Industry Experiences with Small Molecule Continuous Manufacturing

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What Is (and Isn’t) Continuous Manufacturing

For Continuous Manufacturing,

1) Input material(s) are continuously fed into the process
2) The material is transformed within the process,
3) Processed output material is continuously removed from system
4) Requires 2+ pieces of equipment/unit operations in a row

Continuous Manufacturing is Not Necessarily:

1) Single piece of equipment that can run as long as it is being fed
   - Roller compactor, mill, tablet press, encapsulator, extruder
2) Connected batch equipment (high containment transfers)
Small Molecule Continuous Manufacturing Experience

• Application of Continuous Manufacturing ranges from:
  • Continuous from API Starting Materials to finished product
  • Hybrid approach including batch and continuous unit operations
• At least 5 approved applications for drug products
  • Vertex – ORKAMBI (Lumacaftor/Ivacaftor) - NCE
  • Vertex – Symdeko (Tezacaftor/Ivacaftor and Ivacaftor) - NCE
  • Eli Lilly – Verzenio (Abemaciclib) - NCE
  • Janssen – Prezista (Darunavir) – Batch to Continuous Process
  • Pfizer – Daurismo (Glasdegib) - NCE
• Additional products in development and/or regulatory review
• Many CM technical and regulatory publications and presentations
Small Molecule Experience: Drug Substance

• Application of Continuous Manufacturing being considered for drug substance includes:
  • Reactions
  • Extraction
  • Distillation
  • Isolation and drying
  • Crystallization
  • Filtration
  • Milling
Small Molecule Experience: Drug Product

• Most prevalent application of Continuous Manufacturing is Solid Oral Dosage Forms
  • Direct Compression, Dry Granulation and Wet granulation
  • Unit operations include dispensing, blending, granulation, drying and tableting, film coating
• Knowledge base for continuous manufacturing formulations, processes, equipment (both manufacturing and analytical) has grown
• Hybrid approaches are common
Regulatory Landscape

- Approval of 5 products demonstrates continuous manufacturing can be developed and approved under current regulations
- Opportunities for dialogue between Industry and Regulators
  - Meet early and frequently to discuss issues & strategies
- Concerns that global expectations may vary within and between different regulatory agencies
ICH Q13 Continuous Manufacturing

• Harmonization
  • Consistent expectations for market applications and approval

• Topics Covered by Q13 Include:
  • Drug substance and drug product
  • Large and small molecules
  • New products and conversion from batch to continuous manufacturing

• Challenges in Writing the Guideline:
  • Different molecules and drug products have different needs
  • Experience across products ranges from exploratory to implemented

• Balancing the Level of Detail
  • If it’s too high level, useless; if too prescriptive, flexibility can be lost
Talking Points During Implementation

- **Definition of a Batch:**
  - Can be based on time/throughput rate, a discrete quantity (kg, # of units, consumption of ingredient)
    - Allow flexible batch sizes within a validated range (market driven)

- **Stability:**
  - Should there be flexibility for the number and size of ICH stability lots?
    - What does 1/10th scale mean?
  - Number/size of batches for post-approval changes needed
    - Especially where a strong scientific rationale for equivalency to commercial material exists

- **Model Maintenance:**
  - Does it belong in the Pharmaceutical Quality System, or filing?
  - Notification for post approval changes – required or not?
Talking Points for Implementation (Continued)

- **Validation:**
  - 3 batch (traditional) – Required by some markets
  - 3-Stage (Continued Process Verification) and
  - Concurrent approaches
  - Demonstrate control during start-up, shut down and state of control

- **Availability of Product**
  - Product not be approved in some markets due to technology concerns
  - Without a batch manufacturing back-up plan, patients in such markets may not have access to the drug

- **Technology Transfer:**
  - Potential that regulatory agencies will require significant data for technology transfer of “like for like” continuous manufacturing equipment
Talking Points for Implementation (Continued)

• Contingency Plans:
  • Procedures for finishing a batch incase PAT controls are not available
  • Diversion of impacted product, sampling/testing/acceptance criteria

• Soft Sensors:
  • How is the information used? Can anything truly only be for internal use?

• Product Lifecycle
  • Flexibility that can be achieved throughout the product lifecycle
  • How can improvements be implemented with minimal notification?

• Existing Guidance
  • Freedom to apply existing ICH guidance to continuous manufacturing
  • Avoidance of too much interpretation of current guidance that would limit options and freedom for good scientific argument
Similarities for Small Molecule and Biologic Continuous Manufacturing

• Both use QbD via ICH Q8, Q9, Q10 and Q11 during development

• ICH Q8 and Q 11: Development Strategy
  • Define experimental plans to generate process knowledge and understanding
  • Identify relationships between process parameters and quality attributes
  • Identify controls that ensure material of acceptable quality is produced

• ICH Q9: Risk Management
  • Perform risk based assessments to categorize critical and non-critical relationships

• ICH Q10: Pharmaceutical Quality System
  • Identify a Control Strategy that ensures the manufacturing process is capable of consistently producing a quality product
  • The quality requirements don’t change for continuous manufacturing, but the analytical procedures to assess quality attributes may be different (e.g., PAT, models, alarms, APCs)
Similarities for Small Molecule and Biologic Continuous Manufacturing (Continued)

• Bios and small molecule drug substance processes have a lot in common
  • Bio reactors and chemical reactors
  • Harvesting cells versus collecting drug substance
  • They both may use chromatography to purify drug substance
  • Filtrations

• Both may use hybrid processes
Differences Between Small Molecule and Biologic Continuous Manufacturing

• Amount of Process Knowledge and Experience
  • Small molecule is further along

• Terminology
  • Different terminology may be used for Biologicals and small molecules

• Process Monitoring
  • Different analytical methods and acceptance criteria

• System Dynamics
  • Similar dynamics to API processes, but very different when compared to powders (e.g., solid oral dosage forms)
Questions