BIOPHARMACEUTICAL DEVELOPMENT PROGRAM

SOP Title:	**Preparation of the CMC Portion of Pre-IND Read Ahead Packages**
SOP Number:	**24406**
Revision:	**08**

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1. PURPOSE

This SOP defines the content and format of the CMC Portion of Pre-IND Information Packages for submission to the FDA.

2. SCOPE

This procedure applies to Biopharmaceutical Development Program and Regulatory Affairs personnel who are involved in the preparation, review, and approval of CMC Pre-IND Information Packages for the Frederick National Laboratory for Cancer Research (FNLCR) / National Cancer Institute (NCI) at Frederick.

3. RESPONSIBILITIES

3.1 The Associate Director of Regulatory Affairs or designee.

- Defines this procedure.
- Reviews and approves the CMC portion of the Pre-IND Read Ahead Package.

3.2 BQA Regulatory personnel or designee.

- Prepares, reviews, submits (to the Sponsor), and archives the CMC portion of the Pre-IND Read Ahead Packages in accordance with this procedure.

3.3 The Project Scientist, the Manufacturing Director, the PA/QC Director, the BDP Program and Technical Director, the NCI/BRB Project Director, and the NCI/BRB Chief (or their designees)

- Reviews and approves of the CMC portion of the Pre-IND Read Ahead Package.

4. DEFINITIONS

- **Applicant** – an applicant is a person who submits an IND, or an amendment to an IND, to the FDA to conduct clinical investigations with an investigational new drug.
- **Day** – One calendar day.
- **Information Package (briefing package or backgrounder)** – Information provided by an external constituent to Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) as background information for a meeting.
- **Sponsor** – A person who takes responsibility for and initiates a clinical investigation (refer to 21 CFR 312.3).
- **Week** – Seven calendar days.

5. PURPOSE OF THE PRE-IND MEETING

With respect to CMC information, the purpose of pre-IND meetings is to discuss safety issues related to the proper identification, strength, quality, purity, or potency of the investigational drug, as well as to identify potential clinical hold issues.

5.1 Focus of the Pre-IND Meeting

Examples of the CMC issues that could be discussed in pre-IND meetings include, but are not limited to:

- Physical, chemical, and/or biological characteristics
- Manufacturers
- Source and method of preparation
- Removal of toxic reagents
- Quality controls (e.g., identity, assay, purity, impurities profile) or release testing requirements
- Formulation
- Sterility (e.g., sterilization process, release sterility and endotoxin testing, if applicable)
- Linkage of pharmacological and/or toxicity batches to clinical trial batches
- Stability information

5.2 The discussion of safety issues for conventional synthetic drugs is typically brief. For certain types of drugs, such as biotechnological drugs, biological drugs, natural products, complex dosage forms, and drug-device combinations, it may be appropriate to discuss the CMC information in more detail. Examples where detailed discussion may be appropriate include, but are not limited to:

- Drugs from human sources [e.g., appropriate donor screening procedures for tissues, blood, or other fluids; removal or inactivation of adventitious agents (e.g., viruses, bacteria, fungi, and mycoplasma)]
- Drugs from animal sources (e.g., removal or inactivation of adventitious agents, transmissible spongiform encephalopathy (TSE)-free certification)
- Biotechnology drugs, particularly rDNA proteins from cell line sources (e.g., adequacy of characterization of cell banks, potential contamination of cell lines, removal or inactivation of adventitious agents, potential antigenicity of the product)
- Botanical drugs (e.g., raw material source, absence of adulteration)
- Reagents from animal or cell line sources (same considerations as for drugs derived from animal cell or cell line sources)
- Novel excipients
- Novel dosage forms (e.g., characteristics, potential for overly rapid release of dose, if applicable)
- Drug-device delivery systems (e.g., demonstration of device and its characteristics, potential for overly rapid release of dose, particle size distribution considerations, where applicable)

6. GENERAL FORMAT OF THE CMC PORTION OF PRE-IND READ AHEAD PACKAGES

6.1 A pre-IND CMC template is available in the RA files (H:\6QA\QAOnly\RA\Miscellaneous\Templates\PreIND Templates). Using this format makes it easier to build the IND CMC Module 3 in the future since the template is based on eCTD Module 3, but all headings are provided in one document (instead of as separate files). Refer to Attachment 1 for an example eCTD Pre-IND CMC Table of Contents.

6.2 Different templates may be used upon request.

6.3 For a description of the general formatting requirements applicable to the preparation of CMCs for Pre-IND read ahead packages, refer to **SOP 24408 – Preparation of Regulatory Documents**. The document template specific to Pre-IND CMC document should be prepared as follows:

6.3.1 Times New Roman 12 pt is preferred to use for narrative text.

6.3.2 Headers and Footers

6.3.2.1 The font used for headers and footers should be a minimum Time New Roman 8 pt.

6.3.2.2 The header should include the document title and project or product name.

Example Header:

BDP/FNLCR/Leidos Biomedical Research Inc.
Pre-IND CMC for hJAA-F11 Antibody

6.3.2.3 The word “Confidential” is included on the last line of the footer in bold.

6.3.2.4 The month and year of the document approval is also included in the footer. If needed, a placeholder can be added for the date, which should be updated when the final pdf is created.

