SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Applications

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff for issuing Information Request (IR) communications for pending applications and reviewing the applicant's responses to such requests.

II. Scope

A. This SOPP applies to Biologics License Applications (BLAs), Abbreviated/New Drug Applications (A/NDAs), Medical device applications and their respective amendments and supplements.

B. This SOPP applies to products covered by the Biosimilar User Fee Act (BsUFA), the Generic Drug User Fee Act (GDUFA), the Medical Device User Fee Act (MDUFA) and the Prescription Drug User Fee Act (PDUFA) and non-user fee products in these product categories.

III. Background

A. In commitments made in support of the Prescription Drug User Fee Act (PDUFA), FDA undertook to review and act on complete BLAs and NDAs within agreed upon time frames.

B. The Biosimilar User Fee Act (BSUFA) authorized fees and set goals for the review of biosimilar biological product applications, including post market safety activities.

C. The Generic Drug User Fee Act (GDUFA) authorized fees and set goals for the review of generic drug applications.

D. The Medical Device User Fee Act (MDUFA) authorized fees and set goals for the review of medical device applications including BLAs subject under MDUFA.

E. As part of the user fee procedures, FDA instituted the use of two types of letters: action letters and information request (IR) letters. FDA continues to use IR communications (e.g., letters, emails) to request further information or clarification that would assist reviewers during the course of the review or to convey deficiencies identified in the application in advance of the issuance of an action letter.

IV. Definitions

A. Information Request (IR) Communication- A communication sent to an applicant during submission review to request further information or clarification that is needed or would be helpful to complete the review.

B. Letter-ready comments - written comments formulated by the reviewer(s) of a submission written sufficiently well (e.g., correct grammar, spelling, punctuation) to be readily included in a communication (not always a letter) to the applicant.

V. Policy

A. An IR communication is not an action letter and does not stop the review clock. It does not represent a complete review of the submission.

B. For products not covered by user fees, the procedures in this document will be used; however, any applicable performance goals will not apply.

C. Information Request (IR) communication

1. An IR communication may be used to request further information, including a clarification that is needed to complete the discipline review of an original BLA or NDA and their respective amendments and supplements. **Note:** More than

one IR communication may be sent during the review cycle; however, excessive IR communications should not normally occur.

2. An IR communication is issued while the discipline review continues.

3. Information requested in an IR communication should be information that is necessary or would be helpful to complete the review and, as such, is intended to be reviewed during the review cycle in which the communication was issued (if the response is promptly received). **Note:** IR communications should not be sent late in the review cycle.

a. IR communication content should include four essential components (also referred to as Four-Part Harmony):

i. What was provided – acknowledgement of the information submitted by the applicant, including references to sections, page numbers, or tables where appropriate

ii. What is the issue or deficiency – identification of a specific issue or concern[1] with information that was submitted, is missing, or is inadequate

iii. What is needed – explicit request for additional information needed to address the issue and potential alternate ways of satisfying the issue, if applicable

iv. Why it is needed – statement of basis for the deficiency that includes:

a) Effect or impact of the specific issue or concern on the patient or marketing application decision, and

b) Specific reference[2] (when available, applicable and relevant)

4. For simple clarification (e.g., asking where information is located), the reviewer may contact the applicant. If the reviewer contacts the applicant, the reviewer is responsible for documenting the request in the appropriate regulatory system, uploading the document into the appropriate regulatory system through CBER Connect, and notifying the regulatory project manager (RPM) and the Review Committee Chair (Chair).

5. IR communications other than clarifications are handled through the RPM.

6. An IR communication can be issued by telecon, fax, email or letter.

[1] A specific issue or concern can be scientific, clinical and/or regulatory in nature.
[2] A specific reference is an applicable section of a final rule, regulation or statute; applicable section of a final guidance; and/or applicable section of an FDA-recognized consensus standard (unless the entire or most of the rule, regulation, statute, or document is applicable).

7. The Chair reviews IR communications before they are issued.

   a. IR communications may be sent by the RPM or Chair.

   b. An IR communication issued by letter is signed by the Chair.

8. An IR communication does not necessarily reflect upper-level supervisor (i.e., Division or Office Director) concurrence.

9. Immediate supervisor concurrence needed to send an IR communication is as follows:

   a. IR communications meant to clarify information do not require supervisor concurrence.

   b. IR communications (other than for clarification) require concurrence from the discipline reviewer's immediate supervisor.

   c. The supervisor may grant permission to individual reviewers to forward IR communication comments to the RPM without immediate supervisory concurrence for specific files if the reviewer has demonstrated sound judgment based on experience. The RPM and Chair should be notified by the supervisor when this permission is granted.

   d. Supervisory concurrence, when needed, should be documented.

   e. Each Office should determine how immediate supervisory concurrence is obtained and documented, i.e., email, memo.

D. Review of Responses to IR Communications

1. Information requested in an IR communication is intended to be reviewed during the review cycle in which the communication was issued if the response is promptly received.

2. CBER has no obligation to review information submitted in response to an IR communication during the review cycle in which the IR communication was issued.

3. CBER may choose to review such information during the review cycle if time permits and it is determined that such review would not adversely impact the ability to meet the goal date for a first cycle approval.

4. If the agency elects to review the response in the current cycle, the Review Committee will evaluate the responding amendment upon receipt to determine whether it constitutes a major amendment and extends the review clock. Refer to *SOPP 8402: Designation of Amendments as Major* for additional information.

5. If the Review Committee defers the review of a response, and a complete response (CR) letter is issued, the response will be reviewed during the next review cycle as part of the complete resubmission if the applicant references such response in the resubmission.

