Justifying Potency and other Specifications: Justification of Specifications: *What Product and Process Development was all About*

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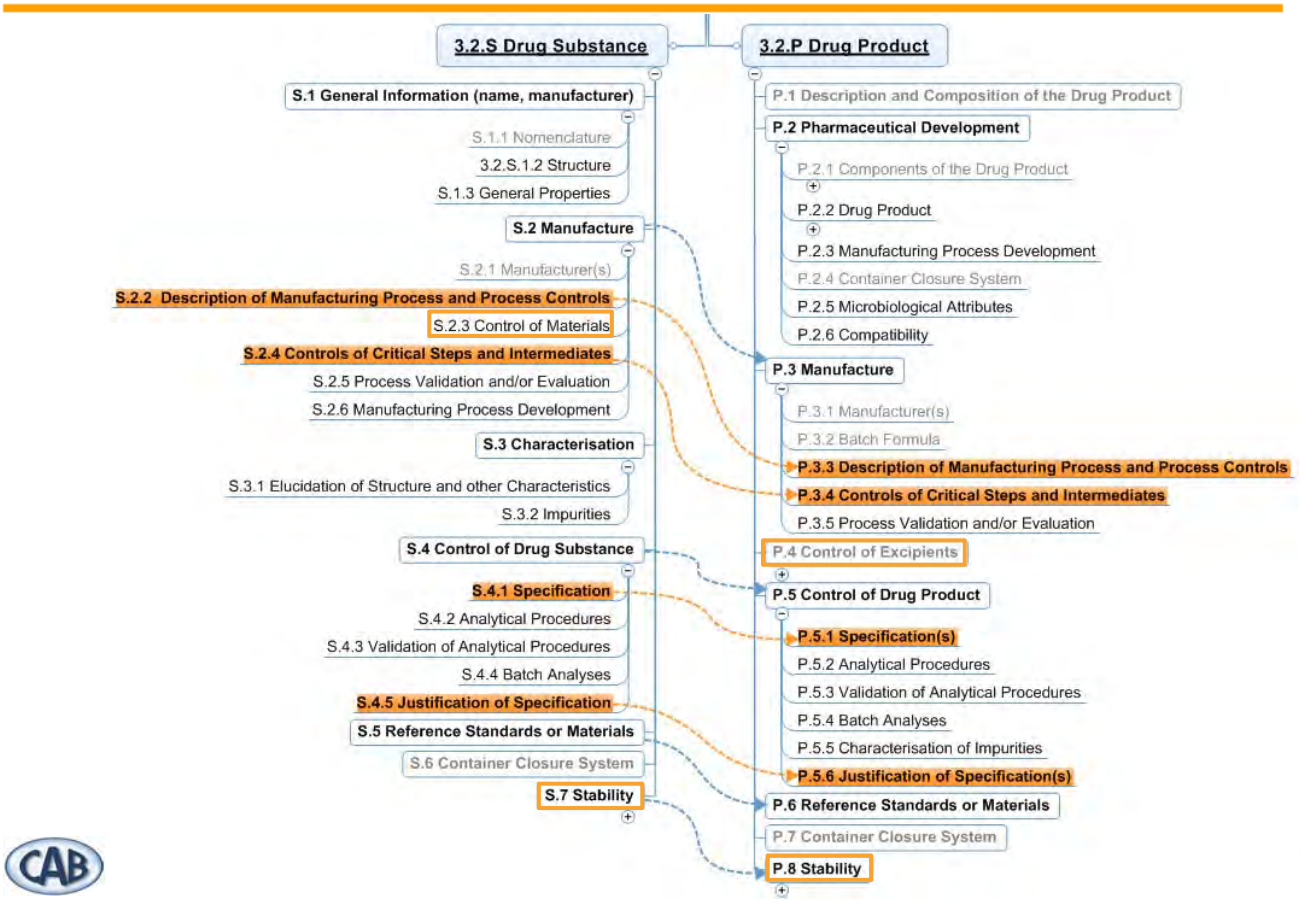
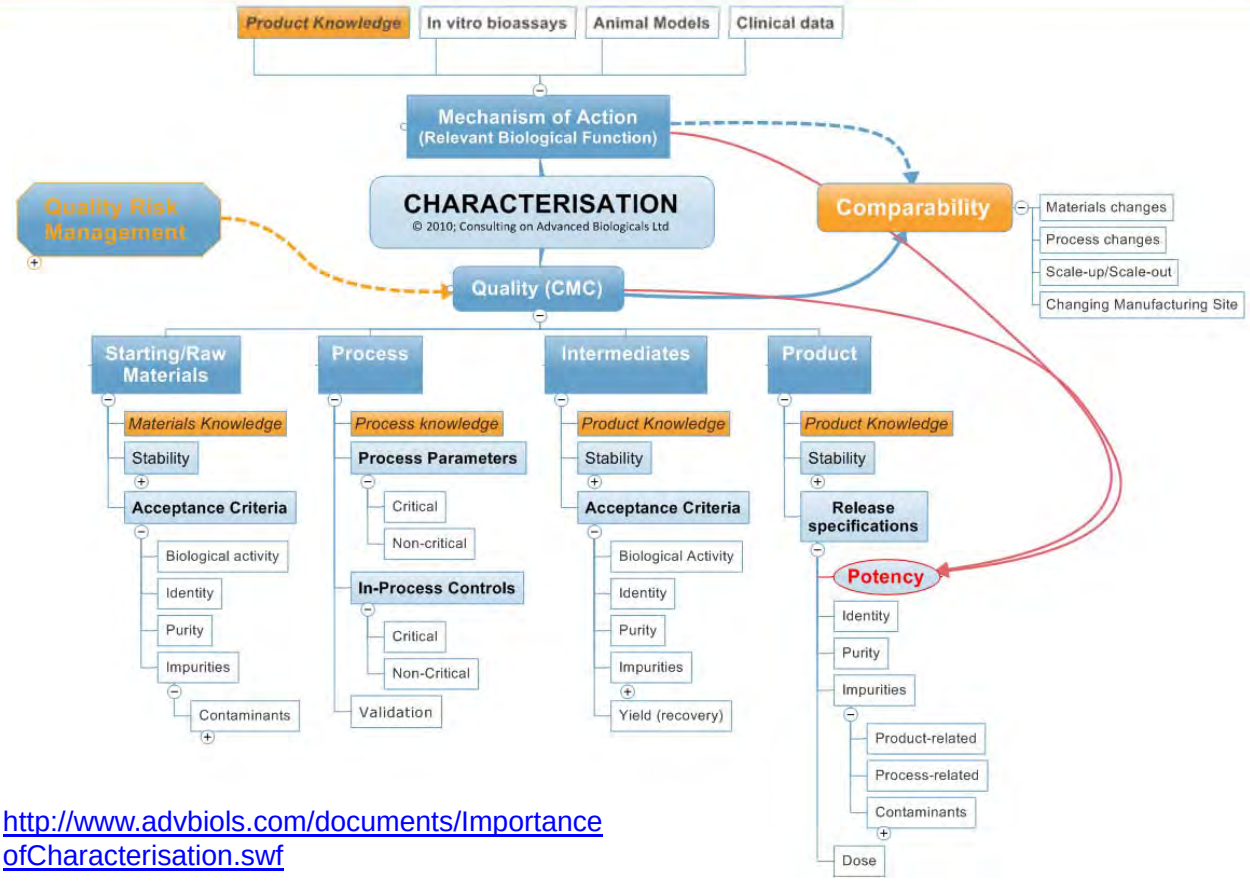
Introduction

