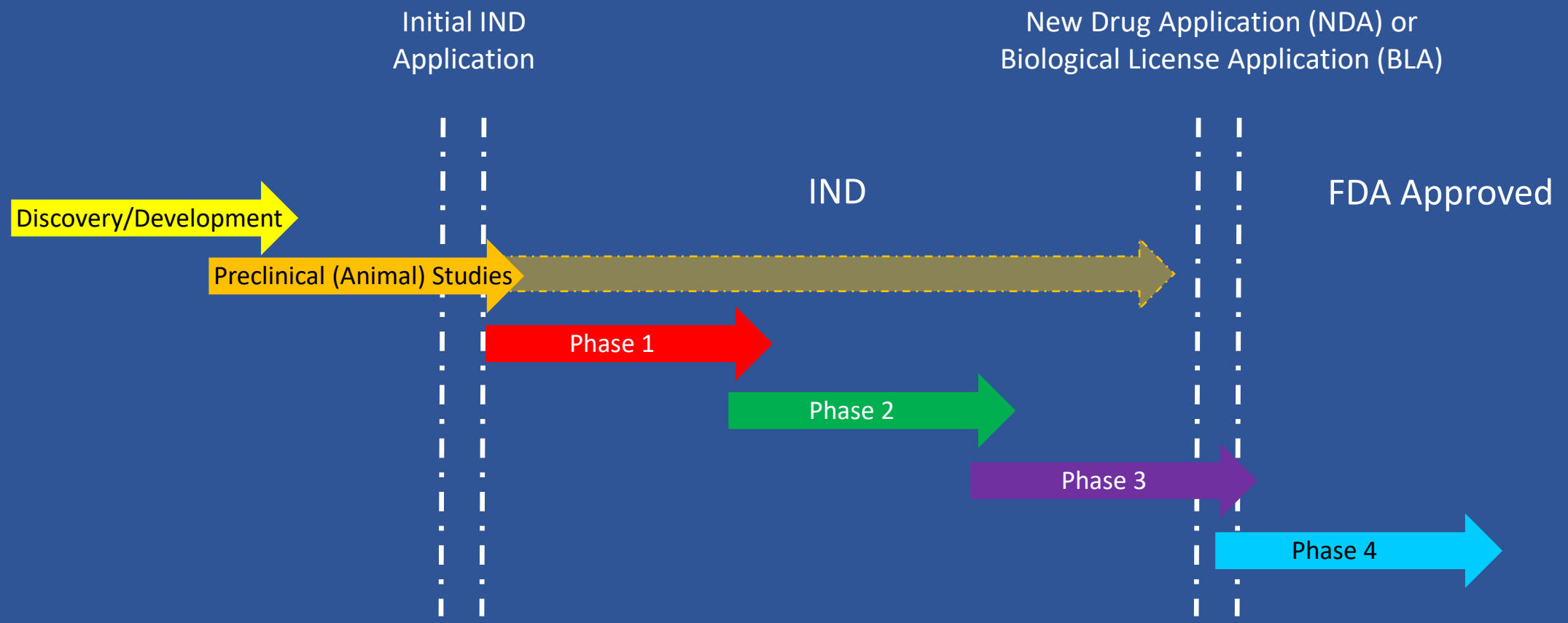
Everything You Need to Know about Holding an IND

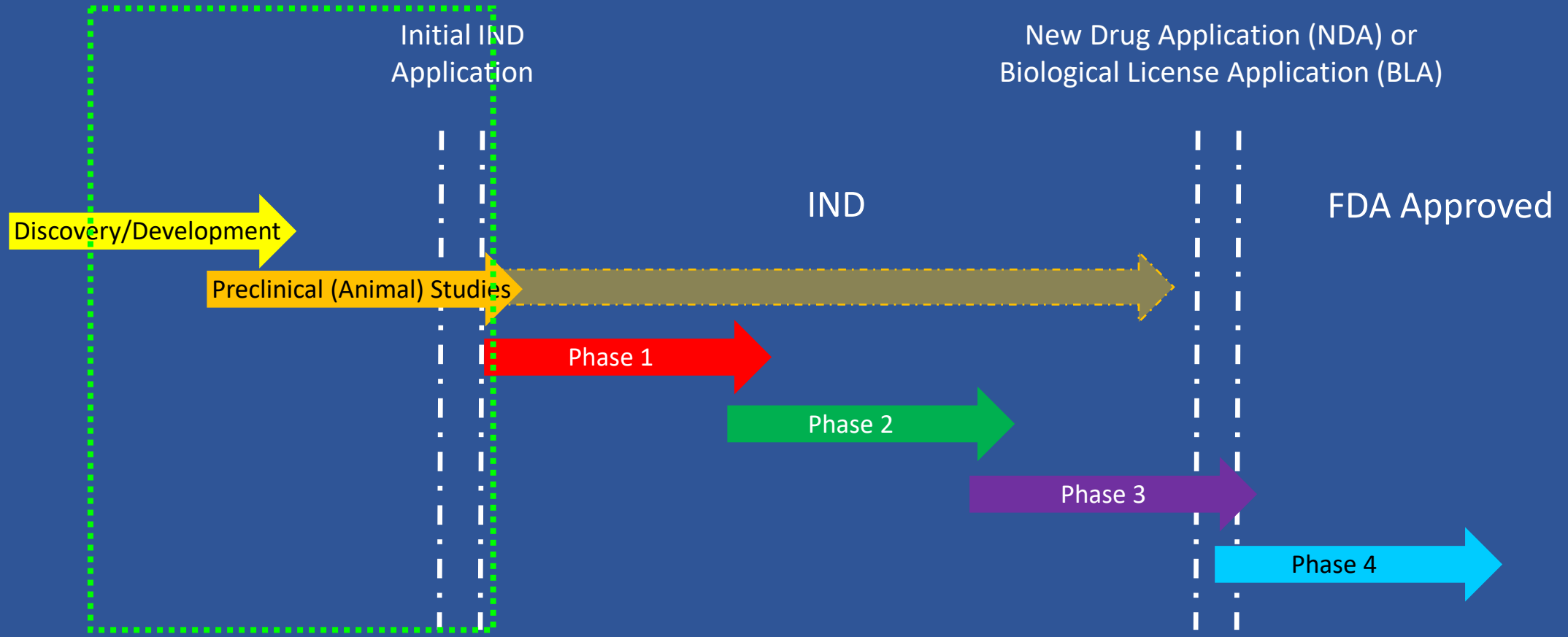
J. Kaitlin Morrison, PhD
Director of UNC Lineberger Sponsored Clinical Research
Assistant Professor of Medicine- Hematology
Kaitlin_Morrison@med.unc.edu

What is an Investigational New Drug Application (IND)?

- A request for authorization from the FDA to administer an investigational drug or biological product to humans
- Gives permission for interstate shipment of an IP



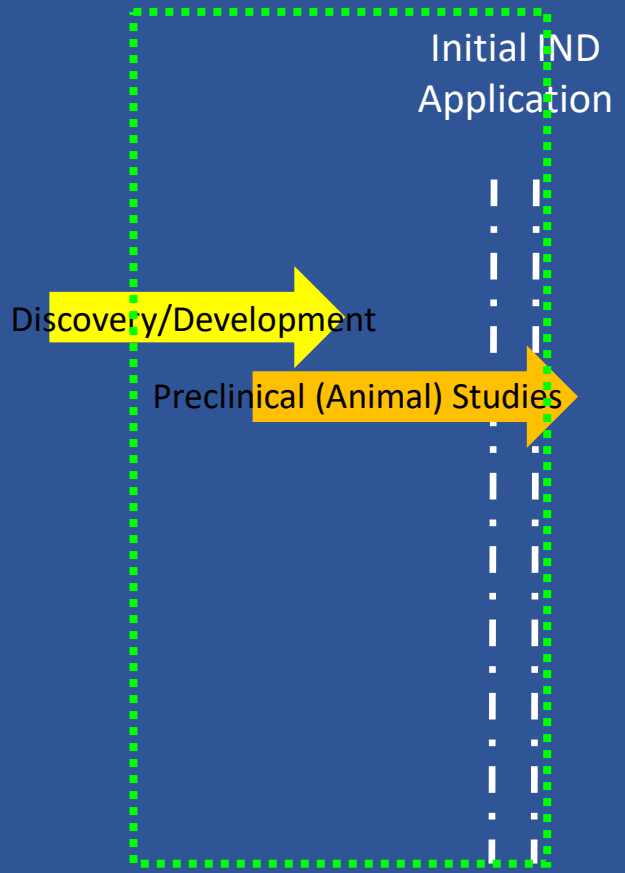
Initial IND Application



Preparation → Drafting IND → FDA Review → Safe to Proceed

Initial IND Applications

PRIOR TO THE IND SUBMISSION: WHAT YOU NEED TO DO



- Determine early if your study may need an IND
- Involve the IND Specialist early
  - Protocol Development meetings, planning, etc.
- Consider having a Pre-IND Meeting with FDA
- If pharma company is the manufacturer, then collect:
  - Letter of Authorization
  - Investigator Brochure
  - Template Risk Language for the ICF (if available)
- If UNC is the manufacturer
  - Finish pre-clinical studies
  - Complete validation of the manufacturing process

Preparation → Drafting IND → FDA Review → Safe to Proceed

Initial IND Applications

IND EXEMPTIONS

Your study must meet all of the following conditions to be exempt:

1. Not intended to support FDA approval of:
   - New indication
   - Significant change in the labeling
2. Not intended to support a significant change in advertising
3. Conducted in compliance with IRB and informed consent regulations
4. Conducted in compliance with promotion and charging for investigational drugs regulations
5. ***Does NOT involve a route of administration or dosage level or using a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks associated with the use of the drug product)***

Be careful! Make sure you refer to the rest of the guidance because FDA provides examples of studies that are NOT exempt:

- Studies with adjuvant chemotherapy
  - One reason why: studied population may have low risk of cancer recurring after surgery so treatment with any toxic therapy may significantly increase risk
- Studies involving substitution of a new agent of unproven activity when standard therapy provides a cure or increase in survival
- New drug combinations UNLESS adequately described in the literature
  - Due to the possible occurrence of synergistic toxicity

Initial IND Applications

EXAMPLE

Study STUDY XXXX does not intend to support FDA approval of a new indication, significant change in labeling or a significant change in advertising for the investigational product. The study will be submitted to the IRB and an appropriate ICF has been drafted. The investigational product is being given in the same way with the same frequency as many other clinical trials. However, when the Investigator submitted to the protocol to the PRC/SRC the following stipulation was received:

> **4) Upon consideration of the IND Exemption Letter provided, as well as the treatments involved, the PRC believes that it will be highly unlikely that this will be IND exempt. Accordingly, it is recommended that the PI consider starting the IND process, to not unduly delay the study.**

Why did this study require an IND?

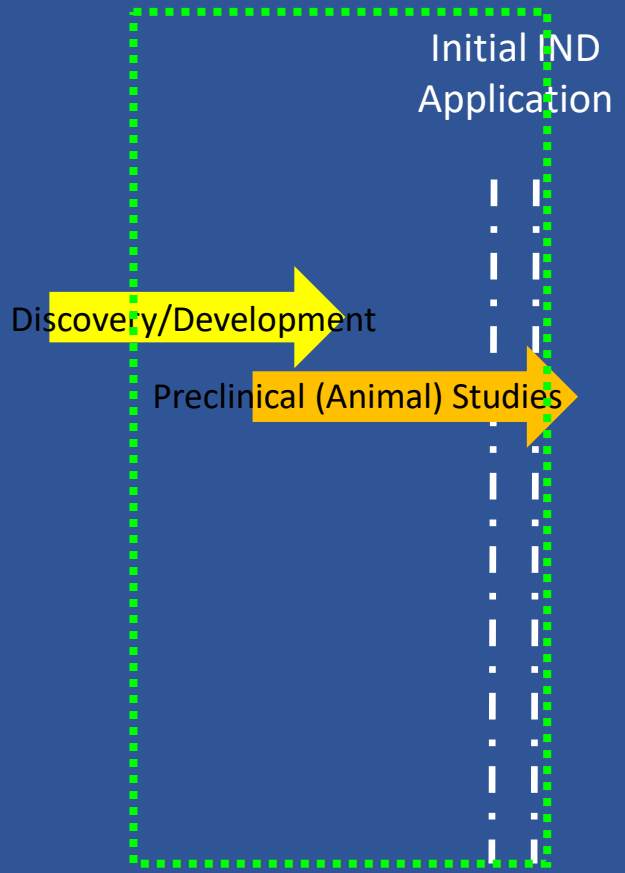
Investigational product = Not FDA Approved

For a study to be IND exempt the study drug used MUST be a commercial product*

*Even if the drug is FDA approved you MUST be using the commercial lot of the product for the study to be IND exempt.

Initial IND Applications

PRIOR TO THE IND SUBMISSION: WHAT YOU NEED TO DO



- Determine early if your study may need an IND
- Involve the IND Specialist early
  - Protocol Development meetings, planning, etc.
- Consider having a Pre-IND Meeting with FDA
- If pharma company is the manufacturer, then collect:
  - Letter of Authorization
  - Investigator Brochure
  - Template Risk Language for the ICF (if available)
- If UNC is the manufacturer
  - Finish pre-clinical studies
  - Complete validation of the manufacturing process

Preparation → Drafting IND → FDA Review → Safe to Proceed

Initial IND Applications
Pre-IND Meeting

What is a Pre-IND Meeting?

