of original submission of the application. If the applicant does not have a BPD Type 4 (pre-351(k) BLA) meeting with FDA, and no agreement exists between FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant's submission is expected to be complete at the time of original submission.

a. All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

b. Any components of the application that FDA agreed at the pre-submission meeting could be submitted after the original application are expected to be received not later than 30 calendar days after receipt of the original application.

c. Incomplete applications, including applications with components that are not received within 30 calendar days after receipt of the original submission, will be subject to a Refuse-to-File decision.

d. The following parameters will apply to applications that are subject to a Refuse-to-File decision and are subsequently filed over protest:

i. The original submission of the application will be subject to the review performance goal as described in section I.A.1.a.

ii. The application will not be eligible for the other parameters of the Program (e.g., mid-cycle communication, late-cycle meeting).

iii. FDA generally will not review amendments to the application during any review cycle. FDA also generally will not issue information requests to the applicant during the Agency's review.

iv. The resubmission goal described in section I.A.1.b. will not apply to any resubmission of the application following an FDA complete response action. Any such resubmission will be reviewed as available resources permit.

e. Since applications are expected to be complete at the time of submission, unsolicited amendments are expected to be rare and not to contain major new information or analyses. Review of unsolicited amendments, including those submitted in response to an FDA communication of deficiencies, will be handled in accordance with the GRMP guidance and the Imminent Action process (see section I.A.7.). The GRMP guidance includes the underlying principle that FDA will consider the most efficient path toward completion of a comprehensive review that addresses application deficiencies and leads toward a first cycle approval when possible.

3. <u>Day 74 Letter:</u> FDA will follow existing procedures regarding identification and communication of substantive review issues identified during the initial filing review to the applicant in the "Day 74 letter." If no substantive review issues were identified during the filing review, FDA will so notify the applicant. FDA's filing review represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle.

For applications subject to the Program, the timeline for this communication will be within 74 calendar days from the date of FDA receipt of the original submission. The planned timeline for review of the application included in the Day 74 letter for applications in the Program will include:

a. the planned date for the internal mid-cycle review meeting,

b. preliminary plans on whether to hold an Advisory Committee (AC) meeting to discuss the application,

c. a target date for communication of feedback from the review division to the applicant regarding proposed labeling and any postmarket requirements or postmarket commitments the Agency will be requesting.

4. <u>Review performance goals:</u> For original 351(k) BLA submissions that are filed by FDA under the Program, the BsUFA review clock will begin at the conclusion of the 60

calendar day filing review period that begins on the date of FDA receipt of the original submission. The review performance goals for these applications are as follows:

a. Review and act on 90 percent of original 351(k) BLA submissions within 10 months of the 60 day filing date.

5. <u>Mid-Cycle Communication:</u> The FDA Regulatory Project Manager (RPM), and other appropriate members of the FDA review team (e.g., Cross Discipline Team Leader (CDTL)), will call the applicant, generally within 2 weeks following the Agency's internal mid-cycle review meeting, to provide the applicant with an update on the status of the review of their application. An agenda will be sent to the applicant prior to the mid-cycle communication. Scheduling of the internal mid-cycle review meeting will be handled in accordance with the GRMP guidance. The RPM will coordinate the specific date and time of the telephone call with the applicant.

The update should include any significant issues identified by the review team to date, any information requests, and information regarding major concerns with the following:

a. The comparative analytical assessment, including the potential relevance of any issues (e.g. data analysis issues or potential clinical impact of observed analytical differences), intended to support a demonstration that the proposed biosimilar biological product is highly similar to the reference product.

b. The data intended to support a demonstration of no clinically meaningful differences, including discussion of any immunogenicity issues.

c. The data intended to support a demonstration of interchangeability.

d. Chemistry, Manufacturing, and Controls (CMC) issues.

In addition, the update should include preliminary review team thinking regarding the content of the proposed REMS, where applicable, proposed date(s) for the late-cycle meeting, updates regarding plans for the AC meeting (if an AC meeting is anticipated), and other projected milestone dates for the remainder of the review cycle.

6. <u>Late-Cycle and Advisory Committee Meetings:</u> A meeting will be held between the FDA review team and the applicant to discuss the status of the review of the application late in the review cycle. Late-cycle meetings will generally be face-to-face meetings; however, the meeting may be held by teleconference if FDA and the applicant agree. Since the application is expected to be complete at the time of submission, FDA intends to complete primary and secondary reviews of the application in advance of the planned late-cycle meeting.

a. FDA representatives at the late-cycle meeting are expected to include the signatory authority for the application, review team members from appropriate disciplines, and appropriate team leaders and/or supervisors from disciplines for which substantive issues have been identified in the review to date.

b. For applications that will be discussed at an AC meeting, the following parameters apply:

   i. FDA intends to convene AC meetings no later than 2 months prior to the BsUFA goal date. The late-cycle meeting will occur not less than 12 calendar days before the date of the AC meeting.

   ii. FDA intends to provide final questions for the AC to the sponsor and the AC not less than 2 calendar days before the AC meeting.

   iii. Following an AC meeting, FDA and the applicant may agree on the need to discuss feedback from the committee for the purpose of facilitating the remainder of the review. Such a meeting will generally be held by teleconference without a commitment for formal meeting minutes issued by the Agency.

c. For applications that will not be discussed at an AC meeting, the late-cycle meeting will generally occur not later than 3 months prior to the BsUFA goal date.

d. Late-Cycle Meeting Background Packages: The Agency background package for the late-cycle meeting will be sent to the applicant not less than 10 calendar days before the late-cycle meeting. The package will consist of any discipline review (DR) letters and IRs issued to date, a brief memorandum from the review team outlining substantive application issues (e.g., deficiencies identified by primary and secondary reviews), the Agency's background package for the AC meeting (incorporated by reference if previously sent to the applicant), potential questions and/or points for discussion for the AC meeting (if planned) and the current assessment of the content of proposed REMS or other risk management actions, where applicable.

e. Late-Cycle Meeting Discussion Topics: Potential topics for discussion at the late-cycle meeting include:

   i. major deficiencies identified to date;

   ii. comparative analytical assessment, including the potential relevance of any issues (e.g. data analysis issues or potential clinical impact of observed analytical differences), intended to support a demonstration that the proposed biosimilar biological product is highly similar to the reference product;

   iii. data intended to support a demonstration of no clinically meaningful differences, including discussion of any immunogenicity issues;

   iv. data intended to support a demonstration of interchangeability;

   v. CMC issues;

   vi. inspectional findings identified to date;

vii. issues to be discussed at the AC meeting (if planned);

viii. current assessment of the content of proposed REMS or other risk management actions, where applicable;

ix. information requests from the review team to the applicant; and

x. additional data or analyses the applicant may wish to submit.

