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 **The Investigational New Drug (IND) Process: *Part 1***

☐ **Session Objectives**

- **Attendees will learn**
  - The differences between a commercial IND and a Sponsor-Investigator IND
  - When an IND is required (and when it is not)
  - If one can promote or charge for an investigational new drug
  - Common Technical Document (CTD) structure related to IND submissions
  - IND content and format



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## >> The Investigational New Drug (IND) Process: Part 1

### ❑ Types of INDs

#### ▪ Commercial INDs

- The Sponsor of the IND is a pharmaceutical/biotech company
- The IND must be submitted electronically via the FDA's electronic gateway
  - ✓ Rules for electronic submissions/anti-viral integrity apply

#### ▪ Sponsor-Investigator INDs

- IND is held by individual
  - ✓ Usually a researcher/physician
- IND can be submitted electronically or in paper format
  - ✓ Electronic submissions can run \$8,000 - \$12,000
- FDA generally allows sponsor-investigator INDs more "flexibility"



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## >> The Investigational New Drug (IND) Process: Part 1

### ❑ When is an IND Required? (IND Regulations: 21 CFR 312)

#### ▪ An IND is required if:

- The clinical study involves an investigational drug that is not lawfully marketed in the United States
- The investigation is intended to be reported to FDA in support of a New Drug Application (NDA) or a change to an approved NDA
  - ✓ Off-label use of an approved drug does not have to be conducted under an IND; however, the results cannot be used to amend labeling (Package Insert)
- The investigation is intended to support a significant change in the advertising for the product
- The investigation involves a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks of an approved product



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## >> The Investigational New Drug (IND) Process: *Part 1*

- ❑ Promotion of an Investigational New Drug
  - A sponsor or investigator shall not represent that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug
    - Relates to “promotional” statements in the Investigators’ Brochure, Informed Consent Form, and advertisements for patient recruitment
    - The FDA takes exception to a sponsor claiming that an investigational drug “is safe and effective” in IND documents like a Clinical Study Report, IB, ICF, or advertisements
  - A sponsor or investigator shall not commercially distribute or test market an investigational new drug, as these are considered “promotional” activities



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## >> The Investigational New Drug (IND) Process: *Part 1*

- ❑ Charging for an Investigational New Drug
  - There are certain situations where a Sponsor can charge for an investigational new drug
    - When the cost of the drug is extraordinary to the sponsor (due to manufacturing, the duration of the clinical trial, etc.)
    - Expanded Access Program:
      - ✓ Expanded Access is a special program to facilitate the availability of investigational drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy
      - ✓ Sponsor can only charge for the actual cost of manufacturing
  - However, in over 35 years of regulatory affairs experience, I’ve never seen a Sponsor charge for an investigational drug



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## >> Phases of Drug Development

### □ Phases of Drug Development

#### ▪ Phase 1 Studies

- The initial introduction of an investigational new drug into humans
- Phase 1 studies are typically controlled and closely monitored studies
- Phase 1 studies may be conducted in patients (like cancer patients) or healthy subjects (typical)
- Typically designed to determine the bioavailability, metabolism and half-life and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on clinical effectiveness
- The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80
- FDA “prefers” that Phase 1 studies be placebo-controlled



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## >> Phases of Drug Development

### □ Phases of Drug Development (cont'd)

#### ▪ Phase 2 Studies

- Includes controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication in patients
- Determine the common short-term side effects and risks associated with the investigational new drug
- Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects
- Should include 3+ doses (logarithmic dosing)
- Again, the FDA “prefers” Phase 2 studies be placebo-controlled but can also be controlled with “standard of care” if placebo is unethical



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## >> Phases of Drug Development

### ❑ Phases of Drug Development (cont'd)

#### ▪ Phase 3 Studies

- Includes studies that are controlled and uncontrolled trials
- Performed after preliminary evidence suggesting clinical effectiveness of the drug has been obtained in Phase 2
- Intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug in a wider patient population
- Provide an adequate basis for physician labeling (Package Insert)
- Phase 3 studies usually include from several hundred to several thousand subjects (per ICH guidelines)



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## >> CTD Structure

### ❑ CTD Structure

- As of May 2018, commercial INDs must be submitted using the FDA's electronic gateway
- In order to use the gateway, the IND must be formatted using the structure outlined in the Common Technical Document (CTD) guidelines
  - However, the CTD was designed for NDAs/BLAs/Marketing Applications
- Many Sponsors try to follow the CTD for both format and content
  - However, many (most) of the sections of the CTD do not apply to INDs
    - ✓ For example: Clinical Overview (Module 2.5)
      - “The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document”
      - How can there be a “critical analysis of clinical data” in an IND for a “first-in-human” study?



