Quality and Regulatory Considerations for Continuous API: a case study

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Disclosures

- The speaker is solely responsible for the content of this presentation
- The views presented here do not necessarily represent the views of GSK
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– Matt Popkin
Content

– GSK Manufacturing Technology Vision and Roadmap
– Continuous Manufacturing
– Continuous API manufacturing platform
– Quality and Regulatory considerations for Continuous Manufacturing
  ▪ GSK approach to Defining a Batch
  ▪ GSK approach to Defining State of Control for an API process
– Summary
Future State - GSK is pursuing an ambitious manufacturing technology vision and roadmap

In our vision of the **Future State**, GSK will have a more agile and responsive supply chain that delivers higher quality and more affordable products to patients at the point of need

- Small high-tech facilities
- Flexible and responsive
- Low Inventory
- Low CAPEX
- High Quality
- Visual performance
- Low Carbon

Flexible spaces that can evolve rapidly as manufacturing technology advances

Modular (continuous) manufacture

Smart intensive standard platforms

Slide from presentation by Mark Buswell, IFPAC Cortona 2014
Achieving the *Future State* represents a significant *Opportunity* for all stakeholders

**Patients**
- Increased access and availability to medicines driven by lower cost and increased supply chain security and reliability
  - Higher quality (and potentially more customised product design)

**Regulators**
- Less oversight and inspection to safeguard patient interest driven technology enable Quality by Design and robust manufacturing

**Reimbursement Agencies**
- More cost effective and economically sustainable healthcare driven by increased efficiency of manufacturing

**Industry**
- Reduced risk profile based on more reliable manufacturing and more agile and responsive supply chains
  - Enhanced economic efficiency (less inventory, lower capital, reduced cost of poor quality)
Continuous process. The material(s) and product are continuously charged into and discharged from the system, respectively, throughout the duration of the process.
Challenges

Internal

- Low equipment utilization
- Large batch equipment
- High inventories
- Labour and capital intensive
- Long lead times

External

- Increasing lower volume products
- Access to emerging markets
- Cost pressures
  - Reduce inventory
  - Reduce development timelines
- Accelerated development (breakthrough therapies)
Features and potential benefits of continuous manufacturing

**Development**
- Reduction in resources to support technology transfer and process scale-up
- Overall reduction in API consumption compared to batch equipment
- Simplified/robust process transfer and scale-up
- Increased process understanding

**Commercial**
- Smaller equipment and facilities
- Reduced inventory
- No storage/shipping costs for intermediates
- Rapid deployment to any part of world
- Better process control and robustness (lower batch-to-batch variations)
- Greater flexibility of batch size
- Fast response to market shortage
Continuous API Manufacturing Platform
Continuous API Manufacturing Platform

Conductivity sensor
uHPLC
+ > 100 process tags

Offline testing
CPPs
Operational controls-
Divert to Waste Valves

MVA Monitoring
Control system
International Symposium on Continuous Manufacturing of Pharmaceuticals

Held at MIT 20-21st May 2014, sponsored by MIT and CMAC
200 participants from industry, academia, regulatory authorities and equipment manufacturers
8 white papers developed at the symposium published in Journal of Pharmaceutical Sciences, March 2015, Vol 104 (3)

1. Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Work-Up and Isolation of Drug Substance
2. Achieving Continuous Manufacturing for Final Dosage Formation: Challenges and How to Meet Them
3. Regulatory and Quality Considerations for Continuous Manufacturing
4. Continuous Bioprocessing
5. Equipment and Analytical Companies Meeting Continuous Challenges
6. Control Systems Engineering in Continuous Pharmaceutical Manufacturing
7. Future supply chains enabled by continuous processing –opportunities and challenges
8. How Development and Manufacturing will need to be structured –Heads of Development/Manufacturing
# Quality and Regulatory considerations for continuous manufacturing

