Chemistry, Manufacturing and Controls: Regulatory Considerations and Resources

Paresma Patel, Ph.D.
Division Director, Division XIX
Office of Product Quality Assessment III,
Office of Pharmaceutical Quality
CDER | US FDA

Clinical Investigator Training Course (CITC) – December 10–12, 2024

Learning Objectives

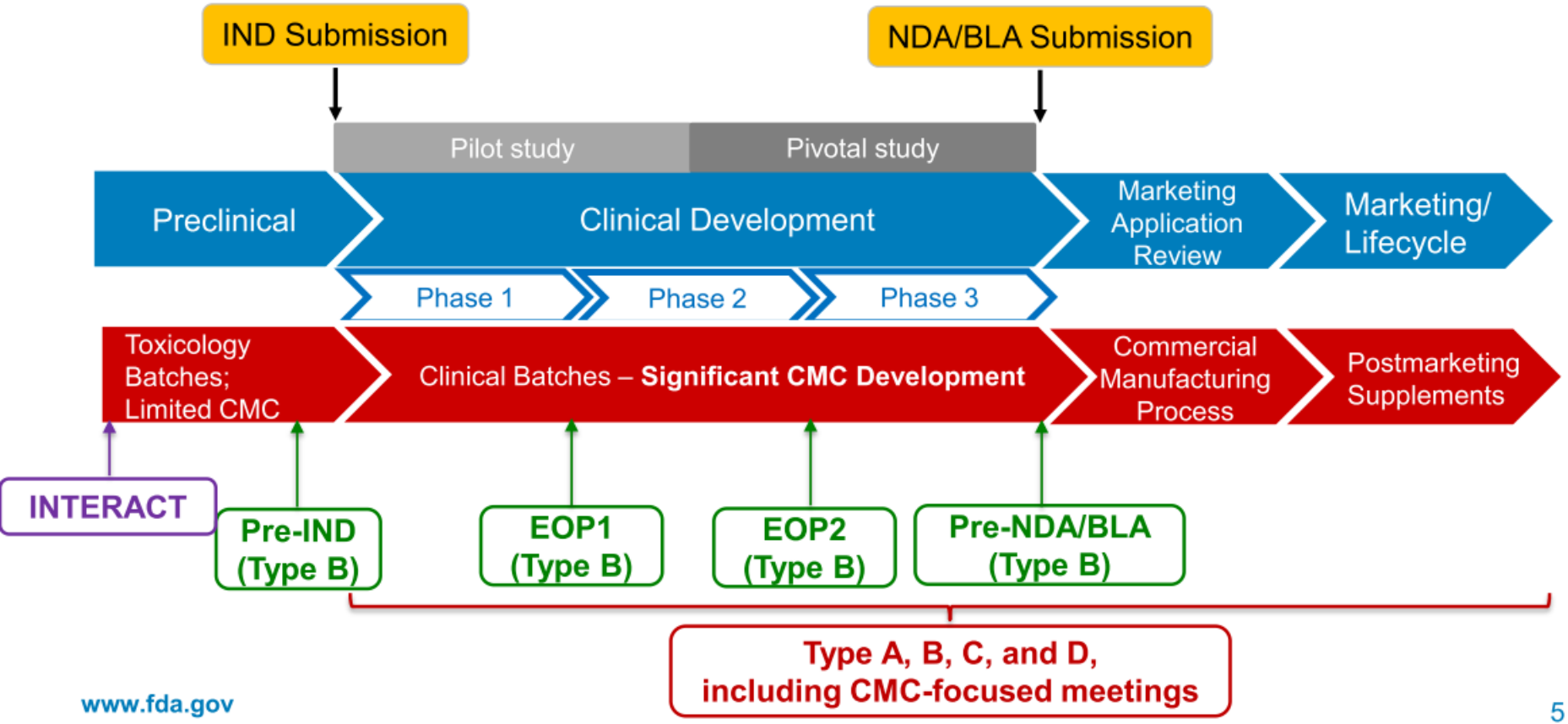
- Understand the regulatory definitions and requirements for drug substances and drug products
- Describe Chemistry, Manufacturing, and Controls (CMC) information for IND submissions
- Name some potential CMC safety concerns for INDs

