IND Exemption, Preparation and Maintenance

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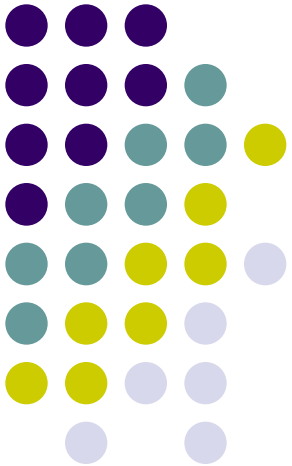


Templates and Guidance

- Best Practices Templates/Instructions
  - http://tiny.cc/d7bpt
- Recorded Webcasts
  - http://tinyurl.com/8n34gr4

Part 1: IND Exemptions

- Definitions
- Studies Using FDA Approved Drugs
- FDA Regulations & Guidance on IND Exemptions
- FDA Review Process
- Special Cases
- 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)). . .

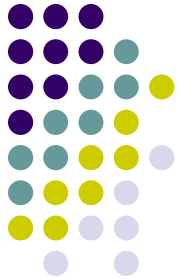
  ". . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. . ."

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

  * Note: "… food used as such (only to provide taste, aroma or nutritive value), or to affect the structure or function of the body, other than by providing nutrition, is not a drug"

  ** 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 Drug?

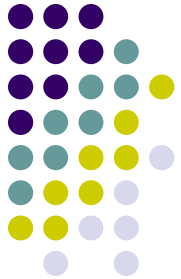


- A drug that is not approved to be marketed in the US
- An approved drug that is not used according to its approved label
- Note: Practice of medicine allows a physician to use any approved drug without prior regulatory approval

IND Exemption Assessment

- Is the drug investigational?
  - It is not approved in the US
  - It is not used according to the label (off-label)
- If the drug is investigational and is used in a clinical study, it is subject to 21 CFR 312
  - Note: Off-label use is common and allowed in the practice of medicine and often may be the standard of care

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

Might Require an IND

On-label

Off-label

IND not required*

It depends!

** Assuming no marketing application planned*

IND Exemption Assessment

- 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

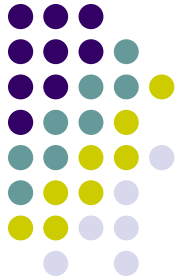
IND Exemption Assessment

- 21 CFR 312.2(b)(1): The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all of the following apply:
  - (i) The investigation is not intended to be reported to the FDA in support of a new indication for use nor intended to be used to support a significant change in the labeling for the product

IND Exemption Assessment

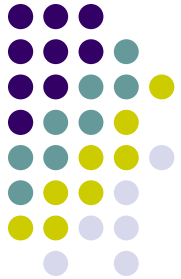
- (ii) . . .the investigation is not intended to support a significant change in the advertising for the product
- (iii) the investigation does not involve a route of administration or dosage level or use in a patient population that **significantly** increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
- (iv) the investigation is conducted in compliance with IRB and informed consent regulations
- (v) the study is conducted in compliance with regulations regarding promotion or distribution of investigational drugs

IND Exemption Assessment



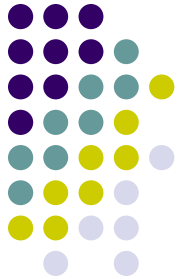
- Evaluate risks associated with the changes in:
  - Patient Population
  - Route of Administration
  - Dose and dosing regimen
  - Drug Combinations

IND Exemption Assessment



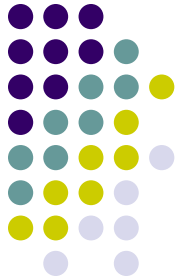
- Studies that generally are exempt:
  - Single-arm, phase 2 trials using marketing drugs to treat a cancer different from that indicated in the approved labeling and using doses and schedules similar to those in the labeling
  - Combinations of drugs, or new routes or schedules that have been described in the professional medical literature

IND Exemption Assessment



- Studies that are generally not exempt:
  - Studies involving substitution of a new agent of unproven activity are generally not exempt in settings where standard therapy provides a cure or increase in survival
  - Initial studies in humans of changes in the schedule of drug administration, new routes of administration or novel combinations of drugs

IND Exemption Assessments



- Modifications to the marketed drug
  - Low-risk modifications to the lawfully marketed drug (e.g. over-encapsulation, changes to color, scoring or size for blinding purposes) are generally acceptable
  - For modifications beyond what is listed above, FDA should be consulted
    - Mechanisms to consult FDA will be discussed later

Question

- Do you have to go to the FDA to get an IND exemption?
  - YES
  - NO

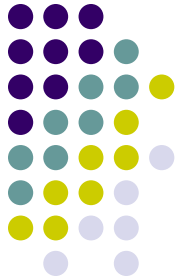
Answer

- No – the IRB can (and the investigator)
  - “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 (due to risk) . . .”
- However, at any time the FDA can be asked if the study meets the criteria for IND exemption.

