Drafting an Investigational New Drug Application (IND)

February 16 and 25, 2021

CARILION CLINIC

Course Objectives

- Identify the different types of INDs and when they are required for a clinical study
- Describe the elements of an IND application
- Define the roles and responsibilities of the sponsor/investigator in an IND study

What is an IND application

- An application that provides the FDA with the data necessary to decide if a new drug and the proposed clinical trial pose a reasonable risk to human subjects participating in the study
- The IND application allows the sponsor to initiate and conduct the clinical studies and transport study drug across state lines (exemption)
- 21 CFR part 312

IND Classifications

- Commercial
  - Permits sponsor to collect data on the clinical safety and efficacy needed for application for marketing in the form of a New Drug Application (NDA)
- Research (Non-Commercial)
  - Permits the sponsor to use the drug in research to obtain advanced scientific knowledge of a new drug
  - No plan to market the drug
- Emergency Use

Definitions

- **Investigational new drug**
  - a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes.
- **Investigator**
  - an individual who conducts a clinical investigation (*i.e.* , under whose immediate direction the drug is administered or dispensed to a subject).
- **Sponsor**
  - the entity who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation
- **Sponsor-Investigator**
  - an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

When is an IND Needed*

- To conduct a clinical trial with an unapproved drug/ new molecular entity (NME)
- If the NME is not approved for the indication under investigation
- If a new dosage level or route of administration is being investigated
- If combined with another drug and the combination is not approved
- All clinical studies where an unapproved drug is administered to human subjects, regardless of whether the drug will be commercially developed

*There are exceptions

When an IND is not needed

- Drug/ NME is not intended for human subjects (pre-clinical studies)
- It is an approved drug, and the study is within the approved indication for use
  - "Off label" studies as long as the dosage and/or route of administration is not changed

If you think your study will require an IND

- Complete the Research and Development application and note that you may need an IND

  https://redcapweb.carilionclinic.org/redcap/surveys/index.php?s=EE7LAYHFDF

- Initiate a discussion with the IRB and go to the Carilion Clinic IRB website (related sites)

https://carilionclinic.org/institutional-review-board#related-sites

Click FDA Information Sheets

"Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices

Clinical investigation of a marketed drug or biologic does not require submission of an IND **if all six** of the following conditions are met: 21 CFR 312.2(b)(1)*

I. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

II. it is not intended to support a significant change in the advertising for the product;

III. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

IV. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

V. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

VI. it does not intend to invoke 21 CFR 50.24.

§ 50.24 - Exception from informed consent requirements for emergency research

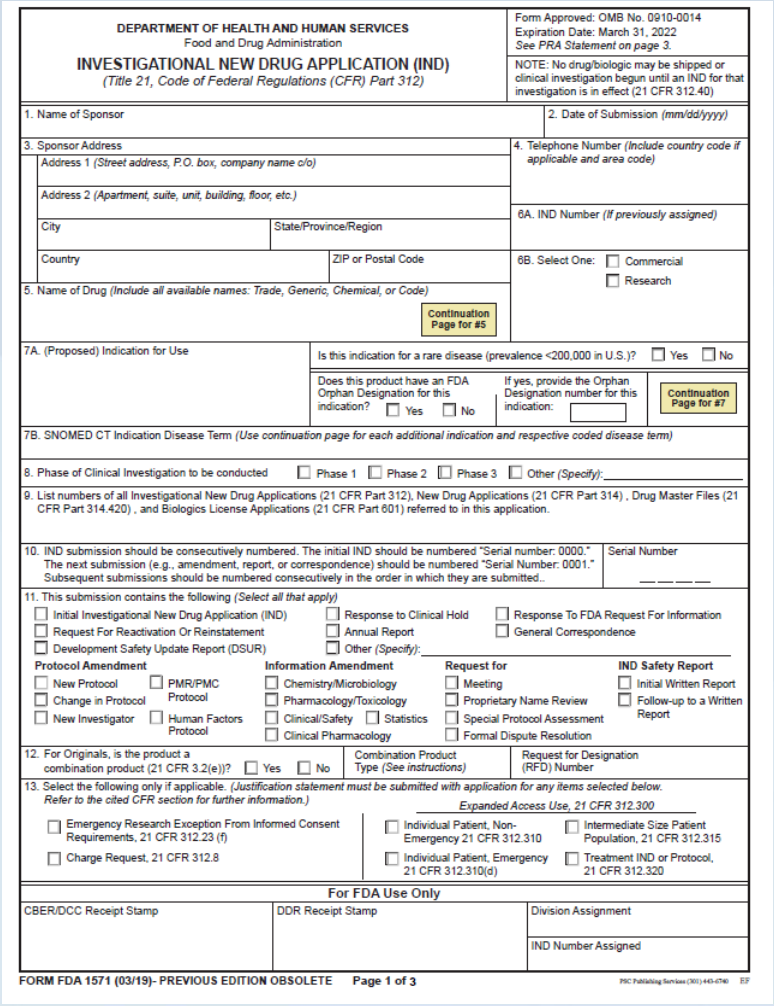
*If all six criteria are met, you may still need to submit an IND per Institutional and/or Carilion Clinic IRB requirement

