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Investigational New Drug Application

Regulatory Sponsor: Name of the Sponsor-Investigator
Department Name
Address
Phone Number

Funding Sponsor: Name of Primary Funding Institution
Address
Phone Number

Study Product: Study Drug Name – Generic, followed by marketed name if applicable

Protocol Number: Protocol Number Used by Sponsor-Investigator

Date:

NOTE: Number of copies: The Sponsor shall submit an **original and two copies** of all submissions to the IND file, including the original submission and all amendment and reports.

1 **FDA Form 1571** [21 CFR 312.23(a)(1)]

The most current FDA forms are located at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm>

2 Table of Contents [21 CFR 312.23(a)(2)]

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This template presents the sections that comprise the IND application and was derived from FDA IND regulations (21CFR312.23) and ICH Good Clinical Practice guidelines.

Don't leave a section blank. If a section does not apply to your study, just enter 'Not applicable'. A few sections may be deleted where indicated.

3 Introduction [21 CFR 312.23(a)(3)]

Brief overview in an introductory statement of the objective of the research plan submitted in this IND. This should include a brief discussion of the disease state to be assessed, objectives and duration of the proposed clinical investigation. The information should place the developmental plan for the investigational agent into perspective and allow FDA to anticipate your needs. The 'Introduction' and 'General Investigational Plan' sections should average 2-3 pages in length.

3.1 Investigational Agent

Provide a brief introductory statement covering the following about the study drug:

- Drug name
- Pharmacological class
- Structural formula (if known)
- All active ingredients

3.2 Dose and Exposure

- Formulation and dose
- Route of administration
- Planned exposure (e.g. duration of study drug administration)

3.3 Overview of Previous Human Experience

Provide a high level summary of prior human experience with the study drug. This is a brief synopsis of a later section of this document entitled "Previous Human Experience with the Investigational Agent." It should include the status of the drug in other countries, if applicable.

Note: If the drug was withdrawn from the market for any reason related to safety or effectiveness, identify the country(ies) where the drug was withdrawn and the reasons for withdrawal.

3.3.1 Reference to previously submitted IND application(s) and/or marketed products

Note: Delete this sub-section if not applicable.

Provide a brief statement that includes the name of the drug, and the name and address of the manufacturer. You may state here: "A letter of Cross Reference authorizing the FDA to review Chemistry, Manufacturing and Control Information on IND xxxxx has been provided by the manufacturer xxxx. It is filed under Additional Information in this application."

Note: For studies *not* using a cross-reference:

Provide a brief introductory statement including the drug name, all active ingredients, pharmacological class, structural formula, formulation and dose, route of administration, and planned exposure to the study drug.

Provide a high level summary of preclinical data to date including mechanism of action, efficacy and safety. Content should be a brief synopsis of the 'Pharmacology and Toxicology Data' section.

Provide a high level summary of prior human experience with the investigational agent. Content should be a brief synopsis of the 'Previous Human Experience' section. Include a statement about whether the drug has been withdrawn from investigation or marketing in any country for reasons related to safety or efficacy. Cite the reason.

3.4 Overview of Preclinical Data

Provide a high level summary of preclinical data to date. This is a brief synopsis of a later section of this document entitled "Pharmacology and Toxicology."

4 General Investigational Plan [21 CFR 312.23(a)(4)]

4.1 Research Rationale and Objectives

Discuss the research rationale for the use of the study agent and the specific study(ies), the indications to be studied, the overall objectives, and the general approach to be followed in evaluating the drug.

4.2 Proposed clinical research

This section should include an overview of the study(ies) proposed for the first year of investigation. This is a general summary of the study design, estimated enrollment, the total number of patients to be exposed to study drug, endpoints, and treatment plan. The actual full protocol(s) is/are to be included as an attachment to this application (see last section below describing attachments).

If research plans are not developed for the entire year, that should be indicated here as well.

Note: A description of the first year of investigation can be a copy of the protocol flow sheet.

4.3 Anticipated risks from study drug

Describe any anticipated risks from the study drug based on *pre-clinical and clinical experience* with this drug.

5 Investigator's Brochure [21 CFR 312.23(a)(5)]

See Section 12, [Attachments](#).

6 Protocol [21 CFR 312.23(a)(6)]

See Section 12, [Attachments](#).

