IND Filing, Timelines, Paperwork and Reports

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A Translational Innovation Forum
Agenda

- IND filing timelines
- UC Davis IND webpage
- IND Cover Letter w/examples
- IND Table of Contents
- Completing Form FDA 1571
- Completing Form FDA 1572
- Binders and where to send
Agenda

- What happens after submission
- IND Amendments
- IND Annual Reports
- IND Safety Reports
Overview of pre-IND Process for academics

- Request pre-IND mtg
- Pre-IND mtg
  - Pre-IND materials due 4 weeks prior
  - 60 days
  - 14 days
- FDA will respond with the date
- Pre-IND mtg
- FDA will send meeting minutes and recommendations
- Prepare and submit IND
  - 30 days
- 60 days
Pre-IND Request (see handout)

- Cover Letter (formal, see example)
  - Product Name
  - Chemical Name
  - Chemical Structure
  - Proposed Indication
  - Type of meeting requested (Type B)
  - Purpose of the meeting
  - Expected Meeting outcomes
  - Preliminary Agenda
  - List of proposed questions
  - Attendees
  - Requested FDA staff
  - Approximate date when the briefing package will be sent
  - Suggested dates and times for the meeting
- Information Package
Art of Writing Questions

- What is it you are concerned about
- Propose the strategy and ask whether FDA agrees with it
- FDA is not going give you solutions

Example:
- Does the Agency agree that the proposed development plan and size of clinical safety database are appropriate?
- Based on an analysis of the PK data, an initial dose of 0.20 mg/kg at an infusion rate of 5 nmol/L/min to attain a steady state serum concentration of 150 nmol/L was selected. Does the Agency concur with this approach?
Meeting Minutes

- FDA will prepare minutes summarizing in bullet form important discussion points, disagreements, issues for further discussion
- Submitted to sponsor within 30 days
- Sponsor should also prepare minutes and send to FDA Project Manager
Pre-IND Consultation Contacts

Overview of IND Process for academics

- IND effective date
- 1 year date

Prepare and submit IND

30 days

Annual Report Due

60 days

Protocol Amendments
Information Amendments
IND Safety Reports
Who Prepares INDs at UC Davis?
Drug Products in UC Davis INDs

- Lawfully marketed Drug (Small Molecule)
- Lawfully marketed Drug (Biologic - protein)
- Lawfully marketed Drug (Biologic – Monoclonal antibody)
- Lawfully marketed Drug (Cellular Therapy)
- Lawfully marketed Device
- Dietary Supplement
- Investigational Drug (not yet approved)
Clinical and Translational Science Center

IND Process: File an IND

1. Register with CTSC by submitting this form to Kate Marusina, kate.marusina@ucdm.ucdavis.edu

2. Prepare IND package. Allow 4-6 weeks for IND preparation, collation, pagination, copying etc. IND application can be very short especially when manufacturing information (CMC Section) can be cross-referenced via letters of authorization from holder of original IND for the investigational drug.

   - Cover Letter (Example)
   - IND (Template, Example)
   - Fill out Form 1571, Investigational New Drug Application (Example). When downloading this form from the FDA website, note the OMB expiration date in the upper right corner. Your form will not be accepted if it is past the expiration date (Example)
   - Fill out Form 1572, Statement of the Investigator (Example)
   - FDA guidance on how to fill out Forms 1571 and 1572
   - Certification Form 3674 if applicable. Typically, you must submit the form 3674 with a new IND. Protocol amendments will require resubmission of this form.
   - For instructions on how to fill out, please see FDA Guidelines, Example

3. Assemble and bind volumes using FDA-approved binders (Binder Format Requirements):

   - Red ("Archival Binder")
   - Green ("Chemistry Binder")
   - Orange ("Pharmacology Binder")

   Each binder must be labeled using the FDA format (Template)

4. Each Submission (binders + forms) need to be submitted in triplicate

5. Send to:

   Food and Drug Administration
   Center for Drug Evaluation and Research
   Central Document Room
   5901-B Ammerdale Rd. Beltsville, MD 20705-1266
IND Package

- Cover Letter
- IND materials
- Form FDA 1571
- Form FDA 1572
IND materials - Table of Contents

