# Best Practice for IND Exemption Studies, IND Preparation and Maintenance

## PART 1: IND Exemption Studies
## PART 2: IND Preparation and Maintenance

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# Our Website
# Templates and Instructions

- Best Practices Templates/Instructions

http://tinyurl.com/b759np3

Recorded Webcasts

http://tinyurl.com/8n34gr4

# Outline for Part 1: IND Exemption Studies

- Definitions
- Studies Using Investigational Drugs
- Studies Using Commercially Available Drugs
- On-label Versus Off-label Use
- FDA Regulations and Guidance on IND Exemptions
- FDA Review Process
- Specific Issues
- Case Scenarios

# What is a Drug?

- A Drug is anything that meets the definition of a drug per the FD&C Act *(201(g)(1))*. . .

  *". . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. . . "*

  *"…a substance (other than food) intended to affect the structure or any function of the body "**

  ** Note: "…compounds administered to blunt or provoke a physiological response or to study the mechanism of action or metabolism of a drug. "*

# What is an Investigational Drugs?

- An article that is not approved (for marketing) in the US as a drug
- An approved drug that is not used according to the approved label (or used in a new combination of approved drugs)

*Note: Practice of medicine allows a physician to use any approved drug without prior regulatory approval*

# What is a Clinical Investigation?

## As defined by 21 CFR 312.2(b):

*"...[an] experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes [of the IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug in the course of medical practice."*

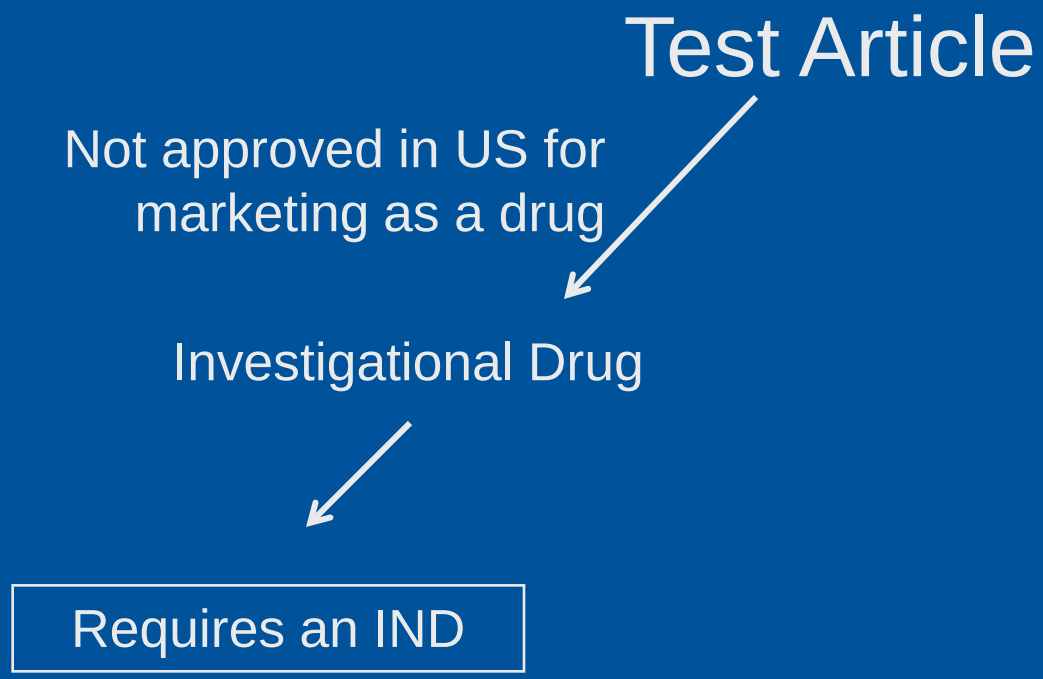
# Outline for Part 1: IND Exemption Studies

- Definitions
- **Studies Using Investigational Drugs**
- Studies Using Commercially Available Drugs
- On-label Versus Off-label Use
- FDA Regulations and Guidance on IND Exemptions
- FDA Review Process
- Specific Issues
- Case Scenarios

# Studies Using Investigational Drugs

- Studies Using Investigational Drugs Require Investigational New Drug (IND) application

  IND application is a request to the FDA for authorization to administer an investigational drug (or biologic) to humans or a marketed drug in a new indication and/or patient population


Test Article
Not approved in US for marketing as a drug
Investigational Drug
Requires an IND

# Outline for Part 1: IND Exemption Studies

- Definitions
- Studies Using Investigational Drugs
- **Studies Using Commercially Available Drugs**
- On-label Versus Off-label Use
- FDA Regulations and Guidance on IND Exemptions
- FDA Review Process
- Specific Issues
- Case Scenarios

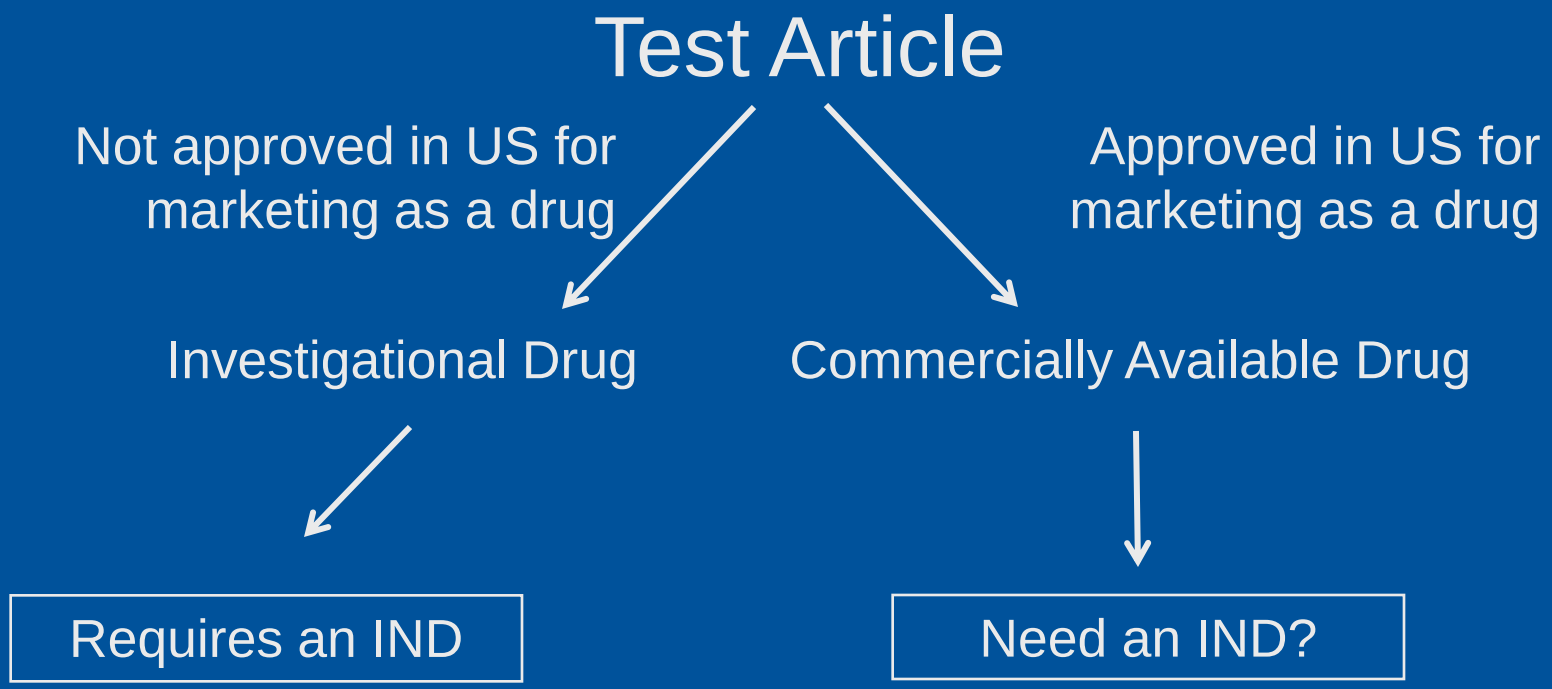
# Studies Using Commercial Drugs

- What are Commercially Available Drugs?
  - Articles that are approved for marketing in the US as drugs

*Note: approval is for marketing a drug in a specific manner as defined by the drug labeling*

- Studies using commercially available drugs may or may not require an IND

*It depends!*


Test Article
Not approved in US for marketing as a drug
Approved in US for marketing as a drug
Investigational Drug
Commercially Available Drug
Requires an IND
Need an IND?

