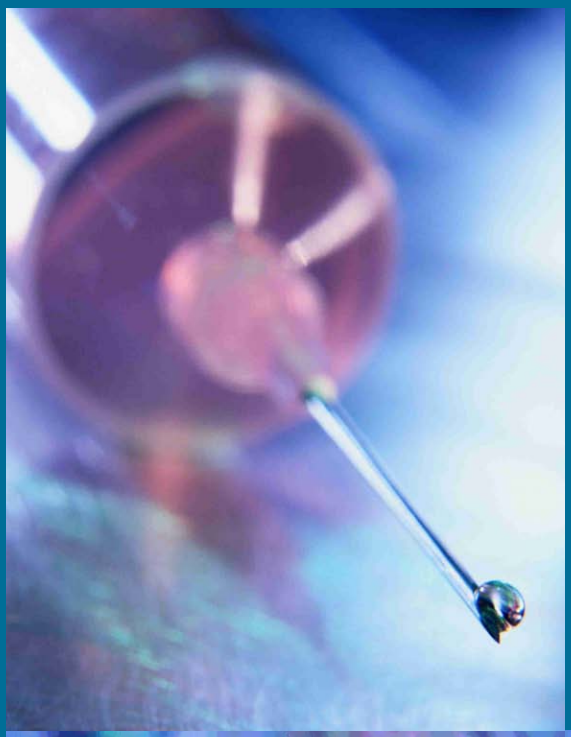

The Sponsor's Guide to Regulatory Submissions for an Investigational New Drug

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Chapter 1

I. Introduction

An Investigational New Drug Application (IND), also known as a "Notice of Claimed Investigational Exemption for a New Drug," is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biologic product to humans. This authorization must be obtained prior to interstate shipment and administration of any new drug or biological product that is not otherwise the subject of an approved New Drug Application (NDA) or Biologics License Application (BLA). Because federal law requires an FDA-approved marketing application prior to the introduction or delivery of a drug into interstate commerce, the IND is a means by which the sponsor can request an exemption from this law to ship investigational products across state lines. This request for exemption is obtained from the FDA through a defined regulatory process. This *Sponsor's Guide to Regulatory Submissions for an Investigational New Drug* is provided to assist with the pre-IND and initial IND submission process. The focus of this guide is the submission process for an investigator-held IND.

In addition to the information contained in this guide, the IND sponsor and clinical investigators must possess a thorough understanding of the regulations pertaining to the use of investigational agents in humans (Title 21 of the *Code of Federal Regulations* [CFR]). The IND regulations are located in 21 CFR 312; the informed consent regulations can be found in 21 CFR 50, Protection of Human Subjects; and regulations regarding Institutional Review Boards are found in 21 CFR 56.

Refer to the following FDA Web sites for additional information regarding the IND: http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm and http://www.fda.gov/cber/ind/ind.htm.

Table 1 contains a list of abbreviations used in this guide.

A glossary is provided in Appendix 1 to define key terms. A short list of government agencies and programs related to drug discovery and development is provided in Appendix 2. A CD-ROM containing an electronic version of this

document is included at the back of this document to provide access to the hyperlinked information.

Table 1: Abbreviations

Abbreviation	Definition
AE	Adverse Experience/Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
BDP	Biopharmaceutical Development Program
BLA	Biologics License Application
BRB	Biological Resources Branch
BRM	Biological Response Modifier
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Control
CGCP	Current Good Clinical Practices
CGLP	Current Good Laboratory Practices
CGMP	Current Good Manufacturing Practices
CRO	Contract Research Organization
CTEP	Cancer Therapy Evaluation Program
DMF	Drug Master File
DTP	Developmental Therapeutics Program
eIND	Electronic Investigational New Drug Application
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IIP	Inter-Institute Program for the Development of AIDS-related Therapeutics
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenously
kD	Kilodalton(s)
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
ORM	Office of Review Management
PDUFA	Prescription Drug User Fee Act
Pre-IND	Pre-Investigational New Drug Application
RAID	Rapid Access to Intervention Development

Table 1: Abbreviations (continued)

Abbreviation	Definition
R*A*N*D	Rapid Access to NCI Discovery Resources
RAPID	Rapid Access to Preventive Intervention Development
RPM	Regulatory Project Manager
SAIC	Science Applications International Corporation
SOP	Standard Operating Procedure
SOPP	Standard Operating Procedures and Policies
The Act	The Federal Food, Drug, and Cosmetics Act
US	United States
USC	United States Code

II. Background

The pharmaceutical development process should be designed and implemented with the goal of a successful license submission in mind. A successful development process collects data regarding the effects of a promising new drug in animals and humans to demonstrate that the new drug is safe and effective when used under specific conditions, and produces a drug product that has been manufactured appropriately. The planning for the most efficient development process should begin by focusing on the goal—plan backward, and execute forward.

Another characteristic of a successful pharmaceutical development process is the need for an integrated team approach. Expertise from project management, manufacturing, nonclinical, clinical, and regulatory disciplines each plays a key role. Assembling the team early in the development process allows for an integrated approach.

The general phases of drug development include discovery, nonclinical development, clinical development, filing for licensure, approval/licensure, and post-approval. The discovery process includes the basic research where drug selection, and preliminary process and analytical methods development occur. The idea of planning backward and executing forward begins at the discovery phase with selection of a drug candidate that has been sufficiently studied to support proceeding further in development.

The nonclinical development phase includes laboratory and animal studies. During the nonclinical development process, the animal model and analytical methods are developed, product is produced, and toxicology and pharmacology

studies are conducted in the appropriate model animals. The test article (drug product) used in nonclinical testing should be characterized according to the guidelines contained in 21 CFR 58 Subpart F. For those toxicology and pharmacology studies that will be used to support the Investigational New Drug Application (IND), the product should be manufactured following the same process as the planned clinical product. Because humans cannot be exposed to risks that have not been evaluated in nonclinical studies, at least a draft of the clinical protocol should be available before the nonclinical plan is prepared. This allows an understanding of the desired clinical conditions so that the nonclinical plan for testing in animals is developed to support these conditions for human testing. Further, the nonclinical development plan must be designed to provide sufficient safety data to support the IND that is submitted to the Food and Drug Administration (FDA) prior to conducting human clinical studies. Early communication with the FDA is a regulatory strategy that can help develop an adequate nonclinical development plan and is discussed further in chapter 2 of this guide.

Nonclinical development is followed by submission of the IND to the FDA. The FDA has 30 days in which to review the IND. The FDA may either allow the investigational new drug to proceed into the clinic or place the drug on clinical hold if safety concerns need to be resolved. The IND is discussed further in chapter 3 of this guide.

The drug is tested for safety and efficacy in humans during the four phases of clinical development. A sound clinical program depends on a planned logical sequence of events that will assure the accuracy and validity of the clinical data while protecting the rights and safety of clinical research subjects. The drug product used in clinical testing should be manufactured according to the Current Good Manufacturing Practices (CGMP) guidelines found in 21 CFR 211.

- A Phase 1 clinical study introduces the investigational drug into humans. In general, Phase 1 studies are conducted to investigate safety/tolerability (maximum tolerated dose in humans) and pharmacokinetics, and occur after animal tissue and whole animal studies have determined that the drug appears safe and effective for its intended use. In terms of new anticancer agents, Phase 1 trials determine a safe dose for Phase 2 trials, define acute effects on normal tissues, and provide evidence of anticancer activity. Anticancer drugs have demonstrated evidence of significant activity in animal models during nonclinical testing, and as such, have therapeutic intent in Phase 1 clinical trials (Christian and Shoemaker 2002).
- Phase 2 clinical studies in general continue safety monitoring and pharmacokinetics assessment. Phase 2 studies of anticancer drugs are used

to confirm that the drug has anticancer activity and to estimate the response rate in a defined patient population (Christian and Shoemaker 2002).

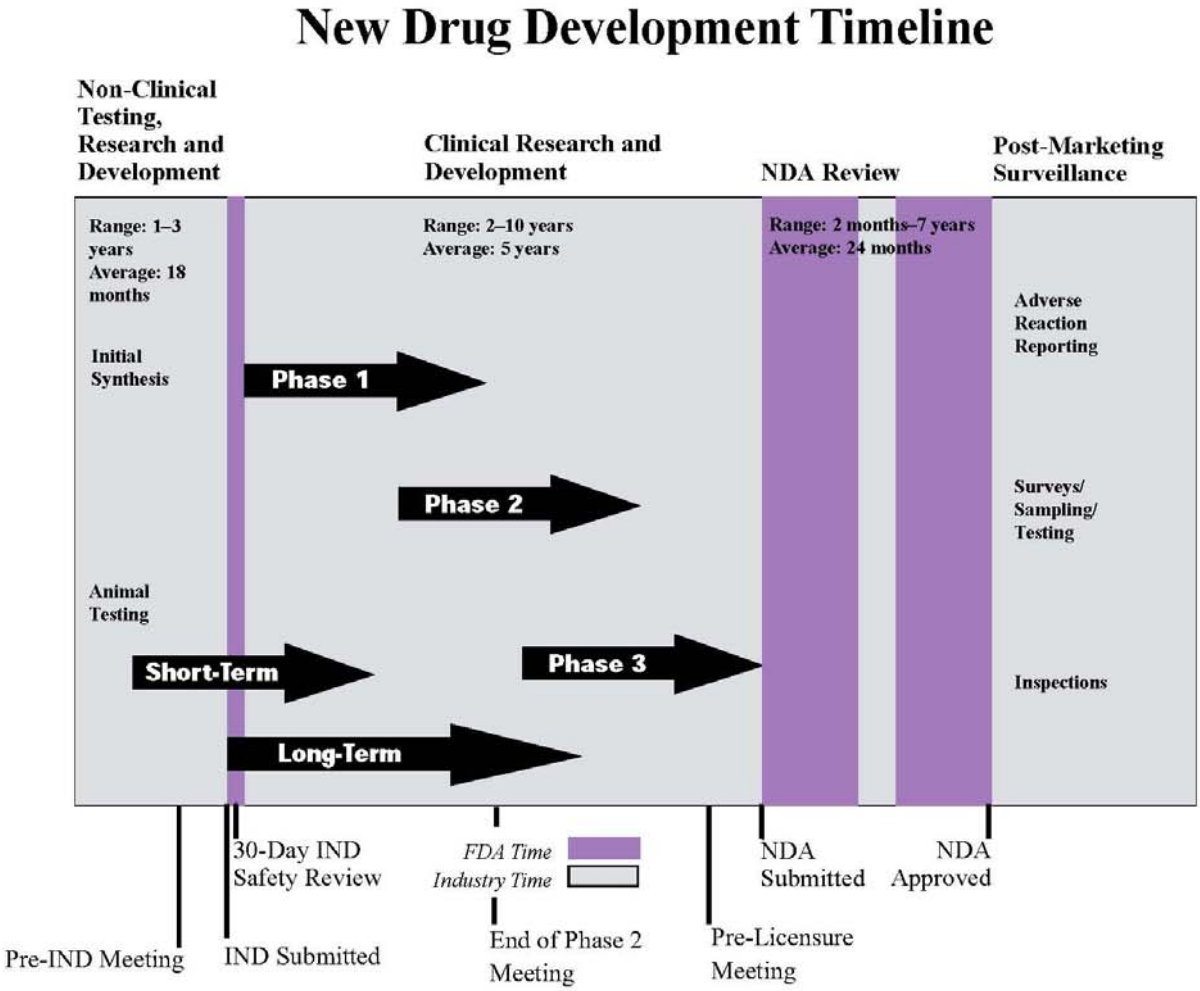
- Phase 3 clinical studies are the pivotal studies used to form the clinical basis for licensure and are designed to evaluate efficacy, safety, and pharmacokinetics. If significant anticancer activity is observed during Phase 2 studies, Phase 3 trials are used to compare the efficacy of the new drug with that of a standard or control to determine if the new drug provides increased patient benefit (Christian and Shoemaker 2002).

At the completion of Phase 3, an application for licensure is submitted to the FDA, using either a Biologics License Application (BLA) or a New Drug Application (NDA). The FDA must be able to determine if the product is: (1) safe and effective as indicated and if the benefits outweigh the risks; (2) labeled correctly; (3) characterized adequately to validate the drug's identity, strength, quality, potency and purity properties; and (4) manufactured according to CGMPs. Phase 4 studies occur after licensure and are designed to track and provide data concerning long-term or less common side effects.

Figure 1 shows a time line and major milestones for the pharmaceutical development process.

In summary, planning ahead and using an integrated team approach to pharmaceutical development are key concepts that can increase the probability of success. Careful consideration of the final goal at each step in the development process can eliminate costly and time-consuming errors. For example, the amount of drug that is manufactured for nonclinical and clinical studies is calculated on the respective clinical and nonclinical protocols. Changes to the clinical plan and/or nonclinical plan after completion of the manufacturing step could be devastating if more drug is needed for the new plan.

Figure 1: New Drug Development Time Line



Reference: http://www.fda.gov/fdac/graphics/newdrugspecial/drugchart.pdf.

III. Chapter References

Reference materials are presented in the order in which they first appear in the text.

1. 21 CFR 312.

2. 21 CFR 50.

3. 21 CFR 56.

4. Investigational New Drug (IND) Application Process. FDA Web site address: http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm.

5. Information on Submitting an Investigational New Drug Application for a Biological Product. FDA Web site address: http://www.fda.gov/cber/ind/ind.htm.

6. 21 CFR 58 Subpart F.

7. 21 CFR 211.

8. Christian M, Shoemaker D. 2002. *The Investigator's Handbook: A Manual for Participants in Clinical Trials of Investigational Agents Sponsored by DCTD, NCI*. Available from: National Cancer Institute, Cancer Therapy Evaluation Program, via the Internet at (http://ctep.cancer.gov/handbook/index.html).

9. New Drug Development Time Line. FDA Web site address: http://www.fda.gov/fdac/graphics/newdrugspecial/drugchart.pdf.

IV. Additional Product Development References

1. *Biologics Development: A Regulatory Overview, Revised Second Edition*. Mark Mathieu, Editor. Parexel, Waltham, MA. 1997.

2. *Expediting Drug and Biologics Development: A Strategic Approach, Second Edition*. Steven E. Linberg, Editor. Parexel, Waltham, MA. 1999.

3. *Good Laboratory Practice Regulations, Third Edition*. Sandy Weinberg, Editor. Marcel Dekker, New York, NY. 2002.

4. *New Drug Development: A Regulatory Overview, Revised Fifth Edition*. Mark Mathieu, Editor. Parexel, Waltham, MA. 2000.

5. *Understanding Biopharmaceuticals—Manufacturing and Regulatory Issues*. Grindley and Ogden, Editors. Interpharm Press, Denver, CO. 2000.

Chapter 2

I. The Pre-Investigational New Drug Application (Pre-IND) Process

A. Overview

Pre-IND meetings are conducted with the appropriate FDA review division (Refer to Chapter 3: Investigational New Drug Application [IND]; Section B. FDA Regulatory Jurisdiction of Products to determine the appropriate review division). The sponsor of the drug typically requests these meetings. Meetings at such an early stage in the drug development process are useful opportunities for open discussion about testing and data requirements, and any scientific issues that may need to be resolved prior to IND submission. Pre-IND meetings are not required by the FDA, but are highly recommended in order to expedite the drug development process. The timing of the pre-IND meeting is dependent on the issues for discussion and is often held from six months to one year prior to the planned IND submission.

Three types of meetings can occur between a drug sponsor and the FDA: Type A, Type B, and Type C. A Type A meeting is one that is immediately necessary for an otherwise stalled drug development program to proceed (for example: clinical hold discussions). Type B meetings include pre-IND meetings, certain end-of-Phase 1 meetings, end-of-Phase 2/pre-Phase 3 meetings, and pre-NDA/BLA meetings. A Type C meeting is any other type of meeting with the FDA that does not fall in the Type A or B categories (for example, discussion of a request for reduced testing of a CGMP drug product).

The sponsor may request a meeting with the FDA prior to submitting the IND (a pre-IND meeting). The purpose of the meeting varies with each product and could include discussion of nonclinical safety study issues; Chemistry, Manufacturing, and Control (CMC) issues; clinical trial design issues related to the investigational drug; or identification of potential clinical hold issues. The meeting may also provide an opportunity for discussing the best approach for presentation and formatting of data in the IND. [21CFR 312.82(a)]. For additional information regarding formal meetings between drug sponsors and the FDA, refer to *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000)*.

The pre-IND process consists of two main submissions to the FDA: (1) the pre-IND meeting request letter and (2) the pre-IND meeting information package. Both of these items are discussed in more detail in the following sections.

B. Pre-IND Meeting Request Letter

The sponsor prepares the pre-IND meeting request letter and sends it to the FDA to obtain a date and time for the pre-IND meeting. The letter contains a brief overview of the purpose of the meeting.

1. Contents of a Pre-IND Meeting Request Letter

The meeting request letter should include adequate information for the FDA to determine if the meeting is necessary and to identify appropriate FDA meeting participants.

The following items should be included in a meeting request. A sample pre-IND meeting request letter can be found in appendix 3.

- Product name and IND application number (if applicable).
- Chemical name (description of molecular entity) and structure.
- Proposed indication(s).
- The type of meeting being requested (Type B).
- A brief statement of the purpose of the meeting. This statement can include a discussion of the types of completed or planned studies or data that the sponsor or applicant intends to discuss at the meeting; the general nature of the critical questions and proposals to be asked at the meeting; and how the meeting fits into the overall development plans.
- A list of the specific objectives expected from the meeting.
- A preliminary proposed agenda, including estimated amounts of time needed for each agenda item and designated speaker(s). It is recommended that very little time be spent introducing the proposed indication/clinical trial and supporting data so that the FDA can spend time responding to the critical questions.
- A draft list of specific questions, grouped by Chemistry, Manufacturing, and Controls (CMC); Nonclinical; and Clinical.
- A list of the individuals (including titles and affiliations) who will attend the proposed meeting from the sponsor's or applicant's organization and consultants.
- A list of FDA personnel or disciplines requested to be present at the meeting.

- The estimated date on which the Pre-IND Meeting Information Package will be sent to the FDA. Generally, it is stated that this information package will be provided four weeks prior to the scheduled meeting date.
- A list of suggested dates and meeting times. The FDA generally schedules Type B meetings to occur within 60–90 days from its receipt of the written request for a meeting. Therefore, suggested dates should be about 60–90 days from when the meeting request letter is sent to the FDA. An information package MUST be sent to the FDA four weeks prior to your meeting date; therefore, when determining suggested meeting dates, it is essential that you take into account when the package will be ready.

2. Submission of a Pre-IND Meeting Request Letter

The drug sponsor who would like to meet with the FDA should submit a written request (letter or facsimile) to the appropriate FDA office as follows:

- Send requests for meetings with the Center for Biologics Evaluation and Research (CBER) to the appropriate applications Division Director in the office with review responsibility for the product. The CBER organizational chart can be found at http://www.fda.gov/cber/inside/orgchart.pdf.
- Send requests for meetings with the Center for Drug Evaluation and Research (CDER) to the appropriate Division Director within the Office of Review Management (ORM). The CDER organizational charts can be found at www.fda.gov/cder/cderorg.htm.
- Direct questions about the assignment of specific products to CBER or CDER to the center jurisdiction officers at:

  CBER Ombudsman 301-827-0379
  http://www.fda.gov/cber/inside/ombudsman.htm

  CDER Ombudsman 301-594-5480
  http://www.fda.gov/cder/ombud/default.htm

Prior to faxing a written request for a meeting, the drug sponsor should contact the appropriate review division to determine to whom the fax should be directed and to arrange for confirmation of receipt of the fax. All faxed meeting requests should subsequently be submitted in hard copy to the review division as described above.

CDER offers a Pre-IND Consultation Program to foster early communications between sponsors and new drug review divisions in order to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class and can each be contacted using the designated Pre-IND Consultation List.

C. Confirmation Letter from the FDA

The FDA will generally respond to a request for a pre-IND meeting within 14 days of receipt of the meeting request letter. The sponsor will receive the response in the form of a letter from the FDA announcing the pre-IND meeting, date, time, meeting leader and other FDA attendees; contact information; whether the meeting will occur in person or as a teleconference; meeting dial-in information if the meeting is to occur as a teleconference; date by which the pre-IND information package should be received at the FDA; and the number of copies of the pre-IND information package required. It is important to note that the date selected by the FDA may or may not be one of the dates and/or times suggested in the sponsor's meeting request letter. In some cases, where a teleconference is selected as the meeting style, dial-in information is not provided (especially if many parties need to dial in) in the FDA meeting confirmation letter. In such case, it is the sponsor's responsibility to arrange for a dial-in number for the scheduled teleconference and notify the FDA (at the contact information listed on the confirmation letter) and all other attendees.

An example FDA meeting confirmation letter is shown in appendix 4.

D. Pre-IND Information Package

1. Description

A Pre-IND Information Package is information provided by a sponsor to the FDA as background information for a pre-IND meeting. The information package should contain all information that the FDA would need to respond to the questions proposed for the meeting. The Pre-IND Information Package must be received at the FDA at least four weeks prior to the scheduled meeting date. 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 frame. If this happens, another meeting request letter must be sent to the FDA to obtain a new meeting date.

2. Contents

Although the contents of the information package will vary, depending on the product, indication, phase of drug development, and issues to be discussed, information packages generally include the items in the following list. Refer to appendix 5 for an example of a table of contents for a Meeting Information Package.

(1) Cover letter. Clearly identify the date, time, and subject of the pre-IND meeting.
(2) Form 1571 (A blank form 1571 is included in appendix 6, and can also be found on the FDA Web site http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1571.pdf.)
(3) Product name and application number.
(4) Chemical name and structure.
(5) Proposed indication(s).
(6) Dosage form, route of administration and dosing regimen (frequency and duration).
(7) A brief statement of the purpose of the meeting. This statement could include a discussion of the types of completed or planned studies or data that the sponsor or applicant intends to discuss at the meeting, the general nature of the critical questions to be asked, and where the meeting fits in overall development plans.
(8) A list of specific objectives/outcomes expected from the meeting.
(9) A proposed agenda, including estimated amounts of time needed for each agenda item and designated speaker(s).
(10) A list of specific questions grouped by discipline.
(11) Clinical protocol and/or data summary (as appropriate).
(12) Nonclinical protocol and/or data summary (as appropriate).
(13) Chemistry, Manufacturing, and Controls information (as appropriate).

The information contained in the Pre-IND Meeting Information Package should contain the most current and accurate information available to the sponsor. If specific guidance regarding the contents of the information package is desired, contact the FDA regulatory project manager (RPM) assigned to the submission. Normally, the RPM is identified in the Pre-IND meeting confirmation letter as the meeting leader. However, if the product is in the early stages of development and no project manager has been assigned, contact the appropriate CBER or CDER office to which the pre-IND meeting request letter was sent.

Sponsors should coordinate the agenda and the content of the information package to expedite review of the material and discussion at the meeting. The FDA will lead the pre-IND meeting and typically does not wish to hear a presentation of the information package. The FDA has already reviewed the information in the package and prefers to address the questions raised by the applicant as listed in the information package. To facilitate the FDA's review, the sponsor should organize the contents of the information package according to the proposed agenda. A fully paginated document with a table of contents, appropriate indices, appendices, cross-references, and tabs differentiating sections is recommended. Paper copies of the information package should be provided for each FDA participant listed in the meeting confirmation letter, with an extra five copies for consultation purposes. The FDA project manager or division contact can advise on the number of copies needed (this information is usually included in the meeting confirmation letter) and whether an electronic copy is appropriate.

E. The Pre-IND Meeting

The pre-IND meeting, usually designated to last for one hour, is a formal meeting between the FDA and the sponsor. Pre-IND meetings are generally held by teleconference unless there are special circumstances. The FDA may send responses to the sponsor's questions and any additional comments in advance of the scheduled pre-IND meeting. If this occurs and if there are no additional concerns, the sponsor has the option of canceling the meeting. This frequently occurs with drugs, but is rare for biologics.

The sponsor should be prepared to discuss any information contained in the Pre-IND Information Package with the FDA at the pre-IND meeting. Representatives who could provide additional information and discussion (for example, manufacturing, nonclinical, and clinical representatives) should be invited to attend the meeting.

The pre-IND meeting is led by the FDA Regulatory Project Manager and generally begins with everyone introducing himself or herself; it then addresses each of the sponsor's questions submitted as part of the pre-IND meeting information package. Do not plan a presentation or overview of the information for the pre-IND meeting. Assume the FDA has read the pre-IND meeting information package and is familiar with the issues.

At the conclusion of the pre-IND meeting, an opportunity is given to allow the sponsor to ask any additional questions, and arrangements are made to provide official FDA meeting minutes within 30 days of the meeting. Even though official

meeting minutes are provided from the FDA, it is a good idea to generate internal meeting minutes in order to begin addressing issues discussed as soon as possible.

II. Chapter References

Reference materials are presented in the order in which they first appear in the text.

1. 21CFR 312.82(a).

2. *FDA Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000)*. FDA Web site address: http://www.fda.gov/cber/gdlns/mtpdufa.pdf.

3. FDA Center for Biologics Evaluation and Research Organizational Chart. FDA Web site address: http://www.fda.gov/cber/inside/orgchart.pdf.

4. FDA Center for Drug Evaluation and Research Organizational Chart. FDA Web site address: www.fda.gov/cder/cderorg.htm.

5. FDA Center for Drug Evaluation and Research Ombudsman. FDA Web site address: http://www.fda.gov/cder/ombud/default.htm.

6. FDA Center for Biologics Evaluation and Research Ombudsman. FDA Web site address: http://www.fda.gov/cber/inside/ombudsman.htm.

7. CDER Pre-IND Consultation Program Pre-IND Consultation List. FDA Web site address: http://www.fda.gov/cder/regulatory/applications/Pre-INDConsultationList.pdf.

8. Form FDA 1571. FDA Web site address: http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1571.pdf.

III. Guidance Documents Applicable to the Pre-IND Process

The following FDA guidance documents can be used for reference in the pre-IND process.

1. *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000)*

2. *Guidance for Industry: IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information*

3. *Guidance for Industry on 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)*.

4. *FDA Guidance for Industry on CMC Content and Format of Investigational New Drug Applications (INDs) for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-derived Products (Draft, February 1999)*.

5. *FDA Guidance for Industry on Fast Track Drug Development Programs: Designation, Development and Application Review (November 1998)*

Chapter 3

I. Investigational New Drug Application (IND)

A. Overview

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 guide outlines the content of an IND according to the US *Code of Federal Regulations* (CFR), 21 CFR 312.23. Related guidance documents are listed at the end of this chapter.

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. Combination products should be discussed with the FDA early in the product development process to determine the proper submission to make.

B. FDA Regulatory Jurisdiction of Products

The regulatory responsibility, review and continuing oversight for drugs and biological products are divided between the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). On June 30, 2003, the FDA transferred to CDER some of the therapeutic biological products that had been reviewed and regulated by CBER. CDER now has regulatory responsibility, including premarket review and continuing oversight, over the transferred products. For additional information, the following FDA Web site is provided: http://www.fda.gov/cber/transfer/transfer.htm.)

The lists below identify general categories of products regulated by CBER and CDER.

CDER regulates:

- Drugs.
- Monoclonal antibodies for in-vivo use.
- Proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics), and other novel proteins,

except for those that are specifically assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products.

- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response).
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells *in vivo* (for the purpose of being harvested for use in the production of a therapeutic cellular or blood product), may be regulated in combination with the therapeutic cellular or blood product, as appropriate. Sponsors of products that fit this description should contact the center jurisdiction officers for guidance on appropriate center assignment.

CBER regulates:

- Cellular products, including products composed of human, bacterial or animal cells (such as pancreatic islet cells for transplantation), or from physical parts of those cells (such as whole cells, cell fragments, or other components intended for use as preventative or therapeutic vaccines).
- Vaccines (products intended to induce or increase an antigen-specific immune response for prophylactic or therapeutic immunization, regardless of the composition or method of manufacture).
- Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests.
- Antitoxins, antivenins, and venoms.
- Blood, blood components, plasma-derived products (for example, albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives (for example, clotting factors), blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations, including radiolabeled or conjugated forms, and certain fibrinolytics such as plasma-derived plasmin and red cell reagents.
- Gene therapy products.

Questions about the assignment of specific products to CBER or CDER, or combination products that may include devices should be directed to the center jurisdiction officers at:

CBER Ombudsman 301-827-0379

CDER Ombudsman 301-594-5480

CDRH Ombudsman 301-827-7991

C. Contents of an IND

The contents of an IND (per 21 CFR 312.23) include the following sections and are discussed in more detail below. An IND template is provided in appendix 7 and contains additional instructions for use in preparing each section of the IND.

Cover Letter
Item 1: Cover Sheet (Form FDA 1571)
Item 2: Table of Contents
Item 3: Introductory Statement and General Investigational Plan
Item 4: Reserved
Item 5: Investigator's Brochure
Item 6: Protocol
Item 7: Chemistry, Manufacturing, and Control Data
Item 8: Pharmacology and Toxicology Data
Item 9: Previous Human Experience
Item 10: Additional Information
Item 11: Relevant Information

In the preparation of an initial IND submission, information that has been previously submitted to the FDA under other INDs or drug master files (DMFs) may be incorporated by reference. For example, manufacturing information may have been previously submitted to the FDA in a DMF format (refer to chapter 4). Using a cross-reference letter that is prepared by the DMF sponsor, submitted to the FDA, and copied to the IND sponsor, this information can be incorporated into an IND. A copy of the cross-reference letter would then be included in the IND in place of the information required. More information regarding DMFs and cross-reference letters can be found in chapter 4.

1. Cover letter

Although not specifically required by the *Code of Federal Regulations*, a cover letter should be included with an IND submission. A templated example of a cover letter is included in appendix 8. This letter should be printed on official letterhead from the IND sponsor. The template includes instructions for the cover letter contents; however, any additional information the sponsor believes is pertinent can be added.

2. Item 1: Cover Sheet (Form FDA 1571) [21 CFR 312.23(a)(1)]

A cover sheet (Form FDA 1571) [21 CFR 312.23(a)(1)] is required. A blank Form FDA 1571 is included as appendix 6. A current Form FDA 1571 and instructions for its completion can be obtained using the following Web site: http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.

A Form FDA 1571 cover sheet for the IND contains the following information:

- The name, address, and telephone number of the sponsor; date of IND submission; the name of the investigational new drug; the IND number if previously assigned; and the indications covered by the IND submission.
- The phase of clinical investigation to be conducted.
- A commitment not to begin the clinical trial until the IND is in effect.
- A commitment that the Institutional Review Board (IRB) will be responsible for the review and approval of the clinical trial in accordance with requirements of 21 CFR 56.
- A commitment to conduct the clinical trial in compliance with all regulatory requirements.
- The name and title of the person responsible for monitoring the clinical trial.
- The name and title of the person responsible for monitoring the safety of the drug being administered in the clinical trial.
- The name and address of the contract research organization (CRO) and the CRO's responsibilities, if applicable.
- The signature of the sponsor or the sponsor's representative. In signing the form, the sponsor agrees to the conditions stipulated on the form.

3. Item 2: Table of Contents [21 CFR 312.23(a)(2)]

This section contains a complete table of contents for the IND. Each major section (item number) should also have a table of contents. The tables of contents should be complete and reflect the correct content and page number of each subsection.

4. Item 3: Introductory Statement and General Investigational Plan [21 CFR 312.23(a)(3)]

This section contains a brief introductory statement (less than ten pages). The brief introductory statement should contain the following basic 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.

The introductory statement also includes a summary of:

- Previous human experience with the drug referencing other pertinent INDs and investigational or marketing experience in other countries;
- Any instances where the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or efficacy including identification of the countries where the drug was withdrawn and the reason for the withdrawal; and
- The investigational plan for the coming year containing the following information:
    - The study rationale,
    - The indication(s) to be 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.

A general investigational plan is also included in this section of the IND. General information regarding the 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.

5. Item 4: [Reserved]

This section is reserved by the FDA for future use. Only provide a cover page for this section; no additional information is required.

6. Item 5: Investigator's Brochure [21 CFR 312.23(a)(5)]

An investigator's brochure (IB) 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 IB 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 IB varies with the stage of the development of the drug. Sponsor-investigators are not required to submit an IB to the IND.

An IB generally contains the following information:

- Drug substance and formulation description, including the structural formula, if known;
- Pharmacological and toxicological effects in animals and if known, in humans;
- Pharmacokinetics and biological disposition of the drug in animals, and if known, in humans;
- Safety and efficacy information in humans summarized from prior clinical studies; and
- Anticipated risks and side effects, precautions or special monitoring to be done.

An outline of an IB is provided in appendix 7 as item 5 of the IND template shown. The *International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6* provides additional general guidance on the preparation and content of the investigator's brochure.

7. Item 6: Protocol [21 CFR 312.23(a)(6)]

The clinical protocol is required to contain specific pieces of information:

- The objective and purpose of the study;
- The name, address, and qualifications of each investigator, subinvestigator, research facility, and Institutional Review Board;
- The number of subjects to be enrolled;
- Inclusion and exclusion criteria for acceptability of study subjects;
- A description of the control group;

- A description of the study design and blinding;
- The method for determining the dose each patient will receive, the planned maximum dose, and the duration of treatment;
- A description of observations and measurements that will be made;
- A description of the plan for monitoring the clinical study; and
- A description of the clinical procedures and laboratory tests to be conducted in association with the study.

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), *International Conference on Harmonisation (ICH) Guidelines* E6 and E8, and The Department of Health and Human Services 45 CFR 46.

This section of the IND (Item 6) should also include the following information:

- A copy of the clinical protocol for the study;
- Each investigator's curriculum vitae;
- The Institutional Review Board (IRB) 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;
- Using Form FDA 1572, information specific to each investigator as part of the investigational site documentation. A blank Form FDA 1572 is included in appendix 9. A current Form FDA 1572 and instructions for its completion can be obtained using the following Web site: http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.
  In signing the Form FDA 1572, the investigator is making certain commitments that are outlined in item 9 of the form. These commitments include agreement to:
  - Conduct the study(ies) according to the relevant, current protocol;
  - Change a protocol only after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of study subjects;
  - Conduct or supervise the investigation personally;
  - Inform study subjects that the drugs are being used for investigational purposes;
  - Ensure the Institutional Review Board approval according to 21 CFR 56 is obtained;
  - Ensure the informed consent process is conducted according to 21 CFR 50;
  - Report adverse experiences that occur during the investigation according to 21 CFR 312.64;
  - Have read and understood the investigator's brochure;

- Assure that all associates, colleagues, and employees assisting in the study are informed about their obligations to meet these commitments;
- Maintain adequate and accurate records according to 21 CFR 312.62 and make the records available for inspection according to 21 CFR 312.68;
- Ensure that a 21 CFR Part 56-compliant Institutional Review Board will be responsible for the initial and continuing review and approval of the investigation;
- Promptly report changes in the research activity and all unanticipated problems involving risks to human subjects or others to the IRB;
- Obtain IRB approval before making any changes to the research except where necessary to eliminate apparent immediate hazards to human subjects; and
- Comply with pertinent 21 CFR 312 requirements.

7.1 The Role of the Institutional Review Board (IRB)

The *Code of Federal Regulations* defines an Institutional Review Board (IRB) as "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" [21 CFR 56.102(h)].

Additional information concerning the IRB and the associated approval process can be found in the following FDA document: *Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update*, and in the *Code of Federal Regulations* 21 CFR 50, 21 CFR 56, and 45 CFR 46.

In order to proceed through the process of administering an investigational new drug in humans, a principal investigator must first gain approval from the IRB. Because IRB procedures/meetings vary among institutions, the investigator should consult his/her institution for specific procedures with respect to IRB submissions. This approval is based on the IRB's review of the clinical protocol that will be used to conduct the study. The criteria by which the IRB evaluates the clinical protocol can be found in the *Code of Federal Regulations* [21 CFR 56.111].

Following its review of the clinical protocol, the IRB can either approve the study, request revisions to the study design, or disapprove the study entirely. The IRB will send a letter to the investigator with its decision, and must identify the study specifically using the IND number, protocol number and any other specific identification. Since IRBs generally meet once a month, any requirements for

revisions to gain approval can result in at least a 30-day delay. This is important because the study cannot begin without IRB approval, even if the FDA has allowed the IND to proceed.

8. Item 7: Chemistry, Manufacturing, and Control Data [21 CFR 312.23(a)(7)]

This section describes the chemistry, manufacture, and control of the drug substance and the drug product to assure the identification, quality, purity, and strength of the investigational drug. The information contained in the Chemistry, Manufacturing, and Control (CMC) section should address both the bulk drug substance and the final drug product. Information pertinent to each includes the name and address of the manufacturer, the methods of manufacture, container and closure system description(s), the acceptance specifications and analytical method descriptions, lot release data, and stability data demonstrating the drug product will be stable throughout the course of the clinical trial.

The information requested in the FDA's March 6, 2000, Gene Therapy Letter should be provided as part of the IND or a drug master file, if applicable. Responses to items 1–5 of that letter can be cross-referenced to the manufacturer's drug master file, if available. Response to item 6 of that letter should be included in item 10 of the IND.

The amount of supporting CMC information varies with the investigational phase, the scope and duration, and the dosage form used for the clinical trial. 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 Well-Characterized, Therapeutic, Biotechnology-derived Products, November 1995*; Phase 2 and 3 studies of drugs in the guidance document entitled *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products—Chemistry, Manufacturing, and Controls Content and Format, February 1999*; and gene therapy products in the guidance document entitled *Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*.

9. Item 8: Pharmacology and Toxicology Data [21 CFR 312.23(a)(8)]

Item 8 includes a discussion of pharmacological and toxicological studies conducted *in vitro* or *in vivo* to demonstrate the safety and possibly the efficacy in

animals of the investigational agent. Most nonclinical safety studies must be conducted in compliance with Good Laboratory Practices as outlined in 21 CFR 58.

Pharmacokinetic effects and mechanism(s) of action studies of the drug in animals may be described in this section. Toxicological effects of the drug should be provided in a report that contains an integrated summary. The summary is written as 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, such as tissue reactivity; and
- A full tabulation of data suitable for detailed review (GLP Study Report).

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 to the IND. Additional pharmacology and toxicology guidance can be found in the guidance document entitled *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products, November 1995*.

10. Item 9: Previous Human Experience [21 CFR 312.23(a)(9)]

This section contains a summary of previous human experience with the proposed investigational drug, if any, including:

- Experience related to the safety of the proposed investigation resulting from previous investigations or marketing with the investigational drug. If the investigational drug is a combination of drugs, then each active drug component is addressed in these terms.
- Information from previous controlled clinical trials relevant to the drug's efficacy for the proposed investigational use. If the investigational drug is a combination of drugs, then each active drug component is addressed in these terms.
- Marketing outside of the US, including a list of the countries where the drug has been marketed. 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.

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

11. Item 10: Additional Information [21 CFR 312.23(a)(10)]

Information on special topics is included in this section, such as:

- Drug dependence and abuse potential;
- Radioactive drugs;
- Pediatric studies;
- Other information to aid in the evaluation of the safety, design, and ability of the proposed study to support marketing of the investigational drug; and
- Pertinent references.

12. Item 11: Relevant information [21 CFR 312.23(a)(11)]

Any other relevant information required for review of the application if requested by the FDA.

D. Submitting and Processing an IND

After the IND is completed and assembled, the final formatting and processing begins as follows.

- Page numbering: The pages are numbered in sequential order. The page number should be accurately reflected in the table of contents (IND item 2). There should also be a table of contents for each item section within the IND with correct page numbering listed.
- Section dividers: Include tabs prior to the first page of each item number in the IND and the table of contents. The tab should be labeled with the section or table of contents title for ease of navigation through the IND.
- Material in a foreign language: An accurate complete English translation is submitted with each part of the IND that is not written in English.
- Number of copies: An original and two copies of all submissions to the IND file, including the original IND and all amendments and reports, are submitted to the FDA.
- Numbering of IND submissions: Beginning with the initial IND, serial numbering with a three digit serial number is required for each submission relating to an IND. The initial IND is numbered 000, and each subsequent submission (amendments, reports, correspondence, etc.) is chronologically numbered.

- Electronic submissions: If an electronic submission is made, no hard copies are needed. Refer to the following Web site for additional information regarding electronic submissions http://www.fda.gov/cber/gdlns/eind.htm. An electronic IND demonstration is available at http://www.fda.gov/cber/ind/ind.htm.
- Address for IND submission: The current address for submission of an IND should be confirmed by consulting the FDA Web site. At the time of publication of this guide, the addresses were as follows:

For a Drug:

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/cber/transfer/transfer.htm)
CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

For a Biologic Regulated by CBER:

Food and Drug Administration
Center for Biologics Evaluation and Research,
HFM-99, Room 200N
1401 Rockville Pike
Rockville, MD 20852-1448

Upon receipt of the IND at the FDA, an IND number is assigned and a regulatory project manager (RPM) receives the IND submission. The RPM will issue a letter to the sponsor within approximately two weeks after receipt of the IND. This letter will indicate the date the FDA received the IND (receipt date), the IND number, and the name and contact information of the RPM. It is important to remember that the 30-day clock is based on the FDA receipt date, not the date

the sponsor sent the IND to the FDA. If the sponsor does not receive a letter of FDA receipt within two weeks after submission, the sponsor should contact the FDA and request a copy of the letter.

The RPM handles the administrative processing of the IND, serves as a regulatory contact, and delegates review team assignments. The review team includes the RPM, a product reviewer, a pharmacology/toxicology reviewer, a clinical reviewer, and a statistical reviewer. The FDA has a 30-day review clock based on the date of receipt of the IND at the FDA. If the RPM has not relayed any comments regarding the IND by the third week after submission, the sponsor should contact the RPM to determine if the FDA has any issues with the IND. The sponsor should contact the RPM again at the 30-day mark to ensure that the FDA agrees it is safe to proceed with the clinical trial.

During this 30-day review period at the FDA, the IND is divided and distributed to the FDA review team. The IND is reviewed with an emphasis on the safety of the pharmaceutical for the study subjects and comments are prepared. The FDA may communicate directly with the sponsor to receive clarification or resolution of issues. The FDA can send comments to the sponsor for resolution. Depending on the severity of the issues on which the FDA comments, the IND may be allowed to go into effect and proceed to the clinical trial at the end of the 30-day review period, or a clinical hold may be issued which does not allow the clinical study to proceed. A complete, easy-to-read, understandable IND with a detailed, accurate table of contents is necessary in order for the FDA to review the IND completely and could result in fewer questions to the sponsor during the 30-day review period.

E. Addressing a Clinical Hold Letter

Upon receipt of an FDA Clinical Hold Letter, a sponsor will prepare an amendment to the IND addressing the clinical hold issues. The appropriate FDA reviewer will evaluate the amendment to determine if the response is complete. When the clinical hold issues are addressed to the satisfaction of the FDA reviewer(s), the FDA responds to the sponsor in writing within 30 days of receipt of the amendment. If the clinical hold issues have not been addressed to the satisfaction of the FDA reviewers, then the product remains on clinical hold.

Additional clinical hold information can be found in:

- *The Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Hold*,

- *CBER SOPP 8201: Issuance of and Response to Clinical Hold Letters for IND Applications*,
- *Submitting and Reviewing Complete Responses to Clinical Holds*, and
- *21 CFR 312.42 Clinical Holds and Requests for Modification*.

F. Amendments to the IND

An IND is a dynamic document that is continually being amended with new information as the drug development proceeds. Many types of submissions are used to update an IND. These can include: protocol amendments, informational amendments, safety reports and annual reports. These updates, which the IND sponsor prepares, should be serially numbered (for example, if the IND was serial no. 000, then the first amendment would be serial no. 001), and should be submitted to the FDA in hard copy format in triplicate (the original and two copies). An appropriately completed Form FDA 1571, indicating the type of amendment, should accompany each submission. A blank Form FDA 1571 is included as appendix 6. A current Form FDA 1571 and instructions for its completion can be obtained using the following Web site: http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.
An amendment to an IND is submitted and processed in the same way as an IND.

1. Protocol Amendments 21 CFR 312.30

A protocol amendment is used by the sponsor after an IND has gone into effect to report a new clinical protocol, changes in an existing clinical protocol, or when a new investigator is added to the study. A protocol amendment submitted to the FDA must be clearly identified as such (for example: "Protocol Amendment: New Protocol," "Protocol Amendment: Change in Protocol," or "Protocol Amendment: New Investigator"). FDA review and IRB approval must be obtained prior to initiation of a new clinical protocol. (Mathieu 2000) FDA review and IRB approval may or may not be required immediately for a revision to an existing protocol if the protocol change is intended to eliminate an apparent immediate hazard to subjects 21 CFR 312.30(b)(2)(ii). In this case, the protocol change may be implemented immediately, provided the FDA is subsequently notified using a protocol amendment and the reviewing IRB is notified within 5 working days according to 21 CFR 56.104(c).

Reporting a new clinical protocol using a protocol amendment is applicable when a sponsor would like to conduct a new clinical study under an existing IND. A copy of the new clinical protocol must be submitted to the FDA prior to initiation

of the protocol; however, there is no 30-day waiting period for the submission of a new protocol to an existing IND.

Changes to an existing clinical protocol are submitted to the FDA in a protocol amendment if a change in a Phase 1 protocol significantly affects the safety of human subjects, or if a Phase 2 or Phase 3 protocol is changed in such a way that the safety of the human subjects, the scope of the investigation, or the scientific quality of the study is significantly affected. The protocol amendment must include a brief description of the change and refer to the active IND that contains the clinical protocol by date and number.

A protocol amendment is used to report a new investigator when the sponsor has added an investigator to conduct a clinical protocol already described in an active IND. The sponsor must notify the FDA using a protocol amendment within 30 days of the addition of a new investigator to an ongoing study. The protocol amendment must include the investigator's name and qualifications to conduct the study, reference to the submission containing the active clinical protocol, and additional information required for all investigators as per 21 CFR 312.23 (a)(6)(iii)(b).

2. Informational Amendments 21 CFR 312.31

An informational amendment is used to submit any pertinent additional information to the FDA not reportable using a protocol amendment, safety report, or an annual report, such as new technical information or responses to FDA comments. When an informational amendment is submitted, the submission must be clearly identified as such (for example: "Informational Amendment: Chemistry, Manufacturing, and Control," "Informational Amendment: Pharmacology-Toxicology," "Informational Amendment: Clinical") and include a statement of the nature and purpose of the amendment, an organized submission of the data, and a request for FDA comments on the information submitted if so desired.

3. Safety Reports 21 CFR 312.32

Safety reports are written reports required for any adverse experience associated with the use of the study drug that is both serious and unexpected. Safety reports are also used to report results from animal testing that suggest a significant risk for human subjects. These reports must be submitted to the FDA as soon as possible, but no more than 15 calendar days after the sponsor is initially notified of the adverse experience. The safety report must be clearly identified as such (for example: "IND Safety Report").

A seven-day reporting period is required for any unexpected fatal or life-threatening experience associated with the use of the drug in clinical studies conducted under the IND. Seven-day safety reports are submitted as soon as possible for no later than seven calendar days after the sponsor is initially notified of the adverse experience.

The sponsor must investigate safety information received as soon as possible and submit a report of the investigation and the results to the FDA in a safety report amendment.

4. Annual Reports 21 CFR 312.33

Each IND sponsor is required to submit an annual report within 60 days of the anniversary date that the IND went into effect. An annual report is a brief report on the progress of the investigation and is submitted as an amendment to the IND. Each annual report should include a brief summary of the status of each study in progress or completed over the last year. This summary must include the following items:

- Title of the study;
- Purpose of the study;
- Identification of the patient population;
- Study status: complete or in-progress;
- Summary of the most frequent and most serious adverse experiences, sorted by body system, in narrative or tabular form;
- Summary of all IND safety reports submitted during the past year;
- List of subjects who died during participation in the investigation, with the cause of death listed for each subject;
- List of subjects who dropped out of the study due to any adverse experience, whether or not thought to be drug-related;
- Description of information obtained pertinent to an understanding of the drug's action(s);
- List of the nonclinical studies completed or in progress during the past year, with a summary of the major findings;
- Summary of significant manufacturing or microbiological changes made during the past year;
- Description of the general investigational plan for the coming year containing information required in 21 CFR 312.23(a)(3)(iv);
- A description of the revised investigator brochure and a copy of the new brochure, if applicable;

- Description of Phase 1 protocol changes made during the previous year and not previously reported in a protocol amendment;
- Summary of foreign marketing developments with the drug during the past year, if applicable; and
- Any outstanding business related to the IND for which the sponsor is requesting a reply, comment, or meeting.

If an annual report is not received, subsequent actions by the FDA will follow, including a Report Request Letter, a Pretermination Letter if the sponsor does not reply within 30 days of the issuance of the Report Request Letter, or a Termination Letter if the sponsor does not reply within 30 days of the issuance of the Pretermination Letter.

G. Closing an IND

In the life cycle of an IND, there are several ways in which the IND can be closed.

- An IND may be inactivated at the request of the sponsor or the FDA if there is no activity (for example, the IND has been on clinical hold for over a year or no subjects have been enrolled for over 2 years) and may be reactivated with proper documentation, subject to a 30-day review clock. Sponsors are not required to submit an annual report to an inactive IND.
- The FDA may terminate an IND that has been inactive for over 5 years.
- An IND can be withdrawn at the sponsor's request. In this case, the IND cannot be reactivated, but can only be resumed with a new IND.
- The FDA can terminate an IND on the grounds of safety; a study not conducted according to the IND; an IND that contains false statements; a product that is not effective (as determined in a Phase 3 efficacy study); or failure to submit progress reports. In this case, the FDA orders the sponsor to end all clinical investigations. The IND can only be reinstated if a hearing is held and all parties are in agreement that the issue has been resolved.

II. Chapter References

Reference materials are presented in the order in which they first appear in the text.

1. 21 CFR 312.2.

2. 21 CFR 312.23.

3. FDA Office of Combination Products. FDA Web site address: http://www.fda.gov/oc/combination/.

4. Center for Biologics Evaluation and Research (CBER) Organizational Chart. FDA Web site address: http://www.fda.gov/cber/inside/orgchart.pdf.

5. Center for Drug Evaluation and Research (CDER) Organizational Chart. FDA Web site address: http://www.fda.gov/cder/cderorg.htm.

6. Transfer of Therapeutic Products to the Center for Drug Evaluation and Research. FDA Web site address: http://www.fda.gov/cber/transfer/transfer.htm.

7. Role of the CDER Ombudsman. FDA Web site address: http://www.fda.gov/cder/ombud/default.htm.

8. Roles and Responsibilities of the CBER Ombudsman. FDA Web site address: http://www.fda.gov/cber/inside/ombudsman.htm.

9. CDRH Ombudsman. FDA Web site address: http://www.fda.gov/cdrh/ombudsman/index.html.

10. 21 CFR 312.23(a)(2).

11. FDA Form-1571. FDA Web site address: http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.

12. 21 CFR 56.

13. 21 CFR 312.23(a)(3).

14. 21 CFR 312.23(a)(5).

15. *International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6*. ICH Web site address: http://www.ich.org/.

16. 21 CFR 312.23 (a)(6).

17. 21 CFR 50.

18. *International Conference on Harmonisation (ICH) Guideline for General Considerations for Clinical Trials E8*. ICH Web site address: http://www.ich.org/.

19. 45 CFR 46.

20. FDA Form-1572. FDA Web site Address: http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.

21. 21 CFR 312.64.

22. 21 CFR 312.62.

23. 21 CFR 312.68.

24. 21 CFR 312.

25. 21 CFR 56.102(h).

26. *FDA Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update*. FDA Web site address: http://www.fda.gov/oc/ohrt/irbs/default.htm.

27. 21 CFR 56.111.

28. 21 CFR 312.23(a)(7).

29. FDA's March 6, 2000, Gene Therapy Letter. FDA Web site address: http://www.fda.gov/cber/ltr/gt030600.htm.

30. *FDA 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, November 1995.* FDA Web site address: http://www.fda.gov/cder/guidance/clin2.pdf.

31. *FDA Guidance Document: INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products-Chemistry, Manufacturing, and Controls Content and Format, February 1999*. FDA Web site address: http://www.fda.gov/ohrms/dockets/98fr/990674gd.pdf.

32. *Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs).* FDA Web site address: http://www.fda.gov/cber/gdlns/cmcsomcell.pdf.

33. 21 CFR 312.23(a)(8).

34. 21 CFR 58.

35. 21 CFR 312.23(a)(9).

36. 21 CFR 312.23(a)(10).

37. 21 CFR 312.23(a)(11).

38. FDA CBER Electronic Investigational New Drug Application (eIND) for a Biological Product. FDA Web site address: http://www.fda.gov/cber/ind/eind.htm.

39. Information on Submitting an Investigational New Drug Application for a Biological Product: Electronic IND Demo. FDA Web site address: http://www.fda.gov/cber/ind/ind.htm.

40. Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs). FDA Web site address: http://www.fda.gov/cder/forms/1571-1572-help.html.

41. FDA CBER Transfer of Therapeutic Products to the Center for Drug Evaluation and Research. FDA Web site address: http://www.fda.gov/cber/transfer/transfer.htm).

42. *Manual of Standard Operating Procedures and Policies Communication Investigational and Marketable Applications Submission of Regulatory Documents to CBER*. FDA Web site address: http://www.fda.gov/cber/regsopp/8110.htm.

43. *FDA CBER Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Hold*. FDA Web site address: http://www.fda.gov/cber/gdlns/clinhld1000.htm.

44. *Manual of Standard Operating Procedures and Policies; Investigational New Drugs; Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications*. FDA Web site address: http://www.fda.gov/cber/regsopp/8201.htm.

45. *FDA Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Holds*. FDA Web site address: http://www.fda.gov/cder/guidance/2362fnl.pdf.

46. 21 CFR 312.42.

47. 21 CFR 312.30.

48. Mathieu, M., *The Investigational New Drug Application (IND) in New Drug Development: A Regulatory Overview, Revised Fifth Edition*: PAREXEL International Corporation. Waltham, MA, USA, 2000.

49. 21 CFR 312.30(b)(2)(ii).

50. 21 CFR 56.104(c).

51. 21 CFR 312.23 (a)(6)(iii)(b).

52. 21 CFR 312.31.

53. 21 CFR 312.32.

54. 21 CFR 312.33.

55. 21 CFR 312.23(a)(3)(iv).

III. Guidance Documents Applicable to INDs

1. *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products, Food and Drug Administration (FDA), November 1995.*

2. *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products–Chemistry, Manufacturing, and Controls Content and Format, FDA, February 1999.*

3. *Guideline for Good Clinical Practice (E6), International Conference on Harmonisation (ICH), June 1996.*

4. *Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*.

Chapter 4

I. Drug Master File Submission [21 CFR 314.420]

A. Drug Master File (DMF)

1. Overview

A Drug Master File (DMF) is an alternate method for submitting product and/or manufacturing information to the FDA. The DMF is a submission of information to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs and biological products. By referencing a DMF, the sponsor submitting an IND can incorporate information from the DMF into the IND (such as from a contract manufacturing organization or an excipient producer), or the sponsor can authorize other entities to reference information without direct disclosure of the information. This is accomplished using a cross-reference letter prepared by the IND sponsor and submitted to the FDA on behalf of his/her IND or on behalf of other entities. The FDA only reviews DMFs when a cross-reference letter has been submitted. While DMFs are neither approved nor disapproved by the FDA, the IND that cross-references the DMF may be placed on clinical hold, due to deficiencies in the DMF.

A DMF is a good regulatory strategy if the study drug will be used in more than one clinical study or for more than one indication. Additional information regarding DMFs can be found at the following Web sites:
Guideline For Drug Master Files or Guidance for Industry Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research .

2. Types of DMF

The type of DMF to be submitted is determined by the subject matter covered in the submission. The following types of DMFs may be submitted:

- Type I: The provision for a Type I DMF has been removed by the FDA as of July 10, 2000.
- Type II: Drug substance, drug substance intermediate, and materials used in their preparation, or drug product. The information contained in the DMF should be limited to a single drug

intermediate, drug substance, drug product, or type of material used in their preparation.

- Type III: Packaging Material. Each packaging material should be identified by the intended use, components, composition, and controls for its release. The names of the suppliers or manufacturers of the components used in preparing the packaging material and the acceptance specifications should also be given. Data supporting the acceptability of the packaging material for its intended use should also be submitted.
- Type IV: Excipient, colorant, flavor, essence, or materials used in their preparation. Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods.
- Type V: Other (for example, a facilities description). An entity wishing to submit information and supporting data in a drug master file (DMF) that is not covered by Types II through IV DMFs must first submit a letter of intent to the Drug Master File Staff at the Food and Drug Administration (5901-B Ammendale Road, Beltsville, MD 20705-1266). The FDA will then contact the entity representative to discuss the proposed submission. Information on the following types of facilities may be submitted in a Type V DMF without submitting a letter of intent:
    i. Facilities for production of gene- or cell-based therapies for Phase1 and 2 clinical trials.
    ii. Contract manufacturing facilities in support of Biologics License Applications or Biologics License Application supplements.

3. Content of a DMF

Administrative information that is included in an original DMF includes:

- DMF holder name and address,
- Corporate headquarters name and address,
- Manufacturing/processing facility name and address,
- Name and address of contact for FDA correspondence, and
- A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

Further detailed information on the content of a DMF can be found in the Web sites mentioned previously, The Guideline for Drug Master Files and the Guidance for Industry Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research .

A DMF must be updated regularly so that it remains current. An annual update should be provided on the anniversary date of the original submission.

4. Submitting a DMF

A DMF is submitted to the FDA in two copies (the original and one copy). Each page contained in the DMF is numbered sequentially, and the DMF contains an updated, accurate table of contents. If the holder of the DMF (the individual, partnership, corporation, or association that owns the DMF) adds, changes, or deletes any information in the DMF, the holder provides written notification to each entity authorized to reference that information.

The DMF must contain a complete list of each entity currently authorized to incorporate by reference any information in the DMF and must be identified by name, reference number, volume, and page number.

Each DMF submission must contain a transmittal letter that contains administrative information about the submission. Information regarding the content of the transmittal can be found in The Guideline for Drug Master Files.

The following address is used to submit a DMF to the FDA (Drug Master Files: Important Address Information):

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

B. Cross-Reference Letter

A Cross-Reference Letter (also known as a Letter of Authorization) permits the FDA to access and review a drug master file (DMF) or portions thereof, on behalf of the person or company referencing the DMF (the applicant). The FDA will review the DMF only when it is referred to in a submission. The person or company who has submitted the DMF (the holder) must submit two copies of the Cross-Reference Letter to the FDA, and send a copy to the applicant. The

applicant then submits the Cross-Reference Letter in his/her IND or other appropriate application. This is the only mechanism triggering the review of the DMF. An example of a cross-reference letter is included in appendix 10.

II. Chapter References

Reference materials are presented in the order in which they first appear in the text.

1. 21 CFR 314.420.

2. US FDA CDER Guideline For Drug Master Files Web site. FDA Web site address: http://www.fda.gov/cder/guidance/dmf.htm.

3. FDA Guidance for Industry: Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research. FDA Web site address: http://www.fda.gov/cber/gdlns/dmfv.htm.

4. Drug Master Files: Important Address Information. FDA Web site address: http://www.fda.gov/cder/dmf/.

III. Guidance Documents Applicable to Drug Master Files

1. *Guideline for Drug Master Files, Food and Drug Administration (FDA), September 1989*.

2. *Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research, Food and Drug Administration (FDA), August 2001*.

Chapter 5

I. Time Line for Pre-IND and IND Process

Table 2 describes pharmaceutical development leading to the clinic and milestones in the pre-IND and IND processes. The table illustrates the interrelated disciplines that participate at each phase, and provides an estimated time frame for each event.

Table 2: Flowchart and Time Line for Pre-IND and IND Process

Development Phase	Applicable Disciplines	Event	Estimated Time Frame
Discovery	Development Scientist	Basic research. Preliminary process and analytical methods development. Sufficient characterization to support proceeding further in development.	1-5 years*
Early Clinical Protocol Development Early Manufacturing (CMC) Early Nonclinical Testing	Development Scientist Clinical Manufacturing Nonclinical Regulatory	Draft clinical protocol. Prepare nonclinical plan to support clinical protocol and to provide sufficient safety data to support the IND. Conduct nonclinical testing. Develop manufacturing process and manufacture material for nonclinical studies.	1-3 years*

*Hughes S, King S. 2001. Drug Development Today: Costs and Development Times. In: Mathieu M, editor. *Pharmaceutical R&D Statistical Sourcebook 2002/2003*. Waltham, MA: PAREXEL International Corporation. P 186.

Table 2: Flowchart and Time Line for Pre-IND and IND Process (continued)

Development Phase	Applicable Disciplines	Event	Estimated Time Frame
Pre-IND Meeting	Clinical Manufacturing Nonclinical Regulatory	The sponsor submits pre-IND meeting request letter	Pre-IND process initiation. The pre-IND is often held from 6 months to one year prior to the planned IND submission.
		The FDA responds with a meeting date	14 days after receipt of the meeting request letter, and usually provides date by which meeting information package is due to the FDA.
		The sponsor submits pre-IND Information Package	At least 30 days before the designated meeting date
		The pre-IND meeting occurs	Usually, 60-90 days after receipt of the meeting request letter, on the date and time specified by the FDA
		A meeting summary is received from the FDA	30 days after the pre-IND meeting
Final Clinical Protocol Preparation Final CMC Final Nonclinical Studies	Clinical Manufacturing Nonclinical Regulatory	Finalize clinical protocol. Conduct nonclinical studies. Manufacture material for clinical studies.	6 months-1 year

Table 2: Flowchart and Time Line for Pre-IND and IND Process (continued)

Development Phase	Applicable Disciplines	Event	Estimated Time Frame
IND Preparation and Submission	Clinical Sponsor Manufacturing Nonclinical Regulatory	The sponsor addresses issues identified at the pre-IND meeting and submits the IND	As soon as the IND is completed and any issues identified at the pre-IND meeting are addressed, the IND can be submitted. *
		After a 30-day IND review period, the FDA allows the IND to proceed or places the product on clinical hold. Comments that don't mandate a clinical hold can also be received from the FDA.	30-day review period
		The sponsor submits an amendment to the IND responding to any clinical hold issues, if applicable.	As soon as the clinical hold issues are addressed
		After a 30-day IND amendment review period of responses to clinical hold items, the FDA allows the IND to proceed or the product remains on clinical hold.	30-day review period
Clinical Trial Initiation	Clinical	Upon resolution of clinical hold issues, the IND is allowed to proceed into Phase 1 studies.	As soon as the clinical hold issues are addressed

*If the pre-IND meeting includes a discussion of the proposed toxicology plans to make sure they are appropriate (correct animal model, dosing, etc.), the toxicology studies can then take at least 6 months to complete after the pre-IND meeting, including time to make revisions to the toxicology protocol (approximately 2 months). In this case, the IND is usually filed approximately 9-12 months after the pre-IND meeting.

APPENDICES

Appendix 1: Glossary

Appendix 2: A Short List of Government Agencies and Programs Related to Drug Discovery and Development

Appendix 3: Sample Pre-IND Meeting Request Letter

Appendix 4: Pre-IND Meeting Confirmation Letter Example

Appendix 5: Sample Pre-IND Information Package Table of Contents

Appendix 6: Form FDA 1571

Appendix 7: IND Template

Appendix 8: Example IND Cover Letter

Appendix 9: Form FDA 1572

Appendix 10: Example Drug/Biologic Master File Cross-Reference Letter

Appendix 1: Glossary

This section defines key terms used in this document. The terms are listed in alphabetical order.

Adverse Experience/Adverse Event (AE)

"Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action." 21 CFR 310.305(b).

Amendment to an Investigational New Drug Application

Additions or changes to an Investigational New Drug Application (IND) or other relevant information are reported to the Food and Drug Administration in an amendment. Amendments to an IND include protocol amendments, informational amendments, safety reports and annual reports and are discussed in further detail in Chapter 3. 21 CFR 312.30 – 21 CFR 312.33.

Biologic

Biologics are regulated by the Public Health Services Act and the Federal Food, Drug, and Cosmetic Act. As such, biologics are subject to both biologic and drug regulations. For the purposes of this document, the term "drug" will refer to both drugs and biologics.

The Public Health Services Act defines biologics as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. Table 3 characterizes and compares general properties of drugs and biologics.

Table 3: General Comparison of Drugs and Biologics

Drugs	Biologics
Synthetic	Extracted from living tissue
Organic compounds	Protein- or carbohydrate-based
Defined structure	Tertiary structure
Chemical characteristics: Molecular weight < 500 kilodaltons (kD)	Chemical characteristics: Molecular weight > 500 kD
Stabile	Labile
Not sensitive to heat	Heat- and shear-sensitive

Clinical Hold
"A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety." 21 CFR 312.42.

A clinical hold may be either a complete clinical hold (a delay or suspension of all clinical work requested under an IND) or a partial clinical hold (a delay or suspension of only part of the clinical work requested under the IND). A clinical hold (including a partial clinical hold) involves the Agency requiring additional information and/or data, reviewing the additional information and/or data, and after the review, informing the sponsor that they can proceed. *Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Holds*.

Clinical Investigation
"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).

Clinical Protocol
A clinical protocol is a written description of the investigational research to be undertaken. The protocol provides the background, rationale, and objectives of the clinical study and describes the design, methodology, and organization of the study. A clinical protocol is reviewed and approved by the principal investigator, IND sponsor, and Institutional Review Board. ICH E6 1.44.

Combination Product
As defined in 21 CFR 3.2(e), the term "combination product" includes:
(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Container Closure System
The sum of packaging components that together contains and protects the drug substance or product. 21 CFR 600.3(bb).

Contract Research Organization
A contract research organization (CRO) consists of 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 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).

Debarment

Two provisions for debarment are made in the United States federal law, mandatory and permissive. A permissive debarment is an action providing restrictions that disqualify an individual, corporation, partnership, or association from providing services in any capacity, directly or indirectly, in relation to an approved or pending product license application. Mandatory debarment applies to both individuals and corporations that have been convicted of a felony under federal law relating to a product license application. In addition to debarment authority, the FDA can impose civil penalties. (Regulatory Affairs Professional Society. *Fundamentals of Regulatory Affairs*. Rockville, Maryland: Regulatory Affairs Professional Society; 2001. 286 p.)

Drug

Drugs are regulated by the Federal Food, Drug, and Cosmetic Act (The Act). The Act defines drugs as articles intended for use in the diagnosis, cure, treatment, or prevention of disease in man and articles other than food that affect the structure or any function of the body of man [21 USC 321(g)(1)]. For the purposes of this document, the term "drug" refers to both drugs and biologics because biologics are regulated by the Federal Food, Drug, and Cosmetic Act, as drugs; and the Public Health Services Act, as biologics. Table 3 characterizes and compares general properties of drugs and biologics.

Drug Master File (DMF)

A Drug Master File is a submission of information to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs and biological products. Additional information about drug master files can be found in Chapter 5. 21 CFR 314.420.

Drug Product

A drug product is a pharmaceutical product type that contains a drug substance, generally, in association with excipients, that is ready for patient administration. A drug product is 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. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo. 21 CFR 314.3(b).

Drug Substance

A drug substance is any substance or mixture of substances intended to be used in the manufacture of a drug product that is or becomes an active ingredient.

Such substances demonstrate pharmacological activity or another direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. The drug substance can be composed of the desired product, product-related substances, and product-related and process-related impurities. The drug substance may also contain excipients including other components such as buffers. The drug substance is subsequently formulated with excipients to produce the drug product. 21 CFR 314.3(b).

Excipient
An inert substance used as a diluent or vehicle for a drug.

Form FDA 1571
The Investigational New Drug Application Form FDA 1571 outlines the information required in an IND by identifying the sponsor, investigational drug, phase of investigation, and parties responsible for monitoring the conduct of the trial. All sections on Form FDA 1571 must be addressed in the original IND submission, and a Form FDA 1571 is required to be submitted with every amendment to the IND.

Form FDA 1572
The Statement of Investigator Form FDA 1572 must be completed by each investigator participating in a study and the original given to the IND sponsor. The form provides a signed statement by each investigator containing his or her contact and Institutional Review Board (IRB) information, and agreement to conduct the study following regulations. The purpose of the form is to demonstrate that the investigator is qualified by training, education, and experience (*ICH Guideline for Good Clinical Practice, E6*).

Good Clinical Practices (GCP)
"A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected." (*ICH Guideline for Good Clinical Practice, E6*).

Good Laboratory Practices (GLP)
Good Laboratory Practices are described in the *Code of Federal Regulations* 21 CFR 58. GLPs are intended for use when conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA, including food and color additives, animal food additives, human and animal drugs, medical devices for

human use, biological products, and electronic products. Compliance with this 21 CFR 58 is intended to assure the quality and integrity of the safety data filed with the FDA. 21 CFR 58.

Good Manufacturing Practices (GMP)
The regulations set forth in the *Code of Federal Regulations* 21 CFR 210 and 211 contain the minimum Current Good Manufacturing Practice (CGMP) for Finished Pharmaceuticals. These sections of the CFR describe methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that the drug meets the requirements of the Federal Food, Drug, and Cosmetic Act (The Act) in regard to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. The failure to comply with any regulation set forth in 21 CFR 210 and 211 in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of The Act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action. 21 CFR 210.1.

Institutional Review Board (IRB)
An Institutional Review Board is "any board, committee, or other group formally designated by an institution [and reportable to the 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 520(g) of the Federal Food, Drug, and Cosmetic Act." 21 CFR 56.102(a).

Investigational New Drug
An Investigational New Drug product for human use is a new drug, antibiotic, or biologic used in a clinical investigation. This term is synonymous with Investigational Drug. 21 CFR 312.3(b).

Investigational New Drug Application (IND)
An Investigational New Drug Application (IND) is required for each Investigational New Drug. The IND is an application that a drug sponsor must submit to the FDA 30 days before beginning clinical studies of new drugs in humans. The purpose of the IND is to request authorization from the FDA to administer an investigational drug in humans and includes the proposed clinical protocol; supporting nonclinical studies; a general investigational plan; and chemistry, manufacturing and control (CMC) information describing the composition,

manufacture and control of the drug. This authorization is required prior to distribution of the investigational drug. 21 CFR 312

Investigator IND
An Investigator IND is submitted by the physician who is initiating and conducting a study using the Investigational New Drug (e.g., the principal investigator). The principal investigator has direct oversight of the dispensation and administration of the Investigational New Drug. The Investigator IND applies to both an Investigational New Drug as well as an approved drug being considered for use in a new indication or in a new patient population.

Investigator
An investigator is an individual who actually 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. "Subinvestigator" includes any other individual member of that team. 21 CFR 312.3(b).

Label
Label means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity. 21 CFR 1.3.

Labeling
Labeling includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce. 21 CFR 1.3.

Life-threatening Adverse Drug Experience
"Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death." 21 CFR 312.32.

Monitoring

"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practices (GCPs), and the applicable regulatory requirements." *(ICH Guideline for Good Clinical Practice, E6)*.

Nonclinical

The term "nonclinical" refers to testing performed prior to entering the Clinical Trial phase of testing in humans. Nonclinical is synonymous with the term "pre-clinical" for the purposes of this document. Nonclinical studies in animals are designed to investigate pharmacological and toxicological properties of a drug. The nonclinical phase of drug development also includes analytical methods development, and production of the CGMP pilot lot of the drug.

Pre-IND Meeting

Part of the IND submission strategy is to confer with the FDA prior to the submission of the IND at a pre-IND meeting. The purpose of a pre-IND meeting is to present to the FDA chemistry, manufacturing and controls (CMC) information and clinical and nonclinical data collected to date; and to seek their guidance on specifically posed questions regarding the information and data presented. The pre-IND meeting allows for early discussion and negotiation with the FDA and can ultimately save time and money in the drug development process by resolving issues prior to the IND filing. *FDA Guidance for Industry: IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information. May 2001* and *FDA Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*.

Serious Adverse Drug Experience

"Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient

hospitalization, or the development of drug dependency or drug abuse." 21 CFR 312.32.

Sponsor
The sponsor of an investigational drug may be an individual, pharmaceutical company, government agency, academic institution, private organization or other organization that takes responsibility for the initiation, management, and/or financing of a clinical investigation. 21 CFR 312.3(b).

Sponsor-Investigator
A Sponsor-Investigator is an individual who is serving as the sponsor of the investigational new drug application and conducts the clinical investigation. The Sponsor-Investigator is the individual under whose immediate direction the investigational drug is administered or dispensed. 21 CFR 312.3(b).

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).

Unexpected Adverse Drug Experience
"Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. 'Unexpected,' as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product." 21 CFR 312.32.

Appendix 2: A Short List of Government Agencies and Programs Related to Drug Discovery and Development

There are many mechanisms to gain access to programs that support the development of promising new drugs. Grants and funding opportunities can be researched on the National Institutes of Health (NIH) Web page at http://www.nih.gov/. Some key agencies and/or programs that are available to assist researchers after funding has been established are described in this section.

Cancer Therapy Evaluation Program (CTEP)

The mission of the Cancer Therapy Evaluation Program (CTEP) is to improve the lives of cancer patients by finding better ways to treat, control and cure cancer. CTEP accomplishes this mission by funding an extensive national program of cancer research and by sponsoring clinical trials to evaluate new anticancer agents, with a particular emphasis on translational research to elucidate molecular targets and mechanisms of drug effects.

CTEP uses a scientific process to accomplish its mission. Promising basic scientific findings are identified and translated into clinical research, both by identifying new agents for evaluation and by identifying biologic characteristics of tumors that may be clinically exploited. Novel anticancer agents with distinctive molecular targets, mechanisms of action, or properties are identified and introduced into clinical trials, with prioritization of agents based on scientific criteria and therapeutic needs. The antitumor activity of new anticancer agents is systematically evaluated in clinical trials. Promising new cancer treatments are rigorously compared to best available treatments in hypothesis-driven clinical trials to reliably define superior treatments for specific types of cancer.

CTEP attempts to forge broad collaborations within the research community and works extensively with the pharmaceutical/biotechnology industry to effectively develop new cancer treatments. CTEP also seeks to involve outside experts and patients or their advocates in the formulation of research priorities. In the selection of clinical research for NCI sponsorship, CTEP attempts to fill critical gaps in the national cancer research effort and to avoid duplication of ongoing private sector efforts. In further efforts to control cancer, active new anticancer agents are made available as rapidly and widely as possible for patients.

CTEP's Web site can be found at http://ctep.cancer.gov/.

Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) is the federal scientific regulatory body responsible for protecting the public health by assuring the safety and efficacy of drugs, biologics, cosmetics, medical devices, food and radiological products.

The FDA's Web site can be found at http://www.fda.gov.

Inter-Institute Program for the Development of AIDS-related Therapeutics (IIP)

The Inter-Institute Program for the Development of AIDS-related Therapies (IIP) is sponsored by the National Institute of Allergy and Infectious Diseases and the National Cancer Institute. The IIP reviews investigators' proposals to receive drug development assistance for specific tasks they otherwise would not be able to perform to translate basic research into clinical practice. The purpose of IIP is to assist AIDS researchers in the nonclinical development of therapies for:

- The treatment of HIV disease, AIDS-associated malignancies, opportunistic infections and tuberculosis associated with AIDS; and
- Microbicide-based HIV prevention strategies.

Some examples of tasks that could apply are:

- High-throughput screen assay development,
- Evaluation in animal efficacy models, and
- CGMP scale-up synthesis of small molecules and biologics, clinical dosage formulation and manufacturing, and current Good Laboratory Practice (CGLP) toxicology.

Additional information is available at the following Web sites:
http://dtp.nci.nih.gov/docs/dart.html and
http://grants.nih.gov/grants/guide/notice-files/NOT-CA-03-038.html.

National Cancer Institute (NCI)/Rapid Access to Intervention Development (RAID) Program

The goal of Rapid Access to Intervention Development (RAID) is the rapid movement of novel molecules and concepts from the laboratory to the clinic for proof-of-principle clinical trials using the NCI's contract research mechanisms. RAID makes available to academic investigators, on a competitive basis, the

nonclinical development contract resources of NCI's Developmental Therapeutics Program (DTP). RAID assists investigators who submit successful proposals by providing any of the nonclinical development steps that may be obstacles to clinical studies, as well as manufacture of CGMP clinical material for Phase 1/Phase 2 clinical studies. Suitable agents for RAID include small molecules, biologics or vaccines. For additional information on the process and procedures of requests for RAID resources, visit the DTP Web site at http://dtp.nci.nih.gov.

National Institutes of Health (NIH)/National Cancer Institute (NCI)/ Developmental Therapeutics Program (DTP)/Biological Resources Branch (BRB)

The Biological Resources Branch (BRB) is one of the extramural arms of the Developmental Therapeutics Program (DTP), NCI. The BRB supports nonclinical and early clinical studies (e.g., Phase 1) of biological response modifiers (BRMs) research in the biomedical community through a program of grants and contracts. These studies assess the effects of novel biological agents and explore relationships of biological responses with antitumor activity. An NCI Nonclinical Repository distributes selected agents for peer-reviewed nonclinical studies performed by both extramural and intramural investigators. Other contracts support the production and *in vivo* evaluation of monoclonal antibodies, immunoconjugates and other biologicals.

The NCI BRB Program staff provides oversight of the Biopharmaceutical Development Program (BDP) at NCI-Frederick. The BDP produces a variety of biopharmaceuticals under current CGMPs for Phase 1/Phase 2 human clinical trials or advanced nonclinical animal testing. The BDP is a government-owned contractor-operated facility. It is operated under contract by Science Applications International Corporation (SAIC)-Frederick, Inc., providing operations and technical support to NCI-Frederick.

The BRB's Web site can be found at http://web.ncifcrf.gov/research/brb/.

National Institutes of Health (NIH)/Rapid Access to Interventional Development (RAID) Pilot Program

The NIH/RAID pilot program has been developed to make certain critical resources available, on a competitive basis, for the development of new small molecule therapeutic agents; and to reduce some of the common barriers

between laboratory discoveries and clinical trials of new therapeutic entities. The resources of the National Cancer Institute's Developmental Therapeutics Program (DTP) will be used for the NIH/RAID pilot program. Services provided may include production, bulk supply, GMP manufacturing, formulation, development of an assay suitable for pharmacokinetic testing, animal toxicology, and regulatory support. While the NIH/RAID pilot program is not a grant program, successful projects will gain access to the government's contract resources, and assistance from the NIH in establishing and implementing a product development plan. Selected projects will be supported by funds from the NIH Roadmap and from individual Institutes in the specific disease areas relevant to their mission. Additional information regarding the NIH/RAID pilot program can be found at the following Web site: http://nihroadmap.nih.gov/raid/.

Rapid Access to NCI Discovery Resources (R*A*N*D)

The R*A*N*D program makes available to academic investigators, on a competitive basis, the discovery, and early nonclinical development contract resources of NCI's Developmental Therapeutics Program. The goal of R*A*N*D is to remove the most common barriers between basic research findings and their use for discovery of new molecular entities. Applications to the program are requests for NCI drug discovery and development resources to conduct specific tasks the applicants themselves are unable to carry out in their efforts to translate basic research findings to the discovery of new drugs. Examples of tasks that may be requested include:

- Production/characterization of molecular target proteins,
- High-throughput screening assay development,
- Natural product isolation/characterization,
- Synthesis of combinatorial libraries,
- Computer modeling, and
- Early pharmacology and *in vivo* efficacy studies.

For additional information on the process and procedures of requests for R*A*N*D resources, visit the following Web site: http://dtp.nci.nih.gov/docs/rand/rand_index.html.

Rapid Access to Preventive Intervention Development (RAPID)

The Rapid Access to Preventive Intervention Development (RAPID) Program makes the contract resources from NCI's Division of Cancer Prevention available to academic and academically affiliated investigators for nonclinical and early clinical drug development. RAPID objectives are to:

- Assist expeditious movement of novel molecules and compounds from the laboratory through Phase 1 clinical trials;
- Assist investigators who submit successful requests by providing any, or all, of the nonclinical and Phase 1 clinical developmental requirements needed to move forward into Phase 2 clinical efficacy trials;
- Support further development of the chemoprevention field;
- Develop prerequisites for filing IND applications to initiate clinical trials; and
- Provide material for proof-of-principle clinical testing.

RAPID accomplishes the tasks that are rate-limiting in bringing discoveries from the laboratory to the clinic. Ordinarily, these tasks will be accomplished by the use of NCI chemopreventive agent development contracts and will be facilitated by direct consultation of the originating laboratory with NCI staff. Such rate-limiting tasks, necessary to accomplish project goals, will vary from project to project and will be evaluated for support on a case-by-case basis. In some cases, RAPID will support only one or two key missing steps necessary to bring a compound into clinical efficacy testing; in other cases, it may be necessary to supply the entire portfolio of development tasks needed to file an IND.

For additional information on the process and procedures of requests for RAPID resources, visit the NCI Web site http://www3.cancer.gov/prevention/rapid.

Type 1 Diabetes – Rapid Access to Intervention Development Program (T1D–RAID)

The T1D–RAID program is designed to assist with the translation of novel therapeutic interventions for type 1 diabetes and its complications (either synthetic, natural product, or biologic) to the clinic. Requests to T1D–RAID are brief, should clearly outline the resources required to ready the proposed therapeutic agent for clinical trials, and are accepted twice yearly, on November 1 and April 1. The requests are reviewed by a panel of extramural experts. Review criteria include strength of the scientific hypothesis, scientific novelty, and cost/benefit considerations afforded by the proposal. While T1D–RAID is not a

grant mechanism, approved requests to T1D–RAID gain access to the drug development contract resources of the National Cancer Institute's Developmental Therapeutics Program (NCI DTP). Resources available to the originating investigator may include GMP synthesized material, formulation research, pharmacological methods, or IND-directed toxicology, for support of an investigator-held IND application and clinical trials. T1D–RAID does not sponsor clinical trials; it sponsors the work needed to get ready to do clinical trials. Additional information regarding the T1D–RAID program can be found at the following Web site: http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D-RAID/.