Outline

- Pharmaceutical Quality
- Chemistry, Manufacturing, and Controls (CMC) – Development Timeline
- Regulatory Definitions
- CMC Considerations
  - Drug Substance
  - Drug Product
- 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 the Lifecycle



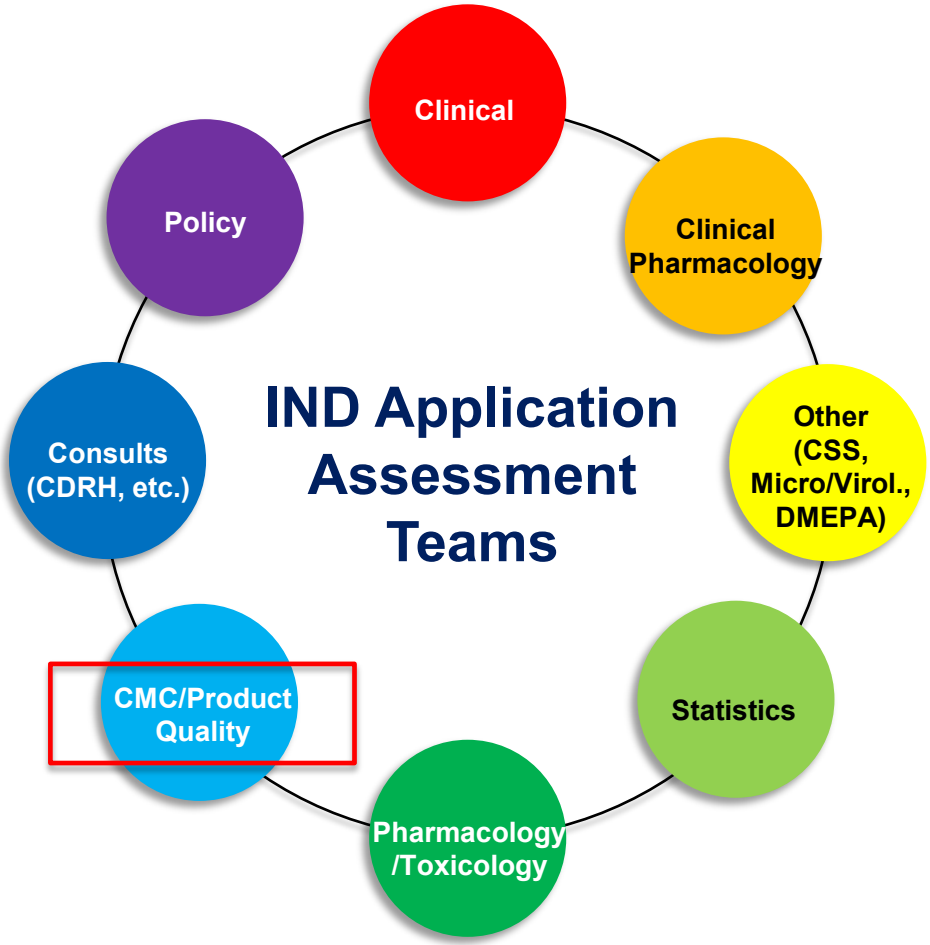
Regulatory Definitions

- Key Definitions in the Code of Federal Regulations 21 CFR 314.3
- **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

- Outlined drug substance and drug product requirements found 21 CFR 312.23 (a)(7)
  - Description, Composition and Controls
  - Manufacturer, Manufacturing Process, Stability
  - Identity, Quality, Purity, and Strength
  - *Emphasis in Phase 1 on the new drug substance and raw materials*
- Guidance Documents
  - Clarifies type, extent, and reporting of CMC information
  - Ensure sufficient data will be submitted to the IND and quality of the proposed clinical studies

