Jefferson
Philadelphia University + Thomas Jefferson University

Sponsor-Initiated Investigational Drug Applications (INDs)

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May 2, 2019

A large portion of original INDs received are from non-commercial sources

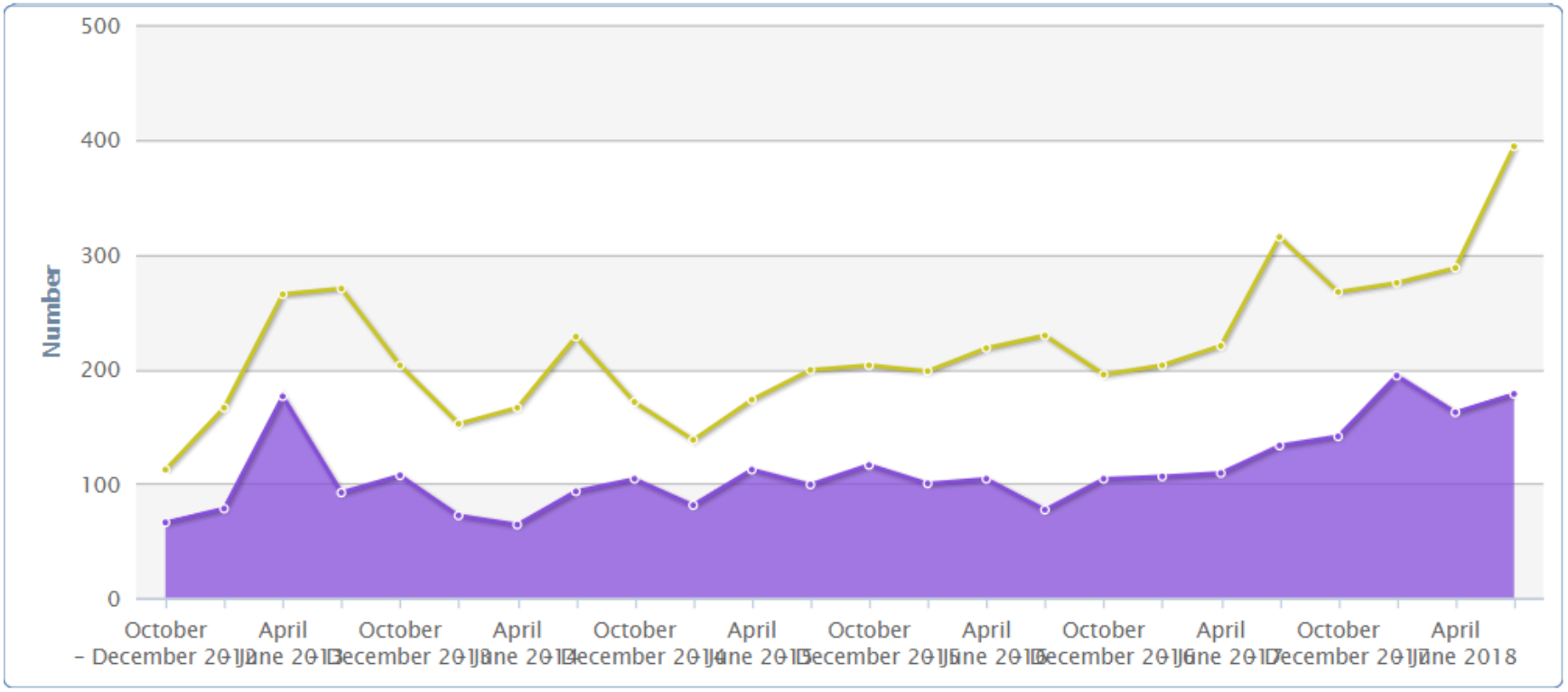
CDER ORIGINAL INDs RECEIVED
CALENDAR YEARS 1986 - 2008

Calendar Year	Commercial	Non-Commercial	Total
1986	332	1286	1618
1987	311	994	1305
1988	371	929	1300
1989	310	1004	1314
1990	382	1123	1505
1991	369	1661	2030
1992	370	2111	2481
1993	384	1848	2232
1994	341	1660	2001
1995	340	1394	1734
1996	389	1194	1583
1997	396	1186	1582
1998	441	1626	2067
1999	425	983	1408
2000	410	974	1384
2001	409	995	1404
2002	417	1338	1755
2003	391	972	1363
2004*	621	1216	1837
2005*	637	1297	1934
2006*	713	1150	1863
2007*	779	1810	2589
2008*	883	1156	2039

* Includes INDs for Therapeutic Biologic Products transferred from CBER to CDER
IND receipt figures exclude INDs meeting the requirements for exemption in accordance with 21 CFR 312.2(b)(4

- ~80-90% of INDs are for non-commercial research
- Emergency use INDs
- Non-profits
- Academia
  - **Sponsor-investigators**

The number of original Investigational New Drug (IND) applications to the US FDA have been steadily rising from 2013-2018



- Knowing how to navigate through the submission process is key to prevent delaying your research!

