

How To Put Together An IND Application

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Learning Objectives

- Definitions
- Content and Format of an IND application
- IND Submission Process
- Best Practices
- Frequently Asked Questions

Challenge Questions



- When is an initial IND application approved?
- What is the FDA Form 1571 used for?
- For combination products (e.g., drug/device product), how do I determine which Center to submit my application to?
- True or False: Can I start my clinical trials 30 days after the FDA receives my IND application?



DEFINITIONS

Definitions (21 CFR 312.3)



Investigational New Drug (IND)

- *“...means a new drug or biological drug that is used in a clinical investigation...also includes a biological product that is used in vitro for diagnostic purposes”*
- Defined by intended use, **NOT** the nature of the product
 - *“...articles intended for use in the diagnosis, cure, mitigation, treatment of prevention of disease...”*
 - *“...articles (other than food) intended to affect the structure or any function of the body...”*

Definitions (21 CFR 312.3)



Clinical Investigation

- *“...means 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 (21 CFR 312.3)

Sponsor

- *“...means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.”*

Definitions (21 CFR 312.3)



Investigator

- *“...means an 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. “Subinvestigator” includes any other individual member of that team.”*

Definitions (21 CFR 312.3)



Sponsor/Investigator

- *“...means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.”*



CONTENT AND FORMAT OF AN IND APPLICATION

What is an IND?



- 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.
- IND may be required even if the results of the clinical investigation will not be used for “commercial purposes”

When is an IND needed?

- Does your research involve a drug (or biologic)?
 - If your research article is an “investigational new drug”, then probably
- Is your research a clinical investigation?
 - “Clinical investigations” are generally not exempt
- Possible exemptions from IND requirements:
 - 21 CFR 312.2(b)(1)(i – v) – Applicability
 - 21 CFR 320.21(b – d) – Requirements for submission of bioavailability and bioequivalence data
 - 21 CFR 361.1 – Radioactive drugs for certain research uses

IND Exemption Criteria



21 CFR 312.2(b)(1)(i – v) – Applicability

- Applies to products “lawfully marketed” in the US
- Must meet **ALL** of the referenced criteria:
 - not intended to be reported as a well-controlled study to support a new indication, nor any significant change in labeling
 - not intended to support a significant change in product advertising
 - does not involve a change in the route of administration or dosage level or use in a population or other factors that significantly increases the risks
 - agreement that the investigation will be conducted in compliance with the requirements of 21 CFR 50, 21 CFR 56, and 21 CFR 312.7

IND Content and Format

21 CFR 312.23 – IND content and format

- Regulatory and Administrative Components
 - 312.23(a)(1 – 5)
- Clinical Components
 - 312.23(a)(6) and (9)
- Nonclinical Components (CMC and Pharm/Tox)
 - 312.23(a)(7 – 8)
- Additional Information
 - 312.23(a)(10 – 11)

IND Content and Format

Regulatory and Administrative Components

- Cover sheet (FDA Form 1571)
- Table of Contents
- Introductory statement and general investigational plan
- Investigator's brochure
- Additional Information
 - Cover letter
 - FDA Form 1572
 - FDA Form 3674
 - Other relevant information

IND Content and Format

Cover letter

- Typically 1 – 2 pages and addressed to Review Division Director
- Identifies the submission as an “Initial IND Application”
- Includes a brief explanation of the intended investigation
 - Study title and type/phase of trial
 - IND name and formulation (e.g., tablets, solution, pre-filled syringe, etc.)
 - Disease/condition under investigation (aka the proposed indication for use)
 - IND manufacturer’s name and contact info (if applicable)
 - Reference to any existing IND application(s) or right or reference (RoR)
- Other relevant information

IND Content and Format



Table of Contents (ToC)

- Should be detailed enough to permit review team to locate pertinent information or items quickly and easily
- Include location information by volume/section and page number
- If hard copy submission, tabbed breaks between sections is recommended

IND Content and Format

Introductory Statement and General Investigational Plan

- Contains pertinent info concerning the IND and all active ingredients and the broad objectives and planned duration of the proposed investigation(s)
- Summary of previous human experience
- Brief description of the overall development plan for the IND
 - Refer to 312.23(a)(3) for additional info

IND Content and Format

Investigator's Brochure (IB)

- Contains detailed and specific information concerning the IND and all active ingredients, including formulation process, animal toxicologic and human pharmacologic data, summary of safety/efficacy profile, and possible risks/anticipated side effects
 - Refer to 312.23(a)(5) for additional info
- Not required if you have a right of reference to an existing IND
 - For investigations involving marketed products, you may submit a copy of the current labeling in lieu of the IB

IND Content and Format

Clinical Components

- A protocol should be submitted for each planned study
 - Refer to 312.23(a)(6) for additional info
- Protocols for subsequent studies not included in the initial IND application are submitted as Protocol Amendments
 - Refer to 312.30 for additional info
- Previous human experience with the IND
 - Summary of prior safety/efficacy information
 - Letter of authorization (with right of reference) is needed if the product already has an existing IND application
 - Refer to 312.23(a)(9) for additional info