Reasons to Go to FDA . . .

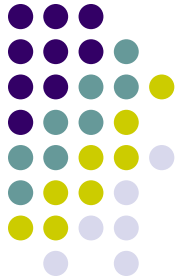
- IRBs as part of multi-site studies may have different conclusions as to whether a study is IND exempt
- Some funding sources (commercial and Federal) may want FDA confirmation of IND exemption status
- You and your IRB disagree on the IND exemption assessment

IND Exemption Assessment by FDA



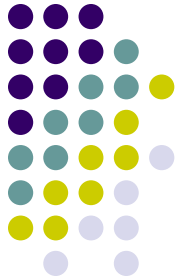
- Formal process
  - The protocol is submitted as part of a complete IND
  - The cover letter explains rational for IND exemption
  - The review is on a 30-day clock
- Informal process
  - Less work up front
  - Not all divisions will provide IND exemption assessments outside of the IND review process
  - Not on a clock, but generally faster

IND Exemption Assessment by FDA



- IND 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)
  - Make sure that your IND application is complete in case you are not exempt
    - IND applications covered later

IND Exemption Assessment by FDA



- Informal Process
  - Start with Pre-IND consultation contacts listed on FDA CDER website
    - http://tinyurl.com/kskl6e
  - For CBER, go to the Organizational Charts website
    - http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.htm
    - Click on the appropriate office that your IND would be reviewed by, e.g.:
      - Office of Vaccines Research and Review
      - Office of Cellular Tissue and Gene Therapies
      - Contact appropriate Division Director or Project Officer

IND Exemption Assessment by FDA

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.)

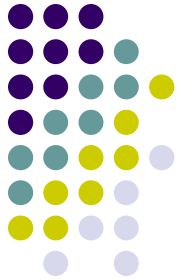
IND Exemption Assessment by FDA

- Informal process
  - Call or email contact and explain situation
  - Ask if they will review the study and determine whether the study meets the IND exemption criteria
  - Email protocol for review
  - FDA typically responds within 2 weeks whether the study meets the IND exemption criteria
  - Use the email response to support IND exemption requests with IRB or other interested parties

Special Cases

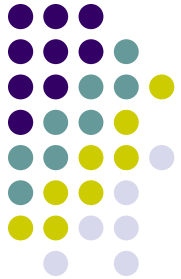
- Endogenous Compounds
- Live Organisms
- Dietary Supplements
- Food

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 no intent to treat or mitigate disease, there is intent to affect the structure or function of the body

Definition of a Drug

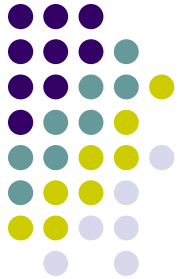


- A drug is anything that meets the definition of a drug per the FD&C Act. . .
  - ". . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. . ."
  - ". . . a substance (other than food) intended to affect the structure or any function of the body. . ."
  - Note: this definition not limited to compounds intended for 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



- Under the Dietary Supplement Health and Education Act of 1994, a dietary supplement is defined as a product taken by mouth that are intended to supplement the diet and contain a dietary ingredient
  - Examples include vitamins, minerals, herbs/botanicals, amino acids, concentrates, metabolites, extracts or combinations of these ingredients

Dietary Supplements

- Under DSHEA, a dietary supplement is **not** considered a drug if the intended use for which it is marketed is only to affect the structure or any function of the body
  - (i.e., not intended to be used for a therapeutic purpose)

Dietary Supplements

- Thus, the need for an IND in a study involving dietary supplements is determined by intent
  - Structure/function study with no therapeutic intent, then no IND is required
- Examples of studies not requiring an IND:
  - Studying the effect of calcium on bone mass
  - Studying the effect of fiber on bowel regularity