# Outline for Part 1: IND Exemption Studies

- Definitions
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- On-label Versus Off-label Use
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# On-label Versus Off-label Use

- What is drug labeling?

  Drug labeling refers to all the printed material that accompanies a drug, including the label, the wrapping and the package insert

  http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

  http://dailymed.nlm.nih.gov/dailymed/about.cfm

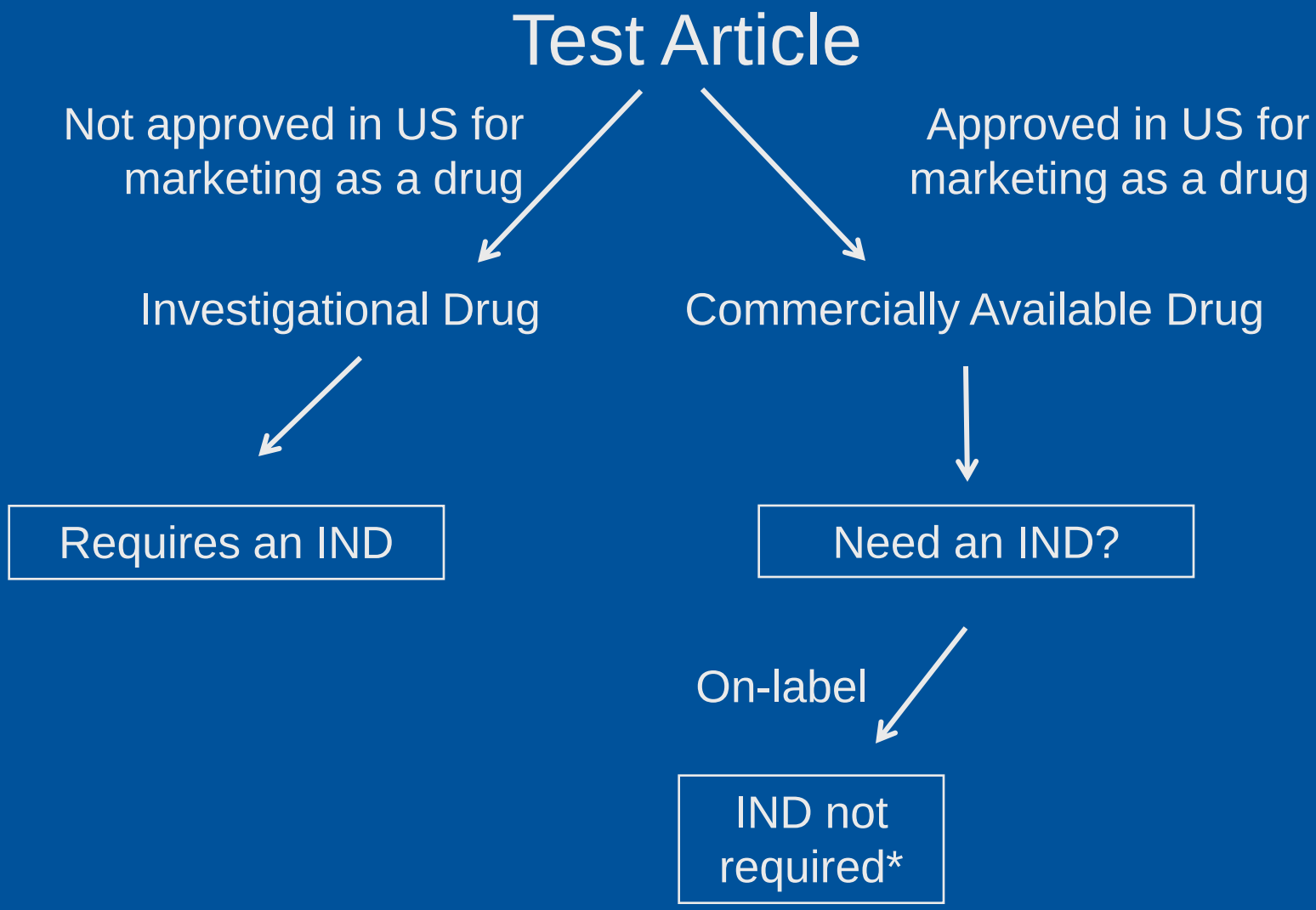
# On-label versus Off-label Use

- On-label Use

  Same indication, same dose, same route of administration, same patient population, same drug formulation

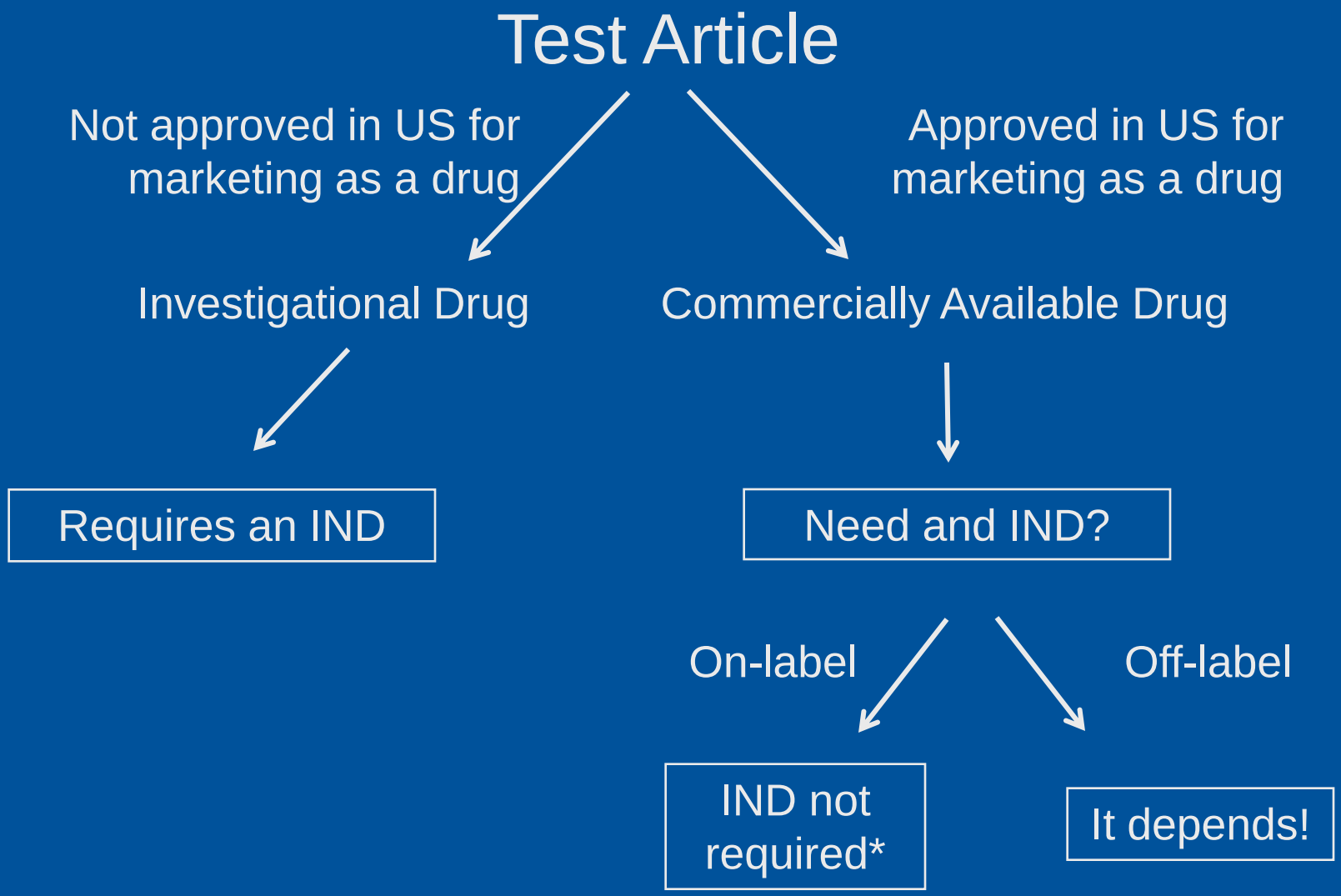
  Studies involving the on-label use of a drug do not require an IND*

