FDA 101 Session: Care and Feeding of an Investigational New Drug (IND)

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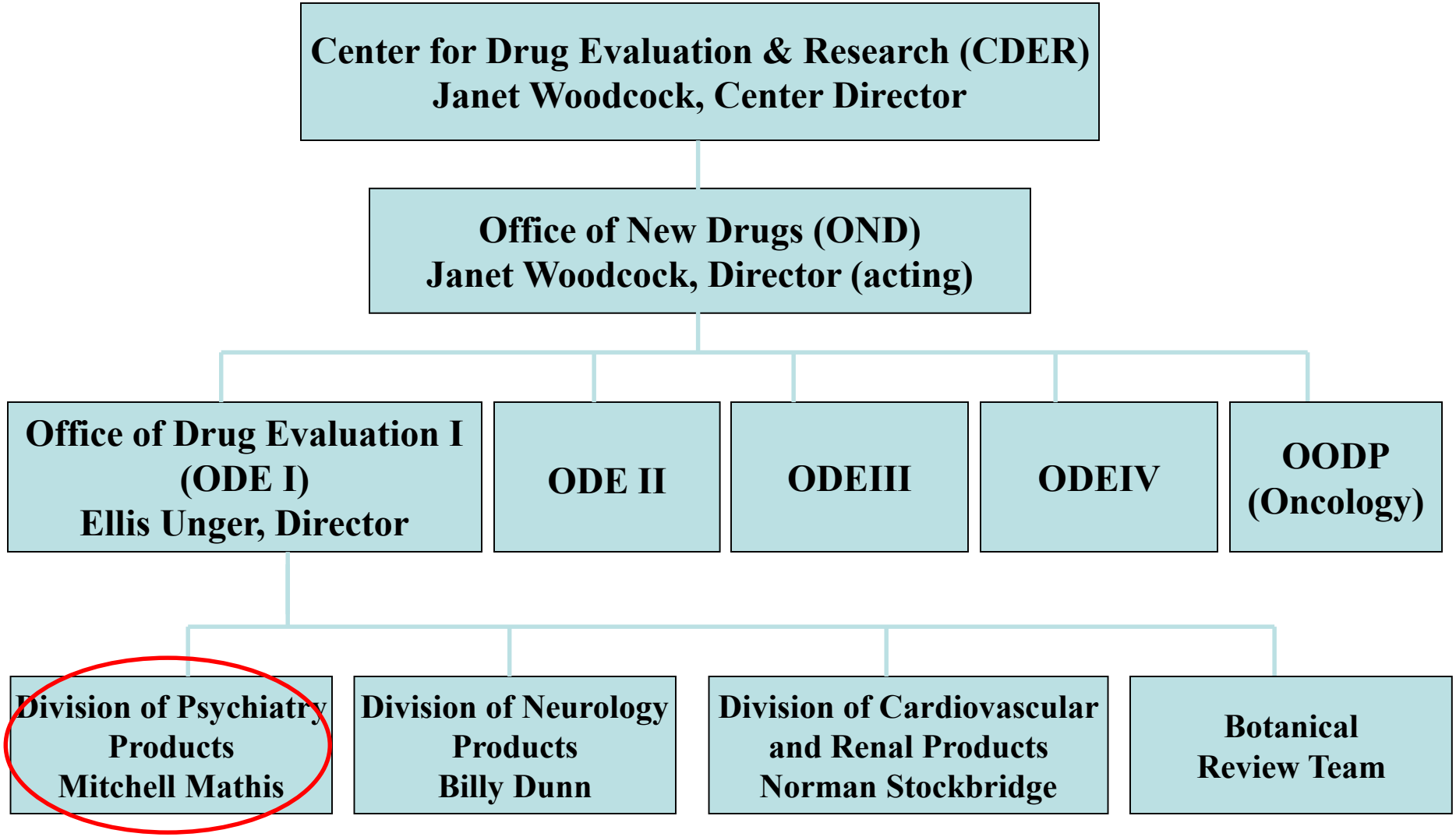
[Note: No conflicts to disclose]

Outline

- Introduction
  - Organization Chart
  - Overview of IND regulations: Definitions
- Investigational New Drugs (IND)
  - Investigator & Sponsor Responsibilities
  - IND Filing
  - IND Exemption
- Point of Contact & Sources of Information


Center for Drug Evaluation & Research (CDER)
Janet Woodcock, Center Director
Office of New Drugs (OND)
Janet Woodcock, Director (acting)
Office of Drug Evaluation I (ODE I)
Ellis Unger, Director
ODE II
ODEIII
ODEIV
OODP (Oncology)
Division of Psychiatry Products
Mitchell Mathis
Division of Neurology Products
Billy Dunn
Division of Cardiovascular and Renal Products
Norman Stockbridge
Botanical Review Team

Division of Psychiatry Products (DPP)

- Workload
  - INDs & NDAs
  - New indications, populations & dosage forms
- Consults (issue & address)
- Indications within DPP and other Divisions
  - Major psychiatric disorders including Schizophrenia, Bipolar, Major Depressive Disorder, Anxiety Disorders, ADHD, Autism, etc.; & sedative/hypnotics
  - Alzheimer's/other Dementias are under the Division of Neurology Products (DNP)
  - Addiction indications are under the Division of Anesthesia and Analgesia Products (DAAP)

IND Regulations

Code of Federal Regulations, Title 21, Part 312
(21 CFR 312)

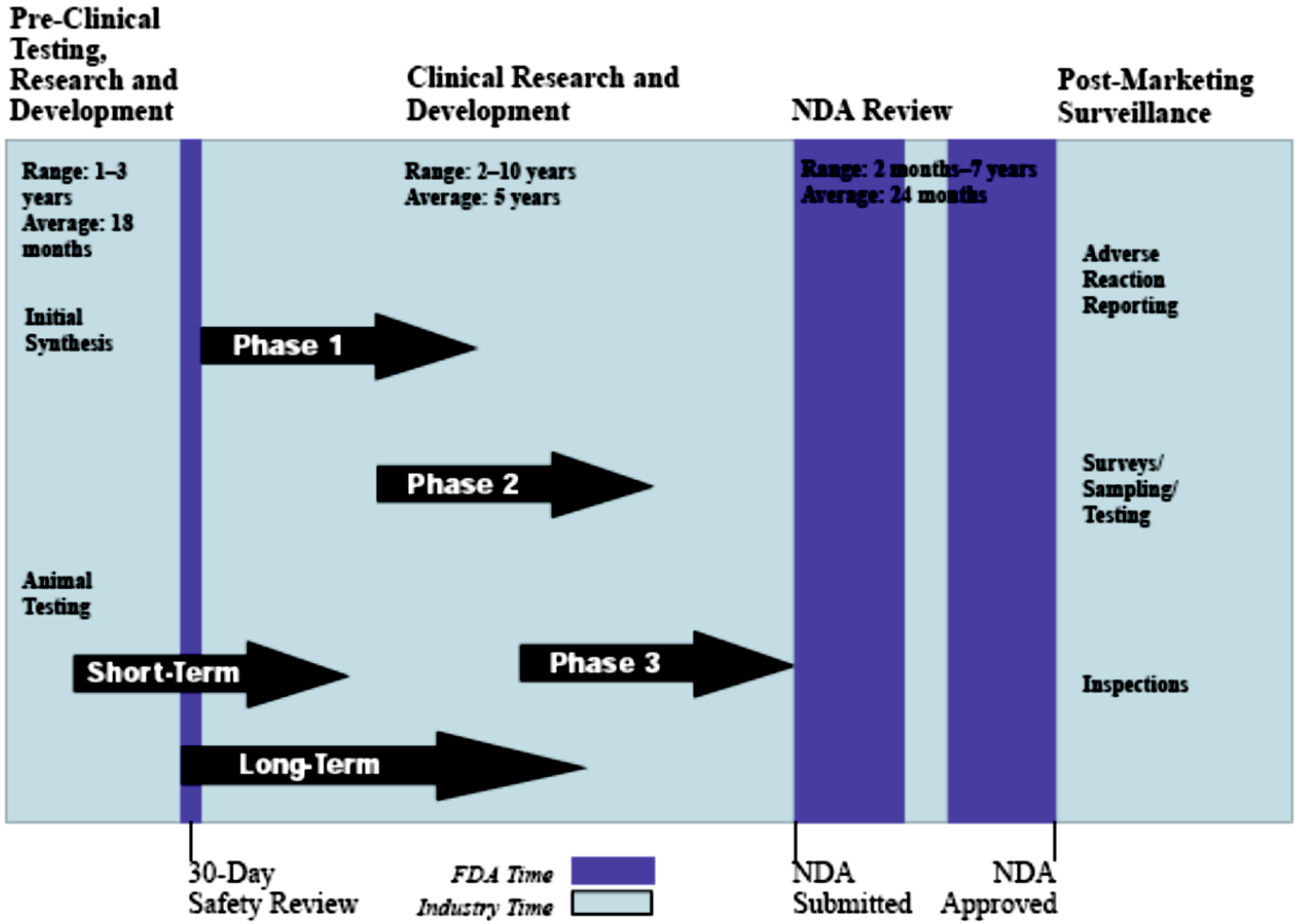
Definitions & Interpretation: 21 CFR 312.3

