Frederick National Laboratory for Cancer Research, Frederick, MD

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Preparation of the CMC Portion of Pre-IND Read Ahead Packages

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Approval/Date: [redacted]

Approval/Date: [redacted]

Table of Contents

1.0 Purpose

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

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

2.0 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 NCI at Frederick.

3.0 Authority and Responsibility

3.1 The Director, Biopharmaceutical Quality Assurance (BQA) Regulatory Affairs or designee has the authority to define this procedure.

3.2 BQA Regulatory personnel or designee are responsible for preparation, review, submission, and archiving of the CMC portion of the Pre-IND Read Ahead Packages. The report preparer has the responsibility for assuring the CMC portion of the Pre-IND Read Ahead Package is consistent with source documents such as Historical Records, Batch Production Records, and Quality Control Testing Reports.

3.3 The Project Scientist or technical designee, the Program and Technical Director or designee, BQA Management, and the NCI/BRB Project Director or designee, are responsible for review and approval of the CMC portion of the Pre-IND Read Ahead Package. The Project Scientist or technical designee, and the NCI/BRB Project Director or designee, are responsible for the review and accuracy of all technical information presented in the CMC portion of the Pre-IND Read Ahead Package. The Process Analytics\Quality Control Director or designee may be asked to review and approve assay descriptions, and testing information.

3.4 BQA Regulatory personnel or designee are responsible for ensuring that the CMC portion of the Pre-IND Information Package documents have correct pagination and section numbering, and follow the Table of Contents prior to document release to clients either as a draft or final version.

3.5 The sponsor or IND applicant is responsible for preparing and submitting the Pre-IND Information Package to the FDA.

3.6 BQA is responsible for quality oversight of this procedure.

4.0 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.

4.1 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

4.2 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)

5.0 General Format of the CMC Portion of Pre-IND Read Ahead Packages

For a description of the general formatting requirements applicable to the preparation of CMCs for Pre-IND read ahead packages, refer to the general formatting section of ***SOP 24408, Preparation of Regulatory Documents***.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

6.0 Content of the CMC Portion of Pre-IND Read Ahead Packages

6.1 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 cover letter of the complete information package four weeks prior to a meeting date.

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

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

6.4 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.

6.4.1 Where possible it is recommended to follow the electronic Common Technical Document (eCTD) format for Module 3 including those sections/information relevant to the PreIND Meeting CMC question discussions. Using this format makes it easier to build the IND CMC Module 3 in the future. Refer to Attachment 1 for an example eCTD PreIND CMC Table of Contents.

7.0 Review and Finalization of the CMC Portion of Pre-IND Read Ahead Packages

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

7.1 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 PreIND CMC will be sent through the NIH Secure Electronic File Transfer (SEFT) system. An electronic PDF copy on a CD-ROM can be provided if necessary

7.2 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.

7.3 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.

7.4 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.

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8.0 Definitions

8.1 **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.

8.2 **Day** – One calendar day.

8.3 **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.

8.4 **Sponsor** – A person who takes responsibility for and initiates a clinical investigation (refer to 21 CFR 312.3).

8.5 **Week** – Seven calendar days.

9.0 References and Related Documents

9.1 **SOP 24408** *Preparation of Regulatory Documents*

Note: For assistance in preparing Pre-IND Read Ahead Packages, the following references and FDA Guidance Documents may prove helpful, and can be obtained by visiting the BQA/Regulatory Group, or the FDA website (www.fda.gov).

9.2 21 CFR 312 Investigational New Drug Application

9.3 21 CFR 610 - General Biological Products Standards

9.4 Section 119 of the Food and Drug Administration Modernization Act (Pub. L. 105- 115)

9.5 Regulations applicable to meetings on investigational products in 21 CFR 312.47

9.6 Guidance for Industry: IND Meetings for Human Drugs and Biologics, Chemistry, Manufacturing and Controls Information (May 2001).

9.7 Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUF Products (Draft Guidance December 2017).

9.8 FDA Guidance for Industry: Content and Format of Phase I Investigational New Drug Applications (INDs) for Phase I Studies of Drugs, Including Well- Characterized, Therapeutic, Biotechnology- Derived Products (November 1995).

9.9 Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products, CBER Standard Operating Policy and Procedure (SOPP) 8101.1 (November 4, 2019.

9.10 FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

9.11 FDA Guidance for Industry: INDs for Phase 2 and Phase 3 Studies – Chemistry, manufacturing, and Controls Information (May 2003).

10.0 Attachments

10.1 **Attachment 1** Sample CMC Pre-IND Information Package Table of Contents

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Attachment 1
Sample CMC Pre-IND Information Package Table of Contents

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