Chemistry, Manufacturing and Controls: Regulatory Considerations Through Clinical Development

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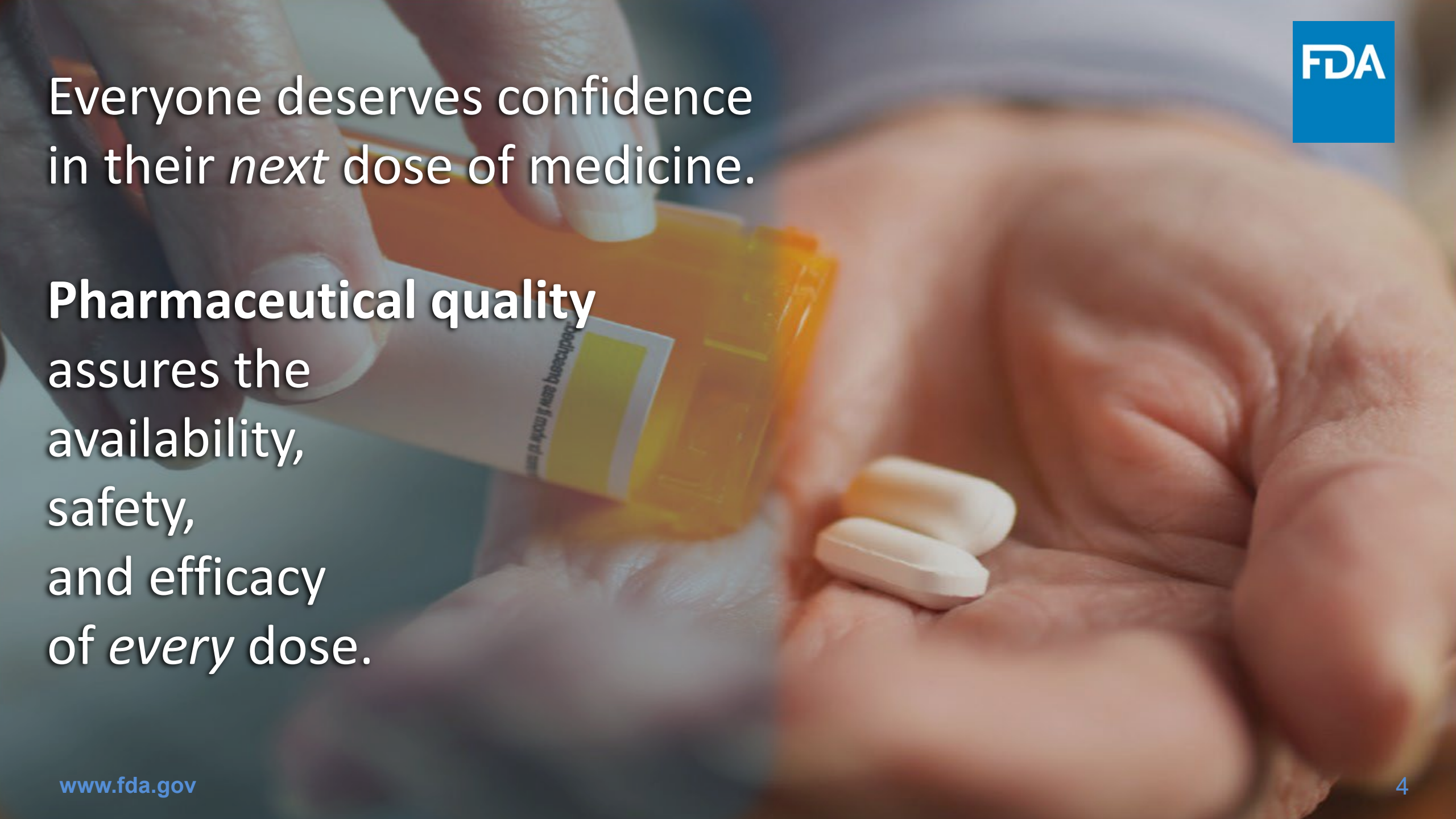
Clinical Investigator Training Course (CITC) – December 6th and 7th 2023

Learning Objectives

- Understand the regulatory definitions and requirements for drug substances and drug products
- Describe Chemistry, Manufacturing, and Controls (CMC) information for IND submissions
- Name some potential CMC safety concerns for INDs

