Investigational New Drug (IND) Application for a Clinical Investigation

Investigator-Initiated IND

Title of Protocol

xx Month 20xx

Sponsor Information:

Name of Sponsor-Investigator

Title/Role, Department

Email

Phone #

Fax #

The Children’s Hospital of Philadelphia

Confidential

(**NOTE**: All blue text is provided for guidance and reference to the regulations. Delete or replace blue text upon completing the application)

*Introduction:*

*An* [*Investigational New Drug Application (IND)*](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.23) *is a request for Food and Drug Administration (FDA) authorization to administer an investigational product, either a drug or biologic, to humans. Such authorization must be secured prior to interstate shipment and administration of any investigational drug that is not the subject of an approved new drug application. For the purpose of this IND application, “drug” will refer to either a drug or biologic.*

*IND regulations are contained in* [*Title 21, Code of Federal Regulations, Part 312*](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312)*. Copies of the regulations, further guidance regarding IND procedures, and additional forms are available from the FDA Center for Drug Evaluation and Research, Drug Information Branch (HFD-210), 5600 Fishers Lane, Rockville, Maryland 20857, telephone (301) 827-4573 or toll free at 1-888-INFOFDA. In addition, forms, regulations, guidances, and a wide variety of additional information are available online on the* [*FDA Web site*](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm)*.*

***FDA Receipt of the IND Application:***

*Upon receipt of the IND application by FDA, an IND number will be assigned, and the application will be forwarded to the appropriate reviewing division. The reviewing division will send a letter to the Sponsor providing notification of the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of the FDA person to whom questions about the application should be directed. Studies shall not be initiated until 30 days after the date of receipt of the IND by FDA unless you receive earlier notification by FDA that studies may begin.*

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# Introductory Statement and General Investigational Plan

## Introductory Statement

This section is typically 2-3 pages long and is intended to place the clinical development plan for the Investigational New Drug into perspective and to help FDA anticipate the needs of the future program. Upon initial submission of an IND application, the detailed developmental plan may not be well established yet and could be contingent on many factors. In this case, the sponsor of the IND application should state this and provide a brief explanation of future plans for clinical development.

Provide a broad overview of the IND application and the primary goals of the project. Include the drug and indication to be studied.

## General Investigational Plan

The general investigational plan should include the following: (1) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a ) The rationale for the drug or the research study; (b ) the indication(s) to be studied; (c ) the general approach to be followed in evaluating the drug; (d ) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (e ) the estimated number of patients to be given the drug in those studies; and (f ) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

### Research Rationale and Objectives

#### Objective 1

#### Objective 2

### Indication(s) to be Studied

#### Indication #1

Describe indication and consider including key eligibility criteria.

#### Indication #2 (if applicable)

Describe indication and consider including key eligibility criteria.

### General Approach to be Followed in Evaluating the Drug

### Trials to be Conducted in the First Year

The kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate).

### Estimated Number of Subjects to be Given the Drug

The estimated number of patients to be given the drug in the study.

### Anticipated Risks

Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

#### Risk 1

#### Risk 2

# Chemistry, Manufacturing and Controls Information

## Drug Substance

### Name of Drug; Name of Manufacturer

# Name of drug. Description of physical, chemical, or biological characteristics and evidence supporting structure and identity of the active pharmaceutical ingredient(s).

# Name and address of manufacturer.

# *Note: The following 3 sections are generally for those investigative teams at CHOP that manufacture the investigational product:*

# Description of the general method of preparation of the drug substance, including a list of the reagents, solvents, and catalysts used. A detailed flow diagram is suggested as the most effective presentation. More information may be needed to assess the safety of biotechnology-derived drugs or drugs extracted from human or animal or plant sources.

# The acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug substance, with a brief description of the test methods used (e.g., Nuclear Magnetic Resonance, Infrared, UV spectra to prove the identity, and High Performance Liquid chromatograms to support the purity level and impurities, etc). Submission of draft certificates of analysis is also suggested.

# Information to support stability of the drug substance during storage in the intended container closure and during the toxicological and clinical studies.

### All Active Ingredients

### Pharmacological Class

### Structural Formula

### Formulation of Dosage

### Route of Administration

### Duration of Exposure for study participants

## Drug Product (if applicable)

For those investigative teams that manufacture, or have knowledge of manufacture of, the investigational product: (For all others, delete section 2.2)

### List of components of manufacturing

A list of all components and composition used in manufacturing process, including reasonable alternatives for inactive compounds used in the manufacture of the investigational drug product. This list is expected to include both those components intended to appear in the drug product and those which may not appear, but which are used in the manufacturing process.