With regard to submission of additional data or analyses, the FDA review team and the applicant will discuss whether such data will be reviewed by the Agency in the current review cycle and, if so, whether the submission will be considered a major amendment and trigger an extension of the BsUFA goal date.

7. **Inspections:** FDA's goal is to complete all GCP, GLP, and GMP inspections for applications in the Program within 10 months of the date of original receipt of the application. This will allow 2 months at the end of the review cycle to attempt to address any deficiencies identified by the inspections.

C. INITIAL PEDIATRIC STUDY PLAN

FDA will open a docket and issue a Federal Register notice no later than December 31, 2027, making available for public comment a biosimilar-specific initial pediatric study plan (iPSP) template. FDA will revise the biosimilar-specific iPSP template as necessary and appropriate in light of any comments received and will publish the template no later than August 31, 2028.

By no later than December 31, 2028, FDA will strive to issue a draft guidance addressing pediatric study plans for biosimilar products and how biosimilar applicants can meet applicable Pediatric Research Equity Act (PREA) requirements. FDA will strive to publish a revised draft or final guidance within 24 months after the close of the public comment period.

D. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

To enhance patient safety, FDA is committed to various measures to reduce medication errors related to look-alike and sound-alike proprietary names and such factors as unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design. The following performance goals apply to FDA's review of biosimilar biological product proprietary names during the BPD phase and during FDA's review of a marketing application:

1. Proprietary Name Review Performance Goals During The BPD Phase

a. Review 90% of proprietary name submissions filed within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.

b. If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

c. If the proprietary name is found to be unacceptable, the above review performance goals also would apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.

d. A complete submission is required to begin the review clock.

2. Proprietary Name Review Performance Goals During Application Review

a. Review 90% of biosimilar biological product proprietary name submissions filed within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

b. A supplemental review will be done meeting the above review performance goals if the proprietary name has been submitted previously (during the BPD phase) and has received tentative acceptance.

c. If the proprietary name is found to be unacceptable, the sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

d. If the proprietary name is found to be unacceptable, the above review performance goals apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.

e. A complete submission is required to begin the review clock.

E. MAJOR DISPUTE RESOLUTION

1. Procedure

For procedural or scientific matters involving the review of biosimilar biological product applications and supplements (as defined in BsUFA) that cannot be resolved at the signatory authority level (including a request for reconsideration by the signatory authority after reviewing any materials that are planned to be forwarded with an appeal to the next level), the response to appeals of decisions will occur within 30 calendar days of the Center's receipt of the written appeal.

2. Performance Goal

90% of such responses are provided within 30 calendar days of the Center's receipt of the written appeal.

3. Conditions

a. Sponsors should first try to resolve the procedural or scientific issue at the signatory authority level. If it cannot be resolved at that level, it should be appealed to the next higher organizational level (with a copy to the signatory authority) and then, if necessary, to the next higher organizational level.

b. Responses should be either verbal (followed by a written confirmation within 14 calendar days of the verbal notification) or written and should ordinarily be to either grant or deny the appeal.

c. If the decision is to deny the appeal, the response should include reasons for the denial and any actions the sponsor might take to persuade the Agency to reverse its decision.

d. In some cases, further data or further input from others might be needed to reach a decision on the appeal. In these cases, the "response" should be the plan for obtaining that information (e.g., requesting further information from the sponsor, scheduling a meeting with the sponsor, scheduling the issue for discussion at the next scheduled available advisory committee).

e. In these cases, once the required information is received by the Agency (including any advice from an advisory committee), the person to whom the appeal was made, again has 30 calendar days from the receipt of the required information in which to either deny or grant the appeal.

f. Again, if the decision is to deny the appeal, the response should include the reasons for the denial and any actions the sponsor might take to persuade the Agency to reverse its decision.

g. Note: If the Agency decides to present the issue to an advisory committee and there are not 30 days before the next scheduled advisory committee, the issue will be presented at the following scheduled committee meeting to allow conformance with advisory committee administrative procedures.

F. CLINICAL HOLDS

1. Procedure

The Center should respond to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of the submission of such sponsor response.

2. Performance goal

90% of such responses are provided within 30 calendar days of the Agency's receipt of the sponsor's response.

G. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

1. Procedure

Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered), the Agency will evaluate certain protocols and related issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

a. The sponsor should submit a limited number of specific questions about the protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., are the endpoints adequate to assess whether there are clinically meaningful differences between the proposed biosimilar biological product and the reference product).

b. Within 45 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the Agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

c. Protocols that qualify for this program include any necessary clinical study or studies to prove biosimilarity and/or interchangeability (e.g., protocols for pharmacokinetics and pharmacodynamics studies, protocols for comparative clinical studies that will form the primary basis for demonstrating that there are no clinically meaningful differences between the proposed biosimilar biological product and the reference product, and protocols for clinical studies intended to support a demonstration of interchangeability). For such protocols to qualify for this comprehensive protocol assessment, the sponsor must have had a BPD Type 2b or 3 Meeting, as defined in section I.I., below, with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.

d. If a protocol is reviewed under the process outlined above, and agreement with the Agency is reached on design, execution, and analyses, and if the results of the study conducted under the protocol substantiate the hypothesis of the protocol, the Agency agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

2. Performance goal

90% of special protocols assessments and agreement requests completed and returned to sponsor within 45 days.

