Manufacturing Process: Common Deficiencies and Recommendations for Information Request Responses

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Outline

- **Introduction**
- **Review Expectations**
- **Common Process Related Deficiencies**
- **Conclusions and Recommendations**

Introduction

- **Purpose of Review - "End in Mind"**
- **Evaluate Adequacy of final Commercial Scale Manufacturing Process**
- **Tools of the Trade**

  Risk based evaluation
- **End Product**
- **A robust commercial manufacturing process with a well-defined control strategy that produces drug product of consistent quality**

Introduction

- **New to OPF**
  - **Integrate process review with facility evaluation**
- **Scope**
  - **The scope is limited to deficiencies cited for solid oral dosage forms**

Review Expectations

Manufacturing Process Development in Product Development Report (3.2.P.2)

- **Demonstrates Process and Product Understanding**
- **Implementation of a risk based approach**

Review Expectations

Executed Batch Record

- **Required by 21CFR314.50(d)(1)(ii)(b) for batches used to conduct bioavailability/ bioequivalence study and/or stability study**
- **Included in Section 3.2.R per ICH M4Q**
- **Establishes baseline manufacturing process and controls for the manufacture of commercial batches**

Review Expectations

Commercial (Master) Batch Record

- **Includes a batch formula, same as that used to manufacture executed batches**
- **Describes a Manufacturing Process that is same/similar to the executed batch record**
- **Identifies equipments adequately, specifies validated process parameter ranges, identifies in-process controls**

Common Process Related Deficiencies

Manufacturing Process Development

Example 1

Deficiency

Process Selection not discussed/ justified; e.g. dry blending vs dry granulation vs wet granulation

Consideration in IR Response

Discuss with data why the proposed process was selected and what measures are in place to mitigate any potential risks

Common Process Related Deficiencies

Manufacturing Process Development

Example 2

Deficiency

- **Process risk vs. Physical Stability (e.g. morphic form)**

Considerations in IR Response

- **Provide data (XRPD, IR) to show no change in API morphic form during processing and shelf-life; discuss analytical method suitability**
- **Discuss API physical characteristics vs in-vivo/in-vitro performance**

Common Process Related Deficiencies

Master Batch Record – Batch Formula

Example 3

Deficiency

- Overage not justified

Considerations in IR Response

- Dosage form design
- Manufacturing process loss; data

Overage because of stability not acceptable

Common Process Related Deficiencies

Master Batch Record – Batch Formula

Example 4

Deficiency

Not all components specified quantitatively; example, the granulating solvent is given as q.s.

Considerations in IR Response

Specify quantitatively all the components; justify if excess prepared (example, coating solution)

Common Process Related Deficiencies

Master Batch Record

Example 5

Deficiency

- **Differences in Executed batch vs. Commercial batch**
  - **variation in equipment % utilization**
  - **process difference (sub-lots)**

Considerations in IR Response

- **Explain/Justify differences**
  - **List equipment %utilization**
  - **Justify process differences as it relates to proposed process parameters; example blend time vs. blender rotation**

Common Process Related Deficiencies

Master Batch Record

Example 6

Deficiency

Yield

- **Low yields not explained/justified**
- **Proposed limits not justified with data**

Considerations in IR Response

- **Low yield explained/justified – additional sampling, batch size**
- **Process issues – low fill capsules, mitigation strategies**

Common Process Related Deficiencies

Master Batch Record

Example 7

Deficiency

Hold Times and Conditions

- **Not identified and justified adequately for high risk intermediates**
- **Tests conducted to justify hold-time and conditions for DP intermediates do not address quality issues e.g. BU of a blend for a low dose drug, microbial limits when wet granulation is used**

Common Process Related Deficiencies

Master Batch Record

Example 7 (Contd.)

Considerations in IR Response

- **Justify Hold Time and Conditions if significant for high risk intermediates**
  - **Identify High Risk Intermediates and Discuss CQA's that may be affected by holding the intermediate for extended periods**
  - **Submit CQA data to support hold time**

Common Process Related Deficiencies

Process Parameters – Commercial Scale

Example 8

Deficiency

- **Ranges Not Specified – TBD?**
- **Ranges Not Justified – Proposed process parameters not supported by established scale-up principles**

Considerations in IR Response

- **Specify ranges based on established scale-up principles**
- **Explain/justify commercial process parameters**

Common Process Related Deficiencies

In-Process Controls

Example 9

Deficiency

Controls not quantitative; subjective vs objective; example - granulation end point

Considerations in IR Response

Include quantitative In-process Controls or Justify

Common Process Related Deficiencies

Microbiological Controls

Example 10

Deficiency

- **Microbiological Controls for Solid Oral Drug Products – CTD-Q 3.2.P.2.5 not addressed adequately**

Considerations in IR Response

- **Microbiological load of components of the DP**
- **Process risk; hold time and conditions**
- **Water activity**
- **Finished product specifications (USP <1111>)**
- **Stability Batch Data**

Conclusions and Recommendations

- **The quality of submissions has greatly improved**
- **Risk analysis is used in making process and controls decisions**
- **Recommend continued use of QbD principles in establishing material controls, CPPs, In-process controls and finished products acceptance criteria**
- **Recommend applicants prepare their applications with adequate data and discussion to demonstrate an understanding of the process and product**

Conclusions and Recommendations

- **Recommend applicants verify that their commercial batch records include clear instructions for the operators; well justified and consistent process parameters (ranges) and in-process controls**
- **Explain if the proposed commercial process deviates from the development and/or executed batches**
- **Explain/justify if the proposed commercial process parameters and controls deviate from those studied during product development studies and/or used in the manufacture of exhibit batches**

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Please evaluate this session:

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