- Introductory Statement
- General Investigational Plan
- Investigator’s Brochure
- Protocol + Form 1572
- CMC
- Pharmacology and Toxicology
- Previous Human Experience
- Additional Information

For lawfully marketed drugs – product label (insert) can be used
For investigational drugs – ask for permission to cross-reference company IND

See handout - Herceptin
Form FDA 1571

- Has to be current, always check
  - [www.fda.gov](http://www.fda.gov), search for “IND”, IND Forms and Instructions (left hand bar)
  - Form Approved OMB No 0910-0014
    
    Expiration Date May 31, 2009 Required with EVERY communication regarding this IND (check different boxes)
  
- Must be signed and dated
- Use Adobe Professional to save changes
- See Handout
Statement of Investigator, Form FDA 1572 (1572): an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic.

Has to be current: [www.fda.gov](http://www.fda.gov), search for “IND”, IND Forms and Instructions (left hand bar)
Form FDA 1572

- Each new investigator has to sign – submit as Protocol Amendment
- Is not required for the studies that are not done under IND
- See handout – Q&A
Cover Letter

- **Address to:**
  - Food and Drug Administration
  - Center for Drug Evaluation and Research
  - Central Document Room
  - 5901-B Ammendale Rd. Beltsville, MD 20705-1266
  - Attn: Division Director (see your handout)

- **Has certain layout:**
  - Drug, indication, phase of investigation
  - Any prior communication (i.e. pre-IND)
  - Contact information
  - Reaffirm that the clinical trial will not start until IND goes into effect
  - Confidentiality statement
Binders

- 3 copies of everything (cover page, 1571, info)
- And Labels

IND. NO. 106756

Safety and Efficacy of the Capsaicin Troche (0.1 mg) in treatment of individuals with dysphagia

Serial 0006

Peter Belafsky, MD

University of California, Davis
FDA Contacts

- **Office of New Drugs**
  - Office of Drug Evaluation I  Robert Temple, MD
    - Cardiovascular, Renal, Neurology, Psychiatry
  - Office of Drug Evaluation II  Curtis Rosebraugh, M.D.
    - Anesthesia, Rheumatology, Endocrinology, Pulmonary and Allergy
  - Office of Drug Evaluation III  Julie G. Beitz, M.D.
    - Gastroenterology, Dermatology, Dental, Reproductive and Urology
  - Office of Antimicrobial Products  Edward M. Cox, MD., M.P.H.
    - Antiinfectives, antivirals and ophthalmology
  - Office of Drug Evaluation IV  Charles J. Ganley, M.D.
    - Non-prescription products, Medical Imaging products
  - Office of Oncology Drug Products  Richard Pazdur, M.D.

See your handouts for the Division Director Names. Your IND is addressed to the Director of the Division.

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ContactCDER/UCM070722.pdf
Botanical Review Team (BRT)

About BRT
Organization
What is a Botanical Drug?
Frequently Asked Questions on Botanical Drug Development
Guidance for Industry
Related Botanical Links
Contact Us

Shaw T. Chen, M.D. Ph.D.
Deputy Director, Office of Drug Evaluation IV
Leader, Botanical Review Team

About the Botanical Review Team

The CDER Botanical Review Team (BRT) provides scientific expertise on botanical issues to the reviewing staff and ensures consistent interpretation of the Guidance for Industry Botanical Drug Products.

What We Do

- The BRT participates in all phases of review, meetings and decision-making processes for all botanical pre-Investigational New Drug (IND) applications, INDs, and New Drug Applications (NDAs).
- The BRT follows the review process for INDs and NDAs for botanical drug products described in MaPP 6007.1 Review of Botanical Drug Products.
- The BRT responds to external constituents who have general botanical drug development questions.
- The BRT responds to issues and meeting requests from FDA’s Office of the Commissioner and works on common botanical issues with
  - the National Center for Complementary and Alternative Medicine
  - the Office of Dietary Supplements at the National Institutes of Health
  - FDA’s Center for Food Safety and Applied Nutrition (CFSAN)
- The BRT serves as an expert resource for CDER on all botanical issues, and
- The BRT works with external regulatory and scientific groups, and presents at and participates in workshops to promote and enhance botanical drug product development and knowledge.
Botanical Drugs

- *Botanical products* are finished, labeled products that contain vegetable matter as ingredients.

