Submitting an IND: What You Need to Know

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Topics

1. IND Application: Content and Format
2. IND Submission: The First 30 Days
3. Responsibilities of Sponsors and Investigators
4. IND Amendments
5. Reporting Requirements
6. Inactivation; Reactivation; Withdrawal; Termination
IND Application: Content and Format

Content

• Requirements outlined in **21 CFR 312.23**
  – Cover Letter
  – Form FDA 1571
  – Form FDA 3674
  – Table of Contents
  – Introductory Statement/General Investigational Plan
  – Investigator’s Brochure
IND Application: Content and Format

• Nonclinical
  – Sufficient data to support clinical protocol
  – Basic exposure data

• Chemistry, manufacturing, and controls
  – Sufficient information to assure proper identification, quality, purity, and strength
  – Sufficient information to assess whether batches can be adequately produced and consistently supplied
IND Application: Content and Format

• Clinical protocol
  – Determine the phase of development
  – Provide supporting data (e.g., from ex-U.S. trials, PK data)
  – Specify how to ensure safety of the subjects/patients in the study (#1 reason INDs are placed on clinical hold)
IND Application: Content and Format

• Bundling: One IND or More?

  – One IND:
    • Early development studies - not sure of indication or dosage form
    • Closely related indications within a single review division
    • Multiple, closely-related routes of administration using same dosage formulation
    • Combination of two or more investigational new drugs for concomitant use
IND Application: Content and Format

• Bundling: One IND or More?

  – Multiple INDs:
    • Two or more unrelated conditions being developed
    • Multiple dosage forms being extensively investigated
    • Multiple routes of administration being extensively investigated
IND Application: Content and Format

Format

• Paper
  – Common Technical Document (CTD) format
  – Regulatory format (21 CFR 312.23)

• Electronic
  – Must use CTD format
  – Physical media
  – Electronic Submissions Gateway (ESG)
IND Application: Content and Format

Mailing address:

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

No user fee required!
IND Application: Resources

How Drugs are Developed and Approved:

IND Application (includes links to all IND guidances):

Small Business Assistance: FAQs on Drug Development and INDs

CTD Format Guidances:
IND Application: Resources

Electronic Submissions:
- Preparation questions: esub@cderv.fda.gov

Electronic Submissions Gateway:
- [http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm](http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm)
- Preparation/Registration/Policy Questions: esgprep@fda.hhs.gov
- Technical Issues: esgreg@gnsi.com

Secure e-mail account:
- Contact Wendy Lee at: wendy.lee@fda.hhs.gov

Pre-assigned application number:
- Send one email per application number request to cderappnumrequest@fda.hhs.gov.
IND Submission: The First 30 Days

- IND arrives in the Central Document Room
  - If electronic: Loaded into the EDR (Electronic Document Room)
  - If paper: Sent to White Oak Document Room
  - Data entered into DARRTS (Document Archiving, Reporting, and Regulatory Tracking System)
  - Review division’s Chief, Project Management Staff (CPMS) notified
IND Submission: The First 30 Days

- Regulatory Project Manager (RPM) assigned
  - Your point of contact with the review division
  - Issues IND Acknowledgement letter (includes IND number; receipt date; address for future submissions; contact information)
  - Performs regulatory/administrative review of IND application for completeness
  - Tracks/manages IND review process
IND Submission: The First 30 Days

- Scientific Discipline Team Leaders notified and reviewers assigned
  - Clinical
  - Nonclinical pharmacology/toxicology
  - Chemistry
  - Clinical pharmacology
  - Biostatistics (if phase 3 protocol)
  - Consult reviewers as needed
IND Submission: The First 30 Days

• Safety Review

  – The review division will determine within 30 days of receipt of your IND whether your study is “reasonably safe to proceed” (active) or will be placed on clinical hold
  – Some review divisions may issue a “safe to proceed” letter; Otherwise, “No news is good news”
  – INDs are not approved
IND Submission: Clinical Hold

- Clinical Hold: [21 CFR 312.42(a)]
  - An order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or suspend an ongoing clinical investigation
    - **Full Clinical Hold**: A delay or suspension of all clinical study under an IND.
    - **Partial Clinical Hold**: A delay or suspension of only part of the clinical study under an IND (e.g., a specific protocol or part of a protocol is allowed to proceed).
IND Submission: Clinical Hold

• Grounds for imposing a clinical hold for phase I trials: [21 CFR 312.42(b)(1)]
  