IND Content and Format

Nonclinical Components – CMC

- Provides sufficient information that accurately describes the composition, manufacture, and control of the drug substance and the drug product to assure the proper identification, quality, purity, and strength of the IND
 - Include placebo formulation information (if applicable) and IND carton/container labeling
 - Refer to 312.23(a)(7) for additional info
- Must also contain environmental assessment or exclusion waiver
 - Refer to 21 CFR 25 for additional info

IND Content and Format

Nonclinical Components – Pharm/Tox

- Contains sufficient pharmacological/toxicological information from animal studies that demonstrates the IND is “...*reasonably safe...*” to justify its use in human clinical trials
- “*The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.*”
 - Refer to 312.23(a)(8) for additional info

IND Content and Format

Additional/Relevant Information

- Additional information may be required based on the nature of the IND application
 - Drug dependence and abuse potential
 - Radioactive drugs
 - Pediatric studies
 - Other information
- Relevant information
 - Other info needed to review the application (e.g., informed consent form)
 - Refer to 312.23(a)(10 – 11) for additional info



IND SUBMISSION PROCESS

IND Submission Requirements



As of 5 May 2018:

- ALL commercial IND applications
 - Must be in electronic Common Technical Document (eCTD) format
 - Fillable forms (FDA Form 1571) are required
 - If the application is ≤ 10 GB, must use the Gateway
 - If > 10 GB, submit as physical media
- Research IND applications
 - While they will be accepted as hard copy submissions, electronic submission is strongly encouraged

Where do I submit my IND?

Drugs

Food and Drug Administration
Center for Drug Evaluation and
Research
Central Document Room
5901B Ammendale Road
Beltsville, MD 20705 – 1266

Therapeutic biologics

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

IND Review: 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)
- INDs are assigned to review division by indication and forwarded to CPMS (Chief, Project Management Staff), who assigns a RPM
 - RPM is your point of contact with the review division
 - Responsible for tracking and managing the IND review process and addressing any regulatory issues/concerns

IND Review: First 30 days



- “Core” Review Team assigned
 - Clinical (clinical data and makes final review determination)
 - Nonclinical (animal pharm/tox data)
 - Clin Pharm (human pharmacologic data)
 - Product Quality (CMC data)
 - Biostats (proposed statistical analyses)
- Other subject matter experts as needed
 - Clinical Microbiology (for antimicrobial and antiviral drugs)
 - CMC Micro (e.g., to evaluate sterility or non-pyrogenicity data)
 - DPMH (if children/pregnant mothers will be allowed to participate)
 - Other review divisions or CBER/CDRH as applicable

IND Review: First 30 days

- The review division team will determine within **30 calendar days of receipt** if your IND application is either:
 - “*Safe To Proceed*”
 - On clinical hold (either full or partial)
- IND applications are not approved!!!
- A Study May Proceed letter may be issued; however, there is no requirement to do so

IND Review: First 30 days



Days 8 – 27:

Conduct review and hold internal safety meeting

Days 0 – 7:

Receipt and Team Assignments

Days 25 – 30:

Final Review Decision and Sponsor Notification

IND Clinical Hold

An IND application may be placed on clinical hold at ANY time

- The review division may attempt to resolve potential-hold issues with the sponsor prior to the internal safety meeting
 - If unable to resolve these issues, an informal teleconference will be scheduled around Days 25 – 27 to discuss the specific reason(s) why the IND is being placed on clinical hold
 - Sponsor will receive a (Full or Partial) Clinical Hold letter with 30 days of the sponsor being notified of the clinical hold
 - Refer to 312.42 for additional info



BEST PRACTICES

Best Practices



- Consider Pre-IND consultation/meeting before submitting IND
- Initial IND submission should (ideally) include one protocol
- Although not required, a cover letter is extremely useful
 - Contact phone # AND an alternate name and phone #
- Secure email address(es) are essential
 - RPMs may **NOT** communicate “confidential information” via unsecure email
- The initial IND submission (and each subsequent submission to the IND) must be accompanied by a Form FDA 1571
- If hard copy submission, ensure it is clear and well organized
 - Provide an informative ToC with distinctive volume/section breaks

Best Practices



- **PROOFREAD YOUR APPLICATION PRIOR TO SUBMISSION!**
- Ensure that you have not only provided sufficient information for us to be able to adequately evaluate the IND's safety and effectiveness, but that we can also find it in your application
- We have 30 days to review your application, so prompt replies to our queries are greatly appreciated!
- Contact your RPM as soon as issues arise so that we can assist/advise you in a timely manner
- **DON'T BE AFRAID TO ASK QUESTIONS EARLY AND OFTEN!**



FREQUENTLY ASKED QUESTIONS

Should I submit a pre-IND before IND?

- A pre-IND is a consultative mechanism to receive early feedback and fosters early communications between sponsors and review divisions by providing guidance on the information necessary for a complete IND submission
- Pre-IND meetings can be in the format of a face-to-face meeting, teleconference, or they can be written responses only (WRO)
 - Review divisions have the final call on meeting format

Should I submit the IND in paper or electronic format?

