Initial IND submission
First 30 days

Judit Milstein
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Judit.milstein@fda.hhs.gov
301-796-0763

FDA Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

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 5, 2018, all commercial INDs have to be in electronic 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-D2S01


FDA
U.S. FOOD & DRUG
ADMINISTRATION