CATALYZE
Accelerating Translation

Development of Chemistry, Manufacturing and Controls (CMC) Module 3 (Quality) for INDs

Carmella S. Moody, PhD
Regulatory Program Director
RTI International

NIH National Heart, Lung, and Blood Institute

CATALYZE Resource For Questions

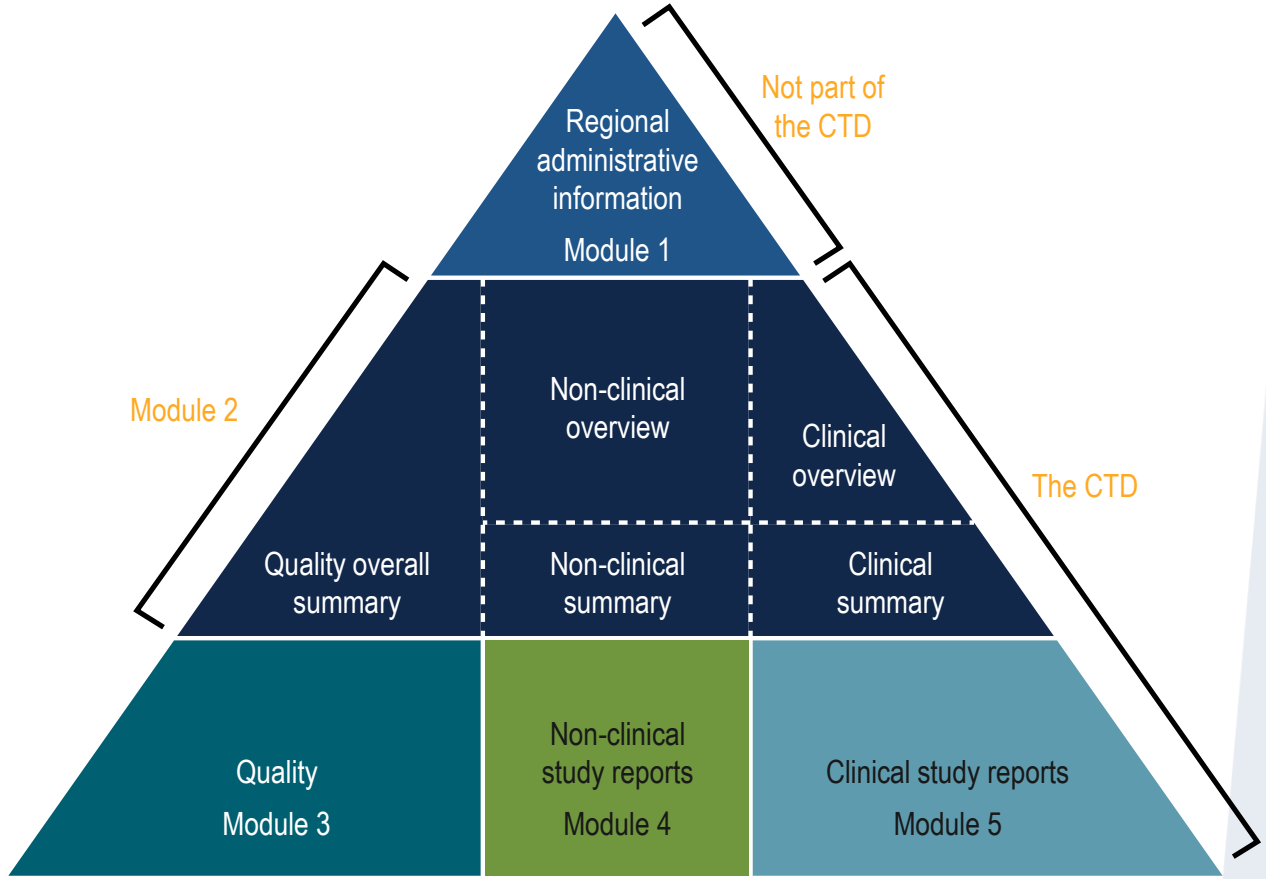
Catalyze_info@rti.org

Critical References for CMC, Module 3 (Quality) for INDs

- IND content and format for Phase 1 studies
- INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information
- Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications; Guidance for Industry
- Guidance for Industry M4Q: The CTD-Quality August 2001: This is mainly to understand the granularity (Quality Sections) of the IND. NOTE: The guidance information is mainly for NDA or BLA so for IND use only for information on the specific **Headings for Module 3.**
- Search for FDA Guidance Documents | FDA

