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Product Development to IND: Chemistry, Manufacturing and Controls (CMC)

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Overview

- Key CMC Points to Consider in Early Development
- Drug Substance CMC Information in CTD Format
- Drug Product CMC Information in CTD Format

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The presentation and information therein does not constitute legal or regulatory advice.

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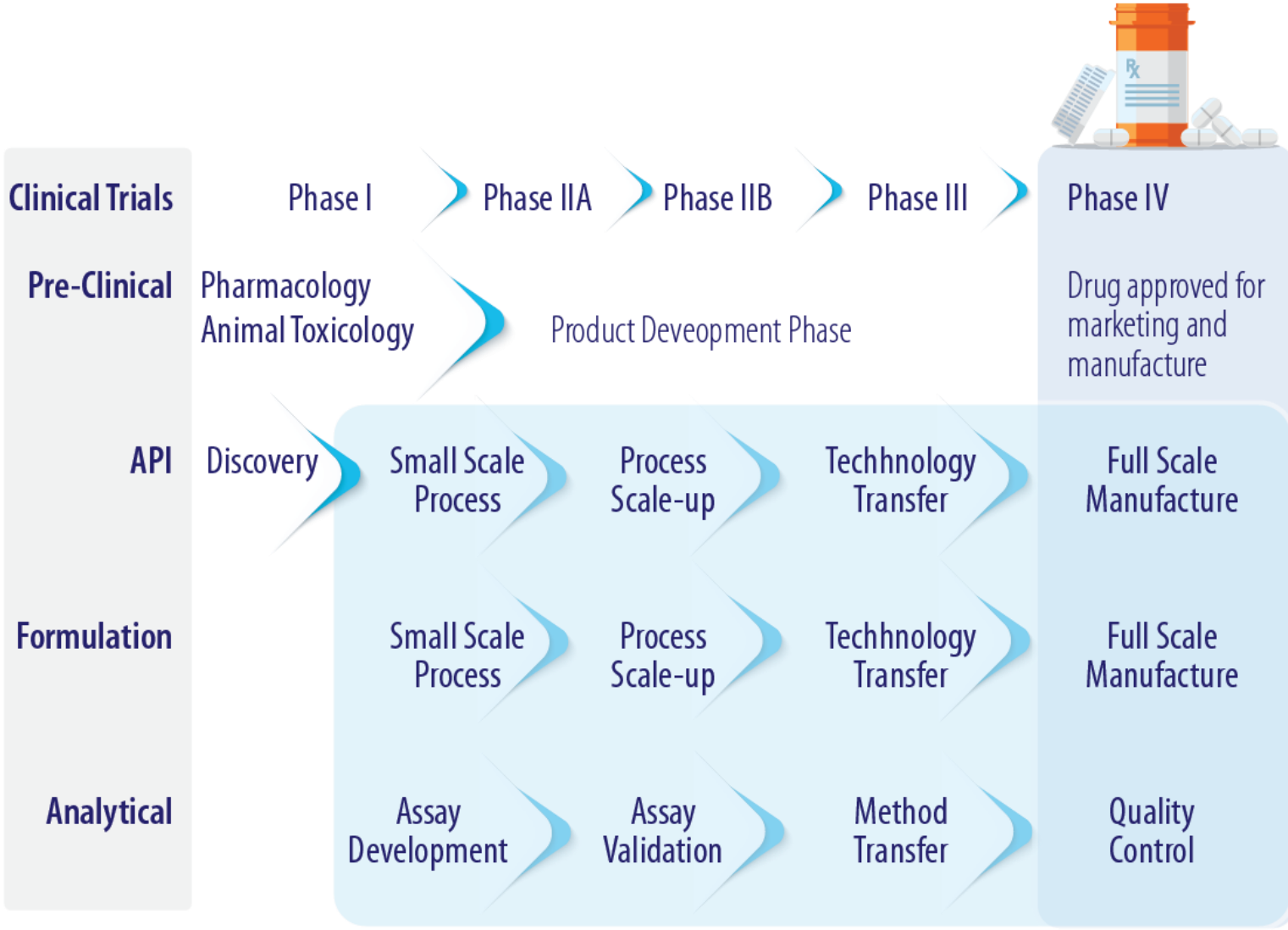
Key CMC Points to Consider in Early Development

Purpose of CMC

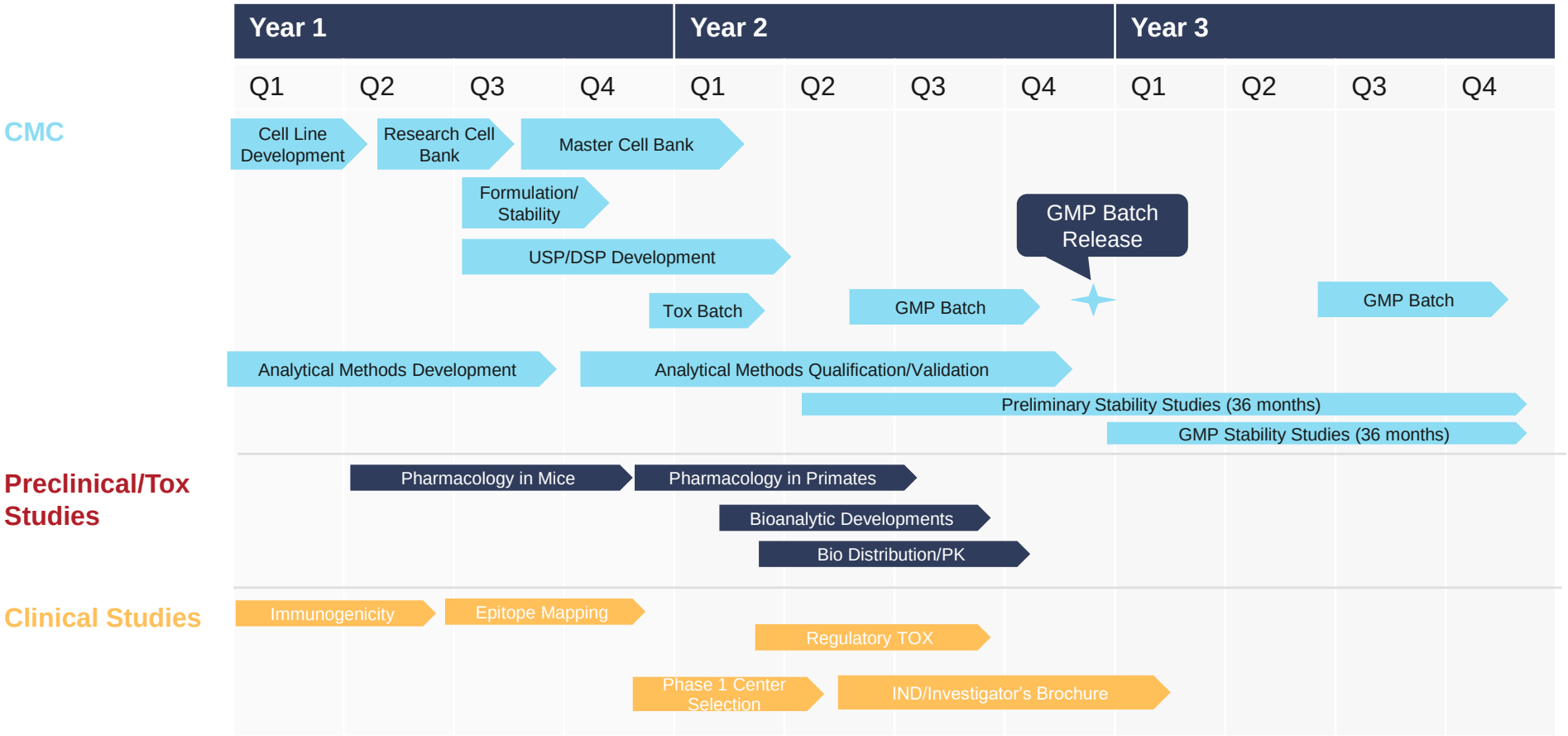
- To assure that the drug sold to the public will have quality attributes similar to those of a drug demonstrated to be safe and effective
- To assure that the quality of the drug meets appropriate standards and is consistent
- To assure that the drug you are using is the drug described in the Prescribing Information