3. Reporting

The Agency will track and report the number of original special protocol assessments and resubmissions per original special protocol assessment.

H. MULTI-DOSE PHARMACOKINETIC AND/OR PHARMACODYNAMIC STUDY AND COMPARATIVE EFFICACY STUDY PROTOCOL REVIEW

During product development when a sponsor submits a protocol for a multi-dose pharmacokinetic and/or pharmacodynamic (PK and/or PD) study to be conducted in patients or a comparative efficacy study (CES) for FDA review, the sponsor will identify the submission as a "Multi-Dose Pharmacokinetic and/or Pharmacodynamic Study in Patients Protocol" or "Comparative Efficacy Study Protocol" in the subject of the cover letter. In cases where the protocol may have been previously discussed during a formal meeting or other formal communication with FDA, the date of the meeting or communication will be noted in the cover letter.

When the cover letter identifies the submission as a multi-dose PK and/or PD study in patients or a CES protocol, documents the planned study start date, and includes any critical questions requiring responses to enable study initiation, FDA will strive to review such protocols consistent with timelines in MAPP 6030.9 and SOPP 8217. FDA will update MAPP 6030.9 and SOPP 8217 by the end of FY 2028.

I. MEETING MANAGEMENT GOALS

1. Formal Meetings

Formal BsUFA meetings between sponsors and FDA consist of BPD Type 1-4 meetings. These meetings are further described below.

- A BPD Type 1 Meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (e.g., meeting to discuss clinical holds, dispute resolution meeting, a complete response letter, a refuse-to-file letter), a special protocol assessment meeting, or a meeting to address an important safety issue.

- A BPD Type 2a Meeting is a meeting focused on a narrow set of issues (e.g., often one, but not more than two issues and associated questions), requiring input from no more than 3 disciplines or review divisions. In order to request a Type 2a meeting, sponsors must first have had another BPD meeting with the Agency. Requests could include:
    - Defined CMC post-approval commitments (e.g., related to analytical methods) discussing the approach in advance of conducting the study to ensure the approach is in line with the Agency's expectations.
    - Immunogenicity testing strategy following prior FDA recommendations/feedback.
    - Feedback on revised study design when revisions are based on prior FDA feedback.
    - To discuss a new issue that arises from a prior meeting upon receipt of WROs, meeting minutes, or correspondence responding to a sponsor's meeting question received after WROs or meeting minutes (i.e., more than just a clarifying question about an FDA response from a prior meeting).

- A BPD Type 2b Meeting is a meeting to discuss questions where FDA will provide advice regarding a proposed or ongoing biosimilar biological product development program (e.g., proposed clinical study design or endpoints). For example, a Type 2b Meeting is appropriate for:
    - initial engagement with FDA to discuss the proposed development program; or
    - to discuss a set of issues that are outside the scope of a Type 2a meeting. This meeting may include substantive review of summary data but does not include review of full study reports.

  When the meeting is the sponsor's first interaction with FDA to discuss a proposed development program, sufficient information should be provided with the meeting request to enable FDA to make a preliminary determination related to potential licensure under section 351(k) and to provide meaningful advice. Preliminary comparative analytical data from the proposed biosimilar or interchangeable biosimilar product compared to the U.S.-licensed reference product are not required for the meeting request. Information provided should include identification of the reference product and a brief summary of completed or planned studies that the sponsor intends to discuss at the meeting plus any additional information to support a useful discussion. Depending on the questions being posed by the applicant, additional information in the background document supporting the meeting request may include:
    - The comparative analytical assessment plan, including preliminary identification of quality attributes and planned characterization methods
    - The indication(s) intended to be sought for licensure
    - A clinical pharmacokinetics study(ies), including intended study population
    - Other clinical study(ies) and rationale for conducting
    - If a sponsor seeks to utilize a non-U.S.-licensed comparator product in a clinical study, the proposed strategy to justify the relevance of the data generated with the non-U.S.-licensed comparator product
    - Any guidance already received from other health authorities on product development
    - Identification of the regulatory status in other jurisdictions

- A BPD Type 3 Meeting is an in-depth data review and advice meeting regarding an ongoing biosimilar biological product development program. This meeting includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding additional studies (if any), including design and analysis.

- A BPD Type 4 Meeting is a pre-submission meeting to discuss the format and content of a complete application for an original biosimilar biological product application under the Program or supplement submitted under 351(k) of the PHS Act. The purpose of this

meeting is to discuss the format and content of the planned submission and other items, including identification of those studies that the sponsor is relying on to support a demonstration of biosimilarity or interchangeability, discussion of any potential review issues identified based on the information provided, discussion of the approach to adequately address PREA, acquainting FDA reviewers with the general information to be submitted in the marketing application (including technical information), and discussion of the best approach to the presentation and formatting of data in the marketing application.

2. <u>Response to Meeting Requests</u>

a. **Procedure:** FDA will notify the sponsor in writing of the date, time, and place for the meeting, as well as expected Center participants following receipt of a formal meeting request and background package. Table 3 below indicates the timeframes for FDA's response to a meeting request.