Electronic Common Document (eCTD) Modules

- **All commercial INDs (which are INDs for products that will eventually be marketed) must be submitted to FDA electronically**
- **All electronic submissions must be in Common Technical Document (CTD) format**
- **CTD Format**
  - **Module 1:** Administrative (Cover Letter and 1571; Introductory Statement and General Investigational Plan; Investigator Brochure)
  - **Module 2:** Summaries (Non-clinical summary; Quality/CMC summary; clinical summary (if applicable))
  - **Module 3:** Quality/CMC data
  - **Module 4:** Non-clinical/pre-clinical study reports
  - **Module 5:** Clinical study reports (Protocol)



Overview of Presentation

- Information is provided for some drug substance and drug product sections, specifically those that may need more explanation of information to be included.
- Note that the Drug Substance and Drug Product Sections are numbered with specific section numbers and corresponding headers.
  - E.g. 3.2.S.1 Characterization, 3.2.P.1 Description and Composition
  - Each numbered section should be a pdf individual file when submitted electronically
- Please also note that this numbering scheme and heading names must be followed and cannot be changed.

Drug Substance CMC (Quality) Information in Module 3 CTD Format

Module 3 CTD Drug Substance Sections

- 3.2.S.1 General information
  - 3.2.S.1.1 Nomenclature
  - **3.2.S.1.2 Structure**
  - **3.2.S.1.3 General properties**
- 3.2.S.2 Manufacture
  - 3.2.S.2.1 Manufacturer(s)
  - **3.2.S.2.2 Description of Manufacturing Process and Process Controls**
  - **3.2.S.2.3 Control of Materials**
  - 3.2.S.2.4 Controls of Critical Steps and Intermediates
  - 3.2.S.2.5 Process Validation and/or Evaluation*
  - 3.2.S.2.6 Manufacturing Process Development*
- 3.2.S.3 Characterization
  - 3.2.S.3.1 Elucidation of Structure and other Characteristics
  - **3.2.S.3.2 Impurities**
- 3.2.S.4 Control of drug substance
  - **3.2.S.4.1 Specifications**
  - **3.2.S.4.2 Analytical Procedures**
  - 3.2.S.4.3 Validation of Analytical Procedures*
  - **3.2.S.4.4 Batch Analyses**
  - **3.2.S.4.5 Justification of Specification**
- **3.2.S.5 Reference standards or materials**
- **3.2.S.6 Container closure systems**
- 3.2.S.7 Stability
- **3.2.S.7.1 Stability Summary and Conclusions**
- 3.2.S.7.2 Post Approval Stability Protocol and Stability Commitment*
- **3.2.S.7.3 Stability Data**

* N/A for Early Phase Development & IND/IMPD Submissions

3.2.S.1.2 Structure

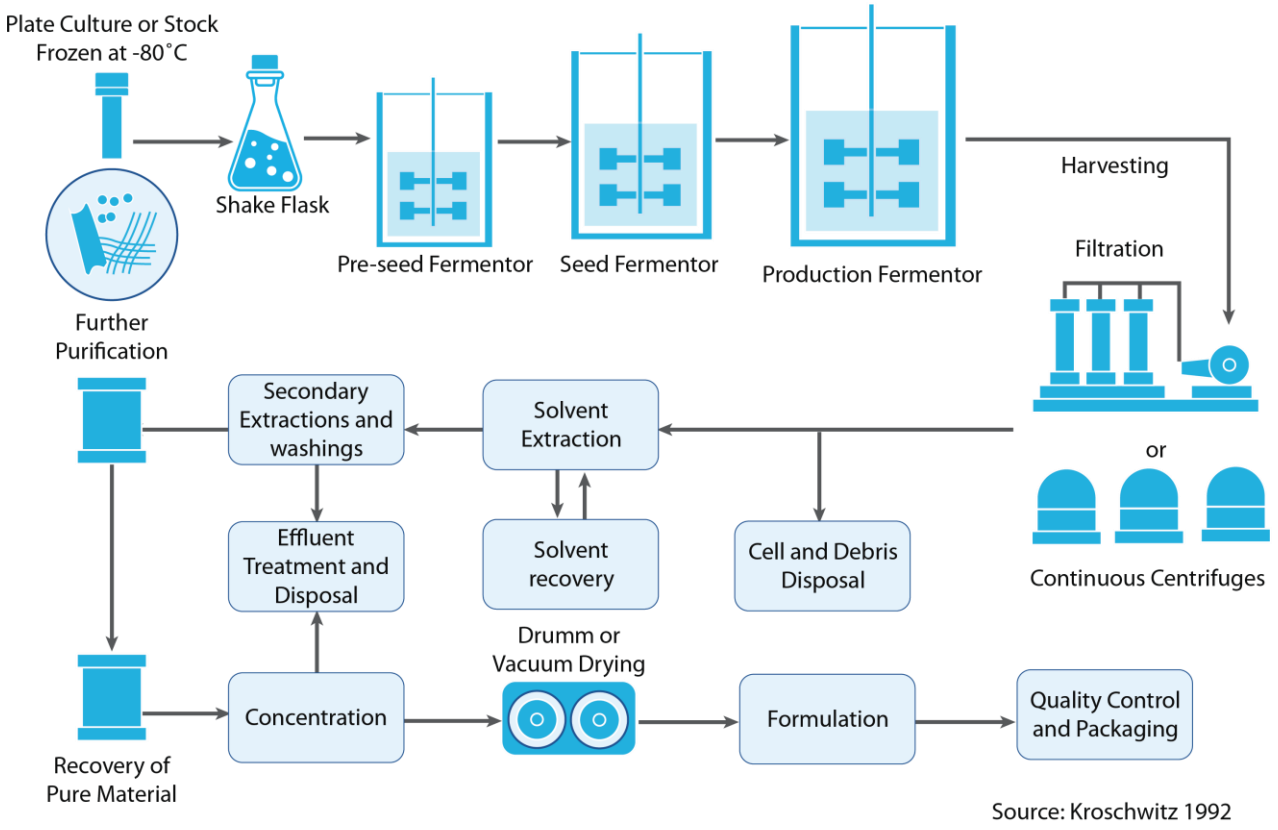
- **Evidence to Support Proposed Chemical Structure**
  - **Small Molecule**
    - ✓Absolute Stereochemistry
    - ✓Molecular Formula
    - ✓Mass Spectrum
  - **Large Molecule (Biologics)**
    - ✓Amino Acid Sequence with Glycosylation Sites (as appropriate)
    - ✓Amino Acid Sequence with any Posttranslational Modifications (as appropriate)
    - ✓Relative Molecular Mass

