Manufacturing Operations Intensification

A new approach

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Outline

• Process Intensification for the Chemical Industry
• What is specific to Pharma and Fine Chemistry Manufacturing?
• Manufacturing Operations Intensification
• Equipment selection to fit Manufacturing needs
• Conclusion
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**Process Intensification for the Chemical Industry**

Process Intensification vision

2010

![Image of a large industrial plant]

2025

![Image of a futuristic, compact plant]

Process intensification will bring a *breakthrough* in chemical processing, leading to a *more competitive and sustainable* chemicals industry.

European roadmap for PI: Cost reduction of 20-50%
Switch to Continuous Process

Focus on Flow Chemistry

Use of new *continuous process technologies* which significantly increase the *economic and ecological efficiency*.

→ Mainly for *specialties, fine chemicals & pharmaceuticals*.
System Engineering

Commercially available flow chemistry solutions

Commercially proven & available

Many

To be adapted from other area's

Some

Reaction → Separation

Analysis & Control

To be adapted for flow

Some
Outline

• Process Intensification for the Chemical Industry
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From dedicated equipment...
...to multipurpose environment
Pharma & Fine Chemicals Production

- A molecule is the output of a sequence made of 10 to 15 reactive and non-reactive steps (Complexity)
- The Unit Operations are mainly discontinuous (Batch)
- Multipurpose environment (Flexibility)
- Significant use of external providers to source raw materials as well as intermediates (Planning)
Quality

Batch Process Quality

Defect rate (ppm)

Process Capability = \(\frac{USL - LSL}{6\sigma}\)

\(= 0.67\)

95.4%

Defect rate = 4.6% = 46000 ppm

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Quality

Batch Process Quality

Defect rate (ppm)

Final Quality to the Customer

Process Capability = \( \frac{USL - LSL}{6\sigma} \) = 0.67

Defect rate = 4.6% = 46000 ppm

Process Capability = \( \frac{USL - LSL}{6\sigma} \) = 2

Defect rate < 1 ppm
**Batch process variability**

<table>
<thead>
<tr>
<th>Batch characteristics</th>
<th>Organic synthesis</th>
<th>Bio process</th>
</tr>
</thead>
</table>
| ❖ Each molecule or each micro-organism inside the batch vessel, is going through an history (TPC...) that can be significantly different from the others. | ❖ Mass transfer  
❖ Heat transfer  
❖ Residence time distribution | ❖ Mass transfer  
❖ Residence time distribution  
❖ Temperature control |
| ❖ The repeatability of this history distribution is low from batch to batch.            |                                                         |                                                       |
| Develop chemistries that are less sensitive  
Develop equipment that are less variable                                  | Use of solvents                                      | Large amount of water used                            |

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Impact

- Batch process variability is responsible for:
  - 5% batch out of specifications (from 1 to 10%)
  - a cost of quality in the order of 25% due to heavy quality controls and rework operations
  - The inability most of the time to deploy Lean Manufacturing and get rid of the non value added operations
What is specific to Pharma and Fine Chemistry Manufacturing?

• 99% operations are batch based

• Batch variability is a main source of not achieving quality, production cycle & cost objectives

• Batch variability is the main barrier to deploy improvement methodologies like Lean Manufacturing and Six Sigma
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Manufacturing Operations Intensification

Manufacturing Process Quality

25% savings by getting rid of non value added rework operations

Final Quality to the Customer
Manufacturing Operations Intensification

• Use of Advanced Manufacturing Technologies to produce manufacturing quality as closed as possible to the final Quality delivered to the customer
  – Continuous processing is part of it

• Manufacturing cost reduced by at least 25%
  – Drastic increase of process capability
  – Elimination of the non value added rework operation
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Equipment selection: Heat Transfer

Reactants

Heat exchange media

Heat generation

Heat removal

\[ \rho C_p \frac{dT}{d\tau} = kA(-\Delta H) - U \cdot \left( \frac{S}{V} \right) \cdot (T - T_c) \]

Chemistry = \( E_a, \Delta H_R, k, C, T \)