- ✓ What does 'justification of specifications' (JOS) mean?
- ✓ How do you justify specifications
  - ✓ During clinical development
  - ✓ For Approval
- ✓ Final thoughts

Common Technical Document (CTD)



The Importance of Characterisation



http://www.advbiols.com/documents/ImportanceofCharacterisation.swf

FDA Common Causes of Hold Actions: Post-Phase 1

- Critical assays (potency, identity, other) are not…
- … validated, reproducible, quantitative, sensitive, specific, biologically relevant
- Stability program inadequate, unsuitable, or absent
- **Characterization data insufficient to establish lot release specifications**
- Comparability not adequately demonstrated
- Safety issues
  - High levels of bioburden resulting from contamination

From: Investigational new drugs submitted to the Food and Drug Administration that are placed on clinical hold: the experience of the Office of Cellular, Tissue and Gene Therapy. Cytotherapy,10:3, 312 – 316; 2006
DOI:10.1080/14653240801910905

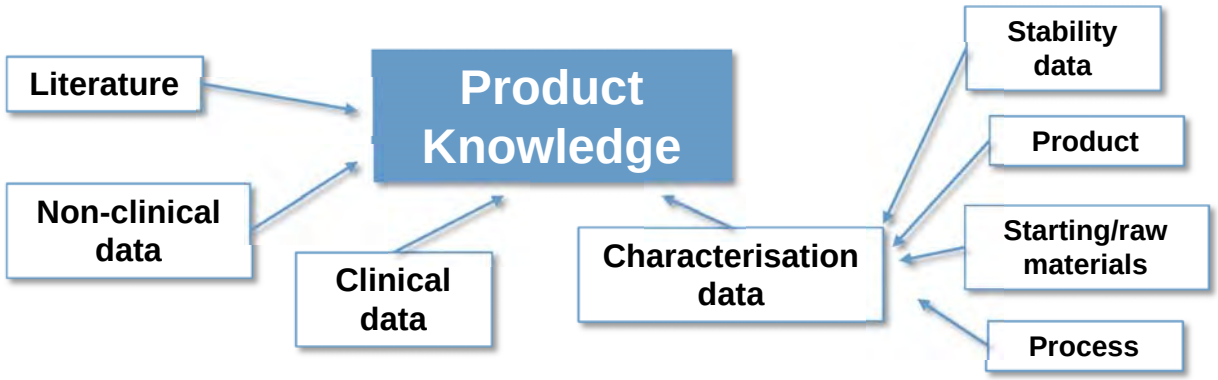
FDA BLA Issues

- Significant change(s) made late in development, without adequate product comparability data
  - Viral clearance evaluation studies may be needed
- Process validation data incomplete, inadequate, or absent
- Inadequate stability studies
- **Characterization data inadequate to support establishing specifications**
- Consistent manufacturing inadequately demonstrated
- Compliance issues - contract manufacturers, finish and fill facilities

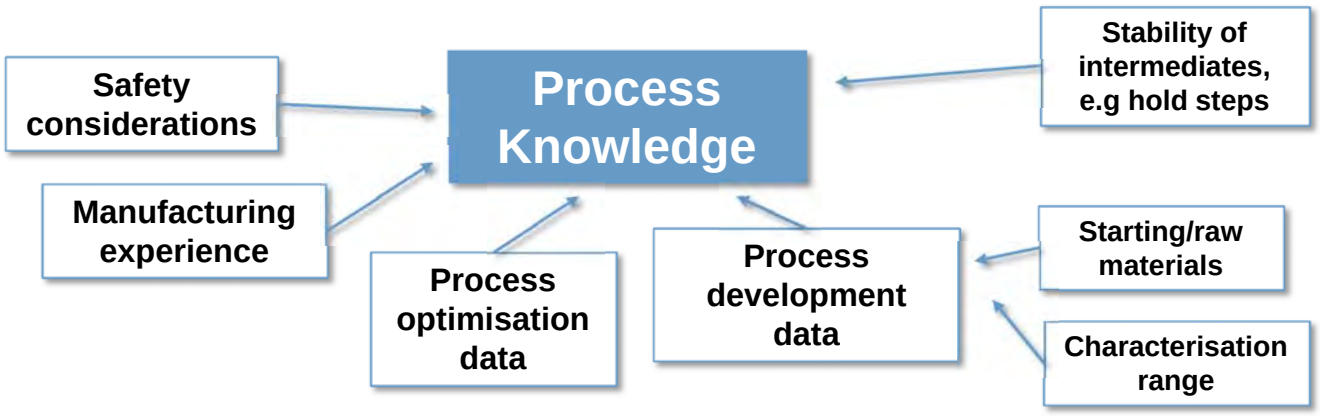
JOS during clinical development

- Specifications preliminary and uncertain
- Limited data to justify specifications
- Early stage focus on safety critical specifications
  - E.g. sterility (no growth), adventitious agents (negative), Endotoxin
- Examples I have seen in IMPD/IND CTD sections
  - N/A !?
  - The specifications of the excipient are based on the CoA (for culture media sold for in vitro use)!?
- While such statements may get approved it is your responsibility to consider whether your specifications are reasonable.

What is JOS: Product Specifications



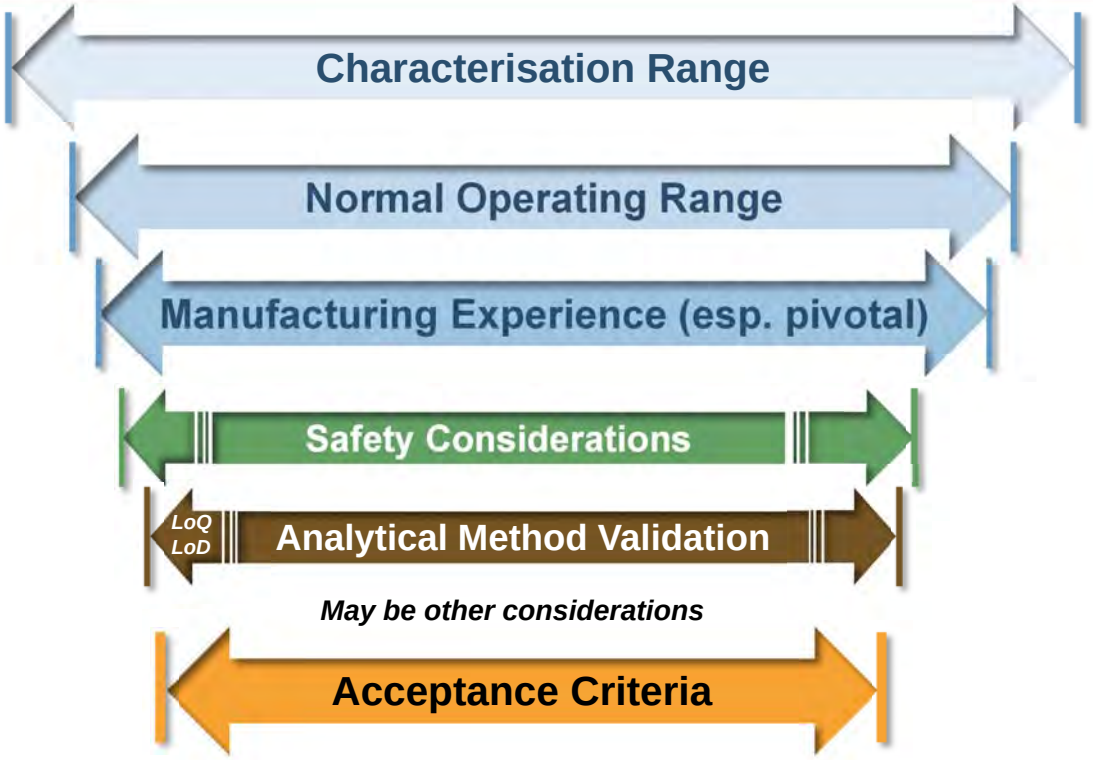
What is JOS: Process Specifications



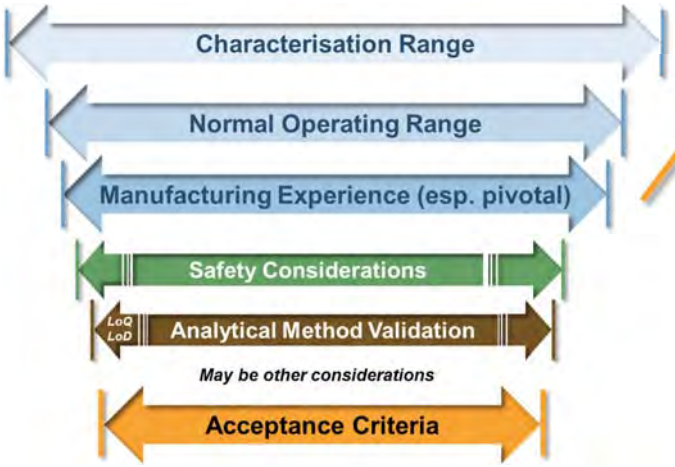
JOS for Market Approval

- Specifications need detailed justifications
- This requires that characterisation is complete and comprehensive
  - Starting/Raw materials specifications
  - Product specifications
  - Intermediates (e.g. cell banks, stored intermediates)
  - Process specifications
  - Stability specifications
  - Process parameters

