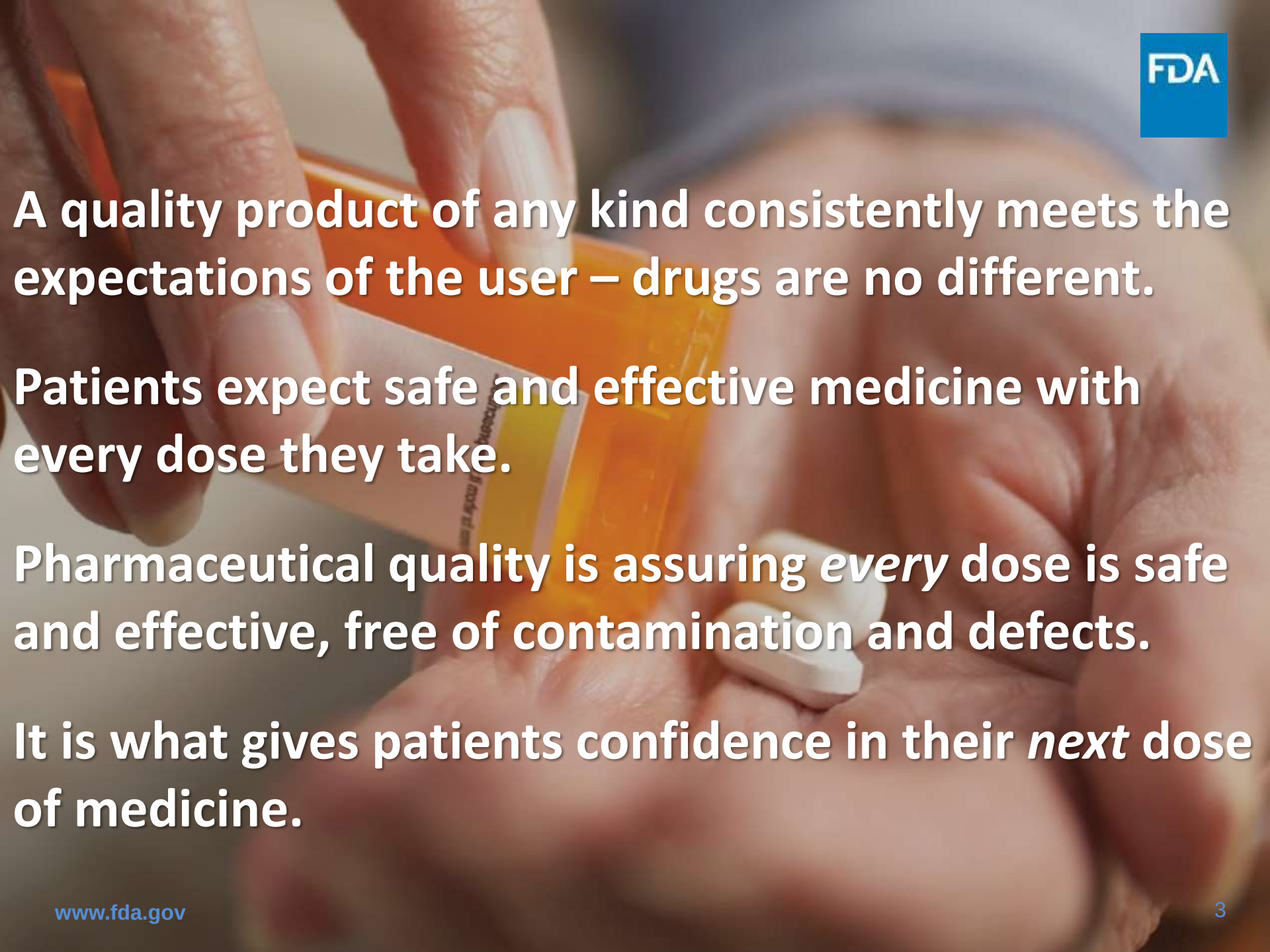
Chemistry, Manufacturing, and Controls: Requirements for Early Clinical Development

Paresma Patel, Ph.D.
Division Director

Office of Pharmaceutical Quality
Office of New Drug Products

Outline

- Pharmaceutical Quality
- CMC Requirements for INDs
  - Drug Substance
  - Drug Product
- Impurities
- Specifications
- Stability
- CMC Safety Concerns
- Guidance Documents and Resources



A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Regulatory Definitions

From 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

21 CFR 312.23(a)(7)

- (7) *Chemistry, manufacturing, and control information.* (i) ***As appropriate for the particular investigations*** covered by the IND, a section describing the ***composition, manufacture, and control of the drug substance and the drug product.*** Although in each phase of the investigation sufficient information is required to be submitted to assure the proper ***identification, quality, purity, and strength*** of the investigational drug, the ***amount of information*** needed to make that assurance ***will vary with the phase of the investigation***, the proposed ***duration of the investigation***, the ***dosage form***, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the ***emphasis in an initial Phase 1 submission*** should generally be placed on the ***identification and control of the raw materials and the new drug substance***. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

IND CMC Regulatory Requirements

21 CFR 312.23(a)(7)

- Composition, manufacture, and control of the drug substance and the drug product.
- Identification, quality, purity, and strength
- 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.

