SOP Title:	**Preparation of Amendments to a Type V Facilities Electronic Drug Master File (CBER Format)**
SOP Number:	**24410**
Revision:	**07**

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1. PURPOSE

This procedure defines the process by which amendments to the Biopharmaceutical Development Program's (BDP's) Type V Facilities Master File (MF) are created for submission to the Center for Biologics Evaluation and Research (CBER) / Food and Drug Administration (FDA) in eCTD (electronic Common Technical Document) format.

2. SCOPE

This procedure applies to BDP personnel that are involved in the preparation, review, and approval of amendments to the Type V Facilities MF for the Frederick National Laboratory for Cancer Research (FNLCR) / National Cancer Institute (NCI) at Frederick. For the purposes of this procedure, amendments are classified as administrative (i.e., Letter of Authorization Updates and Annual Reports) or Quality Amendments (updates to technical information).

3. RESPONSIBILITIES

3.1 The Associate Director of Regulatory Affairs (RA)

- Defines this procedure.
- Reviews and approves both quality and administrative amendments.

3.2 BQA RA (or designee)

- Prepares, reviews, submits, and archives MF amendments in accordance with this procedure.

3.3 The BDP Manufacturing Director, the Process Analytics Director, the QA Engineering/Validation Manager, the Regulatory Compliance/BQA Director, the BDP Program and Technical Director, and the NCI/Biological Branch (BRB) Chief (or their designees)

- Reviews quality amendments.
- Approves quality amendments.

4. DEFINITIONS

- **Amendments** – Amendments are additional electronic documents submitted to the existing Type V Facilities MF. For the purposes of this SOP, there are two types of amendments submitted to the BDP's MF.
  - **Administrative Amendments** – These types of amendments include the following:
    - Letter of Authorization
    - Withdrawal of Letter of Authorization
    - Annual Update

    NOTE: the FDA's Guidance Document Drug Master Files discusses additional types of administrative amendments. If ever applicable, those administrative amendments would be performed following the basic steps outlined in this procedure.
  - **Quality Amendments** – Any changes to technical information should be submitted in a quality amendment.

- **Annual Reports** – Annual reports should not be used to report changes in the DMF. If it is necessary to submit an amendment and an annual report, they must be submitted under separate eCTD sequence numbers. Annual reports help assure FDA that the statement of commitment is current. Failure to submit a report annually may result in the termination of a DMF.

- **Bookmark** – A bookmark is a function in the pdf document. Bookmarks consist of a tree-structured hierarchy, which serves as a visual table of contents for a document. Bookmarks allow the document user to navigate to the targeted place within the document by selecting the bookmarked item.

- **Digital Signature** – A process that can be used to attach a digital code to an electronic message that is unique to the individual signing the message. A digital signature results from the use of a "Private Key" to apply a signature to an electronic message. The "Public Key" on the file with the recipient of the electronic message can be used to verify whether or not the digital signature is valid and whether the message has been altered since it was signed.

- **Master File (MF)** – A MF is a submission of information to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs and biological products. The BDP maintains a Type V Master File on file with the FDA/CBER that describes the manufacturing facilities and operational responsibilities of the BDP at the NCI at Frederick's CGMP biopharmaceutical manufacturing facilities.

- **Letter of Authorization (LOA)** – A LOA permits the FDA to access and review a document in their files, such as a MF, or portions thereof, on behalf of the person or company making reference to the document in their submission. The BDP provides LOAs to their MF on file at CBER in the form of an amendment to the eCTD Master File.

- **Link or Hyperlink** – Links (also known as hyperlinks and hypertext links) within a document allow the user convenient access to other locations within the same document, to other electronic documents, or to websites. By selecting the hyperlinked text, the user has immediate access to the information in the linked location.

- **Portable Document Format (PDF)** – The page description language used in the Adobe Acrobat document exchange system. The MF is created using numerous individual pdf files.

- **Serial Number (eCTD Sequence Number)** – A four-digit number assigned to each submission to the electronic Drug Master File. Serial numbers are assigned sequentially beginning with the serial number 0000 (assigned to the initial submission of the electronic Master File). For example, the first amendment has the serial number 0001). Serial numbers are abbreviated as 00SN throughout this document. Refer to the MF Regulatory File-Correspondence List to determine the next sequential serial number.