Some definitions

- ***Sponsor:*** Responsible for and initiates a clinical investigation
  - Individual, pharmaceutical company, academic institutions, etc.

- ***Investigator:*** Individual who actually conducts the study
  - Under whose immediate direction the investigational drug is administered or dispensed to a subject

- ***Sponsor-investigator:*** Individual who both initiates and conducts an investigation and under who immediate direction the investigational drug is administered or dispensed
  - **Does not include another entity other than an individual**
  - **Assumes responsibility as both sponsor and investigator; comply with FDA regulations as both**
  - **Submission and maintenance of an IND**

The IND is intended to ensure that subjects will not face undue risk or harm

- Primary objective:

- 1) assure safety and rights of subjects in all phases of an investigation and
- 2) In phases 2 and 3, help ensure that the quality of the clinical trial is adequate to evaluate drug effectiveness and safety

Step 1: Do I need an IND?

- Research involves a drug (as defined by the FD&C Act)
- Research is a clinical investigation (as defined in the IND regulations)
- The clinical investigation is not otherwise exempt from the IND requirements

  - ***Drug:*** intended for use in the **diagnosis**, **cure**, **mitigation**, **treatment** or **prevention** of disease

  - ***Clinical investigation:*** an **experiment** where drug administered/dispensed or used in one or more human subjects
    - **Randomized trial evaluating an unapproved marketed drug vs. use of a marketed drug for an unapproved use in practice**

- **If all 3 apply… then yes, you need an IND!**

Broad examples of various types of clinical research which may require an IND as a sponsor-investigator

- Clinical investigation using marketed drugs
- Studies using radiolabeled or cold isotopes
- Studies that may not necessarily be therapeutic, but affect bodily structure & function
  - Studies using endogenous compounds
  - Pathogenesis studies using modified organisms
- Studies using dietary supplements or foods
  - If they fall under the category by definition as a “drug”
- Bioequivalence/bioavailability studies (BA/BE studies)
  - May be exempt if certain criteria are met

Step 2a: How do I prepare for my initial IND submission?

- Sponsor-investigator information
- Investigator's brochure
- Clinical trial protocol
- Chemistry, manufacturing, and control (CMC) information
- Pharmacology & toxicology
- Summary of previous human experience

* In most cases (for marketed Rx or non-Rx drugs) information is provided in the product labeling

