Title: Content of an Investigational New Drug Application (IND)

SOP Number: 24404
Revision Number: 06
Supersedes : Revision 05
Effective Date: NOV 26 2019

Originator/Date: [redacted]

Approval/Date:

Approval/Date:

Table of Contents

1.0 Purpose

This procedure describes the general content of an Investigational New Drug application (IND) submitted to the FDA prior to conducting Phase I or II clinical trials using an investigational new drug.

2.0 Scope

Under current regulations, any use in the United States (US) of a drug product not previously authorized for marketing in the US first requires submission of an IND to the FDA unless exempted per 21 CFR 312.2. This SOP outlines the content of an IND according to the US Code of Federal Regulations, 21 CFR 312.23 and related guidance documents (reference steps 8.1 - 8.6). The specific content of the IND differs for different products and depends on the phase of the investigation, the exten t of human study, the duration of the investigation, the nature and source of the drug substance, and the dosage form of the drug product.

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

3.0 Authority and Responsibility

3.1 It is the responsibility of any Biopharmaceutical Development Program (BDP) personnel preparing an IND or any portion of an IND to follow this procedure.

3.2 It is the responsibility of BDP Staff to notify the Director, Regulatory Affairs, or delegate, whenever they receive a request for assistance in preparing an IND.

3.3 It is the responsibility of the Director, Regulatory Affairs, to provide assistance or designate a person to provide assistance to sponsors requesting help preparing an IND.

3.4 Regulatory Affairs personnel are responsible for managing the preparation of the Chemistry, Manufacturing, and Controls section of an IND per ***SOP 24411 - Preparation of a Chemistry, Manufacturing, and Controls Section in Common Technical Document (CTD) Format.***

4.0 Definitions

4.1 IND: IND means an investigational new drug application. For purposes of this part, "IND" is synonymous with notice of claimed investigational exemption for a new drug, 21CFR 312.3(b).

4.2 Sponsor: The individual, pharmaceutical company, government agency, academic institution, private organization, or other organization that takes responsibility and initiates a clinical investigation. 21 CFR 312.3(b).

4.3 Investigator: An individual who conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event a team of individuals conducts an investigation; the investigator is the responsible leader of the team. "Sub-investigator" includes any other individual member of that team. 21 CFR 312.3(b).

4.4 Sponsor-Investigator: This means an individual person who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed (21 CFR 312.3(b)). The requirements for both a sponsor and an investigator (4.1 and 4.2) apply to a sponsor-investigator.

4.5 Contract Research Organization (CRO): An independent contractor (a person, organization, or corporation) to the sponsor that has entered into a written contractual agreement with a sponsor to perform one or more of the sponsor's responsibilities (such as design of the clinical protocol, selection of the investigators and study monitors, evaluation of reports, and preparation of submissions to the FDA). Because responsibility as well as authority may be transferred, a CRO is subject to the same regulatory actions as sponsors for any failure to perform any of the obligations assumed. 21 CFR 312.3(b).

4.6 Institutional Review Board (IRB): Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 502(g) of the Federal Food, Drug, and Cosmetic Act. 21 CFR 56.102(g).

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

4.7 Clinical Investigation/Study:Any experiment in which a drug is administered or dispensed to,or used involving one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. 21 CFR 312.3(b).

4.8 Test Article: Any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act. 21 CFR 58.3(b}.

4.9 Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. Guidance for Industry:Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation (May 1999).

4.10 Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient. 21 CFR 314.3(b).

4.11 Drug Product: A finished dosage form; for example, tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. 21 CFR 314.3(b).

5.0 Investigational New Drug Application Content

5.1 An IND submission is required by the Code of Federal Regulations (CFR) (21 CFR 312.23) to contain the sections described in this SOP. Although not specifically required by the CFR, a cover letter is generally included with an IND submission and is recommended as part of the electronicCommon Technical Document (eCTD) format (Module 1, Section 1.1). A templated example of a cover letter is included as Attachment 1.

5.2 The specific content of the IND differs for different products and depends on the phase of the investigation, the extent of human study, the duration of the investigation, the nature and source of the drug substance, and the dosage form of the drug product.

