Achieving Quality Beyond Compliance Through Continuous Manufacturing

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The Journey of Quality Beyond Compliance

Managing Quality
Common quality system & standards across all Novartis divisions

Making Medicine
Focus on our products and “how we make medicine”

Continuous Improvement
Manufacturing Strategy/Quality Strategy; Quality by Design

Competitive advantage
Sustainable and reliable supply network of high quality products
Quality Beyond Compliance

Continuous Improvement, Competitive Advantage

People, organizational capability, training

Quality Culture

Products, process, and technology

Quality systems and tools

Cooperation and alignment

External engagement

Managing Quality and Making Medicine

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Supply Patients with Quality Products
Right first time and Every time, Efficiently and Safely

- Offer in depth process understanding and knowledge to manage the risks through product lifecycle
- Deliver quality product through precise systematic process control and confirmed through PAT
- Reduce complexity of the processes (less steps) and product lifecycle
- Ensue product quality at dosage level vs. batch
- Truly achieve product quality by design, rather by analysis
Concept for Continuous Manufacturing

- All continuous unit operations
- Total integration, coupled end-to-end
- Systems approach
- Plant wide control strategy

The process is the product!
Quality Beyond Compliance

Process Transformation

**Batch**

- Mostly **step based**
- **Separation** of DS & DP steps and sites
- Large fragmented footprint, **high CAPEX**
- Long lead times

**Continuous**

- **Simultaneous inlet and outlet** of materials
- Intensified processes with shortened lead times (hours vs. months)
- Increased **supply chain flexibility**
- Reduced plant footprint, **lower CAPEX**
- Quality **quantum leap** by higher level of process control
Process Transformation: Continuous Manufacturing

Continuous Manufacturing is based on Process Intensification which allows more precise process control.

- Maximized material processing in the smallest process space, for example:
Intensification made easy with simultaneous inlet of raws and outlet of products

⇒ Continuous conversion of materials = flow processing

= Continuous Manufacturing

⇒ Flow = Rate Control is key!
Concept ⇆ Pilot ⇆ Reality
End-to-End Pharmaceutical Manufacturing on the Size of a Tennis Court
Magnitude of Technical Challenge

- *New* process technologies for most unit operations
- *New* approaches for end to end integration of process technologies
- *New* development roadmaps for projects
- *New* screening tools to match projects and technologies
- *New* process control strategies
- *New* quality and regulatory pathways
- *New* health safety and environment (HSE) strategies
Role of PAT in Continuous Manufacturing

- Enables one half of CM control strategy
- Faster is better: online, inline, at-line, offline
- Predictable and reliable response time is key
- Non-destructive principles
- Indirect measurements (surrogate test)
- Challenges: impurities, dissolution, micro, polymorphism
New Quality Paradigm
Lead Successful Implementation

*Quality cannot be tested into the product, i.e., quality should be built in by design.*” (ICH Q8) – CM will bring us there...

- Batch definition: *batch vs. lot*
- Start product collection
- Material traceability
- Release decision
- Process validation
What is a batch, lot etc? - 21 CFR 210.3

2) **Batch** means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(10) **Lot** means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.
Batch Definition

- In the discrete manufacturing mode: technical capability $\Rightarrow$ lot size
- In the continuous manufacturing mode:
  - The lot size is completely decoupled from the technical manufacturing framework.
  - The decision for the pre-defined lot size will be based on a balance of acceptable business risk and effectiveness considerations.
Material Traceability and Propagation

Key characteristics:
- Basis step response = cumulative form
- Describes directly amounts of material
- Includes experimental determination and verification
- Can be based on material or events (states)
- Characterized by minimum (e.g. 5%) and maximum (e.g. 95% of material) propagation times
- Determines the area of impact

Area of Impact used for reporting and flagging
Propagations of Material

• Characterize the propagation of materials and events on the basis of step responses per unit operation.

• Propagation dynamics is the basis for a decision at the end of the train to determine conforming vs non-conforming material.

• Lot release data will be based on process data and quality attributes from conforming material.
Handling of Non-Conformity

• Non-conformity e.g. process event or OOS is electronically flagged

• Separation of conforming vs. non-conforming material based on real-time material traceability and material flow property knowledge

• Impacted material will be diverted at the end of the process
Material Traceability and Event Handling

Key characteristics:
- State of control matters, not steady state
- Events (reach or lose state of control) will propagate through system following similar principles like materials
- Events are basis for flagging and diversion decision
- Divert material at end of process to minimize disturbance

Release decision would be based on quality attributes AND process history with time-stamped data
Continuous Quality Verification (CQV) for CM

- Product and process understanding
- Continuous Quality Monitoring and Control
- Process Performance Evaluation
- Release Decision
- Continuous Process Improvement
Integrated Drug Product Specifications

• No separate DS testing and release
• Comprise of some final product testing including traditional DP quality attributes
• Traditional DS quality attributes being evaluated in the final DP
Batch Release Decision

Based on the integrated drug product specification, i.e. on-line, at-line, off-line, in process tests and finished product testing

Start of Shelf-Life

The start (or date) of the continuous manufacturing process lot, specifically the starting point of the collection of the specific lot.
CM Changing the Way Medicines are Made

• Quality beyond compliance
• Ensure patients’ rapid access to breakthrough therapies
• Offer in depth process understanding and knowledge to manage the risks through product lifecycle
• Truly achieve product quality by design, rather by analysis
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Q&A