3.2.S.1.3 General Properties

- Small Molecule Physical-Chemical Properties
  - Color
  - Melting Point
  - Boiling Point
  - Solubility
  - pH
  - Partition coefficient
  - Optical Rotation
  - Particle Size Distribution
  - Polymorphic Form
- Large Molecule
  - Biological Activity
  - Proposed Mechanism of Action

3.2.S.2.2 Description of Manufacturing Process and Process Controls

- The manufacturing process details should cover critical steps, equipment used, in-process controls.
  - Provide a flow chart describing the manufacturing process.
  - Provide a narrative description of each step in the manufacturing process, following the process flowchart.
- **Phase 1**
  - Information very general; equipment defined by function, descriptive process controls, typical process details such as time and temperature provided.
- **Phase 2 and 3**
  - Information should gradually become more specific and detailed, and any deviations or changes made during manufacturing provided.
  - Specific Information on Equipment type
  - Detailed Operating Parameters
  - More specific information on process controls



Typical Process Flow Diagram for Biologics Fermentation Process

3.2.S.2.3 Control of Materials

- **Phase 1**
  - Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process.
  - Biotech: List media components, Monoclonal Antibodies, Enzymes, provide information on Cell Banking System
  - Add information on the quality of the raw material (USP, NF etc.,)
    - ✓ Avoid materials of animal origin and obtain BSE/TSE certification

- **Phase 2:** Structure of Starting Materials**,** Preliminary Specifications
- **Phase 3,** Information demonstrating that materials meet standards appropriate for their intended use (including the clearance or control of adventitious agents) Provide Tighter Specifications.

3.2.S.3.2 Impurities

- Impurity is anything that is not the product!
- **Phase 1**
  - Impurities section generally not included.
  - Address impurities in the Specification (Section 3.2.S.4.1) with appropriate limits to assure safety.
  - It is important to understand the impurities in GLP toxicology batches to obtain “toxicology coverage” of impurities.
- **Phase 2 and Phase 3**
  - Identify, Qualify, Quantify and Report Impurities
  - Tighten specifications as the development program progresses
  - Identify, Qualify, Quantify and Report NEW Impurities
  - Qualify New Impurities as needed in Bridging Toxicology Studies

Inorganic Impurities

- Reagents, ligands, and Catalysts
- Heavy metals or other residual metals
- Inorganic Salts
- Filter Aids, Charcoal and Other Materials

