

How to put together an IND application

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FDA Clinical Investigator Training Course

November 15, 2018



FDA Disclaimer

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Agenda

- Definitions and Interpretations
- Content and Format of initial IND submission
 - Regulatory and Administrative Components
 - Non-Clinical Components
 - Clinical Components
- How to submit an IND
- What to expect after submitting an IND (first 30 days)
- Best Practices/FAQs
- Individual Patient Expanded Access IND



Definitions and Interpretations

(21 CFR 312.3)

- ***Investigational New Drug (IND) Application***

- An application submitted to FDA if a drug (or biological product) not previously authorized for marketing in the US is intended to be used for the purposes of clinical investigation or, in certain cases, for the purposes of clinical treatment when no approved therapies are available.

Definitions and Interpretations

(21 CFR 312.3)

- ***Investigational new drug***

- A new drug or biological drug (approved or not approved) that is used in a clinical investigation.
- A drug is defined by intended use, not the nature of the substance
 - “articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease...” [21 USC 321 (g)(1)(B)]
 - “articles (other than food) intended to affect the structure or any function of the body...” [21 USC 321 (g)(1)(C)]



Definitions and Interpretations

(21 CFR 312.3)

- ***Clinical investigation***

- Any experiment (except for the use of a marketed drug in the course of medical practice) in which a drug is administered or dispensed to, or used involving, one or more human subjects (healthy humans or patients with disease).

More definitions

- ***Investigator***

- Individual who actually conducts a clinical investigation (i.e. , under whose immediate direction the drug is administered or dispensed to a subject).
- In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Sub-investigator" includes any other individual member of that team.

- ***Sponsor***

- The party who takes responsibility for and initiates a clinical investigation, and submits the IND application to the FDA.
- The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

- ***Sponsor-Investigator***

- An individual who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed

An IND is needed when...

- Research involves a drug
- Research is a clinical investigation
- Clinical Investigation is not *exempt* from IND regulations
 - Possible exemptions:
 - Lawfully marketed drug products
 - 21CFR 312.2 (b)
 - Bioavailability or Bioequivalence studies in humans
 - 21 CFR 320.21(b) (c) and (d)
 - Radioactive drugs
 - 21 CFR 361.1



IND Exemption Criteria

(21 CFR 312.2(b))

- The drug product is lawfully marketed in the US AND
- Study is not intended to be reported as a well-controlled study in support of a new indication or significant labeling change AND
- Study is not intended to support a significant change in advertising AND
- Does not involve a route of administration, dosing level, or patient population that significantly increases the risk (or decreases the acceptability of risk) AND
- Study is conducted in compliance with requirements for review of an IRB and informed consent AND
- Study is not intended to promote or commercialize the product

Content and Format

(21 CFR 312.23)



- Regulatory and Administrative Components
 - Cover Letter
 - Regulatory Forms (Form 1571, Form 1572, Form 3674)
 - Table of Contents
 - Introductory Statement and General Investigational Plan
 - Investigator Brochure
- Non-Clinical Components
 - Chemistry, Manufacturing and Controls (CMC)
 - Animal Pharmacology and Toxicology (Pharm/Tox)
- Clinical Components
 - Clinical Protocol
 - Summary of Previous Human Experience
- Other information as necessary

Regulatory and Administrative Components

- **Cover Letter**

- Typically 1 page
- Addressed to the Division Director
- Signed by the sponsor
- Submission identifier- “Initial Investigational New Drug Application”
- Brief explanation of the intended investigation (type and title of the study)
- Investigational New Drug Product’s name and proposed formulation
- Disease or condition under investigation
- IND manufacturer’s name and contact information (if applicable)
- Reference to an existing IND application (if applicable)



Regulatory and Administrative Components

- **Form FDA 1571**

- Administrative information pertinent to the IND application

- Instructions:

- <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm>

- **Form FDA 1572**

- Statement of Investigator

- Guidance:

- <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf>

- **Form FDA 3674**

- Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank

- Instructions:

- <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM354618.pdf>

Regulatory and Administrative Components

- **Table of Contents**

- Detailed enough to permit FDA reviewers to locate items quickly and easily
- Helpful if location information provided by volume and page
- Tabbed breaks between sections