Dietary Supplements

- If the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then an IND is required
- Examples of studies requiring an IND:
  - Effect of a dietary supplement on osteoporosis
  - Effect of a dietary supplement to treat chronic diarrhea or constipation
  - Effect of a dietary supplement on depression or cognitive decline

Food

- Section 201(f) of the FD&C Act (21 U.S.C. 321(f)) defines a food as:
  - (1) articles used for food or drink for man or other animals,
  - (2) chewing gum, and
  - (3) articles used for components of any such articles
- Whether an IND is needed for a clinical study is again determined by intent

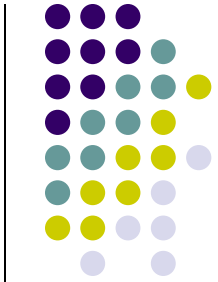
Food

- Food is considered to be a drug if it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. . .
  - An IND would be required if used as part of a clinical study
- Food that is intended to effect the structure or function of the body are not drugs, as long as the intended structure or function effect derives from the product's character as a food; its taste, aroma, or nutritive value
  - No IND needed for such a study

Food

- A study of an edible product to support growth of children
  - No IND is required
- A study of the same edible product used to assess the blocking the absorption of carbohydrates in the gut
  - The product becomes a drug because the primary purpose of consuming it has changed (no longer for its taste, aroma, or nutritive value)
  - An IND would be required

Case Scenario #1



- Investigator plans to do a trial to assess the effectiveness of Vitamin D in the treatment of depression
- Vitamin D manufactured by company X is legally marketed as a drug to treat osteoporosis
- Vitamin D manufactured by company (Y) is legally marketed as a supplement

Case Scenario #1

- Is this a drug study subject to 21 CFR 312?

- If yes, could the study be IND exempt?
  - Using Vitamin D from Company X?

  - Using Vitamin D from Company Y?

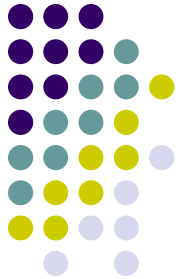
Case Scenario #1

- In case of clinical studies using supplements the need for an IND is determined by intent
  - Structure/function study – no IND required
  - Therapeutic study – IND required

Case Scenario #1

- For IND exemption criterion
  - 21 CFR 312.2(b)(1) – “the investigation of a drug product that is lawfully marketed in the United States” 21 CFR 312.2(b)(1)

Case Scenario #2



- Drug A and Drug B are both FDA approved to be given in a combination for the treatment of colon cancer
- An investigator wants to add Drug C to Drugs A and B in colon cancer
- Drug C is approved for treatment of breast cancer
- Trial design is Drugs A, B and C versus Drugs A and B in colon cancer

Case Scenario #2

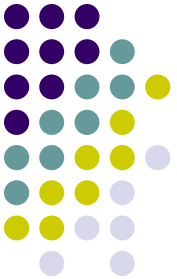
- Is this study eligible for IND exemption?

- What drug(s) is/are used off-label in this study?

Case Scenario #2

- Yes, all drugs are approved and thus eligible for an IND exemption
- Drugs A and B are approved to be give in the combination for this indication, but not approved to be given in combination with Drug C
- Drug C is neither approved to be given in the combo with A and B nor approved for this indication

Case Scenario #3



- Investigator plans to study the structural and functional changes that occur in the eye after the exposure to ragweed
- Ragweed extract is an FDA approved drug for use in the skin prick test to diagnose allergy
- Investigator plans to administer drops of the extract in the eye

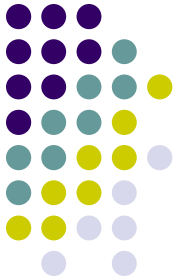
Case Scenario #3

- Is this a drug study subject to 21 CFR 312?
- If yes, could the study be IND exempt?