Organic Impurities

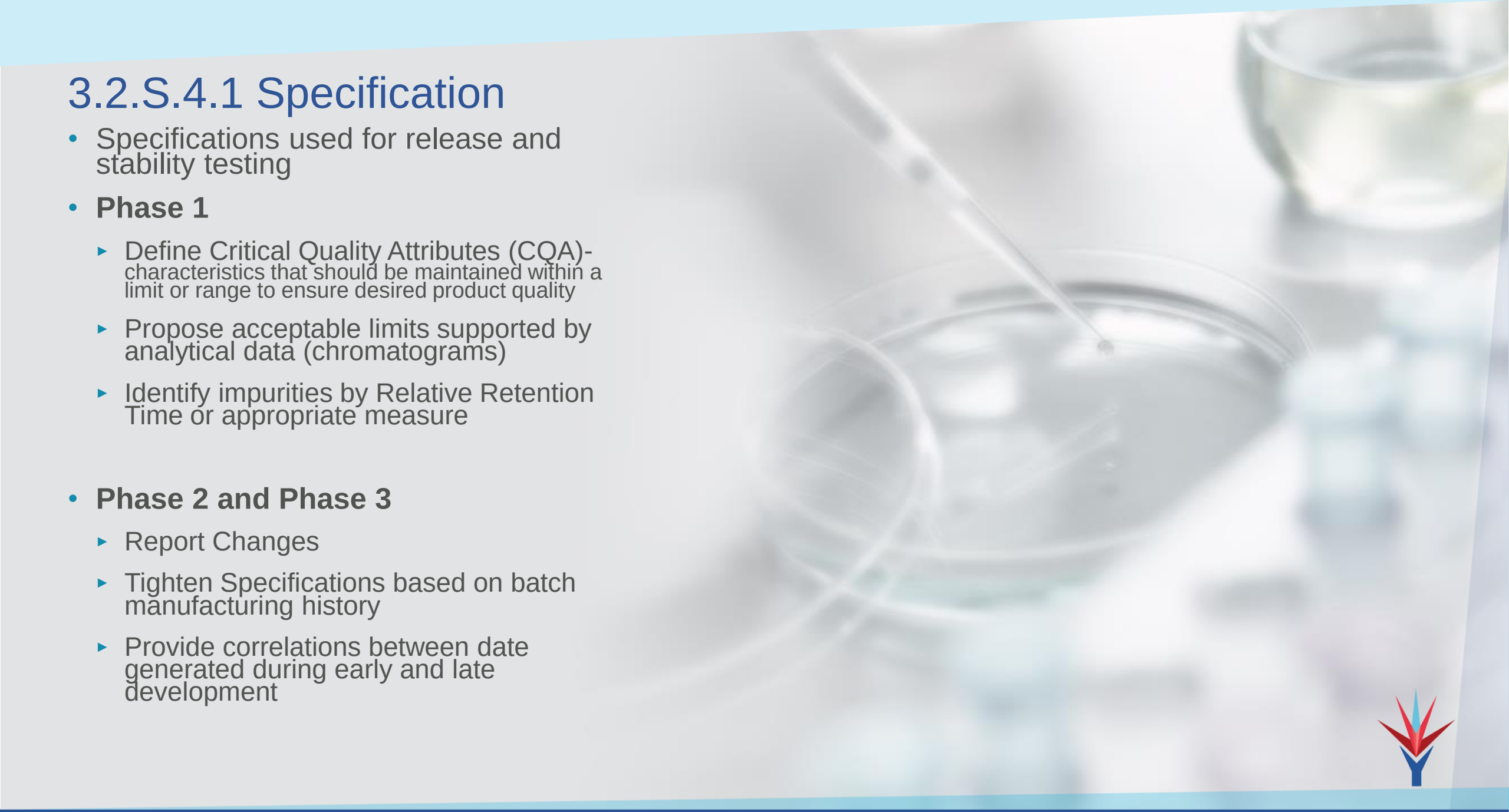
- Starting Materials
- By-Products
- Intermediates
- Degradation Products
- Reagents, Ligands, and Catalysts

Residual Solvents

- Class 1: Solvents to be avoided
- Class 2: Solvents to be limited
- Class 3: Solvents with low toxic potential

3.2.S.4.1 Specification

- Specifications used for release and stability testing
- **Phase 1**
  - Define Critical Quality Attributes (CQA)- characteristics that should be maintained within a limit or range to ensure desired product quality
  - Propose acceptable limits supported by analytical data (chromatograms)
  - Identify impurities by Relative Retention Time or appropriate measure
- **Phase 2 and Phase 3**
  - Report Changes
  - Tighten Specifications based on batch manufacturing history
  - Provide correlations between date generated during early and late development



3.2.S.4.1 Specification (Example Small Molecule)