Regulatory and Administrative Components

- **Introductory Statement and General Investigational Plan**
 - Typically 2-3 pages
 - Brief description of the overall clinical development plan for the Investigational New Drug
 - Helps FDA anticipate the needs of the future program
 - Name of the drug, and all active ingredients, drug's pharmacologic class, structural formula, formulation of dosage form, route of administration, and broad objectives and planned investigations
 - Brief summary of previous human experience

Regulatory and Administrative Components

• Investigator Brochure (IB)

- Description of drug substance and formulation, including structural formula (if known) and formulation
- Summary of pharmacological and toxicological effects of the drug in animals, and to the extent known in humans.
- Summary of the pharmacokinetics and biological disposition of the drug in animals, and to the extent known in humans
- Summary of the safety and effectiveness of the drug in humans
- Description of possible risks and side effects to be anticipated
- IB not required if you have a right of reference to an existing manufacturer's IND application
- IB may be obtained from the IND product's manufacturer

Non-Clinical Components

- **Chemistry, Manufacturing, and Controls (CMC)**
 - Drug Substance
 - Drug Product
 - Placebo Formulation, if applicable
 - Labeling information of the investigational drug
 - Environmental analysis or request for categorical exclusion

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362283.htm>

Non-Clinical Components

- **Animal Pharmacology and Toxicology Information (*Pharm/Tox, PT*)**
 - Adequate information about the drug’s pharmacology and toxicology (in vitro and/or animal studies) to support their use in humans
 - description of the pharmacological effects and the mechanisms of action of the drug in animals and information on the absorption, distribution, metabolism, and excretion of the investigational product, if known
 - Kind, duration and scope of the animal and other studies required will depend on the duration and nature of the proposed clinical investigation
 - Guidance for Industry-Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products
 - Guidance for Industry-M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization of Pharmaceuticals

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362416.htm>

Clinical Components

- **Clinical Protocol**

- should be submitted for each planned clinical study or trial

- Include protocol number and/or title

- Protocols for subsequent studies not submitted with the original IND application can be submitted at a later time as Protocol Amendments

- "Protocol Amendment: New Protocol"

- "Protocol Amendment: Change in Protocol"

- "Protocol Amendment: New Investigator"

- Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362445.htm>

Clinical Components

- **Previous Human Experience**

- If investigational drug has been investigated or marketed, provide summary of previous human experience, including published materials relevant to the drug's safety and efficacy
- If marketed outside US, provide information on all countries where the product has been marketed or withdrawn (and why)
- Letter of authorization, with right of reference, if product is the subject of an another existing IND application
- State if no previous human experience exists

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362446.htm>



IND submission – requirements

- May 5, 2018
- **Commercial INDs**
 - Must be in in electronic Common Technical Document (eCTD) format
 - Less than 10 GB, must use the gateway
 - Larger than 10 GB must use physical media
 - Fillable forms (FDA Form 1571) are required
- **Research INDs**
 - Can be submitted in paper although electronic submission is encouraged

Where to submit an IND?

- **For a Drug:**

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

- **For a Therapeutic Biological Product:**

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 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 (as needed)



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 is placed in clinical hold
- INDs are not approved
- Some Divisions issue a “safe to proceed letter”; Otherwise, no news is good news
- MaPP 6030.9 Good Review Management Principles and Practices for Effective IND Development and Review
 - <https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm349907.pdf>

IND Process from Day 1-30



Day 25-30: Safety Decision and Notification

Day 8-27: Review and Safety Meetings

Day 0-7: Receipt and Assignment of Reviewers

Best Practices

- Consider Pre-IND Consultation before submitting IND
- Initial IND submission with one protocol
- 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)
 - Also helpful to include a CD-ROM with PDF of the submission

More Best Practices

- Clear and well organized (if paper)
 - Divide your submission with tabs, not with colored paper
- Provide a Table of Contents
- Proofread your submission
- Provide assurance on subject safety
- Provide assurance on the adequacy of scientific information to evaluate the drug's safety and effectiveness (Phase 2 and Phase 3 protocols)
- Effectively communicate with the FDA RPM assigned to the IND
 - E-mail Communications- Set up secure email with the Agency
 - Be available for any discussion during the first 30 days
- If you do not get funding, withdraw the IND

Frequently Asked Questions

Should I submit a pre-IND before IND?