IND Application Format

- Cover Sheet
- Table of Contents
- Introductory statement and a general investigative plan
- *Investigators Brochure*
- Protocol
- *Chemistry, Manufacturing and Control Information (CM&C)*
- *Pharmacology and Toxicology Information*
- *Previous human experience with the investigational drug*
- Other relevant information such as prior INDs

May not be needed if you are using a previously assigned IND number

IND Application Form 1571



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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: March 31, 2022
See PRA Statement on page 3.

NOTE: No drug/biologic 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 *(mm/dd/yyyy)*

3. Sponsor Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

4. Telephone Number *(Include country code if applicable and area code)*

6A. IND Number *(If previously assigned)*

6B. Select One: ☐ Commercial ☐ Research

5. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*

Continuation Page for #5

7A. (Proposed) Indication for Use

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #7

7B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*

8. Phase 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 Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics 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 *(Select all that apply)*

☐ Initial Investigational New Drug Application (IND)
☐ Request For Reactivation Or Reinstatement
☐ Development Safety Update Report (DSUR)
☐ Response to Clinical Hold
☐ Annual Report
☐ Other *(Specify)*: _____
☐ Response To FDA Request For Information
☐ General Correspondence

Protocol Amendment
☐ New Protocol ☐ PMR/PMC Protocol
☐ Change in Protocol
☐ New Investigator ☐ Human Factors Protocol

Information Amendment
☐ Chemistry/Microbiology
☐ Pharmacology/Toxicology
☐ Clinical/Safety ☐ Statistics
☐ Clinical Pharmacology

Request for
☐ Meeting
☐ Proprietary Name Review
☐ Special Protocol Assessment
☐ Formal Dispute Resolution

IND Safety Report
☐ Initial Written Report
☐ Follow-up to a Written Report

12. For Originals, is the product a combination product (21 CFR 3.2(e))? ☐ Yes ☐ No

Combination Product Type *(See instructions)*

Request for Designation (RFD) Number

13. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*

Expanded Access Use, 21 CFR 312.300

☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8
☐ Individual Patient, Non-Emergency 21 CFR 312.310
☐ Individual Patient, Emergency 21 CFR 312.310(d)
☐ Intermediate Size Patient Population, 21 CFR 312.315
☐ Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only

CBER/DCC Receipt Stamp | DDR Receipt Stamp | Division Assignment | IND Number Assigned