6.1 Investigator and Facilities Data

6.1.1 Form FDA 1572

6.1.2 Sponsor-Investigator Credentials

6.1.3 Subinvestigator(s) Credentials (CVs)

6.1.4 Disclosure of Financial Interests

6.2 Clinical Trial Registration

7 Chemistry and Manufacturing [21 CFR 312.23(a)(7)]

- Description of drug; include physical, chemical, or biological characteristics
- Name and address of manufacturer of drug product
- **If applicable**, you may state here: "A letter of Cross Reference authorizing the FDA to review Chemistry, Manufacturing, and Control Information on IND xxxxx has been provided by the manufacturer xxxx. It is filed under Additional Information."

7.1 General Method of Preparation and packaging

- General description of how drug is manufactured/prepared
- Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance
- Information sufficient to support stability of the drug substance during proposed human testing
- **NOTE:** Reference to the current edition of the United States Pharmacopoeia – National Formulary may satisfy relevant requirements in this section.

7.2 Drug Components and Drug Product

- **A drug component** is defined as: "any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product." (21CFR210.3)
- **A drug product** is defined as "a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients." (21CFR210.3)
- List all components used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process.
- Where possible, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage
- Packaging procedures as appropriate for the product
- Information sufficient to assure the product's stability during the planned clinical studies
- **NOTE:** Reference to the current edition of the United States Pharmacopoeia – National Formulary may satisfy relevant requirements in this section.

7.3 Placebo Product

Note: if applicable

Include a brief general description of the composition, manufacture, and control of any placebo used in the controlled clinical trial.

7.4 Labeling

Include copies of the label constructed for the study drug and any associated package.

7.5 Environmental Analysis Requirements

The FDA may require an environmental analysis to ensure the study agent does not impose an undue environmental hazard. For products already marketed, it is usually possible to request an exemption from the requirement to conduct an environmental analysis: *“We request a claim for categorical exclusion for this proposed clinical trial as provided for in 21 CFR.25.31 (e) in that the drug shipped under this notice is intended to be used in clinical trials in which the amount of waste expected to enter the environment may reasonably be expected to be non-toxic.”*

8 Pharmacology and Toxicology [21 CFR 312.23(a)(8)]

If applicable, you may state here: “A letter of Cross Reference authorizing the FDA to review Pharmacology and Toxicology on IND xxxxx has been provided by the manufacturer xxxx. It is filed under Additional Information.”

8.1 Pharmacodynamics

8.1.1 Primary pharmacodynamics

Describe the study drug mechanism of action. Include drug activity related to the proposed indication.

8.1.2 Secondary pharmacodynamics

Describe secondary pharmacodynamic effects (if any), their mechanism of action and activity related to the proposed indication.

8.2 Safety pharmacology

Describe the pharmacologic effects on safety including the following as appropriate:

- Neurological effects
- Cardiovascular effects
- Pulmonary effects
- Renal effects
- Gastrointestinal effects
- Abuse liability
- Other effects in addition to the above

8.3 Pharmacokinetics

8.3.1 Absorption

8.3.2 Distribution

8.3.3 Metabolism

8.3.4 Excretion

8.4 Pharmacology Summary

Provide a high-level summary of the pharmacology subsections above.

8.5 Pharmacology Conclusions

Provide a high-level summary of the general conclusions to be drawn from the pharmacology subsections above.

8.6 Toxicology

This section should summarize the toxicology studies conducted. For this section, refer to discussions in the FDA pre-IND meeting where the FDA will clarify guidance and requirements for your submission.

Note: For more detailed guidance, refer to the FDA guidance document: "Guidance for Reviewers Pharmacology/Toxicology Review Format."

(See:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072976.pdf>). Expected content elements for describing specific toxicology studies for this section typically include:

- Study title
- Key findings
- Study drug formulation/vehicle
- Methods
- Dosing
- Study observations
- Results (mortality, clinical signs, etc.)
- Summary
- Conclusions

8.7 Genetic Toxicology

8.8 Carcinogenicity

8.9 Reproductive and Developmental Toxicology

8.10 Special Toxicology Studies

8.11 Toxicology Summary

Provide a high-level summary of the toxicology subsections above.

8.12 Toxicology Conclusions

Provide a high-level summary of the general conclusions to be drawn from the toxicology subsections above.