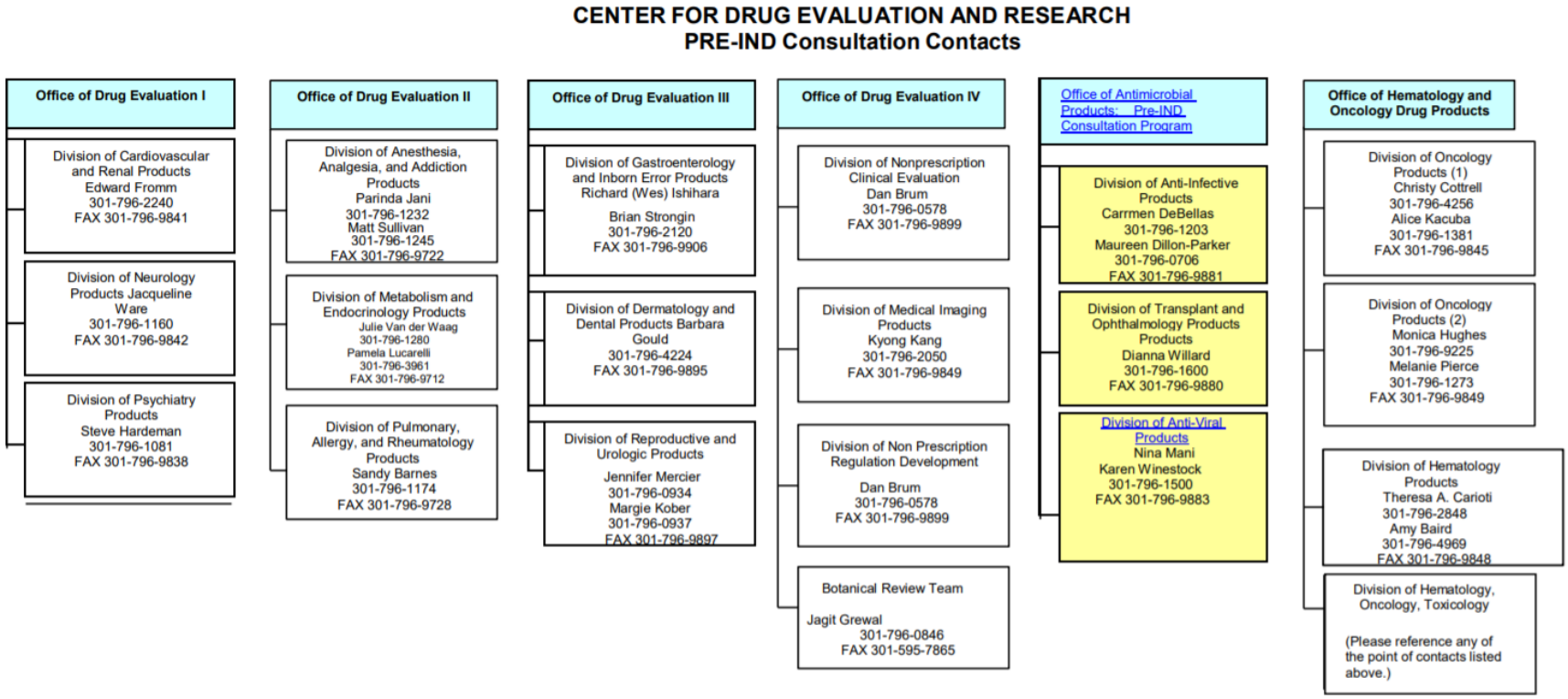
** In other instances (e.g. CMC) the commercial sponsor can provide sponsor-investigator with a letter to cross-reference an existing IND, NDA, or BLA

Step 2b: The FDA is huge… where do I submit (or call for help?)

- Find out who the appropriate center and review division are at the FDA

- **Center for Drug Evaluation and Research (CDER)**
  - Review for most drugs and biologics located in the Office of New Drugs (OND)
- **Center for Biologics Evaluation and Research (CBER)**
  - Review divisions for blood products, cellular, tissue, gene therapies, and vaccines