  * *Note: as long as data will not be used in a marketing application*


Test Article
Not approved in US for marketing as a drug
Approved in US for marketing as a drug
Investigational Drug
Commercially Available Drug
Requires an IND
Need an IND?
On-label
IND not required*
* Assuming no marketing application planned

# On-label versus Off-label Use

- Off-label Use
  - Any difference from what is approved in the label
  - Off-label use is common and allowed in the practice of medicine and often is the standard of care




** Assuming no marketing application planned*

# Outline for Part 1: IND Exemption Studies

- Definitions
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- Studies Using Commercially Available Drugs
- On-label Versus Off-label Use
- **FDA Regulations and Guidance on IND Exemptions**
- FDA Review Process
- Specific Issues
- Case Scenarios

# FDA Regulations and Guidance on IND Exemptions

- 21 CFR Part 312.2(b) – IND Exemptions
- *FDA Guidance Document: "IND Exemptions for Studies of Lawfully Marketed Drug or Biologic Products for the Treatment of Cancer"*

  *http://tinyurl.com/nqkbkd*

- *FDA Guidance Document: "Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND"*

  *http://tinyurl.com/2g7z7kv*

# FDA Regulations and Guidance on IND Exemptions

- **When is an IND not needed for studies involving marketed drugs?**
  - Some studies using commercially marketed drugs
  - Some studies using *in vitro* diagnostic biological products (blood grouping serum, reagent red blood cells, anti-human globulin)
  - Studies using drugs only *in vitro* or in laboratory research animals

*21 CFR Part 312.2(b)*

# FDA Regulations and Guidance on IND Exemptions

- First Hurdle –

21 CFR 312.2(b)(1) - Must be the "investigation of a drug product that is lawfully marketed in the United States" 21 CFR 312.2(b)(1)

# FDA Regulations and Guidance on IND Exemptions

**Five criteria must all be met if a study can be considered exempt from requiring an IND**

1. If the study is not designed to support approval of a new indication or a change in label
2. If the study is not intended to support a significant change in the advertising for the product

# FDA Regulations and Guidance on IND Exemptions

3. If the study does not involve a route of administration, dosage level or patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug
4. The study is conducted in compliance with the IRB and informed consent regulations
5. The study is conducted in compliance with regulations regarding promotion for investigational drugs

# FDA Regulations and Guidance on IND Exemptions

**Evaluate risks associated with the changes in:**

- Patient Population
- Route of Administration
- Dose
- Drug Combinations
- Drug Modification

# Change in the Patient Population…

**V. EXAMPLES OF STUDIES**

The following examples of studies are being provided to illustrate the Agency's current thinking on the types of studies that the Agency considers to be exempt from IND regulation based on a risk assessment.

**A. Studies That Generally Are Exempt**

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely be exempt from IND regulation based on protocol-related issues.

1. Single-arm, phase 2 trials using marketed drugs to treat a cancer different from that indicated in the approved labeling and using doses and schedules similar to those in

*http://tinyurl.com/nqkbkd*

# Change in the Patient Population…

**B. Studies That Generally Are Not Exempt**

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely ***not*** be exempt from IND regulation because of protocol-related issues.

1. Studies of cytotoxic drugs are normally not exempt in patients for whom cytotoxic therapy would not be considered standard therapy and would require special justification. Any use of cytotoxic agents in nonmalignant disease (e.g., rheumatoid arthritis, multiple sclerosis) would, most likely, be considered to alter the acceptability of the risk of the agent.

2. Studies of adjuvant chemotherapy (chemotherapy given after surgery to remove cancer) are likely not exempt for the following reasons:

*http://tinyurl.com/nqkbkd*

# Route of Administration…

- *"For example, there could be a significant increase in risk if marketed drug for oral administration is converted to a dosage form that is to be administered by injection or intravenous, intrathecal, or inhalation route"*

***http://tinyurl.com/2g7z7kv***

# Dosage…

- *"It is possible that a decrease in dose could also significantly increase risk. For example, administering a low dose of a pure polysaccharide vaccine to study subjects can induce hypo-immunologic or non-immunologic responses in the subjects and can also induce tolerance to the vaccine, thus making subjects at risk for the infectious disease the vaccine is intended to prevent"*

***http://tinyurl.com/2g7z7kv***

# Drug Modifications. . .

- The exemption provision was not intended to require use of only the marketed product
- Sponsor-investigator can make low-risk modifications to the lawfully marketed drug (e.g. over-encapsulation, changes to color, scoring or size for blinding purposes)
- Consult FDA and provide detailed manufacturing information such that a determination can be made

***http://tinyurl.com/2g7z7kv***

# Drug Combinations. . .

Remember –the use of new drug combinations not supported by literature are generally not exempt.