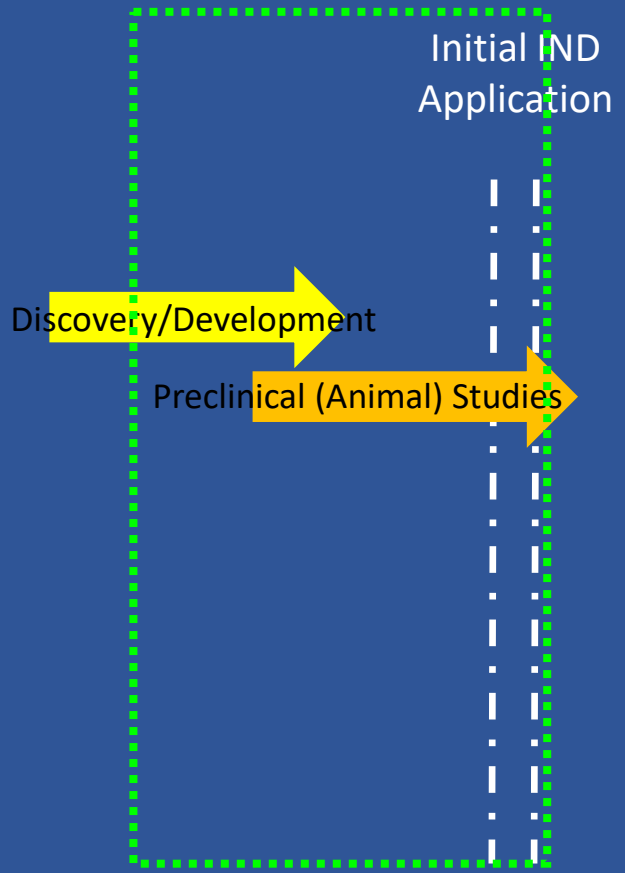
- Your opportunity to discuss your protocols/IND with FDA
- Your opportunity to ask FDA questions

- **How can it save you time?**
  - Identifying and avoiding unnecessary studies
  - Ensuring studies are designed to provide useful information
  - Gain FDA support for proposed strategy
  - Potentially minimizing potential for clinical hold
  - Provides creative exchange of ideas
  - Obtain regulatory insight
  - Minimize costs
  - Clearly defining endpoints and goals
  - Allows early interactions/negotiations with FDA
- **It is important to have one when there is/are:**
  - IP intended to treat a serious or life-threatening disease
  - Novel indication
  - No current guidance documents
  - Sponsors are new to drug development
  - Questions from the sponsor
  - Pharmacologic or toxicologic signals of concern
  - New molecular entity
- **When will the meeting occur?**
  - 6-8 weeks after the request

Preparation → Drafting IND → FDA Review → Safe to Proceed

Initial IND Applications

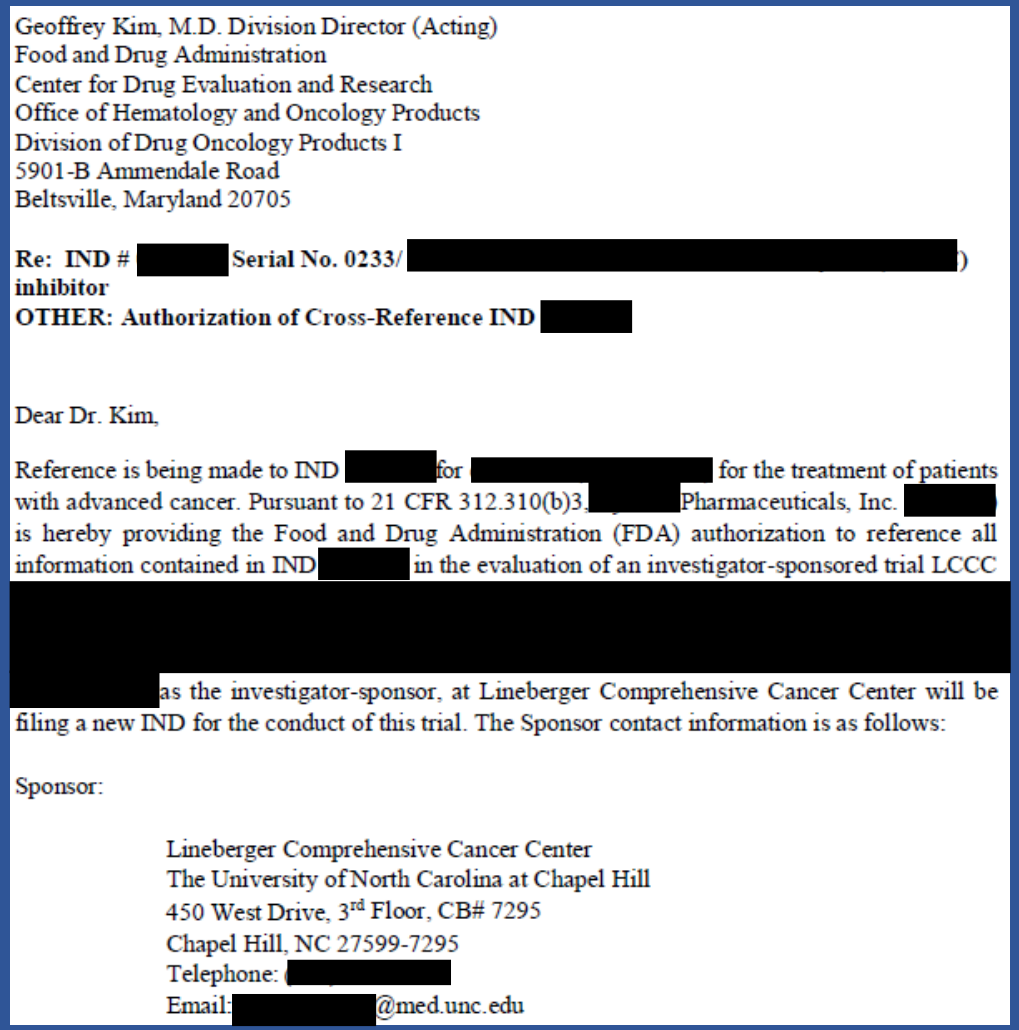
PRIOR TO THE IND SUBMISSION: WHAT YOU NEED TO DO



- Determine early if your study may need an IND
- Involve the IND Specialist early
  - Protocol Development meetings, planning, etc.
- Consider having a Pre-IND Meeting with FDA
- If pharma company is the manufacturer, then collect:
  - Investigator Brochure
  - Template Risk Language for the ICF (if available)
  - Letter of Authorization
- If UNC is the manufacturer
  - Finish pre-clinical studies
  - Complete validation of the manufacturing process

Preparation → Drafting IND → FDA Review → Safe to Proceed

Initial IND Applications
Letter of Authorization



Geoffrey Kim, M.D. Division Director (Acting)
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Drug Oncology Products I
5901-B Ammendale Road
Beltsville, Maryland 20705

Re: IND # [redacted] Serial No. 0233/ [redacted])
inhibitor
OTHER: Authorization of Cross-Reference IND [redacted]

Dear Dr. Kim,

Reference is being made to IND [redacted] for [redacted] for the treatment of patients with advanced cancer. Pursuant to 21 CFR 312.310(b)3, [redacted] Pharmaceuticals, Inc. [redacted] is hereby providing the Food and Drug Administration (FDA) authorization to reference all information contained in IND [redacted] in the evaluation of an investigator-sponsored trial LCCC [redacted] as the investigator-sponsor, at Lineberger Comprehensive Cancer Center will be filing a new IND for the conduct of this trial. The Sponsor contact information is as follows:

Sponsor:

Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
450 West Drive, 3rd Floor, CB# 7295
Chapel Hill, NC 27599-7295
Telephone: [redacted]
Email: [redacted]@med.unc.edu

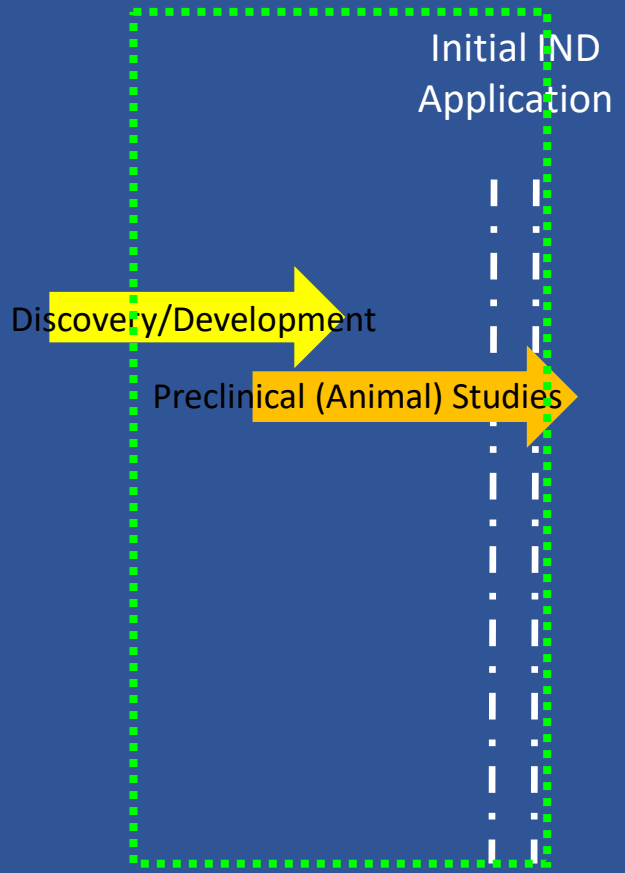
Authorizes FDA to look at the drug manufacturer's IND to review their confidential information in support of our IND:

- Chemistry, Manufacturing and Controls
- Pharmacology Toxicology
- Previous Human Experience

Preparation → Drafting IND → FDA Review → Safe to Proceed

Initial IND Applications

PRIOR TO THE IND SUBMISSION: WHAT YOU NEED TO DO



- Determine early if your study may need an IND
- Involve the IND Specialist early
  - Protocol Development meetings, planning, etc.
- Consider having a Pre-IND Meeting with FDA
- If pharma company is the manufacturer, then collect:
  - Investigator Brochure
  - Template Risk Language for the ICF (if available)
  - Letter of Authorization
- If UNC is the manufacturer
  - Finish pre-clinical studies
  - Complete validation of the manufacturing process

Preparation → Drafting IND → FDA Review → Safe to Proceed

Initial IND Applications

SUBMISSION PREPARATION

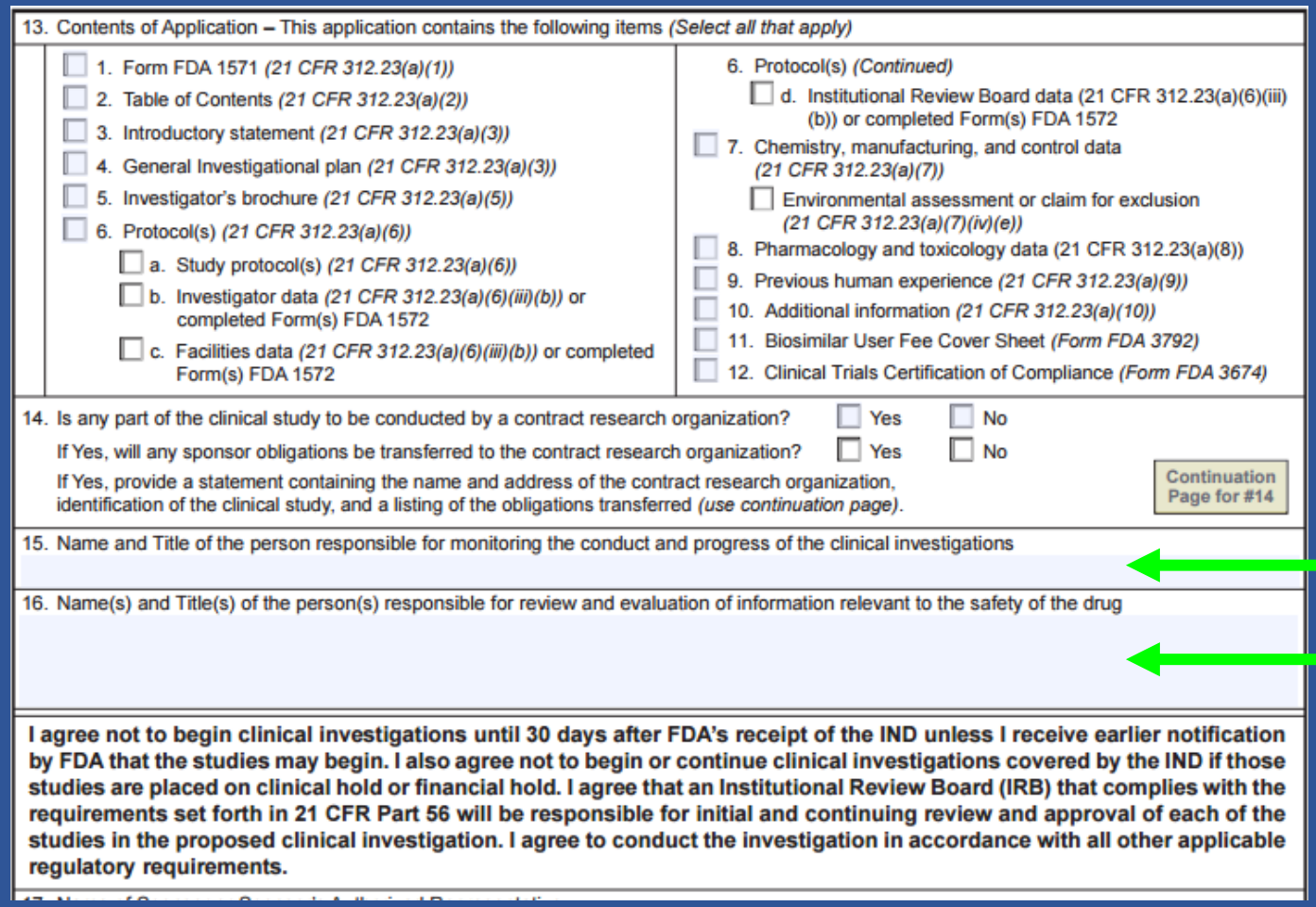
What goes into an initial IND Application?

1. Form FDA 1571
2. Table of Contents
3. Introductory Statement
   a. Name of Drug and active ingredients
   b. Pharmacological Class
   c. Structural formula
   d. Formulation
   e. Route of administration
   f. Objectives and Duration
   g. Status of drug in other countries
4. General Investigational Plan
   a. Rationale
   b. Indication
   c. Approach to evaluate treatment
   d. Drug Related Risks
5. Investigator's Brochure
6. Protocol
   a. Study Protocol
   b. Informed Consent Form
   c. Investigator and Facility Data (Form FDA 1572)
7. Chemistry, Manufacturing and Controls
8. Pharmacology and Toxicology
9. Previous Human Experience
10. Additional Information
    a. Drug Dependence and Abuse Potential
    b. Radioactive Drugs
    c. Pediatric Studies
11. Biosimiliar User Fee Cover Sheet
12. Clinical Trials Certification of Compliance

Preparation → **Drafting IND** → FDA Review → Safe to Proceed

Initial IND Applications

KNOWLEDGE TEST



13. 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(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
- 6. Protocol(s) *(Continued)*
  - ☐ 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))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

14. 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 #14

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

16. 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 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.