5.3 A Cover Sheet (FDA Form-1571) [21 CFR 312.23(a)(2)] should be included. A current FDA Form-1571 can be obtained using the following website: http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm083533.pdf. A cover sheet for the IND contains the following information on FDA Form 1571:

5.3.1 The name, address, and telephone number of the sponsor, the date of the IND, and the name of the investigational new drug.

5.3.2 The IND number if previously assigned. If it has not been previously assigned than this field should be left blank.

5.3.3 The proposed indication of use, whether the indication is for a rare disease, is for commercial or research purposes, and whether the product has an orphan drug designation.

5.3.4 The phase of clinical investigation to be conducted.

This procedureis made available through federal funds from the National Cancer Institute, NIH, under contract --

5.3.5 The numbers of other FDA applications referenced in the IND being submitted.

5.3.6 The serial number of the submission and the type of submission {Initial Investigational New Drug Application should be checked, and the serial number should be "0000").

5.3.7 Check the information that applies in Section 11 of the 1571. For the original IND application, only the box for the "Initial Investigational New Drug Application (IND)" should be checked.

5.3.8 For section 12, fill in anything that applies if it is a combination product.

5.3.9 Anything that applies in Section 13 (Expanded Access Use, Emergency Use, or charge request) of the 1571 should be checked.

5.3.10 Check the information that applies in Section 14 for the sections of the IND that are being submitted. Most of the items should be included in an initial IND submission (items 1-4, 6,7,8,9).

5.3.11 For Section 15, check the appropriate boxes if the clinical study will be conducted by a CRO.

5.3.12 A commitment not to begin the clinical trial until the IND is in effect, or to begin clinical investigation studies if they are placed on clinical or financial hold.

5.3.13 A commitment that the Institutional Review Board (IRB) complies with the requirements of 21 CFR Part 56 and will be responsible for the review and approval of the clinical trial and the investigator will report proposed changes to the IRB.

5.3.14 A commitment to conduct the clinical trial in compliance with all regulatory requirements.

5.3.15 The name and title of the person responsible for monitoring the conduct of the clinical trial.

5.3.16 The name and title of the person responsible under 21 CFR 312.32 for monitoring the safety of the drug being administered in the clinical trial.

5.3.17 The signature of the sponsor or the sponsor's representative and their contact information.

5.4 Table of Contents [21 CFR 312.23(a)(2)]: Each eCTD section over five pages should have a table of contents.

5.5 Per 21 CFR 312.23(a)(4), IND Section 4 is reserved by the FDA for future use. A cover page can be provided for this section; however, no additional information is required.

5.6 Introductory Statement and General Investigational Plan [21 CFR 312.23(a)(3)]: This section (include in eCTD Module 1, Section 1.20) contains a brief (two to three pages) introductory statement, summary of previous human experience with the drug, description of any instances where the drug has been withdrawn from investigation, and the investigational plan for the coming year. A general investigational plan is appropriate for the early phases of clinical study. A more detailed investigational plan can be designed based on the results of initial studies.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract --

5.6.1 A brief introductory statement containing the following information:

- The name of the drug and all active ingredients;
- The drug's pharmacological class;
- The structural formula if known;
- The formulation of the dosage form to be used;
- The route of administration; and
- The objectives and planned duration of the clinical investigation.

5.6.2 A brief summary of previous human experience with the drug referencing other pertinent INDs and investigationalor marketing experience in other countries.

5.6.3 A brief description of any instances where the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or efficacy. Identification of the countries where the drug was withdrawn and the reason for the withdrawal are also included.

5.6.4 A brief description of the overall investigational plan for the drug for the coming year. This description contains the following information:

- The study rationale;
- The indication(s) studied;
- The general approach of the evaluation;
- The kinds of clinical trials to be conducted in the first year;
- The estimated number of patients; and
- The anticipated risks.

5.7 Investigator's Brochure [21 CFR 312.23(a)(5)]: Contains clinical and nonclinical information relevant to the study of the product in humans compiled by the sponsor to provide to the investigators and others involved in the clinical trial. The intent of the Investigator's Brochure is to describe the rationale for key features of the clinical protocol in order to facilitate compliance. The type and extent of information available for inclusion in the Investigator's Brochure varies with the stage of the development of the drug. This section generally describes information contained in the Investigator's Brochure. *The International Conference on Harmonization (/CH) Guideline for Good Clinical Practice E6* (reference this SOP Step 8.3) provides additional general guidance on the preparation and content of the Investigator's Brochure in Section 7. The Investigator Brochure is located in eCTD Module 1, Section 1.14.4.1.

