SOPP 8422: Processing of Trans-BLA Submissions

Version #1

Effective Date: April 18, 2011

I. Purpose

The purpose of this document is to provide guidance to Center for Biologics Evaluation and Research (CBER) staff on administrative procedures for the submission of paper and electronic (roadmap, electronic Common Technical Document (eCTD)) trans-BLAs to the Center for Biologics Evaluation and Research (CBER).

This SOPP will aid CBER staff when responding to inquiries from applicants who are planning to submit trans-BLAs for regulatory action.

Documents submitted in accordance with this SOPP facilitate initial processing by CBER's Document Control Center (DCC) and help ensure prompt delivery to the correct office.

II. Scope

This SOPP addresses a submission containing **identical** changes that affect multiple Biologics License Applications (BLAs). CBER refers to this submission type as a trans-BLA.

III. Background

An applicant may wish to submit **identical** changes to multiple BLAs. In order to accommodate this, CBER initiated the "trans-BLAs process." A single submission meeting this criterion is assigned multiple Submission Tracking Numbers (STNs), one for each BLA affected. The process obviates the need for separate **identical** submissions, eliminating duplicate data entry, and enhancing efficiency. Data Entry is performed once for all submissions in the group.

IV. Definitions

A. CTD: The Common Technical Document (CTD) provides for a harmonized structure and format for new product applications. It is a standard adopted by the International Conference on Harmonization (ICH). Submissions in this format are accepted in either paper or electronic form.

B. eCTD: The electronic Common Technical Document (eCTD) allows for the electronic submission of the CTD from applicant to regulator. While the table of contents is consistent with the harmonized CTD, the eCTD also provides a harmonized technical solution to implementing the CTD electronically. The eCTD specification is based on

Extensible Markup Language (XML) technology. The specification for the XML structure is the Document Type Definition (DTD).

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. eBLA: a Biologics License Application submission in electronic form using any of the following formats: PDF, PDF in CTD format, eCTD.

F. Electronic Submissions Gateway (ESG): the Agency Web portal by which submissions can be received electronically from sponsors and/or applicants. Additional information can be found on FDA's Internet Web page.

G. Trans-BLA: a single submission from an applicant containing **identical** changes pertaining to multiple products (STNs). A trans-BLA can be a supplement (or other submission type, e.g., product correspondence, annual report, PMC submission) pertaining to multiple products. A trans-BLA can not be an original application.

H. Submission Tracking Number (STN): The RMS-BLA sequentially generated tracking number for all BLA submissions. The STN is associated with the manufacturer and a specific product.

1. The *first six digits* represent the original submission tracking number;

2. The *next four digits* represent each supplement to the original submission (the "supplement" portion of the number also represents annual reports, post-marketing commitments, product correspondence, foreign inspections, and promotional materials); and

3. The *final four digits* represent an amendment to the supplement supporting the original submission.

I. SmartForm: a term used to describe an electronic form in portable document format (pdf) with capabilities beyond a traditional paper form, such as electronic completion, dynamic sections, database calls and electronic submission. These forms, e.g., 356h, can be obtained from the FDA forms Website.

J. Guidance Compliant: an eCTD or electronic submission with a roadmap.pdf with active and working hyperlinks. The guidance compliant electronic submission will not have unique paper components.

K. Non-Guidance Compliant: A non-guidance compliant electronic submission is defined as any submission that does not meet the guidance compliant definition. As examples, non-guidance compliant electronic submissions may have a paper component, no roadmap.pdf or non-standard file formats.

L. Primary STN: the Submission Tracking Number (STN) that contains the content applicable to all the STNs in the trans-BLA (paper or electronic).

1. For eCTDs, information submitted will only reside in the BLA eCTD dossier of the primary STN.

V. Policy

A. CBER staff should follow the procedures outlined in this SOPP for submission of trans-BLAs.

B. CBER encourages the use of the Agency's Electronic Submissions Gateway for the submission of regulatory documents to CBER. Additional information on these procedures can be found on FDA's Internet Web page.

1. The appropriate SmartForm should accompany these electronic submissions.

2. This presentation enables data to be stored in a way that facilitates automation. An automated submission load program (the Gateway Interface Application) is part of CBER's Electronic Document Room (EDR) and extracts information from these forms and utilizes it to load CBER submissions.

3. If the appropriate .pdf smart form is not incorporated in the submission, CBER will not be able to leverage the programmatic automation for loading electronic submissions into CBER's EDR and sending load notifications to the appropriate Office and Center staff, thus creating a delay in routing.

C. CBER encourages the submission of a trans-BLA as a single submission from an applicant with **identical** changes that references all impacted BLAs.

1. Communication records for trans-BLAs should be the same.

2. Letters sent in response to a trans-BLA will reference all impacted BLAs. The primary STN is indicated by an asterisk.

3. The review memo will be the same for all impacted BLAs. The memo will be entered only once in RMS-BLA but included in the files for all impacted BLAs.

D. All information submitted as a trans-BLA in eCTD format will reside only in the BLA eCTD dossier of the primary STN.

E. 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.

F. Submissions containing identical changes but submitted individually will be accepted but will not be processed as a trans-BLA.

G. Original Biologics License Applications cannot be processed as trans-BLAs and must be submitted as separate BLAs and processed individually.

VI. Responsibilities

A. Product Office Regulatory Project Manager (RPM)

1. Follows SOPP 8117 regarding pre-assignment of STNs.

2. Ensures that the applicant's cover letter lists all the STNs in the submission.

3. Ensures mailboxes for electronic submissions are monitored and the load notifications are triaged.

4. Ensures that submissions (electronic and paper) are sent to appropriate review personnel.

5. Ensures that STNs are assigned for each product and that an STN Assignment letter is issued. In the STN Assignment letter the primary STN is indicated by an asterisk.