What is this form? Have any of you seen it before?

Form FDA 1571

- FDA's cover letter for all serial submission

Typically, the PI's name goes here for UNC studies

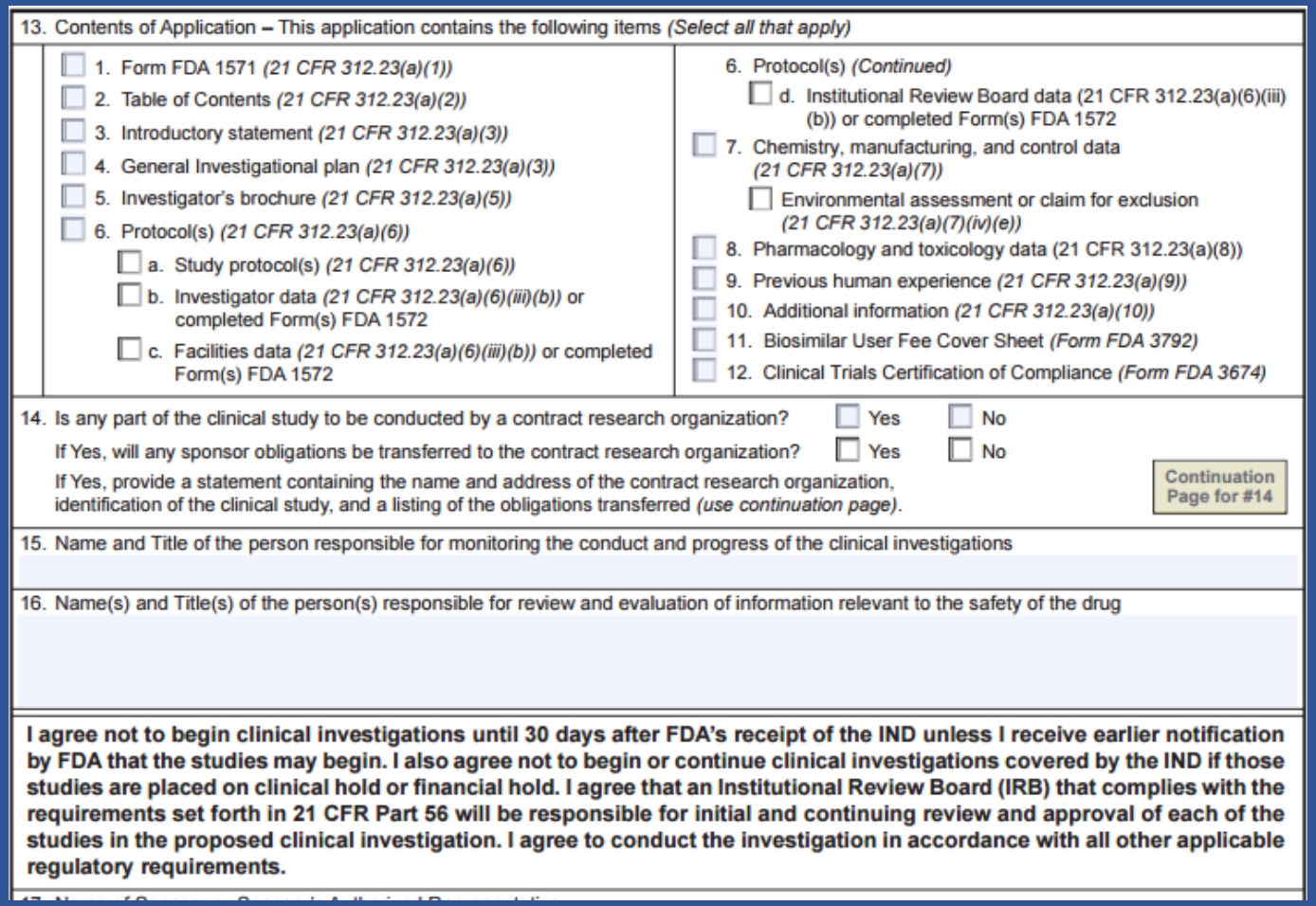
What does this mean?

- Agreeing to monitor conduct and progress of clinical investigations
- Agreeing to review and evaluate information relevant to the safety of the drug

Preparation → **Drafting IND** → FDA Review → Safe to Proceed

Initial IND Applications

FORM FDA 1571



13. 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(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
- 6. Protocol(s) *(Continued)*
  - ☐ 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))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

14. 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 #14

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

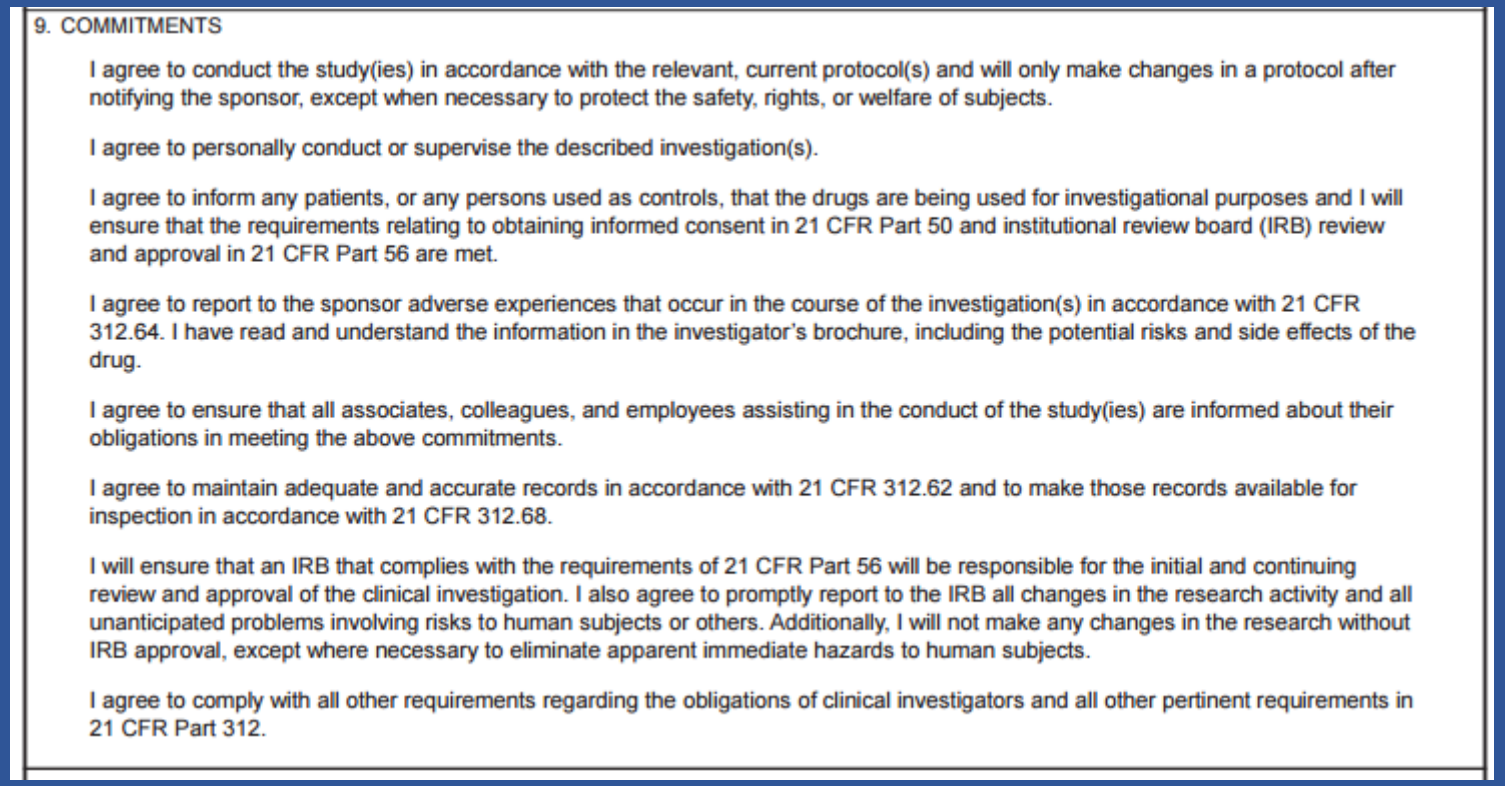
16. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug

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 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.

- What are you agreeing to when you sign it?
  - Not to begin until 30 day initial review is complete
  - Not to begin research if placed on clinical or financial hold
  - Agrees that an IRB that complies with the regulations will be responsible for initial and continuing review and approval of all studies under the IND
  - Agrees to conduct investigation in accordance with the regulatory requirements

Initial IND Applications

KNOWLEDGE TEST



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.

What is this form? Have any of you seen it before?

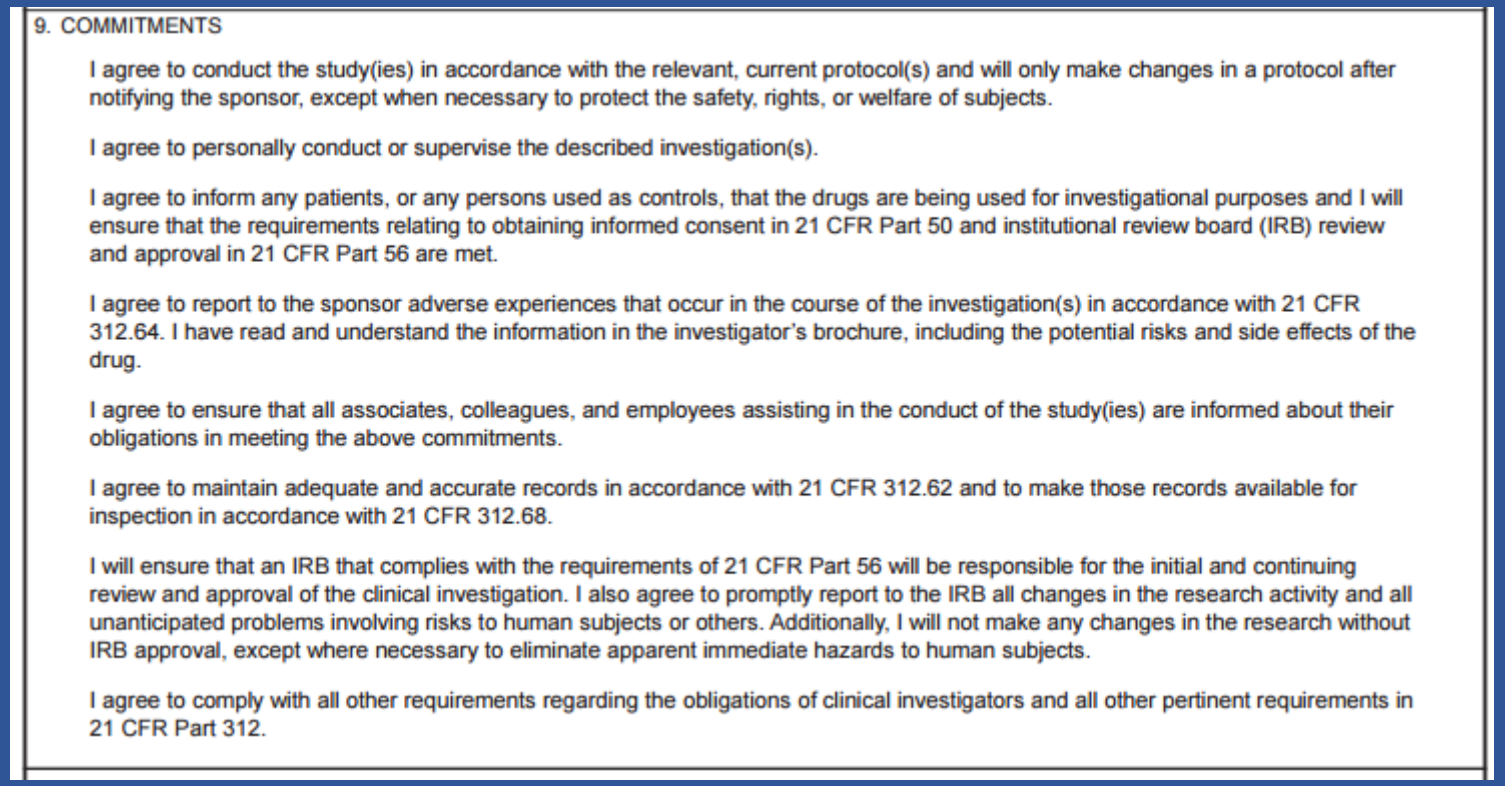
Form FDA 1572

- Statement of Investigator

Preparation → **Drafting IND** → FDA Review → Safe to Proceed

Initial IND Applications

FORM FDA 1572



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.

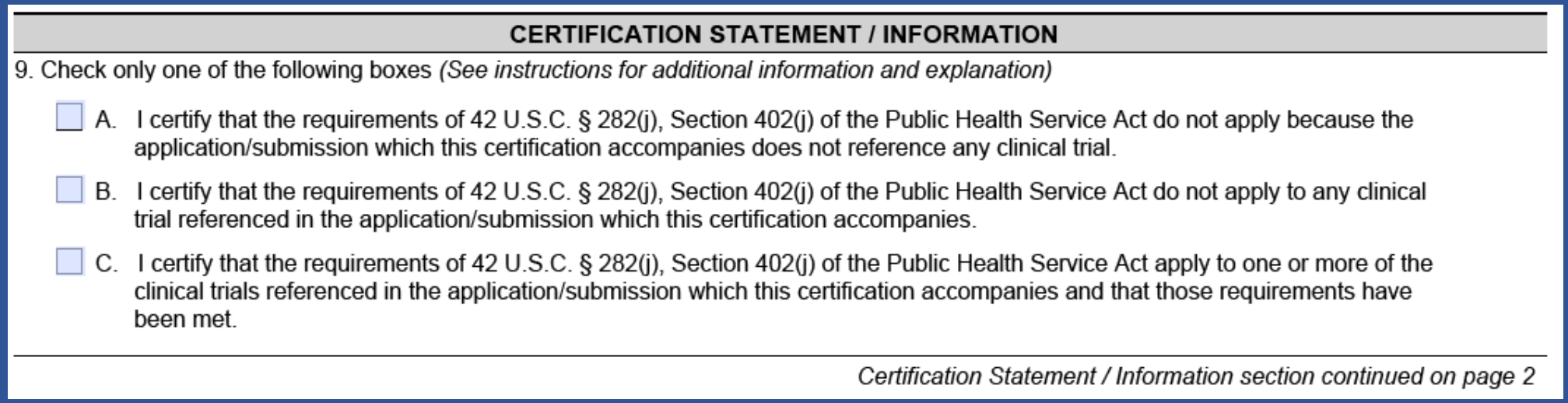
I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

- Conduct study according to protocol
- **Personally** conduct or supervise
- Tell subjects using an IP
- Obtain informed consent
- Obtain IRB review and approval
- Read and Understood the IB
  - Including risks and side effects
- Ensure all associate, colleagues and employees are informed about the obligations
- Maintain adequate and accurate records
- Make records available for inspections
- Report all UPRISOs to the IRB
- Not to make changes to research without IRB approval
  - Except to eliminate apparent immediate hazards to human subjects
- **Follow all IND regulations**

Preparation → **Drafting IND** → FDA Review → Safe to Proceed

Initial IND Applications

KNOWLEDGE TEST



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 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 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 those requirements have been met.

