SAMPLING AND CONTROL: APPROPRIATE CONTROL STRATEGIES FOR CONTINUOUS DIRECT COMPRESSION

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Outline

- MSD’s Approach to Continuous Manufacturing
- PAT Options: RTD Process Model and Blend NIR
- Process Model for Material Tracking and Rejection
- Sampling for Control and Release
- Benefits to Patients and Company
- Moving Towards Worldwide Acceptance of CM
## MSD’s Approach to CM for Oral Solid Doses

<table>
<thead>
<tr>
<th>Why Continuous Manufacturing (CM)?</th>
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<tbody>
<tr>
<td>High assurance of product quality</td>
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<tr>
<td>Lower cost</td>
</tr>
<tr>
<td>Flexibility to meet changing demand</td>
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</table>

<table>
<thead>
<tr>
<th>How we’ll start</th>
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<tbody>
<tr>
<td>Leverage extensive experience with an existing product</td>
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<tr>
<td>Build upon existing RTRT, raw materials monitoring and QbD approaches</td>
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<tr>
<td>Conduct short duration runs with efficient, frequent changeovers between strengths</td>
</tr>
<tr>
<td>Use batch size flexibility to match changing market demand</td>
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<table>
<thead>
<tr>
<th>What we ask of regulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>During global industry shift from batch \rightarrow CM, alternate production methods are required in parallel</td>
</tr>
<tr>
<td>Help us ensure uninterrupted product delivery to patients</td>
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<table>
<thead>
<tr>
<th>What comes next</th>
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</thead>
<tbody>
<tr>
<td>Conversion of other marketed products</td>
</tr>
<tr>
<td>Addition of other continuous technologies (e.g. granulation)</td>
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<tr>
<td>Efficient development and launch of new products</td>
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How We’ll Use CM to Improve Supply Chains

One batch, every cycle, every strength
- Flexible batch size matched to customer demand
- Fast changeovers between products

High demand products
- Higher quality and efficiency due to elimination of start/stop

Low demand products
- Increases shelf life by eliminating overproduction and inventory hold

Volatile demand products
- Avoid shortages by reacting quickly to changes in demand

Monthly vs Weekly Inventory Levels

Monthly
- Deliveries
- Inventory
- Time: Jan, Feb, Mar
- Cycle Stock
- Safety Stock

Weekly
- Inventory
- Time: Jan, Feb, Mar
- Cycle Stock
- Safety Stock
Existing Product & Process Description

Commercial Characteristics

• Available >10yr in most markets
• Multiple strengths
• High overall volume
• Volume dependent on strength
MSD’s Continuous Manufacturing Process: GEA CDC-50, Consigma Coater, Bruker TANDEM
Mapping Different Approaches to CM

- Janssen
- Vertex
- Pfizer
- BMS
- MSD
- Roche
- Bayer
- AZ
- GSK
- Lilly
- Novartis
- Sanofi

Equipment Flexibility / Portability

Portfolio Development Stage (Product Life Cycle)

System Complexity
Comprehensive Control Strategy

Enterprise Resource Planning

Site Manufacturing Execution System

PAT Management System

Supervisory Control and Data Acquisition

PAT Instrumentation

Automatic Controls

Batch defined by number of accepted tablets

Process

Solids Handling Unit

Loss in Weight Feeders (x6)

Blender 1

Blender 2

Tablet Press

Coater 1

Coater 2

Distribution Arm

Finished Product Release

On-Line Tablet Test (W/T/H, Assay by NIR)

Refill

Mass Flow Rates, Blend NIR (development)

Level

Diverted Tablets

Metal detected

Disposition Evaluation

OOS Check

Appearance Check

Suspension/Air Flow Temp, RH

Statistical Process Control, model checks, event checks

Process Validation/Evaluation

Manual controls and procedures

Diversion (potentially non-conforming)

Materials Management

Raw Materials Monitoring

Monitoring

RTD Process Model (potency)

Speed

Speed

Manual controls and procedures

Process Validation/Evaluation

Diversion (potentially non-conforming)

Materials Management

Raw Materials Monitoring

Monitoring
Background on RTD and NIR

1. Perform Experiment
2. Fit Model
3. Check Model Predictions

Blender 1

Blender 2

Entire System

E(t) (1/min)

Time (min)

NIR Tablet Data

Model

API Concentration (% of Target)

Blend NIR

Feeder Output (% API)

Tablet HPLC
Experiments Using Redundant PAT Demonstrate Low Risk If Single Method Used
“All things being equal, the simplest solution tends to be the best one.”