  – Human subjects would be exposed to an unreasonable and significant risk of illness or injury
  – Clinical investigators are unqualified
  – Investigator Brochure is misleading, erroneous, or incomplete
  – Insufficient information to assess risks to subjects
  – Exclusion by gender for life-threatening disease
IND Submission: Clinical Hold

• Grounds for imposing a clinical hold for phase 2/3 trials: [21 CFR 312.42(b)(2)]

  – All the reasons listed for phase 1 trials
  – The protocol is deficient in design to meet its stated objectives
IND Submission: Clinical Hold

• If a deficiency is identified that may be grounds for imposing a clinical hold:
  
  – The review division will attempt to discuss and satisfactorily resolve the matter with you first

  – Many potential holds can be resolved through such discussion (e.g., inadequate patient monitoring)
IND Submission: Clinical Hold

- If a clinical hold is imposed:

  - The review division will notify you by telephone and briefly discuss the clinical hold issues

  - A letter will follow detailing the hold issues and what you must do to resolve them
IND Submission: Clinical Hold

• Your response to the clinical hold letter:

  – Should be complete (i.e., address all the deficiencies identified in the letter)
  – If complete, you will receive an acknowledgement letter
  – If not complete, RPM will notify you
IND Submission: Clinical Hold

• Review division will respond within **30 days** of receipt of your response by either:
  – Removing the clinical hold;
  – Continuing the clinical hold; or
  – Modifying the clinical hold (e.g., full to partial)

• If review team cannot meet the 30-day deadline:
  – Review division will call you and discuss review progress/what is being done to facilitate completion of the review
Sponsor Responsibilities

• General responsibilities [21 CFR 312.50]

  – Select qualified investigators
  – Provide investigators with pertinent information
  – Ensure proper monitoring
  – Ensure that the investigation is conducted according to the general investigational plan/protocol
  – Inform FDA and investigators of significant new adverse effects/risks
Sponsor Responsibilities (cont.)

• Selecting investigators and monitors [21 CFR 312.53]
  
  – Select investigators that are qualified by training and experience
    • Obtain statement of qualifications (CV) from investigators
    • Should not use disqualified/debarred individuals
      (Debarment list: http://www.fda.gov/ora/compliance.ref/debar/default.htm)
  
  – Obtain additional information from investigators
    • Signed Form FDA 1572
    • Clinical protocol to be conducted
    • Financial disclosure [21 CFR 54]
Sponsor Responsibilities (cont.)

• Informing investigators [21 CFR 312.55]
  
  – Provide Investigator’s Brochure
    • Description of drug formulation
    • Pharm/tox effects and PK/PD information in animals and humans
    • Possible risks and side effects
    • Precautions/special monitoring
  
  – Provide new information regarding adverse events and safe use
Sponsor Responsibilities (cont.)

• Review of ongoing investigations [21 CFR 312.56]
  – Monitor the progress of all investigations
  – Review and evaluate evidence of safety and effectiveness of the investigational drug
  – Submit reports to FDA re: safety and progress
  – Assure compliance of investigators
  – Discontinue investigation if drug presents an unreasonable and significant risk (notify FDA, IRB, investigators)
Sponsor Responsibilities (cont.)

• Recordkeeping and record retention [21 CFR 312.57]
  – Receipt, shipment, and disposition of the investigational drug
  – Financial interest paid to investigators
  – Retain records for two years after drug approved OR investigations are discontinued
Sponsor Responsibilities (cont.)

• Permit FDA inspection of records and reports [21 CFR 312.58]
  – Permit inspection of records and reports related to the clinical investigations upon request
  – Provide copies of records and reports upon written request

• Disposition of unused drug [21 CFR 312.59]
  – Assure return of all unused supplies of the investigational drug
  – Ensure safe disposition (does not expose humans to risks)
Transfer of Responsibilities

• You may transfer any or all of your responsibilities to a contract research organization (CRO) [21 CFR 312.52]
  
  – Inform FDA in writing specifying which responsibilities are being transferred
  – CRO must comply with all applicable regulations associated with the transferred responsibilities
Investigator Responsibilities

• General responsibilities [21 CFR 312.60]
  – Ensure that the investigation is conducted according to the protocol and applicable regulations
  – Protect the rights, safety, and welfare of subjects

• Control of the investigational drug [21 CFR 312.61]
  – Administer drug only to subjects
  – Do not supply the drug to anyone not authorized to receive it
Investigator Responsibilities (cont.)