- Are Investigational New Drug (IND) applications required for clinical studies of botanical products that are also lawfully marketed as dietary supplements in the U.S.?
  - Yes. If a lawfully marketed botanical dietary supplement is studied for its effects on diseases in the proposed investigation (i.e., to cure, treat, mitigate, prevent, or diagnose disease including its associated symptoms), then it is an investigational new drug and will be subject to IND requirements. This applies to studies in INDs sponsored for both commercial and academic research purposes.
Botanical Drugs

- Can be approved as a drug under New Drug Application or ANDA and still exist as a dietary supplement on the market
Structure-Function claims

- Structure-function claims describe the effect a dietary supplement may have on the structure or function of the body
  - Promotes cardiovascular health
  - Provides antioxidant protection
Disease Claim

- Disease claim - a claim to diagnose, cure, mitigate, treat, or prevent disease
  - Herceptin is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein...
  - Require FDA approval
  - 10 criteria to decide whether it is a disease claim

- Capsaicin (extract from peppers) formulated in a lozenge (Dr. Belafsky, UCD)
What happens to IND after you send it?

- Received at the Central Doc Rm
- Stamps IND with the receipt date
- IND # assigned
- Assigned to review division
- FDA will send you a Acknowledgement letter with your IND #
- FDA has 30 days to respond
- If you do not hear within 30 days, can start the study, but call first!
...or you get a Clinical Hold letter

- Complete or Partial
- Typically, the FDA attempts to resolve issues first
…or you get a Clinical Hold letter

- Can occur anytime (not only at the start)
  - The IND does not contain sufficient information ... to assess the risks to subjects of the proposed studies (**insufficient information**).
  - Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury (**unreasonable risk**).
  - The plan or protocol for a Phase 2 or 3 clinical investigation is clearly deficient in design to meet its stated objectives (**design flaw**).
  - The investigator brochure (IB) is misleading, erroneous, or materially incomplete (**Misleading IB**).

- See Handout – clinical hold
Essential Requirements to Maintain IND

- Stay current with IND amendments
- Submit Annual reports, even if you did not enroll
- Submit Safety Reports
- Withdraw IND if needed
IND Amendments

- **Protocol Amendments [21 CFR 312.30]**
  - New protocol / Change in the protocol (IRB approval required after submission)
  - New investigator (within 30 days of being added)

- **Information Amendments [21 CFR 312.33]**
  - CMC
  - Pharm/Tox
  - Notice of discontinuance
IND Annual Reports

- 21 CFR 312.33
- Even if did not enroll any patients
- Can include various changes that were not captured in the Information and Protocol Amendments
- Due 60 days prior the IND effective date ("anniversary date")
- See the website for examples and templates
IND Safety Reports

- **21 CFR 312.32**
- See website for submission requirements

- **15-day (calendar) report**
  - Notify FDA & all investigators in writing
  - Any serious and unexpected AE, associated w/ use of drug (including information from non non-IND studies); or,
  - any finding in laboratory animals that suggests a significant risk for human subjects
  - Notify IRB

- **7-day (calendar) report**
  - Notify FDA via phone or fax
  - Any fatal or life life-threatening AE associated w/ use of drug
  - Notify IRB
MedWatch Form 3500A

- Mandatory reporting
- Make sure it is not Form 3500 (Voluntary reporting)
- See handout
CTSU: SAE Processing for UCD Patients

- **UCD PATIENT**
  - SAE is identified by CTSU Staff
    - Study Coordinator completes SAE Report per protocol
    - Fax MedWatch Form to FDA
    - "Acknowledgement of Receipt" Letter from FDA
    - Study Coordinator completes "UCDCC Serious Adverse Event Cover Sheet"
    - Study Coordinator and PI determine event was unanticipated, related and increase risk
    - UCDCC Serious Adverse Event Cover and SAE report submitted to CC Database
  - Study Coordinator submits "Report of Unanticipated Problems Involving Risk to Participants or Others" to IRB

[SAE Report = IND Safety Report or MedWatch Form]
Withdrawing an IND

- 21 CFR 312.38

- Sponsor may withdraw IND at any time w/o prejudice
  - Notify FDA of the reasons
  - End clinical investigations
  - All drug stock disposed of or returned to the drug manufacturer
Questions, comments?