6.3.2.5 If a file is revised, make sure that the revised version should be included in the footer with a month and year of the document approval (ex: January 2022 Rev01)

Example Footer:

NCI **3 of 20**
Confidential **June 2022 Rev 01**

6.4 The associated cover letter to send to the sponsor should contain the contract statement as follows:

6.5 The documents associated with this letter are made available through federal funds from the National Cancer Institute, NIH, under contract XXXXXXXX.

7. CONTENT OF THE CMC PORTION OF PRE-IND READ AHEAD PACKAGES

7.1 The CMC-related questions should be presented in the information package in final form, grouped together and identified. Formulate questions to be as specific, comprehensive, and as precise as possible to identify the critical issues. The questions should be presented in the same relative subject matter order as a typical CMC section of an application or as otherwise appropriate to aid in the review of the information. CMC questions should be presented to the IND sponsor to compile with all the other questions to be addressed at the meeting. The IND sponsor usually submits the final list of questions with the complete information package four weeks prior to a meeting date.

7.2 Provide sufficient CMC background information on the drug to allow the Agency to address the specific questions.

7.3 Where data presentation is appropriate, present a summary of the data (e.g., tables, charts, graphs).

7.4 A sample CMC Pre-IND Read Ahead Package Table of Contents (TOC) is found in Attachment 1. The CMC information may be as detailed as a mini-CMC section or as general as a brief discussion of the manufacturing and testing along with flow diagrams of the process. Sufficient information needs to be submitted to allow the FDA enough information to address specific CMC questions.

8. REVIEW AND FINALIZATION OF THE CMC PORTION OF PRE-IND READ AHEAD PACKAGES

8.1 The Microsoft word files should be provided for review electronically. An email is sent to the following personnel to review the documents. The NCI/BRB chief should be copied on the review email. Additional personnel may review the report at the request of the Associate Director of Regulatory Affairs.

- Project Scientist(s) or designee
- Manufacturing Director or designee
- Process Analytics/Quality Control (PA/QC) Director (or designee)
- Associate Director of Regulatory Affairs or designee
- BDP Program and Technical Director or designee
- NCI/BRB Project Director or designee

8.2 After revisions from the reviewer comments and recommended edits are completed, the final documents are sent with a link to the shared folder for approval. Approvals are completed when signatures below are obtained:

- Project Scientist(s) or designee
- Manufacturing Director or designee
- Process Analytics/Quality Control (PA/QC) Director (or designee)
- Associate Director of Regulatory Affairs or designee
- BDP Program and Technical Director or designee
- NCI/BRB Project Director or designee
- NCI/BRB Chief or designee

Approvers can be changed or other approvals can be added at the discretion of the RA Associate Director.

8.3 Requirements for the review, approval, making an electronic copy, and submitting a Regulatory document can be found in **SOP 24408 – Preparation of Regulatory Documents.**

8.4 BDP Regulatory Affairs will send the completed Pre-IND CMC package to the IND sponsor to submit as part of the entire Pre-IND information Package to the FDA. The pre-IND CMC is typically provided to the customer as an Adobe pdf file; however, Microsoft Word format is also acceptable per the customer's request. The Pre-IND CMC can be sent to the sponsor and/or applicant via encrypted Outlook email or the Secure Email and File Transfer (SEFT). To access the SEFT Service, go to https://secureemail.nih.gov. Alternative methods are acceptable upon sponsor and/or applicant request and at the discretion of RA management.

8.5 It is the responsibility of the sponsor or applicant to submit the information package to the appropriate Division Director in CDER or CBER with product review responsibility.

8.5.1 For a Pre-IND Meeting (Type B), submit the full information package including clear, thoughtful questions at least four weeks prior to the formal meeting.

8.5.2 The FDA may postpone or cancel a meeting if supporting documentation essential for a productive meeting has not been received by the Agency within the prescribed time frames. Failure to submit an adequate information package within the time frames will be considered a request by the sponsor or applicant to cancel the meeting.

9. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
24408	Preparation of Regulatory Documents
21 CFR 312.47	Regulations applicable to meetings on investigational products
N/A	FDA Guidance for Industry: IND Meetings for Human Drugs and Biologics, Chemistry, Manufacturing and Controls Information (May 2001).
N/A	FDA Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (Draft Guidance September 2023).
N/A	CBER Standard Operating Policy and Procedure (SOPP) 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products (current version).
N/A	Guidance Document: Portable document Format (PDF) specifications, September 2016

10. ATTACHMENTS

Attachment 1: Sample CMC Pre-IND Information Package Tale of Contents

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