- Recordkeeping and record retention [21 CFR 312.62]
  - Case histories [e.g., Case Report Forms (CRFs) and supporting data, signed and dated consent forms, medical records]
  - Disposition of the investigational drug (i.e. dates, quantity, and use by subjects)
  - Retain records for 2 years after drug is approved for the indication being investigated or 2 years after the investigation is discontinued
Investigator Responsibilities (cont.)

• Investigator reports to the sponsor [21 CFR 312.64]
  – Progress reports
  – Safety reports
  – Final report
  – Financial disclosure reports

• Assurance of IRB review [21 CFR 312.66]
  – Assure that an IRB is responsible for review and approval of the protocol
  – Report any unanticipated problems involving risk to subjects
  – Not make any protocol changes without IRB approval except to eliminate immediate hazards to subjects
Investigator Responsibilities (cont.)

• Permitting FDA inspection of records and reports [21 CFR 312.68]

• Handling of controlled substances [21 CFR 312.69]
  – Securely locked; limited access
IND Amendments

- Protocol amendments [21 CFR 312.30]

- Information amendments [21 CFR 312.31]
Protocol Amendments

- New Protocol [21 CFR 312.30(a)]
- Changes in Protocol [21 CFR 312.30(b)]
- New Investigator [21 CFR 312.30(c)]
New Protocol [21 CFR 312.30(a)]

• New study may begin provided:
  – Submitted to IND
  – Approved by IRB

• Content and format
  – Copy of the protocol
  – Significant differences from previous protocols
  – Prominent identification (cover letter; form 1571)
  – Reference to any relevant information in IND
  – Request for comment (optional)
Changes in Protocol [21 CFR 312.30(b)]

• Amendment required for:

  – Phase 1: Change significantly affecting subject safety

  – Phase 2/3: Changes significantly affecting safety, scope, scientific quality
Changes in Protocol (cont.)

• Protocol changes may be implemented provided:
  – Change submitted to IND
  – Approved by IRB

• Exception: Change to eliminate an apparent immediate hazard to subjects can be implemented immediately.
Changes in Protocol (cont.)

• Content and Format
  – Description of the change
  – Reference to original protocol submission
  – Prominent identification (cover letter; form 1571)
  – Reference to any relevant information in IND
  – Request for comment (optional)
New Investigator [21 CFR 312.30(c)]

- An amendment is required when a new investigator is added to an ongoing study
  - **Exception**: adding a licensed practitioner to a treatment IND/treatment protocol
- Submit within 30 days of the new investigator being added
- Grouping several new investigators in one submission is permitted
New Investigator (cont.)

- Content and Format
  - Name and qualifications
  - Reference to previously submitted protocol
  - Prominent identification (cover letter; form 1571)
  - Additional info required under 21 CFR 312.23(a)(6)(iii)(b)
Information Amendments

[21 CFR 312.31]

• Amendment required for submission of essential information not within scope of protocol amendment, safety report, annual report
  – New information (e.g., clinical, clinical pharmacology, nonclinical; chemistry, study reports)
  – Discontinuance of study (within 5 days of decision)
Information Amendments (cont.)

• Submit as necessary (but to the extent possible, no more than every 30 days)

• Content and Format
  – Prominent identification (cover letter; form 1571)
  – Statement of nature and purpose
  – Organized in format appropriate for scientific review
  – Request for comment (optional)
IND Reporting Requirements

• Safety Reports [21 CFR 312.32]

• Annual Reports [21 CFR 312.33]
Safety Reports: Definitions
[21 CFR 312.32(a)]

- Associated with the use of the drug: reasonable possibility of causality
- Disability: substantial disruption of ability to conduct normal life functions
- Life-threatening adverse drug experience (ADE): immediate risk of death (based on investigator’s judgment)
- Serious ADE: any dose resulting in death; life-threatening ADE; hospitalization/prolonged hospitalization; disability; congenital anomaly/birth defect; medical event requiring medical/surgical intervention
- Unexpected ADE: specificity/severity inconsistent with known safety profile
Review of Safety Information
[21 CFR 312.32(b)]

• Review all information relevant to the safety of the drug from all sources (foreign and domestic) including:
  – Clinical, epidemiological, and animal investigations
  – Commercial marketing experience
  – Scientific literature reports
  – Unpublished scientific papers
  – Reports from foreign regulatory authorities
Types of Safety Reports

• Written 15-day reports
• Telephone/fax 7-day reports
• Follow-up reports
Written Safety Reports
[21 CFR 312.32(c)(1)]

- Notify FDA in writing of:
  - Any ADE associated with the use of the drug that is both **serious and unexpected**
  - Any finding from tests in lab animals that suggests significant risks for human subjects

- **When?**
  - ASAP; NO LATER THAN **15 days** after receipt of information
Written Safety Reports (cont.)