CMC Relative to Overall Product Development



When and Why is CMC considered?

CMC begins at lead drug candidate selection



CMC and IND Development Timeline Example for Biologics

Critical Elements of CMC

How and where is the drug made?

How are raw materials tested and monitored?

What control procedures are in place to assure product consistency and quality?

Are quality attributes adequately identified and characterized for the product?

Are the test methods used to monitor product quality appropriate?

What controls/How long does the product maintain its quality after it is made (shelf life/expiry)?

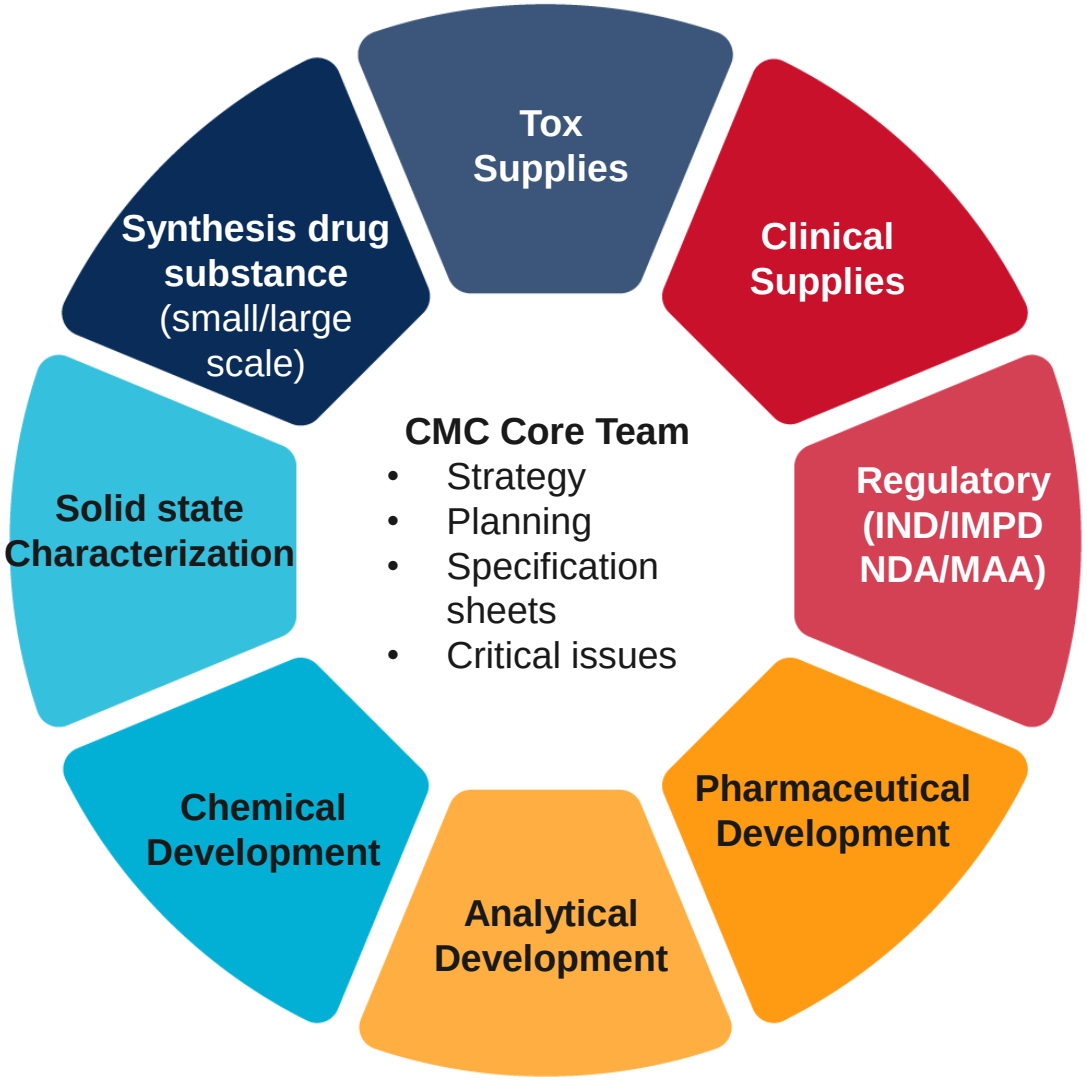
CMC is Specific to the Product

- **Sterile injectable product** – sterility and endotoxin concentration
- **Controlled release product** – release profile of active ingredient over time
- **Oral tablet** – dissolution profile
- **Soluble powder for drinking water** – moisture content as powder, solubility in water
- **Inhaled product**
- **Cell and Gene Therapy Product**
- **Transdermal Product**