Outline

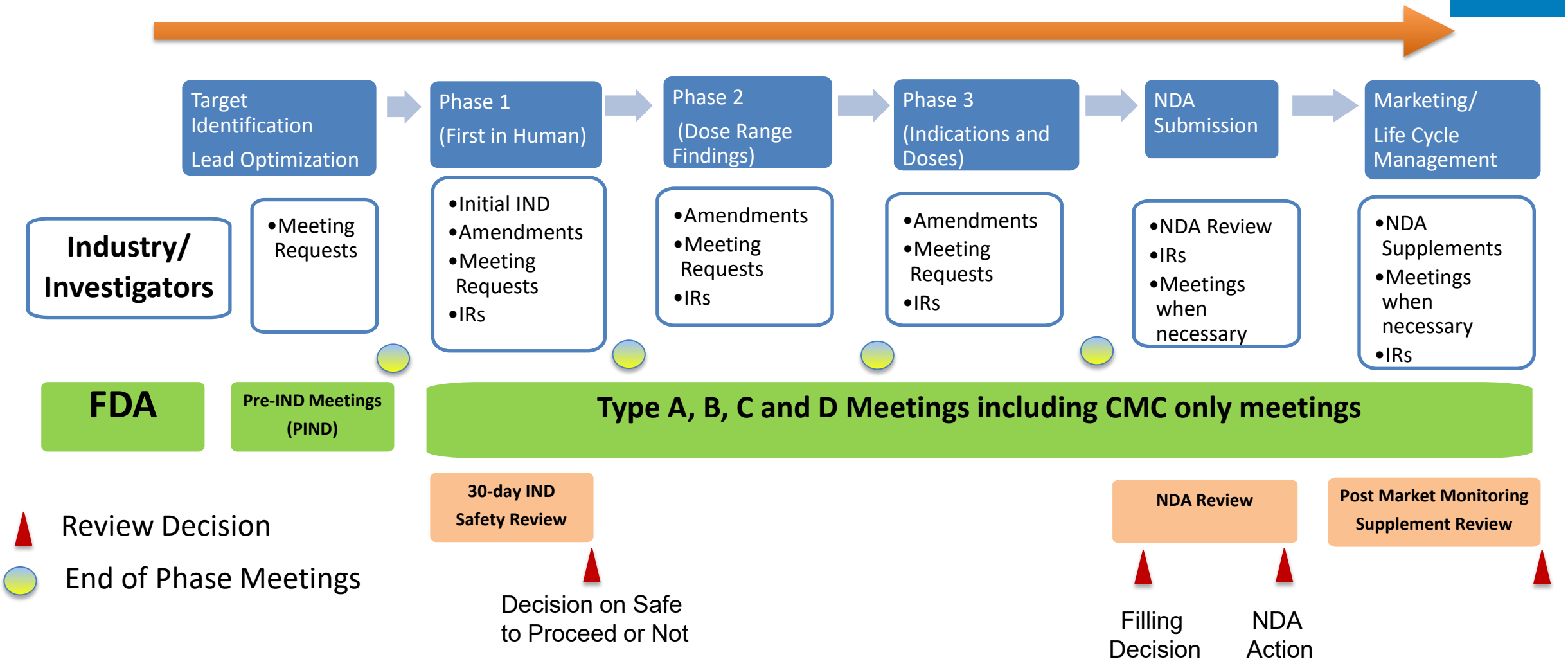
- Pharmaceutical Quality
- Chemistry, Manufacturing, and Controls (CMC) – Development Timeline
- Regulatory Definitions and Requirements
- CMC Requirements for INDs
  - Drug Substance
  - Drug Product
- IND Safety Concerns
- Guidance Documents and Resources



Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

CMC Covers Lifecycle



The challenge for the Quality Review is to assure that the characteristics and performance of the clinical batches will be replicated consistently in the commercial batches.

Regulatory Definitions

- *"**Drug substance*** is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient."
- "***Drug product*** is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients."