Certification Statement / Information section continued on page 2

What is this form? Have any of you seen it before?

Form FDA 3674

- Certification of compliance with clinicaltrials.gov
- Determination of whether your study requires results reporting on clinicaltrials.gov

Initial IND Applications
SUBMITTED TO FDA
What happens next?

1. Start your 30-Day FDA Review- FDA confirms receipt of IND
2. FDA may request additional information

- Better Dose Rationale

Potential Hold Comments:

Regarding the Study Design:

- You propose the starting dose [redacted] at [redacted] Please provide your rationale to support this as the only dose for the first-in-human product. Your justification in the IND submission is based on the Lee publication and fails to address that that product has a different construct ([redacted] Even minor changes in the construct of a [redacted] can affect the safety profile and therefore determination of a tolerable dose with an efficacy signal may be justified.

- Copy of the Informed Consent Form

From: Cross Jr, Frank H [mailto:Frank.CrossJr@fda.hhs.gov]
Sent: Thursday, March 31, 2016 2:26 PM
To: Morrison, Kaitlin <kaitlin_morrison@med.unc.edu>
Cc: [redacted] Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>; Dinin, Jeannette <Jeannette.Dinin@fda.hhs.gov>; Kacuba, Alice <Alice.Kacuba@fda.hhs.gov>
Subject: FDA Request: New IND [redacted]
Importance: High

Dear [redacted]

We have received your new IND [redacted] Please send a copy of the protocol and consent in MS Word, by return e-mail.

Please send by 12:00 pm, EDT, Monday, April 4, 2016.

Please cc all on your response.

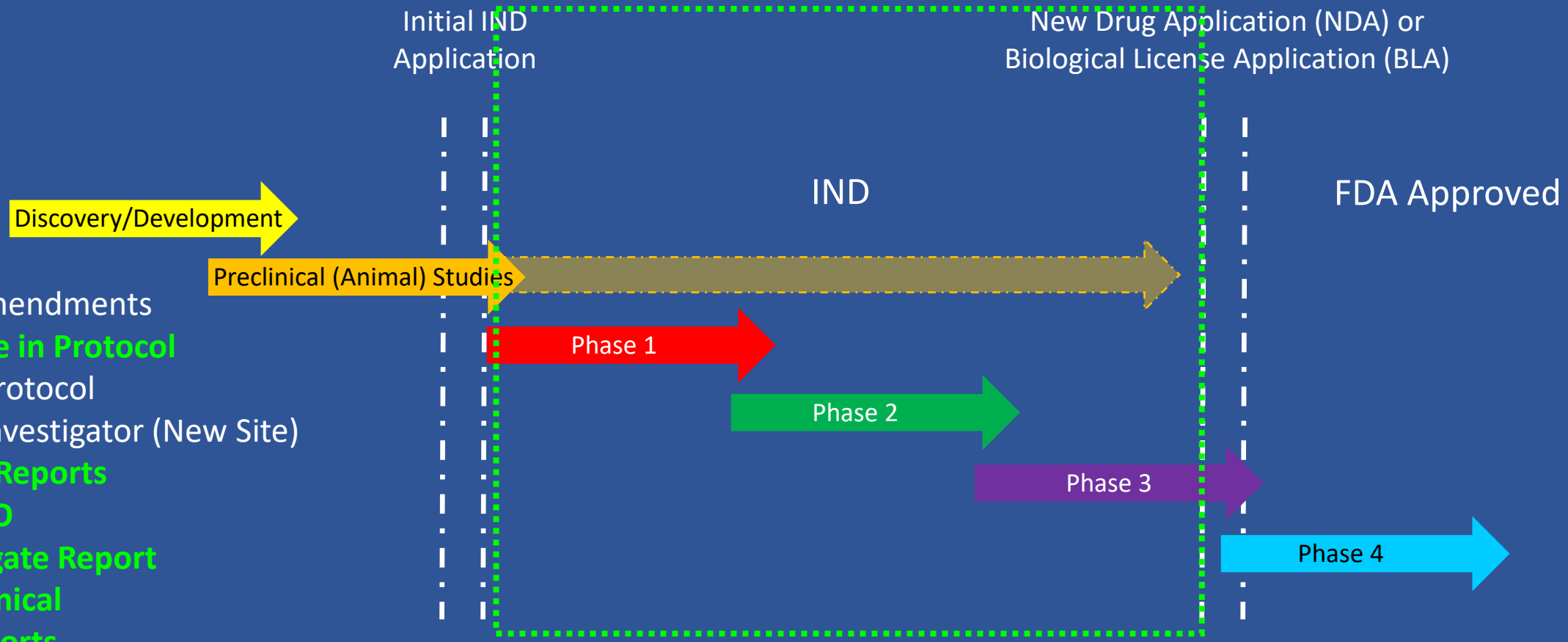
Preparation → Drafting IND → **FDA Review** → Safe to Proceed

Initial IND Applications
SUBMITTED TO FDA
What happens next?

1. Start your 30-Day FDA Review
2. FDA may request additional information
3. 30-day clock ends
   - Safe to Proceed Letter
   - Clinical Hold

Preparation → Drafting IND → **FDA Review** → Safe to Proceed

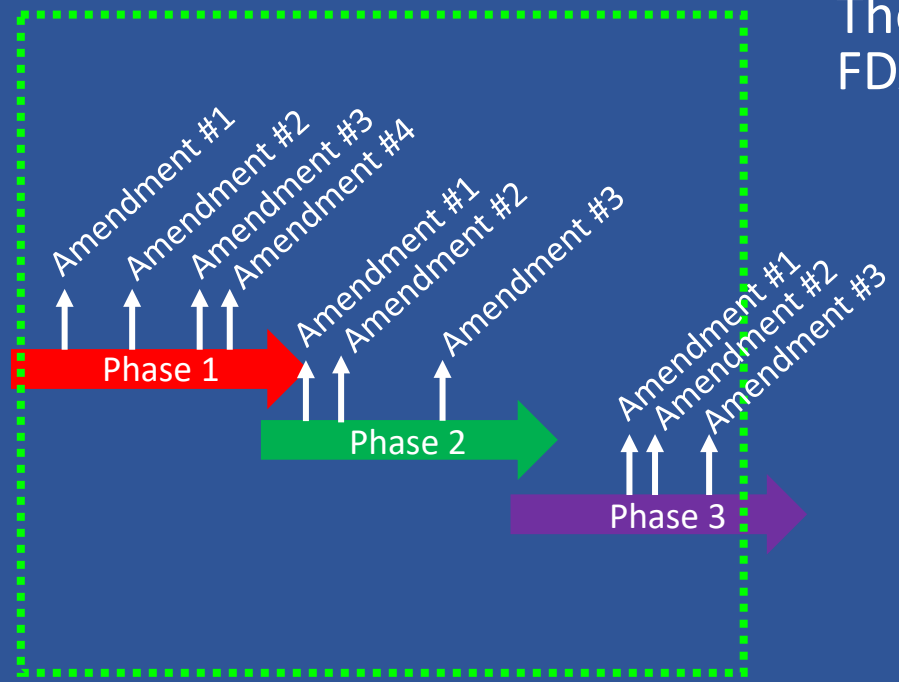
IND Application Maintenance



- Protocol Amendments
  - **Change in Protocol**
  - New Protocol
  - New Investigator (New Site)
- **IND Safety Reports**
  - **UPIRSO**
  - **Aggregate Report**
  - **Pre-clinical**
- **Annual Reports**
- **Continued Communication with FDA**

Preparation → Drafting IND → FDA Review → **Safe to Proceed**

IND Application Maintenance
Protocol Amendment- Change in Protocol



QUIZ

The Following Types of Protocol Amendment MUST be Submitted to FDA:

A: Any Increase in Drug Dosage

B: Significant Increase in # of Subjects

C: Addition of a Control Group

D: Any Significant Change to Study Design

E: Any Increase in Duration of Drug Exposure

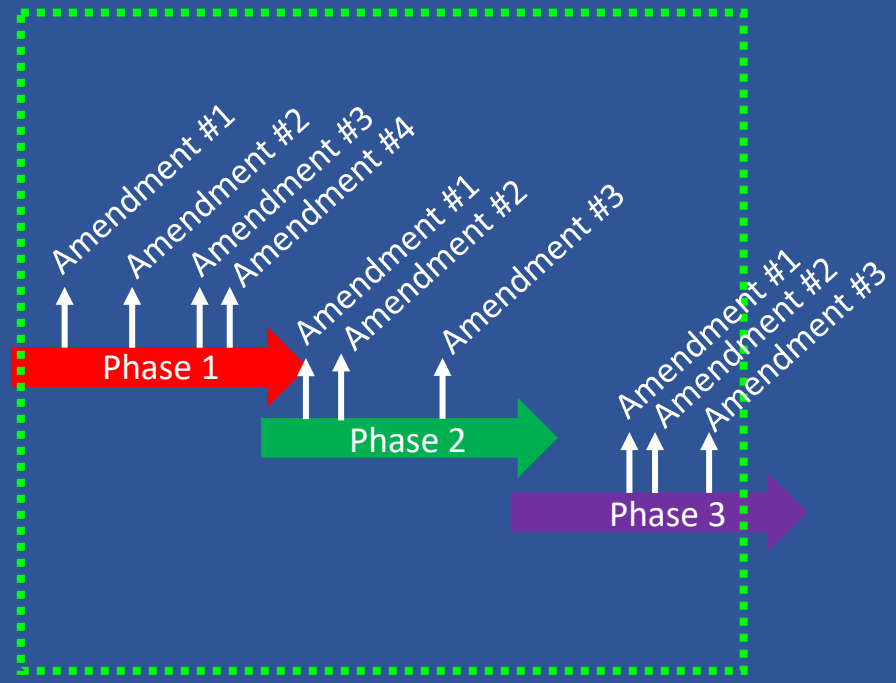
F: Removal of a Control Group

G: Addition of a Test or Procedure to Improve Monitoring For and Reduce Risk of a Side Effect or AE

H: Removal of a Test Intended to Monitor Safety

I: All Protocol Amendments

IND Application Maintenance
Protocol Amendment- Change in Protocol



ANSWER

The Following Types of Protocol Amendment MUST be Submitted to FDA: **Answers A-H**

Although you are not required to submit all protocol amendments to FDA it is highly encouraged and standard practice in the CPO.

IND Application Maintenance
Protocol Amendment- Change in Protocol

KNOWLEDGE TEST

Protocol Amendment: "The frequency of ophthalmic exams was reduced and are now only required at screening and as clinically-indicated due to the presence of ocular symptoms"

Does this protocol amendment require FDA submission?

YES!

This is the Removal of a Test Intended to Monitor Safety

IND Application Maintenance
Protocol Amendment- Change in Protocol

WHAT ACTUALLY HAPPENED

- PI didn't submit to FDA
- In retrospect the PI wouldn't have submitted because for SOC the PI would not have performed the additional eye exams that were removed
- HOWEVER, 6 months later when the protocol amendment was submitted:

From: Cohen, Rebecca [mailto:Rebecca.Cohen@fda.hhs.gov]
Sent: Tuesday, July 26, 2016 5:10 PM
To: [redacted]
Subject: [redacted]-FDA Correspondence-Information Request
Importance: High

Good Afternoon [redacted]

We are currently reviewing the protocol change in the amendment submitted June 9, 2016, for IND [redacted], and have the following Clinical Request for Information. Please address these and provide your response via email to me by close of business Monday, August 8, 2016 (EST). Please ensure that you include a tracked changes version of your protocol, with the changes requested. If after review by the Clinical Reviewer the changes are found acceptable, follow with a formal submission of your revised documents to your IND [redacted]

In order to capture ocular toxicity which may be asymptomatic, please revise the protocol to include ophthalmological evaluations periodically during treatment, in addition to any time a patient reports visual disturbances. Alternatively, provide a rationale including any available data, to support the reduced frequency of ophthalmic examinations.

Please confirm receipt of this email.