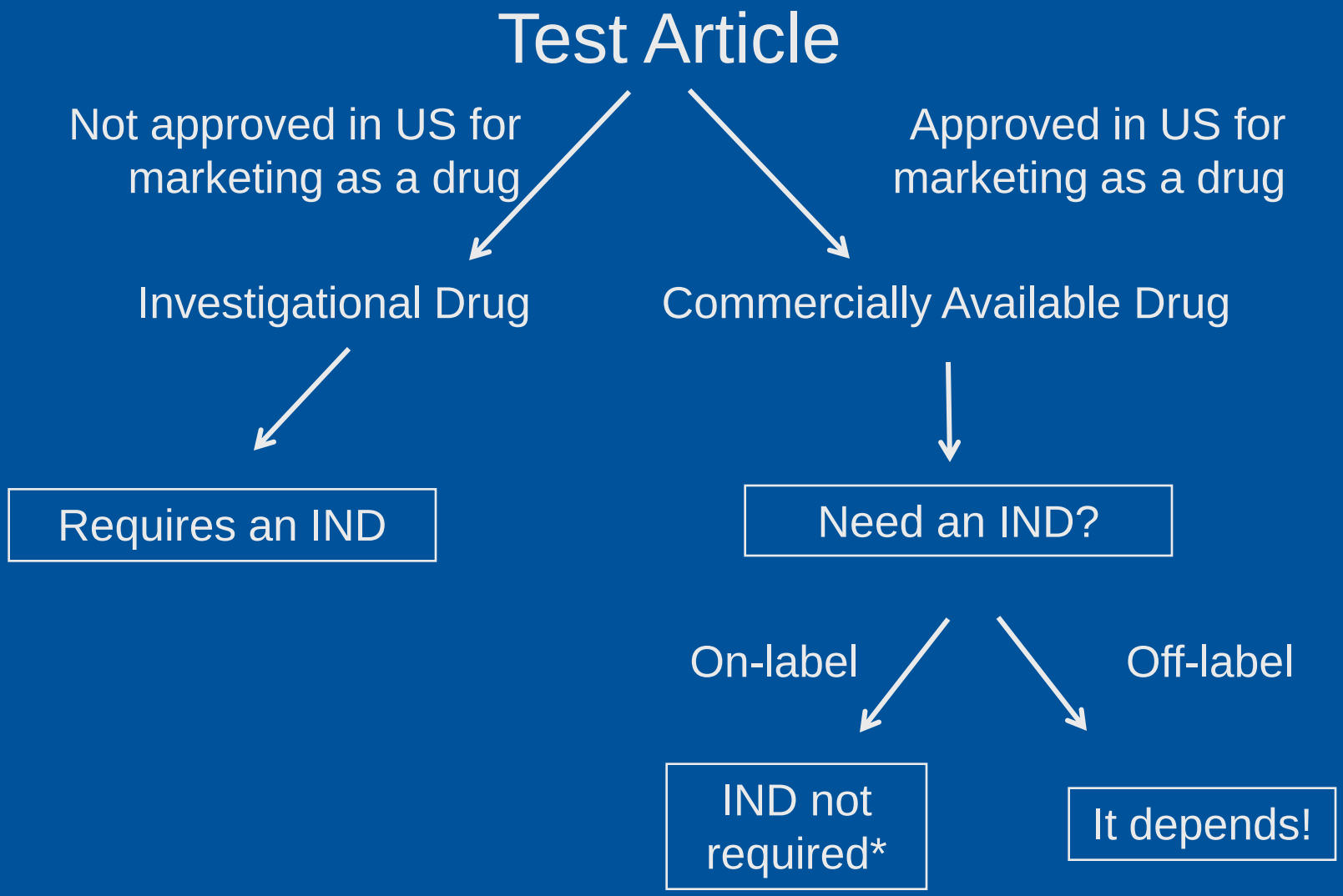
"*Unless adequately described in the literature, initial studies involving new drug combinations should be performed under an IND because of the possible occurrence of synergistic toxicity*."

***http://tinyurl.com/nqkbkd***

# Use of Placebo. . .

*"A clinical investigation involving the use of a placebo is exempt. . . If the investigation does not otherwise require submission of an IND"*

***21 CFR Part 312.2(b)(5)***




** Assuming no marketing application planned*

# Do you have to go to the FDA to get an IND Exemption?

YES

or

NO

# According to the FDA. . .

- "because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption."

*- This statement is found in both FDA Guidance documents on IND Exemptions*

# IRB Submission – First Step!

- Investigator should submit their rationale for why the study is IND exempt directly to the IRB.
  - May use a checklist or a narrative statement
  - Check local IRB policies
- If IRB does not agree – then go to FDA

# Other Reasons to go to FDA

- Time Constraints
- Industry partner requests FDA input before they will donate drug or release funding
- If the situation is unclear from the start
- Your local policy requires FDA input

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# If FDA Evaluates the Study

- **FDA will assess risk by focusing on:**
  - Dose
  - Schedule
  - Route of Administration
  - Patient Population
  - Drug Combinations

# FDA Review Process

- Formal Process
  - On a 30-day review clock
  - If not exempt. . . you will have an active IND
- Informal Process
  - Less work ‘up front’
  - Might get a faster response

# The Formal Process

- Study may be exempt – what should the FDA submission look like?
  - Cover Letter
  - IND
    - IND Document (Important in case you are NOT exempt!)
    - Protocol
    - Consent (optional)
    - Forms 1571, 1572, 3674
    - Letters of Authorization
    - Reprints from the literature (2-3 references are acceptable)

# Cover Letter

- State in the first paragraph that you believe the study may be exempt

- Restate the five exemption criteria and how/why you meet them
  - ✓ Focus on safety (Number 3 of exemption criteria)

# Informal Process for Obtaining Exemption

- Pre-IND Consultation Contacts

  http://tinyurl.com/kskl6e

# CENTER FOR DRUG EVALUATION AND RESEARCH
## PRE-IND Consultation Contacts

### Office of Drug Evaluation I

Division of Cardiovascular and Renal Products
Edward Fromm
301-796-2240
FAX 301-796-9841

Division of Neurology Products
Jacqueline Ware
301-796-1160
FAX 301-796-9842

Division of Psychiatry Products
Steve Hardeman
301-796-1081
FAX 301-796-9838

### Office of Drug Evaluation II

Division of Anesthesia, Analgesia, and Addiction Products
Parinda Jani
301-796-1232
Sara Stradley
301-796-1298
FAX 301-796-9722

Division of Metabolism and Endocrinology Products
Mehreen Hai
301-796-5073
Julie Marchick
301-796-1280
FAX 301-796-9712

Division of Pulmonary, Allergy, and Rheumatology Products
Sandy Barnes
301-796-1174
FAX 301-796-9728

### Office of Drug Evaluation III

Division of Gastroenterology and Inborn Error Products
Richard (Wes) Ishihara
Brian Strongin
301-796-2120
FAX 301-796-9906

Division of Dermatology and Dental Products
Barbara Gould
301-796-4224
FAX 301-796-9895

Division of Reproductive and Urologic Products
Jennifer Mercier
301-796-0934
Margie Kober
301-796-0937
FAX 301-796-9897

### Office of Drug Evaluation IV

Division of Nonprescription Clinical Evaluation
Melissa Furness
301-796-0893
FAX 301-796-9899

Division of Medical Imaging Products
Kyong Kang
301-796-2050
FAX 301-796-9849

Division of Non Prescription Regulation Development
Mary Chung
301-796-0260
David Eng
301-796-2773
FAX 301-796-9899

Botanical Review Team
Geri Smith
301-796-0941
FAX 301-595-7865

### Office of Antimicrobial Products: Pre-IND Consultation Program

Division of Anti-Infective Products
Frances LeSane
301-796-1400
FAX 301-796-9881

Division of Transplant and Ophthalmology Products Products
Dianna Willard
301-796-1600
FAX 301-796-9880

Division of Anti-Viral Products
Victoria Tyson
301-796-1500
Karen Winestock
301-796-1500
Topical Microbicides and other Anti-Viral Diseases
FAX 301-796-9883

### Office of Hematology and Oncology Drug Products

Division of Oncology Products (1)
Frank Cross
301-796-0876
Alice Kacuba
301-796-1381
FAX 301-796-9845

Division of Oncology Products (2)
Karen Jones
301-796-1377
Monica L. Hughes
301-796-9225
FAX 301-796-9849

Division of Hematology Products
Ebla Ali Ibrahim
301-796-3691
FAX 301-796-9848

Division of Hematology, Oncology, Toxicology
(Please reference any of the point of contacts listed above.)