Table 3: Timelines for Responding to Meeting Requests

Meeting Type	Response Time (calendar days)
BPD Type 1	14
BPD Type 2a, 2b, 3 and 4	21

i. For all BPD meeting types, the sponsor may request a written response to its questions, rather than a face-to-face meeting[3] or teleconference. If a written response is deemed appropriate, FDA will notify the sponsor of the date it intends to send the written response. This date will be consistent with the timeframes specified in Table 4 below for the specific meeting type.

ii. For the BPD Type 2a meeting, while the sponsor may request a face-to-face meeting, the Agency may determine that a written response to the sponsor's questions would be the most appropriate means for providing feedback and advice to the sponsor. When it is determined that the meeting request can be appropriately addressed through a written response, FDA will notify the sponsor of the date it intends to send the written response in the Agency's response to the meeting request. This date will be consistent with the timeframe for a Type 2a

[3] A "face-to-face" meeting includes both in-person meetings and virtual meetings on IT platforms that allow for both audio and visual communication.

meeting. If the sponsor believes a face-to-face Type 2a meeting is valuable and warranted, then the sponsor may provide a rationale in a follow-up correspondence explaining why a face-to-face meeting is valuable and warranted, and FDA will reconsider this request. If FDA agrees to grant the face-to-face format, the Agency will strive to schedule the meeting to occur within 60 days of FDA's receipt of the meeting request.

b. **Performance Goal:** FDA will respond to meeting requests and provide notification within the response times noted in Table 3 for 90 percent of each meeting type.

3. <u>Scheduling Meetings</u>

a. **Procedure:** FDA will schedule the meeting on the next available date at which all applicable Center personnel are available to attend, consistent with the component's other business; however, the meeting should be scheduled consistent with the timelines in Table 3 for the type of meeting requested. Table 4 below indicates the timeframes for FDA to schedule the meeting following receipt of a formal meeting request and background package, or in the case of a written response, the timeframes for the Agency to send the written response. If the requested date for any meeting type is greater than the specified timeframe, the meeting date should be within 14 calendar days of the requested date.

Table 4: Timelines for Scheduling Meetings or Sending Written Responses

Meeting Type	Meeting Scheduling or Written Response Time
BPD Type 1	30 calendar days from receipt of meeting request and background package
BPD Type 2a	60 calendar days from receipt of meeting request and background package
BPD Type 2b	90 calendar days from receipt of meeting request and background package
BPD Type 3	120 calendar days from receipt of meeting request and background package
BPD Type 4	60 calendar days from receipt of meeting request*

*Note the background package for BPD Type 4 meetings must be received no later than 14 calendar days after FDA receipt of the meeting request.

b. **Performance goal**

Table 5: Performance Goals for Scheduling Meetings or Sending Written Responses

Meeting Type	Goal
All BPD Meetings	90% of meetings are held or written responses are sent within the timeframe

4. Preliminary Responses

a. **Procedure:** The Agency will send preliminary responses to the sponsor's questions contained in the background package no later than five calendar days before the face-to-face or teleconference meeting date for BPD Type 2b and Type 3 meetings.

b. **Performance goal:**

Table 6: Performance Goal for Sending Preliminary Responses

Meeting Type	
BPD Types 2b and 3	90% of preliminary responses to questions are issued by FDA no later than five calendar days before the meeting date

5. Meeting Minutes

a. **Procedure:** The Agency will prepare minutes which will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted form and need not be in great detail. Meeting minutes are not necessary if the Agency transmits a written response for any BPD meeting.

b. **Performance Goal:** 90% of minutes are issued within 30 calendar days of the date of the meeting.

6. Conditions

For a meeting to qualify for these performance goals:

a. A written request and supporting documentation (i.e., the background package) must be submitted to the appropriate review division or office. The background package

must be submitted at the same time as the written request BPD Type 1, 2a, 2b and 3 meetings. For BPD Type 4 meetings, the background package must be received no later than 14 calendar days after FDA receipt of the written request.

b. The request must provide:

i. A brief statement of the purpose of the meeting, the sponsor's proposal for the type of meeting, and the sponsor's proposal for a face-to-face meeting, teleconference, or for a written response;

ii. A listing of the specific objectives/outcomes the sponsor expects from the meeting;

iii. A proposed agenda, including estimated times needed for each agenda item;

iv. A list of questions, grouped by discipline (For each question there should be a brief explanation of the context and purpose of the question);

v. A listing of planned external attendees; and

vi. A listing of requested participants/disciplines representative(s) from the Center with an explanation for the request as appropriate.

vii. Suggested dates and times (e.g., morning or afternoon) for the meeting that are within or beyond the appropriate time frame of the meeting type being requested.

c. The Agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). However, requests for BPD Type 2b, 3, and 4 Meetings will be honored except in the most unusual circumstances.

The Center may determine that a different type of meeting is more appropriate and it may grant a meeting of a different type than requested.

Sponsors are encouraged to consult available FDA guidance to obtain further information on recommended meeting procedures.

7. Guidance, Clarity, and Transparency

a. Guidance: FDA will strive to issue a revised draft of the existing draft guidance on "Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products" to incorporate information pertaining to Type 2a and Type 2b meetings, as well as the follow-up opportunity, no later than September 30, 2028. FDA will work toward the goal of publishing a revised draft or final guidance within 24 months after the close of the public comment period. FDA will also clarify that meeting requests and background packages only need to include information relevant to the meeting questions. In addition, FDA will update relevant MAPPs and SOPPs.

b. Follow-up opportunity: For all meeting types, to ensure the sponsor's understanding of FDA feedback from meeting discussions or a WRO, sponsors may submit clarifying questions to the Agency. If FDA responds to a sponsor's meeting question in a correspondence after issuance of the meeting minutes or WRO, sponsors may use the follow-up opportunity to seek clarification of FDA's advice. Only questions of a clarifying nature will be permitted, i.e., to confirm something in minutes, a WRO, or such correspondence issued by FDA, rather than to raise new issues or new proposals. FDA may exercise discretion about whether requests are clarifying in nature. If the FDA determines that the follow-up questions are not clarifications of advice provided, FDA may advise the sponsor to request a new meeting to address the issue (e.g., Type 2a). The clarifying questions should be sent in writing as a "Request for Clarification" to the FDA within 20 calendar days following receipt of meeting minutes, a WRO, or correspondence. If FDA agrees that the question(s) is appropriate for a follow-up, FDA will issue a response in writing within 20 calendar days of receipt of the clarifying questions. FDA's response will reference the original meeting minutes, WRO, or correspondence.

J. ADVANCING DEVELOPMENT OF BIOSIMILAR BIOLOGICAL-DEVICE COMBINATION PRODUCTS REGULATED BY CDER AND CBER

1. Use-Related Risk Analysis and Comparative Analyses (URRA/CA)

Sponsors employ Use-Related Risk Analyses (URRAs) and comparative analyses (CAs) to identify the need for risk control strategies and to help design human factors (HF) studies. Based on a URRA or URRA and CA, a sponsor may propose that data from an HF study does not need to be submitted to inform whether the user interface introduces use-related hazards capable of producing clinically meaningful differences in safety, purity, or potency. FDA will maintain the following procedures for review of URRA or URRA and CA for combination products:

a. The sponsor should submit a request for review of their URRA or URRA and CA to the IND (or pIND) or BLA. The submission should include specific scientific or regulatory questions for which the sponsor seeks agreement and justification, if applicable, that data from an HF study does not need to be submitted for FDA review, including any supporting information.

b. Within 60 days of Agency receipt of the URRA or URRA and CA and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the submitted URRA or URRA and CA and answers to the questions posed by the sponsor. If the Agency does not agree that either the URRA or URRA and CA or the sponsor's justification are adequate to support not submitting an HF study report for Agency review, the reasons for the disagreement will be explained in the response.

c. URRA or URRA and CA submission performance goals for FDA beginning in FY 2028 are as follows:

i. Review and notify sponsor of agreement or non-agreement with comments for 90% of filed submissions, within 60 days of receipt of submission.

If information from a URRA or URRA and CA is necessary to support an application or supplement, that information should already be available at the time of submission of the application or supplement. Accordingly, the 60-day goal date for review of a URRA or URRA and CA submitted to a BLA will not apply if a sponsor's initial submission of the URRA or URRA and CA is with the original application or supplement or to a pending application or supplement.

Alternatively, sponsors may request as part of a BPD Type 2b meeting a review of a URRA or URRA and CA submission with specific questions, enabling dialogue at the Type 2b meeting on the underlying URRA or URRA and CA. When a sponsor elects this pathway, review timelines for the URRA or URRA and CA will align with the 90-calendar day timeline applicable to BPD Type 2b meetings (90 calendar days from receipt of meeting request and background package, consistent with section I.I.3.a.). To avail themselves of this option, sponsors should submit the URRA or URRA and CA in the meeting package with the Type 2b meeting request along with specific questions.

2. Human Factors (HF) Protocols

Human factors studies are conducted to evaluate the user interface of a biosimilar biologic-device combination product and can inform whether the user interface introduces use-related hazards capable of producing clinically meaningful differences in safety, purity, or potency.

HF protocols are reviewed with the goal of developing a final finished biosimilar biologic-device combination product that supports the marketing application. To achieve this objective, FDA will establish the following procedures for review of HF protocols:

a. The sponsor should submit a human factors protocol to the IND (or pIND) or BLA with specific questions, including scientific and regulatory requirements for which the sponsor seeks agreement (e.g., are the study participant groups appropriate to represent intended users, is the study endpoint adequate, are the critical tasks that should be evaluated appropriately identified).

b. Within 60 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the Agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

c. Performance goals for FDA will be as follows:

    i. Review and provide sponsor with written comments for 90% of human factors protocol submissions within 60 days of receipt of protocol submission.

If data from an HF study is necessary to support an application or supplement, that data should already be available at the time of submission of the application or supplement. Accordingly, the 60-day goal date for review of an HF protocol submitted to a BLA will not apply if a sponsor's initial submission of the HF protocol is with the original application or supplement or to a pending application or supplement.

Alternatively, sponsors may request as part of a BPD Type 2b meeting a review of an HF protocol submission with specific questions, enabling dialogue at the Type 2b meeting on the underlying HF protocol. When a sponsor elects this pathway, review timelines for HF protocol will align with the 90-calendar day timeline applicable to BPD Type 2b meetings (90 calendar days from receipt of meeting request and background package, consistent with section I.I.3. a.). To avail themselves of this option, sponsors should submit the HF protocol in the meeting package with the Type 2b meeting request along with specific questions.

3. Guidance on Alternative Approaches to Comparative Use Human Factors Studies (CUHFs) for Interchangeable Biosimilars

FDA will strive to issue a draft guidance for review staff and industry on alternative approaches to Comparative Use Human Factors Studies (CUHFs) that may be scientifically appropriate for evaluation of user interface differences for interchangeable biosimilars by no later than September 30, 2028. FDA will work toward the goal of publishing a revised draft or final guidance within 24 months after the close of the public comment period.

K. ADVANCING CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC) FACILITY ASSESSMENT: A RISK-BASED LIFECYCLE APPROACH

To support the timely development and availability of biosimilar biological products, FDA and the regulated industry will focus on enhancing CMC communications during drug development and application review. FDA will continue to utilize user fees to support the use of alternate tools to assess manufacturing facilities in support of pending applications.

Manufacturing facility deficiencies observed on inspection could lead to complete response actions and the need for multiple review cycles. FDA and the regulated industry recognize a need to prevent or mitigate such deficiencies by fostering earlier and more transparent communication on CMC facility topics that could lead to their early resolution. FDA and the regulated industry recognize that additional opportunities for engagement can facilitate transparency, earlier shared understanding of regulatory requirements and expectations for manufacturing facilities, and proactive readiness for facility evaluation and inspection in support of drug applications. FDA and the regulated industry believe that this communication and engagement will provide a more proactive approach to timely address manufacturing facilities deficiencies, which could lead to an increase in first cycle approvals and facilitate the American public's timely access to safe, effective, and high-quality biosimilar biological products.

This BsUFA IV CMC facility lifecycle program is designed to facilitate meeting this objective through new and enhanced engagement mechanisms between FDA and the regulated industry that may happen before, during, and after an application review cycle. Effective use of these engagements aims to prevent or mitigate the occurrence of deficiencies that if unaddressed may lead to multiple review cycles.