• Content and Format
  – FDA Form 3500A (MedWatch) or narrative format identified as “IND Safety Report”
  – Reference previous, similar reports
  – Analyze the significance of the ADE in light of similar adverse events
Telephone/Fax Safety Reports
[21 CFR 312.32(c)(2)]

• Notify FDA by telephone or fax of:
  – Any unexpected **fatal or life-threatening** ADE associated with the use of the drug

• When?
  – ASAP; NO LATER THAN **7 days** after sponsor’s receipt of information
Follow-up Safety Reports
[21 CFR 312.32(d)]

• Submit all relevant follow-up info ASAP

• Missed reports (not initially determined to be reportable): Submit ASAP but NO LATER THAN 15 days from discovery
Safety Reports: Miscellaneous

• Variations [21 CFR 312.32(c)(3)]
  – FDA may request varying frequency and format: Sponsor/FDA agreement

• Results of investigation of other safety information that does not fall under the specific reporting categories are submitted via:
  – Information amendment
  – Annual Report

• Disclaimer [21 CFR 312.32(e)]: You need not admit, and may deny, that the safety report constitutes an admission that the drug caused or contributed to the ADE
Annual Report [21 CFR 312.33]

Report of the progress of the investigation that includes:

• Individual study information
  – Title, purpose, patient population, study status
  – Total # of subjects planned, #entered to date, by age group, gender, and race; the #completed as planned, #drop-outs
  – Study results, if completed
Annual Report (cont.)

• Summary Information
  – Most frequent and most serious ADEs by body system
  – Summary of all IND safety reports submitted during past year
  – Study drop-outs due to ADEs
  – Subjects who died during study; cause of death
  – New info re drug’s actions
  – Completed nonclinical studies; summary of major findings
  – CMC changes
Annual Report (cont.)

- General investigational plan for coming year
- Revisions to the Investigator Brochure
- Phase 1 study modifications not previously reported
- Significant foreign marketing developments
- Log of outstanding business (optional)
Annual Report (cont.)

• Must be submitted within 60 days of the “in effect” anniversary date

• May request bundled annual reports/waiver of anniversary date
  • Multiple applications for the same active moiety
  • Harmonize and consolidate annual report
Inactivation [21 CFR 312.45]

• You or FDA may initiate inactivation if:
  – No subjects entered into studies for >2 years
  – All investigations on clinical hold for >1 year

• If FDA initiates inactivation:
  – Pre-inactivation letter issued to you
  – You have 30 days to respond
Inactivation (cont.)

• If IND inactivated:
  – All investigators notified
  – Stocks of drug returned to you or disposed of properly
  – Annual reports need not be submitted
Reactivation [21 CFR 312.45(d)]

- If you intend to resume clinical investigations under an inactive IND, you must submit a protocol amendment that includes:
  - Proposed general investigational plan
  - Appropriate protocol(s)
  - Additional information supporting the protocol(s)
  - Reference previously submitted information

- Safety review
  - The review division will determine whether your reactivated IND is safe to proceed or will be placed on clinical hold within **30 days** of receipt of your protocol amendment
Withdrawal [21 CFR 312.38]

• You may withdraw an IND at any time
  – Notify FDA
  – All investigations end
  – All current investigators notified
  – All stocks of the drug returned to you

• If IND is withdrawn due to safety reasons:
  – All of the above plus:
    • Notify reviewing IRBs
    • Reasons for the withdrawal
Termination [21 CFR 312.44]

- FDA may terminate an IND based on:
  - Deficiencies in the IND
  - Conduct of an investigation
  - An IND that remains on inactive status for ≥5 years (21 CFR 312.45)

- Pre-termination letter issued: allows you 30 days to respond to our proposal to terminate except where there is immediate and substantial danger to health of individuals
Questions?

- Email: maria.walsh@fda.hhs.gov
- Phone: 301-796-1017
- Mailing Address:
  10903 New Hampshire Ave.
  Building 22, Room 5208
  Silver Spring, MD 20993-0002