5. GENERAL GUIDELINES FOR AMENDMENTS TO THE MF

5.1 A description of general formatting requirements applicable to the preparation of MF amendments in Microsoft Word is included in SOP **24408 – Preparation of Regulatory Documents.**

5.2 MF amendments are prepared for submission using the eCTD software Omnicia according to SOP **24414 – Submitting Documents to the FDA Using BDPs eCTD Software.**

5.3 Create the Source folder under the DMF number folder (ex: eCTDlab\DMF6298\Source) to save all of the source documents for the submission. The folder will be named with the next sequential four-digit serial number. For example, if the last submission was 0019, the folder should be named “0020”.

5.4 Pdf file names must be all lower case with no spaces. Underscores can be used in place of a space; however, other special characters or hyphens should not be used. Examples of appropriate file names include the following:

5.4.1 coverletter_0030

5.4.2 infostate_0030

5.4.3 masterfile_annualreport_2021

5.4.4 form3938_0029

5.4.5 143_0029_authparties

5.4.6 32a1_0029_app1_2021

5.5 Each amendment should include the documents to be sent to the FDA, Form FDA 3938, and a statement that the submission is virus free titled “information statement” with the four-digit sequence number. A cover letter is also included in MF Quality Amendment submissions. Refer to Attachment 2 in SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software** for the list of documents to be sent to the FDA.

6. LETTER OF AUTHORIZATION OR WITHDRAWAL OF LETTER OF AUTHORIZATION AMENDMENT

6.1 BDP will issue a letter of authorization (LOA) to IND sponsors intending to use products manufactured by the BDP in their clinical trial(s). BDP submits the LOA as an amendment to the MF and provides a copy of the LOA to the sponsor for inclusion in their IND, which permits FDA to review the contents of BDP's MF in support of the IND.

6.2 When an IND is withdrawn or closed and the sponsor no longer needs to maintain authorization to reference BDP's MF, a Withdrawal of LOA is submitted as an amendment to the MF. The withdrawal letter should replace the LOA in eCTD section 1.4.1, if applicable. A copy of Withdrawal of LOA is also provided to the sponsor.

6.3 The process for issuing an LOA or a Withdrawal of LOA is the same.

6.4 Draft the letter on FNLCR letterhead using Microsoft Word and save it in the Submission Source folder created in Step 5.3 FDA recommends the use of the templates available on their website for the LOA or Withdrawal of LOA. BDP templates for both letters are available in [redacted]. The letters typically include the following information:

6.4.1 The date of the submission

6.4.2 DMF number

6.4.3 DMF holder's name

6.4.4 DMF title

6.4.5 Submission type (Letter of Authorization or Withdrawal of Letter of Authorization)

6.4.6 Authorized party for whom authorization is being granted or withdrawn

6.4.7 Specific product(s) or section of the MF referenced (Note: the BDP's MF may be referenced in its entirety)

6.4.8 Statement of commitment that the MF is current, and that the MF holder will comply with the statements made in it (for LOA only)

6.4.9 Signature of responsible official

6.4.10 Typed name, title, and contact information of responsible official

6.5 Prepare a pdf copy of the letter and apply a digital signature for the Associate Director of RA (Refer to **SOP 24408 – Preparation of Regulatory Documents**).

6.6 Using the Microsoft Word version of the most recently submitted List of Authorized Parties (eCTD section 1.4.3) found in [redacted]e, add or remove the authorized party and other corresponding information and save the file as a pdf in Submission Source folder created in Step 5.3

6.7 Complete Form FDA 3938 by following the instructions for filling out FDA Form 3938 ([redacted]), which may be used in place of a cover letter for administrative submissions and save it in the Submission Source folder created in Step 5.3. The form should be signed by the Associate Director of RA.

6.8 Place a copy of the "infostate_00SN" pdf file, found in [redacted], in the Submission Source folder created in Step 5.3. This file will not be updated until the submission is compiled with the eCTD software; refer to SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software.**

6.9 After the pdf files and Form FDA 3938 are approved, the submission needs to be put into eCTD format using the Omnicia software; refer to SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software.**

6.10 Refer to Sections 9. and 10. for submission and recordkeeping.

7. ANNUAL REPORT

7.1 MF annual reports are required by the FDA to ensure all information remains current. Changes to technical information should be submitted in a Quality Amendment (refer to Step 8.).

