Overview of the IND Process

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CBER 101 – An Introduction to CBER

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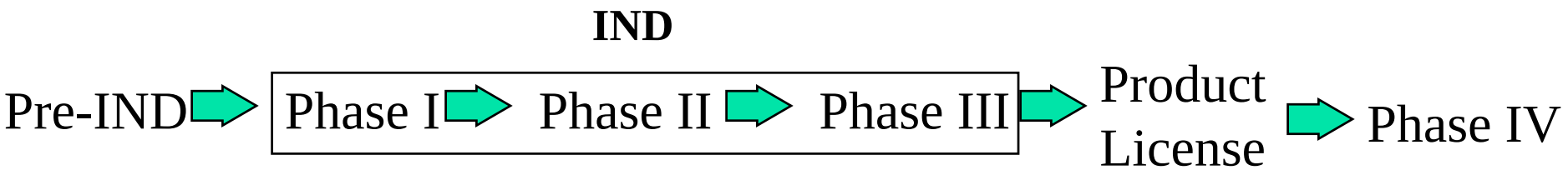
FDA Regulatory Authority

- Statutes – enacted by Congress
  - Public Health Service Act
  - Food Drug & Cosmetic Act
- Regulations – binding interpretations of law
  - Code of Federal Regulations (CFR)
    - 21 CFR 312 – Investigational New Drug Application (IND)
- Guidance – describes agency's policy & regulatory approach to a specific area or issue
  - Not binding on industry, but usually binding on agency

Development of IND



Phases of Investigation
(21 CFR 312.21)

- Phase I Investigational Studies
  - Designed to evaluate safety and side effects
- Phase II Investigational Studies
  - Designed to evaluate efficacy and dose ranging
- Phase III Investigational Studies
  - Expanded study, additional information on efficacy and safety
- Biologics License Application (BLA)

Phases of Investigation (Cont.)

- Can begin studies at any phase
  - *e.g.,* If studies already conducted in other countries, previous studies can support initial submission of a Phase 2 or 3 study, or BLA.
- May skip a phase
  - *e.g.,* If you perform a Phase 1 study, and have appropriate results it is possible to proceed directly to a Phase 3 study.

Pre-IND Meetings
(21 CFR 312.82)

- Request must be submitted in writing (fax is fine) and should include:
  - Description of product
  - Description of clinical indication and approach
  - Identification of purpose, objectives, and draft of specific questions
  - Suggested dates and times for meeting
    - Pre-IND meetings are scheduled within 60 days from receipt of request
- FDA will respond to request within 14 days of receipt of request

Pre-IND Meetings

(21 CFR 312.82) (Cont.)

- Meeting package must be submitted 4 weeks prior to meeting, includes:
  - Pre-clinical data
  - Product manufacturing scheme
  - Data regarding product characterization/proposed specifications
  - Proposed clinical protocol
  - Specific questions grouped by discipline (product, pre-clinical, clinical)

Pre-IND Meetings

(21 CFR 312.82) (Cont.)

- One hour formal meeting held by telephone unless unique situation.
- FDA issues official minutes to applicant within 30 days of formal meeting.

Additional Meeting Information

- Other meetings which may take place during the life-cycle of an IND include:
  - End of Phase 1 meetings (21 CFR 312.82)
  - End of Phase 2/Pre-phase 3 meetings (21 CFR 312.47)
  - Pre-BLA (Biologics Licensing Application) meetings (21 CFR 312.47)
- For more information, please see “Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products”

Ready to Submit IND

- Submit in triplicate if paper submission
- If electronic submission, no hard copies are needed
  - http://www.fda.gov/cber/gdlns/eind
- Address for submission

  CBER/(Appropriate Office)

  Attention: Regulatory Management Staff

  HFM-99, Room 200 north

  1401 Rockville Pike

  Rockville, MD 20852

Required IND Content and Format (21 CFR 312.23)

- Cover Sheet - Form 1571
  - Identifies sponsor, investigational drug, phase of investigation, parties responsible for monitoring conduct of trial
  - Found at http://forms.psc.gov/forms/FDA/fda.html
- Table of Contents
- Introductory Statement & General Investigational Plan

Required IND Content and Format (21 CFR 312.23) (Cont.)

- Investigator's Brochure
  - Required if product is supplied to clinical investigators other than the sponsor
- Protocol for each planned study
- Chemistry, Manufacturing, and Control Information
- Pharmacology and Toxicology Information

Required IND Content and Format (21 CFR 312.23) (Cont.)

- IRB Approved Consent Form
- Previous Human Experience
- Additional Information
  - Cross-reference authorization letters
  - Form 1572
    - Signed statement by each investigator containing their contact & IRB information, and agreement to conduct study following regulations
    - Found at http://forms.psc.gov/forms/FDA/fda.html
- Number Pages

Master File Submission
(21 CFR 314.420)

- Alternative mechanism for submission of product & manufacturing information
- Does not include clinical protocol
- Permits holder to incorporate the information by reference when submitting an IND or
- To authorize other persons to reference information, without direct disclosure

Master File Submission (21 CFR 314.420) (Cont.)

- FDA accesses MF via cross-reference letter submitted to MF and IND
  - Letter obtained from MF holder
- FDA reviews MF only when IND cross-referencing it has been submitted
- MFs are neither approved or disapproved
  - However, a cross-referencing IND may be placed on hold due to deficiencies in a MF

Initial Processing of IND

- IND number is assigned
- Regulatory Project Manager (RPM) receives IND submission.
  - Handles administrative processing of IND
    - Issues acknowledgment letter
    - Titles IND based on final product administered to patient
  - Serves as regulatory contact
  - Obtains review team assignments.
- IND routed to reviewers for review

IND Review Team

- Review team includes:
  - Regulatory Project Manager
  - Product Reviewer
  - Pharmacology/Toxicology Reviewer
  - Clinical Reviewer
  - Statistical Reviewer
- If product includes a device or drug, consult reviewers from CDRH or CDER are assigned if needed, during initial processing.

