

Common CMC Issues for Manufacturing Process and Facility Assessment

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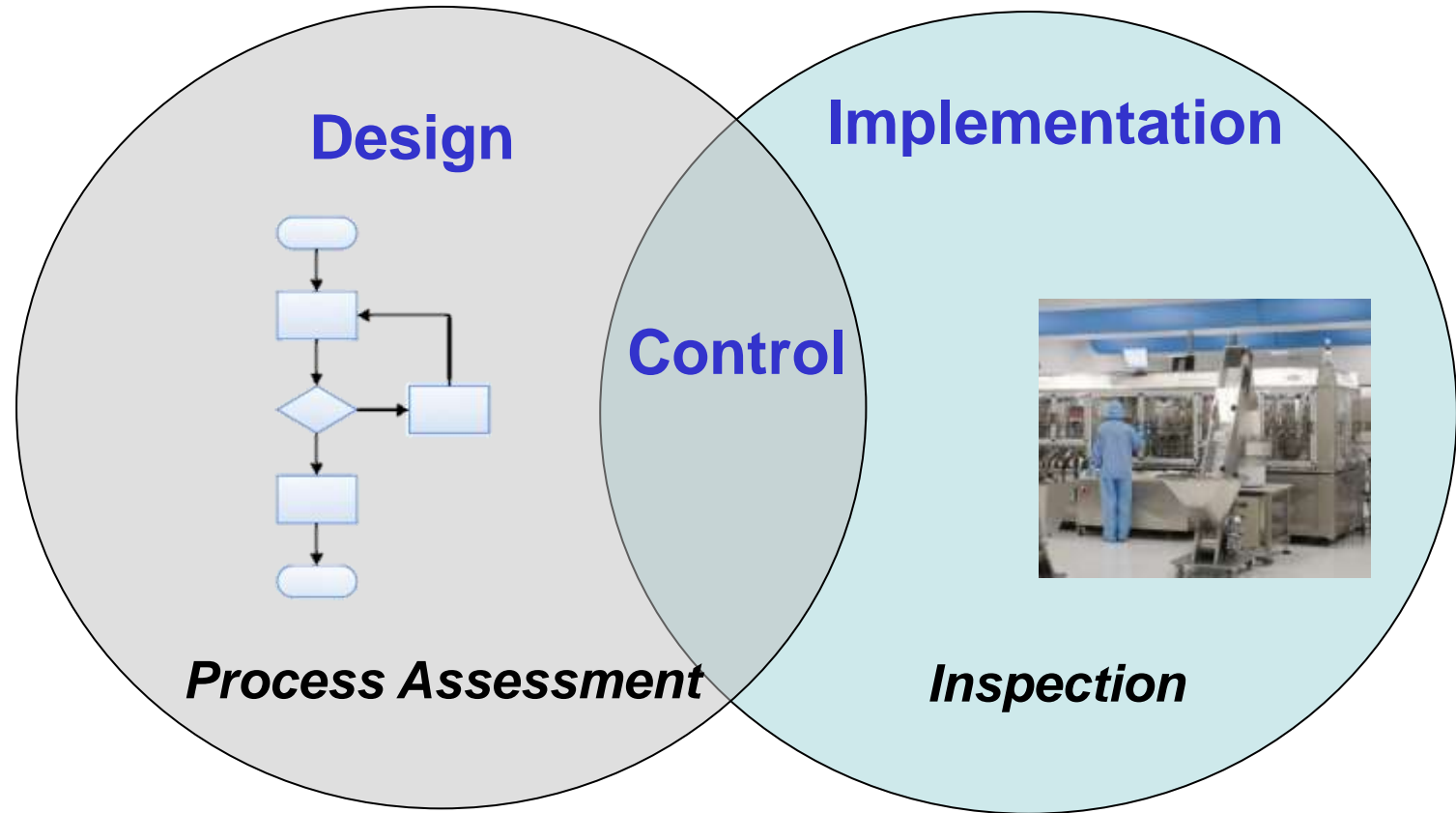
Learning Objectives