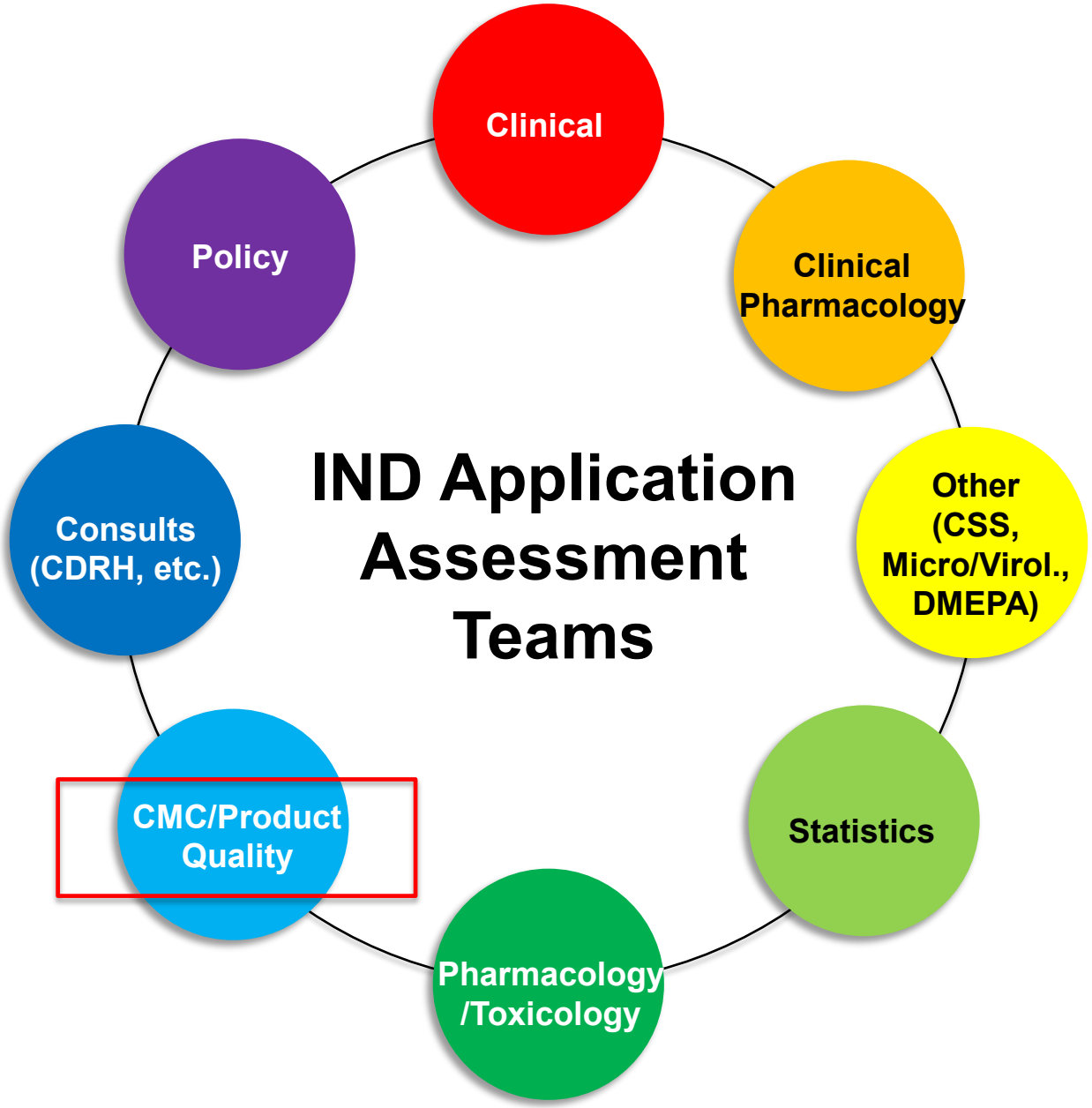
IND CMC Regulatory Requirements

21 CFR 312.23(a)(7)

- Composition and Control of the drug substance and the drug product
- Manufacturer and Manufacturing Process
- Identification, Quality, Purity, and Strength
- Stability
- Amount of information depends on
  - Phase of investigation
  - Dosage form
  - Duration of study
  - Other available information
- Emphasis in an initial Phase 1 submission
  - Identification and control of the raw materials and the new drug substance

FDA has 30 days to review IND submissions

IND Assessment Teams



NDA Product Quality Assessment Teams

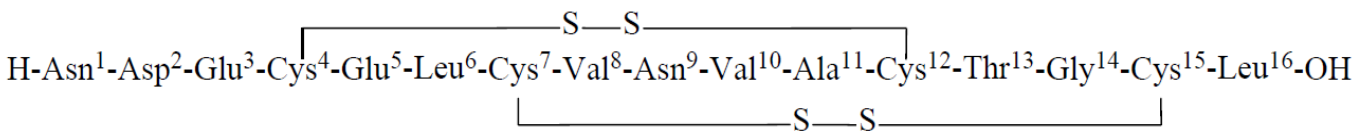
Drug Substance CMC Information

- **General Information**
  - Sources and Complexity
  - Chemical Structure, molecular weight, formula, nomenclature
- **Manufacturing Process**
- **Characterization Data**
  - Structural Characterization
  - Physicochemical Attributes
- **Impurities**
- **Control of Drug Substance** (i.e., Specification for Release)
- **Batch Data** (toxicology and clinical batches)
- **Stability**

