Navigating Through Regulatory Waters: The DOs and DON’Ts of Preparing an Investigational New Drug Application

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- I do not have any financial interest or conflict of interest with any pharmaceutical companies.
Why to Send an Investigational New Drug (IND) Application to FDA?

- Under 21 CFR 312, any use in the US of a drug (or a biological product) not previously authorized for marketing in the US requires submission of an IND application to FDA.

- Any human research study must be conducted under an IND application if:
  - The research involves a **drug** as defined in section 201(g) of the FD&C Act (21U.S.C. 321 (g)(1))
  - The research is a **clinical investigation** as defined in the IND regulations (21CFR 312.3)
  - The clinical research is **not exempt** from the IND requirements
Does Your Research Involve a Drug under Clinical Investigation?

- **DRUG* (201(g)(1)) of FD&C Act**
  - “...An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease... AND
  - An article (other than food) intended to affect the structure or any function of the body...”

  *also applicable to therapeutic biological products

- **CLINICAL INVESTIGATION (21 CFR 312.3(b))**:  
  - ...An experiment in which a drug is administered, or dispensed to, or used involving, **one or more human subjects**, ...except for the use of a marketed drug in the course of clinical practice
Examples of Types of IND Applications:

- IND applications for clinical research
  - Sponsor's (commercial) IND application
  - Investigator's IND application

- Expanded Access IND applications for clinical treatment with investigational drugs of patients with serious and life-threatening conditions
  - Single patient vs. group of patients
  - Emergency use vs. non-emergency use

Final Rule for Expanded Access
DO#1: Decide Whether You Need to Submit an IND Application for Your Research

• To Sail or Not To Sail?
DO#2: Understand When Exemptions From IND Application Requirements Apply to Your Research

Your protocol could be exempt from the IND requirements if your study:

- Involves a lawfully marketed in the US pharmaceutical product AND
  - Conditions for exemption described under 21 CFR 312.2 (b) are met

OR

- Is a bioavailability or bioequivalence (BA/BE) study that investigates a copy of an approved drug product AND
  - Conditions for exemption described under 21 CFR 320.31(b) and (d) are met

OR

- Involves radioactive drugs that are generally recognized as safe and effective for the use that you propose in your study AND
  - Conditions for IND exemption described in 21 CFR 361.1 are met

Your Research Involves a Drug Product Lawfully Marketed in the US

Criteria for exemption from the IND regulations (21 CFR 312.2(b)):

- There is **no intent** to report the investigation to FDA as a **well-controlled study in support of a new indication** and no intent to use it to support any other significant change in the **labeling** of the product

- Your investigation is **not intended** to support a significant change in the **advertising** of the product

- The investigation does **not involve a route of administration, dose, patient population, or other factor that significantly increases the risk** (or decreases the acceptability of the risk) associated with use of the drug product

- The investigation is conducted in compliance with the requirements for review by an **IRB** (21 CFR 56) and **Informed Consent** (21 CFR 50)

- The investigation is **not intended to promote or commercialize** the drug product (21 CFR 312.7)

Two more categories:
• Cold Isotopes
• Dietary Supplements
• DO#3: Check with the FDA if unsure about IND exemptions!
You Have Decided to Submit an IND Application

• To Sail!
DO#4: Know Investigator’s Responsibilities
CFR 312.57 and 312.60-61:

- Ensure that an investigation is conducted according to the signed investigator’s statement (Form 1572), the investigational plan, and the applicable regulations
- Protect the rights, safety, and welfare of subjects under the investigator’s care
- Assume responsibilities for the control of drugs under investigation and maintain adequate records of
  - Drug disposition (shipment, delivery, receipt), quantity, and use
  - Case Report Forms (CRFs) and supporting data including patient data related to protocol occurrences and IND safety reports
  - Any financial interest of investigators
DO#4: Know Investigator’s Responsibilities, cont.
Investigator’s IND Application

As part of IND application processes:

- Submit to FDA an IND application according to the content and format specified in the regulations (21 CFR 312.23)
- Submit information about the trial to ClinicalTrials.gov and obtain a National Clinical Trial (NCT) number
- Respond to inquiries, correspondence, communications about your IND application
- Submit safety reports and amendments to FDA throughout the IND application lifecycle
- Keep all records related to your IND application
  - Retain records for a period of 2 years following the date of approval for marketing, OR
  - Until 2 years after the investigation is discontinued
DO#5: Know IND Application’s Content and Format (21 CFR 312.23(a))

(1) Cover sheet
(2) A table of contents
(3)* Introductory statement and general investigational plan
(5)* Investigator’s Brochure (applicable to multi-center trials)
(6) Clinical protocols
(7) Chemistry, Manufacturing, and Control information
(8) Pharmacology Toxicology information
(9) A summary of previous human experience with the investigational drug
(10) Additional information (e.g. dependence and abuse potential, information related to radioactive drugs)
(11) Relevant information (e.g. reference to previous submissions)

* 21 CFR 312.23(a)(4) is not listed
IND Application: Cover Sheet
21 CFR 312.23(a)(1)

- Forms 1571 & 1572 include:
  - Sponsor's contact information, phase of clinical investigation
  - A commitment not to begin the investigation until the IND application is in effect
  - A commitment that the clinical investigation will be conducted in compliance with relevant IRB and regulatory requirements
  - Signature of the investigator or the responsible sponsor or their authorized representative

- 1571- IND application
  

- 1572- Investigator’s Statement
  
  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf
IND Application:
Introductory Statement and General Investigational Plan
21 CFR 312.23(a)(3)

- Brief, 2-3 page summary
- Intended to place the developmental plan for the drug into perspective and to help FDA anticipate the needs of the future program
- Detailed developmental plan may not be well established yet and could be contingent on many factors; investigator (sponsor) should state this
IND Application: Protocols
21 CFR 312.23(a)(6)

- A protocol for each proposed clinical trial

- Phase 1 protocols may be less detailed, but should provide **all the critical details regarding assessments of safety**, including
  - number of patients, dosing plan, safety exclusion criteria, toxicity stopping rules

- Phase 2 and 3 protocols should provide sufficient details describing all aspects of the trial
  - All potential deviations from trial design should be built in the protocol from the outset
  - Objectives and purposes should be clearly stated
  - A description of the observations and measurements to be made to fulfill the objectives of the trial
  - A description of clinical procedures, lab tests, and all measures to be taken to monitor the effects of the drug

**DON’T** forgo sufficient descriptions of safety monitoring in your protocol
IND Application: Protocols (cont.)

Adverse Event (AE) Recording and Reporting in Clinical Protocols

- For all trial protocols in any phase, AE recording, grading, and reporting should be specified
  - System for AE recording (MedDRA or other)
  - AE grading is important in relation to the studied population
    » Select appropriate AE grading scale for the study
    » Anticipate merging of safety data from multiple trials
    » Have a consistent mechanism for judging relatedness

- AE reporting should be described in protocol and performed according to the respective regulations (21CFR 312.32)
IND Application: Chemistry, Manufacturing, and Controls (CMC)  
21 CFR 312.23(a)(7)

- CMC section should describe composition, manufacturing, and control of the drug substance and drug product

- At the time of IND opening and at any stage of development, the amount of information to be submitted depends on the scope of clinical investigation

- Sufficient information should be provided to allow evaluation of the safety of subjects in the proposed trial
# FDA Guidance Documents for CMC Information

|---|---|
IND Application: Pharmacology and Toxicology Information

21 CFR 312.23(a)(8)

- Adequate information about pharmacological and toxicological studies on the basis of which the sponsor (investigator) has concluded that it is reasonably safe to conduct the proposed clinical investigation

  - Description of the pharmacological effects and mechanisms of actions
  - Information on the absorption, distribution, and metabolism
  - Integrated Summary of data for all studies (21 CFR 312.23(a)(8)(ii)(a))
    » A statement about study conduct (Good Laboratory Practices)
  - Full data tabulation suitable for detailed review

Leveraging Information From Previously Submitted IND Applications

- For IND applications involving investigational products manufactured by other sponsors:
  - IND applicant may obtain a Letter of Authorization to reference the manufacturer’s IND application for the needed CMC or PT information
  - the Letter should be send to FDA with the IND application

- For IND applications involving approved products:
  - IND applicant may obtain a Letter of Authorization permitting to reference the manufacturer’s Drug Master File
  - the proposed investigation may rely on previous findings of acceptability of CMC specifications or PT data

DON’T need to submit detailed CMC or PT information if your investigational product is under another IND application or is an approved drug
DO#6: Know Where to Send Your IND Application
Know Where to Send an IND Application

- Center for Drug Evaluation and Research
- Office of New Drugs
- Respective Review Division
- Center for Biologics Evaluation and Research
- Respective Review Office

Paper or eCTD submissions:

FDA Address for IND applications involving drugs and therapeutic biological products

FDA Address for IND applications involving biological products
DO#7: Know One Useful Tip: A Pre-IND Consultation
Pre-IND consultation

• A consultation provided to sponsors and investigators planning to submit an IND application
  • Pre-IND package may include:
    » IND product’s characteristics
    » manufacturing processes,
    » development plan
    » design of the planned investigation in humans, AND
    » specific questions to the Agency about any or all of the above

1. Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants, May 2009

2. Guidance for Industry: IND meetings for Human Drugs and Biologics, Chemistry, Manufacturing, and Control, May 2001
DO#8: Understand the Procedural Aspects
The Procedural Aspects:

- Under 21 CFR 312.23(d) one original IND application and 2 copies are required.