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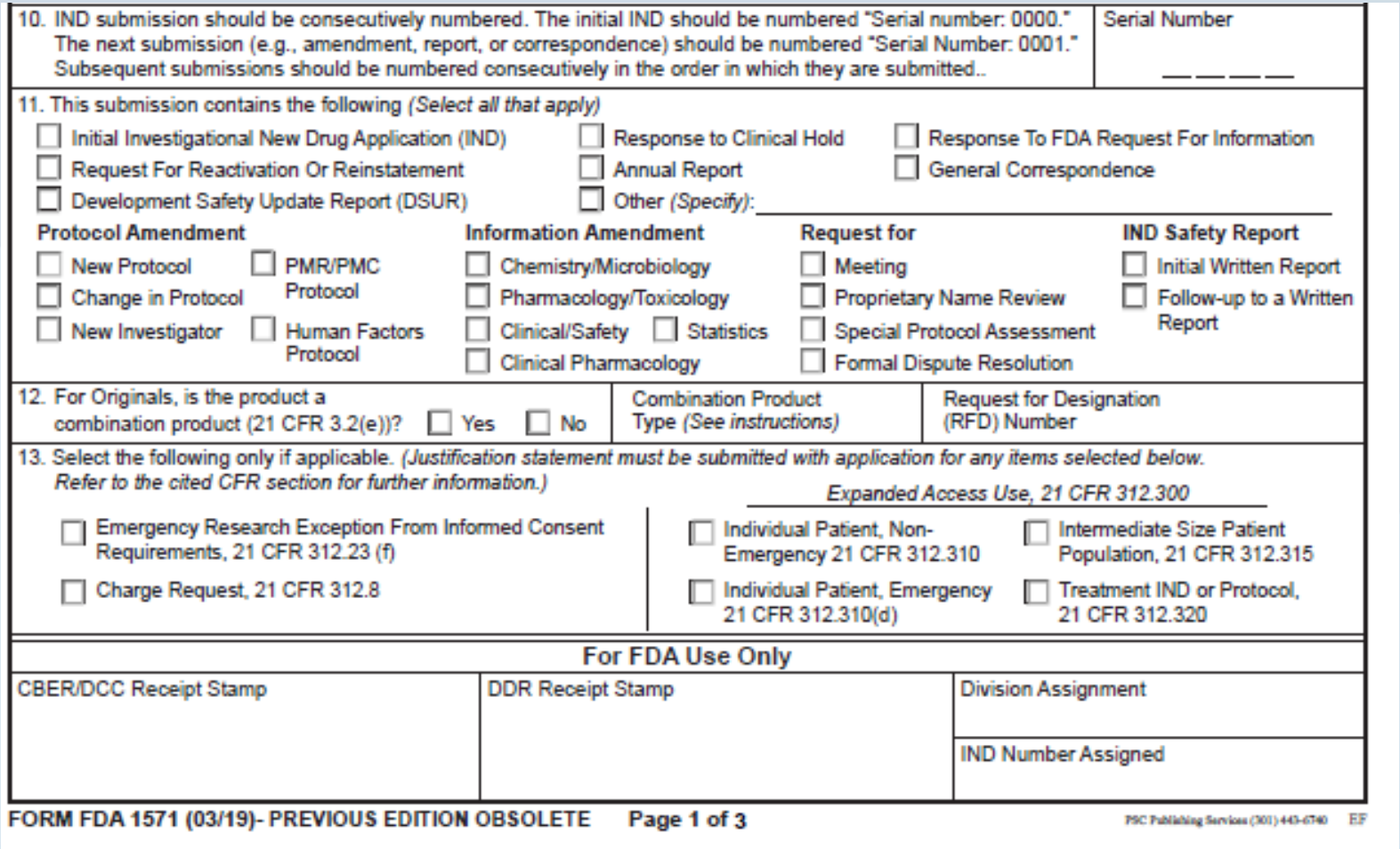
IND Form 1571



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Information Amendment

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CBER/DCC Receipt Stamp	DDR Receipt Stamp	Division Assignment
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14. Contents of Application – This application contains the following items *(Select 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 *(21 CFR 312.23(a)(6))*
  - ☐ a. Study protocol *(21 CFR 312.23(a)(6))*
  - ☐ b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
  - ☐ c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
- 6. Protocol *(Continued)*
  - ☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form 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))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

15. 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, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred *(use continuation page)*.