5.7.1 Drug substance and formulation description, including the structural formula if known.

5.7.2 Pharmacological and toxicological effects in animals and if known, in h1,1mans .

5.7.3 Pharmacokinetics and biological disposition of the drug in animals, and if known, in humans.

5.7.4 Safety and efficacy information in humans summarized from prior clinical studies.

5.7.5 Anticipated risks and side effects, precautions or special monitoring to be done.

5.8 Protocols [21 CFR 312.23(a)(6)] : A copy of the clinical protocol for the study is included in this section. Clinical Protocols are located in eCTD Module 5, Section 5.3.5.2.

5.8.1 Phase I study protocols are acceptably less detailed than Phase II/III study protocols. Phase I study protocols primarily outline the investigation, estimate the number of patients, and describe safety exclusions and the dosing plan. Detailed description within a Phase I study protocol is appropriate for issues critical to safety such as patient monitoring during the clinical trial. Design modifications that do not affect critical safety assessments within a Phase I study are reported in the annual report to the FDA.

5.8.2 Phase II/III study protocols detail all aspects of the study. Alternative or contingency plans to be used when a deviation from the study protocol is needed should be anticipated, planned for, and written into the protocol.

5.8.3 Specific study protocol elements include:

- Objectives and purpose of the study;
- Background information including description of investigational product, summary of non-clinical studies, and any known risks;
- Investigator/Sub-investigatorname(s) and address(es) and a statement of their qualifications;
- Research facility name(s) and address(es);
- Institutional Review Board name(s) and address(es);
- Patient selection/exclusion criteria;
- Estimated number of patients to be selected;
- Study design description including method to eliminate bias;
- Dosing plan description;
- Observations and measurements required; and
- Monitoring plan description.

5.8.4 Study protocols should be written with consideration given to human subject research regulations. Such regulations can be found in the Code of Federal Regulations (21 CFR 50), InternationalConference on Harmonization (ICH) Guidelines E6 and E8, and the Department of Health and Human Services 45 CFR 46.

5.8.5 In addition to a copy of the clinical protocol for the study, this section of the IND should also include the following information:

- Each investigator's curriculum vitae;

- The Institutional Review Board (IRS) approved informed consent form and IRB approval letter, if available. If not available, the form and letter should be submitted in an amendment to the IND when they become available;
- Information specific to each investigator using Form FDA 1572. A current FDA Form-1572 can be obtained using the following website: http://www.fda.gov/media/71816/download.

5.9 Chemistry, Manufacturing, and Control (CMC) Information [21 CFR 312.23(a)(7)]: This section describes the composition, manufacture, and control of the drug substance and the drug product to assure the identification, quality, purity, and strength of the investigational drug. This information is provided in Module 3 of an IND. A detailed description of the content of the Chemistry, Manufacturing, and Control information for the drug substance and the drug product are described separately in ***SOP 24411 - Preparation of a Chemistry, Manufacturing, and Controls Section in Common Technical Document (CTD) Format.***

The amount of supporting CMC information varies with the investigational phase, the scope of, the duration of, and the dosage form used for the clinical trial.

5.9.1 The information contained in the CMC section for both the bulk drug substance and the final drug product should include: description/composition information, name and address of the manufacturer, method of manufacture (including container/closure information), analytical test and specifications(including assay descriptions) to assure the identity, strength, quality, and purity of the drug substance and product, and stability data demonstrating the drug product will be stable throughout the toxicology studies and course of the clinical trial.

5.9.2 For Gene Therapy product IND's, the information requested in the FDA's March 6, 2000, Gene Therapy Letter should be provided as part of the CMC or can be included by reference using a letter of authorization issued by the manufacturer to cross reference their Drug Master File.