### Summary of quantitative composition of investigational product

Summary of quantitative composition of the investigational new drug product, including any reasonable variations that may be expected during the investigational stage.

### Brief description of manufacturing process

Brief general description of the manufacturing process (in the form of a flow diagram is suggested) and packaging procedure, as well as other relevant tests, as appropriate for the product. Final specifications for the drug product intended to be used in toxicological and clinical studies should be included. For injectable products, sterility and pyrogenicity tests, endotoxin levels and particulate matter should be included. Submitting a copy of the certificate of analysis of the clinical batch is also suggested.

### Identity, strength, quality and purity of the drug product

The acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug product.

### Stability of drug product

Information to support stability of the drug product during the planned clinical studies.

## Placebo (if applicable)

This section is expected to include a brief general description of the composition, manufacture, and control of any placebo formulation to be used in the proposed clinical study. The description may be structured similarly to the description of the drug product recommended above.

*Note:* For placebo, the Quality Control test will include the absence of the active pharmaceutical ingredient(s). The physical characteristics of the placebo formulation should be comparable to the actual drug product to enable effective blinding.

## Labeling

Copies of labeling for the investigational product are expected to be provided in this section (or attached as an appendix), when applicable.

### Investigational Product label

The investigational product label will include "Caution: New Drug--Limited by Federal (or United States) law to investigational use" in accordance with 21 CFR 312.6.

## Environmental Assessment

This section is expected to include an assessment of effects of the investigational product on the environment. Environmental Assessment may be obtained from the IND product manufacturer or referenced [External Link Disclaimer](http://www.fda.gov/about-fda/website-policies/website-disclaimer) from an existing IND application.

Most products qualify for a categorical exclusion from such an assessment. In general, exclusion is based upon a variety of considerations, including the following:

1. Environment compartment (soil, air, water) into which the material will partition;
2. Degradation of the material and degree;
3. Safety margin between expected environmental concentration and effect level, for materials that slowly degrade.

Granting of a categorical exclusion will also depend upon the size of study population and amount of active moiety manufactured for the study.

For additional information on environmental assessments consult [Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (PDF - 188KB)](https://www.fda.gov/media/70809/download).

Typical Template Language: I claim a categorical exclusion from environmental assessment requirements (under 21 CFR 25.31[e]) for this IND. To my knowledge, no extraordinary circumstances exist.

# Pharmacology and Drug Disposition

### Pharmacology

This section is generally intended for pharmacology/toxicology information for a study drug that does not have existing data from well-designed studies previously conducted to support marketing of a drug, or for a drug without pharmacology/toxicology data contained in an Investigator’s Brochure. This section is expected to include description of the pharmacological effects and the mechanisms of action of the drug in animals and information on the absorption, distribution, metabolism, and excretion of the investigational product, if known. For those drugs that have comprehensive data from well-designed studies that were previously conducted to support marketing of the drug, or for a drug with extensive pharmacology/toxicology data as contained in an Investigator’s Brochure, this section can cite the FDA product label or the Investigator’s Brochure for relevant pharm/tox data.

### Toxicology

This section is expected to include information on the toxicological effects of the drug in animals and in vitro. For detailed explanation of what should be included in this section, refer to the [Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (PDF - 41KB)](https://www.fda.gov/media/72057/download).

Depending on the nature of the drug and the phase of the investigation, the description is expected to include:

1. the results of acute, subacute, and chronic toxicity tests;
2. the results of tests of the drug's effects on reproduction and the developing fetus;
3. any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and
4. any in vitro studies intended to evaluate drug toxicity.

For each toxicological study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review is expected. This should consist of line listings of the individual data points, including laboratory data points for each animal along with appropriate summary tabulations.

# Investigator’s Brochure

Choose the relevant statement:

The proposed clinical investigation is a single site Sponsor-Investigator study therefore no Investigator’s Brochure is required.

*(2)*

Please find attached the Investigator’s Brochure provided by the drug manufacturer.

*(3)*

Please find attached the draft Certificate of Analysis (CoA) either for each component of the investigational product that will be manufactured, or for the final product.