IND Review Process

- During first 30 days – review ongoing
  - Communication with sponsor
    - clarification
    - resolution of issues

IND Review Process

- Facsimilies
  - Used to make review decisions
  - Not official documents and not filed in an IND application – must be followed up with official hard copy submission
- E-mail
  - Outlook is not a secure email system
  - Can set up secure email with the agency

IND Review Process

- Within 30 days, IND goes into effect or is placed on clinical hold
  - 30-day review clock based on date of receipt in FDA
  - Decision is communicated by telephone
    - If IND is placed on hold, a detailed letter is issued within 30 days of hold telecon
    - If IND is allowed to proceed, a detailed letter is issued only if there are additional non-hold requests for information

Clinical Holds (21 CFR 312.42)

- Hold: An order issued by FDA to delay a proposed clinical investigation or to suspend an ongoing investigation
  - Once active, an IND may be placed on hold if the grounds listed under 21 CFR 312.42(b) are met
- Partial Hold: A delay or suspension of part of the clinical work under an IND
  - *e.g.* IND has 2 protocols, one may proceed & one may not

Response to Hold

- Upon receipt of an amendment entitled "Complete Response to Hold"
  - RPM sends email alerting reviewers to the response and the due dates.
  - The **reviewer** must immediately evaluate the submission to determine if the response is complete.

Resumption of Clinical Investigations [21 CFR 312.42(e)]

- If response addresses all issues detailed in hold letter, response is considered complete, and FDA must respond, in writing, within 30-days of receipt of the submission.
  - 30-day clock does not apply to partial or incomplete responses.

Resumption of Clinical Investigations [21 CFR 312.42(e)]

- FDA either allows study to proceed (remove hold) or continues the hold (response was complete, however inadequately addressed issues).
- For more information please see Guidance for Industry: Submitting and Reviewing Complete Responses to Clincial Hold and CBER SOPP 8201 – Issuance of and Response to Clinical Hold Letters for IND applications, found at http://www.fda.gov/cber/regsopp/8201.htm.

IND Amendments

- Any document, from the sponsor, in support of the IND
- Must be submitted in hard copy
  - In triplicate for INDs
  - Duplicate for Master Files

Annual Reports (21 CFR 312.33)

- Every year, within 60 days of the anniversary date that your IND went into effect, including:
  - Individual study information
  - Summary information
  - Description of the general investigational plan for the coming year
  - Any revisions to the investigators brochure
  - Any significant protocol modifications
  - Foreign marketing development
  - Any outstanding business

Annual Reports (Cont.)

- If we do not receive an annual report, FDA may issue the following letters:
  - Report Request Letter (RR)
  - Pretermination Letter (PT) if the sponsor does not reply within 30-days of the RR letter.
  - Termination Letter if the sponsor does not reply within 30-days of the PT letter.

IND Status (definitions, Cont.)

- Inactivated: IND is subject to no activity, but may be reactivated (21 CFR 312.45).
- Withdrawal: Sponsor requests to end IND, IND cannot be reactivated (21 CFR 312.38).
- Terminated: FDA orders sponsor to end all clinical investigations, IND cannot be reactivated (21 CFR 312.44).
- Exempt: Study does not have to be conducted under IND.

Inactivation (21 CFR 312.45)

- May be performed at request of sponsor or by FDA if certain conditions are met.
  - FDA may inactivate if IND on hold for over 1 year.
    - Once inactive for 5 years, FDA may terminate the IND.
  - FDA may inactivate if no subjects are entered into clinical studies for 2 years or more.

Inactivation (21 CFR 312.45) (Cont.)

- Sponsors not required to submit annual report to inactive IND; however,
- IND still in effect for purposes of public disclosure of information & data under 21 CFR 312.130.
- In general, inactive INDs cannot be cross-referenced.

Inactivation (21 CFR 312.45) (Cont.)

- Reactivation may occur with submission of new protocol, updated manufacturing information, etc.
  - Subject to 30 day review clock
- For gene therapy INDs, sponsor should inactivate rather than withdraw based on requirements for long-term patient follow up.
  - Retroviral INDs have life-long patient follow-up.
  - Adenoviral INDs have 15 year patient follow-up.

Withdrawal (21 CFR 312.38)

- At any time a sponsor may withdraw an IND without prejudice.
- All trials must be ended. These are dead files that cannot be resuscitated; sponsor must submit new IND.

Withdrawal (21 CFR 312.38) (Cont.)

- Withdrawn INDs cannot be cross-referenced.
- FDA does not recommend that sponsors submit information to withdrawn files. Submissions to withdrawn INDS are not tracked by DCC or RPM.

Termination (21 CFR 312.44)

- Termination is initiated by FDA and must be preceded by a proposal to terminate & an opportunity for the sponsor to respond.
- In general FDA doesn't terminate INDs but works with the sponsor to correct deficiencies.
- Most commonly used when IND has been inactive for more than 5 years.

Emergency Use of an IND (21 CFR 312.36)

- Occurs when need for an investigational drug arises in an emergency situation that does not allow for the submission of a complete IND.
  - *e.g.,* patient has few months to live.
  - For treatment of 1 patient, cannot be turned into an IND to treat multiple patients.
  - Not subject to 30-day clock; however, sponsor must submit all information within 30 days.

Information on IND Submissions

- Request CBER IND Packet:
  - Office of Communication, Training, and Manufacturers Assistance (OCTMA) (301) 827-2000 or http://www.fda.gov/cber/ind/ind.htm.