

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

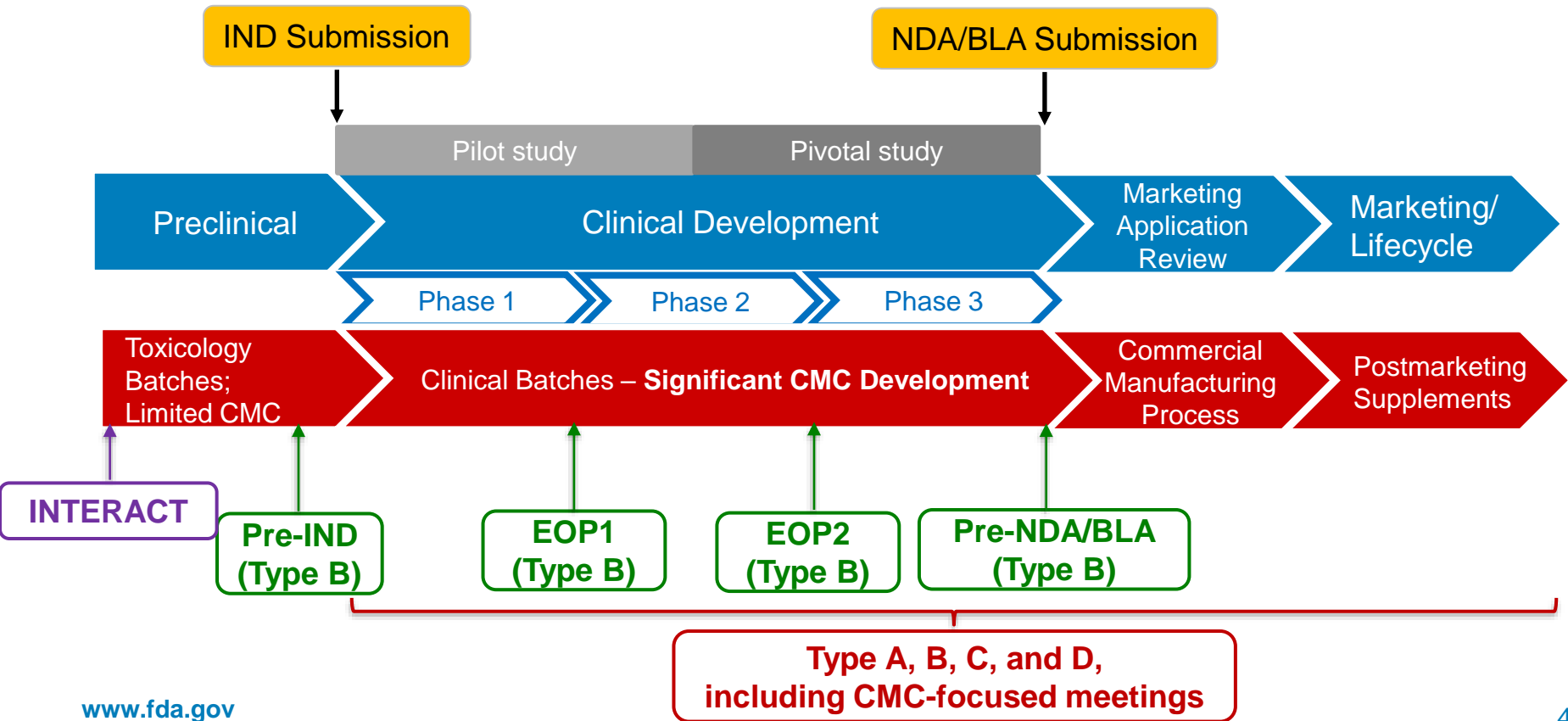
- Pharmaceutical Quality
- Chemistry, Manufacturing, and Controls (CMC) – Development Timeline
- Regulatory Definitions
- CMC Considerations
 - Drug Substance
 - Drug Product
- Guidance Documents and Resources

A close-up photograph of a person's hand holding an open orange pill bottle, pouring three white, oval-shaped pills onto their palm. The background is blurred, focusing attention on the hand and the medication.

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

