

SOPP 8422: Processing and Review of Trans-BLA Submissions

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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 on the administrative procedures for the receipt and review of “trans-BLAs,” i.e., multiple submissions to approved Biological License Applications (BLAs) that contain an identical change (or changes) as a single submission.

II. Scope

This SOPP addresses an **identical** change or changes that affect multiple approved marketing applications. Refer to the Policy section below for additional details on the types of submissions.

III. Background

An applicant may wish to submit an **identical** change (or changes) to multiple approved BLAs, e.g., manufacturing changes, product correspondence, safety reports. To accommodate, CBER initiated the “trans-BLA process” whereby one submission meeting this criterion is assigned multiple Submission Tracking Numbers (STNs), one for each affected BLA. The process obviates the need for

separate identical submissions, thereby eliminating duplicate review and data entry and enhancing efficiency as review and data entry is performed only once for all submissions in the group.

IV. Definitions

- A. Common Technical Document (CTD): A standardized format developed by the ICH for submitting applications to the FDA.
- B. Electronic Common Technical Document (eCTD): A CTD submitted in electronic form with an extensible markup language (XML) backbone.
- C. eCTD dossier: The electronic file containing all eCTD submissions to a specific application for a single product.
- D. eCTD validation: the criteria applied by the commercial product FDA uses to process eCTD submissions.
- E. Electronic Submissions Gateway (ESG): The Agency Web portal by which submissions can be received electronically from sponsors and/or applicants.
- F. Trans-BLA: A single submission from an applicant containing an **identical** change or changes pertaining to multiple products (BLAs).
- G. Submission Tracking Number (STN): A sequentially generated tracking number for all submissions.
- H. Primary STN: The Submission Tracking Number (STN) that contains the content applicable to all the STNs in the trans-BLA.
 - 1. For eCTDs, information submitted will only reside in the BLA eCTD dossier of the primary STN.

V. Policy

- A. Only submissions containing **identical** changes are eligible to be considered a "trans-BLA." CBER encourages the submission of a trans-BLA as a single submission from an applicant with **identical** changes that references all affected BLAs.
 - 1. Communication records for trans-BLAs should be the same.
 - 2. Letters sent in response to a trans-BLA will reference all affected BLAs. The primary STN is indicated by an asterisk (*).
 - 3. The review memo will be the same for all STNs that are reviewed within one office and entered only once in the appropriate regulatory system but included in all STNs of the trans-BLA. Separate memos may be

generated for STNs that are reviewed by different offices, and subsequently, entered into the appropriate regulatory system.

- B.** All information submitted as a trans-BLA in eCTD format will reside only in the BLA eCTD dossier of the primary STN. Refer to “*The eCTD Backbone Files Specification for Module 1*” document for additional information regarding formatting requirements for trans-BLAs. For non-eCTD submissions, the content resides only in the folder of the primary STN.
- C.** Amendments to the trans-BLA should be submitted in the same manner as the original trans-BLA submission, i.e., one submission with **identical** changes pertaining to multiple products.
- D.** Submissions containing identical changes but submitted individually will be accepted and will not be processed as a trans-BLA.
- E.** Original Biologics License Applications cannot be processed as trans-BLAs and must be submitted as separate applications and processed individually.
- F.** A trans-BLA can be a supplement or other submission type to an approved marketing application, e.g., product correspondence, annual report for products regulated within OBRR/DBCD, PMC submission.
- G.** For trans-BLAs where the review responsibilities are not within a single office, at the time of the STN pre-assignment, the Regulatory Information Branch (RIB), in the Division of Informatics and Information Technology (DIIT), Office of Regulatory Operations (ORO) will contact the appropriate staff in the review offices involved and request agreement on which will serve as the lead review office to be responsible for overall management of the trans-BLA.
- H.** If one or more STNs is/are not able to be approved with the rest of the STNs in the trans-BLA, then those specific STNs should be withdrawn and resubmitted as individual requests. In addition, if during the course of the review, additional changes are needed for one or more STNs such that the STN(s) is/are no longer identical to the other STNs in the trans-BLA, then, then those specific STNs should be withdrawn and resubmitted as individual requests (or if applicable, they could be submitted as a different “trans”). In such situations, review staff should contact RIB to facilitate removal of the submission.

VI. Responsibilities

A. Product Office Regulatory Project Manager (RPM)

1. Follows *SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format* regarding pre-assignment of STNs.

2. Ensures that the applicant's cover letter lists all the STNs in the submission and each product has a separate Form FDA 356h.
3. For submissions that have not been pre-assigned, ensures that STNs are assigned for each product.
4. Ensures that an acknowledgement letter is issued. Note: Acknowledgment letters are not issued for all types of submissions, e.g., product correspondence. However, for those submissions for which one is issued, ensure that the primary STN is indicated by an asterisk.
5. Follows *SOPP 8401.2: Administrative Processing of BLA and NDA Supplements* for routine review procedures for supplements.