- **Discuss the integrated process and facility assessment**
- **Explain Review Expectations**
- **Examine Common Process Related Deficiencies**

Introduction

- The Office of Pharmaceutical Manufacturing Assessment (OPMA), performs evaluations of pharmaceutical manufacturing by integrating the assessment of the manufacturing process, facilities, and pre-approval inspection. OPMA's integration of these activities ensures that quality is built into the manufacturing process and facility over the product's life cycle.
- An OPMA reviewer provide a holistic manufacturing assessment of the process, facility, and microbiology (solid oral dose) information in the regulatory submissions.
- Provide enhanced technical knowledge/cross training in both review and cGMP. Make more informed, risk-based decision.

Holistic Manufacturing Assessment



- Adequate process understanding
- Critical controls are in place and well-documented in application

- Facility capable of implementing listed manufacture operations in conformance to cGMP
- Data integrity

Introduction

- **Purpose of manufacturing assessment: Evaluate adequacy of final commercial scale manufacturing process and facilities**
- **Risk based evaluation**
- **A robust commercial manufacturing process with a well-defined control strategy that produces drug product of consistent quality**

Assessment Expectations

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

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

Assessment 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**

Assessment 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

- Potential change in physical form of the API during processing is not evaluated.

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

In Process Controls

Example 2

Deficiency

- Variable blend uniformity (BU) data, justification for BU sampling size, sampling plan, not providing stratified content uniformity (CU) data

Considerations in IR Response

- Process development data to justify BU sampling plan and acceptance criteria
- Establish stratified CU sampling plan and acceptance criteria

In Process Controls

Example 3

Deficiency

- Lack of supporting process development data to justify critical process parameters and in-process controls (i.e. wide range of weight gain control, granule size, moisture content, that were not justified by development data)

Considerations in IR Response

- Process development data to justify critical process parameters and in-process testing acceptance criteria

Common Process Related Deficiencies

Master Batch Record

Example 4

Deficiency

- Differences in Executed batch vs. Commercial batch
 - variation in equipment % utilization
 - process difference

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 5

Deficiency

- Subjective manufacturing process description (... if necessary, add additional amount of granulation fluid...)

Considerations in IR Response

- Process development data to justify amount of granulation fluid, rate of binder addition, and wet massing time and so on
- Establish acceptable granulation end point (i.e. impeller torque, power consumption)

Common Process Related Deficiencies

Master Batch Record

Example 6

Deficiency

Low Yield

- Root cause of low yields not properly investigated/justified
- Proposed limits not justified with batch data

Considerations in IR Response

- Low yield explained/justified (i.e. additional sampling, batch size)
- Process issues – low fill capsules, mitigation strategies to ensure a robust manufacturing process

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

Sub-Lots

Example 9

Deficiency

Inadequate IPC controls for each sub-lot was provided before combining each sub-lot

Considerations in IR Response

Provide sufficient material characterization and process controls for each sub-lot before combining to ensure that variation in sub-lots is not masked by subsequent unit operations.

Common Process Related Deficiencies

Equipment Compatibility

Example 10

Deficiency

Leachable/Extractable study for the polymeric manufacturing components not provided when the product contains cosolvents or surfactant

Considerations in IR Response

- USP<1663>, USP<1664> principles and general approaches
- Demonstrate that all formulation contacting polymeric components are not reactive, additive or absorptive to alter the safety, and quality of the drug product

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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Question 1

Which office in CDER performs evaluations of pharmaceutical manufacturing by integrating the assessment of the manufacturing process, facilities, and pre-approval inspection?

Question 2 (Select the true statement)

- A. The purpose of manufacturing review is to evaluate the adequacy of final commercial scale manufacturing process and facilities**
- B. FDA conducts risk based evaluation for incoming applications**
- C. A robust commercial manufacturing process with a well-defined control strategy that produces drug product of consistent quality is not required for drug application**
- D. All of above**