- A pre-IND is a consultative mechanism to receive early feedback.
- It fosters early communications between sponsors and drug review divisions to provide guidance on the information necessary for a complete IND submission.
- The review divisions are organized generally along therapeutic class
- Pre-IND meetings can be in the format of a face-to-face meeting, teleconference, or they can be written response only (WRO)
 - Some divisions only provide Pre-IND comments as WRO

Frequently Asked Questions

Should I submit the IND in paper or electronic format?

- Commercial IND submissions must be submitted in eCTD format
- Non-commercial are accepted in paper but electronic is encouraged.

Frequently Asked Questions

Will IND number be same as corresponding pre-IND?

- Yes; the Pre (P) will be removed [and status updated]

When will I be assigned an IND number?

- A pre-assigned eCTD IND application number can be requested in advance at:

<http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm163184.htm>.

- However, an IND number will be assigned after the IND application is received by FDA if there is no pre-assigned number.

Frequently Asked Questions

When can I start clinical trials?

- Unless you are informed that you are in clinical hold, you may begin 30-days after FDA receives your IND application.

Frequently Asked Questions

Can my IND cross-reference another IND?

- Yes, an IND can cross-reference another commercial or non-commercial IND provided a **letter of authorization** is submitted to allow for the reference.
- If it is your own IND, it would be helpful to provide direct links/identify location in submission to referenced material.

Frequently Asked Questions

Can another indication be added under same IND?

- Protocols to study additional indications can be submitted under the same IND provided the indications are reviewed by the same review division and there is no change to the product and dosage form.

Can different dosage forms be investigated under same IND?

- Separate INDs should be established
- Exception may be an early in development proof-of-concept study investigating different dosage forms of the same product; IND continues with selected dosage form.

Frequently Asked Questions

I have a combination product-Which is the lead Center?

- Primary Mode of Action (PMOA)
- Request for Designation (RFD)
- <https://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm#assignment>
- combination@fda.gov

Frequently Asked Questions

I am submitting an IND for a drug-device combination product to CDER. What information do I need to include?

- All information on the entire combination product; All the details on the drug and device that typically would be submitted in an IND and IDE

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

Additional Resources

- How Drugs are Developed and Approved
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm>
- IND application (includes links to all IND Guidances)
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>
- Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs
 - <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf>
- Small Business Assistance
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069898.htm>
- Investigator-Initiated Investigational New Drug (IND) application
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm>

Questions?





IND applications for Clinical Treatment (Expanded Access)

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Expanded Access-Regulations

October 13, 2009

- There are three categories of expanded access:
 - **Expanded access for individual patients, including for emergency use (21 CFR 312.310)**
 - Expanded access for intermediate-size patient populations (21 CFR 312.315)
 - Expanded access for large patient populations under a treatment IND or treatment protocol (21 CFR 312.320)

Expanded Access for Individual Patients

- Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options.

Expanded access-considerations

- Patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; and
- The potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context of the disease or condition to be treated; and
- The expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use.

Expanded Access

- Individual Patient Expanded Access
 - Individual Patient Expanded Access for Emergency Use (for situations when an emergency requires that treatment be administered sooner than a written submission can be made to FDA)

Who is the Sponsor?

- The party who (1) submits an expanded access IND application and (2) receives FDA's authorization to use the investigational product is considered ***the sponsor*** of the IND application.
- In the absence of any other sponsor (e.g. pharmaceutical company), the treating physician is the sponsor of the expanded access IND application.
 - Sponsor-Investigator

Expanded access-Sponsor responsibilities

- Protocol amendments
- Information amendments
- IND Safety Reporting
- IND Annual reports
- For single patient access, a written summary at the conclusion of treatment



Expanded Access-Content and format (1)

21 CFR 312.305(b)

- Cover letter
- Table of content
- FDA Forms 1571 and 1572 (for physician sponsored single patient access, Form FDA 3926 may be used instead)
- CMC, nonclinical & other information that may be provided via a Letter of Authorization
- Clinical Protocol/Treatment Plan

