Initial IND submission
First 30 days

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FDA Disclaimer

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IND initial submission
The first 30 days

- FDA's work once your IND submission is received
- Safe to proceed or clinical hold
- Clinical Hold
  - Imposing, responding, and lifting
- Inactivation/termination

IND submission: the first 30 days

- IND arrives to the Central Document Room
  - If electronic: loaded in the Electronic Document Room (EDR)
  - If paper (3 copies): Sent to the White Oak Document Room
  - Data entered into DARRTS (Document Archiving, Reporting, and Regulatory Tracking System
  - IND assigned to Division by indication (endpoints)

IND submission: the first 30 days

- IND forwarded to CPMS (Chief, Project Management Staff)
- RPM (Regulatory Project Manager) assigned
  - Point of contact with the review division
  - Issues acknowledgment letter
  - Tracks/manages IND review process

IND submission: the first 30 days

- Review Team assigned
  - Clinical
  - Non-Clinical Pharmacology and Toxicology
  - CMC (Chemistry, Manufacturing and Controls)
  - Clinical Pharmacology
  - Biostatistics
  - Clinical Microbiology (Antimicrobial and antiviral drugs)
  - Microbiology-Sterility (as needed)
  - Consults

IND submission: the first 30 days

- The Review team will determine within 30 days of receipt of your IND whether your study is
  - "safe to proceed"- IND becomes active or
  - IND is placed on clinical hold
- Some Divisions issue a "safe to proceed letter"; Otherwise, "no news is good news"
- INDs are not approved

Clinical Hold definitions

- **Clinical Hold**: 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).

Grounds for Imposing a Clinical Hold: (1) Phase 1 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 not qualified
- Investigator Brochure is misleading, erroneous, or materially incomplete
- Insufficient information to assess risks to subjects
- Exclusion by gender for life-threatening disease or condition [unless justified/special circumstances]

Grounds for Imposing Clinical Hold: (2) Phase 2/3 Trials

21 CFR 312.42(b)(2)

- Any of the reasons listed above for Phase 1 trials

- The protocol is deficient in design to meet its stated objectives

What to do when you have a Potential Clinical Hold

21 CFR 312.42(c)

- If deficiency(ies) is identified that may be grounds for imposing a clinical hold:
  - FDA will attempt to discuss and satisfactorily resolve the matter with the sponsor first
  - Many potential holds can be resolved through such discussion (e.g., inadequate patient monitoring)

Imposing a Clinical Hold

21 CFR 312.42 (d)

- Division Director (DD) or person with responsibility for review of the IND acting on behalf of the DD makes the final decision to impose a clinical hold

Imposing a Clinical Hold

- Commercial Sponsor:
  - DD and RPM notify sponsor by telephone
  - Reasons for hold are discussed
- Sponsor-Investigator:
  - RPM notifies sponsor by telephone and briefly explains reasons for hold
  - Teleconference with DD is offered if desired by sponsor
- Clinical Hold letter is issued within 30 days of the date of the teleconference
- See details in MaPP 6030.1
  - https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm082022.pdf

Sponsor Responds to Clinical Hold

- RPM consults with review team to determine whether the sponsor's submission is a **complete response** (i.e., addresses all the issues identified in the clinical hold letter)

- If not complete response, RPM notifies sponsor

- If complete response, RPM sends acknowledgment letter and another 30-day cycle begins

Appeal

21 CFR 312.42(f)

If a Sponsor disagrees with the reasons cited for a hold they can:

- Request reconsideration of the decision in accordance with 21 CFR 312.48
- Dispute resolution procedure(s) 21 CFR 312.48
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm343101.pdf

Status Change:
From Hold to Inactive

21 CFR 312.42(g)

- If an IND remains on clinical hold for greater than 1 year the IND may be placed on inactive status by the FDA under 21 CFR 312.45.
- A sponsor is not required to submit annual reports to an IND on **inactive** status. An **inactive** IND is, however, still in effect for purposes of the public disclosure of data and information under 312.130.

Status Change:
From Inactive to Terminated

21 CFR 312.45(e)

- An IND that remains on **inactive** status for 5 years or more may be terminated under 312.44.

Best Practices

- Although not required, a cover letter is extremely useful
  - Contact phone #
  - Alternate name and phone #
  - E-mail addresses
- The initial IND submission (and each subsequent submission to the IND) should be accompanied by a Form FDA 1571
  - If paper, must be submitted in triplicate (1 original and two copies)

Best Practices

- Submission should be in red/orange/green binders
  - U.S. Government Printing Office (GPO)

    Washington DC 20404-0001

    202-512-1800

    Forms 2675, 2675a and b
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

More Best Practices

- Proofread your submission
- Provide a Table of Contents
- Divide your submission with tabs, not with colored paper
- Initial IND submission with one protocol
- Be available for any discussion during the first 30 days
- If you do not get funding, withdraw the IND

IND application-Format

- Paper
  - Common Technical Document (CTD) format
  - Regulatory Format (21 CFR 312.23)
- Electronic
  - Must use CTD format
  - Physical media
  - Electronic Submission Gateway (ESG)
- **May 2018, all commercial INDs have to be in eCTD format**

Where do I send my IND?

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

IND Application-resources

- Electronic Submissions Gateway:
  - http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm
  - Preparation/Registration/Policy Questions: esgprep@fda.hhs.gov
  - Technical Issues: ESGHelpDesk@fda.hhs.gov
- Secure e-mail account:
  - Contact SecureEmail@fda.hhs.gov
- Pre-assigned application number:
  - Send one email per application number request to cderappnumrequest@fda.hhs.gov

Questions?

Please complete the session survey:
surveymonkey.com/r/DRG-D2S02


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