Continuation Page for #15

16. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations

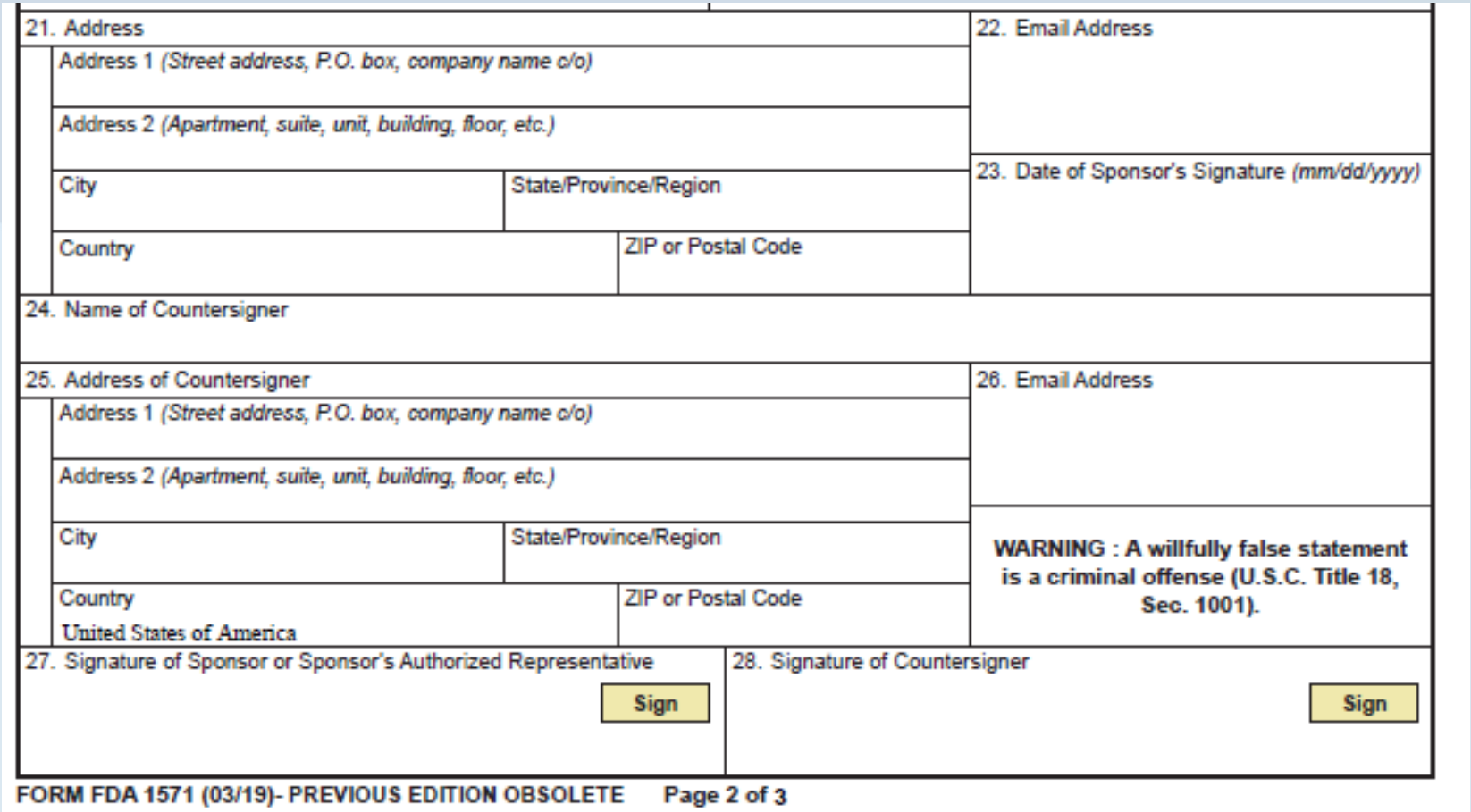
17. Name and Title of the person responsible for review and evaluation of information relevant to the safety of the drug

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 or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth 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.

18. Name of Sponsor or Sponsor's Authorized Representative

19. Telephone Number *(Include country code if applicable and area code)*	20. Facsimile (FAX) Number *(Include country code if applicable and area code)*

IND Form 1571



21. Address			22. Email Address
Address 1 *(Street address, P.O. box, company name c/o)*			
Address 2 *(Apartment, suite, unit, building, floor, etc.)*			23. Date of Sponsor's Signature *(mm/dd/yyyy)*
City	State/Province/Region		
Country		ZIP or Postal Code	
24. Name of Countersigner			
25. Address of Countersigner			26. Email Address
Address 1 *(Street address, P.O. box, company name c/o)*			
Address 2 *(Apartment, suite, unit, building, floor, etc.)*			
City	State/Province/Region		**WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).**
Country United States of America		ZIP or Postal Code	
27. Signature of Sponsor or Sponsor's Authorized Representative **Sign**			28. Signature of Countersigner **Sign**

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Sponsor-Investigator

- Pre-IND Consultation Program
  https://www.fda.gov/drugs/investigational-new-drug-ind-application/pre-ind-consultation-program
- Requesting a Pre-Assigned Application number
  https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number

This request will require a secure email account with FDA

Research and Development has these email accounts

Sponsor-Investigator

- Letter of Authorization
  - Sent to Drug Owner (Pharmaceutical/ Biotech) requesting that the FDA can access the Drug master file (DMF) in support of your IND application
    - FDA will act as the liaison in most cases
- FDA Form 1572 Statement of Investigator

Signed Submission of FDA Form 1571

- ✓ Sponsor-Investigator commits to not initiate the clinical trial until 30 days after acknowledgment that FDA has received the IND and not to begin if the study is put on clinical hold after review of application
- ✓ Sponsor-Investigator commits that study will be initiated approved by IRB and subject to continuing review
- ✓ Sponsor-Investigator will commit to conduct study in accordance with regulatory requirements

Clinical Hold

- Complete
  - Delay or suspension of all clinical work requested in IND submission
- Partial
  - Delay or suspension of only part of clinical work

IND Clinical Hold Response necessary to commence study

Annual Review

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

Individual study information. A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

Annual Review

Summary information. Information obtained during the previous year's clinical and nonclinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

Annual Review

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under § 312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

Useful Websites

- CDER (**Center for Drug Evaluation and Research)**

https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder

- **CBER (Center for Biologics Evaluation and Research)**

https://www.fda.gov/about-fda/fda-organization/center-biologics-evaluation-and-research-cber

- **IND Activity**

https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/ind-activity

- **Drugs**

https://www.fda.gov/drugs