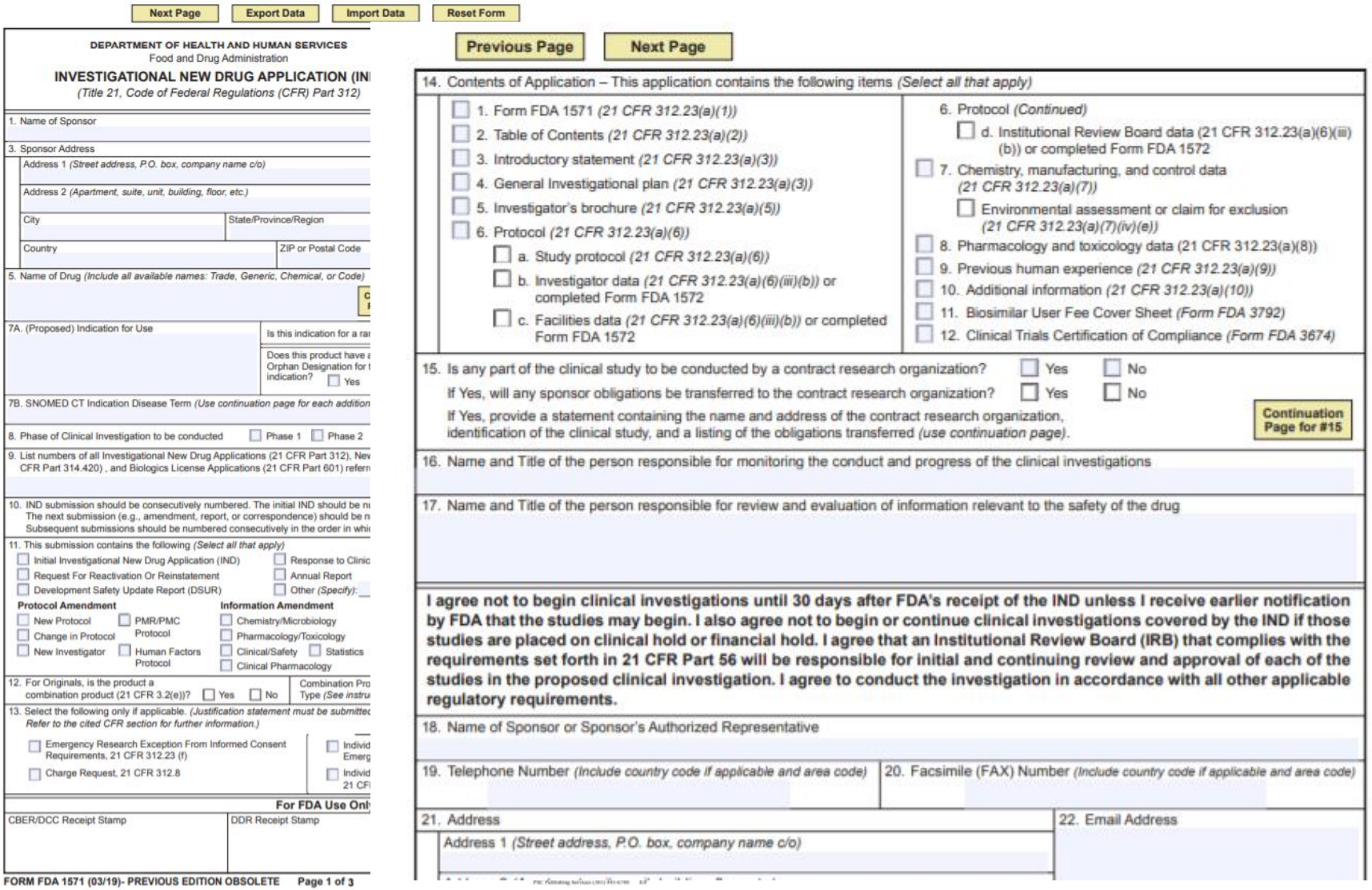
Step 2b: The FDA is huge… where do I submit (or call for help?)



Step 3: I have all my documents and contacts how do I prepare for submission?

- Step 3a: Prepare required forms
  - **Form FDA 1571 Investigational New Drug Application**
    - Sponsor-investigator's agreement to refrain from starting the study until 30 days
  - **Form FDA 1572 Statement of Investigator**
    - Sponsor-investigator agrees to comply with protocol, informed consent, IRB review, recordkeeping & AE reporting
    - **IRB approval does not need to be obtained before IND submission; signature on form 1572 is a commitment to IRB approval**
  - **Form FDA 3674 Certification of Compliance**
    - Require sponsor-investigator to register trials and submit results to clinicaltrials.gov

Form 1571- Sponsor-investigator's agreement



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IN
(Title 21, Code of Federal Regulations (CFR) Part 312)

1. Name of Sponsor

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

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

7A. (Proposed) Indication for Use | Is this indication for a ra | Does this product have a Orphan Designation for t indication? ☐ Yes

7B. SNOMED CT Indication Disease Term *(Use continuation page for each addition*

8. Phase of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2

9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), Nev CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) refer

10. IND submission should be consecutively numbered. The initial IND should be nu The next submission (e.g., amendment, report, or correspondence) should be n Subsequent submissions should be numbered consecutively in the order in whi

11. This submission contains the following *(Select all that apply)*

☐ Initial Investigational New Drug Application (IND) ☐ Response to Clinic
☐ Request For Reactivation Or Reinstatement ☐ Annual Report
☐ Development Safety Update Report (DSUR) ☐ Other *(Specify)*:

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

12. For Originals, is the product a combination product (21 CFR 3.2(e))? ☐ Yes ☐ No | Combination Pro Type *(See instru*

13. Select the following only if applicable. *(Justification statement must be submitte Refer to the cited CFR section for further information.)*

☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8
☐ Individ Emerg
☐ Individ 21 CF

For FDA Use Onl

CBER/DCC Receipt Stamp | DDR Receipt Stamp

FORM FDA 1571 (03/19)- PREVIOUS EDITION OBSOLETE Page 1 of 3

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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)*

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

22. Email Address

Form 1572 & 3674- Sponsor-investigator's statement & NCT registration

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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: February 28, 2019
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