Test Description	Specification	Release testing	Stability testing
Appearance	White to off-white powder	X	X
ID by HPLC	Spectrum conforms to reference	X	-
Counterion	Report results	X	-
Assay	97.0-103.0% anhydrous basis	X	X
Impurities	Individual NMT 1.0% Total NMT 3.0%	X	X
Chiral impurity	NMT 1.0%	X	X
Residual solvents	ICH limits	X	-
Inorganic impurities	NMT EMA limits	-	-
Water content	Report results	-	X
Solid form	Report results	-	X
Particle size	Report results	-	-
ROI	NMT 1.0%	-	-

3.2.S.4.2 Analytical Procedures

- **Phase 1**
  - Provide high level method descriptions
- **Phase 2**
  - Provide more information on method, such that an analyst could repeat the method
  - Development of stability-indicating analytical procedures that will detect significant changes in the quality of the drug substance
  - Qualification/Validation data available
- **Phase 3**
  - Full method descriptions
  - Full validation data included.

Validated analytical methods are not required at Phase 1 but are by Phase 2

3.2.S.4.4 Batch Analysis

- Include lot number, manufacturer, manufacturing site, and the date of manufacture of the drug substance. Include route designation of drug substance, as appropriate
- **Phase 1**
  - Provide Batch Analysis used in GLP Toxicology Studies and to be Used in Phase 1 Clinical Trial Material
  - C of A for Batch of Clinical Trial Material in IND
- **Phase 2 and 3**
  - Batch Analysis with full history of all batches with specifications used in GLP and Clinical Studies

3.2.S.4.5 Justification of Specification

- During clinical development, specifications are preliminary and wide due to limited batch production and process knowledge
- ICH Q6B provides guidance on general principles for setting and justifying specifications

- **Phase 1**
  - Focus should be on safety critical specifications (CQA) and batch history. General

- **Phase 2 & 3**
  - Provide more information on why specific specifications set
  - Justifications based on
    - CQA (Safety)
    - Product characteristics
    - Process capabilities

3.2.S.5 Reference Standards or Materials

- Working Standard-Batch of Drug Substance with Additional Tests Beyond Standard Batch Release for Phase 1.

- Development Progression-Fully Characterized Reference Material becomes Primary Reference Material for use in Comparison of Batches in Clinical Studies.

- Reference Material Generally Highest Purity Possible

3.2.S.6 Container – Closure System

- Sum of Packaging Components that together contain and protect the drug substance
- For IND the packaging information should include
  - A brief description of the components,
  - A description of the assembled packaging system and
  - Any precautions needed to ensure the protection and preservation of the drug substance until formulated into Clinical Trial Material

Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics
CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION, May 1999

3.2.S.7.1 Stability Summary and Conclusions

- **Phase 1**
  - A brief description of Stability Study and Test Methods (if test methods different than methods in 3.2.S.4.2)
  - Not necessary to provide Stability Protocol
  - Conclusions from Stability of Drug Substance (Stability in the Specific Container/Closure from 3.2.S.6)
  - Set retest time points

- **Phase 2 and Phase 3**
  - Description of Stability Program to support DS under Clinical Investigation
    - ✓ List of Tests
    - ✓ Analytical Procedures (if different from procedures in 3.2.S.4.2)
    - ✓ Acceptance Criteria
    - ✓ Testing Time Points
    - ✓ Storage Conditions
    - ✓ Duration of Study
  - ➢ Summary Results of Forced Degradation Studies and Stress Conditions

3.2.S.7.3 Stability Data

- **Stability Data in Tabular Format**
  - **Phase 1**
    - ✓ Preliminary Tabular Data
    - ✓ Include lot number, manufacturer, manufacturing site, and the date of manufacture of the drug substance.
  - **Phase 2**
    - ✓ Preliminary Tabular Data
    - ✓ Any available stability data for clinical material from Phase 1 not reported in annual reports
    - ✓ Stability data from representative clinical trial materials used in Phase 2
  - **Phase 3**
    - ✓ Changes in the drug substance stability program from that described for phase 2
    - ✓ Any stability data for CTM in phase 2 studies that were not reported during phase 2 in annual reports or amendments
    - ✓ Stability data for representative clinical trial materials used in phase 3 not provided in annual reports
    - ✓ Include lot number, manufacturer, manufacturing site, and the date of manufacture of the drug substance.