1. Readiness For Pre-Approval Inspection (PAI) or Pre-License Inspection (PLI)

To provide greater transparency on FDA's requirements and expectations and support regulated industry readiness for facility evaluation and inspection supporting a 351(k) BLA, including supplements, FDA will publish guidance, described in section I.K.8. below, describing the manufacturing facility readiness attributes that should be met, prior to facility evaluation and inspection. The guidance will describe how the regulated industry can use this information to self-assess facility readiness to reduce the probability of deficiencies that often cannot be corrected during the review cycle, and to ensure meaningful and timely manufacturing facility evaluation and inspections. The readiness criteria set forth in the guidance may also facilitate eligibility for post-PLI meetings, when warranted.

2. CMC Facility Pre-submission Meeting for a 351(k) BLA, Including CMC Supplements Related to Manufacturing Facilities[4]

Applicants may request a single CMC Facility Pre-submission meeting to discuss manufacturing facilities for a proposed application submission. Transparent sharing and discussion of this information can facilitate applicant and facility readiness, as well as FDA's assessment of the application with respect to facility evaluation and inspection. Such meetings shall include FDA representatives from relevant functions and are generally expected to occur 3-6 months before an application submission, though they may occur earlier or later.

Topics for this meeting may include, but are not limited to, information regarding manufacturing supply chain with focus on the relationships and interdependence of manufacturing facilities and the operations intended for the application product, awareness and mitigation of associated risks, and learnings from prior inspections conducted by FDA and other regulators. FDA's advanced awareness and assessment of other relevant quality information about the facilities and their operations will inform FDA's risk-based approach in making decisions for facility evaluations and inspections. The proposed topics should not focus on content suited for other existing meeting types or other engagement (e.g., Pre-Operational Review, BPD meetings).

3. Enhancing Inspection Communication for 351(k) BLA Applicants, Not Including Supplements

FDA and the regulated industry believe enhanced communication between review teams and the regulated industry on certain pre-license inspections can facilitate an efficient application review process.

When FDA determines for an application, not including supplements, that it is necessary to conduct a pre-license inspection at a time when the product identified in the application is being manufactured, FDA's goal is to communicate its intent to inspect a manufacturing facility at least 60 days in advance of the pre-license inspections and no later than mid-cycle. FDA reserves the right to conduct manufacturing facility inspections at any time during the review cycle, whether or not FDA has communicated to the facility the intent to inspect.

[4] Throughout Section I.K., this includes Category 2 supplements, as appropriate.

4. Post-PLI Meeting for Original 351(k) BLAs, Not Including Supplements

The intent of the post-PLI meeting is to ensure transparency and enable resolution where possible of any outstanding deficiencies by the original action date. After FDA completes a PLI for a 351(k) BLA and reviews findings, FDA intends to inform the applicant when observations communicated to a facility on the Form FDA 483 may result in a complete response action. Upon such notification, an applicant may request a meeting to discuss inspection findings that impact application approval and corrective actions to those findings, with the goal of facilitating transparency on whether corrective actions are responsive to the issues identified that may impact application approvability. FDA reserves the right to defer comment on acceptability of the corrective actions and approvability of the application but will strive to provide specific and actionable feedback. FDA shall include representatives from relevant functions in the post-PLI meeting. When FDA grants a post-PLI meeting, FDA will strive to complete the meeting to facilitate first cycle approval by the originally assigned BsUFA Action Date but may extend the goal date per section I.A.5. of the commitment letter.

5. Post-Action Meetings for 351(k) BLAs, Including CMC Supplements Related to Manufacturing Facilities

When FDA issues a complete response letter for a 351(k) BLA, including CMC supplements, due to deficiencies observed on a PAI or PLI, an applicant may request a CMC Facility Post-Action meeting to discuss and gain understanding of those deficiencies that should be corrected before the application can be approved.

6. Meeting Procedures

a. **Regarding post-PLI meeting requests**, FDA intends for timelines and procedures to take application specific circumstances (e.g., inspections that occur later in the review cycle) into consideration to facilitate meaningful discussion within the review cycle with the goal of implementing corrective actions that facilitate application approval.

b. **Meeting Requests**: The format and content of meeting requests should adhere to the recommendations outlined in the guidance "Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products."

c. **Responses to Meeting Requests**: FDA will notify the requester in writing of the date, time, and place for the meeting, as well as expected Center participants following receipt of a meeting request. FDA will strive to meet the timeframes listed below for responding to meeting request.

Table 7: Timelines for Responding to Facility Lifecycle Meeting Requests

MEETING TYPE	RESPONSE TIME (CALENDAR DAYS)
CMC Facility Pre-submission	21
Post-PLI	14
Post-Action	14

d. **Scheduling the Meeting Requests**: The meeting should be scheduled consistent with the type of meeting requested. FDA will strive to schedule the meeting within the timeframes listed below.

Table 8: Timelines for Scheduling Facility Lifecycle Meetings

MEETING TYPE	MEETING SCHEDULING (CALENDAR DAYS FROM MEETING REQUEST)
CMC Facility Pre-submission	60
Post-PLI	30
Post-Action	30

e. **Meeting Background Packages**: The timing of the Agency's receipt of the sponsor background package for each meeting type is specified in Table below.

Table 9: Timelines for Agency Receipt of Facility Lifecycle Meeting Background Packages

MEETING TYPE	RECEIPT OF BACKGROUND PACKAGE
CMC Facility Pre-submission	30 calendar days before the date of the meeting
Post-PLI	At the time of the request
Post-Action	At the time of the request

f. **Preliminary Responses to Questions**: The Agency will send preliminary responses to the applicant's questions 2-5 calendar days prior to the meeting.

g. **Sponsor Notification to FDA**: Prior to the date of the meeting, the applicant will notify FDA of whether the meeting is still needed, and if it is, provide the anticipated agenda at least 1 business day in advance of the meeting.

h. **Meeting Minutes**: The Agency will prepare minutes that will be available to the applicant not later than 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting. Meeting minutes need not be provided if the Agency transmits a written response for any meeting type.

7. CMC Facility Lifecycle Workshop and Third-Party Assessment

FDA will contract with an independent third party to conduct a public workshop which will be held no later than September 30, 2030. The public workshop will focus on program implementation and its impact on facility readiness and reduction of facility deficiencies. The topics for the workshop will be informed by the third-party assessment and include, but are not limited to, impact on the goals of inspection readiness and reduction in facility deficiencies, program operations (e.g., rate of meetings granted or denied, denial reasons, timing of meetings relative to significant milestones) and feedback from both FDA and the

regulated industry on learnings to date. A third party will separately engage both FDA staff and individual sponsors through contractor-led interviews to assess the effectiveness of the facility lifecycle program. This third party will also assess the impact of the facility lifecycle program on facility-issue driven complete responses.

Following the close of the public comment period for the public workshop, the third-party that conducted the assessment described above will assess feedback from the workshop and draft a report summarizing the findings from the workshop, its assessment, and engagement with FDA and individual sponsors and identify best practices and areas for improvement for the regulated industry and FDA to enhance the CMC facility lifecycle program. The next steps may include proposed timeframes to develop or revise, as appropriate, relevant MAPPs and/or SOPPs and other applicable documents to incorporate lessons learned. FDA will publish the final report on the FDA's website no later than 9 months after the close of the comment period following the public workshop.

8. Guidance for Regulated Industry

By October 1, 2028, FDA will strive to publish draft guidance describing the implementation of this CMC facility lifecycle program. Such guidance will convey topics including, but not limited to, attributes that describe readiness for a PAI or PLI (as described in section I.K.1.), CMC Facility Pre-submission, Post-PLI, and Post Action meeting procedures, timelines, meeting type designation, criteria that FDA will consider when determining eligibility for each meeting (e.g., compliance classification, readiness for PLI criteria, meeting package completeness), best practices when submitting meeting request packages, and considerations regarding goal date extensions. FDA will strive to finalize the guidance within 24 months following close of the comment period.

L. REGULATORY SCIENCE TO ENHANCE THE DEVELOPMENT OF BIOSIMILAR AND INTERCHANGEABLE BIOLOGICAL PRODUCTS

The goals for the BsUFA Regulatory Science pilot program were met, and the pilot concluded at the end of BsUFA III.

Should FDA or regulated industry subsequently identify biosimilar-specific scientific or regulatory topics that would benefit from targeted research, when possible, such proposed topics will be discussed between FDA and regulated industry. If FDA conducts research using BsUFA operating funds during BsUFA IV, FDA will notify regulated industry and shall make such research results publicly available, as appropriate.

M. BLA REVOCATION AND REISSUANCE

To facilitate the transfer of a 351(k) BLA(s) between applicants, FDA will establish a 180-day timeline for completing license revocation and reissuance following receipt of a complete request to transfer a 351(k) BLA(s). This timeline will not apply in instances where (1) the transfer request includes both CDER- and CBER-regulated BLAs or (2) there are outstanding facility issues.

Applicants may include in their 351(k) BLA transfer request cover letter a request that FDA refrain from making the 351(k) BLA transfer effective before a certain date within the 180-day

timeline. FDA may act on the request prior to the 180-day goal date but will not make the transfer effective before the date specified by the applicants, provided that such date is not later than the 180-day goal date.

FDA will post each FY on its website, using a consistent, publicly disclosed reporting methodology:

- the number of applicable 351(k) BLA transfer requests
- the number of those requests completed within the 180-day timeline

N. ASSESSMENT OF THE BSUFA REVIEW PROGRAM FOR PRE-INDS, INDS, AND BLAS

Beginning in FY 2028 and continuously through the end of the assessment, FDA will contract with an independent third party with expertise in assessing the quality and efficiency of the biosimilar development and regulatory review program to assess pre-IND, IND and 351(k) BLA development and first cycle review processes, outcomes, and FDA-sponsor communications.

The third party will assess the completeness, consistency, and timing of key review process milestones, communications, and materials exchanged between FDA and sponsors during first-cycle BLA review from BsUFA III (as applicable and feasible) and BsUFA IV, particularly how, when, and whether significant issues were identified, communicated, and addressed. The third party will also assess adherence to key process milestones (e.g., completion of primary and secondary review, inter-center consults) as documented within relevant statute, and FDA MAPPs, SOPPs, guidances and this letter and attempt to identify the root cause of any delays.

The third party will also assess processes related to provisional determinations, including publication of exclusivity-related information to determine the ELAD as it relates to RFAs, as well as PD amendment submission and review.

Key communications assessed will include information requests, new target action dates, feedback on sponsor-submitted materials, labeling (including REMS), and formal meetings and letters. For major amendments, other clock extensions, and imminent action, the third party will characterize the rationale FDA uses for employing these mechanisms and timing of the determination. For complete response outcomes, the third party will summarize the basis for these outcomes and characterize significant review and/or process issues.

The third party will also evaluate the timing of communications related to iPSPs, amended iPSPs, IND clinical protocols and protocol amendments during development from BsUFA III and IV. The evaluation will be conducted to assess the elapsed time between submission and FDA's response (including initial and any subsequent comments), any related process bottlenecks, and whether sponsors consistently provided required information. For iPSPs and amended iPSPs, the evaluation will also assess the elapsed time between submission and FDA agreement.

The third party will be expected to collect and analyze data and, for all first-cycle BLAs submitted during BsUFA IV, review communications between FDA and sponsors and conduct interviews with sponsors and review teams. The third party will use the data to provide actionable recommendations to help FDA and sponsors increase the effectiveness and efficiency of key review processes, communications, and materials, limit first cycle complete responses (for

applications that are ultimately approvable), limit missed goal dates, and assess the use of imminent action, new target action dates, and review clock extensions.

In addition to the above, for all supplements submitted during BsUFA IV for which the Imminent Action mechanism is employed, the third party will be expected to characterize the rationale used and the timing of the determination. No other metrics shall be assessed for supplements.

Deliverables:

a. Prior to beginning the assessment, FDA will publish the statement of work for this assessment for public comment.

b. By March 31, 2030, FDA and the third party will publish an interim assessment report for public comment.

c. By June 30, 2030, FDA and the third party will hold a public workshop to discuss the interim assessment report. Stakeholders may share feedback on increasing the effectiveness of key review processes and FDA-sponsor communications and reducing complete responses, missed goal dates, and review clock extensions.

d. By March 31, 2032, FDA and the third party will publish a final report on FDA's public website. This report will include findings from the assessment as well as recommendations for increasing the effectiveness of key review processes and FDA-sponsor communications and reducing complete responses, missed goal dates, and review clock extensions. The report will also incorporate feedback from the public workshop in section (c).

II. CONTINUED ENHANCEMENT OF USER FEE RESOURCE MANAGEMENT

FDA is committed to ensuring the sustainability of BsUFA program resources and to enhancing the operational agility of the BsUFA program. FDA will build on the financial enhancements included in prior authorization cycles to ensure optimal use of user fee resources and the alignment of staff to workload. FDA will also continue activities to promote transparency of the use of financial resources in support of the BsUFA program.

A. RESOURCE CAPACITY PLANNING

FDA will continue operating the Agency's resource capacity planning function, including utilization of modernized time reporting, to support enhanced management of BsUFA resources in BsUFA IV and help ensure alignment of user fee resources to staff workload.

B. FINANCIAL TRANSPARENCY

1. Five-Year Financial Plan

FDA will publish a BsUFA 5-year financial plan on or before the end of the 2nd quarter of FY 2028. FDA will publish updates to the 5-year plan on or before the end of the 2nd quarter of each subsequent fiscal year. The plan and its annual updates will include the following topics:

a. **Shared Services**

i. A discussion of Agency efforts to provide Shared Services in support of the process for the review of biosimilar biological products. Shared Services programs support Agency-wide activities (such as human resources) with costs proportionally allocated across programs, including BsUFA, based on the proportion of those costs that support the process for the review of biosimilar biological product applications. This discussion will cover: the types of services that have been consolidated, the financial impact on the BsUFA program, and ongoing or planned consolidation efforts.

ii. The planned user fee obligations for FDA's Shared Services program for the five years represented by the BsUFA IV authorization. The annual updates to this plan will provide actual amounts for the preceding fiscal year, as well as updated planned amounts for the remaining fiscal years.

iii. Discussion to address factors contributing to any variation from planned to actual amounts in excess of 10%.

b. **Index of financial and personnel related reporting**

FDA will add an appendix that will list current sources of personnel and / or financial reporting, including the financial report, performance report, and various pages on the

FDA website, to explain distinctions between the personnel or other financial data provided in various reports.

2. Annual Financial Report

FDA will include the following items in the annual Financial Report submitted to Congress each year:

a. An accounting of appropriated user fee funds included in the operating reserve at the end of each fiscal year.

b. How any new capacity planning adjustment (CPA) fee revenues are being allocated.

c. A discussion of the operating reserve tracking, reserving, and reporting (OR TRR), as related to section 744H(f)(2)(E) (as in effect on October 1, 2027) of the Federal Food, Drug, and Cosmetic Act and FDA's objective to hire and retain staff, including:

i. The OR TRR payroll target for the year.

ii. A comparison of the actual payroll to the OR TRR payroll target.

iii. A discussion of whether FDA has met the OR TRR payroll target.

iv. If FDA has not met the OR TRR payroll target, the amounts in the operating reserve that are set aside for payroll for hiring and retaining staff.

v. In addition to the current table that provides overall BsUFA fee payroll and operating spending broken out by Center, enhanced reporting on:

- Personnel compensation and benefits to include payroll, awards, overtime, and benefits for personnel.

- Operating expenses by major object class codes that have BsUFA fee obligations.

3. Technical Staff Meeting

FDA is committed to transparency and supporting understanding of the BsUFA program finances. FDA will commit to offering one technical staff meeting per year with regulated Industry. These meetings will be expected to:

a. Occur after the publication of the fee-setting Federal Register Notice each fiscal year in the August – September timeframe, with the first meeting in 2028.

b. Include topics relevant to the fee-setting or finances of the BsUFA program.

Within 30 calendar days after the conclusion of each technical staff meeting, FDA will publish meeting minutes to its website. The meeting minutes will describe, in sufficient detail, the topics and significant points discussed in each meeting.

III. TRANSPARENCY IN FDA HIRING AND RETENTION OF REVIEW STAFF

The biosimilar biological product review program requires that FDA maintain sufficient numbers and types of technical and scientific experts to efficiently conduct reviews of 351(k) applications.

During BsUFA III, FDA experienced attrition among technical and scientific experts involved in the review process. To deliver on BsUFA IV commitments, FDA is committed to sharing updates on the status of restaffing the BsUFA program, including prioritizing staffing for review functions and on specific BsUFA IV enhancements.[5]

During BsUFA IV, FDA will share quarterly updates on BsUFA hiring via the PDUFA and BsUFA quarterly hiring webpage. FDA will also maintain the CDER and CBER net hiring webpage.

[5] To deliver on specific BsUFA IV enhancements in Supplement Review, Facility Lifecycle Management, and Provisional Determinations, FDA will, as part of its restaffing hiring efforts, reserve positions for certain offices in CDER (12 positions), during FY 2028 and will report out on the status of hiring for these enhancements in quarterly updates on FDA's webpage.

IV. DEFINITIONS AND EXPLANATION OF TERMS

1. The term “review and act on” means the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

2. A resubmitted original application is a complete response to an action letter addressing all identified deficiencies.