BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017

FDA proposes the following goals contingent on the allocation of resources for each of the fiscal years 2013-2017 of at least the inflation-adjusted value of $20 million in non-user fee funds, plus collections of biosimilar user fees, to support the process for the review of biosimilar biological applications.

BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017

The performance goals and procedures of the FDA Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the authorization of the biosimilar biological product user fee program are summarized below.

I. REVIEW PERFORMANCE GOALS

A. Biosimilar Biological Product Application Submissions and Resubmissions

FY 2013

1. Review and act on 70 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 70 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2014

1. Review and act on 70 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 70 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2015

1. Review and act on 80 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 80 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2016

1. Review and act on 85 percent of original biosimilar biological product application submissions within 10 months of receipt.

2. Review and act on 85 percent of resubmitted original biosimilar biological product applications within 6 months of receipt.

FY 2017

1. Review and act on 90 percent of original biosimilar biological product application submissions within 10 months of receipt.

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

B. Supplements with Clinical Data

1. Review and act on 90 percent of original supplements with clinical data within 10 months of receipt.

2. Review and act on 90 percent of resubmitted supplements with clinical data within 6 months of receipt.

C. Original Manufacturing Supplements

1. Review and act on 90 percent of manufacturing supplements within 6 months of receipt.

D. Goals Summary Tables

Original and Resubmitted Applications and Supplements

SUBMISSION COHORT	PERFORMANCE GOAL				
	2013	**2014**	**2015**	**2016**	**2017**
Original Biosimilar Biological Product Application Submissions	70% in 10 months of the receipt date	70% in 10 months of the receipt date	80% in 10 months of the receipt date	85% in 10 months of the receipt date	90% in 10 months of the receipt date
Resubmitted Original Biosimilar Biological Product Applications	70% in 6 months of the receipt date	70% in 6 months of the receipt date	80% in 6 months of the receipt date	85% in 6 months of the receipt date	90% in 6 months of the receipt date

Original Supplements with Clinical Data	90% in 10 months of the receipt date
Resubmitted Supplements with Clinical Data	90% in 6 months of the receipt date
Manufacturing Supplements	90% in 6 months of the receipt date

II. FIRST CYCLE REVIEW PERFORMANCE

A. Notification of Issues Identified during the Filing Review

1. Performance Goal: For original biosimilar biological product applications and supplements with clinical data, FDA will report substantive review issues identified during the initial filing review to the applicant by letter, teleconference, facsimile, secure e-mail, or other expedient means.

2. The timeline for such communication will be within 74 calendar days from the date of FDA receipt of the original submission.

3. If no substantive review issues were identified during the filing review, FDA will so notify the applicant.

4. 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.

5. FDA will notify the applicant of substantive review issues prior to the goal date for 90% of applications.

B. Notification of Planned Review Timelines

1. Performance Goal: For original biosimilar biological product applications and supplements with clinical data, FDA will inform the applicant of the planned timeline for review of the application. The information conveyed will include a target date for communication of feedback from the review division to the applicant regarding proposed labeling, postmarketing requirements, and postmarketing commitments the Agency will be requesting.

2. The planned review timeline will be included with the notification of issues identified during the filing review, within 74 calendar days from the date of FDA receipt of the original submission.

3. The planned review timelines will be consistent with the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products (GRMPs), taking into consideration the specific circumstances surrounding the individual biosimilar biological product application.

4. The planned review timeline will be based on the application as submitted.

5. FDA will inform the applicant of the planned review timeline for 90% of all applications and supplements with clinical data.

6. In the event FDA determines that significant deficiencies in the application preclude discussion of labeling, postmarketing requirements, or postmarketing commitments by the target date identified in the planned review timeline (e.g.,

failure to demonstrate a biosimilar biological product is highly similar to the reference product, significant safety concern(s), need for a new study(ies) or extensive re-analyses of existing data before approval), FDA will communicate this determination to the applicant in accordance with GRMPs and no later than the target date. In such cases the planned review timeline will be considered to have been met. Communication of FDA's determination may occur by letter, teleconference, facsimile, secure e-mail, or other expedient means.

7. To help expedite the development of biosimilar biological products, communication of the deficiencies identified in the application will generally occur through issuance of a discipline review (DR) letter(s) in advance of the planned target date for initiation of discussions regarding labeling, postmarketing requirements, and postmarketing commitments the Agency may request.

8. If the applicant submits a major amendment(s) (refer to Section VIII.B for additional information on major amendments) and the review division chooses to review such amendment(s) during that review cycle, the planned review timeline initially communicated (under Section II.B.1 and 2) will generally no longer be applicable. Consistent with the underlying principles articulated in the 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.

    - If the review division determines that the major amendment will result in an extension of the biosimilar biological product review clock, the review division will communicate to the applicant at the time of the clock extension a new planned review timeline, including a new review timeline for communication of feedback on proposed labeling, postmarketing requirements, and any postmarketing commitments the Agency may request.

    - In the rare case where the review division determines that the major amendment will not result in an extension of the biosimilar biological product review clock, the review division may choose to retain the previously communicated planned review timeline or may communicate a new planned review timeline to the applicant.