<table>
<thead>
<tr>
<th>Control Strategy</th>
<th>Manufacture product of the intended quality in a reproducible way</th>
</tr>
</thead>
<tbody>
<tr>
<td>API and Product Specifications</td>
<td>Same for batch and continuous processes</td>
</tr>
<tr>
<td>Start-up and shut-down</td>
<td>Must be defined for each continuous process</td>
</tr>
<tr>
<td>Process monitoring and sampling</td>
<td>Opportunity to incorporate more direct real-time analytics</td>
</tr>
<tr>
<td>Raw materials and intermediates</td>
<td>May require additional raw material control</td>
</tr>
<tr>
<td>Product collection or rejection</td>
<td>Criteria will be defined during temporary upsets or disturbances and start-up and shut-down</td>
</tr>
<tr>
<td>Batch definition</td>
<td>Defined fraction of the production, either a fixed quantity or an amount produced in a fixed time</td>
</tr>
<tr>
<td>Material traceability</td>
<td>Link the raw materials to a specific quantity of product</td>
</tr>
<tr>
<td>Risk assessment and failure modes</td>
<td>In line with QbD principles, apply to both batch and continuous processes</td>
</tr>
<tr>
<td>DS &amp; DP Stability</td>
<td>Stability requirements are the same for batch and continuous process</td>
</tr>
</tbody>
</table>
Essential Concepts of Continuous Processing

- **Residence time**
  - Ratio of volume of reactor system to flow rate of materials through reactor system
  - Changes in material input have delayed response in output!

- **Dispersion**
  - Instantaneous change at input mixes forwards and backwards
  - Dispersion is a measurable characteristic of the reactor system

- **Productivity Rate**
  - Equipment intended to perform at 80% to 120% of nominal annual capacity requirements
  - Impacts Residence time and potentially mixing and Dispersion
Batch Definition
GSK accepted definition and implications

“A Batch is an amount of material prepared at Controlled State, independent of volume (mass), time of collection or intervening process disturbances, which is processed to product within the demonstrated stability time of the material (based on start of collection)”

“Regulatory and Quality Considerations for Continuous Manufacturing” white paper explains the four definitions for a batch in a continuous operation. For this case study GSK has chosen the above batch definition.

This definition provides maximum flexibility for all potential continuous processes but requires additional case-by-case amendment for specific projects

Each case by case amendment simplifies some aspects of process operation but comes at a cost of complexity elsewhere
Batch Definition on Example Product
Potential Options – all acceptable

1. Defined by volume (e.g. 200L)
   - Uniform size; simplified development and stock management
   - Variable time; complicated pedigree

2. Defined by time (e.g. 24h)
   - Simplified operations and batch paperwork
   - Variable scale; scalability risk for isolation; complicated pedigree

3. Defined by input batch
   - Aligned to one input; simplifies pedigree (slightly)
   - Other inputs not factored in pedigree; variable volume; complicated pedigree
**Batch Definition – Potential Options**

All acceptable, BUT for example product Option 1 is optimal

<table>
<thead>
<tr>
<th>Option</th>
<th>Definition</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Defined by volume (e.g. 200L)</td>
<td>Uniform size; simplified development and stock management</td>
<td>Variable time; complicated pedigree</td>
</tr>
<tr>
<td>2</td>
<td>Defined by time (e.g. 24h)</td>
<td>Simplified operations and batch paperwork</td>
<td>Variable scale; scalability risk for isolation; complicated pedigree</td>
</tr>
<tr>
<td>3</td>
<td>Defined by input batch</td>
<td>Aligned to one input; simplifies pedigree (slightly)</td>
<td>Other inputs not factored in pedigree; variable volume; complicated pedigree</td>
</tr>
</tbody>
</table>
Batches implicated in a Quality deviation can implicate batches prepared before and/or after introduction of the deviation.