# Informal Process

- Call consultation contact and explain situation (we feel the study meets exemption criteria but need some guidance)
- Ask if they will consider reviewing the study
- Send cover letter, protocol synopsis and full protocol for review
- You should receive a decision within two weeks (response might be verbal or written from FDA)

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- Studies Using Investigational Drugs
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- FDA Regulations and Guidance on IND Exemptions
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# Specific Issues

- Endogenous Compounds
- Live Organisms
- Dietary Supplements
- Research with Noncommercial Intent

# Endogenous Compounds

- **Endogenous compounds (those naturally found in the body)**
- **Often used in challenge studies to evoke physiological response, characterize a disease or establish mechanism of action**
- **These studies require an IND!**

*Note:* Although there is not intent to treat or mitigate disease, there is intent to affect the structure or function of the body.

# What is a Drug?

- **A Drug is anything that meets the definition of a drug per the FD&C Act. . .**
  - *". . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. . ."*
  - *". . .articles intended to affect the structure or any function of the body. . ."*

*Note:* not limited to compounds intended for a therapeutic purpose

# Live Organisms

- Challenge studies with live organisms (viruses, bacteria and fungi) administered to study pathogenesis or host response require INDs

*Note: Although there is no therapeutic purpose, there is intent to affect the structure/function of the body*

# Dietary Supplements

- Dietary Supplements are defined as products taken by mouth that are intended to supplement the diet and contain a dietary ingredient
- Examples include vitamins, minerals, herbs/botanicals, amino acids, metabolites (including extracts or combinations of these things)

# Dietary Supplements

**Need for an IND is determined by intent. . .**

**Structure/Function Study = no IND Required**

**Examples:**

- **Studying the effect of calcium on bone mass**
- **Studying the effect of fiber on bowel regularity**

# Dietary Supplements

Need for an IND is determined by intent. . .

Therapeutic Studies require INDs (treat, diagnose, cure, mitigate. . . )

Examples:

- Studying the effect of calcium on osteoporosis prevention
- Studying the effect of fiber to treat diarrhea

# Research with Noncommercial Intent

The IND regulations apply to investigations regardless if the intent of the study is commercial or non-commercial

# Case Scenarios

# IND Best Practices

## PART 2
## How do You Establish and Maintain an IND?

*Erin K O'Reilly, PhD, RAC*
*Associate Director, Regulatory Affairs*

Duke Translational Medicine Institute

*June 10th and 11th, 2014*

# Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- Standard Paper IND Format and Content
- Forms
- Filing and FDA Review Process
- Other IND Formats
- IND Maintenance
- Case Scenarios

# Definitions

- Sponsor is an individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation
- Investigator is an individual who conduct a clinical trial-under whose immediate direction a drug is administered or dispensed
- Sponsor-Investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction a drug is administered or dispensed

# Definitions: Types of INDs

- Commercial IND

  Ultimate goal is to obtain marketing approval

- Sponsor-Investigator IND (Investigator- Initiated IND)

  Primarily research-driven (goal is publication)

# Definitions: Types of INDs

Expanded Access:

- Individual patients, including emergencies
- Moderate sized populations
- Large populations under a treatment IND/protocol

# Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- IND Format and Content
- Forms
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- Other IND Formats
- IND Maintenance
- Case Scenarios

# IND Format & Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigators Brochure
6. Protocols
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information

http://tinyurl.com/b759np3

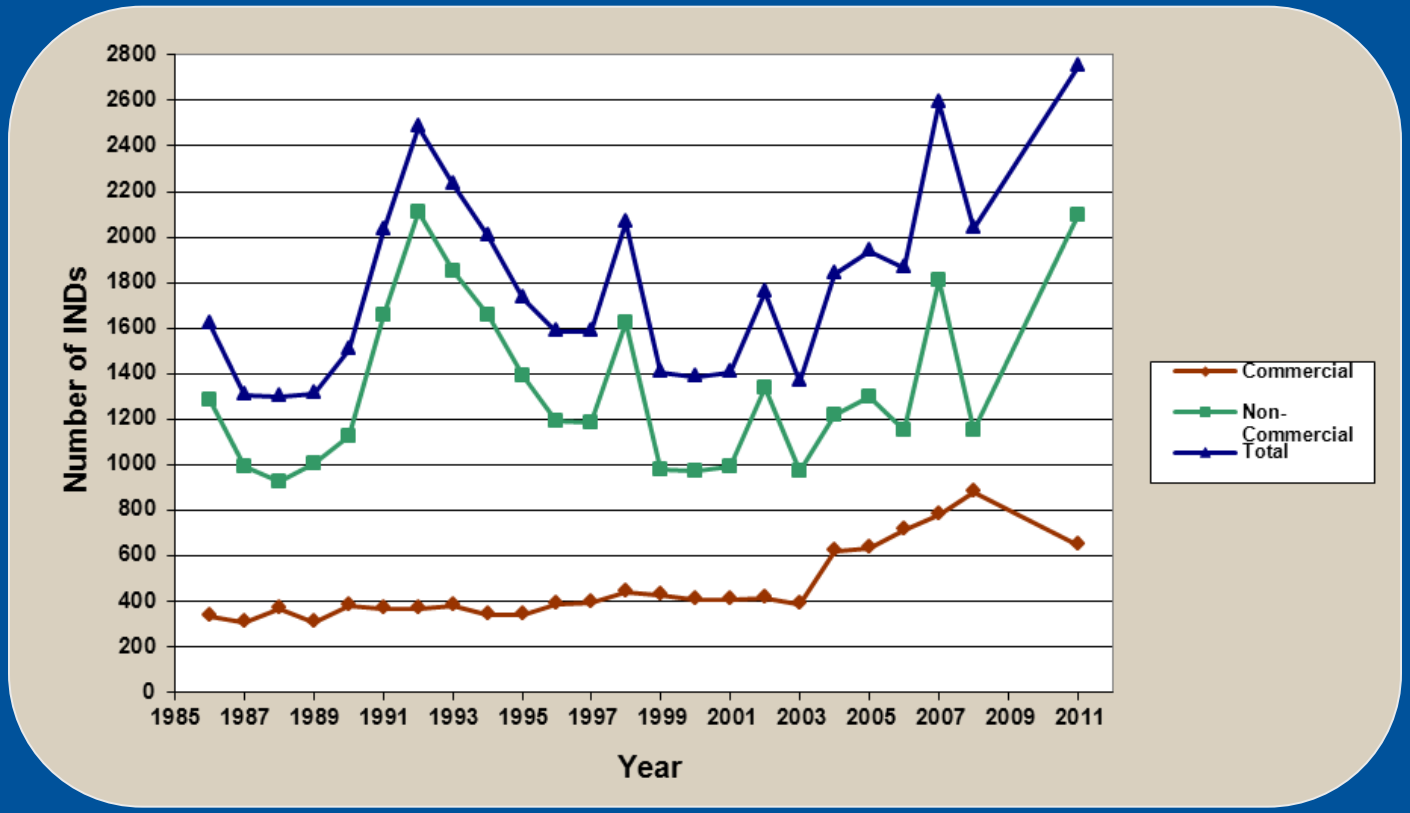
# IND Content for Sponsor-Investigator

It is best practice to ‘follow the script’ and maintain these standard headings.

Why??

# Original INDs Received

- CDER




FDA-TRACK

# IND Content for Sponsor-Investigator

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigators Brochure
6. Protocols
7. CMC
8. Pharm/Tox
9. Previous Human Experience
10. Additional Information

# What Information Do I Need for Each Section?

- FDA-Approved Drug – off label
- Investigational Drug (non-FDA approved) – from company
- Investigational Drug (non-FDA approved) – you control manufacturing
- Cellular Therapy Product

# IND Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigators Brochure
6. Protocols
7. CMC
8. Pharm/Tox
9. Previous Human Experience
10. Additional Information

Can be referenced to drug labeling or to letters of authorization (cross reference letter).