- **IND** - Investigational new drug application
- **Investigational new drug** – A new drug or biological drug that is used in a clinical investigation.
- **Clinical investigation** – Any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Definitions (Cont.)

- **Sponsor** - Is the person who takes responsibility for and initiates a clinical investigation. The Sponsor may be a pharmaceutical company, a private or academic organization, or an individual.
- **Sponsor-Investigator** - An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- **Investigator** - An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject).
- **Sub-investigator** - Includes any other individual member of that team.

New Drug Development Timeline



See 21 CFR 312.21 regarding phases of an investigation.

Your Involvement with INDs

- Investigator(s) in multicenter clinical trials (Commercial IND)
  - Investigator/sub-investigator
  - Sponsor holds IND & you sign the Form 1572
  - Specific responsibilities
- Sponsor-investigator (Research IND)
  - Clinical research with marketed drugs
  - File an IND
  - Sponsor & investigator responsibilities

Investigators in Clinical Trials

Investigator Responsibilities

- Sponsor is the “holder” of the IND
- Completes and signs Form FDA 1572
  (Statement of the Investigator)
  - Name/address of the investigator
  - Education, training, and experience of the investigator
  - Name and address of facility where the investigation will be conducted and the clinical laboratory facilities
  - Name and address of IRB responsible for review
  - Name of sub-investigators
  - A copy of Protocol and CV

Investigator Responsibilities

Upon signing the Form FDA 1572, the investigator agrees to:

- Conduct the study in accordance with the current protocol;
- Personally conduct or supervise the described investigation;
- Inform any patients that the drugs are being used for investigational purposes;
- Understand the information in the investigator's brochure;
- Ensure that those involved in the study are informed about their obligations;
- Ensure that an IRB that complies with the requirements of 21 CFR Part 56.

Investigator Responsibilities

- Report to the sponsor adverse experiences that occur in the course of the investigation (21 CFR 312.64)
  - Safety reports:
    - Serious Adverse Events: Immediately report to the sponsor
    - Non-serious Adverse Events: Report to the sponsor as specified in the protocol
- Disclosure of Financial Interests (21 CFR Part 54)
  - Financial disclosure reports
    - Investigators and sub-investigators who are directly involved in the treatment or evaluation of research subjects must submit financial disclosure information to the sponsor

Investigator Responsibilities

- Maintain adequate and accurate records
  (21 CFR 312.62)
- Make those records available for inspection
  (21 CFR 312.68)
  - Drug Disposition
  - Case Histories
  - Record retention
- Handling of controlled substances
  (21 CFR 312.69)
  - If the investigational drug is subject to the Controlled Substances Act, adequate precautions must be taken to limit theft or diversion.

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and

Individual Investigators as Sponsor-Investigator

Investigational New Drug Application (IND)

- Request for FDA authorization to administer an investigational drug to humans

- IND is submitted by Sponsors when proposing to study an unapproved drug, or an approved product for a new indication or in a new patient population

Investigator IND Content and Format (21CFR312.23)

- Signed Form FDA-1571 (Cover Sheet) and Form 1572
- Table of Contents
- Introductory Statement and General Investigational Plan
- Clinical Protocol with Form 3674 to certify registration
- Chemistry, Manufacturing and Control Information
- Pharmacology/Toxicology Information (if appropriate)
- Summary of Previous Human Experience (and supporting data)

What Happens After I Submit an IND?

- Upon receipt of IND FDA issues an acknowledgement letter
  - Sponsors can obtain supplies of investigational drug
- Studies may not begin under the IND until 30 days after receipt of IND or later if clinical hold order is issued
  - Division determines whether study is safe to proceed or a clinical hold order should be issued
  - Collaborative effort often requires input from many disciplines
  - Discussions may lead to questions for the Sponsor during the review period (Keep an open direct line of communication)
- Division of Psychiatry Products (DPP) will issue a Study May Proceed letter following the 30-day review period with or without comments

What Happens After I Submit an IND?

- Clinical Hold order may be issued during the 30-day review

- Grounds for imposing clinical holds (21 CFR 312.42):
  - **Human subjects would be exposed to unreasonable and significant risk of illness or injury in the proposed investigation**
  - Clinical investigator not qualified by reason of scientific training/experience
  - Investigators Brochure is misleading, erroneous or incomplete
  - **There is insufficient information required under 312.23 to assess the risks to subjects of the proposed studies**
  - Plan or protocol for the investigation is clearly deficient in design

  **Inadequate CMC information in the submission is also a clinical hold issue

- Clinical investigations under an IND can be suspended at any time as safety data accumulates during the drug development program

I Have an IND in Effect – Now What?

- Sponsors are required to amend the IND as drug development progresses
- Protocol amendments include new protocols and changes to protocols [21 CFR 312.30]
  - Form 3674 for new clinical protocols
- Safety Reports [21 CFR 312.32]
  - Any suspected adverse reaction that is both serious and unexpected must be reported in 15 days
  - All unexpected fatal or life threatening suspected adverse reactions must be reported within 7 days

I Have an IND in Effect – Now What?

- Submit Annual Report within 60 days of the anniversary date that the application went into effect [21 CFR 312.33]
  - Includes brief summary of the status of each study, total number of subjects, number of drop-outs, and summary of most frequent and most serious adverse experiences
- Sponsors can inactivate or withdraw an IND at any time if decided not to continue clinical investigation [21 CFR 312.45]

I Have an IND in Effect – Now What?

- General responsibilities of sponsors [21 CFR 312.50]
  - Select qualified investigators and provide them with information needed to conduct the investigation properly
  - Ensure proper monitoring of the investigation
  - Conduct the investigation according to the protocol
  - Ensure that FDA and all participating investigators are promptly informed of significant adverse effects or risks
- Record keeping and retention [21 CFR 312.57]
  - Records of receipt, shipment or other disposition of the drug
  - Records of any financial interest in 54.4(a)(3) paid to investigators
  - Retain records until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been notified
  - Retain reserve samples of any test article and reference standard used in BE/BA studies

Tips/Reminders

- Include a Cover Letter
  - Submission identifiers, type and title of study, IND number, investigational drug products name and proposed formulation, disease or condition under investigation and contact information
- Letter of Authorization to refer to existing information
- Secure Email: SecureEmail@fda.hhs.gov
- Paper submissions or correspondence in triplicate
- Questions prior to submitting an IND contact Chiefs
  - paul.david@fda.hhs.gov or steven.hardeman@fda.hhs.gov
- Include a track changes version of submissions for reviewers when appropriate, e.g., protocol changes
- Submit well organized submissions, be specific and clear to minimize delays

How Do I Know If I Need an IND?