B. Document Control Center (DCC)

1. Processes paper submissions according to current procedures.

2. Processes electronic submissions received on media or not loaded automatically via the FDA Electronic Submissions Gateway and notifies the appropriate Electronic Submission Coordinator (ESC).

3. Maintains the original submission (paper or electronic received on media) in DCC as an uncirculated archival copy.

C. Electronic Submission Coordinator (ESC)

1. Ensures mailboxes for electronic submissions are monitored and the load notifications are triaged.

2. Reviews electronic submission for "readability."

3. Ensures access of the submission in the EDR for all review committee members.

D. Electronic Document Room (EDR) Team

1. Confirms eCTD validation.

2. Ensures all submissions received via the FDA Electronic Submissions Gateway are appropriately stored on CBER's network.

3. Ensures all submissions received via the FDA Electronic Submissions Gateway are sent to CBER's DCC for processing.

VII. Procedures

A. Electronic (steps 1-4 are specific for eCTD submissions received via Gateway)

1. Ensure that the applicant obtains pre-assigned STNs from CBER per *SOPP 8117: Issuing Submission Numbers in Advance of the Receipt of the Electronic Submission*. The applicant should identify the primary STN of the trans-BLA in the cover letter. **[RPM]**

    a. Ensure that the primary STN is an eCTD if the trans-BLA group is mixed (eCTD and paper). **[RPM]**

    b. Ensure the applicant uses the next eCTD sequence number for the primary STN only. **[RPM]**

2. Validate that the applicant uses the primary STN in the backbone us-regional.xml. **[EDR Team eCTD validation**]

3. Ensure that any follow-up correspondence (amendments) to this submission reference the primary STN. **[EDR Team and RPM]**

4. Ensure that electronic fillable 356h forms for all the STNs are included in the Module 1 folder per eCTD Guidance. The naming convention is:

    a. Primary STN = 356h.pdf form

    b. Child STN1 = 356h_STN1.pdf

    c. Child STN2 = 356h_STN2.pdf

    d. etc. for each child STN [**EDR Team eCTD validation**]

    e. The form can be found on the Agency's Internet Web page.

5. Ensure that the cover letter lists all the STNs in the submission. **[RPM]**

6. Process electronic submissions and notify the appropriate Electronic Submission Coordinators (ESCs) per *DCC Procedure Guide 22: Procedures for Processing, Routing, and Storing Electronic Submissions*. **[DCC]**

7. Ensure Office specific mailboxes for electronic submissions are monitored and load notifications are triaged **[RPM, ESC]**

8. Ensure load notifications are sent to appropriate review personnel **[RPM]**

9. Review electronic submissions for "readability," i.e., structure, format, presence of bookmarks, hyperlink functionality, etc., throughout the entire submission. **[ESC]**

10. Ensure that a Submission Tracking Number (STN) is assigned for each product in the RMS-BLA database and the STN Assignment letter is issued per *SOPP 8401.2: Administrative Processing of Biologics License Application Supplements (BLSs)[Except Blood, Blood Components, and Source Plasma]*. [**RPM]**

11. Ensure that the submission can be found under the assigned STN in CBER's Electronic Document Room (EDR). [**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 submission.

12. Ensure access of the electronic submission in CBER's EDR for all review committee members. **[ESC]**

B. Paper

1. Receive, process, log into CBER's Document Accountability Tracking System (DATS), and route to the appropriate Office all submissions and extra reviewer copies. DCC will route the submission based on the product name as reported by the applicant on the Form FDA 356h or parent STN following existing DCC routing procedures per *SOPP 8110: Submission of Paper Regulatory Applications to CBER.* **[DCC]**

2. Route submissions to all committee members using the Marketing Applications Request System (MARS) application in RMS-BLA. [**RPM]**

3. Maintain the original copy of the submission in DCC as an uncirculated record copy. **[DCC]**

4. Ensure that a Submission Tracking Number (STN) is assigned for each product in the RMS-BLA database and the STN Assignment letter is issued per *SOPP 8401.2: Administrative Processing of Biologics License Application Supplements (BLSs)[Except Blood, Blood Components, and Source Plasma]*. **[RPM]**

VIII. Appendix

N/A

IX. References

A. References below are located on FDA's Internet Web Page

1. Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications - 6/2008
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf

2. The eCTD Backbone Files Specification for Module 1
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf

3. Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations - 10/22/2003
http://www.fda.gov/RegulatoryInformation/Guidances/ucm124737.htm

4. Guidance for Industry: Part 11, Electronic Records; Electronic Signatures - Scope and Application - 8/3/2003
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf

5. SOPP 8007: DCC Binding Procedures for Regulatory Documents
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109596.htm

6. SOPP 8110: Submission of Paper Regulatory Applications to CBER
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079467.htm

7. SOPP 8117: Issuing Submission Numbers in Advance of the Receipt of the Electronic Submission
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109641.htm

8. SOPP 8401.2: Administrative Processing of Biologics License Application Supplements (BLSs) [Except Blood, Blood Components, and Source Plasma]
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073082.htm

9. International Conference on Harmonization – M4: The Common Technical Document http://www.ich.org/products/ctd.html

10. FDA's Electronic Submission Gateway
http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

11. Electronic 356h Form
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/BiologicForms/default.htm

X. History

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