Drug Substance Regulatory Requirements

21 CFR 312.23(a)(7)

- (iv)(a) Drug substance.
- Physical, chemical, or biological characteristics;
- Manufacturer
- Method of preparation
- Identity, strength, quality, and purity
- Stability

Drug Product Regulatory Requirements

21 CFR 312.23(a)(7)(iv)

- (b) Drug product.
- List of all components
- Quantitative composition
- Drug product manufacturer
- Description of the manufacturing and packaging procedure
- Identity, strength, quality, and purity
- Stability

Drug Substance CMC Information

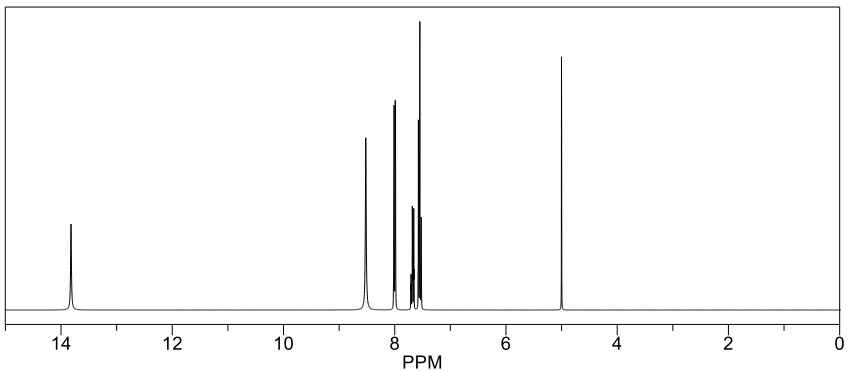
- Manufacturing Process
- Characterization Data
  - Structural Characterization
  - Physicochemical Properties
- Impurities
- Specification for Release
- Stability

Drug Substance: Manufacturing Process

- Brief Description of Manufacture
  - Written and detailed flow diagram
  - Include all reagents, solvents, catalysts, etc.
  - In-process Controls (e.g. tests for reaction completion)
  - Controls for input materials, raw materials, intermediates
- Differences in synthesis of toxicology and clinical batches
- Use of the same batch for toxicology and clinical batches

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)

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)
- Impurities and Specification
- Stability

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
- **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

Impurities

- Control strategy for potential impurities
- Address differences in impurities between toxicology and clinical batches
- List of process impurities, degradants, and potentially mutagenic impurities
  - Include reference to nonclinical data (e.g. AMES or QSAR)
  - Address risk of potentially mutagenic impurities based on manufacture process

Drug Substance and Drug Product Specification

- Test methods and limits to assure identity, strength, quality and purity
- Description of analytical test methods or reference to compendial tests
- Proposed limits based on available analytical testing, toxicology, and clinical batch data
- Batch data for proposed clinical batches with data on purity level and impurity profile

Drug Substance and Drug Product Specification

- Specification tests and limits are likely to change as development proceeds
  - Methods are being developed and validated
  - Manufacturing process is being optimized
  - Commercial process and scale is being developed

Drug Substance and Drug Product Stability

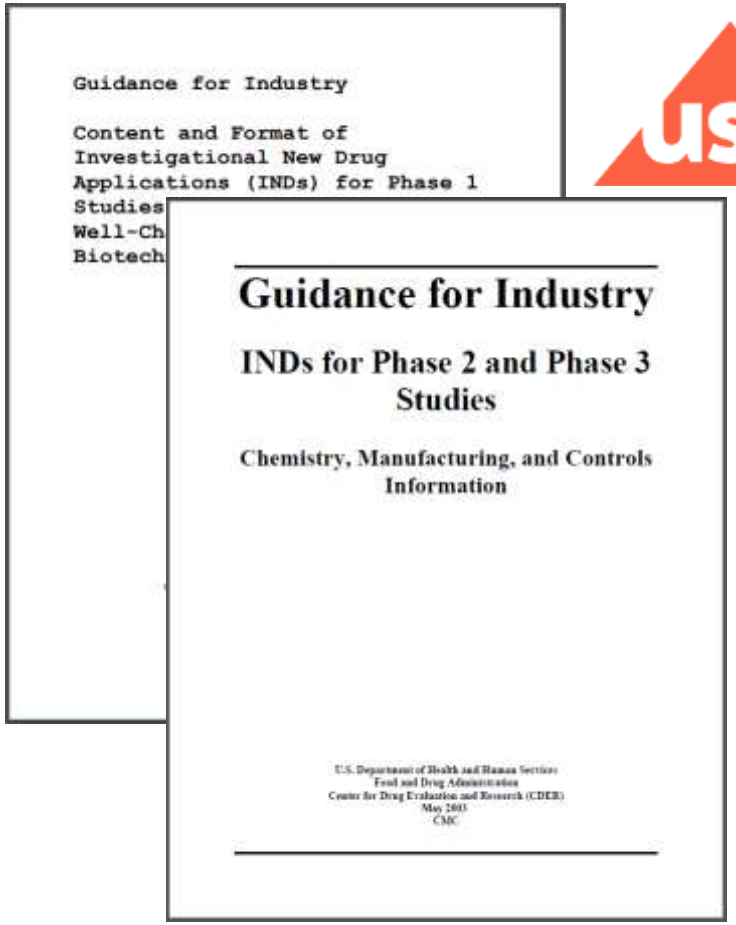
- How much data?
  - Preliminary data on representative material (e.g. technical batches, nonclinical batches)
  - Submit available data on clinical batches
- Provide information on the tests used to monitor stability
- Stability commitment

CMC Safety Concerns

- Drug substance or drug product manufactured with impure/unknown materials
- Impurity profile insufficiently characterized
- Impurities of known or potentially high toxicity
- Unreliable analytical methods undermine confidence in data
- Insufficient batch data
- Stability issues (significant changes in assay)
- Lack of sterility assurance or endotoxin control (e.g., injectable drug products)

Resources

- Guidance Documents
- USP/NF Monographs
- Pre-IND Meetings



References

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION