Quality by Design (QbD) for the Continuous Manufacturing of Solid Oral Dosage Forms

David Emiabata Smith, 16th September, 2014
Vertex Continuous Manufacturing Approach
Vertex’s Path to Continuous Manufacturing

Individual unit operations allows manufacture in a “discontinuous” mode

- Wet granulation
- Utilized for process development, clinical, and formal stability

ConsiGma-25 unit allows for continuous batch manufacture

- Wet granulation, fluidized bed drying & compression
- Utilized for process development, clinical, and formal stability

Development & Launch Rig allows for fully continuous manufacture

- Raw material blending to tablet film coating
- PAT equipped: process monitoring /control & RTRT
- Utilized for process development, clinical, and formal stability
Vertex’s Continuous Manufacturing Rig

Much Smaller Footprint

- Smaller scale equipment
- All unit ops in one room

Coated Tablets Out
Continuous Monitoring, Control & RTRT
Continuous Manufacturing and PAT are Ideally Suited for the CMC Development of Breakthrough Therapies

Early finalization of formulation on commercial scale equipment
- Commercial product equivalent to product used for clinical development

“Data rich” commercial design space can be explored with limited API as part of a Quality by Design (QbD) approach

Impact of upstream variables on downstream process and final product quality easier to assess

Highly consistent product quality is produced with continuous monitoring and control

CM facilitates streamlined QbD development and NDA submission
Vertex Approach to Quality by Design (QbD)
1. Define Quality Target
   Product Profile

2. Identify Potential CQAs

3. Perform Initial Process and Material Risk Assessment

4. Determine Criticality

5. Establish Design Space and Control Strategy

6. Perform Process Risk Assessment

7. Continual Improvement

- **Initial risk assessment**
  - Risk based on SME evaluation and existing data on probability of occurrence
  - Determines which process parameters and material attributes need to be studied

- **Determine criticality**
  - Set desired manufacturing range and thresholds for criticality
  - Design and execute experiments
  - Develop process models and assess criticality

- **Establish Design Space & Control Strategy**
  - Define Design Space Limits (DSL)
  - Material attributes and CPP’s
  - Define IPCs
  - Finalize specifications
Criticality Determined using Pre-defined Criteria

- Desired Manufacturing Range (DMR, $\Delta X$)
  - Commercially relevant range of a process parameter
- Threshold for Criticality
  - The minimum change in a CQA considered to be a significant impact
  - Determined by a team of experts
  - Generally set as a small fraction of the CQA’s acceptance range
- Experiments and Process Models
  - Multivariate experiments across the DMR
  - Statistical analysis of main effects and interactions result in process models
- Criticality Analysis
  - Determine effect on CQA ($\Delta Y$) across the DMR
  - If $\Delta Y$ exceeds the Threshold, the process parameter is critical
Example of Criticality Assessment

• IF no statistically significant effect → Non-Critical
• IF significant and $\Delta Y < \text{Threshold}$ → Non-Critical
• IF significant and $\Delta Y \geq \text{Threshold}$ → Critical
Approach to Setting Design Space Limits

- The DMR becomes the DSL if a process parameter does not cause a CQA to fail across the DMR
  - DSL is reduced if the parameter can cause failure of a CQA
  - Equipment limitations can also limit the DSL
- For materials, if variability of an attribute within the specifications (DMR) causes a CQA to fail, appropriate specifications will be put in place
Example of High Level Approach to QbD Experiments

- Designed experiments with individual unit operations
  - All processes, except drying and milling

- Designed experiments with grouped unit operations
  - Granulation, drying, and milling

- Process models developed from all unit operation experiments to assess criticality

- Combined predictive models developed to confirm findings with continuous experiments across DMR

- Fully continuous experiments using entire DLR
  - Component feeding through film coated tablets

- Next slides show example of unit op screening experiments, grouped unit ops experiment, and outcome of confirmation experiments
Example: Screening Study for Wet Granulation

- Initial risk assessment wet granulation
  - Potential impact on CQAs of appearance, degradation products, dissolution, content uniformity, and physical form
- 20 experiment design including material attributes and process parameters on commercial scale equipment

- Summary of results
  - No impact on CQAs except:
    - API A $D_{50}$ affects milled granule fines, thereby impacting dissolution
    - API B SDD bulk density impacts dissolution

<table>
<thead>
<tr>
<th>Material Attributes</th>
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<tbody>
<tr>
<td>API A $d(0.5)$ (µm)</td>
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<tr>
<td>API B SDD bulk density (g/cc)</td>
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<td>Formulation (1/2)</td>
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<tr>
<th>Process Parameters</th>
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<tr>
<td>Water added during TSWG (%)</td>
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<tr>
<td>Degree of fill (%)</td>
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<tr>
<td>Line rate (kg/hr)</td>
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Example: Experimental Design Grouped Unit Ops