Investigators may obtain the Investigator’s Brochure (IB) from IND product’s manufacturer. For investigator-initiated IND applications that have a right of reference to an existing manufacturer’s IND application, submission of the IB is not required. IB is updated as the development program progresses and new information becomes available.  IB is expected to contain the following information:

* Brief description of the drug substance and the formulation, including the structural formula, if known
* Summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans
* Summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans
* Summary of information relating to safety and effectiveness in humans obtained from prior clinical studies
* Description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug. Adverse Events (AEs) described in the IB help determine whether an AE that occurs during a clinical trial is “expected” and, if so, how it will be reported to FDA.

*(4)*

Please find attached the drug Package Insert.

# Protocol(s)

Reference from the FDA on [Clinical Protocols](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362445.htm)

## Protocol

Protocol Title:

Protocol IRB#:

Protocol version date:

## CV of Investigator

# Previous Human Experience with the Investigational Agent

## Safety and Efficacy: Prior human marketed experience

There is no specific format for describing previous human experience with an investigational drug in an IND application. Shown below are some helpful points to consider when writing a summary of previous human experience:

* If no previous human experience exists, this should be stated in this section of the IND application.
* If an investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation’s rationale should be included in this section. A summary of previous human experience should contain all relevant information about previous investigations or marketing, including clinical trial reports and published material relevant to the product’s safety and effectiveness.
* If the product has been marketed outside of the United States, all countries where the product has been marketed or withdrawn from any of those markets (and why) should be listed.
* For an IND application with investigational new drug that is subject to another existing IND application (e.g., an IND application sponsored by the investigational new drug’s manufacturer), the investigator-sponsor may obtain a Letter of Authorization from the existing IND sponsor with the right of reference to the information contained in the existing IND application, including information related to any previous human experience.
* If an investigational new drug is a combination of drugs previously investigated or marketed, the description of human experience should be provided for each active drug component. However, if any component in such combination is an approved marketed product, submission of a copy of prescribing information leaflet may be sufficient. Additional published material about the approved drug may need to be submitted, if such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

# Additional Information

In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

## Drug dependence and abuse potential

If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals. Reference the [FDA Guidance](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf).

The investigational product, XXXXX, has/does not have known psychotropic or abuse potential.

## Radioactive drugs

If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

This IND application does not include radioactive drugs.

## Pediatric studies

Plans for assessing pediatric safety and effectiveness.

This IND application includes pediatric studies.

## 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.

## Charge Request

U.S. regulations prohibit charging a patient for an investigational drug unless FDA gives authorization to do so. A request to charge must be made if the sponsor or pharmacy plans to charge the patient or health insurance provider for the cost of the drug. In this case, cost recovery would extend only to the cost of the drug and associated shipping costs. Commercialization of an investigational drug is prohibited.

IND Sponsor-Investigators who wish to recover the cost of an investigational drug must submit a request to do so in the IND application. Sponsors may request to charge under 21 CFR 312.8 by selecting “Charge Request” in box 12 of FDA Form 1571. The FDA will respond in writing with the authorization to charge. Note that under 21 CFR 312.8, the price charged may not be larger than necessary to recover direct costs; and that under 21 CFR 312.8, authorization to charge for an investigational drug may be withdrawn by FDA if conditions underlying the authorization are no longer satisfied.

Permission is requested, under 21 CFR 312.8, to charge for the investigational drug, XXXX, for the duration of the IND for all protocols under the IND and until the IND is withdrawn. Justification for this request is included below:

* 1. Clinical benefit and significant advantage:
  2. Assurance that data will support a significant change in label:
  3. Justification that the trial could not be conducted without charging for the product:
  4. Calculation of costs accompanied by a statement by an independent CPA:

# Relevant Information

If requested by FDA, any other relevant information needed for review of the application.

## Information previously submitted

The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

No information previously submitted is referenced.

## Material in a foreign language

The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

No foreign language material is included in this application.

## Numbering of IND submissions

Each submission relating to an IND is required to be numbered serially using a single, four-digit serial number. The initial IND is required to be numbered 0000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

IND submissions will be numbered serially using a single, four-digit serial number. This initial IND application is 0000 and each subsequent submission will be incrementally numbered chronologically in sequence.

## Identification of exception from informed consent

If the investigation involves an exception from informed consent under 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in 50.24 of this chapter.

Either delete section 8.5, indicate that no exception from informed consent is requested, or if exception from informed consent is integral to the study, provide more information concerning the regulatory process to obtain approval.