Novartis Approach to Continuous Manufacturing (API and Drug Product)

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Outline

• Motivation

• Blue Sky Vision and Approach

• Benefit and Examples
From Batch to Continuous Manufacturing

A radical transformation in operational performance

- **Operations**: Major efficiency gains have been implemented. Additional quantum leap efficiency gains are unlikely
- **Compliance**: Many manual checks, deviations/investigations, difficult root cause analysis
- **Quality**: Reliance on in process and end product testing

**TPT** = Troughput time
**OAE** = Overall asset effectiveness

Traditional: 200-300 days
Lean: 100-200 days
Continuous: <10 days

2005 - 2010 - > 2015

Quality: Seamlessly integrated and well characterized processes

Operations:
- Major efficiency gains have been implemented. Additional quantum leap efficiency gains are unlikely
- Compliance:
  - Many manual checks, deviations/investigations, difficult root cause analysis
- Quality:
  - Reliance on in process and end product testing
Blue Sky Vision: A Radical Transformation

11 Research and Technology Areas to create a modular technology toolbox

1. Bench Scale unit at MIT to study process integration, steady state & control strategy

→ the ultra LEAN Manufacturing

Continuous reaction and separation of DS
Integration DS and DP
DP finishing

End to end quality by design integration
Novartis-MIT Blue Sky Vision

Continuous Manufacturing: A radical transformation

- Full Integration of Quality by Design concept
- Quality is assured by designing quality control measurements into the process system
- A new product development process integrating chemistry and pharmaceutics
- New methodologies, technologies and equipment
- New streamlined facility lay-outs
- Major changes in technical skills and mindset
- Major changes in organizational structures for cohesive development, quality and technical operations
Quality by Design
Better process and product quality through increased process understanding

Process Understanding Pyramid

1. Principles
2. Mechanistic Understanding
3. MVDA Models
4. Empirical Understanding
5. Decisions Based on Univariate Approach
6. Data Derived From Trial-N-Error Experimentation

From batch to continuous manufacturing
Approach: Integration of chemistry and engineering

- Implementation of principles of continuous flow synthesis (e.g., recycling, membrane separation, high temperature and pressure regimes)
- Chemically compatible, easily integrated continuous flow reactors with operation conditions that can be scaled from research to production
- Knowledge based design, in-line monitoring and optimization approaches of synthesis, workup, and purification steps
- Different scale flow reactors to validate scaling principles
- Immobilization and recycling of catalysts
- Development of workup techniques for integration with reaction sequences and when economically advantageous, recycle of regents
- Methods for handling (addition, formation, separation,…) of solids in continuous flow reactors
Advantages of Flow Chemistry

- Quality by Design (QbD): Integrated continuous flow reactors, work-up, and process analytics & control
- Safe handling of highly reactive systems and reduced quantities of hazardous materials
- Limited unstable intermediate accumulation
- Less raw material (solvents, starting materials, catalysts)
- Faster and predictable scale-up from efficient small continuous flow reactors
- Opportunities for reaction chemistry and conditions not easily accessed in batch
- Potential for “greener” and more sustainable operation
Upstream – CM Main Objective

Faster reaction times and higher yield

Feed

Reaction

Quench

Residence Time

Product
**Downstream CM Main Objectives**

*Reduce number of unit operations*

<table>
<thead>
<tr>
<th>Batch Process</th>
<th>Multiple CM Blue Sky Technology Approaches...</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crystallization</td>
</tr>
<tr>
<td>2</td>
<td>Isol./Drying</td>
</tr>
<tr>
<td>3</td>
<td>Milling/Sieving</td>
</tr>
<tr>
<td>4</td>
<td>Dispensing</td>
</tr>
<tr>
<td>5</td>
<td>Formation of Granules</td>
</tr>
<tr>
<td>6</td>
<td>Drying</td>
</tr>
<tr>
<td>7</td>
<td>Milling/Sieving</td>
</tr>
<tr>
<td>8</td>
<td>Blending</td>
</tr>
<tr>
<td>9</td>
<td>Forming</td>
</tr>
<tr>
<td>10</td>
<td>Coating</td>
</tr>
</tbody>
</table>
Expected Benefits

Continuous Manufacturing: A radical transformation

Significant benefits can be expected:

- Increase of product quality enabled by consistent application of QbD and steady state operation
- Reduction of asset footprint (40-90%)
- Reduction in capital expenditure (25-60%)
- Reduction of operational costs (25-60%)
- Reduction of inventories
- Reduction of overall drug substance and drug product development times, improving time to market
## Example 1: Reduction in Development Time

<table>
<thead>
<tr>
<th>Today</th>
<th>CM Setup</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS</td>
<td>Upstream</td>
</tr>
<tr>
<td><strong>Bench/Lab</strong></td>
<td>Formulation / Synthesis development &amp; Process development</td>
</tr>
<tr>
<td><strong>Pilot</strong></td>
<td>Process Development &amp; Scale up</td>
</tr>
<tr>
<td><strong>Launch</strong></td>
<td>Process Validation</td>
</tr>
</tbody>
</table>

### Table:
- **Today**:
  - DS: Bench/Lab, Pilot, Launch
  - Lab: <100 g, kg, <1 kg, 200 kg, >200 kg
  - DP: Lab, Pilot, Launch
  - Lab: <1 kg, <100 kg

### CM Setup Diagram:
- Upstream: Lab, Pilot, Launch, Market scale
- Downstream: Lab, Pilot / Launch, (Market scale)**
Example 2: Reduction of Asset Footprint

Set up here is a 2 stage synthesis that is capable of producing >1T per annum
Example 3: Dangerous Chemistry

Diazomethane synthesis

(i) Headspace nitrogen dilution; (ii) Diazald addition port; (iii) potassium hydroxide addition port; (iv) subsurface nitrogen sparge; (v) diazomethane monitoring (photoacoustic FT-IR); (vi) packed column with liquid recycle

Example 4: Faster Synthesis Metoprolol

<table>
<thead>
<tr>
<th>Continuous</th>
<th>Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time 15 sec, yield 91%</td>
<td>Reaction performed at reflux for 2-5 hours, 65-70% yield</td>
</tr>
<tr>
<td>Maximum yield at high excess of amine, Inexpensive, volatile amine is easily separated</td>
<td></td>
</tr>
<tr>
<td>7.0 g/h (61 kg/yr) with a single microreactor</td>
<td></td>
</tr>
</tbody>
</table>
Example 5: Benefit
Commercial Example from Fine Chemicals

- Comparison of reaction: Lithiation & Coupling

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Reaction Condition</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
<td>@ -76°C/-76°C for 5hrs</td>
<td>&lt; 70%</td>
</tr>
<tr>
<td>Continuous</td>
<td>@ -10°C/-30°C for 1minute</td>
<td>&gt; 85%</td>
</tr>
</tbody>
</table>

- Economic Comparison of Batch and Continuous Process

<table>
<thead>
<tr>
<th></th>
<th>Batch</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity</td>
<td>20 MT/yr</td>
<td>20 MT/yr</td>
</tr>
<tr>
<td>Overall yield</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>Investment cost</td>
<td>$1,000,000</td>
<td>$270,000</td>
</tr>
<tr>
<td>Raw material cost</td>
<td>$300/ kg product</td>
<td>$200/ kg product</td>
</tr>
<tr>
<td>Labor cost</td>
<td>$240,000/yr</td>
<td>$120,000/yr</td>
</tr>
<tr>
<td>Total production cost</td>
<td>$550/ kg product</td>
<td>$350/ kg product</td>
</tr>
</tbody>
</table>

- 73% - 33% - 50% - 36%

Source: SK Corporation Korea / BU: Company Manufacturing Service
Presentation to Novartis: „Use of Continuous Process for the Synthesis of Pharmaceutical Intermediates“
Example: Current Batch Route

Reactors

Reagents

Solvents

Waste

Filter

Dryer

Crystallizer

Centrifuge

Tablet Press

Tablet Coater

DP (Tablets)

Wet Granulator

Blender

Coating

Excipients

Waste

Solvents

Reagents

Waste

Distillation Column

LLE

Waste

Reagents

Solvents

Waste

Reagents

Solvents

Waste

Reagents

Solvents

Reagents

Solvents

Waste

IFPAC Cortona, W. Bisson Novartis Sept. 21, 2010
Example: New Route
Process Map and CM Control Strategy

Dynamic Process Data Collection

Incoming Raw Material
CPP1 – CQA3
CPP4 – CQA4
CPP5 – CQA1,3
CPP6 – CQA5
CPP7 – CQA1
CPP8 – CQA2

Residual Solvent
• Extract Organic Solvent

Freebase
• Purity

Salt Form
• Salt-formation

Filter
• Yield

Moisture/Polymorph
• Dry

Processing
• Final Form

Shaping
CPP9 – CQA5
CPP10 – CQA2,3
CPP11 – CQA1
CPP12 – CQA2,3
CPP13 – CQA1
CPP14 – CQA4
CPP15 – CQA5
CPP16 – CQA2

CQAs

Batch Level Analysis of Granulation Process
R²X₁ = 0.5656
R²X₂ = 0.298283

Ellipse: Hotelling T² (0.95)

S₀₀₁₀⁻Ｂ_₈₅
S₀₀₁₁⁻Ａ_₈₅
S₀₀₁₁⁻Ｂ_₈₅
S₀₀₁₂⁻Ａ_₈₅
S₀₀₁₂⁻Ｂ_₈₅
S₀₀₁₃⁻Ａ_₈₅
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S₀₀₁₆⁻Ａ_₈₅
S₀₀₁₆⁻Ｂ_₈₅

CQAs

• Reaction
Correct Transformation

CPP2 – CQA2
CPP3 – CQA1,4

FMEA/DoE

FMEA/DoE

FMEA/DoE

FMEA/DoE

FMEA/DoE

FMEA/DoE

FMEA/DoE

FMEA/DoE

FMEA/DoE
The Integrated Way Forward
Operationalize Continuous Manufacturing in Development and Manufacturing

Past

Initiate

- MIT- Novartis Technical Collaboration
- High level FDA – Novartis alignment
- Business, Organization, Regulatory Challenges Workshop

Next 3-5 years

Operationalize

- Develop 2015 detailed technology and business plan
- Implement in Development and Manufacturing
- Build flexible organization & new capabilities to leverage the value from the scientific breakthroughs
- Strong alignment with regulatory stakeholders

Long-term

Embed

- Expand to full range of NCE portfolio
- Expand global regulatory framework
- Significant quality gains and productivity delivers top- and bottom-line results
Acknowledgement

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Thank you!

Questions & Answers