- Regulatory review and all interactions with an IND applicant must occur within 30 days of the receipt date:
  - Information Requests
  - Teleconferences
  - Additional data submissions
  - Protocol modifications

- By Day 30, the FDA will notify the applicant that the IND application (studies):
  - May proceed, OR
  - Will be placed on “hold”
Clinical Hold or No Sailing
DO#9: Understand the Grounds for Imposition of Clinical Hold (21 CFR 312.42)

- Phase 1 protocols:
  - Human subjects are exposed to an unreasonable and significant risk of illness or injury
  - Clinical investigators are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND application
  - Investigator Brochure is misleading, erroneous, or incomplete
  - IND application does not contain sufficient information to assess the risks to subjects
  - IND application is for the treatment of a life-threatening or serious disease affecting both genders and only one gender is included in the proposed trial and there are no plans to include both genders in subsequent trials

- Phase 2 and 3 protocols:
  - Any of the above, OR
  - The protocol is deficient in design to meet its stated objectives
Clinical Hold: Examples

- CMC: Identification of a safety concern or insufficient data to make an evaluation of safety, for example:
  - Product with chemical structures of known or highly likely toxicity

- Pharmacology Toxicology:
  - Data from animal studies are not sufficient to support the anticipated exposure (dose/duration) for the proposed clinical trial

- Clinical:
  - Previously observed toxicities are not addressed by the proposed safety assessments
Release from Clinical Hold or How to Return to Sailing

- A letter is sent by FDA stating the reasons for hold and how to address them
- IND applicant submits a written response to be reviewed within 30 days
- If the response is adequate, the protocol is released from hold and the IND application is in effect
DO#10: Understand the Terms and Conditions of Adverse Event Reporting
Adverse Event Reporting: Definitions
21 CFR 312.32(c)(1)(i)(A) and (B)

• Adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related

• Adverse reaction means an adverse event caused by a drug

• Suspected adverse reaction is any adverse event for which there is a “reasonable possibility” that the drug caused the adverse event
  • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  • One or more occurrences of an event otherwise uncommon in the population exposed to the drug
  • An aggregate of specific events generally expected in the given population but observed to occur in a clinical trial in the drug group more frequently than in the control group

Guidance for Industry: Safety Reporting Requirements for INDs and BA&BE Studies, Dec 2012
Adverse Event Reporting: Definitions, cont.
21 CFR 312.32

• Unexpected:
  • Not listed in the investigator’s brochure at all or not listed at the specificity or severity observed, OR
  • Not consistent with the risk information described in the general investigational plan or elsewhere in the application

• Serious:
  • Death
  • Life-threatening
  • Leading to hospitalization
  • Resulting in significant disability
  • Resulting in congenital anomaly
Adverse Event Reporting: Expedited Mandatory Reporting

- 21 CFR 312.32(c)(1) Submit a report to FDA within 15 calendar days after the IND sponsor’s initial receipt of information if:
  - Suspected adverse reaction AND
  - Serious AND
  - Unexpected

If you are not the IND sponsor, send the report to the IND sponsor “promptly” (usually within 72h or as specified in the protocol)

- 21 CFR 312.32(c)(2) Submit a report to FDA as soon as possible but no later that 7 calendar days after the IND sponsor’s initial receipt of information if:
  - Unexpected fatal suspected adverse reaction OR
  - Unexpected life-threatening suspected adverse reaction

If you are not the IND sponsor, send the report to the IND sponsor “immediately” (usually within 24 h or as specified in the protocol)
Adverse Event Reporting: Expedited Mandatory Reporting, cont.
21CFR 312.32(c)(2)

- Initial form of communication may be telephone, fax, or e-mail to the Regulatory Project Manager in Review Division
- Send a written report on form 3500A

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm#obtain_and_send

- Include analysis of all safety reports previously filed with the IND concerning similar experience
- Send a follow up IND safety report as more information becomes available
DO#11: Understand Procedures for IND Application Maintenance

• Keeping Afloat!
IND Application Amendments and Annual Reports
21CFR 312.30-31 and 21CFR 312.33

• IND application Amendments may include any new information for any section of the application
  • submit when necessary, but to the extent feasible, not more than every 30 days

• IND application Annual Reports
  • Should be submitted annually within 60 days of the date when an IND went into effect
    – Individual study information (brief summary of study status and available results)
    – Summary information from the previous year’s clinical and nonclinical investigations

DON’T Send Numerous Minor IND Amendments
DON’T be late with Annual Reports
IND Application’s Status

- **Active (ongoing)**
- **Inactivated (upon FDA’s or sponsor’s proposal)**
- **Reactivated**
  - If activities under the IND application have restarted
- **Withdrawn (upon sponsor’s request)**
  - Studies are not showing effectiveness
  - A safety issue has emerged
- **Terminated (upon FDA’s proposal)**
  - Human subjects would be exposed to unreasonable or significant risk
  - Manufacturing processes are inadequate to establish and maintain appropriate standards
  - Other grounds for termination under 21 CFR 312.44
Additional References:

- 21 CFR 312
- Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well-Characterized, Therapeutic, Biotechnology-derived Products, Nov 1995
- Information for Investigators
- FDA Small Business Assistance