Appendix 3: Sample Pre-IND Meeting Request Letter

Date

[Dr. John Smith]
Division of Application Review and Policy
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
c/o Document Control Center (HFM-99)
Woodmont Office Center, Suite 200N
1401 Rockville Pike
Rockville, MD 20850

RE: Request for a Pre-IND Meeting (Type B) for [*Add Product Name*] as a Treatment for [*Add Treatment Type*]

Dear [*Dr. Smith*]:

We would like to request a Pre-IND meeting with the FDA to discuss a proposed IND to develop [*Add product name]* as a treatment for [*add treatment type*.] [*Next, you can briefly discuss current therapies for this disease and the benefits of your product.*]

The purpose of the proposed initial clinical study is to _____ [*Mention safety and pharmacokinetics that will be evaluated. Mention the indication and patient population to be studied. Keep this paragraph short—only a few sentences.*]

[*Product name*] is _____ [*provide a brief description of the product and its primary mode of action to be investigated*].

[*This third paragraph should briefly discuss the product, what it is or what it reacts with that makes it useful. Identify anything unique about the product. Include chemical name and structure.*]

The purpose of this pre-IND meeting is to discuss issues concerning _____ [*nonclinical toxicology studies, proposed clinical trial design, any CMC issues. This statement could include a discussion of the types of completed or planned studies or data that the applicant intends to discuss at the meeting, the general nature of the critical questions to be asked, and where the*

meeting fits in the overall development plans. Lastly, add a statement about what objectives/outcomes you expect to get from the meeting. This can be a general statement that you hope to gain input from the FDA concerning the nonclinical tox studies, clinical trial protocol design, and CMC issues; or you can state any specific issues you have.] A proposed agenda is attached, including the estimated amounts of time needed for each agenda item and the designated speaker. Also included is a list of the individuals who plan to attend the meeting, and the proposed FDA staff that we would like to participate in the meeting. Finally, a draft list of specific questions to be addressed at the meeting is attached.

We would like to schedule a meeting for one of the following dates if possible:_____ [*list at least 4–5 dates and times—morning or afternoon—for the meeting; the dates should be scheduled to occur within 60 days of the Agency's receipt of the written request for a meeting. Remember, for a Type B meeting, the meeting information package must be submitted at least 4 weeks prior to your assigned meeting date by the FDA or they can cancel the meeting; usually people pick dates 6–8 weeks out so they have at least two weeks to submit the information package from the time they send in the letter. Just make sure you will be ready to submit your information package at least four weeks prior to your first proposed meeting date!*] The meeting information package will be submitted at least four weeks prior to the meeting date.

We appreciate your consideration of this Pre-IND meeting request. Please contact _____ at _____ to discuss meeting dates. If you need any additional information in the interim, please do not hesitate to call me.

Sincerely,

Dr. [*fill in name*]
[*title*]
[*affiliation*]

Sample Meeting Agenda and List of Participants Format

Product Name **PRE-IND MEETING AGENDA**

I.	Introduction/Background	Dr. *name*	3 minutes
II.	Discussion on List of Questions • CMC Issues • Nonclinical Issues • Clinical Trial Design	All	57 minutes

LIST OF PROPOSED ATTENDEES

(*List names of proposed attendees with their titles)*

LIST OF PROPOSED FDA PARTICIPANTS

(List of any FDA individuals or specialty areas from which you would like FDA personnel to participate in your meeting).

DRAFT List of Specific Questions for *Product Name* Pre-IND Meeting

(List the questions and/or proposals you want addressed by the FDA. Questions and/or proposals must be as specific, comprehensive, and precise as possible to identify critical issues. You can list as many questions as you think can be addressed within your meeting time frame.)

CMC Questions and/or Proposals:

1.

2.

3.

Nonclinical Questions and/or Proposals:

4.

5.

6.

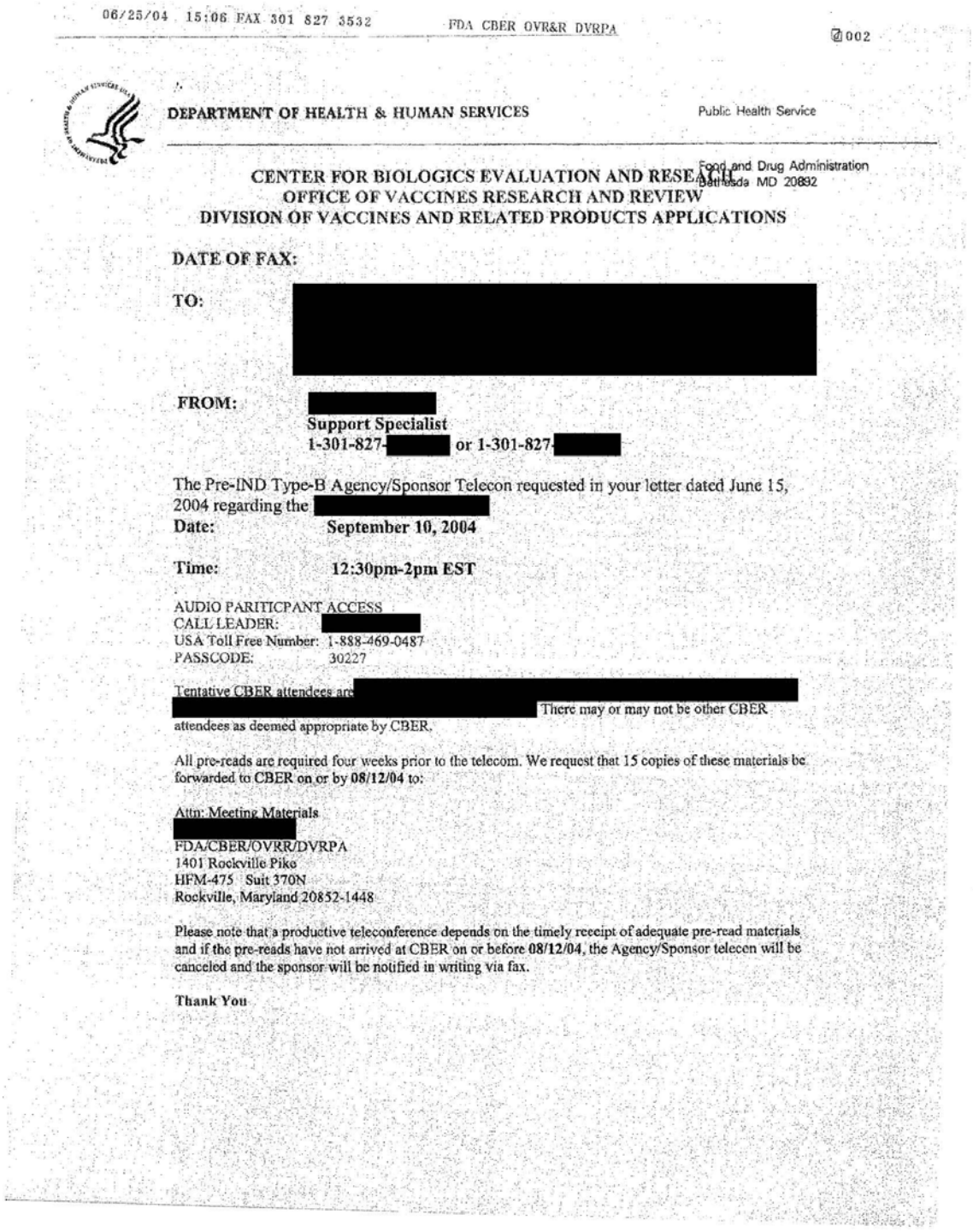
Clinical Trial Design Questions and/or Proposals:

7.

8.

9.

Appendix 4: Pre-IND Meeting Confirmation Letter Example



06/25/04 15:06 FAX 301 827 3532 FDA CBER OVR&R DVRPA 002

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Bethesda MD 20892

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS

DATE OF FAX:

TO: [redacted]

FROM: [redacted]
Support Specialist
1-301-827-[redacted] or 1-301-827-[redacted]

The Pre-IND Type-B Agency/Sponsor Telecon requested in your letter dated June 15, 2004 regarding the [redacted]
Date: **September 10, 2004**

Time: **12:30pm-2pm EST**

AUDIO PARITICPANT ACCESS
CALL LEADER: [redacted]
USA Toll Free Number: 1-888-469-0487
PASSCODE: 30227

Tentative CBER attendees are [redacted] There may or may not be other CBER attendees as deemed appropriate by CBER.

All pre-reads are required four weeks prior to the telecom. We request that 15 copies of these materials be forwarded to CBER on or by **08/12/04** to:

Attn: Meeting Materials
[redacted]
FDA/CBER/OVRR/DVRPA
1401 Rockville Pike
HFM-475 Suit 370N
Rockville, Maryland 20852-1448

Please note that a productive teleconference depends on the timely receipt of adequate pre-read materials and if the pre-reads have not arrived at CBER on or before **08/12/04**, the Agency/Sponsor telecon will be canceled and the sponsor will be notified in writing via fax.

Thank You

Appendix 5: Sample Pre-IND Information Package Table of Contents

Sample Pre-IND Information Package Table of Contents

Cover Letter
Form FDA 1571
Table of Contents
1.0 Introduction/background Information
2.0 Product name and application number
3.0 Chemical name and structure
4.0 Proposed indication
5.0 Dosage form, route of administration, and dosing regiment
6.0 Purpose of the meeting
7.0 Specific objectives/outcomes expected from the meeting
8.0 Agenda, attendees, and list of questions
    8.1 Agenda
    8.2 Attendees
    8.3 List of questions
        8.3.1 CMC questions
        8.3.2 Nonclinical questions
        8.3.3 Clinical trial design questions
9.0 Chemistry, Manufacturing, and Control Information
10.0 Nonclinical study summaries
    10.1 Summary of nonclinical studies
        10.1.1 Reactivity of [product name] with normal human tissues
        10.1.2 *In vitro* studies
        10.1.3 Animal experiments
    10.2 Proposed Toxicology Protocol
11.0 Clinical study design

Note: This table of contents is provided as one example of a Pre-IND Information Package Table of Contents. Other formats are acceptable if the information content of the pre-IND information package is complete as outlined in the *FDA Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*, and the table of contents accurately reflects the organization of the document.

Appendix 6: Form FDA 1571

A current FDA Form-1571 and instructions for its completion can be obtained using the following Web site:
http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.

Next Page | Export Data | Import Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
2. DATE OF SUBMISSION
3. ADDRESS *(Number, Street, City, State and Zip Code)*
4. TELEPHONE NUMBER *(Include Area Code)*
5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
6. IND NUMBER *(If previously assigned)*
7. INDICATION(S) *(Covered by this submission)*
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
   ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER *(Specify)*
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
   ☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
   ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

FORM FDA 1571 (1/03) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

FSC Media Arts (301) 443-1090 EF

Previous Page

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE Sign	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

FORM FDA 1571 (1/03) **PAGE 2 OF 2**

Save Data Print

Appendix 7: IND Template

ITEM 1. Form FDA 1571

Instructions: This form can be downloaded from the FDA Web site at:
http://www.fda.gov/opacom/morechoices/fdaforms/cder.html

ITEM 2. TABLE OF CONTENTS

[Note: volume numbers should be included in the table of contents where multiple volumes are used.]

Item Page

ITEM 3. INTRODUCTORY STATEMENT AND GENERAL INVESTIGATIONAL PLAN

[The text of Item 3 should be no more than 5 pages. Keep "Previous Human Experience" to no more than 1 paragraph and "Rationale" to about 1 page. Include minimal information on nonclinical toxicology and pharmacology studies, just enough to justify dose, schedule, and route. Refer to *Investigator's Brochure* for this information, if applicable.]

INTRODUCTION

The introductory statement should be brief and include the name of the drug and all of the active ingredients, the drug's structural formula (if known), and the drug's pharmacological class. Also include the formulation of the dosage form to be used, the route of administration, and the duration and objectives of the planned clinical trial.

A sample introductory paragraph follows:

This Investigational New Drug Application (IND) is being submitted to conduct clinical studies of xxxxxx. Xxxxxx is a ... It blocks progression from the G_1 phase to the S phase of the cell cycle... Xxxxxx has shown activity against...

The proposed phase x study will assess the antitumor activity of xxxxxx, as determined by progression-free survival, in patients with xxxxxx. Xxxxxx will be administered intravenously (IV) using a ... schedule. Clinical and laboratory toxicities will be characterized at each dose level.

AGENT DESCRIPTION

Name:	[Chemical or agent name; include all active ingredients]
Code Name[s]:	[NSC XXXXXX and/or other names]
Description:	[Describe]
Molecular Formula:	[Formula]
Chemical Structure:	[If applicable]

Pharmacologic Class:	[Name the class]
Bulk Drug Substance:	[Company, city, state] [Biologic agent]
Product:	[Company, city, state]
Formulation:	Each 30 mL vial of [agent] contains the following:
Route of Administration:	[Route]
Storage and Stability:	XXXXXXX

PREVIOUS HUMAN EXPERIENCE

Make a statement about whether the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or efficacy and the reason for the withdrawal.

RATIONALE

CLINICAL STUDY

Indications to Be Studied

Study Objectives

Eligibility Criteria

Study Design

Estimated Number of Patients

Potential Adverse Experiences

FUTURE PLANS

REFERENCES

ITEM 4. [RESERVED]

ITEM 5. INVESTIGATOR'S BROCHURE

GENERAL OUTLINE FOR INVESTIGATOR'S BROCHURE

[Sponsor-Investigators are not required to submit an investigator's brochure (IB).]