Plan for Success with the Right Expertise on the CMC Team

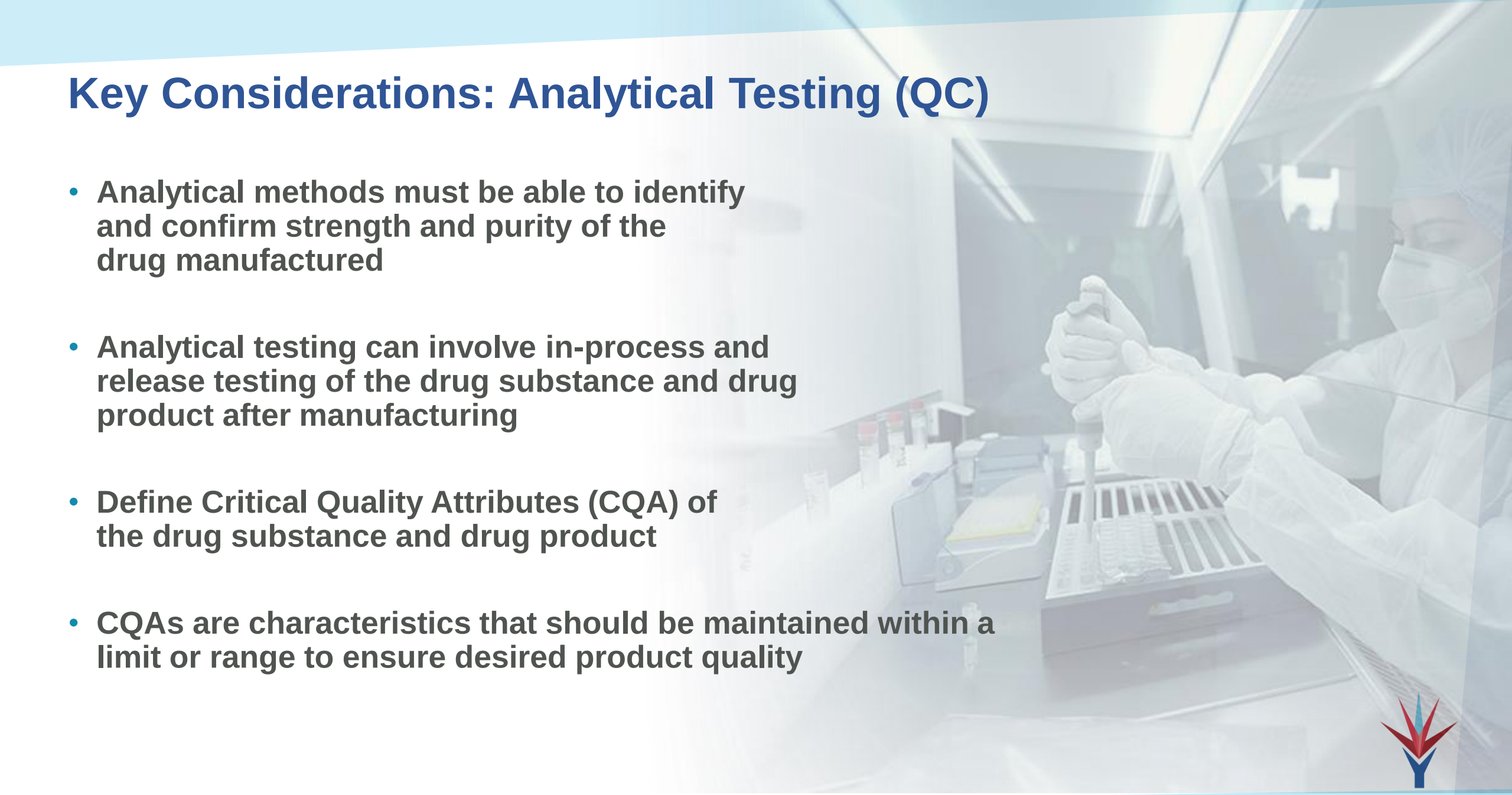
For an effective and efficient development program, the CMC team should consist of an interdisciplinary team with expertise focused on specialized disciplines.

To fulfil this need, start-up pharmaceutical companies often use CMC consultants and/or a small number of employees with expertise covering several disciplines.



Key Considerations: Analytical Testing (QC)

- Analytical methods must be able to identify and confirm strength and purity of the drug manufactured
- Analytical testing can involve in-process and release testing of the drug substance and drug product after manufacturing
- Define Critical Quality Attributes (CQA) of the drug substance and drug product
- CQAs are characteristics that should be maintained within a limit or range to ensure desired product quality



Key Considerations: Control of Raw Materials

- **Develop manufacturing processes with pharmaceutical grade materials (e.g., USP, NSF, Ph.Eur.)**

- **cGMP/pharmaceutical grade raw materials are tested and comply to more stringent quality requirements than research grade.**
  - Define grade and purity of raw materials via specifications with the vendor
  - Avoid materials of animal origin and obtain BSE/TSE certification
  - Perform use tests

- **Identify and qualify multiple suppliers of key raw materials**

Key Considerations: Manufacturing

Define manufacturing processes that are readily scalable:

- Consider changes in equipment processing parameters between laboratory, pilot and commercial manufacturing scale
- Define critical process parameters (CPPs) and determine proven acceptable ranges (PARs)

DO NOT make process ranges too tight in early process development

Process ranges should tighten as development progresses

Utilize Quality by Design (QbD) principles to accelerate CMC knowledge

Drug Master File (DMF)

Drug Master Files are submitted to maintain the confidentiality of the information.

Drug Master Files contains Chemistry, Manufacturing and Control related information.

Drug Master File

Type II DMFs are submitted for drug substance

Type III DMFs are submitted for packaging material

Type IV DMFs are submitted for excipients, colorants or flavors

Drug Master Files are submitted in the eCTD format

Key Considerations: Quality Assurance (QA)

- Releases drug substance and drug product batches manufactured for non-clinical and clinical use
- Approves SOPs and IOQ protocols
- Approves release of raw materials for use in manufacturing
- Reviews batch records, deviations, CAPAs and validation protocols

Supports retained and reference sample collection with QC.