Name of Clinical Investigator

Address 1	Address 2		
City	State/Province/Region	Country	ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select one of the following.)*

☒ 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 — CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

Address 1	Address 2		
City	State/Province/Region	Country	ZIP or Postal Code

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY — CONTINUATION PAGE for Item 4

Name of Clinical Laboratory Facility

Address 1	Address 2		
City	State/Province/Region	Country	ZIP or Postal Code

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

Name of IRB
Thomas Jefferson University - Institutional Review Board

Address 1	Address 2		
1015 Chestnut Street	Ste 1100		
City	State/Province/Region	Country	ZIP or Postal Code
Philadelphia	PA	USA	19107

6. NAMES OF SUBINVESTIGATORS *(If not applicable, enter "None")*

CONTINUATION PAGE – for Item 6

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 (2/16) PREVIOUS EDITION IS OBSOLETE. Page 1 of 3

Form Approved: OMB No. 0910-0616. Expiration Date: 3/31/2021. See PRA Statement below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance

Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. Name of Sponsor/Applicant/Submitter
2. Date of the Application/Submission
3. 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 and Fax Numbers *(Include country code if applicable and area code)*
   - (Tel):
   - (Fax):

PRODUCT INFORMATION

5. **For Drugs/Biologics:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).
For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)

Continuation Page for #5

APPLICATION / SUBMISSION INFORMATION

6. Type of Application/Submission Which This Certification Accompanies

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☐ 510(k) ☐ PDP ☐ Other

7. Include IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/ Other Number *(If number previously assigned)*
If BLA was selected in item 6, provide Supplement Number

8. Serial Number Assigned to Application/Submission Which This Certification Accompanies

CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes *(See instructions for additional information and explanation)*

☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, including 42 CFR part 11, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that the requirements of 42 U.S.C. 282(j), including any applicable provisions of 42 CFR part 11, have been met.

Certification Statement / Information section continued on page 2

Step 3: I have all my documents and contacts how do I prepare for submission?

- **Regulatory checklist**
  - **Forms 1571, 1572, & 3674**
  - **Cover letter**
  - **Table of Contents**
    - Introductory statement and general investigational plan
    - Investigator's Brochure
    - Protocol
    - CMC
      - Statement on drug packaging for **"Caution New Drug – Limited by Federal (or United States) law to investigational use"**
      - Statement requesting **categorical exclusion from an environmental assessment**
    - Pharmacology & Toxicology
    - Previous human experience with the investigational drug
    - Other important information
      - Drug dependence & abuse potential

Cover letter and table of contents

[Month XX, 201X]

Food and Drug Administration
Center for Drug Evaluation and Research
Division of [Therapeutic Area]
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

RE: **Initial Investigator New Drug Application**
Serial Number 0000

Dear Dr. [Division Director]:

We are submitting this initial application for a Sponsor-Investigator IND. We propose to evaluate [Drug generic name (Trade Name®)] under this IND for safety and efficacy for the treatment of [disease or condition].

This submission also contains the initial study protocol [Study Number] Protocol v. 1.0*/* entitled, "[XXX]." Approximately [XX] patients will be enrolled in this study.

[A brief description of the protocol]

[If applicable, Pharmaceutical Company] has agreed to provide study drug [XXX] for the duration of the above referenced research study at no charge to the study participants or to their insurance providers. In addition, they have provided a letter authorizing the FDA to refer to all relevant data included in their IND #[XXX].

If you have any questions regarding this submission, please contact myself or [Name of Sub-Investigator, MD] at [phone number] or [email address]. Dr. [Name of Sub-Investigator] can act on my behalf on any issue relating to this IND.

Per 21 CFR 312.20, please find three copies (1 original and 2 photocopies) of

- Investigational New Drug Application for [title of the study].
- Form FDA 1571

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4.2.3 Manufacture 10

Step 4: Time to submit!

- REMEMBER!
  - Send **3 paper copies** of your IND (1 original, 2 copies)
  - Can send a compact disk/USB drive to supplement paper copies
  - Divide submission with tabs and not colored paper
  - Be available for discussions via the phone
  - The FDA has **30 days** from the date of receipt to review the application
    - Within that time a project manager is assigned and review team assembled
    - Safe to proceed or clinical hold
  - Snail-mail via USPS to the appropriate center or review division
    - Electronic communications require certification

Summary Roadmap to submitting a sponsor-investigator IND