Rebecca Cohen, RN, MPH, OCN
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Oncology Products 2/ Office of Hematology and Oncology Products
Center for Drug Evaluation and Research/ Food and Drug Administration
Rebecca.Cohen@fda.hhs.gov

IND Application Maintenance
Protocol Amendment- Change in Protocol

WHAT ACTUALLY HAPPENED

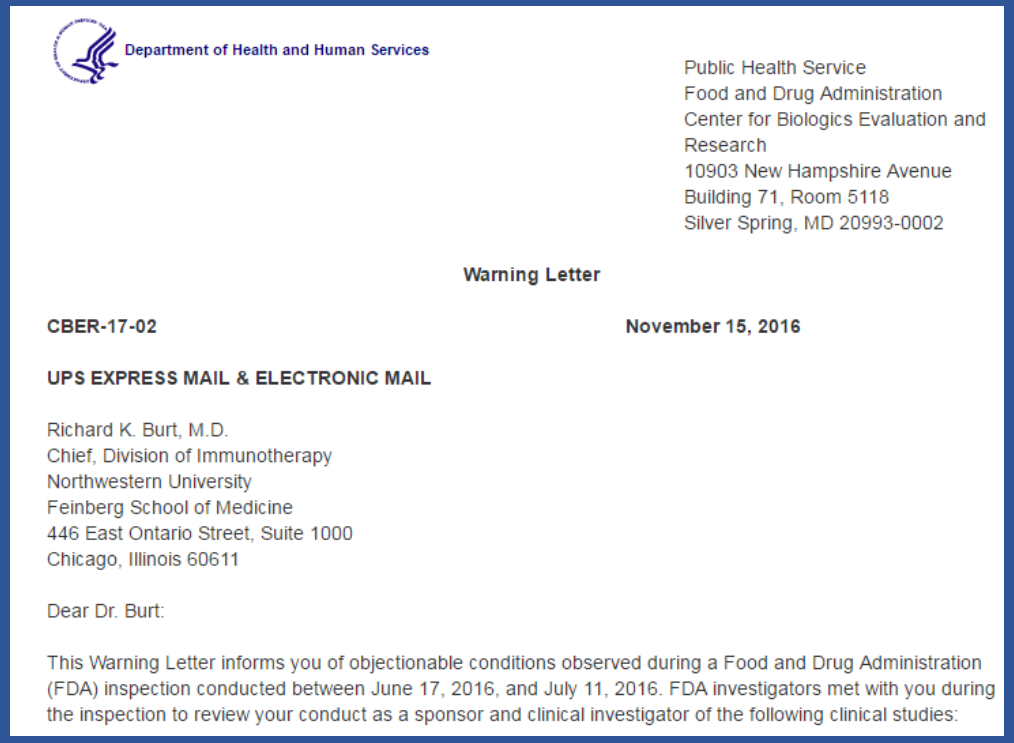
- PI didn't submit to FDA
- In retrospect the PI wouldn't have submitted because for SOC the PI would not have performed the additional eye exams that were removed
- **Helpful Hint:** Before amending the protocol, make sure that you are not eliminating anything FDA specifically asked for:

We are currently reviewing your IND submission (IND [redacted] for "[redacted]". Our Clinical Reviewer has the following clinical comments (potential hold comments) and requests for protocol revision. Please provide your response to me (revised document in tracked changes) via email by close of business, **Thursday, June 28, 2012**, or sooner if possible. If after review these changes are found acceptable by the Clinical Reviewer, please follow with a formal submission of your final revised protocol to the IND ([redacted]).

Potential Hold Comments:

1. The protocol proposes on page 44, Table 6.1, Time and Events, an ophthalmologic exam at baseline. Considering the available experience with [redacted] and [redacted] inhibitors, revise the protocol to include additional periodic monitoring for visual acuity, ophthalmologic evaluation, and/or imaging studies to assess for ocular complications. Alternatively, provide justification for not performing additional periodic ophthalmic examinations in order to mitigate the risk of developing retinal venous occlusion or central serous retinopathy.

IND Application Maintenance
Protocol Amendment- Change in Protocol
WHAT COULD HAVE HAPPENED



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Building 71, Room 5118
Silver Spring, MD 20993-0002

Warning Letter

CBER-17-02 **November 15, 2016**

UPS EXPRESS MAIL & ELECTRONIC MAIL

Richard K. Burt, M.D.
Chief, Division of Immunotherapy
Northwestern University
Feinberg School of Medicine
446 East Ontario Street, Suite 1000
Chicago, Illinois 60611

Dear Dr. Burt:

This Warning Letter informs you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted between June 17, 2016, and July 11, 2016. FDA investigators met with you during the inspection to review your conduct as a sponsor and clinical investigator of the following clinical studies:

2. You failed to submit a protocol amendment to FDA when there was a significant change in protocol design. [21 CFR § 312.30(b)(1)(ii) and 312.30(b)(2)(i)(a).] Further, you failed to submit a protocol amendment to FDA when new investigators were added to carry out a previously submitted protocol within 30 days of the investigators being added. [21 CFR § 312.30(c).]

IND Application Maintenance
Protocol Amendment- Change in Protocol

KNOWLEDGE TEST

Study Drug: Pembrolizumab

Protocol Amendment: Switching From Investigational Lot to Commercial Supply

Does this protocol amendment require FDA submission?

YES!

You also need to cross reference the NDA instead of the IND

IND Application Maintenance
Protocol Amendment- Change in Protocol

EXAMPLE

- FDA initially asks questions about the drug supply, so we need to be sure to update them when it changes:

I am Regulatory Project Manager assigned to IND [redacted] for Keytruda, for which you serve as the authorized representative on behalf of [redacted]

The Clinical reviewer has the following questions regarding [redacted]

Please provide a response to the below requested information as soon as possible:

1. What is the source of Keytruda that is being supplied for your study (i.e. commercial sponsor, pharmacy, etc.)?

2. If the manufacturer is supplying the drug for your study, how does the product that you are proposing to use in your study differ from the lawfully marketed product?

3. Is the product being supplied for the study made in an FDA approved manufacturing facility using an FDA approved manufacturing process?

Kindly provide an electronic response to the above requested information to Ruth.Maduro@fda.hhs.gov by **3:00pm on Tuesday, September 1, 2015**, or sooner if possible.

I can be reached at Ruth.Maduro@fda.hhs.gov and (240)402-4232. Kindly confirm receipt of this email communication.

IND Application Maintenance
Protocol Amendment- Change in Protocol
QUIZ

When Is the Earliest That You Can Act on a Protocol Amendment:

A. 30 Days After FDA Receipt
B. 30 Days After FDA Receipt and After IRB Approval
C. After IRB Approval
D. After FDA Receipt and IRB Approval

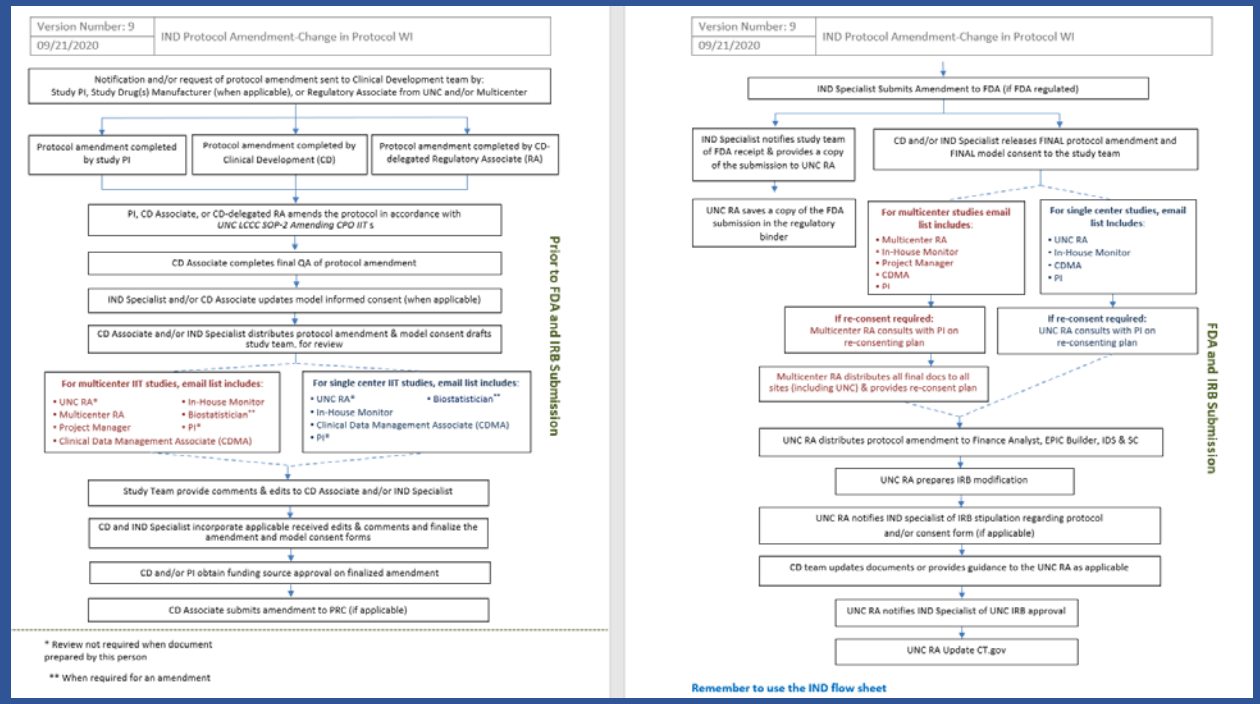
ANSWER: D- After FDA Receipt and IRB Approval

However, it is **always recommended** that you check in with your FDA Project Manager **first.**

IND Application Maintenance
Protocol Amendment- Change in Protocol

WHAT YOU NEED TO DO:

- Amend the protocol and ICF
- Goal to submit to FDA prior to the preparation of the IRB submission
  - Clean and Tracked protocol
  - Clean and Tracked consent form
- Recommend checking in with the FDA project manager about any initial comments or concerns
- Implement the amendment after BOTH IRB approval and FDA receipt



IND Application Maintenance
Protocol Amendment- Change in Protocol

WHAT ABOUT SINGLE SUBJECT EXCEPTIONS?

Points to Consider:

- Are you changing the protocol in any of the ways that require FDA approval?
- SSEs don't make the protocol deviation "magically disappear" FDA still considers them to be deviations

EXAMPLE

Protocol Language: "Adequate pulmonary function with FEV1, FVC and DLCO >50% of expected corrected for hemoglobin. Exceptions may be allowed for patients with pulmonary involvement after discussing with PI"

FDA's Response: "Section 4.3.10 describes **intent to violate the protocol** by **enrolling ineligible patients**. This language should not appear in the protocol as it is **not compliant** with Good Clinical Practices."

One of the most frequent reasons for an Investigator to receive a Warning letter is for the enrollment of ineligible subjects

IND Application Maintenance
Protocol Amendment- Change in Protocol

KNOWLEDGE TEST

Subject 048 comes to clinic for consideration of Cycle 17. Her scans show a 30% increase in her liver lesions. She, however, has no new lesions. The protocol indicates that treatment may only continue until “disease progression.” The treating physician believes that the patient is still receiving clinical benefit and has requested that the subject remain on study. What should you do:

A. Write a Note-to-File granting the SSE. The PI has the final say on IITs.
B. Have the treating physician submit a SSE to their IRB. Once approved they may proceed.
C. Contact your FDA project manager to determine if FDA has any concerns prior to granting the SSE

ANSWER: C- Contact your FDA project Manager!

This is an increase in the duration of drug exposure.

IND Application Maintenance
Protocol Amendment- Change in Protocol

WHAT ACTUALLY HAPPENED

- IND Specialist and PI reached out to the FDA project manager at 2:03 PM
- At 2:40 PM the FDA project manager replied:

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, October 13, 2016 2:40 PM
To: LCCC_IND
Cc: [redacted]
Subject: RE: IND[redacted]

Hello Dr. Morrison,

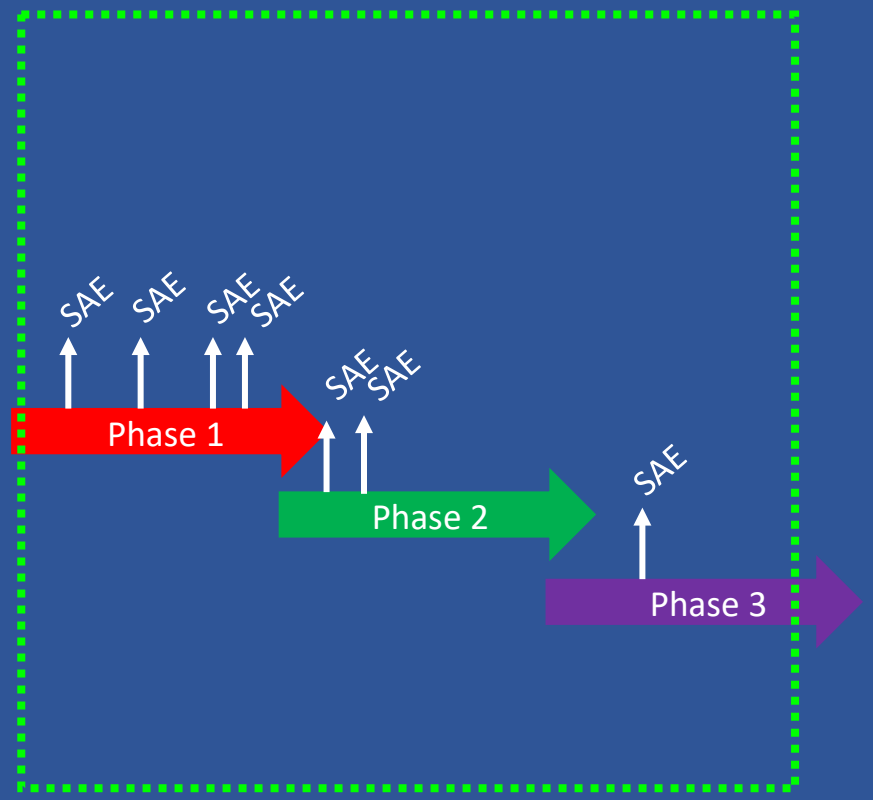
For your situation, you will need to submit a request for a single patient IND (SPI) and use the attached document on steps to take and documents to provide for your submission. You may use the fax number provide in my signature block.