7.2 An annual report template is available on FDA's DMF website and a BDP template is available in [redacted].

7.2.1 The annual report should contain the following information:

7.2.1.1 A statement of commitment signed by the MF holder stating that the MF is current, and that the holder will comply with the statements made in the MF. This statement can be included in eCTD section 1.2 and referenced in the annual report.

7.2.1.2 Confirmation that the administrative information in eCTD section 1.3 is up to date. An updated eCTD section 1.3 should be provided, if needed.

7.2.1.3 Dates of any quality amendments submitted since the last annual report.

7.2.1.4 Confirmation that the list of authorized parties in eCTD section 1.4.3 is up to date. An updated eCTD section 1.4.3 should be provided, if needed.

7.2.1.5 A list of parties whose authorization has been withdrawn and the dates of withdrawal.

7.3 Prepare a pdf copy of the annual report and apply a digital signature for the Associate Director of RA (Refer to SOP **24408 – Preparation of Regulatory Documents).**

7.4 Complete Form FDA 3938, which may be used in place of a cover letter for administrative submissions. The form should be signed by the Associate Director of RA.

7.5 Place a copy of the "infostate_00SN" pdf file, found in [redacted], in the Submission Source folder created in Step 5.3. This file will not be updated until the submission is compiled with the eCTD software; refer to SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software.**

7.6 After the pdf files and Form FDA 3938 are completed and signed, the submission needs to be put into eCTD format using the Omnicia software; refer to SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software.**

7.7 Refer to Sections 8. and 9. for submission and recordkeeping.

8. QUALITY AMENDMENT

8.1 A Quality Amendment is typically reviewed annually for any facility changes, including revising Section 4.0 (Response to March 6, 2000, FDA Letter to Sponsors of INDs or Master Files Manufacturing Gene Therapy Products) as discussed in Step 8.2.4.

8.2 Preparation of MF Sections for Review

8.2.1 Copy the current version of the DMF files from the [redacted] folder and place them in shared review network folder. This includes Sections 1-4, Appendices 1-3, cover letter and the facility diagram files/table of major equipment in Appendix 2.

8.2.2 Open each Microsoft Word file copied to the MF Amendment source folder and make any revisions known. The font used for text is Arial 12pt. If a file is revised, make sure the headers and footers are updated. Headers and footers remain unchanged if no revisions are made.

8.2.2.1 The header format for each Microsoft Word file appears in Arial 10-point font on each page of each section as follows:

Example Header:

BDP MF BB-MF 00XXXX 2019 Amendment
Leidos Biomedical Research, Inc. /FNLCR
3.2.A.1 Facilities and Equipment
Section 1.0 Introduction

8.2.2.2 Update the year on the first line of the header to reflect the current year of the Amendment.

8.2.2.3 Confirm the "####" entry on the first line of the header reflects the MF FDA identification number.

8.2.2.4 The second line of the header is the company name: Leidos Biomedical Research Inc./FNLCR.

8.2.2.5 Confirm the third line and fourth lines of the header reflect the title of the section being updated. The FDA suggested the BDP Facility Type V Master File be submitted under Section 3.2.A.1 Facilities and Equipment using the eCTD format.

8.2.2.6 The footer format for each Microsoft Word file appears in Arial 10-point font on each page of each section and has the following format. The number 1 represents the sequential page number, and the word "Confidential" appears in bold with all capital letter font as follows:

8.2.2.7 Appendix 2 contains approximately 28 separate facility diagrams and one table. The facility diagrams are each separate figures so if one is updated, then only that figure needs to be replaced in the amendment. Figures may have a slightly different header that does not include the third line of "3.2.A.1 Facilities and Equipment" to get the information to fit. The words "Appendix 2 – Building A/B" are included.

8.2.2.8 Save and close each file when revisions are complete and update the file name to the appropriate sequence number and year of the amendment.

