Chemistry, Manufacturing and Controls: Regulatory Considerations and Resources

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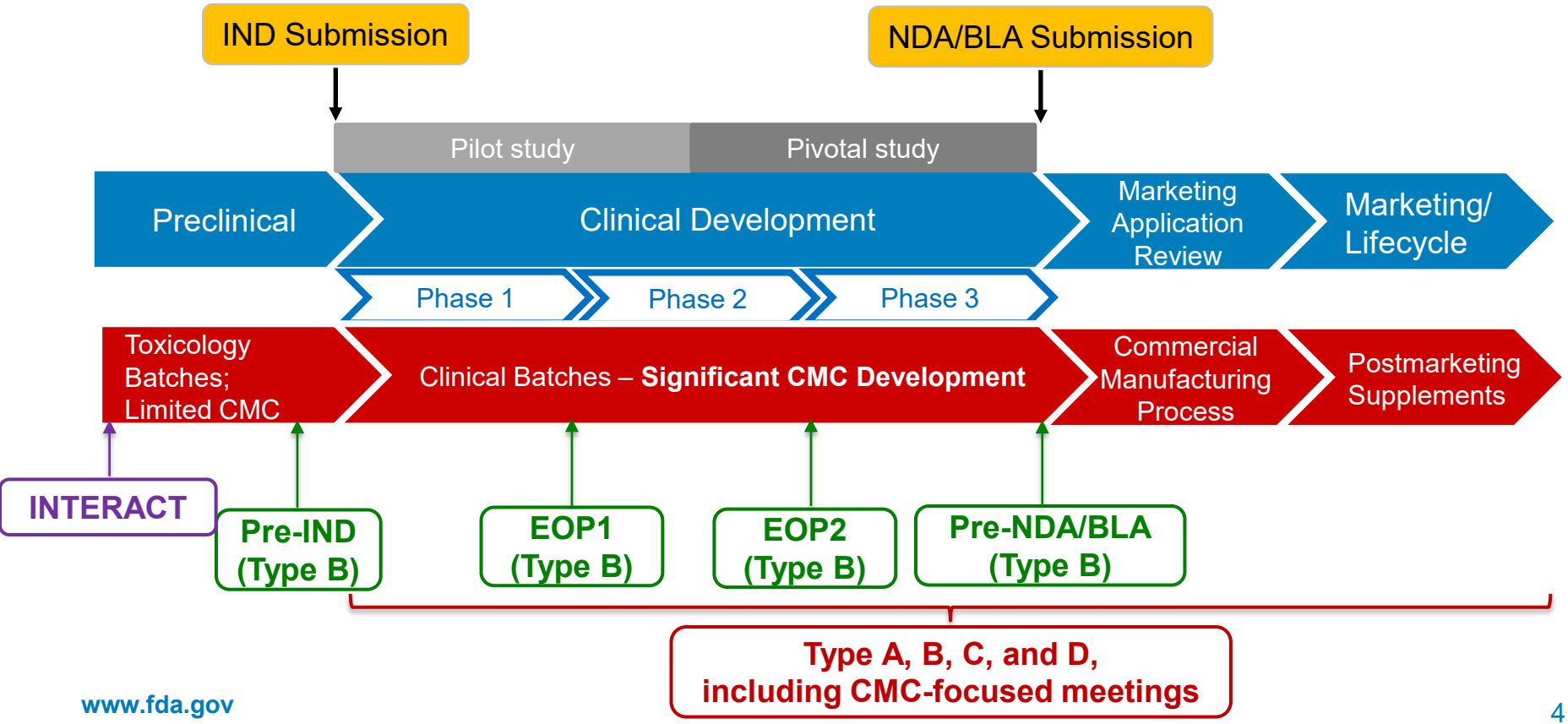
Regulatory Do's and Don'ts: Tips from FDA – September 4, 2024

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

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 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]

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

Regulatory Do's and Don'ts

Do's

- ✓ Read and apply available guidance documents
- ✓ Meet and engage with FDA early, especially for complex products with little applicable guidance
- ✓ Ask focused regulatory questions during meetings
- ✓ Address FDA advice and comments
- ✓ Engage CMC team in CMC-focused meeting
- ✓ Assure quality suppliers and CGMP requirements

Don't: Ignore FDA advice and input!

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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