- This question usually arises with individual investigators who are studying a marketed drug in a clinical trial.
- The FDA makes the determination as to whether an IND is needed (IRBs do not make this determination).
- The clinical investigation of a drug product that is lawfully ***marketed*** in the US is "***exempt***" if all the following apply [21 CFR 312.2(b)]:

How Do I Know If I Need an IND?

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.

3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

I Don't Think I Need an IND

- If meet all of the exemption criteria, you may not need an IND
  - Your IRB may require that you submit paperwork from the FDA stating that you are exempt
- Make your case to FDA
  - State why you believe you are exempt (based on CFR IND exemption criteria) in your cover letter
  - Include copy of protocol
- FDA can usually determine whether exemption criteria are met or not, you should be informed within 30 days of FDA receipt
  - You can contact the project manager to find out status.
  - Helpful hint: clinical trials involving higher doses than are in current product labeling and/or potentially vulnerable populations will probably not be exempt

Do I Need an IND?

- Botanicals include plant materials, algae, macroscopic fungi, and combinations thereof
  - Numerous botanical preparations are marketed in the US as dietary supplements
  - Dietary Supplement: a product (other than tobacco) intended to supplement the diet that contains one of more of the dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; …or a concentrate, metabolite, constituent, extract or combination of any above ingredients
  - Typically regulated by CFSAN (Center for Food Safety and Applied Nutrition).

Do I Need an IND?

- If a marketed dietary supplement is studied for its effects on diseases in the proposed investigation (e.g., cure, treat, mitigate, prevent, or diagnose disease including its associated symptoms), an IND is required
- If a marketed dietary supplement is studied for its dietary supplement use (i.e., structure and/or function claims), an IND is not required.
- FIJT (Food, Dietary Supplements, and Cosmetics IND Jurisdiction Team) – may find CFSAN related products being studied as drugs EXEMPT
- See 21 CFR 101.93 (f) and (g): defines what types of claims are structure/function claims and disease claims.
- Guidance: Determing Whether Human Research Studies Can Be Conducted Without an IND - https://www.fda.gov/downloads/drugs/guidances/ucm229175.pdf

Sources of Information

IND Regulations: Title 21, Code of Federal Regulations (CFR), Part 312
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=312

FDA Guidance Documents
http://www.fda.gov/RegulatoryInformation/Guidances/default.htm

FDA Forms and Directions for completing them
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

About CDER
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm

FDA Home Page
http://www.fda.gov/

Sources of Information

Office of Scientific Investigations
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090085.htm

Clinical Investigator Inspection List
http://www.accessdata.fda.gov/scripts/cder/cliil/index.cfm

Clinical Investigators-Disqualification Proceedings
http://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm

Most Useful Links Ever

FDA's Clinical Investigator Training Course

Past trainings (with video links)

http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/SpotlightonCPIProjects/ucm201459.htm

FDA's Pediatric Investigator Training Course

Past Training (with slides)

www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm392506.htm

Most Useful Links Ever

- **One-Stop Shop for IND-Related Links**
- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm

Investigator-Initiated Investigational New Drug (IND) Applications

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This table provides links to information for investigators about submitting Investigational New Drug (IND) applications to FDA. The resources for application reporting and applications procedures apply to IND applications for both clinical research and clinical treatment.

IND Applications for Clinical Investigations (*Product Development*)	IND Application Reporting	IND Application Procedures	IND Applications for Clinical Treatment (*Expanded Access*)
Overview	Overview	Overview	Overview
Contents and Format	Protocol Amendments	Exemptions from IND Requirements	Contents and Format
Regulatory and Administrative Components	Information Amendments	Interactions with FDA	Treatment of a Single Patient in Emergency Setting
Non-clinical Components	Safety Reports	Clinical Hold	Treatment of a Single Patient in Non-emergency Setting
Clinical Components	Annual Reports	Investigator's Responsibilities	Treatment of a Group of Patients