Equipment = \( U, S/V \)
**Reactor / Reaction Fit Coefficient**

*(Laurent Falk – ENSIC Nancy – 2010)*

1. Estimation of the potential hot spot in order to control reaction exothermicity \( \frac{dT}{d\tau} = 0 \)

2. Keep the ratio \( \Delta T_{ad} \times \left( \frac{t_{exch}}{t_{react}} \right) \) as small as possible
   - \( t_{exch} = \text{Heat exchange characteristic time} \)
   - \( t_{react} = \text{Reaction characteristic time} \)

3. Reactor / Reaction Fit coefficient

\[
\frac{k \cdot C_A \cdot D}{U_{exch}}
\]

- Kinetic coefficient = \( f(\text{chemistry}) \)
- Concentration = \( f(\text{chemistry}) \)
- Characteristic dimension = \( f(\text{reactor}) \)
- Heat exchange coefficient = \( f(\text{reactor}) \)
# Equipment Data

<table>
<thead>
<tr>
<th>Reactor</th>
<th>0.5 L Batch</th>
<th>100 L Batch</th>
<th>6 m³ Batch</th>
<th>Metal Flow Reactor</th>
<th>Glass Flow Reactor</th>
<th>SiC Flow Reactor</th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>Falk &amp; al., 2010</td>
<td>Prat &amp; al., 2005</td>
<td>Barthe &amp; al., 2008</td>
<td>Gourdon &amp; al, 2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat transfer coefficient ( U ) (W/m².K)</td>
<td>1200</td>
<td>800</td>
<td>400</td>
<td>2500</td>
<td>600</td>
<td>10000</td>
</tr>
<tr>
<td>Typical dimension ( D ) (m)</td>
<td>0.08</td>
<td>0.5</td>
<td>2.3</td>
<td>0.008</td>
<td>0.0015</td>
<td>0.003</td>
</tr>
<tr>
<td>Surface / Volume ratio ( S/V ) (m²/m³)</td>
<td>40</td>
<td>8</td>
<td>1.74</td>
<td>400</td>
<td>2750</td>
<td>2000</td>
</tr>
<tr>
<td>Heat exchange capacity ( US/V ) (kW/m³.K)</td>
<td>48</td>
<td>6</td>
<td>1</td>
<td>1000</td>
<td>1650</td>
<td>20000</td>
</tr>
</tbody>
</table>

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**Start with Lab Chemistry**

- Higher Reactor / Reaction fit coefficient means:
  - Lower probability of manufacturing feasibility
  - Higher safety risks
  - Lower product performance

- Lower Reactor / Reaction fit coefficient means:
  - Higher probability of manufacturing feasibility
  - Lower safety risks
  - Higher product performance

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Equipment impact
(Chemistry kept constant)

Reactor type
- kCD/U
- SiC Flow Reactor
- Glass Flow Reactor
- Metal Flow Reactor
- 0.5 L Batch Reactor
- 100 L Batch Reactor
- 6 m3 Batch Reactor

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To double the heat transfer coefficient requires:

• x10 the heat exchange circuit pumps power
  or,
• x13 the mixing power
  or,
• add an external heat exchanger plus transferring pumps

Equipment impact (Chemistry kept constant)
Equipment impact
(Chemistry kept constant)

For the Metal Flow Reactor
Impact of decreasing the channels diameter from 8 to 2 mm

Reactor type

Glass Flow Reactor
Metal Flow Reactor
SiC Flow Reactor

6 m³ Batch Reactor
100 L Batch Reactor
0.5 L Batch Reactor

kCD/U

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Equipment impact
(Chemistry kept constant)

For the Glass & SiC Flow Reactors
Impact of increasing the Heat Exchanger flow

Reactor type

Glass Flow Reactor  Metal Flow Reactor
SiC Flow Reactor

kCD/U

6 m3 Batch Reactor
100 L Batch Reactor
0.5 L Batch Reactor

For the Glass & SiC Flow Reactors
Impact of increasing the Heat Exchanger flow

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Equipment impact
(Chemistry kept constant)