Regards,
Rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

IND Application Maintenance

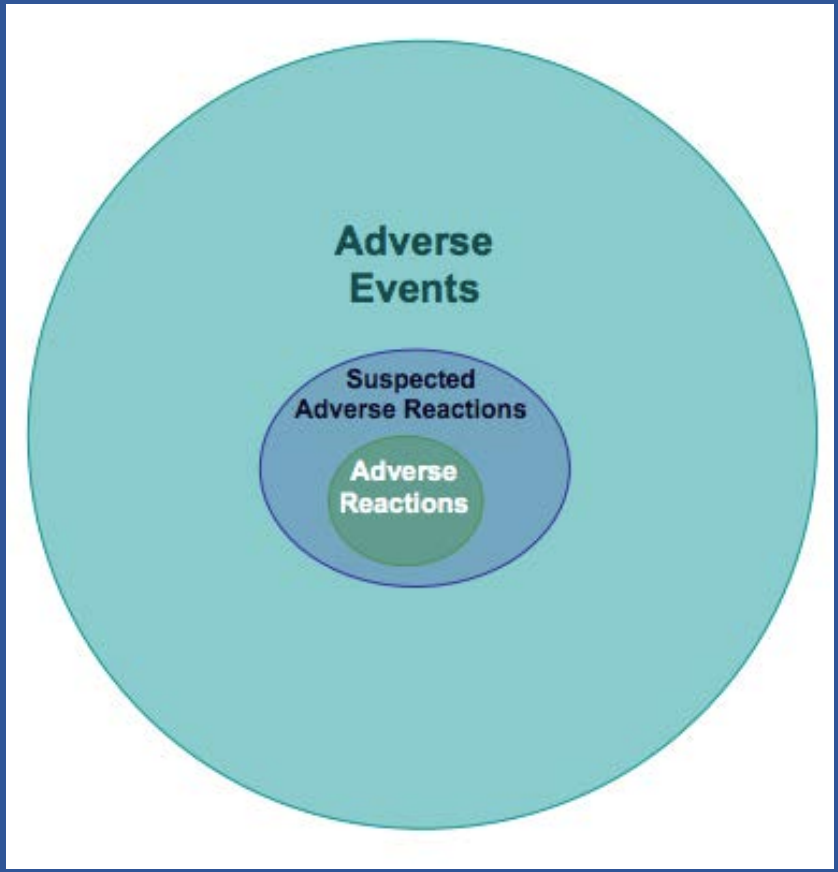
IND Safety Reports- Individual Clinical Events



WHAT 3 QUESTIONS DO I NEED TO ASK?

1. Is it serious?
   - Death, Life-threatening, Inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity, substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect, may require medical or surgical interventions to prevent one of the aforementioned results
     - Example: development of drug dependency or abuse
     - Example: allergic bronchospasm requiring intensive treatment in an emergency room
2. Is it related?
   - "reasonable possibility" that the drug caused the adverse event
     - aka: evidence to suggest a causal relationship between the drug and the adverse event
     - You don't have to be 100% sure
3. Is it unexpected?
   - Not listed in the IB
     - If there isn't an IB, then not listed in the IND
     - At the same specificity
     - At the same severity
     - As occurring with this specific IP

IND Application Maintenance
IND Safety Reports- Individual Clinical Events



IS IT RELATED?

Historically, investigators have over reported to FDA…so much that FDA issued a Guidance on this

- Single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - Angioedema
  - Hepatic Injury
  - Stevens-Johnson Injury
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
  - Strong temporal association
  - Recurs on re-challenge
  - Ex: Tendon rupture or heart valve lesion in young adults
- An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

IND Application Maintenance
IND Safety Reports- Individual Clinical Events

QUIZ

Which of the following would require an IND safety report?

A. A subject on trial X has a cerebral thromboembolism that is determined to be related to the IP. The IB indicates that cerebral vascular incidents are expected.

This is unexpected because the event is more specific than listed in the IB

B. A subject on trial Y has hepatic necrosis that is determined to be related to the IP. The IB indicates that elevated hepatic enzymes are expected.

This is unexpected because the event is more severe than listed in the IB

C. A subject experiences serious symptom B. Symptom B generally doesn't occur in this patient population and isn't listed in the IB. Symptom B isn't normally associated with drug exposure.

Single events that are not commonly associated with drugs are not reportable

D. You submitted an IND safety report for Stevens-Johnson syndrome because it is strongly associated with drugs and was unexpected. A second patient experiences Stevens-Johnson syndrome.

Have you updated the IB? If not, then this would still be unexpected

IND Application Maintenance
IND Safety Reports- Individual Clinical Events

FDA MAY REQUIRE ADDITONAL REPORTING

Regarding the Safety Reporting Plan:

21. We recommend that you report grade 4 or greater product infusion reactions, cytokine release syndromes and/or neurologic toxicity in an expedited fashion in addition to all Serious Unexpected Adverse Reactions (SUSARs).

IND Application Maintenance
IND Safety Reports- Findings from Other Studies
QUIZ

You receive an action letter from Merck indicating that 2 patients on the KN-011 trial have developed fatal interstitial lung disease for which there is a causal relationship to pembrolizumab. Merck has instructed you to update both your exclusion criteria in your protocol and your ICF risk information based on these events. Does this need to be reported to FDA via an IND safety Report?

Answer: YES!

Findings from other studies that suggest significant risk in humans exposed to the drug.

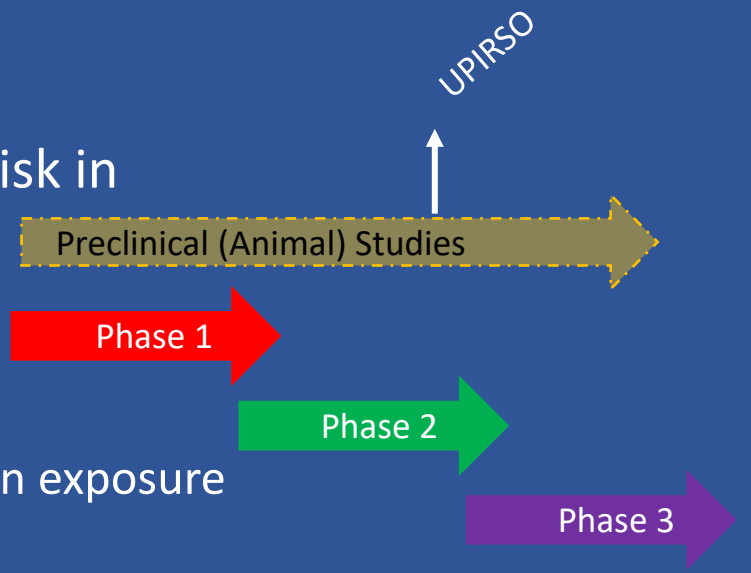
- Even if not conducted under an IND
- Even if conducted by a different sponsor
- Ordinarily would result in a safety-related change in the protocol, ICF, IB

The sponsor should conduct literature searches regularly.

This is one reason why the DSMC asks you to ”attach copies or references of significant literature reporting developments that may affect the safety of participants or the ethics of the study”

IND Application Maintenance
IND Safety Reports- Other Types of Reporting

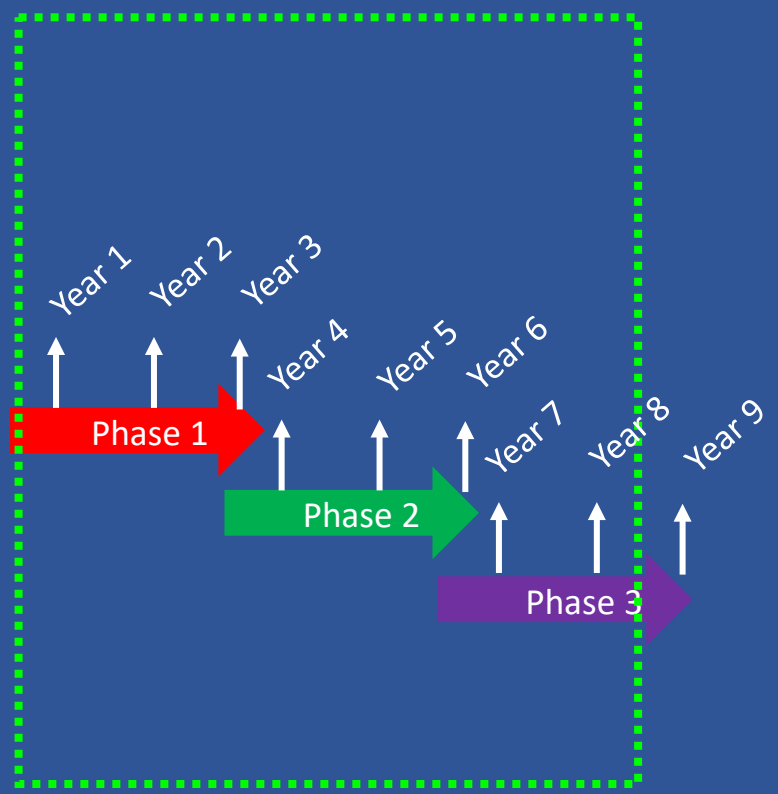
1. Reporting from Other Studies
2. Aggregate Reporting
   - Sponsors should have a systematic approach for safety surveillance:
     - Process for reviewing, evaluating, and managing accumulating safety data
     - From the entire clinical trial database—at the level of the IP (meaning across studies)
     - At appropriate intervals
3. Pre-Clinical Findings
   - Findings in animal or *in vitro* testing that suggest significant risk in humans exposed to the drug
     - Mutagenicity
     - Teratogenicity
     - Carcinogenicity
     - Reports of significant organ toxicity at or near the expected human exposure
   - Even if conducted by a different sponsor



IND Application Maintenance
IND Safety Reports
WHAT YOU NEED TO DO:

- Fill out a MedWatch Form
- Evaluate SAEs at both UNC **and multicenter sites**
- Don’t forget:
  - Action Letters
  - Evaluations or other literature
- Write a cover letter and Form FDA 1571
- Submit to the IND
- Timelines:
  - If life-threatening or fatal: **7 days**
  - Other qualifying events: **15 days**
- **Don’t confuse a MedWatch submission with a serial submission to the IND**

IND Application Maintenance
Annual Reports



- Update FDA on what has gone in on the last year:
  - Summary of study status
    - # of subjects enrolled by age, gender and race
    - # of subjects that have dropped out for any reason
    - Most frequent and most serious adverse events by body system
    - Summary of IND safety reports
    - Subject deaths with cause of death
    - Subjects that have dropped out due to AE, whether or not thought to be drug-related
  - Brief description of what, if anything, was obtained that is pertinent to understanding of the drug's actions:
    - Dose response
    - Information from controlled trials
    - Bioavailability
  - Brief description of study results (if available)
  - List of preclinical studies and summary of findings
  - Investigational plan for the coming year
  - Summary of revisions to:
    - IB
    - Protocol
  - Foreign marketing developments
  - Outstanding business with FDA

- Due within 60 days of the anniversary of when the IND went into effect

IND Application Maintenance
Annual Reports
EXAMPLES

- What if FDA does not receive all the required information?

From: Patel, Anuja <Anuja.Patel@fda.hhs.gov>
Sent: Wednesday, August 17, 2016 11:52:03 AM
To: [redacted]
Cc: [redacted]
Subject: FDA Information Request- IND 110556- Annual report dated July 7, 2016

Dear Dr [redacted]

We refer to your amendment dated July 7, 2016, received on July 11, 2016, containing your annual report for protocol [redacted]

We have the following comment from our clinical team:

- **Please submit a final study report when available for this study when available.**

Please acknowledge receipt of this email and feel free to contact me if you have any questions.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9872 (fax)
anuja.patel@fda.hhs.gov (email)

IND Application Maintenance
Annual Reports
LCCC EXAMPLES

- What happens if FDA receives the report and has questions?
  - FDA sends a Request for Information:

From: Wall, Laura
Sent: Wednesday, March 1, 2017 11:41:37 AM (UTC-05:00) Eastern Time (US & Canada)
To: [redacted]
Cc: Wall, Laura
Subject: IND 114035 - FDA Information Request - Please respond within 60 days

Dear [redacted] and Kaitlin,

The clinical team requests that you respond to the following Information Request:

1. Please provide a separate table listing grade 3 and 4 AE or note that no grade 3-4 AE occurred, if appropriate.

Please send me the requested information via e-mail and officially to your IND within 60 days.

Kindly confirm receipt.

Thank you,

Laura

IND Application Maintenance
Annual Reports
KNOWLEDGE TEST

Your IND annual report was due in May 2016, but you got super busy and didn't end up submitting it until December 2016. So, now May 2017 is coming up what should you do:

A. No worries, you recently updated FDA, so you don't need to update them again until December 2017

B. FDA just needs to have a general idea of what is going on, so as long as you need them an annual report every couple of years you will be okay, so you can skip this one if you are busy

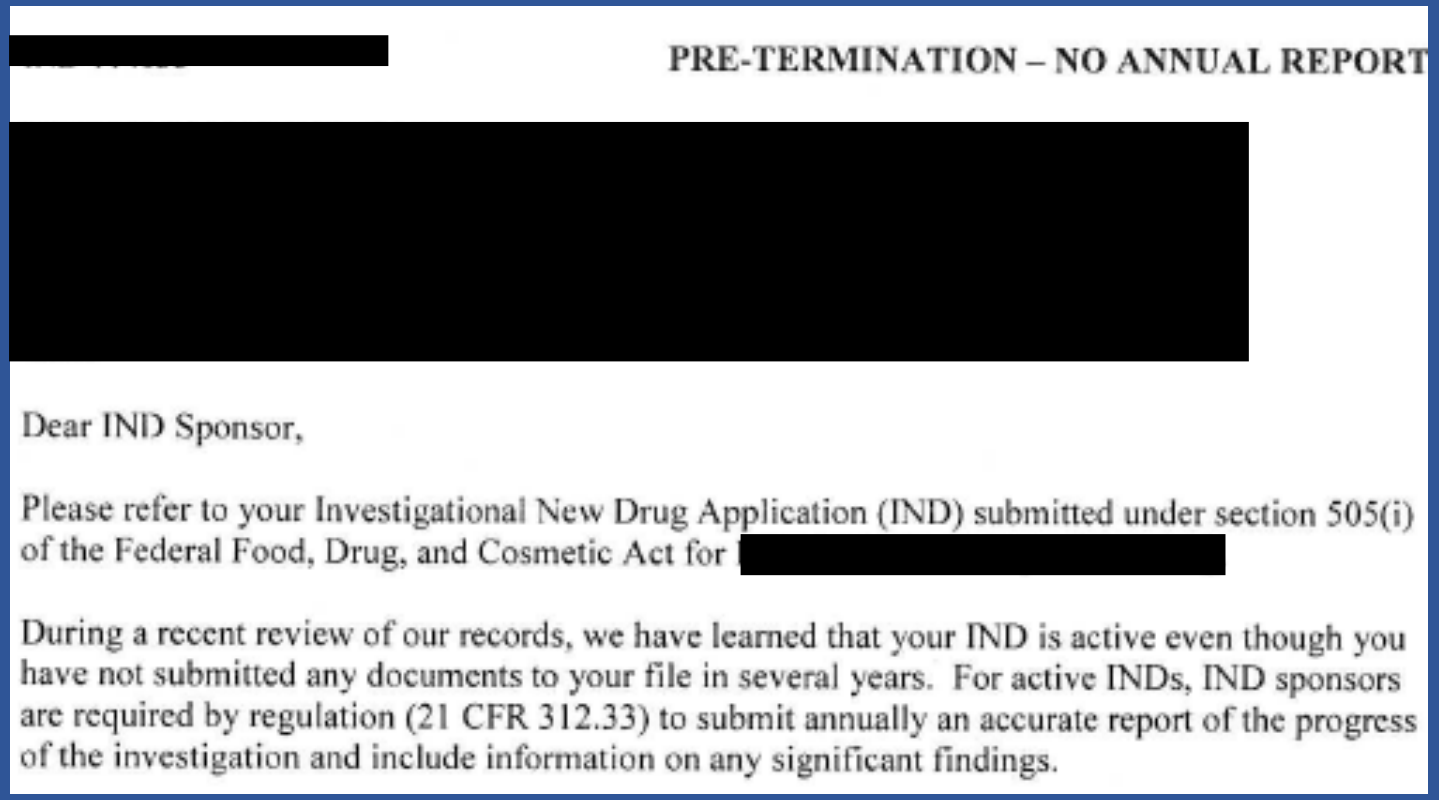
C. You need to submit the IND annual report by May 2017