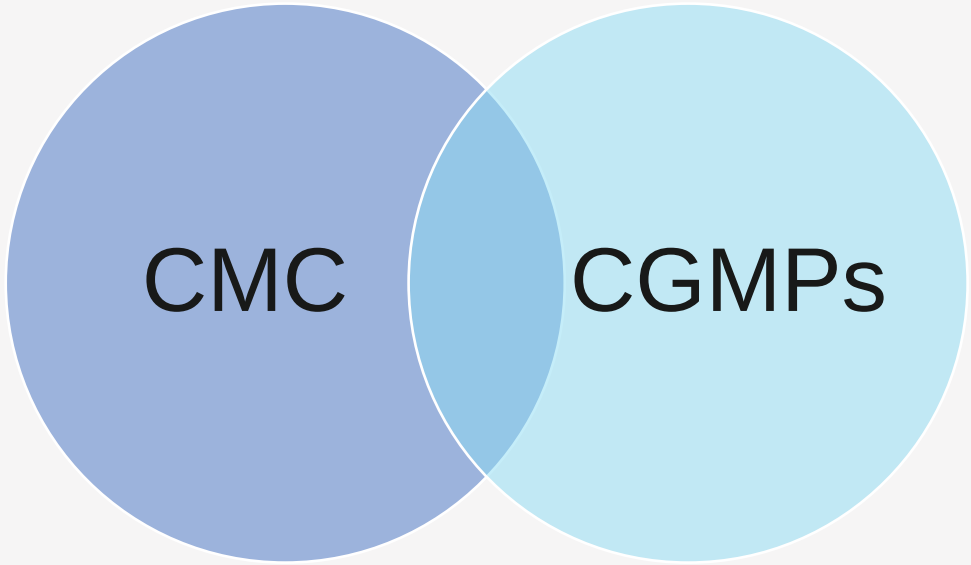
Retained samples are stored for identification purposes.

Reference standards are stored as a comparator for the purpose of analysis of manufactured batches.

Key Considerations: CGMPs

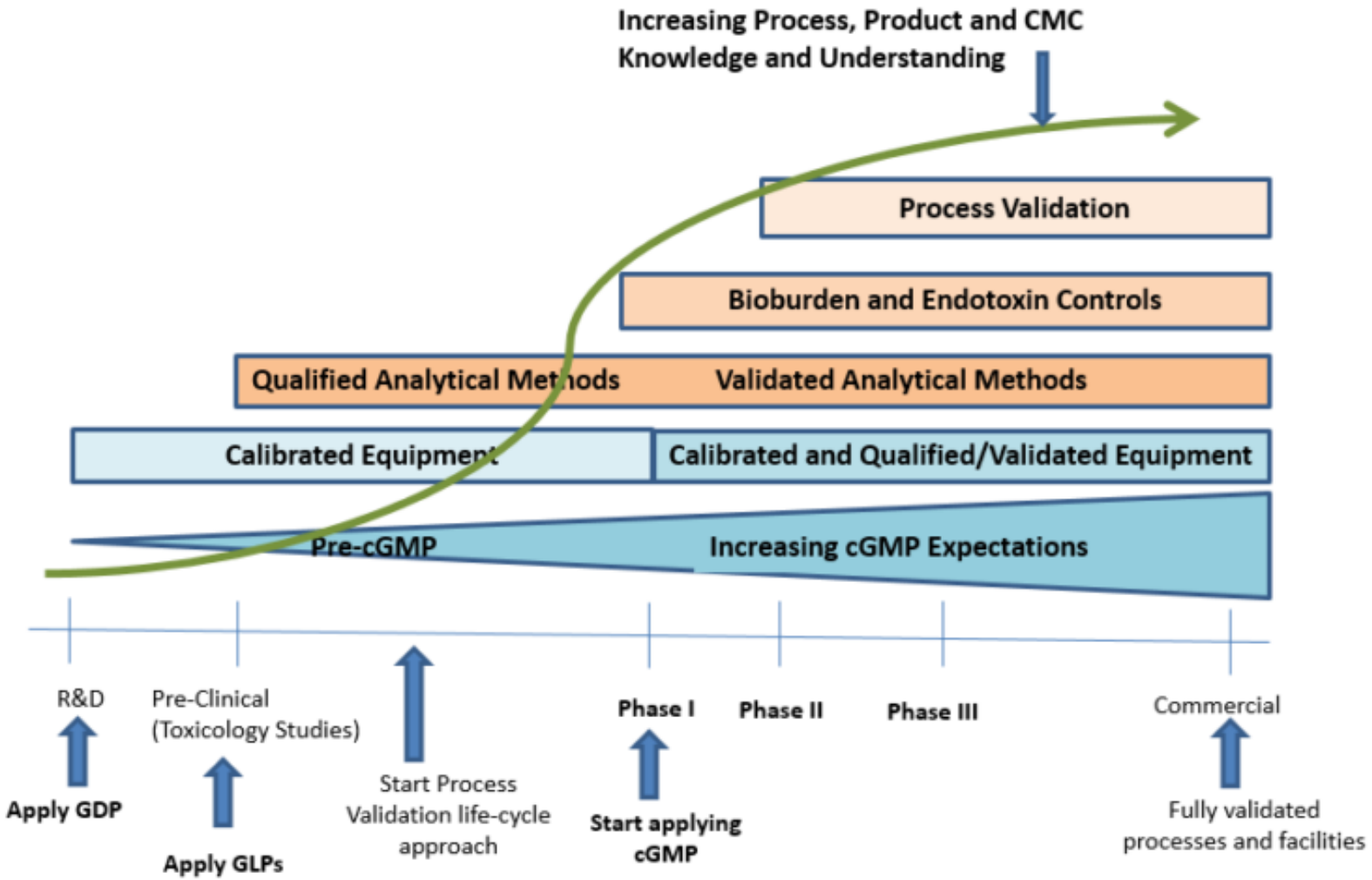
- **CGMP goals are to assure that the product is the same or similar to product determined to be safe and effective in clinical studies**
- **Assures the manufacturing process consistently results in a product that meets appropriate quality attributes**
- **Assures the drug product will maintain its quality attributes throughout shelf life**

CMC review and CGMP Compliance Overlap but are not the same



Chemistry, Manufacturing, and Controls (CMC) and Good Manufacturing Practices (GMPs): The Big Picture of a Long-term Commitment
Elizabeth Pollina Cormier, Ph.D. Review Chemist, Division of Manufacturing Technologies FDA/CVM/ONADE

Phase Appropriate cGMPs for CMC



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Drug Substance CMC Information in 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