See general outline below for an Investigator's Brochure (IB). Refer to ICH Guideline E6: Guideline for Good Clinical Practice for additional information regarding the content of an Investigator's Brochure.

TITLE PAGE

TABLE OF CONTENTS

SUMMARY

INTRODUCTION
- **General Approach**
- **Mechanism of Action (Biologic activity for biologic IB)**

PHYSICAL, CHEMICAL AND PHARMACOLOGICAL PROPERTIES AND FORMULATION
- **Names and Description**
- **Dosage Formulation (or how supplied)**
- **Route of Administration**
- **Storage and Handling**

NONCLINICAL STUDIES
- **Introduction/Summary of Nonclinical Studies**
- **Pharmacology (or efficacy)**
  - Pharmacological Aspects/Significant Metabolites Studies
  - Therapeutic Activity and Safety Assessment Studies
  - Example: *In Vitro* Antitumor Studies or *In Vitro* Efficacy Studies, and *In Vivo* Antitumor Studies or *In Vivo* Efficacy Studies
- **Pharmacokinetics and Drug Metabolism in Animals (this section usually does not apply to biologic IBs and can be omitted)**
  - A summary of the pharmacokinetics and biological transformation and disposition including:
    - Analytical Methods
    - Pharmacokinetics in Mice

Pharmacokinetics in Dogs
Summary of Nonclinical Pharmacokinetics or Conclusions

Toxicology

A summary of toxicological effects such as:
Toxicology in Mice
Toxicology in Dogs
Summary of Nonclinical Toxicology or Conclusions

EFFECTS IN HUMANS

Pharmacokinetics and Product Metabolism in Humans

Clinical Trials/Published Data
Sponsored Clinical Trials
Other (indicate type) Studies

Safety and Efficacy

Safety Information from Clinical Trials: A 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.

Marketing Experience

Identify countries where investigational drug did and did not receive market approval, and a summary of information resulting from the marketed use.

SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

Provides the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial.

REFERENCES

ITEM 6. PROTOCOL

Page

6a. Study Protocol

6b. Investigator Data

6c. Facilities Data

6d. Institutional Review Board Data

Instructions for Item 6:

- A separate title page should be included in each section.
- Item 6a—include the protocol, informed consent, and Institutional Review Board approved consent if available.
- Item 6b—Include investigator information—Form FDA 1572, CV, any other qualifications.
- Item 6c—List the institution where this study will be taking place and the principal investigator's name and title. Also, indicate established procedures for determining the adequacy of the facilities used for the conduct of clinical trials (i.e., peer review, etc.)
- Item 6d—Please indicate established procedures for ensuring that the research conducted under this IND is properly reviewed by an appropriately constituted Institutional Review Board (IRB). Each investigator who participates in NCI-supported clinical research must conduct the research in an institution with an approved assurance from the Department of Health and Human Services Office for Human Research Protections (OHRP) at the National Institutes of Health. This is in accordance with the *Code of Federal Regulations*, Title 45 Part 46, and Title 21, Parts 50 and 56. Include IRB approval if available at IND submission.

ITEM 7. CHEMISTRY, MANUFACTURING, AND CONTROL DATA

Page

7a. Drug Substance [Biologic Agent]

1. Letter of Authorization to Cross-Reference IND XX,XXX [BB-IND for biologics]: [Drug company name], if applicable.
2. Description and Characterization
3. Name and Address of the Manufacturer
4. Methods of Manufacture
5. Analytical Methods and Specifications
6. Stability

7b. Drug Product [Biologic Product]

1. Components and Composition
2. Name and Address of the Manufacturer
3. General Manufacturing and Packaging Description
4. Analytical Methods and Specifications
5. Stability

7c. Response to Gene Therapy Letter [gene transfer INDs only]

7d. Environmental Analysis Requirements/Claim for Exclusion

Instructions:

For Item 7d, see next page

If chemistry, manufacturing, and control services were provided by RAID, a document will be provided for inclusion in the appropriate section of the IND.

ITEM 7d. Environmental Analysis Requirements/Claim for Exclusion

The [add sponsor name] requests a claim for categorical exclusion for this proposed clinical trial as provided for in 21 CFR 25.31(e), in that the agent shipped under this IND 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 nontoxic. Furthermore, it is understood that the clinical supplies of [agent] are to be used under the direction of qualified investigators (physicians, as well as pharmacists and nurses) knowledgeable in the use and handling of investigational anticancer agents.

[Describe procedures for drug disposition of unused clinical supplies of the agent. Also describe waste handling and control procedures for the agent.]

ITEM 8. PHARMACOLOGY AND TOXICOLOGY DATA

Page

8a. Nonclinical Efficacy

8b. Pharmacology

1. Nonclinical Pharmacology Summary

8c. Toxicology

1. Nonclinical Toxicology Summary

For gene transfer INDs, add the following statement to Item 8c:

All animal safety information provided to [sponsor name] has been submitted as described in 21 CFR 312.32-33.

Instructions:

If pharmacology and toxicology services were provided by RAID, a document will be provided for inclusion in the appropriate sections of the IND.

ITEM 9. PREVIOUS HUMAN EXPERIENCE

[If the IND is a cross-reference and an investigator's brochure is included in the IND, the text of Item 9 should be limited to 1 or 2 short paragraphs. Refer to investigator's brochure and summarize only clinical information that supplements the brochure.]

[If the IND is not a cross-reference, the text of Item 9 should be limited to no more than 1 page and used to summarize any relevant clinical information available.]

ITEM 10. ADDITIONAL INFORMATION

Page

.

Instructions:
Add any additional pertinent information in this section, such as relevant publications, letters of cross-reference (if not already included in other sections), etc.

ITEM 11. RELEVANT INFORMATION

Instructions:
Add any other relevant information required for review of the application if requested by the FDA.

Appendix 8: Example IND Cover Letter

[Date]

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

Steven K. Galson, M.D., M.Ph.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

or

Jesse Goodman, M.D.
Director
Center for Biologics Evaluation and Research
Attn: Office of Compliance and Biologics Quality
c/o Document Control Center (HFM-99)
Office Center, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

Subject: Notice of Claimed Investigational Exemption for a New Drug (IND) Serial No. [0000] Vol. 1, pp. 1–xxx; Vol. X, pp. 1–xxx; Title of IND

Dear Dr. Galson or Dr. Goodman:

[Company/Institution Name] hereby submits one original and two copies of 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].

Steven K. Galson, M.D., M.Ph.; or Jesse Goodman, M.D.
[Date]
Page 2

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 principal investigator], M.D. A signed Form FDA 1572 and investigator's curricula vitae are included as attachments to this letter.

[Add any pertinent information to which you would like to call to 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 under item 7.

2. The adjuvant [adjuvant's name] was manufactured by [adjuvant manufacturer's name, city, state]. A cross-reference letter to the company's drug master file [DMF number] is enclosed under Item 7 of this filing.

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 Product License Application is approved.

Please address all correspondence to:

[Sponsor's name, affiliation, address, and contact information]

If you have any questions regarding this submission, please contact [name of contact person] at [contact person's phone number] or [contact person's e-mail address].

Sincerely,

[Name, title and affiliation of IND applicant]

Enclosure

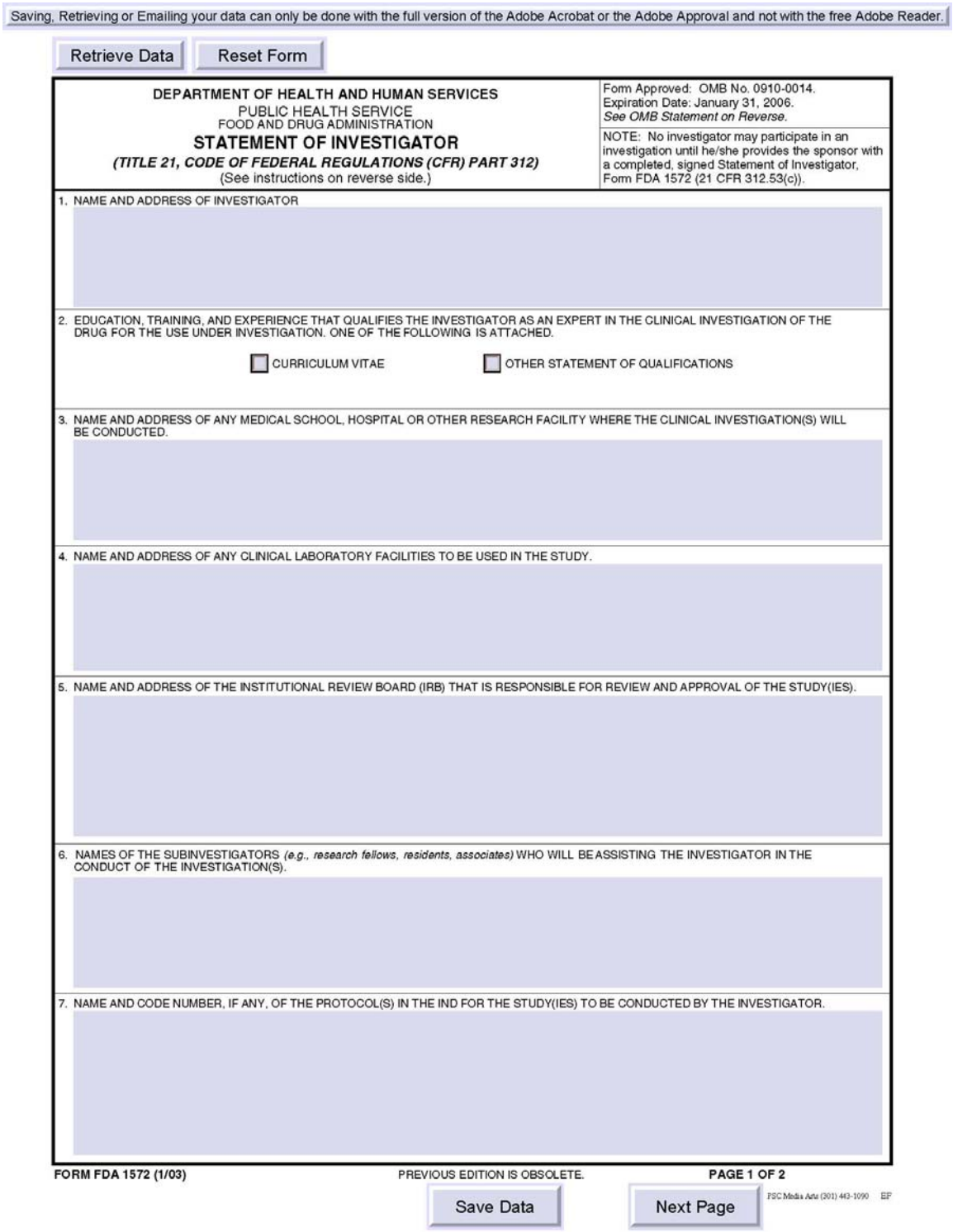
pc:

For gene transfer INDs, add:

The information requested in the FDA's March 6, 2000, Gene Therapy Letter has been provided. Responses to items 1–5 of that letter can be found in the cross-referenced manufacturer's master file, BB-MF XXXX. Response to item 6 can be found in [add this information to item 10 of the IND]. Lastly, all animal safety information provided to [add sponsor name] has been submitted as described in 21 CFR 312.32-33 (response to item 7).

Appendix 9: Form FDA 1572

A current Form FDA 1572 and instructions for its completion can be obtained using the following Web site:
http://www.fda.gov/opacom/morechoices/fdaforms/cder.html.



Saving, Retrieving or Emailing your data can only be done with the full version of the Adobe Acrobat or the Adobe Approval and not with the free Adobe Reader.

Retrieve Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

FORM FDA 1572 (1/03) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

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PSC Media Arts (301) 443-1090 EF

Previous Page

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

FORM FDA 1572 (1/03) **PAGE 2 OF 2**

Save Data Print Email Form

Appendix 10: Example Drug/Biologic Master File Cross-Reference Letter

May 6, 2003

Jesse Goodman, M.D.
Director, Center for Biologics Evaluation and Research
Attn: Office of Compliance and Biologics Quality
c/o Document Control Center (HFM-99)
Office Center, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

Subject: **BB-MF-[redacted], Type V Biologics Master File, Serial No. 012**
Letter of Authorization to Cross-Reference Biologics Master File

Dear Dr. Goodman:

This authorization letter is in reference to the Type V, Biologics Master File (BB-MF-[redacted]) entitled [Drug Master File Title] submitted by [Company Name]. The most current version of the Master File was submitted to the FDA/CBER on October 23, 2002.

We authorize the institution listed below to cross-reference [Company Name] Biologics Master File (BB-MF-[redacted]) as described below in support of their Investigational New Drug Applications IND# [redacted]. The final biological product for this IND was manufactured using the buildings, equipment, utilities, and flows of personnel, raw materials, product, process, components, and waste described in BB-MF [redacted] and, therefore, the entire master file may be referenced.

Institution: [redacted]

Product(s): [redacted]

IND Title(s): [redacted]

Institution Address: [redacted]

Institution Representative: [redacted]

Institution Representative Phone Number: [redacted]

Jesse Goodman, M.D.
May 6, 2003
Page 2

We certify that the information contained in BB-MF [redacted] is current and that the [Company Name] complies with all of the statements made therein.

Please note the information contained in our BB-MF [redacted] is proprietary and confidential and may not be distributed to anyone without the written consent of the [Company Name]. The legal protection of such confidential material is hereby claimed under applicable provisions of 21 CFR 601.51 and 21 CFR 314.430.

Please contact me at [redacted] if you have any questions.

Sincerely,

Manager, Regulatory Affairs
[Name of Company]

The Sponsor's Guide to Regulatory Submissions for an Investigational New Drug

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