ANSWER: C-Your IND annual report is due every year on the same date-within 60 days of the IND anniversary date (the date on which you were safe to proceed)

IND Application Maintenance
Annual Reports

WHAT REALLY HAPPENED

- It was assumed that an IND annual report didn't need to be submitted if FDA had been communicated with recently and didn't take notice that one was not submitted.
- 4 years later:



[redacted]

PRE-TERMINATION – NO ANNUAL REPORT

[redacted]

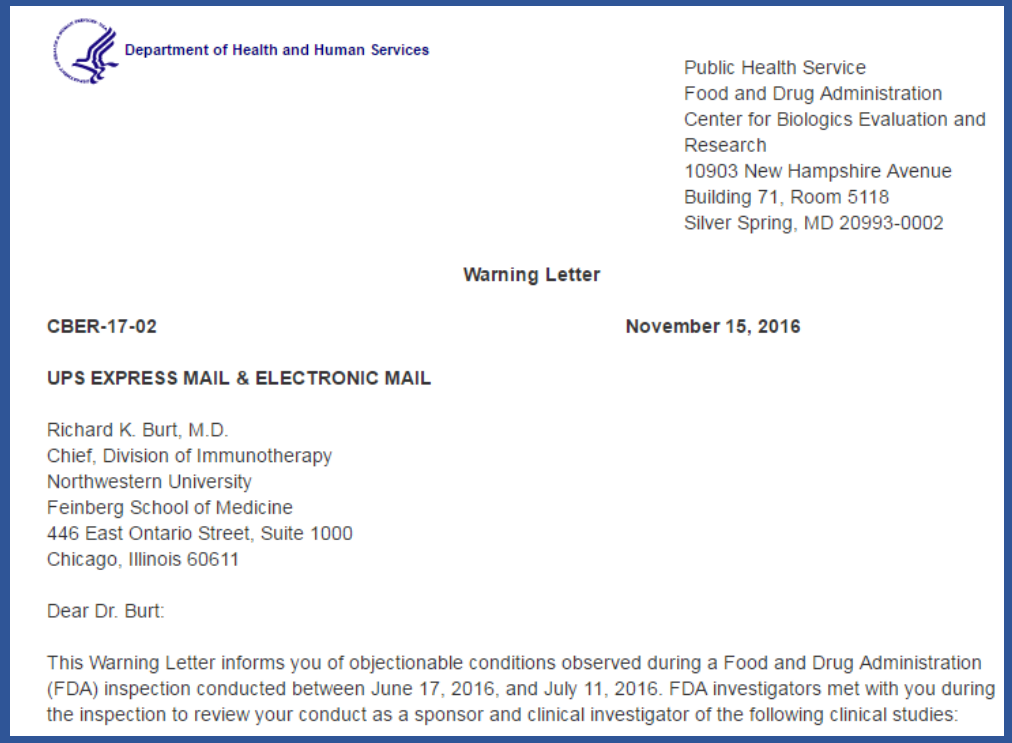
Dear IND Sponsor,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [redacted]

During a recent review of our records, we have learned that your IND is active even though you have not submitted any documents to your file in several years. For active INDs, IND sponsors are required by regulation (21 CFR 312.33) to submit annually an accurate report of the progress of the investigation and include information on any significant findings.

IND Application Maintenance
Annual Reports

WHAT COULD HAPPENED



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Building 71, Room 5118
Silver Spring, MD 20993-0002

Warning Letter

CBER-17-02 **November 15, 2016**

UPS EXPRESS MAIL & ELECTRONIC MAIL

Richard K. Burt, M.D.
Chief, Division of Immunotherapy
Northwestern University
Feinberg School of Medicine
446 East Ontario Street, Suite 1000
Chicago, Illinois 60611

Dear Dr. Burt:

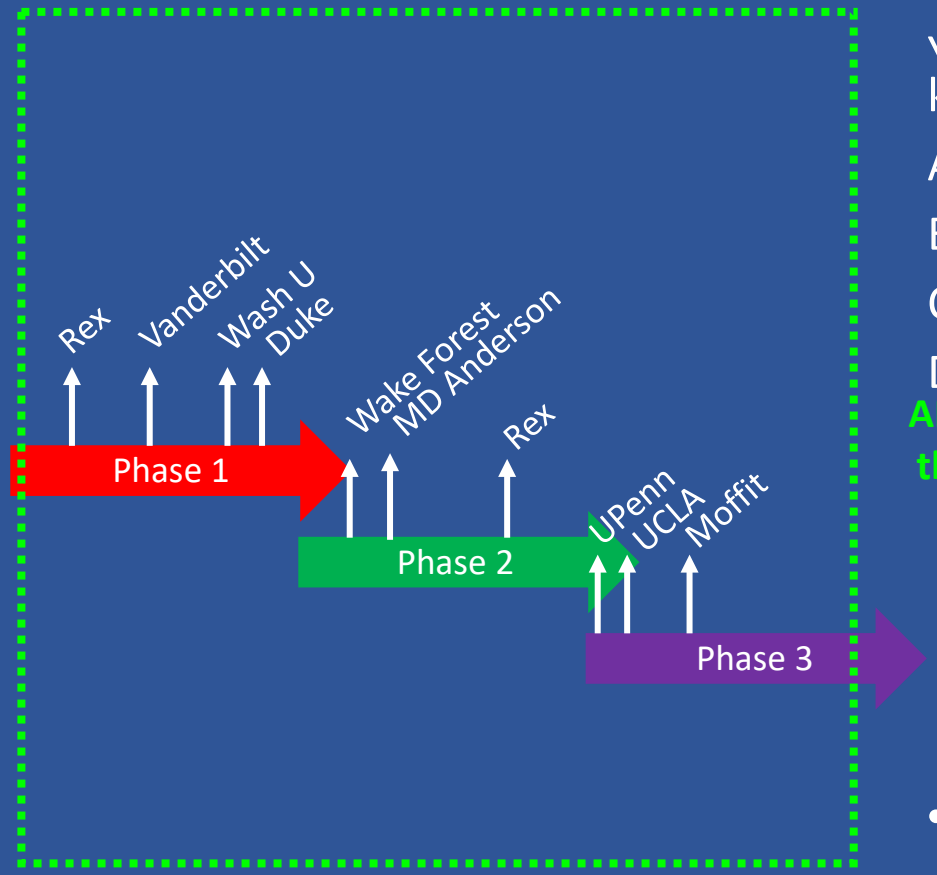
This Warning Letter informs you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted between June 17, 2016, and July 11, 2016. FDA investigators met with you during the inspection to review your conduct as a sponsor and clinical investigator of the following clinical studies:

7. You failed to make adequate annual reports to FDA as required by § 312.33. [21 CFR § 312.56(c)].

IND Application Maintenance
Annual Reports
WHAT YOU NEED TO DO:

- Draft an annual report
- Draft a cover letter and Form FDA 1571
- Submit to FDA
  - Recommended timeframes:
    - 60-day warning- you should have the draft report by now
    - 30-day warning- the submission should be on its way to FDA by now

IND Application Maintenance
Protocol Amendment- New Investigator



QUIZ

You are adding a new site to your trial, when do you need to let FDA know?

A. Within 30 days of the investigator being added
B. At the time of annual report
C. Whenever you have another submission that needs to go
D. When you send the final study data

ANSWER: A- Once an investigator is added to the study, the IP may be shipped, and the investigator may begin participating in the study. The sponsor must notify FDA of the new investigator within 30 days

YOUR PART:

- Send FDA a Form FDA 1572 for the new site and the new PI's CV
- Make sure that you have seen an FDA submission adding the site prior to conducting the site's SIV

IND Application Maintenance
Protocol Amendment- New Investigator

WHAT ACTUALLY HAPPENED:

- FDA has been notified at the time of annual report or years later
  - This is NOT in accordance with the regulations
  - FDA can’t properly inspect if it doesn’t know where the investigations are occurring
- For example, study XXXXX added 21 sites during the 2015 annual report

IND Application Maintenance
Protocol Amendment- New Investigator

WHAT COULD HAVE HAPPENED:

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Building 71, Room 5118
Silver Spring, MD 20993-0002

Warning Letter

CBER-17-02 **November 15, 2016**

UPS EXPRESS MAIL & ELECTRONIC MAIL

Richard K. Burt, M.D.
Chief, Division of Immunotherapy
Northwestern University
Feinberg School of Medicine
446 East Ontario Street, Suite 1000
Chicago, Illinois 60611

Dear Dr. Burt:

This Warning Letter informs you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted between June 17, 2016, and July 11, 2016. FDA investigators met with you during the inspection to review your conduct as a sponsor and clinical investigator of the following clinical studies:

2. You failed to submit a protocol amendment to FDA when there was a significant change in protocol design. [21 CFR § 312.30(b)(1)(ii) and 312.30(b)(2)(i)(*a*).] Further, you failed to submit a protocol amendment to FDA when new investigators were added to carry out a previously submitted protocol within 30 days of the investigators being added. [21 CFR § 312.30(c).]

A. You failed to submit a protocol amendment within 30 days of adding the following five clinical investigators at four investigational sites to the **(b)(4)** Protocol:

- Dr. J.S. (Canada Site 102) who enrolled 2 subjects between 2009 and 2010.
- Dr. J.V. and Dr. C.O. (Brazil Site 103) who enrolled 3 subjects between 2009 and 2014.
- Dr. J.B. (Sweden Site 104) who enrolled 14 subjects between 2011 and 2016.
- Dr. B.S. (United Kingdom Site 105) who enrolled 11 subjects between 2014 and 2016.

During the inspection, we found that you prepared new protocol versions when you added new investigators; however you failed to submit these protocol amendments to FDA.

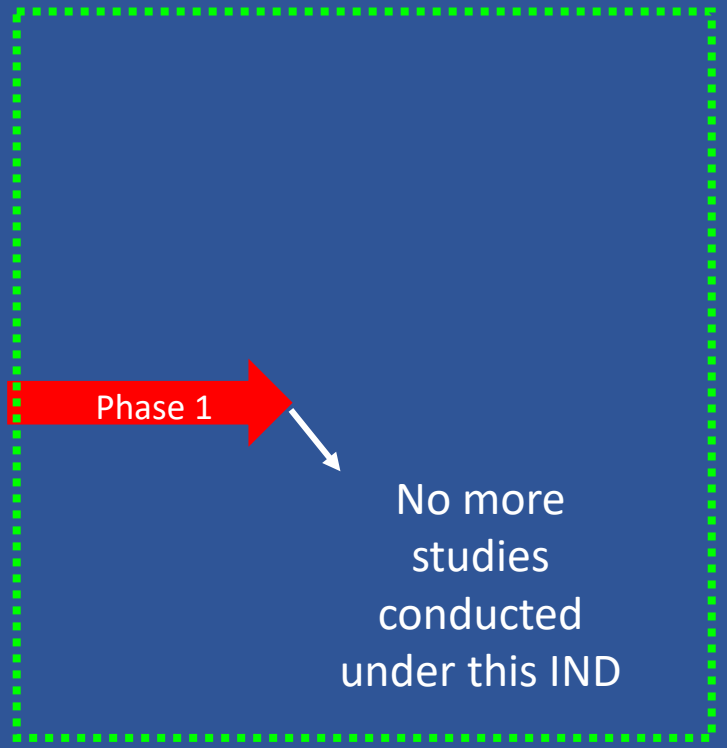
Version Number	Version Date	Investigator Addition
7	6/25/07	Added clinical investigators from two new sites, Brazil and Canada
15	12/11/13	Added clinical investigator from two new sites, Sweden and the United Kingdom
17	9/25/14	New clinical investigator in Brazil

Your response letter states that you submitted a Form FDA 1572 and curriculum vitae for the investigators at the current enrolling sites to FDA on July 12, 2016. Your response is not acceptable because you did not indicate that you have put a corrective action plan in place to prevent similar violations in the future.

IND Application Maintenance
Continued Communication with FDA

- FDA should be viewed as part of the study team
- They can help with questions:
  - How about this protocol amendment?
  - Can we start enrolling pediatric patients?
  - Can we decrease the safety window between enrollment of subjects?
- Some example comments about desired continued communication:
  - “After completion of the dose finding study on the initial subjects…we recommend that you submit the data to the FDA for review prior to the use of additional doses.”
  - “Once the dose of…is determined, the protocol can be revised to determine the best dose of….to address CRS”
  - “This may be reassessed after you have an established safety profile for…”

What Happens When All of Your Studies Under the IND are Complete?