5.9.3 The FDA provides guidance for the content of CMC information for Phase 1 studies of drugs in the guidance document entitled *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Wei/-Characterized, Therapeutic, Biotechnology-derived Products, November 1995;* and Phase 2 and 3 studies of drugs in the guidance document entitled *INDs for Phase 2 and 3 Studies of Drugs-Chemistry, Manufacturing, and Controls Information, May 2003.*

5.10 Pharmacology and Toxicology Information [21 CFR 312.23(a)(8)]: Discussion of pharmacological and toxicological studies conducted in animals or *in vitro* used by the sponsor to support the safety and possibly the efficacy of the proposed investigational study. The extent of the pharmacological and toxicological study requirements varies with the phase of the clinical study. As drug development proceeds, the sponsor submits updated pharmacology and toxicology information in an amendment. Additional pharmacology and toxicology guidance can be found in the guidance document entitled *Content and Format of Investigational New Drug Applications (INOs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products,*

November 1995. Pharmacology and Toxicology information is located in eCTD format Module 4.

5.10.1 Information to be included in the pharmacology and toxicology section includes:

- A brief description of each study design;
- A systematic presentation of the findings with a full tabulation of the data;
- Identity and qualifications of the person(s) evaluating the pharmacology and toxicology data to determine the safety of the proposed study;
- Where and when the pharmacology and toxicology studies were conducted;
- Where the pharmacology and toxicology study records are maintained;
- A statement that the study was conducted in compliance with Good Laboratory Practices outlined in 21 CFR 58; or if not conducted in compliance with Good Laboratory Practices, provide a reason for the noncompliance.
- A rationale for the animal model selected.

5.10.2 Pharmacology and Drug Disposition: Pharmacological effects and mechanism(s) of action of the drug in animals are described including absorption, distribution, metabolism, and excretion data.

5.10.3 Toxicology: Toxicological effects of the drug in animals and *in vitro* are provided in an integrated summary. The summary is written appropriate to the investigational phase and considers such elements as:

- Acute, subacute, and chronic toxicity tests;
- Tests of the effect on reproductive health and the developing fetus;
- Tests related to the mode of administration or conditions of use;
- Any *in vitro* studies; and
- A.full tabulation of data suitable for detailed review.

5.11 Previous Human Experience with the Investigational Drug [21 CFR 312.23(a)(9)]: Previous Human Experience with the investigational drug is located in eCTD Module 5. This section contains a summary of previous human experience with the proposed investigational drug, if any, including:

5.11.1 Experience related to the safety of the proposed investigation resulting from previous investigations or marketing with the investigational drug.

5.11.2 Information from previous controlled clinical trials relevant to the drug's efficacy for the proposed investigational use.

5.11.3 If the investigational drug is a combination of drugs, then each active drug component is addressed in terms of Step 5.11.1 and 5.11.2.

5.11.4 If the investigational drug has been marketed outside of the United States, then a list of the countries where the drug has been marketed is included. A list of the countries where the drug has been withdrawn from the market is included where the reason for withdrawal pertains to safety or efficacy.

5.11.5 A statement should also be made if there is no previous human experience with the proposed investigational drug.

5.12 Additional Information [21 CFR 312.23(a) (10)]: Information on special topics is included as needed in the relevant eCTD section:

5.12.1 Drug dependence and abuse potential;

5.12.2 Radioactive drugs;

5.12.3 Pediatric studies; and

5.12.4 Other information to aid in the evaluation of the safety, design, and ability of the proposed study to support marketing of the investigational drug including pertinent references.

5.13 Relevant Information [21 CFR 312.23(a) (11)]: Any other relevant information required for review of the application if requested by the FDA is included as needed in the relevant eCTD section.

5.14 Clinical Trials Certification of Compliance Form 3674 should be filled out and included in the IND. The form can be found at the following FDA website and should be included in eCTD format Module 1: . **https://www.fda.gov/media/69901/download**

5.15 eCTD format also includes Module 2 Summaries. Phase I IND's may or may not include these summary sections since most of this information may be a duplicate to the actual other Modules 3-5. This is left up to the discretion of the IND sponsor.

5.16 IND Submission

5.16.1 Information previously submitted: Information that has been previously submitted to the FDA may be incorporated into the IND by reference.

5.16.2 Material in a foreign language: An accurate and complete English translation is submitted with each part of the IND that is not written in English.

5.16.3 Unless submitting a noncommercial IND, an IND must be submitted in eCTD format unless the submission is exempted or waived.

5.16.4 Numbering of IND Submissions: Beginning with the initial IND, serial numbering with a four-digit serial number is used for each submission relating to an IND. The initial IND is numbered 0000, and each subsequent submission (amendments, reports, correspondence, etc.) is chronologically numbered.

