Continuous Manufacturing for Solid Oral Dosage Forms

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Christine M. V. Moore, Ph.D.
Global Head and Executive Director
GRACS CMC Regulatory Policy, MSD
Agenda

• Background on continuous manufacturing
• MSD’s approach for continuous manufacturing for solid oral dosage forms
• Challenges for continuous manufacturing
• Opportunities: collaboration and communication
What is Continuous Pharmaceutical Manufacturing?

A manufacturing scheme where the material(s) and product are continuously charged into and discharged from the system, respectively, throughout the duration of the process.
Continuous Processes vs. Unit Operations

Many common drug product single unit operations run in a continuous mode, for example:

- Tableting
- Roller compaction
- Hot melt extrusion

In current terminology, “continuous manufacturing” is commonly used to describe:

- For drug product: connected manufacturing, most commonly for solid oral dosage form, even if run for a discreet period of time
- For API: single flow chemistry reaction or crystallization steps
- For biotechnology product: single or connected unit operations, for upstream or downstream processing
Continuous Manufacturing is not new!

"Whereas batch operation was common in the early days of the chemical industry, most processes have been switched completely or partially to continuous operation"

Exponential Growth

Publications using the terms "Pharmaceutical" and "Continuous Processing"
Current Regulatory Landscape

- At least 2 products made by continuous manufacturing have been approved by health authorities*:
  - Vertex’s Orkambi – New drug approved in US, EU, Canada, Australia & Switzerland
  - Janssen’s Prezista – Batch to continuous conversion approved in US and EU

- Many large innovator companies have programs for continuous manufacturing of SODs
  - Several investigational drugs are being produced by continuous manufacturing

- US, Europe and Japan regulatory agencies all have specialized groups to help facilitate new manufacturing technology:
  - EU Process Analytical Technology (PAT) Team
  - FDA Emerging Technology Team (ETT)
  - PMDA Innovative Manufacturing Work Group (IMWG)

http://investors.vrtx.com/releases.cfm?view=all
Pharmaceutical Industry Shifts

- Large, centralized facilities
- Few campaigns of large batches

- Smaller volume products
- Small and agile local plants
- Many campaigns, quick turnaround
Continuous Manufacturing Advantages

Agility
- Flexible batch sizes to respond to patient demand
- Decreased cycle times and fast turnarounds

Predictability
- High process reliability and robustness
- Decreased potential for quality related drug shortages

Quality Assurance
- Integrated measurement and control in real time
- Potential for decreased variability
- Inherently better mixing and segregation control
Traditional vs. New – Which would you choose?

Blending Operations

Traditional Batch

Continuous

Scale of mixing ≈ 100-200cm

Bin blender versus

Continuous blender

Scale of mixing ≈ 5-10cm

Content Uniformity Evaluation

Thief sampling versus

In-line monitoring

Spectroscopy

Continuous is clearly the more modern manufacturing approach!
MSD Strategy for Continuous Manufacturing of Solids Oral Drug Products

• MSD views Continuous Manufacturing as an enabler for modernized drug product manufacturing
  - Efforts ongoing in solid oral drug (SOD) products, small molecule drug substances, and biotechnology products (upstream & downstream)
• For SODs, MSD intends to demonstrate the technological and regulatory approaches via a proof-of-operations for an already approved drug designed with QbD and utilizing RTRT
  - MSD plans to file the new control strategy for the product worldwide
  - Experience gained will help shape MSD’s developing roadmap for future applications of Continuous Manufacturing
• Subsequent products could be other existing products or new molecular entities
Continuous Manufacturing Vision: To create a small, flexible, replicable, multiproduct facility operating in sync with customer demand

- ~1 billion tab/yr to serve worldwide markets
- < 90 day lead time formulation to patient
- Production at rate of consumption
- Footprint ~⅓ the size of a traditional facility
- Template for the future

Proof of Operations: Merck’s Continuous Direct Compression + Film Coating Facility
Continuous Oral Solid Dosage Process
Direct Compression + Film Coating (GEA Video)

LINKS:
https://www.youtube.com/watch?v=BqDdkMMQR9k
https://www.youtube.com/watch?v=FXRjt1RZ3CQ
Continuous Manufacturing and Real Time Release Testing

Real Time Release Testing (RTRT)

The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process parameters

ICH Q8(R2)

- Raw Materials
  - Vacuum Conveyors
    - Loss in Weight Feeders (n=4)
    - Loss in Weight Feeders (n=2)
  - Blender 1
    - Blender 2
      - Tablet Press
        - Coating Pans
          - Product tablets
  - Level sensor
  - At-line Disintegration (in lieu of dissolution)
  - Bruker TANDEM (weight, assay, hardness)
  - Residence Time Distribution Model
  - Segregation of potentially non-conforming tablets
  - NIR (for model development)
4-hr Tablet Continuous Process Run

**Tablet Weight**

- Startup checks
- Steady production
- Process pause
- Steady production

**Blend Composition & Tablet Assay**

- Blend Composition by NIR (% of target, 10s avg)
- Tablet Assay by HPLC (% of target)
- Start and stop of product collection

**Graphs**

- Tablet Weight graph showing average weight (±StDev) in mg, with upper control limit (UCL) and lower control limit (LCL).
- Blend Composition & Tablet Assay graph showing percent of target composition with time in minutes from 0 to 360.
Blending and Segregation
Steady State Uniformity Measurements

Comparison between optimized batch process and first two continuous process runs for tablets