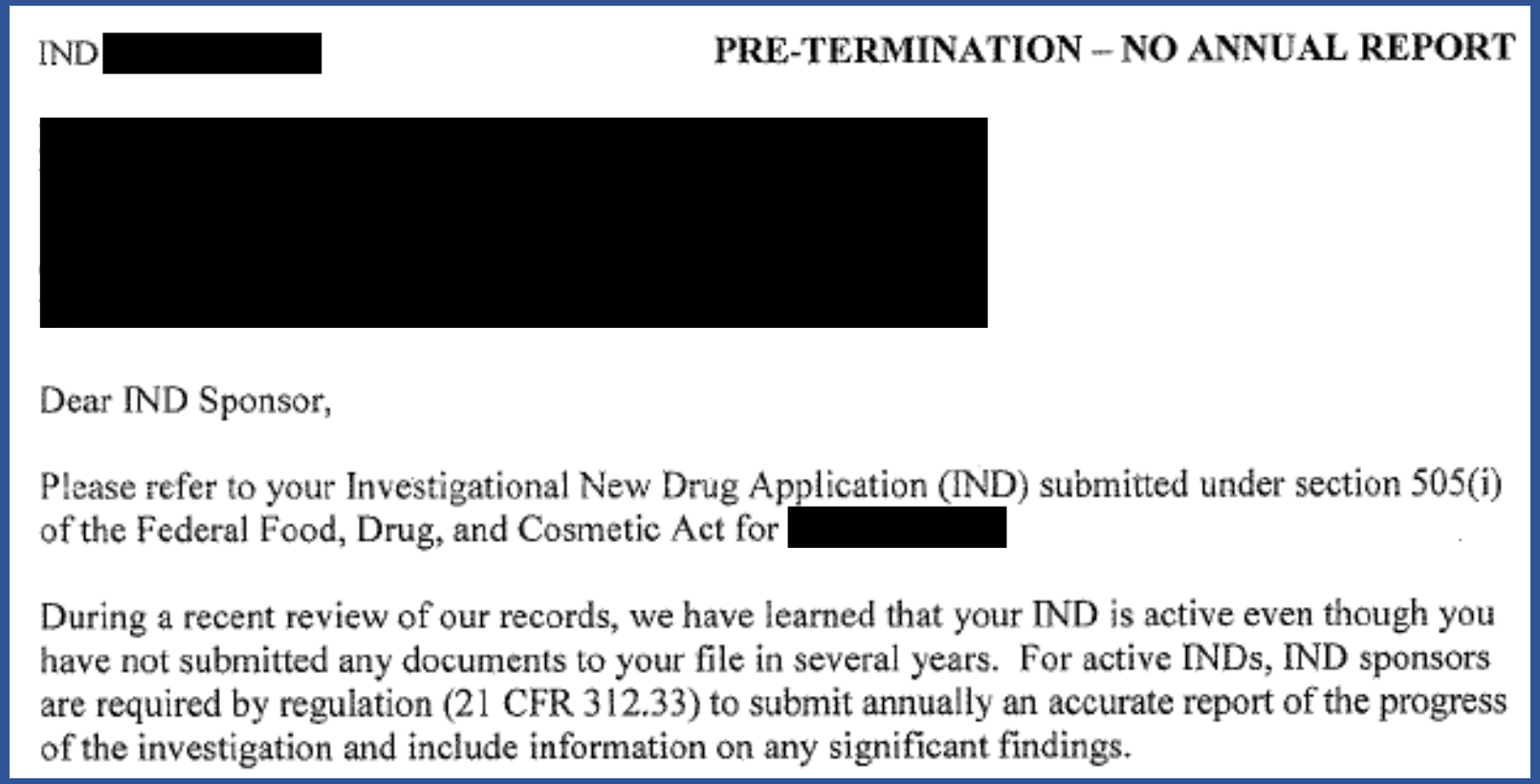
WITHDRAW YOUR IND

- Before you withdraw make sure of the following:
  - Data collection complete
  - Data analysis final
  - IRB application closed
  - All clinical investigations have stopped
  - All current investigators have been informed
  - IP has either been return or destroyed
- Tell FDA
  - Send FDA your final study data
  - In the form of a final annual report
- You can NOT reinstate a withdrawn IND so make sure you want to withdraw it
- If withdrawn for a safety-related reason
  - Tell FDA
  - Tell all reviewing IRBs

What Happens When All of Your Studies Under the IND are Complete?

WHAT REALLY HAPPENED

- Study is closed with IRB and everyone thinks that everything is complete
- Two years later:



IND [redacted] **PRE-TERMINATION – NO ANNUAL REPORT**

[redacted]

Dear IND Sponsor,

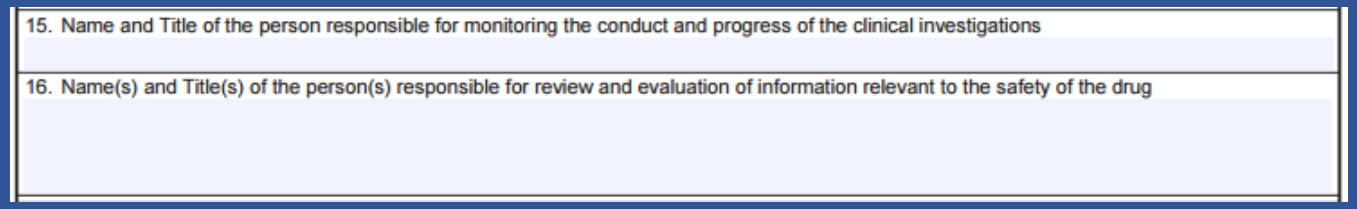
Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [redacted]

During a recent review of our records, we have learned that your IND is active even though you have not submitted any documents to your file in several years. For active INDs, IND sponsors are required by regulation (21 CFR 312.33) to submit annually an accurate report of the progress of the investigation and include information on any significant findings.

IND Sponsor Transfers and New Medical Monitors

WHAT TO DO WHEN A PI LEAVES

- If UNC holds the IND:
  - Needs a new medical monitor (person on the 1571)



  - Need a new PI
  - IF granted approval by department head may be transferred to PI and taken to new institution

- **If PI holds IND:**
  - **IND will need to be transferred to a new PI OR**
  - **If IND is being taken to new institution, contact information needs to be updated with FDA**

IND Sponsor Transfers and New Medical Monitors

WHAT ACTUALLY HAPPENED

- Several of the INDs from were not properly transferred to UNC from the Investigator

From: Wall, Laura [mailto:Laura.Wall@fda.hhs.gov]
Sent: Wednesday, March 01, 2017 11:42 AM
To: [redacted]
Cc: Wall, Laura <Laura.Wall@fda.hhs.gov>
Subject: IND [redacted] - FDA Information Request - Please respond within 60 days

Dear [redacted]

The clinical team requests that you respond to the following Information Request:

1. [redacted] currently listed as investigator sponsor. Please submit a request for sponsor transfer to [redacted]

Please send me the requested information via e-mail and officially to your IND within 60 days.

Kindly confirm receipt.

Thank you,

Laura

IND Sponsor Transfers and New Medical Monitors

WHAT ACTUALLY HAPPENED

- An investigator left UNC and the IND was not transferred
  - FDA only contacted the old investigator when they did not receive timely annual reports
  - The old investigator received IND pre-termination notices and an IND termination notice
    - Aka the FDA shut down the trial
  - The new investigator did not know that there were any problems with the IND

From: "Maduro, Ruth" <Ruth.Maduro@fda.hhs.gov>
Date: April 25, 2016 at 9:30:14 AM EDT
To: [redacted]
Cc: "Maduro, Ruth" <Ruth.Maduro@fda.hhs.gov>
Subject: IND [redacted] Termination

Dear [redacted]

I am providing this email communication to you regarding IND [redacted]

Please note the following regarding IND [redacted]

1. IND [redacted] was terminated on October 30, 2015, following Pre-termination (No Annual Report) notification of July 22, 2015, which stated the following:
   - "If you wish for your IND to remain active, please provide, within 30 days of receipt of this letter, an annual progress report."
   - "You may choose to not respond to this letter. If you do not respond, we will assume that you do not object to the FDA's termination of this IND. In that case, you will be notified by mail that the IND has been terminated."

As a reminder, the October 30, 2015, Termination letter stated that "According to 21 CFR 312.44, FDA is terminating this IND since we have not received an annual report for your investigations for at least two years."

The below link is included here for your referencing http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM446695.pdf.

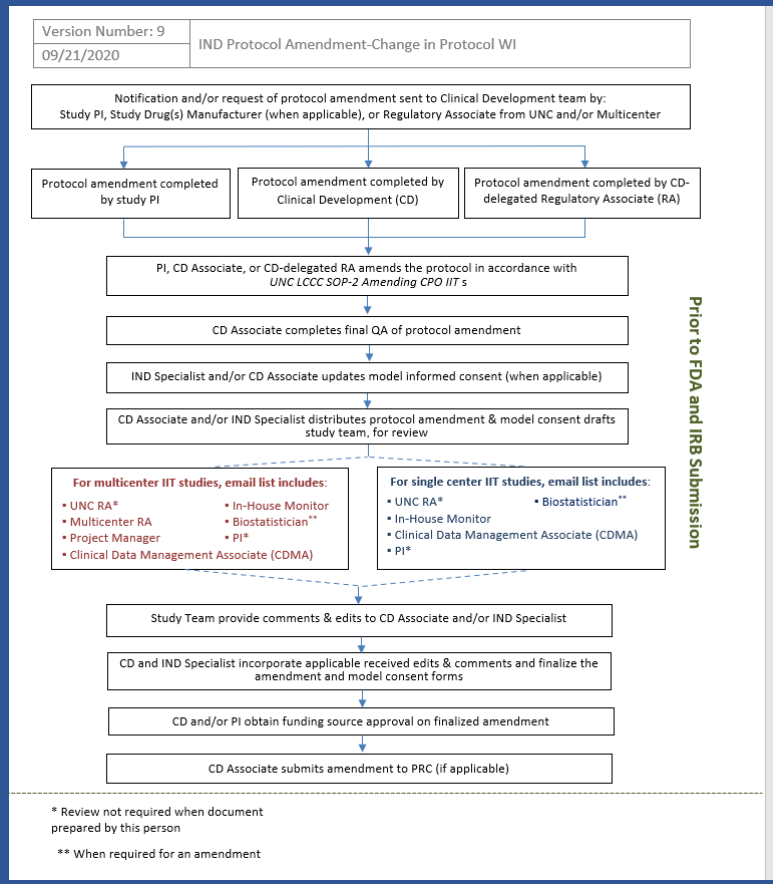
In addition, February 26, 2016, email communication to [redacted] informed that transfer of ownership was not submitted as an amendment to IND [redacted]

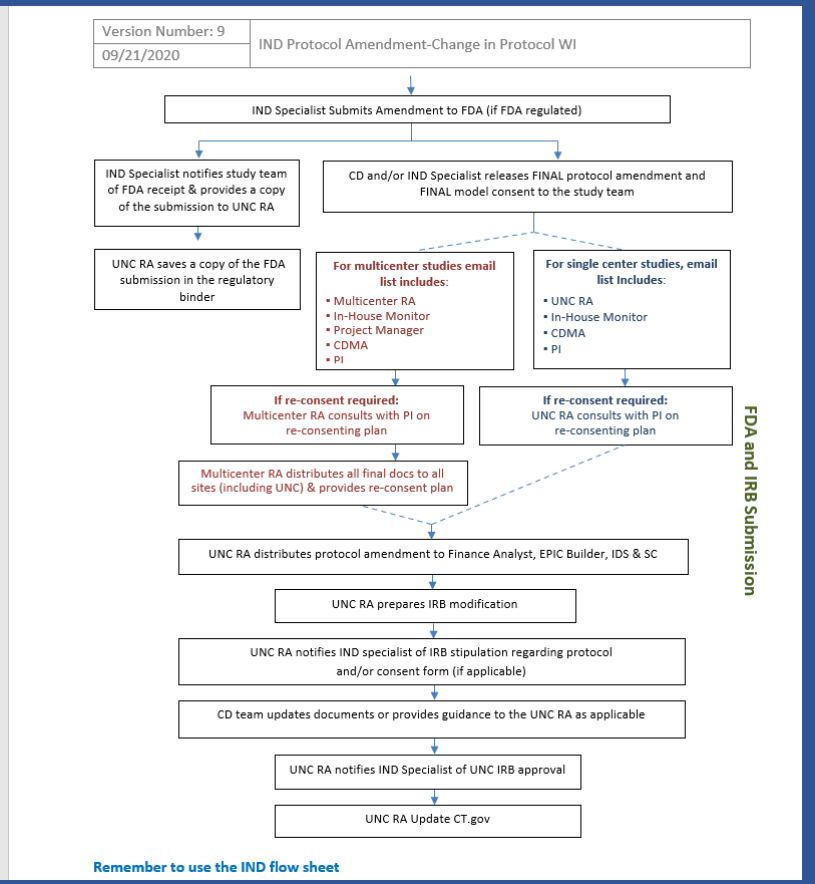
Kindly confirm receipt of this email communication.

Regards,
Ruth

IND Resources

- People
  - NC TrasC IND support: request at https://tracs.unc.edu/request
  - Lineberger Comprehensive Cancer Center IND support: request at LCCC_IND@unc.edu
- LCCC SOPs (complete with working instructions and templates)
  - **Protocol Amendments:**
    - SOP-2 Amendment CPO IIT
    - SOP-4 Administrative Letters
    - SOP-54 LCCC IND Protocol Amendment Change in Protocol
  - **New Sites:**
    - SOP-55 LCCC IND Protocol Amendment New Investigator
  - **Communication from FDA:**
    - SOP-53 LCCC IND Distribution of FDA Emails
  - **Annual Reports**
    - SOP-45 LCCC IND Annual Reports
  - **Determining if your study requires an IND**
    - SOP-3 Determining IND Status
  - **Changes in PI, Sponsor or Medical Monitor**
    - SOP-43 Change in Principal Investigator (updated)
    - SOP-57 LCCC IND Change in Sponsor, MM or PI
    - SOP-56 Change in Multi-Center PI
  - **Safety**
    - SOP-5 Action Letters
    - SOP-13A and B LCCC IND Safety Reporting
  - **IND Withdrawal**
    - SOP-58 LCCC IND Withdrawal
  - **Updating Form FDA 1572**
    - SOP-16 LCCC IND Updated FDA Form 1572
  - **Investigator's Brochures**
    - SOP-30 Drafting and Amending of Investigator's Brochures
  - **Protocol Review Meetings**
    - SOP-34 IIT Protocol Review Meetings
- Training/Education
  - https://unclineberger.org/iit/
  - http://regardd.org/





Questions???

Always feel free to email me: Kaitlin_Morrison@med.unc.edu