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## CTD Structure

- ❑ CTD Structure (cont'd)
  - Important to understand that the FDA has adopted the CTD format (not content) to allow for the electronic submission of the IND
  - IND content is dictated by 21 CFR 312.23



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## Sponsor-Investigator INDs

- ❑ Sponsor-Investigator INDs
  - Do not have to follow CTD format
    - Can follow 21 CFR 312.23 (IND content and format)
      - ✓ Chemistry/Manufacturing/Controls
      - ✓ Pharmacology/Toxicology
      - ✓ Previous Human Experience
  - Can be submitted in paper format



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## >> The Investigational New Drug (IND) Process: Part 1

❑ Questions?



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## >> The Investigational New Drug (IND) Process: Part 1

❑ IND Content and Format Covered in 21 CFR 312.23

❑ Format of an IND

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- In order to use the gateway, the IND must be formatted using the structure outlined in the Common Technical Document (CTD) guidelines
  - However, the CTD was designed for NDAs/BLAs/Marketing Applications
- Many Sponsors try to follow the CTD for both format and content
  - However, many (most) of the sections of the CTD do not apply to INDs
    - ❖ For example: Clinical Overview (Module 2.5)
      - ✓ "The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document"
      - ✓ How can there be a "critical analysis of clinical data" in an IND for a "first-in-human" study?



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## >> The Investigational New Drug (IND) Process: *Part 1*

- ❑ **IND Content and Format Covered in 21 CFR 312.23**
  - ❑ Even though 21 CFR 312.23 is for “content and format”, format applies to Sponsor-Investigator INDs only (commercial INDs must follow CTD format)
- ❑ **Format of an IND**
- ❑ **As summarized on subsequent slides, the general contents of an IND are based on 21 CFR 312.23 (IND content and format)**
  - The FDA has adopted the CTD format (not content) to allow for the electronic submission of the IND
  - That means the various IND documents (content) are “mapped” to a location in the CTD structure/format.
  - For example, the Introductory Statement maps to CTD module 2.2 (Introduction to Summaries), the Investigator’s Brochure maps to Module 1.14.4.1, etc.



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## >> IND Content

### ❑ IND Content

IND Content	IND Comments	“Maps to” CTD Location
Cover Letter	All IND-related submissions require a cover letter. The cover letter will serve as a “road map” for the submission and introduce the FDA to the application.	1.2 / Cover letters
Form FDA 1571	Standard form that accompanies all IND submissions.	1.1.1 / Application form: FDA form 1571
Form FDA 3674	Certificate of compliance with Clinicaltrials.gov	1.1.2 / Forms

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Introductory Statement	The <u>brief</u> introductory statement provides: name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug, the formulation of the dosage form, the route of administration, the broad objectives and planned duration of the proposed clinical investigation, and brief summary of previous human experience (if applicable). This is usually ~2 pages.	2.2 / Introduction to Summary

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
General Investigational Plan	A <u>brief</u> description of the overall plan for investigating the drug product for the upcoming year. This is usually 1-2 pages. It is non-binding. The purpose is to give the FDA an idea of sponsor's development plans for the upcoming year. It is <u>not</u> meant to summarize the protocol(s) that are submitted with the IND.	1.13.9 / General Investigational Plan

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Investigator's Brochure	The IB should summarize the development activities (brief summary of the indication to be studied; chemical name, structure, dosage form; preclinical pharmacology, PK, and toxicology; previous human experience (if applicable); and a section entitled: Summary of Data and Guidance for the Investigator. This section should include an integrated toxicology summary (and clinical summary, if available) with an overall conclusion regarding toxicity/safety implications to humans.	1.14.4.1 / Investigator's Brochure

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Protocol	The final, full protocol (or protocols) to be included in the IND and investigator documentation (CV and 1572 Form)	5.3 / Clinical Study Reports and Related Information

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## IND Content

### IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Pharmacology / PK Summaries	<p>It is recommended that the pharmacology and PK summaries that are included in this section of the IND be identical to the summary of pharm/PK summaries that are included in the IB</p> <p>Brief summaries will suffice for nonclinical studies and should include, at a minimum: introduction, materials, methods, data, and brief conclusion</p>	<p>2.6.2 / Pharmacology Written Summary</p> <p>2.6.4 / PK Written Summary</p> <p><i>Note: IND <u>does not</u> require "tabulated" summaries.</i></p>

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## IND Content

### IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Toxicology Summary	<p>As noted above, it is recommended that the summary of the toxicology studies be identical to the summary of toxicology studies that are included in the IB</p> <p>Please note: All toxicology studies conducted with the API should be included. That includes pilot studies, non-GLP studies, and GLP studies. An integrated toxicology summary with an overall conclusion regarding toxicity implications to humans is expected.</p>	<p>2.6.6 / Toxicology Written Summary</p> <p><i>Again, a Toxicology Tabulated Summary is not required.</i></p>