IND Assessment Teams



NDA Product Quality Assessment

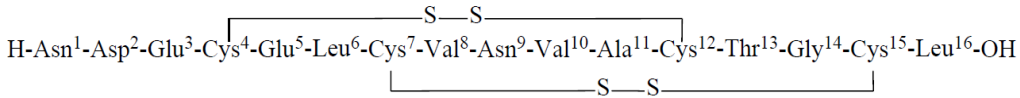
Drug Substance

- General Information [3.2.S.1]
  - Sources and Complexity
  - Chemical Structure, molecular weight, formula, nomenclature
- Manufacturer and Manufacturing Process [3.2.S.2]
- Characterization Data [3.2.S.3.1]
  - Structural Characterization
  - Physicochemical Attributes
- Impurities [3.2.S.3.2]
- Control of Drug Substance [3.2.S.4] (i.e., Release Specification)
- Batch Data [3.2.S.4.4] (toxicology and clinical batches)
- Stability [3.2.S.7]

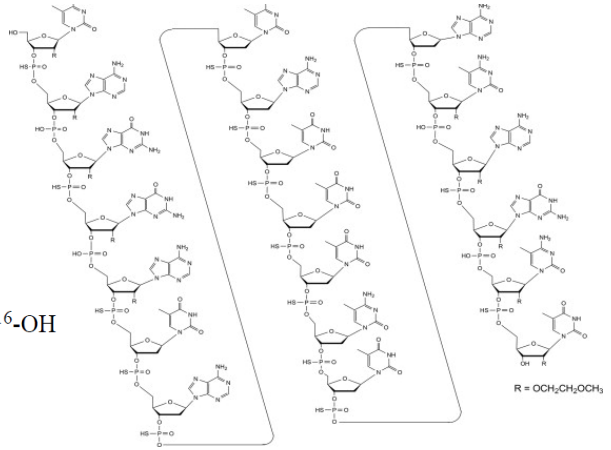
Drug Substance Sources and Complexity

Manufactured by Chemical Synthesis

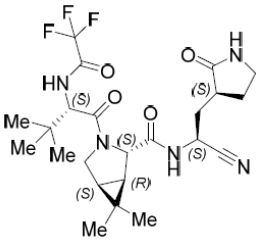
- Small Molecules
- Peptides
- Oligonucleotides



