Transforming Pharmaceutical Manufacturing
Continuous: The Ultra Lean Way of Manufacturing

Bernhardt Trout
Director of Center and Department of Chemical Engineering, MIT
## Acknowledgements

### MIT - Professors
- Paul Barton: Chem E
- Richard Braatz: Chem E
- Steve Buchwald: Chemistry
- Jung-Hoon Chun: Mech E
- Charles Cooney: Chem E
- Marty Culpepper: Mech E
- Timothy Jamison: Chemistry
- Klavs Jensen: Chem E
- Allan Myerson: Chem E
- Greg Rutledge: Chem E
- Alex Slocum: Mech E
- Bernhardt Trout: Chem E

### Novartis
- Thomas van Laar
  *Head Global Techn. Operations*
- Juan Andreas
  *Head Group Quality*
- Steffen Lang
  *Head Global Techn. R&D*
- Berthold Schenkel
  *Chemical Development*
- Norbert Rasenack
  *Pharmaceutical Development*

+ students and Post-docs
Agenda

- Current Status of Pharmaceutical Manufacturing: Batch
- Blue Sky Vision Continuous Manufacturing
- Case study – new process
- Case study – economics
- New Drug Product Technologies (selected)
Starting Point: Current State of the Art

Additional quantum leap improvements are unlikely to happen with traditional manufacturing concepts

- **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
Batch Processes - Disadvantages

Disconnected, long throughput times, end product testing

- Defined batch size (output quantity driven by batch size)
- Multiple, sequential process steps, end to end
- Many interruptions between/during process steps
- Long waiting times between single process steps
- Numerous transport steps between process steps
- Lengthy throughput times from start to finish
- High levels of raw material and intermediate inventories required
- Extensive validation and scale-up activities needed
- Physical and organizational separation in operations and development
- Quality measured by in process sampling/control and end product testing
Transforming Manufacturing to “Continuous”
Our Definition of “Continuous” (ultra QbD)

- Flow
- Integration (end to end)
- Systems approach
- Integrated control strategy
Focus on New Technologies

- Want leaps in improvement, not incremental steps.

- Exploit new technological opportunities that come with “Continuous,” while also overcoming new challenges.

- Open up mental frameworks for mindset change.
Novartis-MIT Center for Continuous Manufacturing

- ~60 MIT students and post-docs
- 20 Novartis staff and 12 MIT Professors from Chemical Engineering, Chemistry, and Mechanical Engineering
- 90% of research performed in each professor’s lab
  - Chemistry
  - Reactor Designs
  - Separations
  - Formation of Final Dosage Form
- 10% in dedicated facility for bench scale unit
Novartis-MIT Blue Sky Vision
Integrated Continuous Manufacturing: A radical transformation

→ the ultra LEAN Manufacturing

From start of chemical synthesis through final pharmaceutical dosage form
Road Map for Pharmaceutical Manufacturing

Paradigm shifts in manufacturing and quality envisioned

Traditional Manufacturing

Target 2010

LEAN - ePO - eBPR - 6σ - QUALIMETRICS

Toyota of Pharma

Disconnected process steps

Process steps and their impact understood

Quality by Design

Blue Sky Vision: Continuous Manufacturing

Seamlessly integrated and well characterized processes

Current

2012

> 2020
LEAN: increasing throughput rates

Traditional Manufacturing

Past

OAE 20 – 40%

2010

LEAN Manufacturing

OAE 40 - 60%

Continuous Manufacturing

OAE >> 80%

OAE: Operational Asset Effectiveness

Novartis/MIT, All Rights Reserved
LEAN: decreasing throughput times

Traditional Manufacturing

Past

200-300 days

LEAN Manufacturing

2010

100-150 days

Continuous Manufacturing

> 2015

< < 10 days

Inventory Turns/Free Cash Flow

TPT  Throughput Time Pharmaceutical Manufacturing

13  |  Novartis/MIT, All Rights Reserved
## Benefits

<table>
<thead>
<tr>
<th>Value Attribute</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Scale Up</td>
<td>6-12 mo shorter process development</td>
</tr>
<tr>
<td>Reduced Footprint</td>
<td>Reduction of 40-90%</td>
</tr>
<tr>
<td>Linkage with PAT</td>
<td>More flexibility within design space</td>
</tr>
<tr>
<td>Flexible Supply Size</td>
<td>Supply to demand, reduced inventory</td>
</tr>
<tr>
<td>Flexible Dose Form</td>
<td>Fast market response, reduced inv.</td>
</tr>
<tr>
<td>CapEx/OpEx</td>
<td>Reduction 25-60%</td>
</tr>
<tr>
<td>Continuous Process Verification</td>
<td>Lower QC cost, reduced waste</td>
</tr>
<tr>
<td>Continuous Production &amp; Release</td>
<td>Reduced inventory and QC costs</td>
</tr>
<tr>
<td>No WIP or Quality Holds</td>
<td>Reduced inventory and QC costs</td>
</tr>
<tr>
<td>Linkage of Info &amp; Material Flow</td>
<td>Lower QA/QC costs</td>
</tr>
<tr>
<td>Continuous Improvement</td>
<td>Faster reduction in COGS</td>
</tr>
</tbody>
</table>
Integrated Continuous Manufacturing:

- Integration of full Quality by Design concepts
- Implementation of a new product development process (integrated chemistry and pharmaceutics)
- Utilization of new methodologies, technologies and equipment
- Development of a new streamlined facility lay-out
- Major change in technical skills and mindset
- Major change in organizational structures for cohesive development, quality and technical operations
Summary of Challenges

- Mindset/Organizational
- Regulatory
- Technological
Case Study: Integrated Drug Substance and Drug Product Manufacturing
Existing Process - Upstream