# What is a Letter of Authorization?

- This is a letter from a sponsor (company) to their IND (or IDE or DMF) stating that confidential information from their submission can be used in support of your submission.
- Thus, the FDA has “permission” to reference the named materials in support of your IND.
- Get copies of the letters to include in your submission

# Do you need a Letter of Authorization?

- For use of an investigational drug?

Probably

- For use of a commercially marketed drug?

Probably Not

# IND Format & Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigators Brochure
6. Protocols
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information

# Section 6 - Protocols

- Can submit more than one
- Things that go in this section. . .
  - Protocol (Section 6.1)
  - Informed Consent (Section 6.2)
  - CVs for principal investigator(s) and FDA Form 1572(s) (Section 6.3)

# IND Format & Content

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigators Brochure
   5.1 Letter of Authorization
6. Protocols
   6.1 Protocol
   6.2 Informed Consent
   6.3 Investigator and Facilities Data
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information

# Previous Human Experience

- May not be any previous human experience if drug is completely new
- May be able to refer to published literature
  - Same indication
  - Different indication

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# FORMS

- 1571 (Section 1)
- 1572 (Section 6.3)
- 3674 (Section 1 or 10)

Make sure that you have the right version!

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

# Key components of the FDA Form 1571

- Contractual agreement between sponsor and FDA
- Name of person responsible for conduct and progress of the study (Item 14)
- Name of person responsible for the review and evaluation of safety information on the drug (Item 15)
- Sponsor agrees to conduct investigation in accordance with all applicable regulatory requirements (Item 16)
- Must be submitted with each submission to your IND.

# Key components of the FDA Form 1572

- Contractual agreement between an Investigator and the Sponsor
- Name of person responsible for conduct an investigation and their credentials (Items 1 & 2)
- Listing of the facilities and labs that are participating in the investigation (Items 3 & 4)
- Listing of the IRB responsible for reviewing/approving study (Item 5)
- Listing of additional Sub-Investigators (Item 6)
- Investigator agrees to conduct investigation in accordance with all applicable regulatory requirements (Item 9 - Commitments)
- Should submit when you have information to update

# FDA Form 3674

- Requirement as of December 2007
- Form is a Certification of Compliance that all requirements of the Public Health Service Act (42 USC § 282(j)) have been met.

In other words, certification of registration at http://clinicaltrials.gov

Find Help: http://prsinfo.clinicaltrials.gov

# FDA Form 3674

**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, enacted by 121 Stat. 823, Public Law 110-85, 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, enacted by 121 Stat. 823, Public Law 110-85, 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, enacted by 121 Stat. 823, Public Law 110-85, 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.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/ SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*

NCT Number(s): _____ _____ _____ _____ _____

# Which drug trials must be registered?

## "Applicable Clinical Trials"

- Interventional studies (drugs, biologics, devices)
- Phase 2 – 4 (not typical phase 1 drug – safety)
- US FDA jurisdiction (e.g., IND/IDE or US site)
- Studies initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007

The law also requires results reporting for a subset of these studies.

Note: ICMJE requires more broad registration than the law.

# Deadline(s) for Registering Trials

- ICMJE Policy – Study must be registered prior to enrollment of first subject.
  In other words, if the PI wants to publish the data – you should follow this practice.

- LAW – No later than 21 days after enrollment of the first subject.
  This is required by US Public Law, you must do this!

# IND Content for Sponsor-Investigator

1. Forms 1571 & 3674
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan

} Mainly take from protocol

5. Investigators Brochure
   - 5.1 Letter of Authorization and/or product labeling
6. Protocols
   - 6.1 Protocol
   - 6.2 Informed Consent
   - 6.3 Form 1572 & CV
7. CMC
8. Pharm/Tox
9. Previous Human Experience

} 'L of A' and/or product labeling

10. Additional Information (Reprints)

# Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
- IND Format and Content
- Forms
- Filing and FDA Review Process
- Other IND Formats
- IND Maintenance
- Case Scenarios

# Filing the IND

- Cover Letter (it is a good idea to get second contact name on the cover letter)

- An original and two copies
  - Less than 3 copies may result in delays
  - Original in a grey ACCO-like report cover
  - 2 copies in different colors other than grey
  - Must be paginated uniquely throughout

# Filing the IND

- Where to send initial submission?

For a Drug (CDER):

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901 Ammendale Road
Beltsville, MD 20705-1266
Attn: [Name of Div. Dir.]

For a Biologic (CBER):

U. S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Room
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002
Attn: [Name of Div. Dir.]

- Who to address?
  - Usually the Division Director in the Initial IND Submission

# Filing the IND

- CDER – Can request a pre-assigned application number (3 business days)
- Email cderappnumrequest@fda.hhs.gov

**Subject:** Request for a Pre-Assigned *<insert Application Type>* Number

**Text:**

- Name of Applicant that will be on form (FDA 1571 or 356h) or transmittal letter (Master File)
- Applicant Address (street, city, state, zip code)
- Name of US Contact, Phone Number, Fax Number, Email Address
- Name of drug or Subject of Master File *<insert Established Drug Name (if applicable); or sponsor code name with short description of product, Dosage Form, Strengths if applicable >*
- Drug Trade Name (if applicable)
- Indication
- Review Division (if known)

http://tinyurl.com/pdafv3h

# What happens after you submit?

- FDA to respond within 30 days
- Sponsor receives ‘acknowledgement’ letter with IND number
  - Name of ‘project manager’ (address this person in future correspondence)
  - Save this letter!
- If no issues are identified by day 30, the IND is considered to be in effect (“approved”)
  - FDA does not routinely send letter stating that IND is in effect
  - This 30th day after receipt is your ‘effective date’!!

# What if there are issues with the IND?

- The FDA's primary objective in all reviews is to ensure the safety and rights of subjects
- Commitments in writing will often preclude a clinical hold (This would be submitted as an amendment to the IND)
- If issues cannot be resolved within this 30 day period, the FDA places the study (or IND) on "clinical hold"
- When hold is lifted – verify the 'effective date'

# Outline for Part 2: Preparation and Maintenance of an IND

- Definitions and Types of INDs
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# IND Format & Content - CTD

1. Module 1 – Administrative
2. Module 2 – Summary
3. Module 3 – Quality
4. Module 4 – Safety
5. Module 5 – Efficacy

1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigators Brochure
6. Protocols
7. CMC
8. Pharm/Tox
9. Previous Human Experience
10. Additional Information

Enables electronic submissions to FDA

# IND Format & Content – Expanded Access

- Single-patient IND (30 day review, AR)
  - Cover letter and 1571
  - Patient History
  - Proposed Treatment Plan
  - CMC & Pharm/Tox
  - Informed Consent
  - Investigator Qualification Info (1572/CV)

http://tinyurl.com/muzd2c

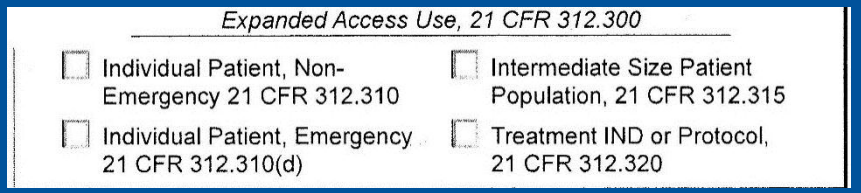
- Emergency IND (EIND)

Checklist and eligibility tool available on FDA website → http://tinyurl.com/k2tskkh