Case Scenario #3

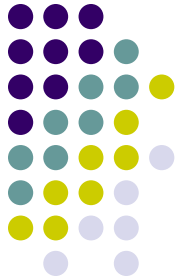
- Yes, this is a drug study (structure – function study)

- Yes, the study is eligible for IND exemption



Break

IND Preparation and Maintenance



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

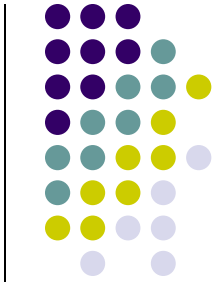
Definitions

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

Definitions

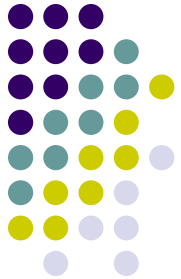
- Sponsor-Investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction a drug is administered or dispensed
- Commercial IND
  - Ultimate goal is to obtain marketing approval
- Sponsor-Investigator IND (Investigator-Initiated IND)
  - Primarily research-driven (goal is publication)

IND Format and Content



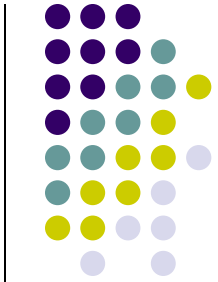
1. Form 1571 (cover sheet)
2. Table of Contents
3. Introductory Statement
4. General Investigation Plan
5. Investigators Brochure
6. Protocols
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Other Information
11. Biosimilar User Fee Cover Sheet
12. Clinical Trials Certification of Compliance

IND Content and Format



- Usual IND types
  - FDA approved drug
    - Use drug label to support IND
  - Non-FDA approved drug from company
    - Letter of Authorization to support IND
  - Non-FDA approved drug; sponsor is manufacturer
    - Sponsor is responsible for all information

IND Content and Format



- FDA Guidance on Content and Format of INDs
  - http://www.fda.gov/downloads/Drugs/.../Guidances/ucm074980.pdf
- Introductory Statement and General Investigational Plan
  - 21 CFR 312.23(3)
  - Sections usually separated into Sections 3 and 4 in IND as listed on Form 1571
  - This information usually derived from Protocol
  - Investigational Plan lists broad objectives and planned duration of the proposed clinical investigation(s)
    - This section is updated in each year's Annual Report

IND Content and Format

- Investigator's Brochure
  - 21 CFR 312.23(5) (Content of IB)
  - 21 CFR 312.55 (Requirements for IB)
    - IB not required if it is a Sponsor-Investigator IND and a single site study
  - ICH E6 (Proposed content and format of IB)

IND Content and Format

- Protocol
  - 21 CFR 312.23(6) (Content of Protocol)
  - ICH E6 (Proposed content and format of protocol)
  - 6.1 Protocol
    - More than one protocol can be submitted to IND
    - INDs are drug and indication specific, so multiple protocols must all pertain to the same drug and indication
  - 6.2 Informed Consent
  - 6.3 Form 1572 & CV

IND Content and Format

- CMC
  - 21 CFR 312.23 (7)
  - Approved drug labeling, Letter of Authorization or Sponsor provides information
  - Content of CMC section discussed later
- Pharmacology and Toxicology Information
  - 21 CFR 312.23 (8)
  - Approved drug labeling, Letter of Authorization or Sponsor provides information

Letter of Authorization

- This is a letter (amendment) from a sponsor or company to their IND, IDE or DMF stating that confidential information in their submission can be used in support of your IND
- Thus, the FDA has “permission” to reference the named submission to access information as part of the review of your IND
- A copy of the amendment is included in your submission in the appropriate section of the IND (CMC, Pharm/Tox)

Letter of Authorization

- Required for all non-approved drugs unless sponsor is providing necessary information
- It is not required for FDA-approved drugs, even if drug manufacturer has an open IND
- It is not necessary to obtain permission of drug manufacturer to use drugs in research studies
- Research is also exempt of license/patent status of drug

CMC Section

- FDA Guidance on cGMP for Phase 1 Drugs
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf
- Drug Substance
  - Manufacturer
  - Raw Materials
  - Manufacturing Process
  - Analytical Testing (in-process and release)
  - Release specifications
  - Certificate of Analysis
  - Stability data and protocol

CMC Section

- Drug Product
  - Manufacturer
  - Manufacturing Process
  - Analytical Testing
  - Specifications
  - Certificate of Analysis
  - Stability data and protocol
  - Container Closure
  - Labeling

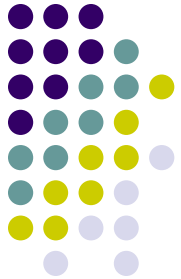
CMC Section, Biologics

- Components and Materials
  - Cells, reagents, excipients
- Procedures
  - Preparation of MCB, WCB, final formulation
- Product Testing
  - Sterility, mycoplasma, identity, contaminants, endotoxin, potency, viability, cell dose/number