Expanded Access-Content and format (2)

Form FDA 3926

Designed specifically for use by physicians when submitting requests for single patient expanded access to investigational drugs, including in emergencies. It is also for certain subsequent submissions to FDA after the initial application is received

Form FDA 3926

- Patient Initials
- Date of Submission
- Investigational Drug Name
- Clinical Information
- Treatment Information
 - Investigational Drug Name
 - Name of entity that will supply the drug
 - FDA Review Division
 - Treatment plan, including dose, route and schedule of dosing, planned duration and monitoring procedures.



Form FDA 3926

- Letter of Authorization
- Physicians Qualification Statement
- Physicians Name, Address and contact information
- 10.a- Request for authorization to use form 3926
- 10.b-Request for authorization to use alternative IRB review procedures

Where do I send the request?

- OND Division
 - CDER Central Document Room



Mailing Address for Expanded Access

Drug Products

- ***Individual Patient IND Requests and Follow-up Reports submitted by a licensed physician using FDA Form 3926***
- Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
ATTN: [appropriate Review Division]
“EXPANDED ACCESS SUBMISSION”
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266



Mailing Address for Expanded Access

Biologic Products

- ***Individual Patient IND Requests and Follow-up Reports submitted by a licensed physician using FDA Form 3926***
- Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Bldg. 71, Rm. G112
Silver Spring, MD 20993-0002



Mailing Address for Expanded Access

Medical Devices

- ***Individual Patient Expanded Access Requests and Follow-up Reports (including Emergency Use Reports)***
- Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center
10903 New Hampshire Avenue
Bldg. 66, Rm. G609
Silver Spring, MD 20993-0002

If an IDE exists for the device, include the IDE number in the request.

Review Process

- Upon receipt of the single patient expanded access IND application, FDA will review to make a decision.
 - The FDA will either allow the treatment to proceed or
 - Place the IND on hold.
- An IND number will be assigned and communicated to the sponsor
- FDA allows over 99% of single patient expanded access requests to proceed.
 - 2017 cohort --461/461 Expanded Access Emergency Use
 - --1107/1111 Expanded Access Individual Patient
- FDA may contact the physician to request more information or clarification in order to avoid placing the IND on hold.

When can I treat the patient?

- 30 days after FDA receives the IND application or on earlier notification by FDA that the expanded access use may begin.

Individual Patient Expanded Access

- Form 3926
- IRB Approval
- Informed consent

Individual Patient Expanded Access for Emergency Use

- Phone call
- Agreement to submit an IND within 15 working days
- Communicate to IRB within 5 working days

Completion of Treatment

- Upon completion of treatment, the sponsor of a single-patient IND application is expected to send to FDA a summary of treatment results including patient's response, all adverse events, drug disposition, and other relevant information.
- When submitting this summary report, the sponsor of the application may request FDA to withdraw the IND application.

References

- <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm351748.htm>
- <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf>
- <https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>
- <https://www.fda.gov/RegulatoryInformation/Guidances/>
 - Individual Patient Expanded Access Application-Form FDA 3926
 - Expanded Access to Investigational Drugs for Treatment Use-Qs & As

Need Help?

- **For specific questions during normal business hours (8 AM-4:30 PM, ET, Weekdays)**
 - **Investigational drugs:** 301-796-3400 or druginfo@fda.hhs.gov [CDER's Division of Drug Information], or contact the appropriate [review division](#), if known
 - **Investigational medical devices:** 301-796-7100 or DICE@fda.hhs.gov [CDRH's Division of Industry and Consumer Education]
 - **Investigational biologics:** 240-402-8020 or 800-835-4709 or industry.biologics@fda.hhs.gov [CBER's Office of Communication, Outreach and Development]
 - For **general questions**, or if you are unsure of who to contact, contact the Patient Affairs Staff at 301-796-8460 or patientaffairs@fda.hhs.gov.
- **After 4:30 p.m. ET weekdays and all day on weekends**
 - For **emergency requests** for all medical products (drugs, biologics, and medical devices) contact **FDA's Emergency Call Center** at 866-300-4374.



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