- Intermediate Size Population
- Treatment IND

Note: Protocol to Existing IND feasible

http://tinyurl.com/mau5hco



*Expanded Access Use, 21 CFR 312.300*

| | |
|---|---|
| ☐ Individual Patient, Non-Emergency 21 CFR 312.310 | ☐ Intermediate Size Patient Population, 21 CFR 312.315 |
| ☐ Individual Patient, Emergency 21 CFR 312.310(d) | ☐ Treatment IND or Protocol, 21 CFR 312.320 |

# Outline for Part 2: Preparation and Maintenance of an IND

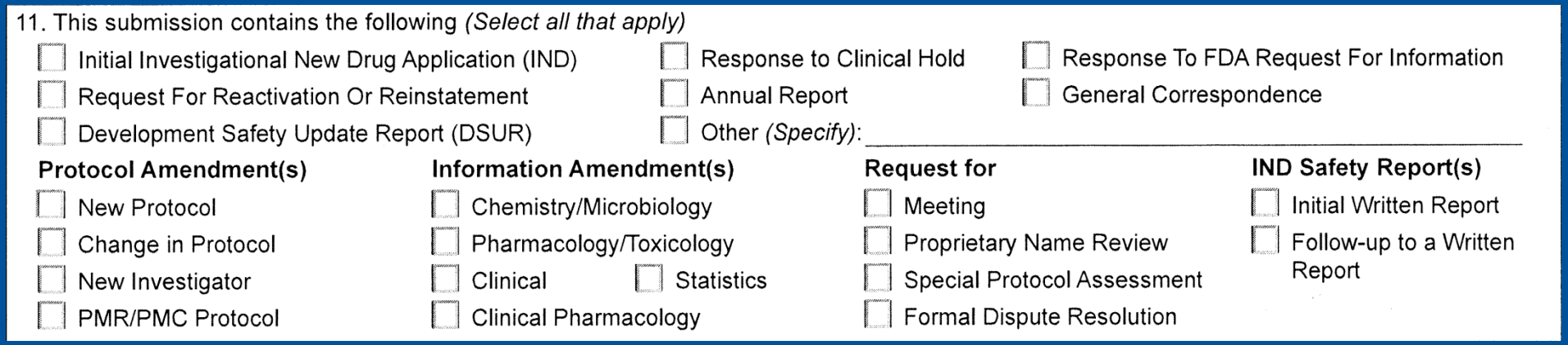
- Definitions and Types of INDs
- IND Format and Content
- Forms
- Filing and FDA Review Process
- Other IND Formats
- IND Maintenance
- Case Scenarios

# Caring for and Feeding Your IND

# IND Maintenance

- IND Amendments (Protocol, Information, Safety, Annual Reports)
- Notes on Multi-center Studies
- Cover Letters
- Financial Disclosure
- Ending an IND

# IND Maintenance



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(s)**

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol

**Information Amendment(s)**

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical
- ☐ Statistics
- ☐ Clinical Pharmacology

**Request for**

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

**IND Safety Report(s)**

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

## FDA Form 1571: Box 11

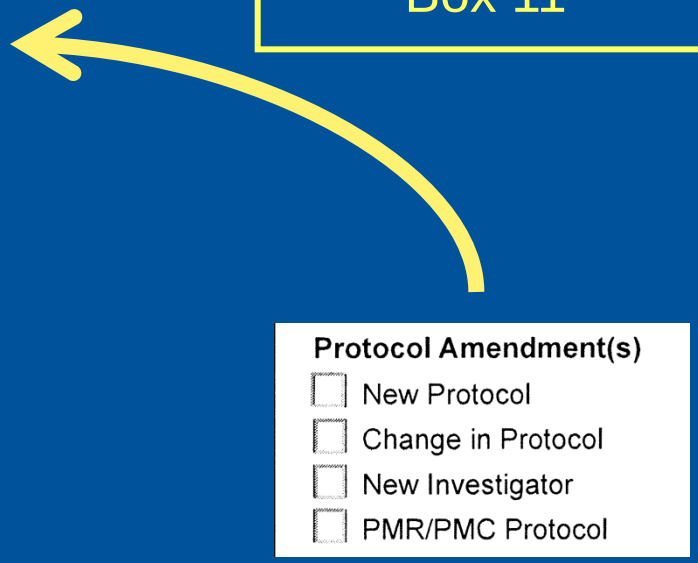
Maintenance of an IND includes any and all of the above types of submissions.

# Protocol Amendments

Four Kinds. . .

1. New Protocol
2. Change in Protocol
3. New Investigator
4. ~~PMR/PMC Protocol~~

From Form 1571: Box 11



# Protocol Amendments

New Protocols & Protocol Changes

- Can be submitted to an existing IND
- Must include a brief summary of the differences between new/revised protocol and previous protocol(s)
- No 30 day clock with FDA submission– Must have IRB approval before beginning
- You are strongly encouraged to check with your FDA project manager
- FDA & IRB submissions may occur in any order
- Should send IRB approval letters to FDA

# Protocol Amendments

## Change in Protocol (cont.)

What changes must be reported (regulation):

- Phase 1: changes that significantly affect the safety of subjects
- Phase 2 or 3: changes that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study

# Protocol Amendments

## Change in Protocol (cont.)

What changes should be reported (best practice):

Phase 1: all changes

Phase 2 or 3: all changes

# Protocol Amendments

- EXCEPTION: a change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided subsequent FDA and IRB notification

# Protocol Amendments

New Investigator

- Relevant for multi-center studies
- FDA must be notified of the new principal investigator (i.e. a site opening) within 30 days of them enrolling their first subject
- Sponsor must collect and submit the 1572 and CV of the PI from each site to the FDA
- Sponsor must collect the IRB approval letter from each site prior to shipping drug and should submit to FDA

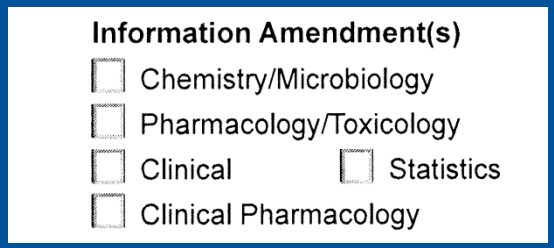
# Information Amendments

## Five Kinds. . .

Select review discipline to which submission applies.

1. Chemistry/Micro
2. Pharm/Tox
3. Clinical
4. Statistics
5. Clinical Pharmacology

From Form 1571: Box 11



# Information Amendments

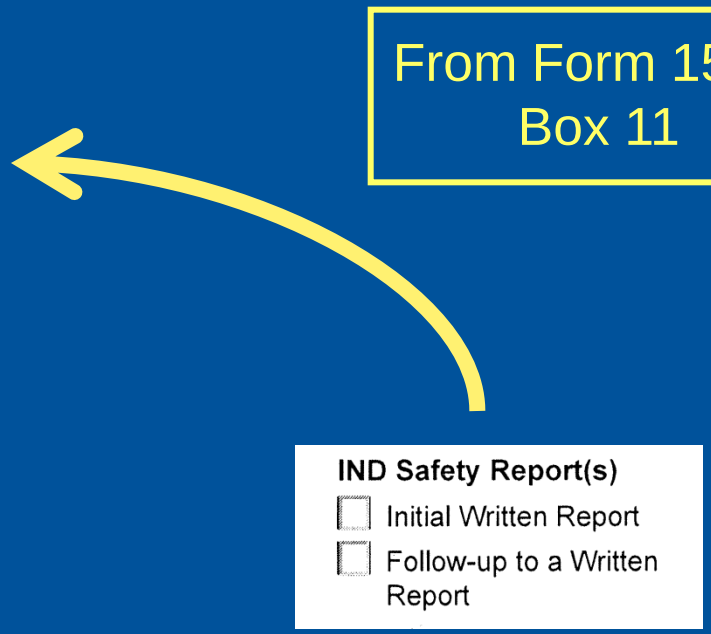
- Generally comprised of new technical information
- Statement identifying the nature and purpose of the amendment
- Note: Discontinuation of a clinical study can be submitted as an Information Amendment under “clinical”
- Submit information amendments as needed but, if possible, not more than every 30 days.