8.2.3 BQA RA (or designee) is responsible for updating and revising Section 4.0 (Response to March 6, 2000, FDA Letter to Sponsors of INDs or Master Files Manufacturing Gene Therapy Products). Section 4.0 consists of an introduction and responses to seven questions from the FDA Letter. RA reviews the response to each question, investigates the current status, and updates/edits the response to the question to provide the most current information.

8.2.4 RA sends out a link for the shared review network folder to the following BDP individuals (or their designees) so they can review each of the sections relevant to their areas. Required reviewers may be modified at the discretion of the Associate Director of Regulatory. Reviews are performed using the track changes feature of Microsoft Word.

- Director, Manufacturing Operations
- Director, Biopharmaceutical Process Analytics/Quality Control (PA/QC)
- Director, Regulatory Compliance/BQA
- BQA, Quality Engineering/Validation Manager
- BQA Auditing Manager

NOTE: The list of reviewers can be modified at the discretion of Regulatory Affairs management.

8.2.5 As the reviews are completed:

8.2.5.1 Resolve all reviewer comments and update the document's Table of Contents (if applicable). A track change version of the file should be saved separately for reference during approval.

NOTE: The version sent to the FDA will not have the tracked changes on it. It will be the final approved version.

8.2.5.2 Ensure the headers are updated for all documents being revised; refer to Step 8.2.2. If updates are required for the facility diagrams in Appendix 2, the PDF text should be updated to reflect the current amendment.

8.2.5.3 Any significant changes should be added to the table of revisions in the cover letter. Be sure to include section numbers, page numbers, paragraph, etc., as applicable to indicate the location and nature of the change.

8.3 Approval of the Quality Amendment

8.3.1 Once the reviews are complete and any revisions are finished, any files not being updated should be removed from the shared review drive as they will not be included in the Quality Amendment submission.

8.3.2 Generate an approval page with digital signature blocks per SOP **24408 – Preparation of Regulatory Documents.** Approvers should include, at a minimum, the following individuals:

- Director, Manufacturing Operations
- Director, Biopharmaceutical Process Analytics/Quality Control (PA/QC)
- Director, Regulatory Compliance/BQA
- Associate Director, Regulatory Affairs
- BQA, Quality Engineering/Validation Manager
- BDP Program and Technical Director
- BRB Branch Chief

8.3.3 RA sends out a link to the approvers listed above to the shared review network folder containing the revised files, updated cover letter listing the changes and signature page. A link to the track change version of each revised file may also be provided.

8.3.4 Once the Quality Amendment is approved, the cover letter should be signed by the Associate Director of RA.

8.3.5 Complete Form FDA 3938 and obtain signature from the Associate Director of RA.

8.3.6 Move the files to be included in the submission to the Submission Source folder created in Step 5.3. Create a subfolder for the Microsoft Word versions.

8.3.6.1 Place a copy of the "infostate_00SN" pdf file, found in [redacted], into the Submission Source folder. This file will not be updated until the submission is compiled with the eCTD software; refer to SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software.**

8.3.6.2 The approval signature page is not submitted to the FDA and therefore is not moved to the Submission Source folder. It should be included in the compiled submission described in Step 10.3.2.

8.3.7 Ensure all references in the text to appendices, figures, and tables are in blue font (Royal Blue 255).

8.3.8 Ensure internal (inter-document) hyperlinks have been created.

8.3.9 Convert the Microsoft Word documents to pdf and create bookmarks and links per SOP **24408 – Preparation of Regulatory Documents.**

8.3.9.1 For external (between documents) hyperlinks, be sure to set the correct destination for external hyperlinks. Some links will point to previous submissions, if the files were not updated for the current submission.

8.3.9.2 Creating external links between documents:

Open the PDF file from the source folder (i.e., [redacted]). Right click on the word that you want to create a link and select "Create a link". Choose link type as "Invisible Rectangle" and "Go to a page view" for a link action then click "Next". A "Create Go to View" box will be popped up.

All external hyperlinks should point to the file in the output folder (i.e., [redacted]) not to the file in the source folder. To create the link destination, open the PDF file from the output folder then click "Set Link" from the pop-up window. If external hyperlinks point to the current sequence prepared for submission, the target file should be rendered first to point to the link in the output folder. All files should be rendered again once hyperlinks are completed.

Accordingly, some of the files must be published per SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software** before the external hyperlink can be created.

8.3.10 Refer to Steps 9. and 10. for submission and recordkeeping.

8.4 Authorized Party Notification

8.4.1 In accordance with 21 CFR 314.420(c), DMF holders must notify authorized parties of any DMF changes, deletions, or additions.

8.4.2 Using the template found in the DMF folder on the QA drive, a notification should be created that can be distributed to all authorized parties.

8.4.3 The notification should be converted to pdf and digitally signed by the Associate Director of RA.

8.4.4 The signed notification should be emailed to the institutional contact for each authorized party, as noted in the Excel spreadsheet of authorized parties.

8.4.4.1 Prior to sending the signed notification, a distribution form should be requested according to SOP **21417 – Distribution of Documents to External Recipients**

8.4.5 Refer to Step 9. for recordkeeping.

9. ECTD PUBLISHING AND FDA SUBMISSION

9.1 Compile the submission according to SOP **24414 - Submitting Documents to the FDA using BDPs eCTD Software.**

9.2 Submit the eCTD files to the FDA according to SOP **24302 - Establishment and Use of an FDA Electronic Submissions Gateway (ESG) Account.**

9.3 Prior to submission, a distribution form should be requested according to SOP **21417 – Distribution of Documents to External Recipients**.

10. RECORDKEEPING

10.1 LOA or Withdrawal of LOA

10.1.1 Request a distribution form according to SOP **21417 – Distribution of Documents to External Recipients.** The approved distribution form can be saved in the Source folder.

10.1.2 Provide a copy of the LOA or Withdrawal of LOA to the sponsor

10.1.3 Include the LOA/Withdrawal of LOA letter and associated communications in the project correspondence file.

10.1.4 A LOA can also be provided to the sponsor along with the Chemistry, Manufacturing, and Controls information/Manufacturing Report.

10.1.5 Update the DMF Regulatory Correspondence File with a link to the Source folder containing the final files and the ESG receipt/acknowledgement. Include the serial submission number in the correspondence log. The distribution form can be saved to the Source folder.

10.1.6 Make the appropriate additions or deletions to the list of authorized parties Excel file on the QA drive.

10.2 Annual Update

Update the DMF Regulatory Correspondence File with a link to the Source folder containing the final files and the ESG receipt/acknowledgement. Include the serial submission number in the correspondence log. The distribution form can be saved to the Source folder.

10.3 Quality Amendment

10.3.1 Update the DMF Regulatory Correspondence File with a link to the Source folder containing the final files and the ESG receipt/acknowledgement. Include the serial submission number in the correspondence log. The distribution form can be saved to the Source folder.

10.3.2 Merge the individual pdf files of the entire MF, along with the approval page, into a single pdf file. The combined file should contain the current version of each section of the MF.

10.3.3 Note: Form FDA 3938 is a protected document and cannot be merged with the other files. It is acceptable to maintain it as a separate file along with the combined file.

10.3.4 Create bookmarks and hyperlinks as described in **SOP 24408 – Preparation of Regulatory Documents.**

10.3.5 Add a copy of the combined file to the DMF folder on the QA drive and add a corresponding link to the DMF Regulatory Correspondence File.

10.3.6 Add a copy of the MF Annual Update file to [redacted]\Drug Master File BB-MF ####. Delete the previous year's DMF Annual Update File BB-MF #### so that only the most current version is available on the H:\drive.

10.3.7 Update the DMF Section Updates Excel file on the QA drive to indicate which files were updated in the submission.

10.4 Authorized Party Notification

10.4.1 Each email sent to the authorized parties should be saved as an individual pdf file in the DMF folder on the QA drive. A copy of the signed memo and distribution form should also be saved in the same folder.

10.4.2 Update the DMF Regulatory Correspondence File with a link to the folder created above.

10.4.3 Add the date of the notification sent to the authorized parties Excel file on the QA drive.

11. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
21417	Distribution of Documents to External Recipients
24302	Establishment and Use of an FDA Electronic Submissions Gateway (ESG) Account
24408	Preparation of Regulatory Documents
24414	Submitting Documents to the FDA Using BDP's eCTD Software
N/A	FDA Draft Guidance for Industry: Drug Master Files, October 2019