Drug Product CMC (Quality) Information in Module 3 CTD Format

3.2.P Drug product [name, dosage form, manufacturer]

- **3.2.P.1 Description and composition of the drug product**
- 3.2.P.2 Pharmaceutical development
- 3.2.P.3 Manufacture
  - 3.2.P.3.1 Manufacturer(s)
  - **3.2.P.3.2 Batch Formula**
  - **3.2.P.3.3 Description of Manufacturing Process and Process Controls**
  - 3.2.P.3.4 Controls of Critical Steps and Intermediates
  - 3.2.P.3.5 Process Validation and/or Evaluation*
- 3.2.P.4 Control of excipients [name]
  - **3.2.P.4.1 Specification(s)**
  - 3.2.P.4.2 Analytical Procedures
  - 3.2.P.4.3 Validation of Analytical Procedures*
  - 3.2.P.4.4 Justification of Specifications
  - **3.2.P.4.5 Excipients of Human or Animal Origin**
  - **3.2.P.4.6 Novel Excipients**
- 3.2.P.5 Control of drug product
  - **3.2.P.5.1 Specification(s)**
  - **3.2.P.5.2 Analytical Procedures**
  - 3.2.P.5.3 Validation of Analytical Procedures*
  - 3.2.P.5.4 Batch Analyses
  - 3.2.P.5.5 Characterization of Impurities
  - 3.2.P.5.6 Justification of Specification(s)
- 3.2.P.6 Reference standards or materials
- **3.2.P.7 Container closure system**
- 3.2.P.8 Stability
  - **3.2.P.8.1 Stability Summary and Conclusion**
  - 3.2.P.8.2 Post approval Stability Protocol and Stability Commitment*
  - **3.2.P.8.3 Stability Data**

* N/A for Early Phase Development & IND/IMPD Submissions

3.2.P.1 Description and Composition of the Drug Product

- **Table listing of all Components used in manufacture of drug product**
  - Include all component intended to appear in DP and those which may be used up in manufacturing process
  - **Phase 1**
    - ✓ Tabular format
    - ✓ Include Quality of Inactive Ingredients (USP, NF, ACS etc.)
  - **Phase 2**
    - ✓ Include all information from Phase 1 plus quantitative composition on a per unit basis only for components that appear in final DP
  - **Phase 3**
    - ✓ Update information from information reported in Phase 1 and Phase 2

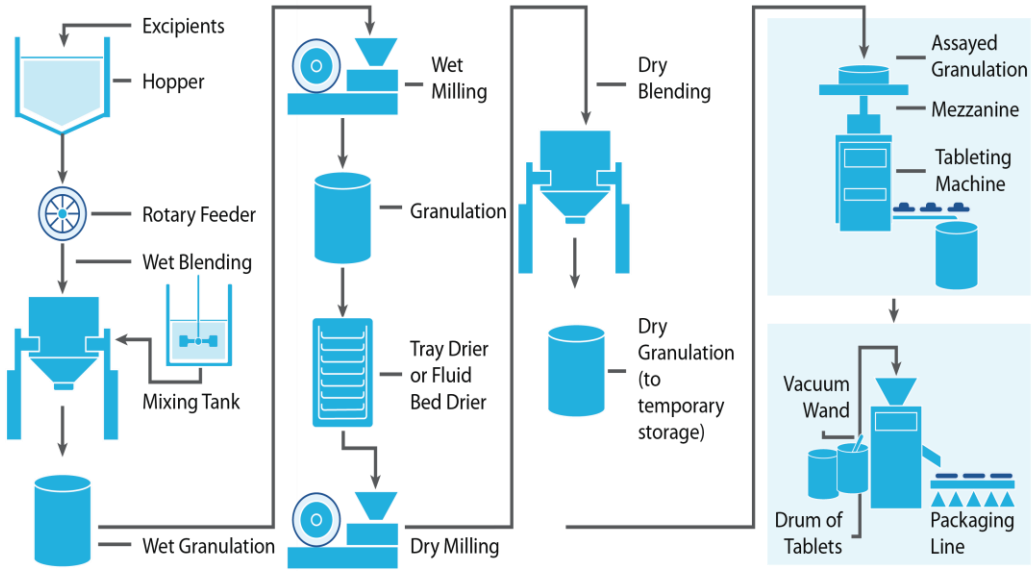
3.2.P.3.2 Batch Formula

- **Phase 1**
  - Quantitative Information for all batch components whether or not the component appears in the final DP batch
- **Phase 2**
  - Update as necessary from Phase 1 batches
  - Quantitative Information for all batch components whether or not the component appears in the final DP batch
- **Phase 3**
  - Update representative batch formula from Phase 2 batches
  - Quantitative Information for all batch components whether or not the component appears in the final DP batch

3.2.P.3.3 Description of Manufacturing Process and Process Controls

- **Phase 1**
  - Generalized Process Flow diagram
  - Brief narrative of unit operations linked to Process Flow Diagram
  - Information on sterilization process, as appropriate

