Advancements in Continuous Manufacturing Technology

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Discussion Items

• Continuous Manufacturing: An Overview

• Continuous Manufacturing: Advantages and Limitations

• Process Simplification: Enabler for Continuous manufacturing
Pharmaceutical Continuous Manufacturing (PCM) was identified as national priority technology by US Congress.

US congress has authorized funding to support PCM.

FDA has created ETT (emerging technology team) to assist industry implement continuous manufacturing.

Pharmaceutical Companies Pursuing Continuous Manufacturing

<table>
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<th>Company</th>
<th>Initiative</th>
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| Vertex       | • Introduced continuous manufacturing of drug substances and drug products  
               • Obtained FDA & EU approval for cystic fibrosis medications' ORKAMBI in 2015, and SYMDEKO in 2018 |
| Janssen      | • Obtained FDA approval for antiretroviral medication (PREZISTA) in 2016 |
| Eli Lilly Co.| • Obtained FDA & PMDA approval for breast cancer medication (VERZENIO) in 2017 |

Source: Mitsui & Co Global Strategic Studies Institute
Advantages and Limitations

Advantages:
• Increased Worker Safety
• Standardization
• Economies of Scale
• Higher Production Rates

Limitations
• Requires High Investment
• Require Extremely Careful Design
• Lack of Flexibility
• May Lead to Excess Inventory
New Technologies: An Enabler for Continuous Manufacturing

Process Simplification / Efficiency Improvement / Capacity Enhancement
Simplification of Granulation: Conversion to Single Pot

- Wet granulation
- Wet Milling
- Fluid Bed Drying
- Milling
- Blending
- Compression
- Coating

Single Pot
(High Shear Granulator)

Compression
Coating
Key Enablers

Results: Particle Growth
Conversion to Direct Compression: Glidant Mixing Process

- Conversion of multi-stage processes to direct compression
- Glidant grades, and high shear are key enablers:
  - reduce Van der Waals
  - produce ball-bearing action

Application: Remediation of a DRL Commercial Product

Challenges:
- Very poor bulk flow
- COPE due to physical defects, excursions in-process parameters
- Longer processing times
- Low throughput

Improvements:
- Excellent bulk flow
- Elimination of physical defects
- Increase of compression speed from 20 to 40 rpm
- 75% reduction in process time
Continuous Manufacturing: Direct Compression and Coating

Continuous Coater
Benefits

- Operators Delight: elimination of major powder exposure/handling operations (sifting, milling, blending and drying)
- Improves product quality – eliminates thermal and shear stresses
- Reduction in energy usage – greener process
- No CapEx requirement
- ~ 75% reduction in process time
- Consolidation of operations – reduction in manufacturing areas/equipment usage
- Amenable for conversion to continuous manufacturing

Limitations

- Increase in raw materials (excipients) cost in some cases
- Difficult to implement for formulations that have hydrophobic drugs in large concentrations