The continuous process provides the same or less variability than batch
### MSD Experience – Technical Feasibility Studies

**Continuous Direct Compression**

<table>
<thead>
<tr>
<th>Product</th>
<th>Product A</th>
<th>Product B</th>
<th>Product C</th>
<th>Product D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch Process</td>
<td>Direct Compression</td>
<td>Direct Compression</td>
<td>Wet Granulation</td>
<td>Wet Granulation 10% Drug load</td>
</tr>
<tr>
<td>Drug Load Tablet Weight</td>
<td>33% 150mg</td>
<td>fixed dose combo 5%/20% 250mg</td>
<td>5% 200mg</td>
<td>10% 200 mg</td>
</tr>
<tr>
<td>Experiment time</td>
<td>1.5 days</td>
<td>2 days</td>
<td>3.5 days</td>
<td>Discontinued – Poor feeding</td>
</tr>
<tr>
<td>Demonstrated Throughput</td>
<td>25-40 kg/hr</td>
<td>25-50 kg/hr</td>
<td>25-40 kg/hr</td>
<td></td>
</tr>
<tr>
<td>API usage</td>
<td>25 kg</td>
<td>10 kg API A 42kg API B</td>
<td>12 kg</td>
<td></td>
</tr>
</tbody>
</table>

**Comparative Batch API Usage**

- ~800 kg
- ~100 kg/500 kg
- ~100 kg
Some Regulatory Considerations for Continuous Manufacturing

• Definition of “batch”
• Tracking of disturbances and segregation of potentially nonconforming material
• Flexibility of operation: batch size, manufacturing process, formulation
Definition of “Batch”

Batch (or Lot) – ICH Q7 Definition
• A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits.
• In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

General expectations:
• Batch can be based upon a pre-determined amount of material entering or exiting the system or by time
• Flexibility of batch size should be attainable within validated ranges (fixed per run)
• Raw material tracking is important if needed for batch traceability
Disturbances in Continuous Manufacturing

- Disturbances introduced in the system propagate and become wider and less intense as material travels down the line.

- The dynamic behavior of the system to disturbances is usually determined through Residence Time Distribution (RTD) Studies where a deliberate change is made, measured, and mathematically modeled.
Segregation of Potentially Non-Conforming Material

- Sections of the batch impacted by the disturbance can be segregated as “potentially non-conforming material”
  - Detected by in-line measurements or through process models
  - Can be removed from the system at a point that minimized downstream disturbances
  - May still be of acceptable quality; material is either discarded or investigated for potential acceptance
- Partial batch rejection is justifiable
  - Because of the high level of understanding and control, partial lot rejection does not implicate the quality of the whole batch
  - Typically, a minimum yield would be expected to be met to demonstrate a “state of control”
Flexibility needs for Continuous Manufacturing

**Flexible Batch Size**
- Validation of at least one batch at maximum batch size
- Continuous verification
- Flexibility to operate at varied run length / batch size

**Flexible Production Processes**
- Ability to have both batch and continuous manufacturing in the same application
- Could be same or different sites
- Consistent with ICH Q8/9/10 Points to Consider (2011)

**Flexible Formulations**
- Ability to adjust the formulation between batch and continuous processes to ensure robust processes
- Need to ensure same:
  - Product performance
  - Product appearance
  - Product label

To best serve our patients, we want the **flexibility** to deliver our medicines to any patient **worldwide, rapidly**
Continuous Manufacturing: Unprecedented Collaboration

- Multiple academic consortium
- Numerous conferences and workshops
- Manufacturing site visits (at industry and academic facilities)
- Several collaborative white papers
- Regulator-regulator discussions
- Early industry-regulator dialogue

ANVISA is encouraged to join in the conversations!
Continuous Manufacturing Resources

Academic Consortia Information:

• Engineering Research Center for Structured Organic Particulate Systems (C-SOPs):
  http://docs.wixstatic.com/ugd/0da418_05eee9e6a42e42bebceac64e7823ccfd.pdf

• Continuous Manufacturing and Crystallization (CMAC) Future Manufacturing Research Hub:
  http://docs.wixstatic.com/ugd/0da418_0125c4a7520543efb015755f2b56cfe9.pdf

• Research Center Pharmaceutical Engineering (RCPE):
  http://docs.wixstatic.com/ugd/0da418_d51e1e99dcec40e6a7c3b5e9edd5846d.pdf

• Synthesis and Solid State Pharmaceutical Centre (SSPC):
  http://docs.wixstatic.com/ugd/0da418_7ff8070cc02b47afbf0899a12a469fef.pdf

White Papers and Conference Summaries:

• 2014 – 1st International Symposium on Continuous Manufacturing of Pharmaceuticals (White Papers)
  https://iscmp2016.mit.edu/2014-white-papers

• 2016 ISPE Continuous Manufacturing Conference (Summary) – Pharm Eng, V 37 (3), 2017

• 2016 – 2nd International Symposium on Continuous Manufacturing of Pharmaceuticals (White Paper)
  https://iscmp2016.mit.edu/regulatory-white-paper

• 2017 – International Institute for Advanced Pharmaceuticals Summit (Summary)
  http://www.csops.org/malta-summit-summary
Conclusions

• Continuous manufacturing offers benefits to manufacturers and to patients through quality, agility and flexibility

• MSD is applying continuous manufacturing to an already approved product as a proof-of-concept in support of achieving World Class Supply

• Continued collaboration and communication between industry, academics and regulators will help to move this technology forward
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