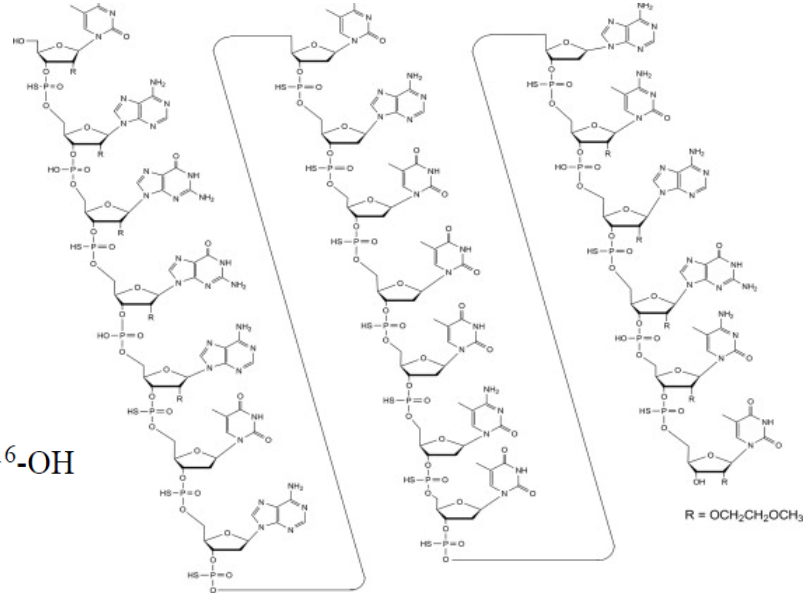
Drug Substance Sources and Complexity

Manufactured by Chemical Synthesis

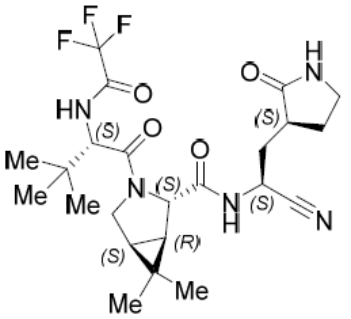
- Small Molecules
- Peptides
- Oligonucleotides