Preferred as implicates forward batch only.
Batch Pedigree
Defined by volume

<table>
<thead>
<tr>
<th>200 L Collection</th>
<th>Days input lasts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Reagent 1 Feed Bx 1</td>
<td></td>
</tr>
<tr>
<td>Reagent 2 Feed Bx 1</td>
<td></td>
</tr>
<tr>
<td>Reagent 3 Bx 1</td>
<td></td>
</tr>
<tr>
<td>Reagent 4 Bx 1</td>
<td></td>
</tr>
<tr>
<td>Reagent 5 Bx 1</td>
<td></td>
</tr>
<tr>
<td>Reagent 6 Bx 1</td>
<td></td>
</tr>
<tr>
<td>Gas cylinder 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
</tr>
<tr>
<td>Bx 2</td>
<td></td>
</tr>
<tr>
<td>Bx 2</td>
<td></td>
</tr>
<tr>
<td>Reagent 3 Bx 2</td>
<td></td>
</tr>
<tr>
<td>Reagent 4 Bx 2</td>
<td></td>
</tr>
<tr>
<td>Reagent 5 Bx 2</td>
<td></td>
</tr>
<tr>
<td>Reagent 6 Bx 2</td>
<td></td>
</tr>
<tr>
<td>Gas cylinder 2</td>
<td></td>
</tr>
</tbody>
</table>

Each change over leads to dispersion of that input blurring pedigree further

For a telescoped end-to-end process with this many feeds, there will NEVER be a clean solution!
Batch Pedigree
Defined by volume: Investigation and Recall

Essential to have efficient time stamping of feed change over

Recall will implicate multiple batches depending on origin of Quality Deviation
Control Strategy for continuous manufacturing

Manufacturing process produces product of the intended quality in a reproducible way

- Traceability
- Specifications
- Product collection or rejection
- Uniform quality and character of product
- Process monitoring and sampling
- Raw materials and intermediates
- Risk assessment and failure modes
- Equipment
- State of control

Control Strategy
State of Control

• In accordance with the definition provided in Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production, Journal of Pharmaceutical Innovation, Sau L. Lee et al (March 2015), **GSK defines state of control as: Operating within conditions where controls consistently assure product quality and continued process performance.**

• May be interpreted differently for specific products and platforms:
  One approach is to operate within conditions that assure product quality (i.e., within the registered design space)
  – The design space will consist of a multi-dimensional combination of registered ranges for CPPs and PPs and input material attributes.
Attaining state of control at Start-up

When do you call it?

- Flow rate case dependent
- % from set point, ranges
### Example CPP’s from Stage 1 of a Continuous Process

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Set point</th>
<th>Proposed variance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 productivity (Rgt 1 soln flow) rate</td>
<td>30 gmin⁻¹</td>
<td>± xx% (± yy gmin⁻¹)</td>
</tr>
<tr>
<td>Input 1 in DMAc Solution concentration</td>
<td>25% w/w</td>
<td>(± 1.5% w/w)</td>
</tr>
<tr>
<td>Input 2 in DMAc Solution concentration</td>
<td>15% w/w</td>
<td>(± 1.25% w/w)</td>
</tr>
<tr>
<td>Stage 1a residence time</td>
<td>controlled by other parameters</td>
<td>&gt;10 min</td>
</tr>
<tr>
<td>Relative Input 2 in DMAc flow rate</td>
<td>1.0 rel. gmin⁻¹</td>
<td>(± 0.070 rel. gmin⁻¹)</td>
</tr>
<tr>
<td>Stage 1b residence time</td>
<td>controlled by other parameters</td>
<td>&gt;10 min</td>
</tr>
<tr>
<td>Stage 1 temperature</td>
<td>25 °C</td>
<td>± 2.5 °C</td>
</tr>
<tr>
<td>Stage 1 pressure</td>
<td>4 barg</td>
<td>&gt; 3 barg</td>
</tr>
<tr>
<td>N₂ flow rate</td>
<td>2 Lmin⁻¹</td>
<td>± 50% (± 1 Lmin⁻¹)</td>
</tr>
</tbody>
</table>
Ensuring State of Control

• Example controls in order to assure state of control (performance within the design space):
  – Alarms at tighter ranges than design space limits for CPPs (pressure, temperature, flow rates)
  – Monitoring and multi-variate modelling of process equipment performance of non-quality related parameters (e.g., pump demand, differential pressures)
Start Up State of Control