JOS: Process Specifications

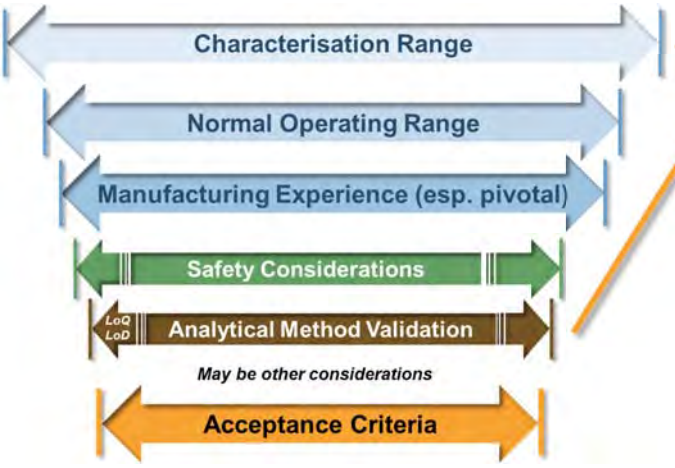


JOS: Process Specifications



- Process Drift
- Trending
  - PP
  - IPC
  - intermediates and product acceptance criteria
- Product Reference Material

JOS: Process Specifications



- Analytical Method Drift
  - Trending
  - Measurement Reference Material (calibrator)
    - Certified reference material
    - In-house
  - Don't forget
    - Stability of test samples

Product Specification (hard)Example: Potency

- ✓ Characterisation range
  - ✓ Hard to determine
  - ✓ Helpful to have *in vivo* pharmacology model/potency assay
    - ✓ Ability to test non/sub-potent product
    - ✓ Confirm *in vitro* potency/surrogate potency measures can identify non/sub-potent product
  - ✓ *Ex vivo* organ/tissue culture models
  - ✓ Bioassays
  - ✓ Surrogate potency measures
- ✓ Identify at least a threshold for potency (potent or not)
- ✓ Look for correlation to clinical outcome measures

Warning!

Just because your potency assay is quantitative for an analyte doesn't mean it is quantitative of potency.

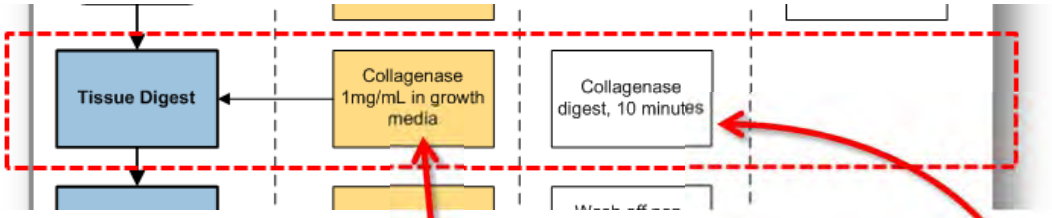
- The *measurand* may also not directly correlate to potency
- Potency determination may need to be multi-parameter
- Not all parameters will be quantitative measurements
  - E.g. threshold when measuring mRNA or cytokine/GF level of cell population

Process Parameters Example: Enzyme

Assuming you want to retain the *in situ* characteristics of the cells but release them from the tissue.

Characteristics	Parameters
phenotype/genotype - *cellular active* - *cellular impurity* viability proliferative capacity cell yield biological activity indicators of early cell damage	Time/duration pH temperature size of tissue pieces reaction media composition co-enzymes Stability of enzyme in solution

Optimised process parameters



Collagenase raw material specification:
CDU: 1,000 – 3,000 /mg
FALGPA : 4-10 U/mg
Other enzymes: <1 U/mL
etc.

Collagenase Solution:
Collagenase: 900 – 1,100 CDU/mL
in optimised reaction buffer solution

Reaction buffer specification:
HBSS
buffered pH: 7.4 ± 0.2
indicator dye
supplements etc.
Stability >6 hours at 4±2 C

Collagenase step parameters:
Collagenase solution: 1.8 – 2.2 mL/mg tissue
Digest time: 12 ± 2 minutes
Temperature 37 ± 0.5 C
CO_2: 5 ± 0.5 %

Conclusions

- ✓ Specifications are set to control and confirm the quality of the product for a specific qualified/validated process.
- ✓ Specifications are set based on manufacturing experience and all other relevant information.
- ✓ Specifications should be justified (sound reasons that can be explained).
  - ✓ Important to record reasons (development is a long process, key staff may turn-over)
  - ✓ Detailed JOS will be needed for approval and most will require data beyond averages from batch records.