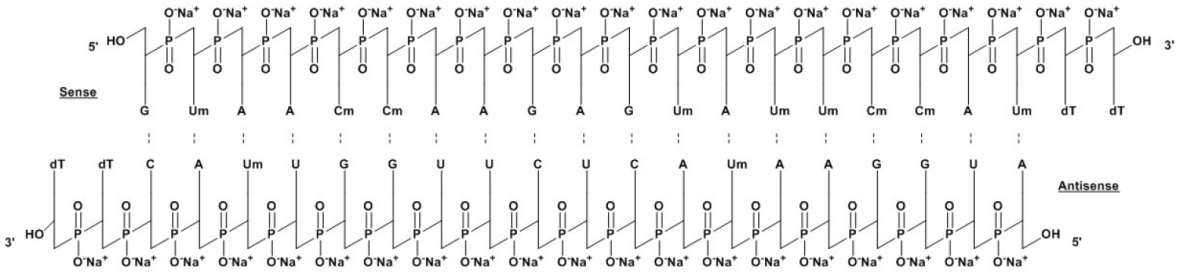
Plecanatide



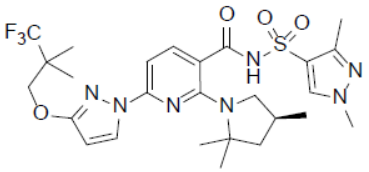
Tofersen



Nirmatrelvir



Patisiran Sodium

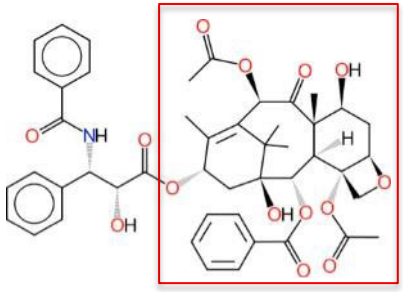


Elexacaftor

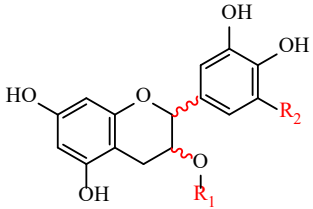
www.fda.gov

Drug Substance Sources and Complexity

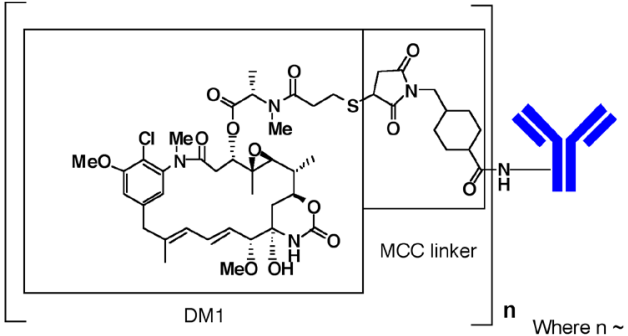
- Fermentation products
- Semi-synthetic
- Isolated from natural sources
- Antibody Drug Conjugates



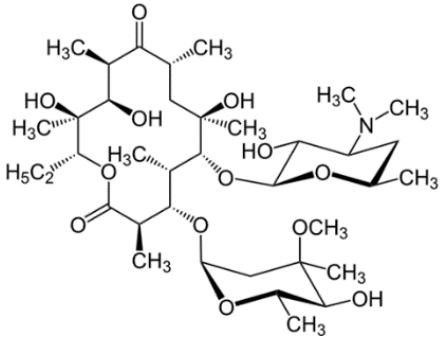
Paclitaxel
(semi-synthetic)



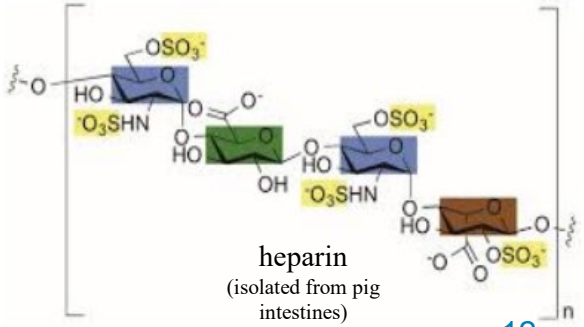
sinecatechins
(from green tea)



ado-trastuzumab emtansine
(Biotechnology/Synthetic)



erythromycin
(from fermentation)



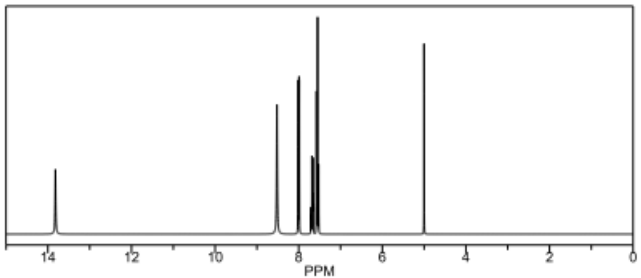
heparin
(isolated from pig intestines)