• Example start-up procedure:
  – Each part of the process will be brought online in sequence (stage 1 -> stage 2 -> stage 3)
  – During each start-up procedure, material will be fed to waste until defined state of control has been reached.
  – Once a state of control (i.e. operation within the design space ranges) has been achieved, material will continue to be fed to waste until material produced out of state of control has been purged from the reactor (set point #3 in example).
  – Only after this condition has been met may material be fed to the subsequent unit operation (i.e. Stage 1 start-up and control complete and Stage 2 start-up begun).
  – A single time for each reactor (for a given productivity rate) can be defined according to the equation below.

\[
\text{Time before forward processing} = \text{residence time at 80\% productivity rate} + \text{back mixing time}
\]
Forward Processing
Residence Time, Productivity Rate and Back Mixing

Residence time \( (s) = \frac{\text{Volume of reactor (mL)}}{\text{Volumetric flow rate (mL/s)}} \)

\[ = \frac{\text{Volume of reactor (mL)} \times \text{density of material (g/mL)}}{\text{Mass flow rate (g/s)}} \]

Productivity rate \( = \frac{\text{Operational flow rate}}{\text{Nominal flow rate}} \times 100 \)

Time before forward processing

\[ = \text{residence time at 80% productivity rate} + \text{back mixing time} \]
# Forward Processing Time

Real world example for sequential start-up times

<table>
<thead>
<tr>
<th>Reactor¹</th>
<th>Residence time at 80% productivity rate (min)</th>
<th>Forward and back mixing (min)</th>
<th>Time before starting next feed (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>20.4</td>
<td>2.3</td>
<td>22.7</td>
</tr>
<tr>
<td>2</td>
<td>15.3</td>
<td>2.3</td>
<td>17.6</td>
</tr>
<tr>
<td>3a</td>
<td>59.3</td>
<td>4.4</td>
<td>63.7</td>
</tr>
<tr>
<td>Reactor 1 and Reactor 2</td>
<td>59.3</td>
<td>4.4</td>
<td>63.7</td>
</tr>
</tbody>
</table>
Productivity Rate

\[ Time \text{ before diverting} = residence \text{ time at } 120\% \text{ productivity rate} - back \text{ mixing time} \]

\[ Time \text{ before recollection} = residence \text{ time at } 80\% \text{ productivity rate} + back \text{ mixing time} \]

- Precise conditions will be platform/equipment specific, not product specific
- Must be defined and approved in the file
Questions?
Back-up Slides
Control Strategy for continuous manufacturing

Manufacturing process produces product of the intended quality in a reproducible way

State of control

Raw materials and intermediates

Risk assessment and failure modes

Equipment

Specifications

Product collection or rejection

Uniform quality and character of product

Traceability

Process monitoring and sampling

Control Strategy
Example Deviations

<table>
<thead>
<tr>
<th>Type of Disturbance</th>
<th>Impact</th>
<th>Action</th>
<th>Likely Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momentary spiking of process parameter with return to set point</td>
<td>Low</td>
<td>Confirm time-delay for parameter not exceeded</td>
<td>Electrical surges and/or vibration, bubbles in process stream</td>
</tr>
<tr>
<td>Prolonged spiking of process parameter or Change to stable performance away from set point</td>
<td>Medium</td>
<td>Investigation; divert to waste/quarantine if outside Design Space</td>
<td>Meter failure or process input change</td>
</tr>
<tr>
<td>Continual drift from parameter set point</td>
<td>High</td>
<td>Diversion to waste leading to plant shutdown</td>
<td>Key component failure (filter blockage, pump motor failure, etc)</td>
</tr>
</tbody>
</table>
Considerations for Deviations

- Length of time before alarm is triggered
- Length of time before material is diverted to waste?
- Quarantine considerations and reintroduction criteria?
- Time before re-collection?
Summary

- Regulatory expectations for quality assurance and reliable manufacturing are the same for both batch and continuous processes
- Regulatory and quality framework is developing – still work to be done
- Develop an appropriate control strategy for continuous process
  - Define state of control
  - Define start-up/shut-down procedure
- Opportunities to design appropriate controls in-line/at-line (move away from end product testing)
- GSK are also developing API continuous manufacturing processes