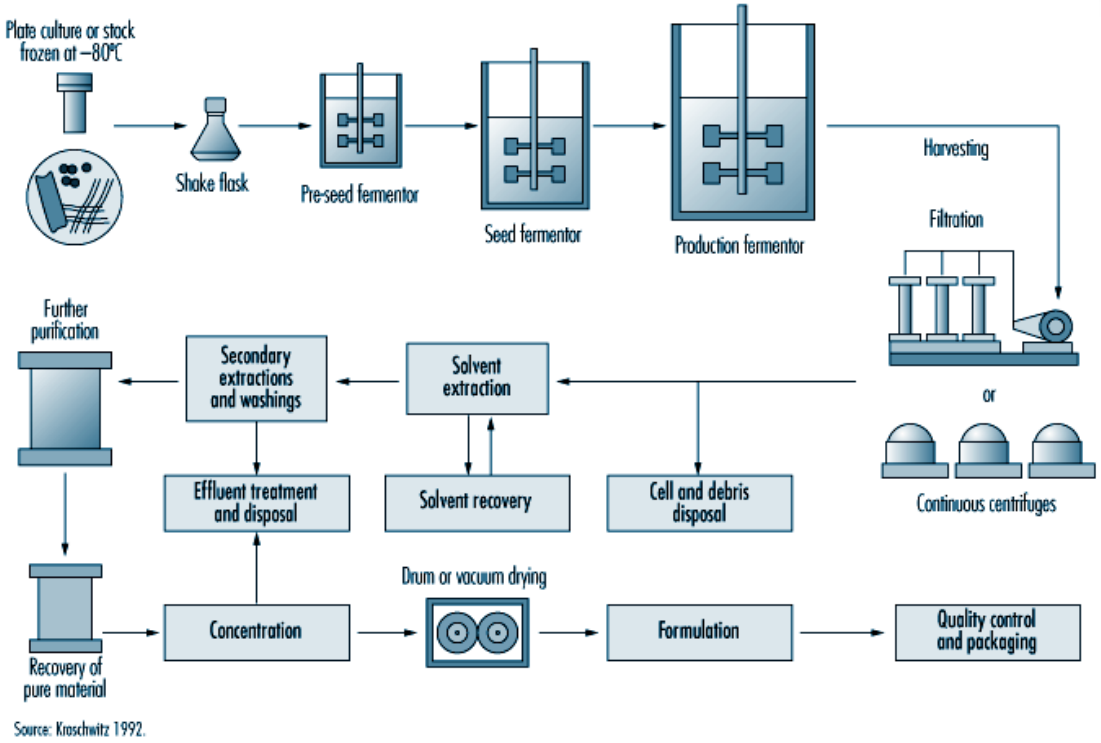
3.2.S.2.2 Description of Manufacturing Process and Process Controls

Process flow diagram of the process is provided with unit operations, reactant quantities, yields, solvents and operating conditions

Detailed narrative description of each step in the manufacturing process

Detailed analysis of the manufacturing process

Review of raw materials and safety concerns



Typical Process Flow Diagram for Biologics Fermentation Process

3.2.S.3.2 Impurities

Manufacturing process developed to remove process and product related impurities

- An impurity is anything that is not the product!
- Provide test procedures in the IND with appropriate limits to assure safety
- Tighten specifications as the development program progresses

Consider impurities in GLP toxicology batches to obtain “toxicology coverage” of impurities

3.2.S.4.1 Specifications

- Proposed acceptable limits for each test supported by analytical data
- Include Certificates of Analysis (COAs) with clinical and non-clinical GLP toxicology batches
- Specifications are used for release and stability testing
- Validation data and established specifications ordinarily are not submitted at the initial stage of drug development

3.2.S.4.1 Specifications

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

3.2.S.4.2 Analytical Procedures

- Analytical procedures should be used to ensure identification, quality, purity, and strength of the drug substance
- Brief description of analytical test methods used
- Use USP/NF methods when possible
- Limited precision & robustness studies can occur during Phase 3

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

3.2.S.4.5 Justification of Specification

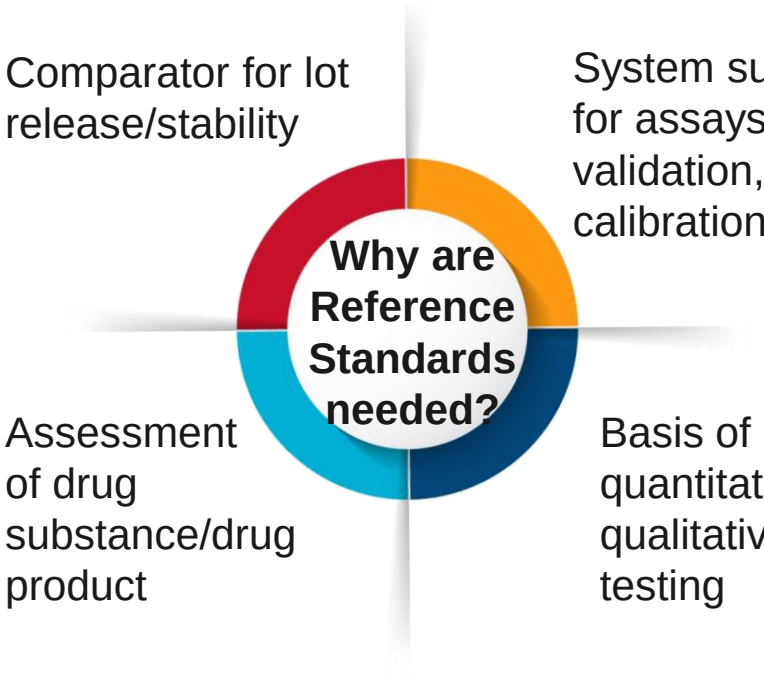
During clinical development, specifications are preliminary and wide due to limited batch production and process knowledge

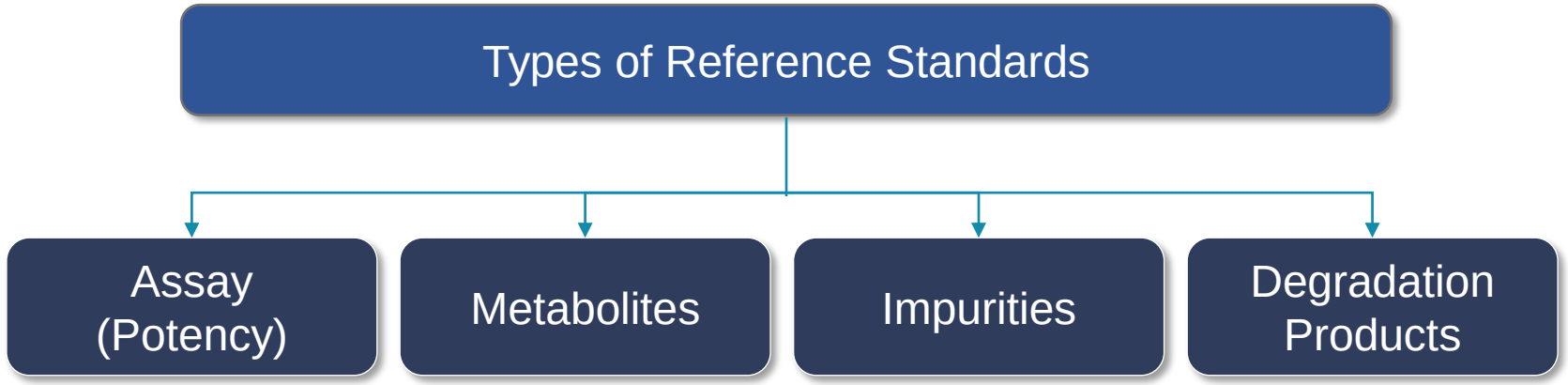
- Early-stage focus should be on safety critical specifications for drug substance and drug product

Justifications should be based on:
- Product characteristics
- Process capabilities

- ICH Q6B provides guidance on general principles for setting and justifying specifications

3.2.S.5 Reference Standards or Materials





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Drug Product CMC Information in 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

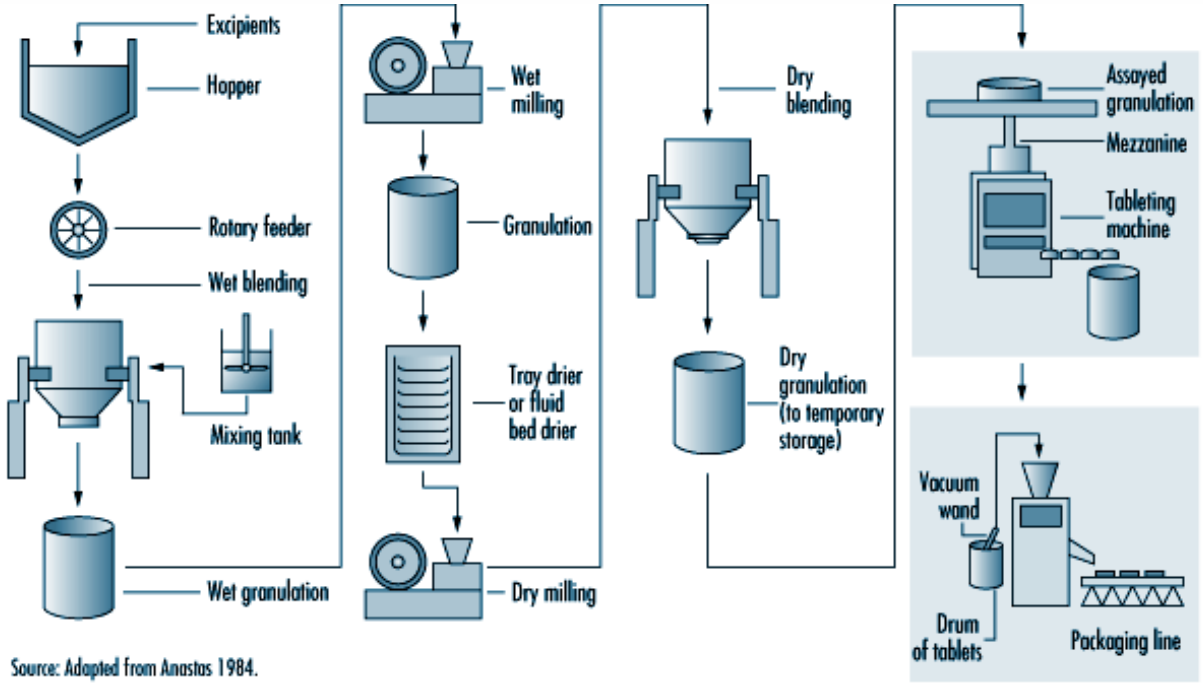
* N/A for Early Phase Development & IND/IMPD Submissions

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

Process flow diagram of the process is provided 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)



Typical Oral Tablet Manufacturing Process Flow

3.2.P.3.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process should be provided to ensure that the process is controlled

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided

3.2.P.4 Control of Excipients [name]

Qualified excipients

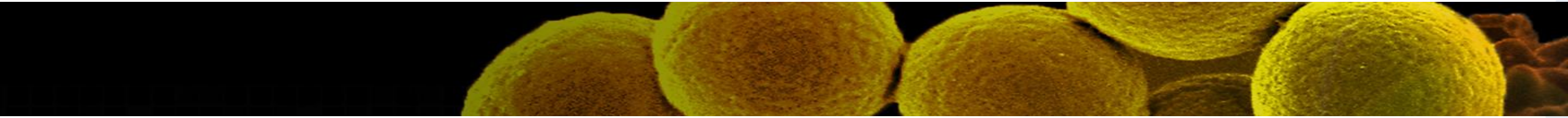
- USP-NF, Ph.Eur. and JP compendial excipients
- Excipients listed in FDA Inactive Ingredient List (IID)
- Manufactured under GMP
- Avoid using novel excipients as additional safety testing is needed

3.2.P.5.1 Specification(s)

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.8.1 Stability Summary and Conclusion

Stability of the drug product is a critical quality attribute of a pharmaceutical product



- **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)

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Thank You and Helpful Links

Helpful Links

cGMPs for Phase 1 Investigational Drugs
https://www.fda.gov/media/70975/download

Content and Format of INDs for Phase 1
https://www.fda.gov/media/72057/download

ICH Q6B Specifications

https://www.fda.gov/media/71510/download

ICH M4Q(R1)

https://www.gmp-compliance.org/files/guidemgr/MEDIA556.pdf

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Current Good Manufacturing Practices

GMP Summary

Key GMP Aspects

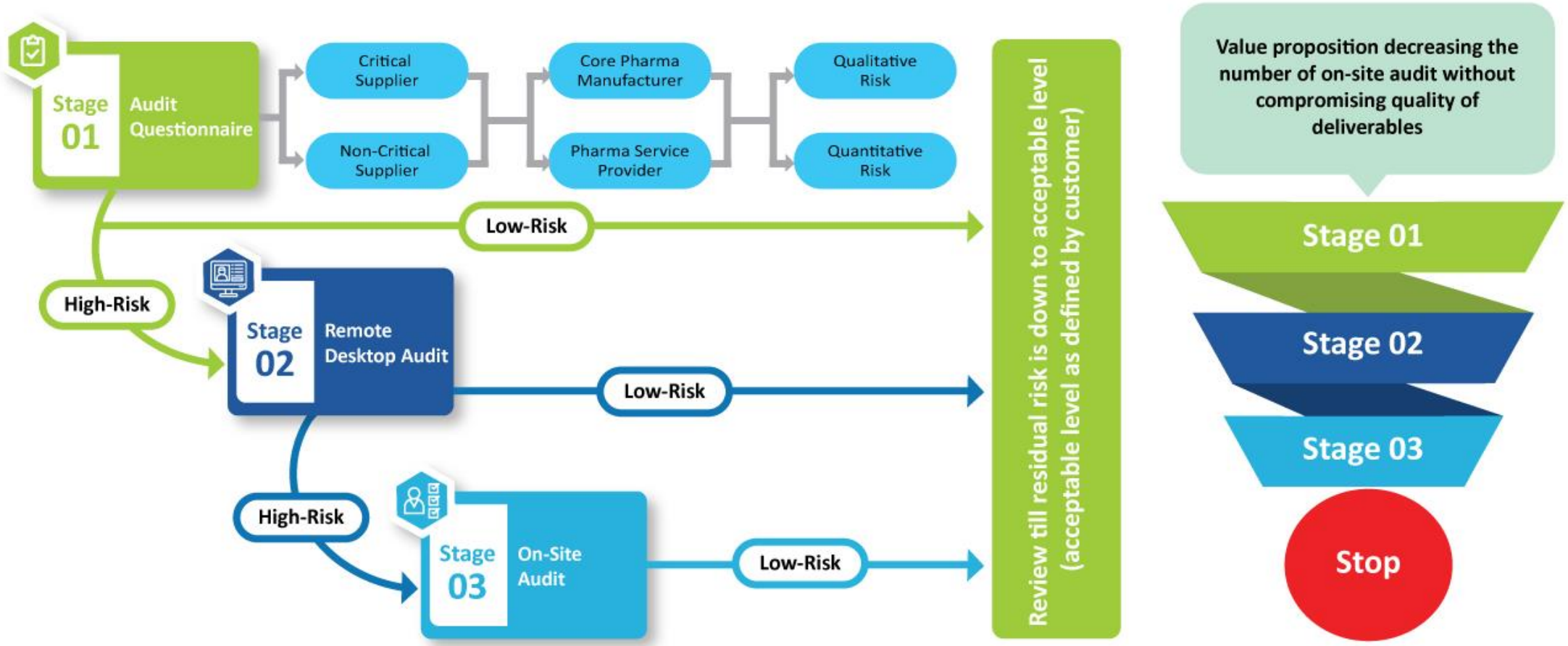
- Training covering equipment, facilities and personnel
- Creating SOPs for equipment and facilities
- Recording and Documentation
- Developing standard test methods

What is Process Validation?

- The FDA defines process validation as, *"…the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product"*.

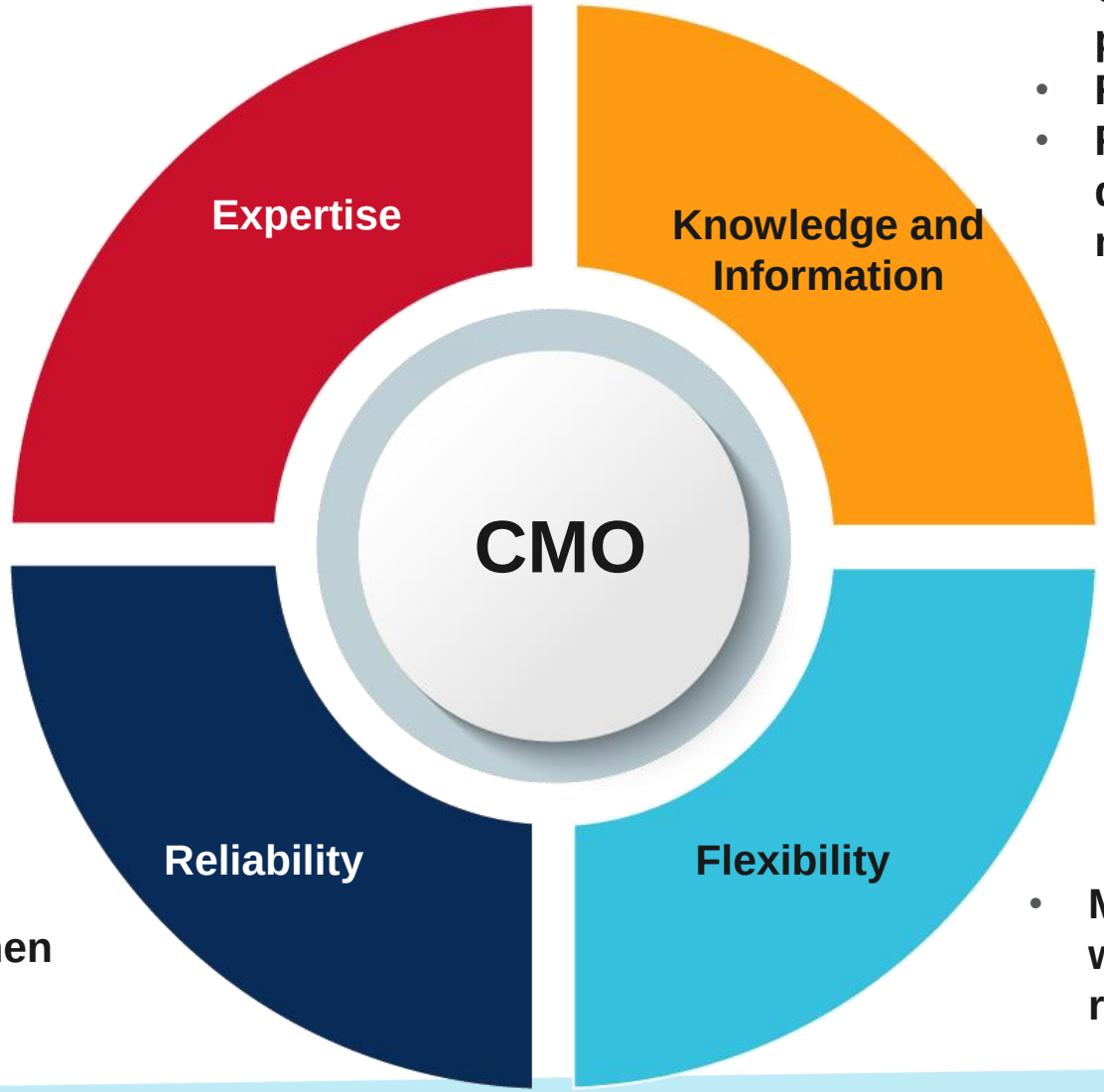
- The 3 stages of process validation are:
- **Process Design** – The commercial manufacturing process is **defined**.
- **Process Qualification** – The design is **evaluated** to determine whether the processes meet demands of reproducibility.
- **Continued Process Verification** – Ongoing assurances that all processes remain in a **state of control.**