- Commercial IND submissions must be submitted in eCTD format
- Research INDs are accepted as hard copy submissions, but electronic submission is encouraged
 - When providing hard copy submissions, always confirm receipt with your RPM as it will take some time to receive something that was mailed in
 - When possible, an emailed courtesy copy PDF is always appreciated

Will the IND number be same as corresponding PIND number?

- Yes; the “P” will be removed once the initial IND application is received and the status will change from “Presubmission” to “Pending” while under the 30 day review period
- Once the 30 day review has been completed (and assuming the IND is determined to be “safe to proceed”) the status will be updated to “Active” in our system
 - Remember, as long as your IND status is “Active” in our system you’re required to continue submitting IND annual reports per 21 CFR 312.33
 - You may withdraw an IND if you’re no longer actively investigating it

When will I be assigned an IND number?

- A pre-assigned eCTD PIND application number can be requested prior to submitting your initial IND application
- If no pre-assigned number exists when the initial IND application is received, an IND number will be assigned

When can I start my clinical trial(s)?

- Thirty days after we receive the application, unless we notify you that the investigations described in your application are subject to a clinical hold under 312.42
- Although you may ship the IND to investigators named in the application prior to the 30 days review being completed, they may not begin the clinical trial until the 30 day review period has expired (assuming that a clinical hold is NOT placed on your IND application)

Can my IND cross-reference another IND?

- An IND application can cross-reference another commercial or research IND application provided an appropriate letter of authorization is submitted to allow for right of reference
- If you're the sponsor of the cross-referenced IND application, it is advantageous to provide direct hyperlinks/identify the location in submission to the cross-referenced material

Can another indication be added under same IND?

- Generally speaking, 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
- Contact your review division for advice prior to submitting another indication

Can different dosage forms be investigated under same IND?

- Separate IND applications should be submitted for each dose form to be investigated
- Exceptions could be made in an early development, proof-of-concept study investigating different dosage forms of the same product; however, the IND would eventually proceed with selected dosage form
- Contact your review division for advice prior to submitting another dosage form

How is the Lead Center determined for combination products?

- The Primary Mode of Action (PMOA) determines the Center where the product will be reviewed
- PMOA is the single mode of action of a combination product that provides the most important therapeutic action
 - Combo products with PMOA of a drug are assigned to CDER
 - Combo products with PMOA of a device are assigned to CDRH
 - Combo products with PMOA of a biological product are assigned to CBER
- Sponsors can submit a request for designation (RFD) to the Office of Combination Products if unsure

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

- Information for the entire combination product; i.e., all the necessary information on the drug that would be needed to support an IND application **AND** the corresponding information for the device that would be included in an investigation device exemption (IDE)
 - Refer to 312.23 for additional info on IND applications
 - Refer to 812.25 for additional info on IDE investigational plans



Learning Objectives

- Definitions
- Content and Format of an IND application
- IND Submission Process
- Best Practices
- Frequently Asked Questions

Challenge Questions



- When is an initial IND application approved?
 - **NEVER!**
- What is the FDA Form 1571 used for?
 - Provides pertinent admin info on the submission/application
- For combination products (e.g., drug/device product), how do I determine which Center to submit my application to?
 - PMOA determines the Lead Center
- True or False: Can I start my clinical trials 30 days after the FDA receives my IND application?
 - True, **but with a very big caveat!!!**

Questions?





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ADMINISTRATION

Additional Resources

- [CDER Small Business & Industry Assistance \(SBIA\)](#)
 - Information on the CDER SBIA program
- [Investigational New Drug \(IND\) Application](#)
 - Information on the content, format, and submission of an IND application
- [Forms & Submission Requirements](#)
 - Links to the various forms the FDA uses for applications (e.g., Form 1571, 1572, etc.) and instructions for completing them
- [Electronic Regulatory Submission and Review](#)
 - Information on providing electronic submissions to the FDA

Additional Resources

- [Requesting a Pre-Assigned Application number](#)
 - Instructions for requesting a pre-assigned IND number
- [FAQs about Combination Products](#)
 - Information about combination products, including the RFD process and contact info for CDER Office of Combination Products (OCP)
- [Laws, Regulations, Policies and Procedures for Drug Applications](#)
 - Links to the applicable regulations for IND, NDA, BLA, and ANDA applications
- [Device Advice: Comprehensive Regulatory Assistance](#)
 - Links to the applicable regulations for device applications

Additional Resources

- [Guidances \(Drugs\)](#)
 - Searchable database of all FDA guidance documents
- [CDER Manual of Policies & Procedures | MAPP](#)
 - Searchable database of all CDER SOPs
- [6030.1 – IND Process and Review Procedures \(Including Clinical Holds\)](#)
 - CDER OND SOP on placing/removing IND clinical holds
- [6030.9 – Good Review Management Principles and Practices for Effective IND Development and Review](#)
 - CDER OND SOP on conducting an IND review