- **Phase 2**
  - Updated flowchart
  - Brief step by step narrative of unit operations (e.g. blending) rather than individual manufacturing steps
  - No reprocessing procedures and controls, unless safety related.
  - Include changes to DP Sterilization Process, validation data not required
- **Phase 3**
  - Process flow diagram with unit operations, excipient quantities, operating conditions and batch size
  - Detailed narrative description of each step in the manufacturing process
    - ✓ **Equipment** (homogenizer, blender)
    - ✓ **Process parameters** (pH, blending time, mixing speed)
    - ✓ **Environmental conditions** (humidity, oxygen)
    - ✓ **Sterilization Process** description with any changes
    - ✓ **Biologics**, provide sterilization validation processes



Source: Adapted from Anastas 1984

Typical Oral Tablet Manufacturing Process Flow

3.2.P.4.1 Specifications

- Use excipients as provided in FDA Inactive Ingredient Database (IID)
  - Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions | FDA
  - Inactive Ingredient Search for Approved Drug Products
  - Avoid using novel excipients as additional safety testing, equivalent to information needed for drug substance is required
- **Phase 1**
  - Provide list of compendial excipients with reference to Quality Standards (USP, NF)
- **Phase 2**
  - Update list of compendial excipients and update reference to quality standards if changed from Phase 1
- **Phase 3**
  - Update information on compendial excipients and add additional testing beyond compendium as necessary

3.2.P.4.5 Excipients of Human or Animal Origin

- Provide BSE/TSE Certifications
- Provide Letter of Cross Reference to relevant Drug Master Files

- If no information available, provide information regarding Adventitious Agents
  - sources,
  - specifications,
  - description of the testing performed,
  - viral safety data.
  - Provide details in Appendix 3.2.A.2.

3.2.P.4.6 Novel Excipients

- Provide full description of the
  - characterization,
  - manufacture,
  - control,
  - analytical procedures, and
  - acceptance criteria
  - EQUIVALENT TO THAT SUBMITTED FOR DRUG SUBSTANCE

- Alternatively, a reference with authorization to a DMF can be provided.

3.2.P.5.1 Specifications

- **Phase 1**
  - Provide test methods and proposed acceptable limits for CQA for Identity, Strength/Potency, Quality and Purity

- **Phase 2**
  - Detailed listing of all the tests performed on the drug product and the tentative acceptance criteria
  - Summary table of test results and analytical data (e.g., chromatograms) from batch release of representative clinical trial materials
  - Data updates on the degradation profile should be provided so safety assessments can be made.
- **Phase 3**
  - Detailed listing of all tests performed and acceptance criteria
  - Summary table of test results and analytical data (e.g., chromatograms) from batch release of representative clinical trial materials
  - Data updates on the degradation profile should be provided so safety assessments can be made.

3.2.P.5.1 Specification(s)-Example

Test Description	Tentative Specifications
Appearance	Round, white tablets
ID by HPLC	Spectrum conforms to reference
Content Uniformity	Meets USP criteria
Assay	90.0 to 110.0%
Enantiomeric Purity	NMT 0.5%
Related Compounds	Compound A: NMT 0.5% Compound B: NMT 0.5% Compound C: NMT 0.5% Compound D: NMT 1.0% Individual unknown impurity: NMT 0.2% Total impurities: Report Results
Moisture	Report Results
Dissolution	Q> 80% at 30 minutes
Residual Solvents	Acetone: NMT 5000 µg/tablet.
Endotoxin	NMT 5.0 EU/kg
Microbial Enumeration Test (USP<61>)	Total aerobic count (CFU/g): <100 CFU/g Total yeast and mold (CFU/g): <10 CFU/g

3.2.P.5.2 Analytical Procedures

- **Phase 1**
  - Provide high level method descriptions
  - Validation data not required but should be available by Phase 2

- **Phase 2**
  - Provide more information on method, such that an analyst could repeat the method
  - Develop stability-indicating analytical procedures that will detect significant changes in the quality of the drug product
  - Qualification/Validation data available
- **Phase 3**
  - Full method descriptions
  - Full validation data included.
  - Degradation products should be identified, qualified, quantified, and reported, as appropriate.

3.2.P.7 Container-Closure System

- **Sum of packaging component that together contain and protect the Drug Product**
  - **Phase 1**
    - Provide summary information on primary container/closure system. May provide high level diagrams
    - Provide reference to compendial standards (glass, polyethylene containers)
    - Provide diagrams of atypical delivery systems (MDIs, auto-injectors etc.)
  - **Phase 2**
    - Update information on primary container/closure system if any changes could affect product quality
  - **Phase 3**
    - Update information on primary container/closure system if any changes could affect product quality
    - Atypical delivery systems (MDIs, auto-injectors etc.) should be similar to marketed product

3.2.P.8.1 Stability Summary and Conclusion

- Stability of the drug product is a critical quality attribute (CQA) of a pharmaceutical product.
- Provide a brief description of the stability study. Include
  - Storage conditions (temperature, humidity)
  - Test methods used to monitor stability (if different than methods provided in 3.2.P.5.2)
  - Container-closure
  - Testing time points
- Provide summary statement relative to best storage conditions (temperature, humidity) based on data provided in 3.2.P.8.3.
- Provide information on retest date.
- Note: There is no specific requirement that the stability study include routine storage, intermediate and accelerated conditions, however, most studies do include if there is enough material in compliance with ICH Q1A (R2).