CMO Audit Process



CMO Vendor Selection Criteria

- Technical
- Regulatory
- Innovation



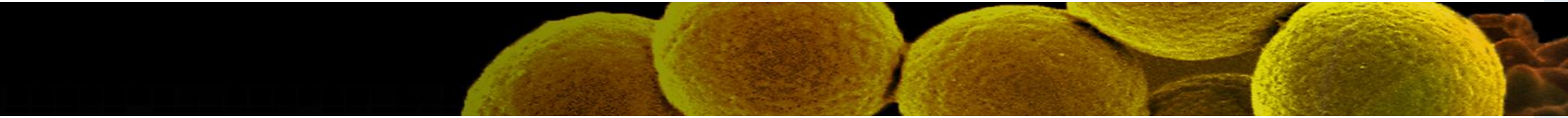
- Clear project scope
- Updates on progress
- Recommendations
- Reports on development and manufacture work

- Proficiency at implementation
- Do what they say, when they say they'll do it

- Modify plans in line with project requirements

cGMP Requirements for Vendor Qualification

- Vendors selected are evaluated for compliance against regulations.
- Results of audit reviewed and need for a site follow-up visit.
- Site qualifications are done on a cyclical basis (every 24 months).
- Stringency of process increases as development program advances.



Benefits

- Ability to evaluate systems vendor uses to produce a regulated product
- Identify gaps in quality systems and ask for corrective action.

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Additional Slides if Time Allows

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Chemistry, Manufacturing and Controls
21 CFR 312.23 (7)

- **Chemistry Manufacturing and Controls (CMC**) concerns the composition, manufacture, and control of the drug substance and the drug product

- **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 (21 CFR 314.3)

- **Drug product** means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo. (21 CFR 210.3 (4))

3.2.S.4.1 Specification

Test	Acceptance Criteria
Description (solid)	[Define a color range] solid.
Description (Liquid)	[Clear/translucent, Color range] liquid.
Identification	
[DS] by IR	The spectrum of the sample is concordant with that of the [DS] reference material.
[DS] by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the [DS] reference material chromatogram.
[DS] by Capillary Electrophoresis	The relative migration time of the principal peak in the electropherogram of the sample, with respect to the internal standard peak, corresponds with that of the principal peak in the [DS] reference material electropherogram.
[DS] by TLC	The Rf value of the principal spot in the sample chromatogram corresponds with that of the principal spot in the [DS] reference material chromatogram.
[DS] by UV	The spectrum of the sample is concordant with that of the [DS] reference material.
Solid state form [by XRPD]	[The spectrum of the sample is concordant with that of authentic Form X material].
Specific optical rotation $[\alpha]^{20}_{D}$	Concordant with that of [DS] reference material.

3.2.S.4.1 Specification (cont.)

Test	Acceptance Criteria
[Counterion] by [method]	Positive.
[DS] content by [method], (% w/w, [corrected to water- and solvent-free basis])	[X.X] – [Y.Y]
Drug-related impurities content by [method], ([units]) [aaaaaa/SB-XXXXX] [bbbbbb/SB-YYYYY] [Unidentified impurity, RRT X.X] [cccccc/SB-ZZZZZ] [Unidentified impurity, RRT Y.Y] Any unspecified impurity Total	 Not greater than [X.X] Not greater than [X.X] Not greater than [X.X] Not greater than [X.X] Not greater than [X.X] Not greater than [X.X] Not greater than [X.X]
Enantiomer ([xxxxx/SB-XXXXX]) content by [method], ([units])	Not greater than [X.X]
[Impurity Name] content by [method] ([units])	Not greater than [X.X]
Residual solvents contents by [method], ([ppm]) [Solvent 1] [Solvent 2] Any other residual solvent Total solvents	 Not greater than [XX] Not greater than [XX] Not greater than [XX] Not greater than [XX]

3.2.S.4.1 Specification (cont.)

Water content by [method], ([units])	Not greater than [X.X]
Residue on ignition (% w/w)	Not greater than [X.X]
Heavy metals ([ppm])	Not greater than [X]
Specific optical rotation $[\alpha]^{20}_{D}$	[XX.X]° – [YY.Y]° or [XX.X]° ± [Y.Y]°
pH of solution	[X.X – Y.Y]
Color and clarity of solution	[Color range], [Clear]
Melting point by [method] (°C)	[XXX] – [YYY]
Polymorph content by [method] ([units]) [Form X] [Form Y] [Ratio of Form X : Form Y]	 Not greater than [XX] Not greater than [XX] [X – Y]
Crystallinity by [method] ([units]) Amorphous:crystalline ratio	 [Not less than] [Not greater than] [XX]
Tapped bulk density of [milled] [micronized] [conditioned] [DS] ([units])	[X.X – Y.Y]
Particle size of [milled] [micronized] [conditioned] [DS] by [method] (μm) Mass median diameter [10%] of particles [90%] of particles	 [X.X – Y.Y] Not greater than [X.X] Not greater than [X.X]
Specific surface area of [milled] [micronized] [conditioned] [DS] ([units])	[X.X – Y.Y]

3.2.S.4.1 Specification (cont.)

Microscopic examination / image analysis of [milled] [micronized] [conditioned] [DS] Crystal habit Particle dimensions ([units])	 [X.X – Y.Y]
Bacterial endotoxins(IU/g)	Not greater than [X.X]
Microbial limits test Total aerobic count ([cfu/g or cfu/ml]) Total fungi ([cfu/g or cfu/ml]) Specific organisms *Staphylococcus aureus* *Escherichia coli* *Salmonella* *Pseudomonas aeruginosa*	Complies with [Pharmacopoeia] Not greater than [X^n] Not greater than [X^n] Absent in [1g] of bulk material. Absent in [1g] of bulk material. Absent in [1g] of bulk material. Absent in [1g] of bulk material.
Sterility	Complies with [Pharmacopoeia].