    - The division will notify the applicant promptly of its decision regarding review of the major amendment(s) and whether the planned review timeline is still applicable.

III. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

To enhance patient safety, FDA will utilize user fees to implement 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.

A. Review Performance Goals – Biosimilar Biological Product Proprietary Names

1. Proprietary names submitted during the biosimilar biological product development (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 names submitted with biosimilar biological product application

    a) Review 90% of biosimilar biological product application 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.

IV. MAJOR DISPUTE RESOLUTION

A. 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.

B. Performance goal: 90% of such answers are provided within 30 calendar days of the Center's receipt of the written appeal.

C. Conditions:

1. 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.

2. 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.

3. 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.

4. 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).

5. 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.

6. 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.

7. 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.

V. CLINICAL HOLDS

A. 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.

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

VI. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

A. 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.

1. 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 clinical endpoints adequate to assess whether there are clinically meaningful differences between the proposed biosimilar biological product and the reference product).

2. 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.

3. Protocols that qualify for this program include any necessary clinical study or studies to prove biosimilarity and/or interchangeability (e.g., protocols for comparative clinical trials 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 trials 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 2 or 3 Meeting, as defined in section VIII (F and G), 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.

4. 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 trial 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.

B. Performance goal:

For FY 2013, 70% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2014, 70% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2015, 80% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2016, 85% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

For FY 2017, 90% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes.

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

VII. MEETING MANAGEMENT GOALS

A. Responses to Meeting Requests

1. **Procedure:** Within 14 calendar days of the Agency's receipt of a request and meeting package from industry for a BPD Type 1 Meeting, or within 21 calendar days of the Agency's receipt of a request and meeting package from industry for a Biosimilar Initial Advisory Meeting or a BPD Type 2, 3, or 4 Meeting, as defined in section VIII(D-H), below, CBER and CDER should notify the requester in writing of the date, time, place, and format (i.e., a scheduled face-to-face, teleconference, or videoconference) for the meeting, as well as expected Center participants.

2. **Performance Goal:** FDA will provide this notification within 14 days for 90 percent of BPD Type 1 Meeting requests and within 21 days for 90 percent of Biosimilar Initial Advisory Meeting and BPD Type 2, 3 and 4 Meeting requests.

B. Scheduling Meetings

1. **Procedure:** The meeting date should reflect the next available date on 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 type of meeting requested.

a) Biosimilar Initial Advisory Meeting should occur within 90 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

b) BPD Type 1 Meetings should occur within 30 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

c) BPD Type 2 Meetings should occur within 75 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

d) BPD Type 3 Meetings should occur within 120 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

e) BPD Type 4 Meetings should occur within 60 calendar days of the Agency receipt of the sponsor-submitted meeting request and meeting package.

2. **Performance goal:**

For FY 2013, 70% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2014, 70% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2015, 80% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2016, 85% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

For FY 2017, 90% of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings are held within the timeframe.

C. Meeting Minutes

1. **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.

2. **Performance Goal:** FDA will provide meeting minutes within 30 days of the date of the meeting for 90 percent of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings.

D. Conditions

For a meeting to qualify for these performance goals:

1. A written request (letter or fax) and supporting documentation (i.e., the meeting package) should be submitted to the appropriate review division or office. The request should provide:

   a) 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 or a teleconference;

   b) A listing of the specific objectives/outcomes the requester expects from the meeting;

   c) A proposed agenda, including estimated times needed for each agenda item;

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

   e) A listing of planned external attendees; and

   f) A listing of requested participants/disciplines representative(s) from the Center.

   g) 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.

2. 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 2, 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, which may require the payment of a biosimilar biological product development fee as described in section 744B of the Federal Food, Drug, and Cosmetic Act before the meeting will be provided. If a biosimilar biological product development fee is required under section 744B, and the sponsor does not pay the fee within the time frame required under section 744B, the meeting will be cancelled. If the sponsor pays the biosimilar biological product development fee after the meeting has been cancelled due to non-payment, the time frame described in section VII.A.1 will be calculated from the date on which FDA received the payment, not the date on which the sponsor originally submitted the meeting request.

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

3. FDA will develop and publish for comment draft guidance on Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings by end of second quarter of FY 2014.

VIII. DEFINITIONS AND EXPLANATION OF TERMS

A. 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.

B. Goal Date Extensions for Major Amendments

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

2. A major amendment may include, for example, a major new clinical safety/efficacy 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.

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

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

5. Consistent with the underlying principles articulated in the 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.

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

D. A Biosimilar Initial Advisory Meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service Act may be feasible for a particular product, and, if so, general advice on the expected content of the development program. Such term does not include any meeting that involves substantive review of summary data or full study reports.

E. 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 special protocol assessment meeting, or a meeting to address an important safety issue.

F. A BPD Type 2 Meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing biosimilar biological product development program. Such term includes substantive review of summary data, but does not include review of full study reports.

G. A BPD Type 3 Meeting is an in depth data review and advice meeting regarding an ongoing biosimilar biological product development program. Such term 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, including design and analysis.

H. A BPD Type 4 Meeting is a meeting to discuss the format and content of a biosimilar biological product application or supplement submitted under 351(k) of the PHS Act.