Manufacturing Process Development

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Manufacturing Process Development: S2.6

• Current status

  • No reason or justification for selecting the current manufacturing process.

  • Not applicable

  • 3 validation batches manufactured.
ICH Q11

- Q11 to clarify principles of Q8, Q9, and Q10 as they relate to drug substance and provide examples

- ICH Guidelines
  - Q8 Pharmaceutical Development
  - Q9 Quality Risk Management
  - Q10 Pharmaceutical Quality System

- Concepts of these guidelines apply to DS as well as DP

- Unique to the manufacturing process of DS Process - purification
Manufacturing Process Development

- **Goal:** Consistently obtain API of intended quality
- **What to submit?** Summary overview (~20 pages)
- **How you get there**
  - Scientific understanding (literature, expertise, references)
  - DS CQA
  - Starting material selection
  - Selecting an appropriate manufacturing process
  - Approach to development
  - Identify Control strategy
- **Relevance of development studies to the commercial process**
- **Knowledge gained** - Connect back to DS CQA
Critical Quality Attributes (CQA) of DS

- Prior knowledge
- CQA of DS
  - DP QTPP
  - Characteristic (physical, chemical, microbiological)
  - Impurities
  - Polymorph or PS
  - Not same as specification

- How were CQAs determined? What is a justification?
- Basis of selection of SM and manufacturing process.
Starting Material

- Manufacturing Process starts with starting material.
  - Most deficiencies are cited
    - Choice of starting material, Justification?
      - Well Characterized
      - Q11 principles
      - Is it appropriate?
    - CMA (impurity, stability, handling)
      - Justification for impurities not tested in the DS
  - Source
    - Commercially available, contract synthesis, well defined in literature, economics etc.
Starting Material

• Justification-

“Forms a significant structural fragment of the active substance”
Selection of starting material (SM)

• All general principles should be considered

• **General principles** (paraphrased)
  1. Changes in the early **steps** has lower potential impact on API
  2. Describe enough to understand
     where and how impurities in the API are formed and
     why proposed Control Strategy is suitable
  3. **Steps impacting impurity profile** should normally be included.
  4. Convergent synthesis may have one or more starting materials
  5. Substance with defined chemical properties and structure.
  6. Significant structural fragment -context is other than cat., reagents, solvents etc.
Manufacturing process development

- Define manufacturing process
  - Synthetic route selection?
  - Optimization studies
  - Significant changes – from lab to production scale

- Discuss approaches used to optimize process.

- Identify CPP & Control strategies
Approaches to process optimization

• Traditional Approach
  – Defined set points and operating ranges for process parameters
  – Drug substance control strategy typically based on
    • Demonstration of process reproducibility
    • Testing to meet established acceptance criteria

• Enhanced Approach
  – Risk management and more extensive scientific knowledge
    used to select process parameters and unit operations.
  – Studies performed to establish parameters
  – Control strategies applicable over the lifecycle of the drug
    substance

• Company can choose either or combination of both.
Control Strategy: Definition

“A planned set of controls, derived from current product and process understanding that ensures process performance and product quality…..”

ICH Q8 (R2) & Q10

“The Control Strategy is a comprehensive plan for ensuring that the final product meets critical requirements, and therefore the needs of the patient.”

Control Strategy: What & Why?

- A planned set of controls
- Stems from product and process understanding and risk management
- Leads to product quality assurance
- Is not optional (21CFR314.50)

What?

Why?
Control Strategy (Q10)

• Assures
  – Process performance and product quality (risk management)

• Every process
  – traditional or enhanced or combination of both

• Include
  – Material attributes (starting material, raw material, solvents, reagents, catalyst, packaging, etc)
  – Process (order of addition, molar ratios, concentrations, purification step)
  – In-process controls

• Specifications
Process validation (Q7)

- Required by Law: All manufacturing processes to be validated prior to product commercialization.

- Provides assurance of DS quality

- Definition:
  - “Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes”
Manufacturing process development

- What is process development.
  - History of how the process was developed.
- Where: In S.2.6 section of eCTD format.

- How should it be included?
  - Brief summary of the study (~20 pages)
  - Study conducted on lab scale, pilot scale batches is ok
  - No raw data or spectra
  - Provide conclusion from each stage of study.

- What should be included?
  - Critical process parameters for each step or stage.
  - How are they optimized (Different conditions or sets of conditions)
  - What is the outcome.
Thanks
ICH Q11

1. Introduction
2. Scope
3. Manufacturing Process Development
4. Description of Manufacturing Process
5. Selection of Starting Material
6. Control Strategy
7. Process Validation/Evaluation
8. Submission in CTD Format
9. Lifecycle Management
10. Illustrative Examples
11. Glossary

Format:
General principles