William of Ockham
# PAT Summary: Examining Operations & Robustness of RTD Model and Blend NIR

<table>
<thead>
<tr>
<th>Factor</th>
<th>RTD Process Model</th>
<th>Blend NIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method Basis</strong></td>
<td>First principles calculation</td>
<td>Empirical multivariate calibration</td>
</tr>
<tr>
<td><strong>Scale of Scrutiny</strong></td>
<td>Average prediction for &gt;10 tablets</td>
<td>Sample size ≈ 1/4 tablet</td>
</tr>
<tr>
<td><strong>Prediction Location</strong></td>
<td>Predicts blend and tablet API concentration</td>
<td>Measures API concentration in blend at feed frame entrance</td>
</tr>
<tr>
<td><strong>Model Robustness</strong></td>
<td>Sensitive to material properties and process parameters that affect flow or blending</td>
<td>Sensitive to physical properties and process parameters that affect sample presentation</td>
</tr>
<tr>
<td><strong>Blind Periods</strong></td>
<td>Flow rate assumption during ~3 s feeder refill</td>
<td>No measurement during ~2 min probe cleaning</td>
</tr>
<tr>
<td><strong>Signal to Noise Ratio</strong></td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Fouling / Equipment</strong></td>
<td>Low risk to feeder load cells</td>
<td>Dependent on adhesion properties of product</td>
</tr>
<tr>
<td><strong>Model Maintenance Requirements</strong></td>
<td>Updates required based on bulk density, flowability, or process parameter changes</td>
<td>Updates required based on probe, spectrometer, material property or process parameter changes</td>
</tr>
<tr>
<td><strong>Universal Applicability</strong></td>
<td>Can predict concentration of any component as needed</td>
<td>Applicable for components with characteristic NIR bands with sufficient specificity</td>
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</table>
RTD vs. NIR Deep Dive

Sample Fraction per Second

RTD vs. NIR

Signal to Noise Ratio Compared with HPLC Results

Assumptions:
- Blend NIR
- Feeder Output (% API)
- RTD Model Prediction
- HPLC
RTD vs. NIR Deep Dive

Model Accuracy vs. HPLC

- **API Feeder**
  - Method error ≈ 0.46

- **RTD Model**
  - Method error ≈ 0.08

- **Blend NIR**
  - Method error ≈ 1.98

- **Tablet NIR**
  - Method error ≈ 1.55

- **Tablet HPLC**
  - Method error ≈ 0.76

Model Maintenance

- **50kg/hr, 315rpm Blender 1, 300rpm Blender 2**
- **NIR Predicted API Concentration (%)**
  - **RTD Model - June, 50mg**
  - **RTD Model - November, 100mg**
  - **Tablet HPLC - June, 100mg**
  - **Tablet HPLC - November, 100mg**

- **Time (min)**
  - **Jan-15**
  - **Nov-15**
  - **Jun-16**
RTD Model for Raw Material (RM) Tracking
Model provides exquisite ability to track RM from start to end

Tablet Diversion System:
- Raw Materials
- Feeders
- Blenders
- Tablet Press
- Tablet Coater
- Diverted Tablets
- Bulk Tablets

Material Tracking System:
- Time (min)
- Mass Flow Rate = 60 kg/hr
- Drum Size = 30kg

<table>
<thead>
<tr>
<th>Time</th>
<th>RM Lot 1</th>
<th>RM Lot 2</th>
<th>Drum</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>RM Lot 1</td>
<td>RM Lot 2</td>
<td>Drum A</td>
</tr>
<tr>
<td>2</td>
<td>RM Lot 1</td>
<td>RM Lot 2</td>
<td>Drum A</td>
</tr>
<tr>
<td>10</td>
<td>RM Lot 2</td>
<td></td>
<td>Drum B</td>
</tr>
<tr>
<td>15</td>
<td>RM Lot 2</td>
<td></td>
<td>Drum B</td>
</tr>
</tbody>
</table>
Implementation of the RTD Process Model for Material Rejection

API Concentration from Feeders
RTD Model Prediction at Tablets
Tablet Action Limit
Tablet Rejection Limit for Model Prediction

- API spike
- Yellow shaded regions indicate conservative diversion of tablets
- Red shaded region indicates diversion of tablets predicted to be outside of acceptable limits

(a) beginning of tablet rejection
(b) first predicted average tablet potency outside acceptable limits
(c) predicted average tablet potency returns to acceptable range
(d) tablet rejection ends

Yellow shaded regions indicate conservative diversion of tablets
Red shaded region indicates diversion of tablets predicted to be outside of acceptable limits
Preliminary Thoughts on Sampling During CM

- Most monitoring & control loops operate at f ≥ 1Hz
- TANDEM used for control and release: weight / hardness / composite assay
- Sampling must be statistically representative
- If process is capable (Cpk>1.3) and in state of control:
  - Strict criteria on sampling interval not needed
  - Risk between samples is to the business, not the patient
- Monte Carlo modeling will inform final decision
Moving Towards Acceptance of Continuous Manufacturing Technology

What Industry Can’t Do

– We cannot run different control strategies for different regulatory regions
– We cannot maintain different RTRT models for same test for different markets
– We cannot develop a single technology platform without assurance of global acceptance

We embrace O’Connor, Yu and Lee’s proposal (Int. J. Pharm. 509 (2016) p. 492)
– “international harmonization of approaches for expediting the global adoption of emerging technologies.”

An Ethical Dilemma?

– We want the highest assurance of quality of drugs for patients
– We want the most economical manufacturing to benefit our shareholders
– We want to be able to supply all markets

Failure to gain approval of any of these components in any regulatory region sinks the entire ship
To best serve our patients, we want the **flexibility** to deliver our medicines to any patient **worldwide**.
Conclusions

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

Collaboration is needed to overcome obstacles and allow patients to reap the benefits of CM
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