Troublesome Issues Seen in Biologics Development in Academic Spaces and Small Startup Companies

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Licenses of Intellectual Property

Cell Lines
Vectors
Promoter Sequences

- Perpetual
- Exclusivity
- Research Use Only or Commercial

Manufacturing Process

- Drug Substance
- Drug Product (Formulation)

Procedures

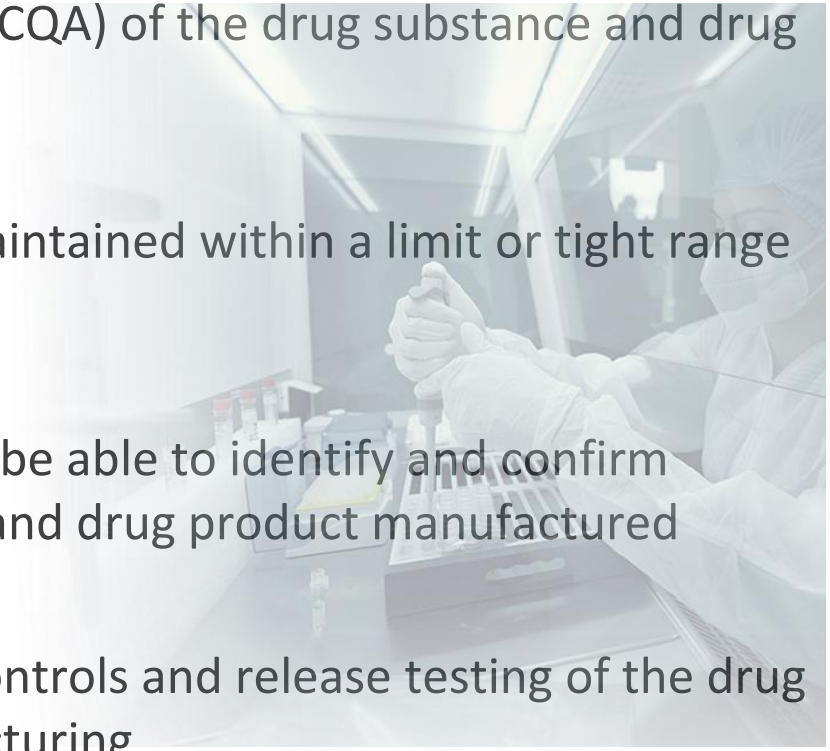
- Fixed, written laboratory procedures, which can be easily converted into draft SOPs, are worth any amount of time spent on them.
- Repeatability of the process is one of the first requirements for biologics development.
- Verifiable assays for determining purity, product stability, impurity identification, quantitation, and potency.

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"*.

Key Considerations: Analytical Testing (QC)

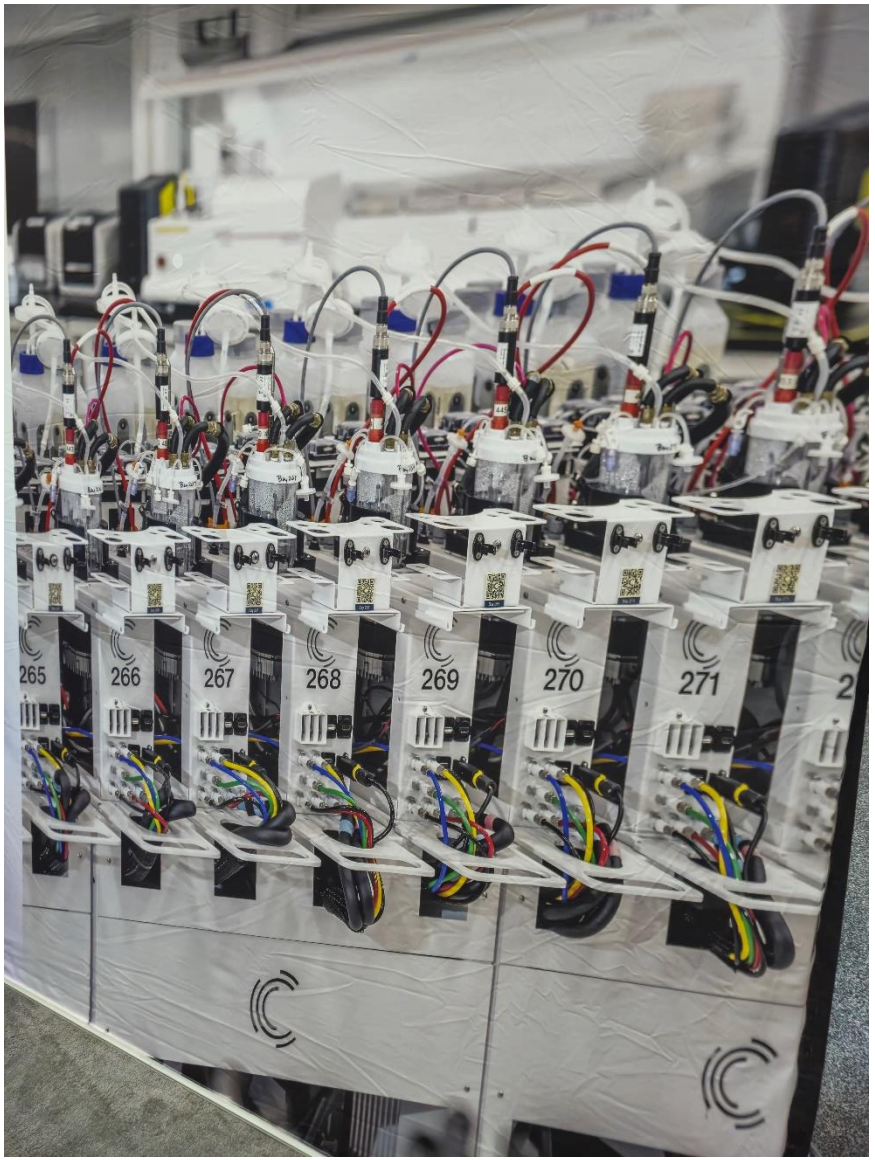
- Begin to define Critical Quality Attributes (CQA) of the drug substance and drug product
- CQAs are characteristics that should be maintained within a limit or tight range to ensure desired product quality
- Even preliminary analytical methods must be able to identify and confirm potency and purity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



Key Considerations: Manufacturing

Manufacturing processes may not work when scaled up:

- Consider changes in equipment processing parameters between laboratory, larger manufacturing scale
- Define critical process parameters (CPPs), determine proven acceptable ranges (PARs), determine minimum and maximum hold times
- Scale out is often required



Key Considerations: Control of Raw Materials

- **Develop manufacturing processes with pharmaceutical grade materials (e.g., USP, NF, JP, EP aka 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**

3.2.S.3.2 Impurities

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

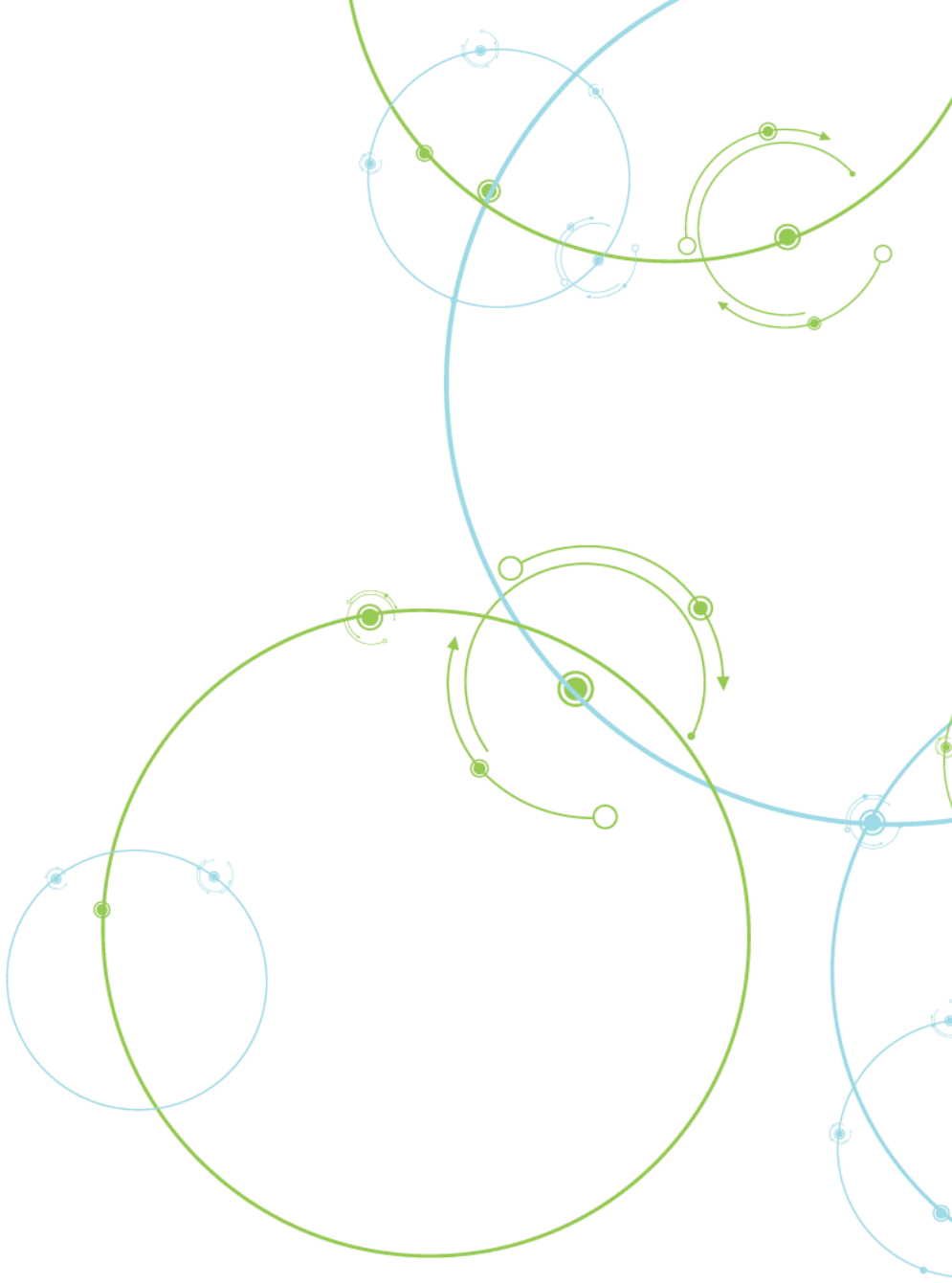
Tighten specifications as the development program progresses

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
- Multiple batches of DS and DP are determining the specification ranges/limits.

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
- EP methods must be quickly revalidated
- Limited precision & robustness studies can occur during Phase 3



3.2.S.4.5 Justification of Specification

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

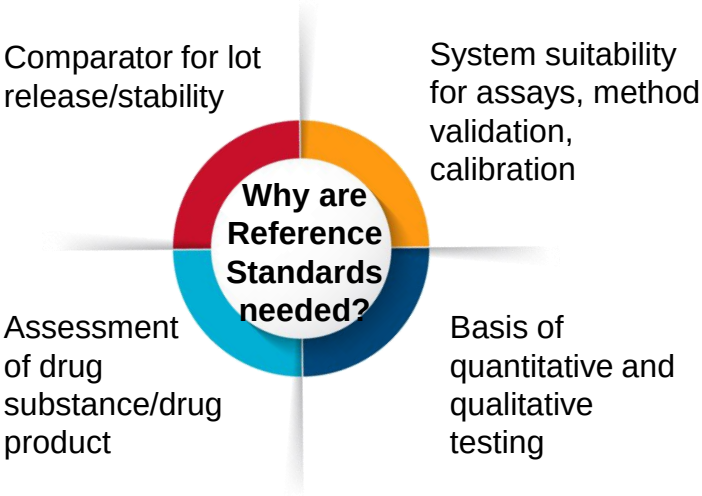
- Early-stage focus should be on safety critical specifications for drug substance and drug product

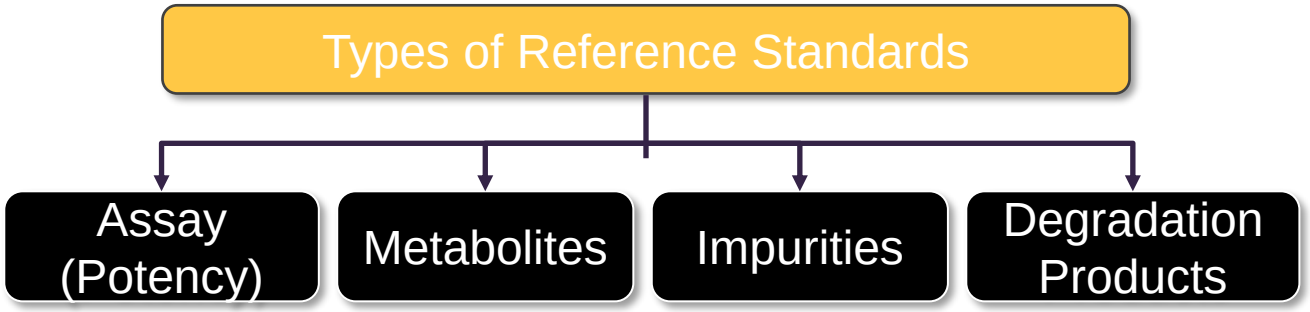
- ICH Q6B provides guidance on general principles for setting and justifying specifications

Justifications should be based on:

- Product characteristics
- Process capabilities

3.2.S.5 Reference Standards or Materials





3.2.P.8.1 Stability Summary

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)

Thank you

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