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Drug Substance / Drug Product	This section will describe the composition, manufacture, and control of the drug substance (active pharmaceutical ingredient, API) and the drug product in sufficient detail to assure the proper identification, quality, purity, and strength of the investigational drug. Available stability data (API and drug product) are to be included. Information on lot(s) of API used in toxicology studies needs to be included. Similarly, information on lot(s) used in clinical study needs to be included.	Module 3  <i>Note: A summary of CMC information is not required. Nor is a "Quality Overall Summary".</i>

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Placebo	This section should also describe the manufacture of the placebo that will be used in clinical trial, if applicable.	Part of Module 3
Investigational Label	The only <u>required</u> wording is: "Caution: New Drug--Limited by federal (or US) law to investigational use"; however, most labels include the name of the investigational drug, manufacturer, retest/expiry date, sponsor, contact phone number, and directions for use	1.14.4.2 / Investigational Drug Labeling

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Environmental Assessment	<p>A claim for categorical exclusion under 21 CFR 25.32 regarding environmental assessment is required. This is a standard statement.</p> <p>"In accordance with 21 CFR 25.32, the Sponsor requests a categorical exclusion from providing an environmental assessment."</p>	1.12.14 / Environmental analysis

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## » IND Content

### ❑ IND Content (cont'd)

- Detailed structure of Module 3/Drug Substance:
  - 3.2.S Drug Substance
    - 3.2.S.1 General Information
    - 3.2.S.2 Manufacture
      - 3.2.S.2.1 Manufacturer(s)
      - 3.2.S.2.2 Description of Manufacturing Process and Process Controls
      - 3.2.S.2.3 Control of Materials
      - 3.2.S.2.4 Controls of Critical Steps and Intermediates
      - 3.2.S.2.5 Process Validation: Not applicable for INDs
      - 3.2.S.2.6 Manufacturing Process Development
    - 3.2.S.3 Characterization
    - 3.2.S.4 Control of Drug Substance
    - 3.2.S.5 Reference Standards or Materials
    - 3.2.S.6 Container Closure Systems
    - 3.2.S.7 Stability
  - Repeats for 3.2.P (Drug Product)

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## » IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Nonclinical Full Reports: Pharmacology PK Safety Pharm Toxicology	<p>Full reports of the nonclinical studies required.</p> <p>Note: FDA will review nonclinical reports, especially safety pharmacology and toxicology, and compare to the IB to make sure all studies are included in both the IB and Module 4.</p> <p>Data from toxicology and safety pharmacology studies must comply with the Standards for Exchange of Nonclinical Data (SEND) format.</p>	Module 4

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## » IND Content

### ❑ IND Content (cont'd)

#### ▪ Detailed content of Module 4

#### 4.2 Study reports

##### 4.2.1 Pharmacology

##### 4.2.1.1 Primary pharmacodynamics

##### 4.2.1.2 Secondary pharmacodynamics

##### 4.2.1.3 Safety pharmacology

##### 4.2.2 Pharmacokinetics

##### 4.2.2.1 Analytical methods

##### 4.2.2.2 Absorption

##### 4.2.2.3 Distribution

##### 4.2.2.4 Metabolism

##### 4.2.2.5 Excretion

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## >> IND Content

### ❑ IND Content (cont'd)

#### ▪ Detailed content of Module 4 (cont'd)

##### 4.2.3 Toxicology

4.2.3.1 Single dose toxicity [Species and route of administration]

4.2.3.2 Repeat dose toxicity [Species, route, duration]

4.2.3.3 Genotoxicity

4.2.3.4 Carcinogenicity

4.2.3.5 Reproductive and developmental toxicity

4.2.3.6 Local tolerance

4.2.3.7 Other toxicity studies



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## >> IND Content

### ❑ IND Content (cont'd)

IND Content	IND Comments	"Maps to" CTD Location
Previous Human Experience	A <u>summary</u> of previous human experience is to be included. It is acceptable to replicate the clinical section of the Investigators' Brochure for this section. If the IND protocol is "first-in-human", this section is NA.	2.7 / Clinical Summary
	<p><i>Full clinical reports are not required.</i></p> <p>If full clinical reports are to be submitted, they should be placed in the appropriate section of Module 5.</p>	Module 5

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## Next Session

- ❑ Questions on IND content or format?
- ❑ Next Session: IND Process: Part 2
  - Attendees will learn about
    - Clinical Holds
    - Protocol Amendments/Information Amendments
    - Annual Reports
    - Overview of IND Safety Reporting Requirements
    - Review the responsibilities of both sponsors and investigators conducting studies under an IND
    - Review of expedited drug development programs for serious conditions



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