# IND Safety Reports

Two Kinds. . .

1. Initial Written Report
2. Follow-Up to a Written Report

From Form 1571: Box 11



# IND Safety Reports

- Serious and Unexpected Adverse Events associated with the use of the drug must be reported ‘quickly’
- Further, any findings from animal studies that suggest a significant risk for human subjects must also be reported ‘quickly’
- The sponsor-investigator must notify the FDA and all participating investigators

# IND Safety Reports

Serious Adverse Drug Experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse drug experience,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/ incapacity
- or a congenital anomaly/birth defect.

# IND Safety Reports

Unexpected Adverse Drug Experience:

- Any event in which the specificity or severity of which is not consistent with the current investigator brochure (IB) or package insert;
- or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the application

Note: 'expected' does not include events anticipated based on pharmacological properties (*i.e.* not theoretical expectedness)

# IND Safety Reports

| Type of SAE | FDA Timeline |
|---|---|
| **Unexpected fatal or life-threatening adverse drug experience** | 7 calendar days |
| **Serious and unexpected adverse drug experience** | 15 calendar days |
| **New animal findings that suggest significant risk to human subjects** | 15 calendar days |
| **Follow-up reports** | As relevant information is available |

# Use the Correct MedWatch Form

FDA Form 3500 (Voluntary MedWatch):

- For use by healthcare professionals, consumers, and patients. Submit by mail, fax or online

FDA Form 3500A (Mandatory MedWatch):

- For use by IND reporters, manufacturers, distributors, importers, user facilities personnel

# IND Safety Reports

- May submit via FDA Form 3500A or in a narrative format (foreign events may use CIOMS I form)
- In the report, identify all safety reports previously filed to the IND for similar adverse experience, and analyze the significance of the adverse experience in light of the previous, similar reports.

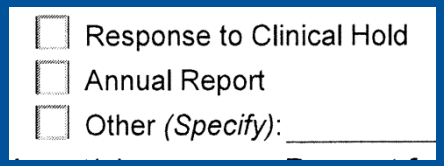
# Case Studies. . .(if time allows)

## IND Safety Reports and IND Maintenance

# Annual Reports

Due within 60 days of the anniversary of your IND (Effective Date)

From Form 1571: Box 11

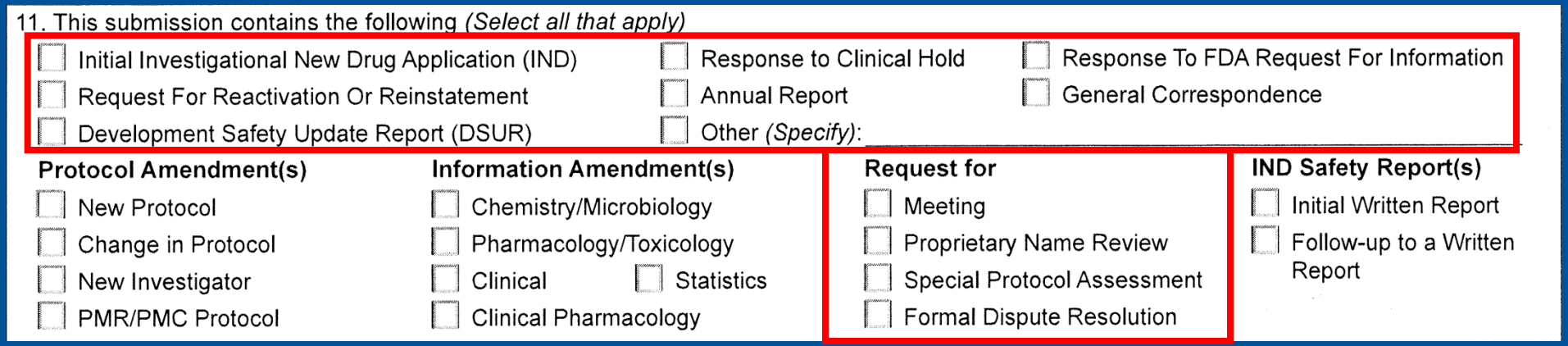



Templates can be found at our website

# Annual Reports - Content

1. Individual Study Information
2. Summary Information (Safety)
3. General Investigational Plan
4. Investigator Brochure
5. Protocol Modifications
6. Foreign Marketing Developments
7. Outstanding Business

# IND Maintenance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- ☐ Special Protocol Assessment
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**IND Safety Report(s)**

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

## FDA Form 1571: Box 11

Submissions should be filed as needed but, if possible, not more than every 30 days.

# IND Maintenance

- IND Amendments (Protocol, Information, Safety, Annual Reports)
- **Notes on Multi-center Studies**
- Cover Letters
- Financial Disclosure
- Ending an IND

# Multi-Center Studies

As a sponsor you. . .

- Must obtain 1572 & CV of PI from each site
  - Must submit to the FDA within 30 days of the site's first enrollment
- Must obtain the IRB approval letter from each site
  - Should submit to the FDA
- Must monitor your study at each site
  - In person, by mail or electronically

# Multi-Center Studies

As a sponsor you. . .

- Must send IND safety reports to each site (in addition to the FDA)
  - Each PI must also submit to their IRB

- Should request information early for annual reporting requirements
  - This makes life easier for you

Always remember, you have ultimate responsibility!

# IND Maintenance

- IND Amendments (Protocol, Information, Safety, Annual Reports)
- Notes on Multi-center Studies
- **Cover Letters**
- Financial Disclosure
- Ending an IND

# Cover Letters

- Ideally dated the date of submission
- Should summarize the content of your submission
- May ask questions or ask for FDA comment on items
- Important to list an alternate contact person

# IND Maintenance

- IND Amendments (Protocol, Information, Safety, Annual Reports)
- Notes on Multi-center Studies
- Cover Letters
- **Financial Disclosure**
- Ending an IND

# Financial Disclosure Forms

21 CFR Part 54

- Applies only to studies that will be used in support of a marketing application (NDA or BLA) or
- Any study in which a single investigator makes a significant contribution to the demonstration of safety

# Financial Disclosure Forms

Therefore, in general. . .

- Phase I Studies – Not Applicable
  - Unless they are critical for demonstrating efficacy (in a marketing application)
- Sponsor-Investigator Studies – Not Applicable

In any case, they are never submitted to INDs (only with marketing applications)

# IND Maintenance

- IND Amendments (Protocol, Information, Safety, Annual Reports)
- Notes on Multi-center Studies
- Cover Letters
- Financial Disclosure
- **Ending an IND**

# The End of an IND

- Withdrawal - Initiated by the sponsor
  - If withdrawn for safety reason, IRB must be notified
- Inactive Status – Initiate by FDA or sponsor
  - FDA may inactivate IND if no subjects are entered into clinical studies in 2 years or an investigation remains on clinical hold for >1 year (or sponsor can request this action)
  - A sponsor is not required to submit an annual report
  - An inactive IND can be reactivated via a protocol amendment
  - INDs inactive for > 5 years may be terminated by the FDA
- Termination – Initiated by the FDA
  - based on safety issues, deficiencies in the IND or in the conduct of an investigation
  - sponsors usually have a chance to respond

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

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

# Questions???