6.0 Submitting the IND to the FDA

6.1 Electronic Submissions: When making an electronic submission refer to the following Web sites for additional information:

- CDER: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm.
- CBER: http://www.fda:gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm163685.htm.

6.2 IND submissions and subsequent amendments to the IND should be accompanied by a Form 1571.

6.3 IND submissions should be made electronically using the FDA's Electronic Secure Gateway (ESG). The current address for cover letters for IND submissions should be confirmed by consulting the FDA Web site (http://www.fda.gov). At the time of approval of this SOP, the addresses were as follows:

For a Drug

(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm):

U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Central Document Room

5901-B Ammendale Road

Beltsville, Md. 20705-1266

For a Therapeutic Biological Product Regulated by CDER

(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm):

(http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133463.htm)

U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Therapeutic Biological Products Document Room

5901-B Ammendale Road

Beltsville, MD 20705-1266

For a Biologic Regulated by CBER

(http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/ucm094309.htm):

U.S. Food and Drug Administration

Center for Biologics Evaluation and Research

Document Control Center

10903 New Hampshire Avenue

W071, G112

Silver Spring, MD 20993-0002

7.0 Storage of INDs at the Biopharmaceutical Development Program

7.1 If a sponsor provides the BDP with a courtesy copy of an IND, the IND is filed in the appropriate project Regulatory Correspondence electronic folder.

7.2 Regulatory Affairs personnel (or designee) update the project's Regulatory Correspondence File to reflect the receipt of the IND copy.

8.0 References

8.1 *FDA Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including We/I-Characterized, Therapeutic, Biotechnology-derived Products, November_1995.*

8.2 *FDA Guidance for Industry: INDs for Phase 2 and Phase 3 Studies - Chemistry, Manufacturing, and Controls Information, May 2003.*

8.3 *FDA Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to /CH E6(R1) March 2018.*

8.4 *FDA Guidance for Industry: Container Closure* Systems *for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation, May 1999.*

8.5 CBER website with Information on Submitting an Investigatio nal New Drug Application: http://www.fda.gov/BiologicsBloodVaccines/Deve lopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/ucm094309.htm .

8.6 CDER website with Information on Submitting an Investigational New Drug Application: http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm

9.0 Attachments

9.1 **Attachment 1** Example IND Cover Letter

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

Attachment 1

Example IND Cover Letter

[Date]

[FDA address: This will vary, depending on the nature of the product and the disease indication.]

[redacted] **M.D.**
Director
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

or

- MD, Ph.D.
Director
U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

Subject: **Notice of** Claimed Investigational Exemption for a New Drug **{IND)**
IND # XXXXX Serial No. [0000]
[Insert Title of IND Here]

Dear [redacted]

[Company/Institution Name] is submitting a Notice of Claimed Investigation Exemption for a New Drug (IND) for [insert IND title here].

[Company/Institution Name] is sponsoring this IND to evaluate the administration of [name of drug or biologic] for the treatment of [name of disease or condition].

The proposed initial study under this IND will be conducted at the [name of clinical site]. The Principal Investigator of this study is [name of principle investigator], M.D. A signed Form FDA 1572 and Investigator's Curricula Vitae are included in the IND submission.

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

Attachment 1 (Continued)

Example IND Cover Letter

[redacted]

[Date]
Page 2

[Add any pertinent information to which you would like to call the FDA's attention; some examples are given below]:

1. [Drug name] was manufactured by [manufacturer's name]. Information concerning the manufacture of this product is contained in Module 3.

2. The adjuvant [adjuvant's name] was manufactured by [adjuvant manufacturer's name, city, state]. A cross-reference letter to their Drug Master File [Drug Master File Number] can be found in Module 1.

3. Clinical trials will not be initiated prior to thirty (30) days after receipt of this IND by your Center. We will notify your Center if and for what reason the investigation is discontinued. In addition, we will notify each investigator if the investigation is discontinued or a New Drug Application or Biologics License Application is approved.

[Company/Institution Name] has established secure email with the FDA. For questions concerning this submissionplease contact XXX-by phone at XXX, or email at XXX.

Sincerely,

[Name, Title and Affiliation of IND Applicant]

Enclosure

pc:

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