VI. Responsibilities

A. Product Office Regulatory Project Manager (RPM)

1. Responsible for overall management of IR communications.

2. Determines, along with the Chair, the method of IR communication for requests other than simple clarification.

3. Ensures IR communications are documented in the appropriate regulatory system.

4. Makes applicant response to IR communications available to the appropriate reviewer(s).

B. Reviewer

1. Performs review of all assigned areas of the submission and relevant amendments.

2. May contact the applicant for simple clarification request. If the reviewer contacts the applicant, the reviewer is responsible for documenting the request in the appropriate regulatory system by uploading the document through CBER Connect and notifying the RPM and Chair.

3. Drafts letter-ready comments and/or questions for IR communications other than simple clarification requests; obtains appropriate supervisory clearance.

4. Reviews and concurs on draft IR communication prior to issuance.

5. Reviews applicant response to IR communication.

C. Review Committee Chair

1. Determines, along with the RPM, the method of IR communication for requests other than simple clarification.

2. Reviews letter-ready IR comments prior to issuance; may send IR communications issued by telecon, email or fax.

3. Signs IR communication issued by letter.

D. Immediate Supervisor

1. Notifies the RPM and Chair when permission is granted to individual reviewers to proceed with comments for IR communications for specific files without prior approval.

2. Performs review and notes concurrence, or gives justification of non-concurrence, of draft letter-ready comments for IR communications, as appropriate, and DR letter.

VII. Procedures

A. IR Communications

1. Determine level of supervisory review and concurrence needed for communication. **[Reviewer/RPM]**

2. Preparation and Issuance of IR Communications with no Supervisory Concurrence

   a. Determine the method of communication (e.g., email, telecon, fax, or letter). **[Reviewer/RPM]**

      i. Refer to *SOPP 8104: Documentation of Telephone Contacts with Regulated Industry* for additional information.

      ii. Refer to *SOPP 8119: Use of Email for Regulatory Communications* for additional information.

   b. Ensure communication is entered into the appropriate regulatory system through CBER Connect. **[Reviewer/RPM]**

3. Preparation and Issuance of IR Communications with Supervisory Concurrence

   a. Determine method of communication (e.g., email, telecon, fax, or letter). **[RPM/Chair]**

   b. Prepare letter-ready comments and/or questions for applicant based on the principles of Four-Part Harmony. **[Reviewer]**

   c. Forward draft letter-ready comments to RPM; include immediate supervisor for concurrence. **[Reviewer]**

   d. Perform review and concurrence of draft letter-ready comments. **Note:** Offices may determine method of concurrence. **[Immediate Supervisor]**

   e. Draft communication to applicant with proposed response date, as appropriate, and forward to reviewer, reviewer's supervisor and Chair for review and concurrence. **[RPM]**

f. Review and comment on the draft communication within the timeframe requested by the RPM. **[Reviewer, Reviewer's Immediate Supervisor, Chair]**

i. IR communication comments from more than one office will need review from all affected offices.

ii. If the method of communication is a letter, refer to CBER's Letter Template SharePoint Online site for the most recent approved letter template.

g. Sign IR communication letter, if appropriate. **[Chair]**

h. Refer to *SOPP 8116: Use of Electronic Signatures for Regulatory Documents* and *JA 820.01: Guide for CBER's Electronic Signature Process* for additional information.

4. Issue communication to applicant. **[RPM]**

5. Ensure communication is entered into the appropriate regulatory system through CBER Connect. **[RPM]**

B. Responses to IR Communications

1. Review of Responses to IR communications

a. Receive notification of response to an IR communication and make the submission available to the appropriate reviewer(s). **[RPM]**

b. Perform initial review of response to determine if it can be reviewed within the current review cycle. **[Reviewer]**

c. **Note:** make sure the correct option in the action letter is included if the response cannot be reviewed within the current review cycle.

2. Determine if the information is a major amendment. **[Review Committee Members]**

a. If yes, follow the procedures for a major amendment.

b. Refer to *SOPP 8402: Designation of Amendments as Major* for additional information.

VIII. Appendix

N/A

IX. References

A. References below are CBER Internal:

1. JA 820.01: Guide for CBER's Electronic Signature Process

2. Letter Template SharePoint Online Site

B. References below can be found on the Internet:

1. Biologics Price Competition and Innovation (BPCI) Act of 2009

2. Guidance Documents

a. Guidance for Industry: Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act, November 2001

b. Guidance for Review Staff and Industry: Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications

3. User Fee Information

a. Biosimilar User Fee Act (BsUFA)

b. Generic Drug User Fee Act (GDUFA)

c. Prescription Drug User Fee Act (PDUFA)

d. Medical Device User Fee Act (MDUFA)

4. CBER SOPPs

a. SOPP 8104: Documentation of Telephone Contacts with Regulated Industry

b. SOPP 8116: Use of Electronic Signatures for Regulatory Documents

c. SOPP 8119: Use of Email for Regulatory Communications

d. SOPP 8402: Designation of Amendments as Major

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Lynch	Darlene Martin, MS, PMP ORO/DROP Director (Acting)	September 28, 2022	6	Updated for PDUFA VII, BSUFA III, and MDUFA V
Monser	N/A	December 11, 2020	5	Technical Update for retirement of EDR and replacement of “database” with “system”
Monser	N/A (reviewed by Template Coordinator)	December 20, 2019	4	Technical Update to current format/font and corrections to reference titles and hyperlinks and grammatical errors.
Linda Dixon	Christopher Joneckis, PhD	January 29, 2018	3	Updated for 2017 user fee implementation; added GDUFA
SOPP 8401.1 working group	Robert Yetter, PhD	November 9, 2012	2	Updated to implement PDUFA V commitments
Leonard Wilson, RMCC	Robert Yetter, PhD	June 11, 2001	1	Original Prepared to implement PDUFA commitments