3.2.P.8.3 Stability Data

- **Stability data is required for all phases of an IND to:**
  - Determine appropriate storage conditions
  - Demonstrate the drug product is within specifications for the planned duration of clinical studies
  - Support selection of a container closure system
  - Determine how the product changes over time under different environmental conditions (e.g., temperature, moisture and light)

- **Phase 1**
  - Include at least 1-3 months of data on the CTM batch at the proposed storage condition in the IND.
  - Commit to monitoring to support the stability of the clinical trial material from the date of manufacture until the DP batch is used in the clinical study.
  - Commit to removing CTM from clinical study if stability goes outside defined specifications.

- **Phase 2**
  - Provide any stability data for the clinical material used in the phase 1 study that were not reported during phase 1. Provide stability data for Phase 2 representative CTM in annual reports.
  - Provide data from studies used to assess effect of high temperature, humidity, oxidation, photolysis and/or thermal cycling
- **Phase 3**
  - Provide stability protocol
  - Stability data for representative clinical material to be used in phase 3
  - Include batch number, manufacturing site, date of manufacture of the drug product, and relevant information on the drug substance (e.g., lot number, manufacturer) used to manufacture the drug product.

1.12.14 Environmental Analysis

- Claim for Categorical Exclusion for IND

"The requested action qualifies for a categorical exclusion from the requirement to prepare an EA, per 21 CFR § 25.31(b), because the estimated concentration of the substance at the point of entry into the aquatic environment is estimated to be below 1 part per billion. To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA."

1.14.4.2 Investigation Drug Labeling

- Primary Container Label for Clinical Trial Material
  - The only information required by FDA on the immediate container label for clinical trial material is the caution statement
  - **"Caution: New Drug - Limited by Federal (or United States) law to investigational use."**
  - 21 CFR 312.6: The label or labeling of an investigational new drug **shall not bear any statement that is false or misleading** in any particular and **shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated**.

1.14.4.2 Investigational Drug Labeling (cont).

- No FDA requirement to include an expiration date on the primary container label for clinical trial material

  - FDA understands that it may be possible to extend the expiration date based on additional stability data as they are generated.

  - Not including the expiration date on the primary label makes it unnecessary to over-label or relabel clinical supplies as the expiration date is extended.

  - Especially important for clinical trial materials stored at refrigerator or freezer temperatures as the containers cannot be allowed to reach room temperature to apply the new label.

CATALYZE
Accelerating Translation

QUESTIONS Provided Before Presentation

NIH National Heart, Lung, and Blood Institute

Questions-PreIND

- What level of CMC needs to be completed for a pre-IND and for an IND meeting with the FDA? What level of GLP study design is required?

- What kind of drug product manufacturing and analytical testing documentation is needed for my small molecule pre-IND filing?

Questions-IND

- Specific differences between phase 1 and phase 2/3 CMC requirements
- What is required of a CMC section for the IND
- Do you need to produce cGMP drug substance/product to be used in the proposed human study BEFORE IND submission?
- What are the differences in CMC requirements for IND vs. Phase 1 clinical.
- General understanding of the whole process

Questions-Devices-Diagnostics

- What is needed for a successful IDE submission for a 510(k) technology
- Diagnostics embedded within apps or medical devices
- What early experiments, performance metrics, or sample handling factors are needed for FDA validation of a diagnostic platform?

Questions-Other

- Specifically, I have questions around any external manipulation to loading therapeutic biomolecules or delivery of nuclei acids.
- What guidance is available for the development and qualification of a novel analytical method?
- It seems like things could change re:CMC with the new US Administration. I'd like any insights you have on the changing landscape
- Particularly interested in transdermal delivery systems / drug-device combinations

Questions-Toxicology

- What toxicology study is needed for a newly discovered mammalian steroid hormone?

Thank You

Carmella S. Moody, Ph.D.
Regulatory Affairs Program Director

RTI International
3040 E. Cornwallis Road
PO Box 12194
Research Triangle Park, NC 27709-2194

CATALYZE

Accelerating Translation

NIH National Heart, Lung, and Blood Institute