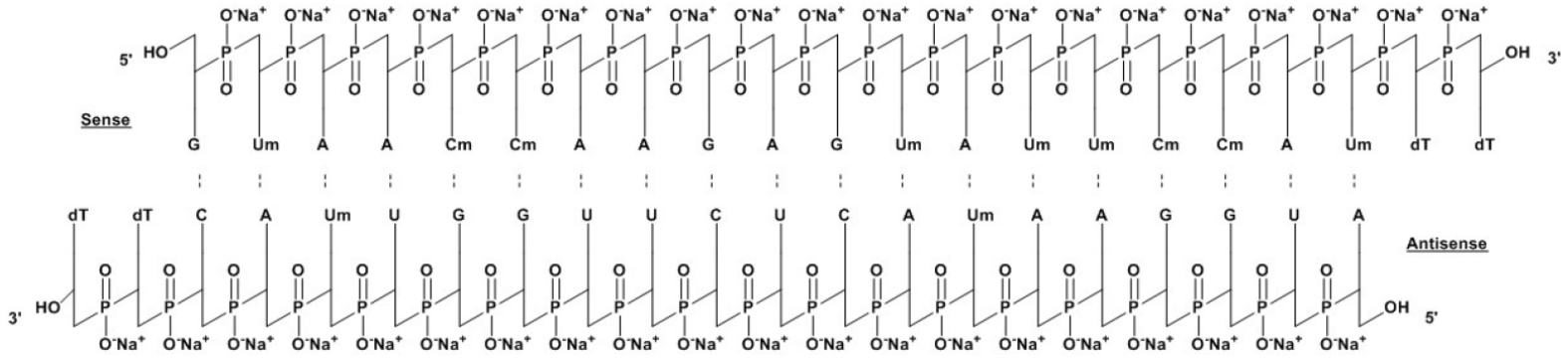
Plecanatide



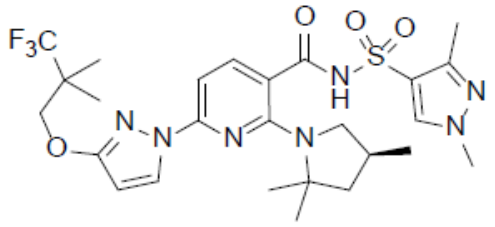
Tofersen



Nirmatrelvir



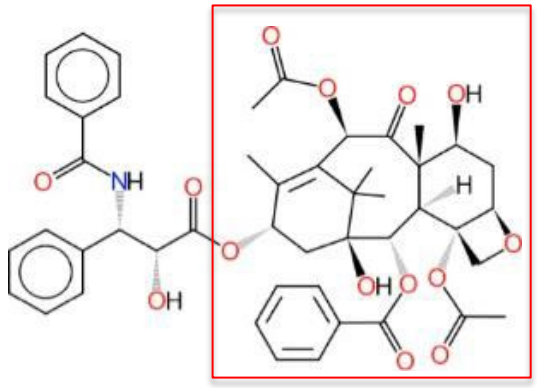
Patisiran Sodium



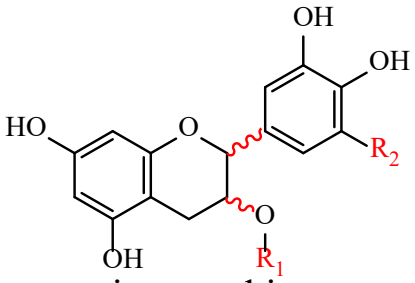
Elexacaftor

Drug Substance Sources and Complexity

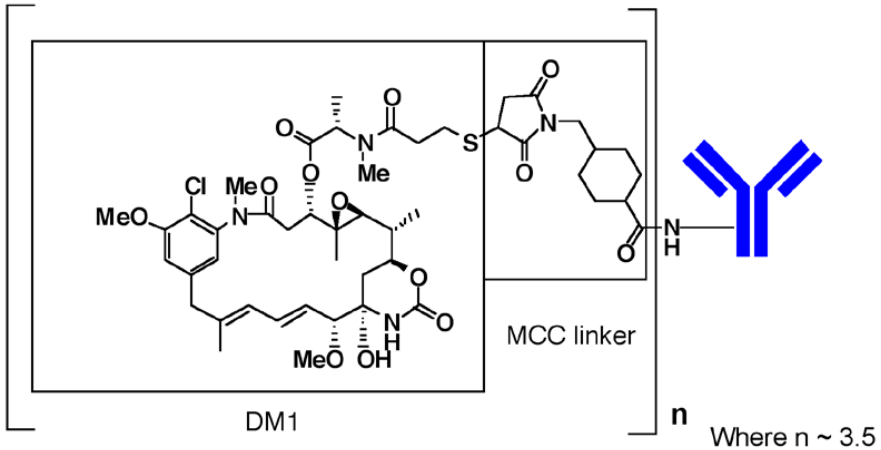
- Fermentation products
- Semi-synthetic
- Isolated from natural sources
- Antibody Drug Conjugates



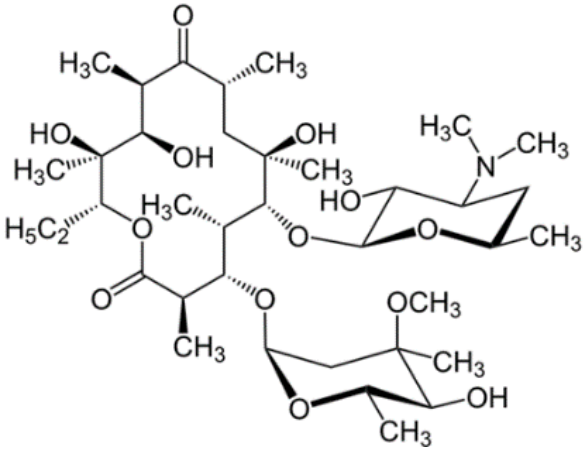
Paclitaxel
(semi-synthetic)



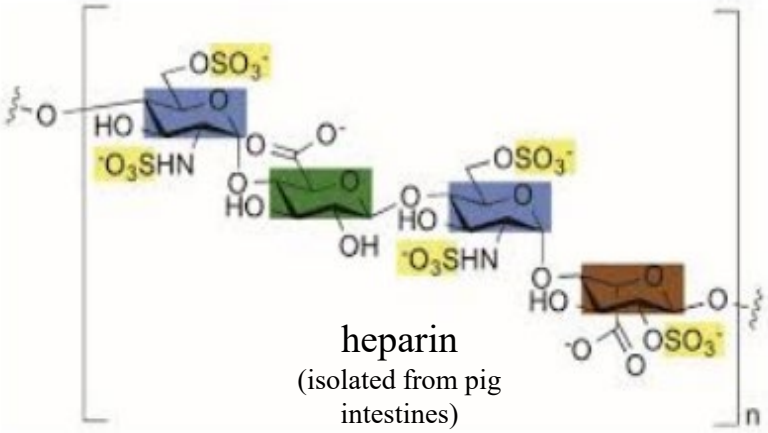
sinecatechins
(from green tea)



ado-trastuzumab emtansine
(Biotechnology/Synthetic)



erythromycin
(from fermentation)



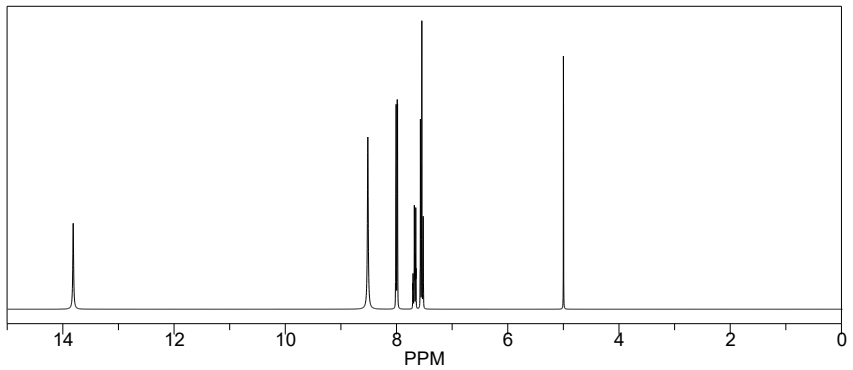
heparin
(isolated from pig intestines)

Drug Substance: Manufacturing Process

- Brief Description of Manufacture
  - Written and detailed flow diagram
  - Reagents, solvents, catalysts, etc.
  - Controls for input materials, raw materials, intermediates
  - Any In-process Controls (e.g., tests for reaction completion)
- Emphasis on differences between toxicology and clinical batches
- Process Optimization Beyond Phase 1
  - Increase scale of manufacture
  - Optimization of steps, yield, purity
  - GMP manufacturing process to support late stage development
  - CMC focused meeting (end-of-phase 2 or earlier)

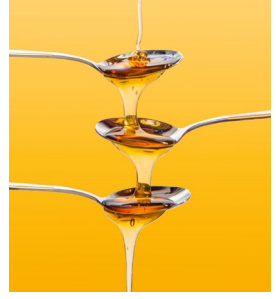
Drug Substance: Structural Characterization

- Data to support the proposed structure (e.g. NMR, IR, UV)
- Structural data may be limited at early stages of development
- Raw spectral data alone is not sufficient
- Your interpretation (e.g. peak assignments) is expected
- We will evaluate interpretation of spectral and other characterization data
- Some ambiguity can be justified for impurities present at low levels

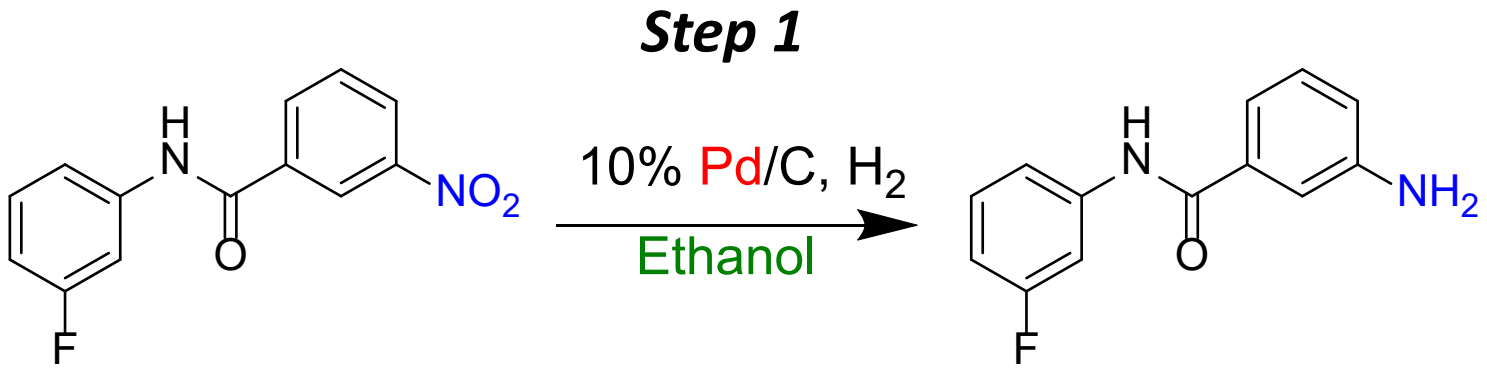


Drug Substance: Physicochemical Characterization

- Drug Substance Attributes
  - Appearance and Physical Form (e.g. solid, oil, etc.)
  - Solubility (aqueous and in organic solvents)
  - Particle Size Distribution
  - Polymorphic Forms
  - Hygroscopicity
- Understand Criticality to Drug Product
- Monitor and characterize critical attributes (e.g., dissolution, disintegration, polydispersity index, particle size, water content)

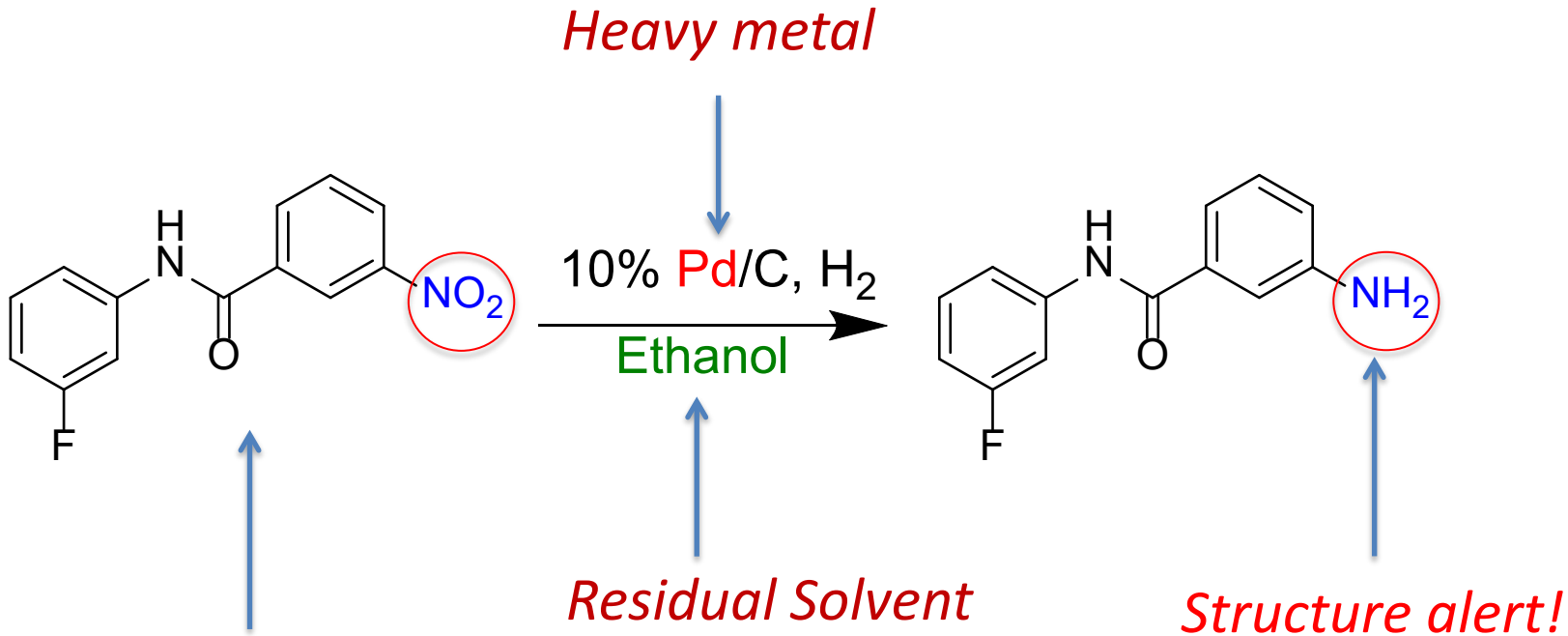


Impurities



Any *component* of the drug substance that is *not the chemical entity*

Impurities



- Control strategy and sources for potential impurities
- Address differences in impurities between toxicology and clinical batches

Impurities

Any *component* that is *not the chemical entity*

- **Organic impurities**
  - ICH Q3A(R2) – Impurities in New Drug Substances
  - ICH Q3B(R2) – Impurities in New Drug Products
  - Reporting, identification and qualifications thresholds
- **Mutagenic Impurities**
  - ICH M7(R1) – Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk
  - Control of Nitrosamine Impurities in Human Drugs
- **Residual solvents**
  - ICH Q3C(R6) – Impurities: Residual Solvents
- **Elemental impurities**
  - USP<232>, <233>, and ICH Q3D(R2) – Elemental Impurities
- **Microbial contaminants**
  - USP<61> Microbial limits; USP<85> Bacterial endotoxins

Drug Product

- Description of the Dosage Form
  - Justify novel technology or complex formulation
  - Administration information
- Quantitative Composition
  - Inactive ingredients (include quality or compendial status)
  - Novel excipients (additional information may be needed)
  - Animal derived excipients require evaluation
- Manufacturing Process
  - Written Description and Flow Diagram
  - Sterilization process (if applicable)
- Degradation Products (Drug Product Impurities)

Control of Drug Substance and Drug Product

- Test methods and limits to assure *identity, strength, quality and purity*
- Description of analytical test methods
- Proposed limits based on analytical development and batch data
- Monitor critical attributes (e.g., dissolution, disintegration, polydispersity index, particle size, water content)
- Specification tests and limits change as development proceeds
- Batch data for proposed clinical studies

Example Drug Substance Specification

Test/Attribute	Test Method	Acceptance Criteria
Appearance	Visual	White solid
Identification	Retention time (HPLC) FT-IR	Conforms to Reference
Assay	HPLC	98 – 102%
Purity Related substance impurities Residual solvents Elemental impurities	 HPLC GC ICP-MS	 NMT 0.10% 5000 ppm ICH Q3D/USP <232>/<233>
Water content	Karl Fisher/USP <921>	NMT 2%
Polymorphic Form	XRPD	Crystalline
Particle Size	In-house	Report D10, D50, D90
Bacterial endotoxins	USP <85>	USP <85>
Microbial limits	USP <61>/<62>	USP <61>/<62>

Drug Substance and Drug Product Stability

- How much data?
  - Preliminary data on representative material (e.g. technical batches, nonclinical batches)
  - Submit available data on clinical batches
- Provide information on the tests used to monitor stability
- Stability commitment