CMC, Biologics

- In-process and release specifications,
- Certificate of Analysis
- Stability data, protocol
- Container/Closure
- Labeling
- Guidance for Cell Therapy CMC
  - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm

Pharmacology/Toxicology

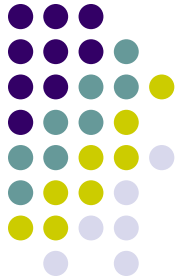


- Animal safety studies are required for IND application (IND enabling toxicity studies)
  - Nonclinical safety studies must be done according to Good Laboratory Practice (21 CFR Part 58)
  - ICH Guidance M3 lists nonclinical studies that must be performed by phase of drug development
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292340.pdf
- LOA or drug label may be sufficient for this section

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

Required Forms



- 1571
  - Goes in Section 1
- 1572
  - Goes in Section 6.3 along with CV
- 3674
  - Formerly placed in Section 10, now goes in Section 12 of new 1571
- Obtain updated forms at FDA website
  - http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

FDA Form 1571

- Key Components
  - This is a legal commitment to comply with regulations covering clinical trials conducted under IND
    - “WARNING: A willfully false statement is a criminal offense”
  - Instructions to fill out form found on FDA website:
    - http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM182850.pdf
  - Must be submitted with each submission to your IND
  - Name of the Sponsor (person) who takes responsibility for and initiates clinical investigation (Field 1)
  - For Sponsor-Investigator IND, the person should be named and sign the form (Field 25)

FDA Form 1571

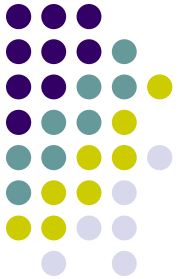
- Key Components
  - If a pharmaceutical company will be supplying the drug, but will not itself be submitting the IND (with that protocol), the company is not the sponsor
  - The date of submission on the form (Field 2) should match the date on the cover letter
  - The date of the Sponsor's signature (Field 22) can be different from the date of the submission (Field 2)
  - The order of the items listed in Field 13, Contents of Application, should be followed in your IND
  - The form can be on separate pages

FDA Form 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)*

FDA Form 1572



- Key Components
  - Investigator is named in Field 1 and signs in Field 11
  - Contractual agreement between an Investigator, the Sponsor and the FDA
    - "I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312"
    - "WARNING: A willfully false statement is a criminal offense"
  - Subinvestigators are listed in Field 6
    - These are individuals who will assist the investigator and make a direct and significant contribution to the data
    - This section must be updated as needed and the amended 1572 submitted to the IND

FDA Form 3674

- Certification of Compliance that all requirements for registration of applicable clinical trials on clinicaltrials.gov have been met
- Field 9: Certification
  - Box A is checked if the clinical trial is not subject to the registration requirements
  - Box B is checked if the registration requirements do not apply at the time of the submission of the IND
    - Checked if it is an applicable clinical trial but the CT.gov registration is not complete

FDA Form 3674

- Field 9, Certification
  - Box C is checked if the study has been registered
    - Provide the National Clinical Trial (NCT) number
  - So if you have an applicable trial at the time of submission, but have not registered, you can either:
    - Check B with the initial submission and the resubmit 3674 when you have an NCT number (checking C this time)
    - Or Check C with the initial submission and write ‘Pending’ in the space for the NCT number
      - You will need to write “Pending” physically as the field will only accept 8 digits

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 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.

FDA Form 3674

- What clinical trials must be registered?
  - Applicable clinical trials are:
    - Interventional studies (drugs, biologics, devices)
    - Phase 2 – 4, Phase 1 drug safety studies are not required
    - 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

FDA Form 3674

- ICMJE requires public trial registration at time of first patient enrollment if clinical data will be accepted for publication
- The Public Health Service Act requires registration no later than 21 days after enrollment of the first subject
  - Penalties up to a $10,000 fine for failing to submit or for submitting fraudulent information to ClinicalTrials.gov
  - After notification of noncompliance, the fine may go up to $10,000 per day until resolved
  - For federally funded grants, penalties may include the withholding or recovery of grant funds

Filing the IND

- Cover Letter
  - 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
- Submit original and two copies of IND
  - Less than 3 copies may result in delay of review
  - Typically original is in a grey ACCO-like report cover
  - 2 copies are in different colors (other than grey)

Filing the IND

- Where to send the initial IND application?
  - CDER (for drugs or protein therapeutics)