9 Previous Human Experience with the Investigational Agent [21 CFR 312.23(a)(9)]

9.1 *Marketed experience*

Note: Delete this sub-section if not applicable.

Overview any FDA-approved marketed indications for the study drug. Reference to the FDA drug labeling for approved indications should be noted here, with copies of such labeling included in the attachment section of this IND application.

Note: If the drug was withdrawn from the market for any reason related to safety or effectiveness, identify the country(ies) where the drug was withdrawn and the reasons for withdrawal.

9.2 *Prior Clinical Research Experience*

Note: if applicable.

Summarize any clinical research studies using the investigational agent. This includes research studies conducted by you, published research, and any available unpublished research with the investigational agent.

9.3 *Clinical Care Experience*

Note: if applicable.

It is not uncommon for marketed drugs to be used in clinical care settings to treat patients for indications that do not have an FDA approval. This is often termed “off-label” use. Any published literature on the safety of the drug in that setting, and if available, published practice guidelines of the use of the drug for standard-of-care and the associated safety information could be referenced here. This is particularly relevant if the patient population treated with this off-label use of the drug is similar to the proposed study population for this IND application.

10 Additional Information [21 CFR 312.23(a)(10)]

In certain application information on special topics may be needed. That information should be submitted in this section. Examples of additional information that would be relevant if applicable to the planned IND work are noted below.

Note: Delete any of the following sub-sections that are not applicable.

10.1 *Drug dependence and abuse potential*

10.2 *Radioactive drugs*

10.3 *Pediatric studies*

10.4 *Other information*

A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug

11 Bibliography

Typically each protocol will contain its own bibliography. However, sections of this IND application may have additional references. If that is the case, then this section should be added and the appropriate bibliography provided.

12 Attachments

The following lists the attachments to this IND application:

- Cover letter
- Investigator's Brochure [21 CFR 312.23(a)(5)]
- Package insert
- FDA Form 1572 [21 CFR 312.23(a)(6)]
- FDA Form 3674 [21 CFR 312.23(a)(6)] (if appropriate)
- FDA Form 3455 [21 CFR 312.23(a)(6)] (if appropriate)
- Protocol(s) [21 CFR 312.23(a)(6)] (include copies of all protocols to be conducted under this IND application)
- Consent Form(s) [21 CFR 312.23(a)(6)] (if applicable, include copies of consent forms)
- CVs of all investigators [21 CFR 312.23(a)(6)] (listed on the 1572)
- Letter of Cross Reference from (drug supplier) [21 CFR 312.23(a)(10)]

INVESTIGATOR'S BROCHURE

[21 CFR 312.23(a)(5)]

Sponsor-Investigators are not required to submit an Investigator's Brochure for a single-center study. However *it is required for multi-center studies*

A cross-reference letter or package insert may be submitted in lieu of required information for the IB. Package inserts may be found in the Physician's Desk Reference (PDR), the FDA website or the US Pharmacopoeia—National Formulary

PACKAGE INSERT

(if applicable)

FDA Form 1572

[21 CFR 312.23(a)(6)]

Attach the 1572 form for the Principal Investigator(s) for the proposed IND studies.

The most current FDA forms are located at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm>

FDA Form 3674

[21 CFR 312.23(a)(6)]

This form is the 'Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank'. Most trials must register with the ClinicalTrials.gov database that was established by the NIH and FDA to increase public awareness of clinical trials. In addition, the International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition for publication of research results. One form per protocol must be registered. Any questions about ClinicalTrials.gov can be addressed to angela.lee@mssm.edu.

The most current FDA forms are located at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm>

FDA Form 3455

[21 CFR 312.23(a)(6)]

This is the 'Disclosure: Financial Interests and Arrangements of Clinical Investigators' form which must be sent to the FDA *if* there is a conflict of interest with any of the investigators listed on the Form FDA 1572.

The most current FDA forms are located at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm>

PROTOCOL(S)

[21 CFR 312.23(a)(6)]

List all protocols by title on this attachment face sheet in the order they are attached.

INFORMED CONSENT FORM(S)

[21 CFR 312.23(a)(6)]

CURRICULA VITAE OF ALL INVESTIGATORS

[21 CFR 312.23(a)(10)]

Provide for all investigators as listed on the 1572.

LETTER OF CROSS REFERENCE FROM (DRUG SUPPLIER)

[21 CFR 312.23(a)(6)]