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

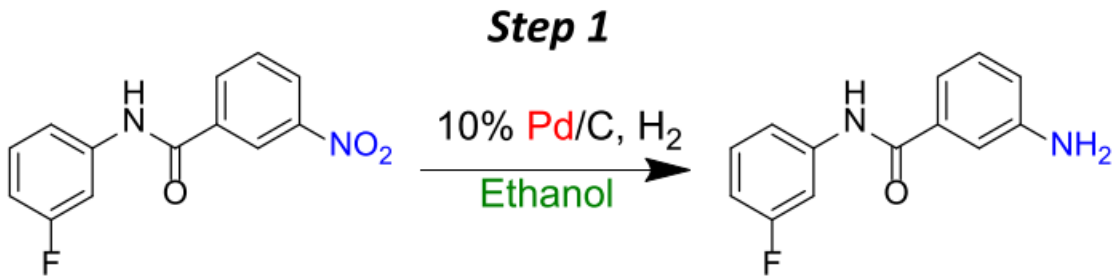
- Data to support the proposed structure (e.g. NMR, IR, UV)
- Structural data may be limited at early stages of development
- Raw spectral data alone is not sufficient
- Interpretation (e.g. peak assignments) is expected
- Assessor will evaluate interpretation of spectral and other characterization data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



Drug Substance: Physicochemical Characterization

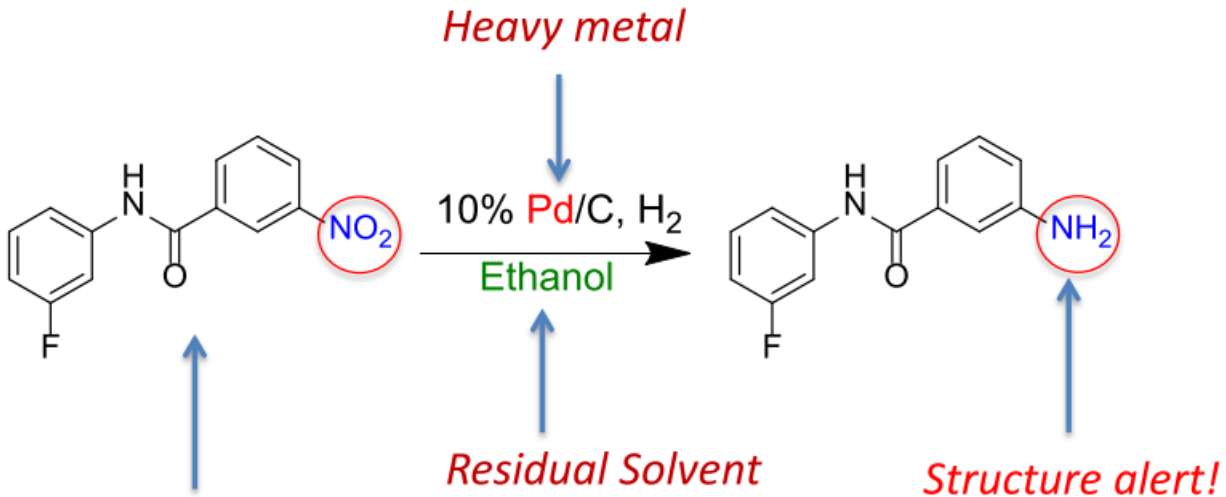
- Drug Substance Attributes
  - Appearance and Physical Form (e.g. solid, oil, etc.)
  - Solubility (aqueous and in organic solvents)
  - Particle Size Distribution
  - Polymorphic Forms
  - Hygroscopicity
- Understand Criticality to Drug Product
- Monitor and characterize critical attributes (e.g.,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

Control of Drug Substance

- 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 Stability

- How quality varies with time under the influence of a variety of environmental factors (e.g., temperature, humidity, and light).
- Establish retest period or shelf life
- Testing of attributes susceptible to change, and likely to influence quality, safety, efficacy (e.g., appearance, purity, impurities, water content, polymorphism)
- Long term (recommended storage) and Accelerated (increased temperature/rate of chemical degradation) Conditions
- Provide information on the tests used to monitor stability
- How much data?
  - IND Submissions:
    - Preliminary data on representative material (e.g., technical batches, nonclinical batches)
    - Submit available data on clinical batches

Drug Product

- Description of the Dosage Form [3.2.P.1]
  - Justify novel technology or complex formulation
  - Administration information
  - In-use compatibility
- Quantitative Composition [3.2.P.1], [3.2.P.4]
  - Inactive ingredients (include quality or compendial status)
  - Novel excipients (additional information may be needed)
  - Animal derived excipients require evaluation
- Manufacturing Process [3.2.P.3]
  - Written Description and Flow Diagram
  - Sterilization process (if applicable)
- Control of Drug Product [3.2.P.5] (i.e., Release Specification)
  - Degradation Products (Drug Product Impurities)
  - Batch Analyses
- Container Closure System and Stability [3.2.P.7 and 3.2.P.8]

Drug Product Information for INDs

- Product label required as per 21 CFR 312.23(a)(7)(iv)(*d*)
  - Statement of “Caution: New Drug Limited by Federal Law to Investigational Use”
  - Investigational brochure
- 21 CFR 312.23(a)(7)(iv)(*e*) *Environmental analysis requirements.*
  - Claim for categorical exclusion under 25.30 or **25.31(e)**

Drug Product Specification

Attribute	Analytical Procedure	Acceptance Criteria
Identity	IR or HPLC/UV	Matches Standard
Appearance	Visual	Color, Imprint
Assay	HPLC	90-110%
Impurities (Related substances)	HPLC	NMT 0.1% Total: NMT 1%
Osmolality	USP	280 – 320 mOsm/kg
Dose Uniformity	HPLC or Weight	Statistical Criterion (USP)
Particulate Matter	USP	NMT #
Water Content	Chemical or weight loss	Few %
Microbial Limits or sterility	USP	NMT # cfu/g; absence of pathogenic organisms; Sterile
Bacterial Endotoxins	USP	NMT #
Reconstitution Time	Visual Inspection	NMT # seconds

Drug Product Stability

- Packaging components that contain, protect, and deliver the dosage form (primary and secondary packaging components)
- Establish shelf life and expiration dating period
- Testing of attributes susceptible to change, and likely to influence quality, safety, efficacy (e.g., appearance, purity, impurities, water content, dissolution)
- How much data?
  - IND Submissions:
    - Preliminary data on representative material (e.g. technical batches, nonclinical batches)
    - Submit available data on clinical batches
    - In-use compatibility, reconstitution stability, and data to support hold times

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)
- CGMP Issues with Facilities

Pre-IND Meetings

Pre-IND meeting to discuss the readiness of IND

- One pre-IND meeting
- Meeting package with background information
- CMC pre-IND focus areas
  - Manufacturing process and characterization
  - Drug substance and drug product specifications
  - Stability data and study design
  - Impurity controls
  - Adequacy of clinical and toxicology batches
  - Potential gaps or hold issues

Resources

- Code of Federal Regulations: https://www.ecfr.gov/
- US Pharmacopeia (USP)
- IND Guidance Documents:
  - Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products.
  - INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information Guidance for Industry.
  - Exploratory IND Studies Guidance for Industry, Investigators, and Reviewers.
  - Current Good Manufacturing Practice for Phase 1 Investigational Drugs Guidance for Industry.
  - Botanical Drug Development
- ICH Guidelines
  - ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and Drug Products
  - ICH Q11 Development and Manufacture of Drug Substances
  - ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
  - ICH Q1A Stability Testing of New Drug Substances and Products
- Expedited Programs
  - MAPP 5015.13 Quality Assessment for Products in Expedited Programs
  - Expedited Programs for Serious Conditions | Drugs and Biologics
  - Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP) Program

Resources – Impurities

- **Organic impurities**
  - ICH Q3A(R2) – Impurities in New Drug Substances
  - ICH Q3B(R2) – Impurities in New Drug Products
- **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
  - Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities
- **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

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

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Paresma R. Patel
Division Director
Office of Pharmaceutical Quality
CDER | US FDA

Paresma.patel@fda.hhs.gov