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

Filing the IND

- Where to send the initial IND application?
  - CBER

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

    Address to the Attention of the Division Director

IND Review by FDA

- Sponsor receives acknowledgement letter with IND number 10-14 days after submission
  - The letter contains the name of the project manager – this will be your contact person for the IND
  - Save this letter
- Approximately 7-10 days before decision, FDA may contact sponsor if there are issues that need to be resolved
  - Be available and respond quickly
  - You can email responses to FDA, but you need to formally submit responses to IND

IND Review by FDA

- By regulation, FDA must complete its review within 30 days of receipt of the submission
- If no issues are identified by day 30, the IND is considered to be in effect (“approved”)
- FDA does not routinely send a letter stating that IND is in effect
- This 30th day after receipt of the IND is your ‘effective date’
  - This date is important as the Annual Report is due each year within 60 days (+/-) of this date

IND Review by FDA

- The FDA's primary objective in all reviews is to ensure the safety and rights of subjects
  - All components of the IND maybe responsible for safety concerns; the clinical protocol, the manufacturing process/ drug product, or the pharmacology toxicology data
- To address FDA concerns, commitments in writing may sometimes preclude a clinical hold
  - E.g., revise protocol, submit CoA for drug product, etc
  - This would be submitted as an amendment to the IND

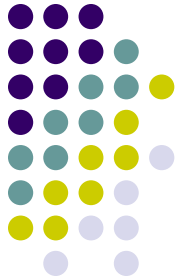
IND Review by FDA

- If issues cannot be resolved within this 30 day period, the FDA places the study (or IND) on "clinical hold"
  - This will be communicated by phone or email by the 30th day
  - The official letter will listing the clinical hold issues will arrive in approximately 30 days

IND Review by FDA

- FDA is not bound by a defined period of time to review responses to clinical hold issues
- When the clinical hold is lifted – the ‘effective date’ is now the date on the letter from FDA stating that you may now proceed

Other Types of INDs



- Single patient IND
  - Often referred to as ‘compassionate use’
  - This IND is used when patient cannot be enrolled in a clinical trial for a variety of reasons:
    - Patient does not fit inclusion/exclusion criteria
    - Current protocols are no longer enrolling
    - Pharmaceutical industry has concerns as data from these patients must be submitted as part of NDA/BLA review

Other Types of INDs

- Emergency Use IND
  - There is not sufficient time to submit IND prior to giving drug to patient
  - Must contact FDA and get approval
  - IND is submitted as soon as possible
- Treatment IND
  - Non-drug manufacturer opens IND to allow patient access to drug during NDA/BLA preparation or FDA review
  - Treatment protocol is opened under manufacturer's IND

Maintenance of the IND

- IND Amendments
  - Protocol, Information, Requests, Safety, Annual Reports
- Ending an IND
  - Inactivation
  - Withdrawal
  - Termination

Maintenance of the IND

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

Maintenance of the IND

- Protocol amendments
  - New protocol
  - Change in protocol
  - New investigator
  - Post Marketing Requirement/Post Marketing Commitment (PMR/PMC)

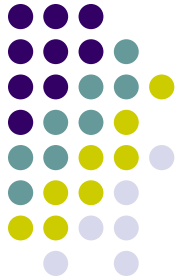
Maintenance of the IND

- Protocol amendments – changes to an existing protocol
  - A brief summary of the changes between the revised protocol and previous version is a nice reviewer aid
    - It is not necessary to provide clean and tracked-change versions
  - The amended protocol is official as soon as it is received at FDA
    - There is no defined review time for of amendments to the IND
    - However, if there are changes that could be construed as having a safety impact, it is recommended that the sponsor hear from FDA that the changes in the protocol are acceptable
    - IRB approval of the amended protocol is also required

Maintenance of the IND

- Protocol amendments – changes to existing protocol
  - Exception
    - When a change is necessary to eliminate an apparent immediate safety hazard to subjects, this can be implemented without prior IRB or FDA review
    - Both IRB and FDA must be notified as soon as possible

Maintenance of the IND



- New investigator
  - The signed 1572 and CV of a new principal investigator at a new site must be submitted to the IND within 30 days of the site enrolling their first subject
  - It is good regulatory practice for the sponsor to collect the 1572, CV and IRB approval letter from the site prior to shipping drug

