Continuous Pharmaceutical Manufacturing: CGMP, Process Validation, and Inspectional Considerations for Implementation

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Outline

• Continuous manufacturing in the Regulatory and CGMPs framework

• CGMP considerations
  – Quality Unit
  – Equipment & computer systems

• Process Validation Approach
  – Assessing process robustness
FDA View of Continuous Pharmaceutical Processing

• FDA supports continuous processing for pharmaceutical manufacturing
  – Offers potential advantages in both development and manufacturing

• Continuous manufacturing is consistent with FDA Quality Initiatives
  – More modern manufacturing approach
  – Potential to improve assurance of quality and consistency of drugs
  – Enables quality to be directly built into process design
The Commissioner is keenly aware that the general CGMP regulations must apply to a wide variety of drug products. Therefore, the CGMP regulations in Part 211 are intended to be:

• general enough to be suitable for essentially all drug products,
• flexible enough to allow the use of sound judgment and permit innovation, and
• explicit enough to provide a clear understanding of what is required.

Preamble to 21 CFR 210 & 211, March 1979
CGMPs & Continuous Manufacturing

- CGMP’s are intended to be flexible and amendable to new technology
  - Production and Process Controls
  - Equipment, Laboratory Controls, Records
- In implementing CM, the Quality Assurance Unit may appear to have the greatest challenges adapting.
  - Compressed timeframes
  - Immediate decision-making on in-process and finished materials
  - New ways of thinking about old business processes
Responsibilities of the QC Unit

• 21 CFR 211.22 – “The Quality Control Unit shall have the responsibility and authority to”… approve and reject all incoming components, in-process materials, and final product.

• Materials are isolated and individually approved
• Hold time studies allow for investigation periods if needed
Responsibilities of the QC Unit

• 21 CFR 211.22 – “The Quality Control Unit shall have the responsibility and authority to”… approve and reject all incoming components, in-process materials, and final product.

• Material is constantly generated and moved forward
• Rapid transmission of material requires an adequate control strategy and significant process development
• But most importantly, **QC oversight must be built into process decision-making.**
QCU and Automation

• CM equipment is highly reliant on automation software for control and monitoring

• Quality decision making must be programmed into the automation:
  – Interlocks, communication checks, recipe integrity, data collection frequency
  – Monitoring, Alert & alarm limits, segregation points, automatic stops
  – Start up sequence, restart, material collection criteria, and shut-down processes

• Some oversight is delegated to the automation but the QCU is ultimately responsible for the product
Importance of Automation Validation

• 21 CFR 211.63 – *Equipment must be suitable for intended use.*

• User requirements include both technical and quality functionality.

• Installation / Operational / Performance Qualification should consider both unit component functionality as well as the entirety of the integrated system.

• OQ/PQ should consider the relative risk and impact to product of the automation design specifications
Maintenance of Automation

- 21 CFR 211.67 – *Equipment shall be maintained as appropriate according to procedures to prevent malfunction that would alter the drug product.*

- Robust change control process for code improvements
  - Design, testing, implementation, & confirmation

- Monitoring of automation performance
  - QCU should be auditing the “delegated” responsibilities

- Version control, back-ups, and security
Deviation Preparation

• 21 CFR 211.22 & 192 – *Failure to meet any specification shall be thoroughly investigated.*

• Proactive QCU

• Deep understanding of process is required
  – Have identified potential failure modes
  – Detectability: process parameters & PAT signals
  – Clear plan of action justified and determined in advance
  – Overall batch quality: What is acceptable control?

• This decision-making also feeds into Quality Control Strategy and automation
Control and Process Risk

- Monitoring of process parameters & PAT measurement of attributes
- State of control vs. flux and impact on material collection
Control and Process Risk

• Risk to Product
  – Detect and remove OOS or potentially OOS material

• Risk to Process
  – Maintaining a state of control, establish thresholds for “in control”
  – Does limited control over the entire batch manufacturing period pose an indirect threat to product quality?

• Batch review
  – Percent yield and state of control
  – Time in control, frequency of rejection

• Examine process and variability through robust Process Validation
Process Validation

• **Process Validation** – The collection and evaluation of data, from the process design stage through commercial production, which establishes *scientific evidence that a process of capable of consistently delivering quality products.*

• **Process Qualification** – Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing.

Process Validation - Stage 1

• Process Design
  – Equipment
  – Material inputs and attributes
  – RTD Studies, system dynamics

• Control Strategy
  – Parameter monitoring and acceptable ranges
  – PAT points, sampling rates, models
Process Validation - Stage 2a

• Qualification of equipment and automation
• Operates in accordance with the process requirements over the entire anticipated operating range
  – Expected conditions, stresses, duration
Process Validation - Stage 2b

- Understand the Process Design
- Material Attributes established
- Process Parameters set
- PAT points and models
- Facilities and Equipment have been adequately qualified

- Confirm process design and control strategy for the intended scale of manufacturing
- **Demonstrate capability to reproducibly manufacture commercial product**
Process Performance Qualification

- Seeks to **confirm effectiveness of control strategy**
- Evaluate adequate performance of process with expected variability of inputs and process to **confirm robustness**
- For CM especially, demonstrate that the process can achieve and maintain a **state of control**
- Pre-determined in PPQ Protocol
  - Length of CM run and number of batches
  - Attributes to be monitored
  - Acceptance criteria: for each attribute and for the batch
  - Definition of a “successful” batch
Assessing Robustness

• Unlike batch processes, the quantity of material produced by CM is directly related to the amount of time operating in a state of control
• To assess robustness during PPQ, there should be some expectation for yield in a CM process
• But..... may not be as simple as percent yield
  – Number of diversion vs. time of each diversion
  – Start up losses and inherent waste
• Definition of “yield” must be very clear
• Measure of PPQ “success” must be determined in advance
PPQ Protocol

- Should include typical operations
  - Start up, pauses, & restarts if part of the process
  - Run length
  - Expected interventions
    - PAT probe cleaning or replacement, refill events

- Sources of variability
  - Incoming materials
  - Equipment fatigue
Continued Process Verification

- Establish a program to collect and analyze product and process data related to product quality
  - Establish Monitoring plan
  - Frequency of trending and analysis
  - Attributes
- Understanding of remaining variability
- Detect abnormalities
- Statistical approach highly recommended
Summary

• Continuous Manufacturing is highly compatible with CGMPs
  – Quality oversight is a universal expectation
  – Suitability and performance of physical and electronic equipment

• Thorough Process Validation enhances the robustness of processes designed and intended to remain in a constant state of control
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