Justification of Specifications (JOS): What Product and Process Development was all About

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The Importance of Characterisation

http://www.advbiols.com/documents/Importance ofCharacterisation.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
What does 'justification of specifications' (JOS) mean?

How do you justify specifications

During clinical development

For Approval

Final thoughts

Dossier sections potentially contributing to JoS

3.2.5 Drug Substance

3.2.6 Drug Product

P.1 Description and Composition of the Drug Product

P.2 Pharmaceutical Development

P.3 Manufacture

P.4 Control of Excipients

P.5 Control of Drug Product

P.6 Control of Drug Substance

5.1 General Information (name, manufacturer)

5.2 Manufacture

5.2.1 Manufacturing

5.2.2 Description of Manufacturing Process and Process Controls

5.2.3 Control of Materials

5.2.4 Controls of Critical Steps and Intermediates

5.2.5 Process Validation and/or Evaluation

5.2.6 Manufacturing Process Development

5.3 Characterisation

5.4 Control of Drug Substance

5.4.1 Specification

5.4.2 Analytical Procedures

5.4.3 Validation of Analytical Procedures

5.4.4 Batch Analysis

5.4.5 Justification of Specification

5.5 Reference Standards or Materials

5.6 Container Closure System

5.7 Stability

5.7.1 Stability Summary and Conclusions

5.7.2 Pre-approval Stability Protocol and Stability Commitment

5.7.3 Stability Data

NonClinical Data

Clinical Data
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

- Literature
- Non-clinical data
- Clinical data
- Characterisation data
- Product Knowledge
- Stability data
- Product
- Starting/raw materials
- Process
What is JOS: Process Specifications

- Safety considerations
- Manufacturing experience
- Process knowledge
- Stability of intermediates, e.g. hold steps
- Starting/raw materials
- Characterisation range
- Process optimisation data
- Process development data
- Starting/raw materials specifications
- Product specifications
- Intermediates (e.g. cell banks, stored intermediates)
- Process specifications
- Stability specifications
- Process parameters

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: Specifications

- Specifications
  - Final Acceptance Criteria
  - Manufacturing Experience (esp. pivotal)
  - Normal Operating Range (NOR)
  - Characterisation Range
  - Operating Range
  - Safety Considerations
  - Analytical Method Validation
    - May be other considerations
    - Final Acceptance Criteria

Defining Specifications

- Operating Range (OR)
  - [Proven acceptable range (PAR)]
- Normal OR (NOR)
  - [Acceptance Criteria]
- Critical quality attribute (cQA)
- Action Limits
- Process Parameter (PP)
- Characterisation Range
  - [Characterised/knowledge space]
- Characterisation data
- Batch data
- cQA Range
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
ICH Q6B: JOS

• The setting of specifications for DS and DP is part of an overall control strategy which includes control of raw materials and excipients, IPC, process evaluation/validation, adherence to GMP, stability testing, and testing for consistency of lots. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes.

• Specifications are linked to a manufacturing process.

• Specifications should account for the stability of DS and DP.

• Specifications are linked to preclinical and clinical studies.

• Specifications are linked to analytical procedures.

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.