CMC IND Safety Concerns

- Manufactured with impure/unknown materials (i.e., adulterated)
- Impurity profile insufficiently characterized
- Impurities of known or potentially high toxicity
- Unreliable analytical methods undermine confidence in data
- Insufficient batch data
- Stability issues (e.g., significant changes in assay)
- Lack of sterility assurance or endotoxin control (e.g., injectable drug products)
- Issues with formulation (e.g., particulate matter)
- GMP Issues with Facilities

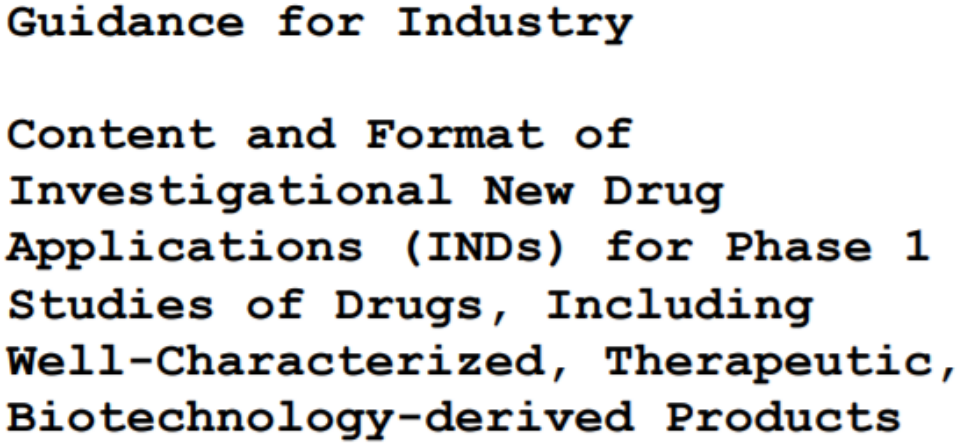
Pre-IND Meetings and Guidance

Pre-IND meetings

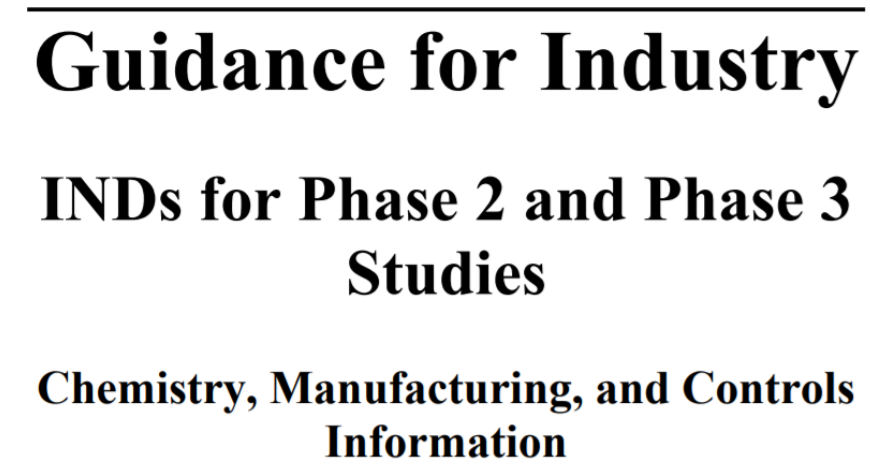
- Discuss the readiness of IND
- Specific questions for various review disciplines
- CMC pre-IND focus areas: manufacturing, specifications, impurity controls, batch data, potential gaps

Guidance Documents

- FDA's current thinking on a topic
- Ensure sufficient data will be submitted
- Clarifies type, extent, and reporting of CMC information


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

INDs for Phase 2 and Phase 3 Studies

Chemistry, Manufacturing, and Controls Information

Guidance Documents

1. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-and-format-investigational-new-drug-applications-inds-phase-1-studies-drugs-including-well
2. INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/inds-phase-2-and-phase-3-studies-chemistry-manufacturing-and-controls-information
3. Exploratory IND Studies Guidance for Industry, Investigators, and Reviewers. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exploratory-ind-studies
4. Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-q7a-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients
5. Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice
6. Current Good Manufacturing Practice for Phase 1 Investigational Drugs Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-phase-1-investigational-drugs

Challenge Question #1

The regulatory term for an 'active ingredient intended to furnish the pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body' is:

A. Drug Product
B. Impurity
C. Drug Substance
D. Intermediate

Challenge Question #2

The following are CMC Safety Concerns, except which one:

A. Impurities of known or potentially high toxicity
B. Insufficient batch data
C. Lack of sterility assurance or endotoxin control
D. The manufacturing process route for the marketing application has not been finalized

Questions?

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