B. Document Control Center (DCC)

1. Documents the receipt of paper and hybrid submissions by date stamp and data entry to the appropriate system.
2. Performs document scanning and quality control in accordance with FDA and CBER guidelines.
3. Performs manual load of scanned and electronic submissions received on media to CBER's Electronic Repository (CER).
4. Performs manual loads of submissions received via the FDA Electronic Submissions Gateway ESG that failed to automatically load to CER.
5. Notifies the Electronic Submissions Coordinator (ESC) and the CBER Electronic Repository Team of submissions that could not manually load to CER.

C. Office of Regulatory Operations (ORO), Division of Informatics (DI), Regulatory Information Branch (RIB)

1. Pre-assigns STNs in accordance with *SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format*.
2. Contacts appropriate staff in review offices to initiate determination of lead review office for trans-BLAs that involve more than one office.

D. CBER Electronic Repository (CER) Team

1. Reviews eCTD validation report and accesses any failed submission at its server location.
2. Determines if the failure to load is caused by technical error or a failure to adhere to eCTD validation criteria.

3. Notifies the ESC via e-mail of submissions that fail to load because of potential eCTD or other guidance related issues.
4. Identifies and resolves technical issues and load submission to CER.
5. Ensures all the submissions received via the FDA Electronic Submissions Gateway are appropriately stored on CBER's servers and appropriate network environment.

E. Electronic Submission Coordinator (ESC)

1. Ensures mailboxes for electronic submissions are monitored and submissions are processed in accordance with requirements.
2. Reviews appropriate guidance, CBER regulatory systems and validation tools to identify trans-BLAs.
3. Consults with the eCTD data and eSubmissions subject matter experts for validation and guidance.
4. Prepares rejection notice and, if needed, consults with the review office regarding the issue.
5. Ensures access of the submission in CER.

F. Review Committee Members

1. Reviews the submissions (refer to *SOPP 8401.2: Administrative Processing of BLA and NDA Supplements* for supplements) within required timelines and provides letter ready review comments (if relevant) to the RPM.

G. Lead Review Office

1. Manages the trans-BLA overall, including interactions (e.g., regulatory communications, such as letters and teleconferences) with the applicant.
2. Ensures that review timelines are adhered to.

VII. Procedures

A. General Information:

1. Pre-assign STNs as requested for submissions that are required to be submitted in eCTD format per *SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format*. **[RIB]**

2. Ensure that any follow-up correspondence (amendments) to the submission references the primary STN. **[RPM]**

B. Submission Receipt and Processing:

1. Process the submission and notify the offices via the load notification per established procedures. **[DCC]**
2. Ensure that the cover letter lists all the STNs/products in the submission and the submissions contains a separate Form FDA 356h for each product. **[RPM]**
3. For submissions that were not pre-assigned any STNs, ensure that STNs were assigned for each product in the appropriate regulatory system. **[RPM]**
4. Ensure that the STN Acknowledgement letter is issued, if applicable, per *SOPP 8401.2: Administrative Processing of BLA and NDA Supplements*. **[RPM]**
5. Ensure that the submission can be found under the assigned STN in the CER. **[RPM]**
 - a. For eCTD, the submission will only be present under the BLA eCTD dossier of the primary STN.
 - b. Data is entered once for the primary STN; the information should be visible for all STNs in the trans-BLA.
6. Ensure access of the electronic submission in CER for all review committee members. **[ESC]**
7. Upon receipt of submission, review supplements in accordance with procedures in *SOPP 8401.2: Administrative Processing of BLA and NDA Supplements*. Review other types of submissions in accordance with expected review timelines, if established. **[Review Committee Members]**

C. Specific Procedures for trans-BLAs that contain STNs managed by different review offices

1. Upon receipt of an STN pre-assignment request, contact appropriate review staff of involved offices and request that offices determine lead. **[RIB]**
2. Determine lead review office, taking expertise into consideration, when contacted by RIB and respond to RIB within one business day. **[Review Offices]**

3. Identify lead review office in the appropriate regulatory system. **[RIB]**
4. Provide concurrence on action letters and any information request letters (if the content of the information request is applicable to all offices). **[Division Director of non-lead office]**

VIII. Appendix

N/A

IX. References

A. References below can be found on the Internet:

1. [The eCTD Backbone Files Specification for Module 1](#)
2. [SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format](#)
3. [SOPP 8401.2: Administrative Processing of BLA and NDA Supplements](#)
4. [International Conference on Harmonization – M4: The Common Technical Document](#)
5. [FDA's Electronic Submissions Gateway](#)
6. [Electronic FDA 356h Form](#)

X. History

Written/Revised	Approved By	Approval Date	Version Number	Comment
Monser	N/A	February 27, 2023	5	Technical update due to 2023 CBER Reorganization and corrected hyperlinks
Monser	N/A	February 27, 2022	4	Technical update due to 2022 CBER Reorganization
Monser	Christopher Joneckis, PhD	December 13, 2021	3	Update to current procedures and new review procedures for cross-office review
Monser	N/A	December 11, 2020	2	Technical Update for retirement of the EDR and replacement with CER, replaced "database" with "system" and updated references/hyperlinks

Written/ Revised	Approved By	Approval Date	Version Number	Comment
BPS/RMCC	R. Yetter	April 18, 2011	1	First issuance of this SOPP