Reactor 1

KI; Reagents

Filter 1

Dryer 1

Reagents

Solvents

Waste

Reactor 2

Filter 2

LLE

Distillation Column 1

Solvents

Solute

Waste

Filter 3

Crystallizer 1

Centrifuge 1

Filter 4

Dryer 2

Waste

Reagents

Solvents

Solute

Waste

Distillation Column 2

Dedicated Facility
Existing Process - Downstream

Manufactured at 2 facilities to support different markets
New Continuous Process
Chemical Step 1: Solvent Free Synthesis

NVS Route

90 °C, 6 h then 60 °C, 42 h (93%)

CCM Route (Melt Chemistry)

120 °C, 50 min (84-86% yield)

Recycle
Chemical Step 2: Rapid Synthesis

NVS batch Route

0 °C, 3 h, run as a slurry (93%)

CCM Route (Not possible in batch)

25 °C, 5 min, in solution (98% yield)
Process Understanding Pyramid

1st Principles

Mechanistic Understanding

MVDA Models

Empirical Understanding

Decisions Based on Univariate Approach

Data Derived from Trial-N-Error Experimentation

Data Derived from Trial-N-Error Experimentation

Decisions Based on Univariate Approach

Empirical Understanding

MVDA Models

Mechanistic Understanding

1st Principles

Process Understanding Pyramid

DATA DERIVED FROM TRIAL-N-ERROR EXPERIMENTATION

DECISIONS BASED ON UNIVARIATE APPROACH

EMPIRICAL UNDERSTANDING

MECHANISTIC UNDERSTANDING

1st Principles
Process Map

CM Control Strategy

Dynamic Process Data Collection

Incoming Raw Material

CPP1 – CQA3

FMEA, DoE

Residual Solvent

CPP4 – CQA4
CPP5 – CQA1,3

FMEA, DoE

Salts Form

CPP8 – CQA2

FMEA, DoE

Moisture/

CPP10 – CQA2,3
CPP11 – CQA1

FMEA, DoE

Drug Product

CPP16 – CQA2

Form

CPP12 – CQA2.3
CPP13 – CQA1
CPP14 – CQA4
CPP15 – CQA5

FMEA, DoE

Batch Level Analysis of Granulation Process:

R2X[1] = 0.5656
R2X[2] = 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
S0013-B_85
S0014-A_85
S0014-B_85
S0015-A_85
S0015-B_85
S0016-A_85
S0016-B_85

CPP1 – CQA3

FMEA, DoE

Correct Transformation

CPP2 – CQA2
CPP3 – CQA1,4

FMEA, DoE

Purity

CPP6 – CQA5
CPP7 – CQA1

FMEA, DoE

Yield

CPP9 – CQA5

FMEA, DoE

S0015-B_85

S0016-B_85

S0016-A_85

S0015-A_85

S0014-B_85

S0014-A_85

S0013-B_85

S0013-A_85

S0012-B_85

S0012-A_85

S0011-B_85

S0011-A_85

S0010-B_85

S0010-A_85

S0015-B_85

S0015-A_85

S0016-B_85

S0016-A_85

S0014-B_85

S0014-A_85

S0013-B_85

S0013-A_85

S0012-B_85

S0012-A_85

S0011-B_85
Video
## Economic Comparison

<table>
<thead>
<tr>
<th></th>
<th>Blue Sky CM (% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CapEx</strong></td>
<td>61-68</td>
</tr>
<tr>
<td>Material Handling</td>
<td>50-60</td>
</tr>
<tr>
<td>QA/QC</td>
<td>25-50</td>
</tr>
<tr>
<td>Waste</td>
<td>40-60</td>
</tr>
<tr>
<td>Utilities</td>
<td>40-60</td>
</tr>
<tr>
<td>Labor</td>
<td>25-50</td>
</tr>
<tr>
<td>Raw Materials</td>
<td>0-46</td>
</tr>
<tr>
<td>Present Cost</td>
<td>15-50</td>
</tr>
</tbody>
</table>

Simulation based on peak demand production and the savings in a number of key areas are based on our assumptions as to how a single dedicated CM would compare with multiple batch facilities.
Summary of Innovations

• 1\textsuperscript{st} step: Solvent free synthesis
• 2\textsuperscript{nd} step: fast, new chemistry (cannot do in batch)
• 3\textsuperscript{rd} step: eliminate unit operations, reduction in processing time and increased yield
• New filtration and drying approaches
• Solvent free coating
• Eliminated granulation/blending
• Integration
• Route for QbD for CM process
New Drug Product Technologies (selected)
Selected DP Technologies

- Thin Film
- Electro Processing
- Extrusion Molding
Thin Films
From Films to Tablets
Electro Processing
Electrospinning of Drug and Excipient

1) Dissolve drug and polymer in solvent

2) Electrospin to produce fibers

3) Process mat into tablets
Spinning Suspension using Free-Surface Electrospinning

Drug crystal slurry from upstream

Polymer solution

Mixing and sonication

Pump

40 kV

feed to folding, cutting
Dissolution Testing

- Tablets prepared from electrospun material and compressed powder blends
- Dissolution performed using standard USP tests
- N=3
Extrusion Molding
Melt Extrusion-Molding

Injection Molding with Turntable

Temperature

Mold

Extruder die

Powder

Tablet

9 mm
Melt Extrusion Molding

![Diagram showing Melt Extrusion Molding process](image)

![Graph showing percent dissolved over time](image)

- Percent $X_A$ or $X_B$ Dissolved vs Time (min)

![Images of extrusion equipment and molded product](image)
Summary of Challenges

- Mindset/Organizational
- Regulatory
- Technological