- Design includes material attributes, granulation, FB drying and milling
- Initial risk assessment on combined processes
  - Potential impact on CQAs of appearance, assay, degradation products, dissolution, content uniformity, physical form, and water content
- 20 experiments on commercial scale equipment
  - Separate unit ops to allow sampling between processes
  - Incoming material attributes defined as “granule properties”
Example: Experimental Design Grouped Unit Ops

• Summary of Results
  – No impact on CQA’s except:
  – Drying parameters significantly affect CQA of water content
  – API A dissolution affected by granule properties, water added during granulation, and mill speed
  – API B dissolution affected by granule properties, water added during granulation, & dryer inlet temperature and airflow

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<th>Material Attributes</th>
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<tr>
<td>Granule properties</td>
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<td>Formulation (1/2)</td>
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<td>Line rate (kg/hr)</td>
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<td>Fluid bed dryer inlet temperature (ºC)</td>
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<td>Fluid bed dryer inlet air flow (m³/hr)</td>
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<td>Fluid bed dryer fill time (min)</td>
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<td>Mill speed (rpm)</td>
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Drying Time Constrained due to Equipment Limitations

- Upper drying time limit dependent on fill time of FBD
  - Cell has to be empty before next product mass can be charged
  - For “short” FB dryer fill time, the max drying time is 16 minutes
  - For “long” FB dryer fill time, the max drying time is 22 minutes

- Drying time was regressed against variables studied
  - Wet product mass has largest impact on drying time
    - Combination of fill time, water added, and line rate
API B Dissolution Affected by Material Attributes and Process Parameters

- Largest effect from API B SDD bulk density
- Decreased dissolution with water added during granulation
- Increased dissolution with mill speed
API A Dissolution Affected by Material Attributes and Process Parameters

- Decreased dissolution with water added during granulation
- Increasing dissolution with API A $D_{50}$
  - Consistent with screening study
- Drying parameters showed impact on dissolution when water added during granulation was high
Confirmation Experiments Spanned DMR

• Six development batches were processed continuously on the DLR

• Significant parameters from the unit ops studies were varied
  – See table below

• Core tablet samples were tested and projected on the combined unit ops dissolution models

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<tr>
<th>Formula</th>
<th>Granule Property</th>
<th>Blender 1 Speed</th>
<th>Water Added</th>
<th>Line Rate</th>
<th>Inlet air flow</th>
<th>Inlet air temp</th>
<th>FBD Fill time</th>
<th>Mill speed</th>
<th>Blende 2 Speed</th>
<th>Press speed</th>
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Unit Ops Models Representative for Continuous Runs

Process models appropriate to assess criticality and define DSL

- Process models generated from combined data sets
- Predicted dissolution values for API A and API B
- Results show good comparison between unit ops and continuous runs
Process Control Strategy (Summary)

**Blending (IG Phase)**
- Parameters: - Line Rate - Blender speed
- IPC: - Individual Components Feed Rate

**Granulation**
- Parameters: - Line Rate - Binder Feed Rate

**Drying**
- Parameters: - Line Rate; - Solution Pump Rate - Inlet Air Temp. & Flow Rate - Dryer Fill Time - Drying Time
- IPC: - Product Temp. - Moisture Content (NIR)

**Milling**
- Parameters: - Mill Speed

**Blending (EG Phase)**
- Parameters: - Granule Feed Rate
- IPC: - Granule Potency (NIR)

**Core Compression**
- Parameters: - Compression Force - Press Speed
- IPC: - Individual Components Feed Rate - Blend Potency (NIR)

**Film-Coating**
- Parameters: - Pan Load - Spray Rate & Spray Time - Inlet Air Flow Rate - Polish Time
- IPC: - Weight - Thickness - Hardness
Conclusions

• Vertex Approach to CM Development
  – CM can provide opportunity for accelerated development - Ideal for Breakthrough Therapies
  – Sequential unit ops and fully continuous experiments can provide opportunities for streamlined QbD development
  – Data rich design space can be developed using commercial scale equipment with limited API

• Vertex Approach to QbD
  – Risk assessment and prior knowledge determines studies needed
  – Defining DMR and criticality thresholds up front, before experiments, eliminates uncertainty in identifying CPP’s
  – Process Models (from DoE’s) were used to assess criticality
  – Design Space Limits (DSL) were determined by utilizing DoE’s and resulting process models (across the DMR)
Acknowledgements

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  – CMC Regulatory
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  – Facilities

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