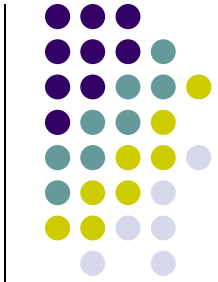
Maintenance of the IND

- Information Amendments
  - Chemistry/Microbiology
  - Pharmacology/Toxicology
  - Clinical
  - Statistics
  - Clinical Pharmacology

Maintenance of the IND

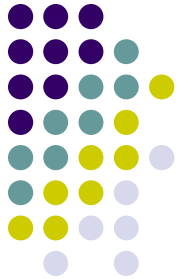
- Information Amendments
  - Generally comprised of new technical information
  - Statement identifying the nature and purpose of the amendment in the cover letter is recommended
  - Submit information amendments as needed but, if possible, not more than once every 30 days
  - Amended 1572 forms can be submitted as clinical amendments
- You can bundle different types of amendments in the same submission

Maintenance of the IND – IND Safety Reports



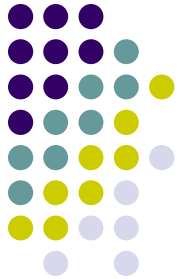
- Types
  - Initial Written Report
  - Follow-up to a Written Report
- Reporting requirements
  - Serious and Unexpected Adverse Events associated with the use of the drug must be reported within a defined period of time
  - The sponsor must notify the FDA and all participating investigators
- FDA Guidance:
  - "Safety Requirements for INDs…." Dec. 2012
  - http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf

Maintenance of the IND - IND Safety Reports



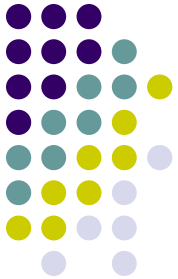
- An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes
  - death
  - a life-threatening adverse drug experience,
  - inpatient hospitalization or prolongation of existing hospitalization,
  - a persistent or significant disability/incapacity
  - a congenital anomaly/birth defect

Maintenance of the IND - IND Safety Reports



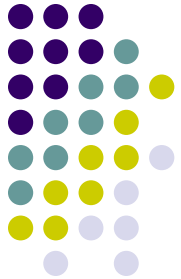
- Unexpected SAE
  - Any event in which the specificity or severity of the event is not consistent with the current investigator brochure (IB), package insert or protocol
- The assessment of relatedness/possible relatedness to the use of the drug is made by both the sponsor and the investigator
- The investigator is responsible for reporting unexpected SAEs to the IRB

Maintenance of the IND - IND Safety Reports



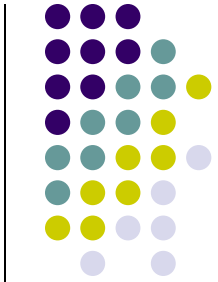
- Reporting to FDA
  - Unexpected fatal or life-threatening AE must reported within 7 calendar days
  - Serious and unexpected adverse drug experience must be reported in 15 calendar days
  - New animal findings that suggest significant risk to human subjects must be reported in 15 calendar days
  - Follow-up IND safety reports are submitted as relevant safety information is available

Maintenance of the IND - IND Safety Reports



- Reporting to FDA
  - IND safety reports are usually reported using the MedWatch FDA Form 3500A
  - The sponsor (or FDA)may propose a different reporting format and frequency for safety reporting
    - Must be approved in advance by FDA to be acceptable

Maintenance of the IND - Annual Reports



- Annual reports are due with 60 days of the anniversary of the effective date of the IND
- Content (21 CFR 312.33)
  - Individual Study Information
  - Summary Information (Safety)
  - Updated General Investigational Plan
  - Investigator Brochure (if changed)
  - Protocol Modifications (if not already submitted)
  - Foreign Marketing Developments
  - Outstanding Business

Ending the IND

- Withdrawal - Initiated by the sponsor
  - If withdrawn for safety reason, IRB must be notified
- Inactive Status – Initiated by FDA or sponsor
  - Sponsor - at any time
  - FDA – if no subjects enrolled in 2 years, investigation remains on clinical hold for >1 year or IND is inactive for >5 years
- INDs can be reactivated by submission of a new protocol
- As long as an IND is active, an Annual Report is due

Ending the IND

- Termination – Initiated by the FDA
  - Based on safety issues, deficiencies in the IND or in the conduct of an investigation
  - Rare occurrence, but FDA will do this if they feel subjects in the study are at unacceptable risk

Contact Information

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