Reactor type
glass Flow Reactor
SiC Flow Reactor
Metal Flow Reactor
0.5 L Batch Reactor
100 L Batch Reactor
6 m3 Batch Reactor

kCD/U

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## Chemistry impact

*(Equipment kept constant)*

---

<table>
<thead>
<tr>
<th>Reactor Type</th>
<th>Volume (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiC Flow Reactor</td>
<td>0.5</td>
</tr>
<tr>
<td>Glass Flow Reactor</td>
<td>10</td>
</tr>
<tr>
<td>Metal Flow Reactor</td>
<td>100</td>
</tr>
<tr>
<td>100 L Batch Reactor</td>
<td>0.5</td>
</tr>
<tr>
<td>6 m3 Batch Reactor</td>
<td>100</td>
</tr>
</tbody>
</table>

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**Graph:**

- x-axis: kCD/U
- y-axis: Units

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Impact of dilution and/or slower dosage (C→ C/10)

Dilution increase = need for more separation
Dosing = productivity decrease & secondary reactions

Reactor type

kCD/U

1,000,000
100,000
10,000
1,000
10
1

0.5 L Batch Reactor

100 L Batch Reactor

6 m3 Batch Reactor

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Chemical Engineering

Impact of working at lower temperature
- 20° : $k \longrightarrow k/4$
- 40° : $k \longrightarrow k/16$

Working at lower temperature = negative impact on yield and selectivity

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Chemistry impact

(Equipment kept constant)

Impact of:
- Diluting and,
- Dosing and,
- Lowering the temperature

This is what batch scale up is all about:
To adapt the Chemistry to the Reactor......
.....if acceptable by the chemistry

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Impact of concentrating and/or removing solvents (C---3C)

Chemistry Impact (Equipment kept constant)

- SiC Flow Reactor
- Glass Flow Reactor
- Metal Flow Reactor
- 0.5 L Batch Reactor
- 100 L Batch Reactor
- 6 m³ Batch Reactor

kCD/U

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Chemical Engineering

Impact of working at higher temperature

+ 40° : k ---> 16k

Reactor type

- SiC Flow Reactor
- Glass Flow Reactor
- Metal Flow Reactor
- 0.5 L Batch Reactor
- 100 L Batch Reactor
- 6 m3 Batch Reactor

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Chemistry impact

(Equipment kept constant)

Adapting the Chemistry to the Reactor = lower Chemistry performances

Increased Chemistry performances

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Pharma & Fine Chemicals
Production needs

• New Markets
  – Manufacturing of future molecules and potential new products
  – New means higher performances than existing product performances
  – This search will start early on in Research
  – The challenge will be:
    • to invent such products,
    • to develop processes likely requiring more heat and mass transfer
    • to lower the entry Capex to minimize risks

Continuous reactors with higher mass and heat transfer capability, where the chemistry will continue to deliver higher performances
Reactor / Reaction fit:

New Markets

- Higher product performances
- Higher probability of manufacturing feasibility
- Lower safety risks
Pharma & Fine Chemicals

Production needs

• New Products
  – Manufacturing of new molecules under development
  – Due to manufacturing overcapacity, they would have to be produced using existing facility and equipment,
  – The challenge will be:
    • To overcome the scale up
    • To be able to integrate the new processes into the existing manufacturing structure and equipment
    • To be able to maintain the existing manufacturing efficiency after the integration of the new processes

Continuous reactors with higher mass and heat transfer capability where the chemistry will not have to be adapted
Reactor / Reaction fit: New Products

- Higher probability of manufacturing feasibility
- Lower safety risks
Pharma & Fine Chemicals
Production needs

• Maintenance of Business
  – Manufacturing of existing & established molecules
  – Under significant pressure due to generics and eastern low cost producers
  – Batch variability is the main barrier to deploy improvement methodologies
  – The chemistry has been already adapted to the reactor
  – The challenge will be:
    • To re-engineer manufacturing processes and structure in order to lower manufacturing costs by 30%

Continuous Reactors where the existing chemistry will be implemented with minimum adaptation
**Reactor / Reaction fit:**

**Maintenance of Business**

- Decrease manufacturing costs by removing batch process variability
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Continuous mode production

Manufacturing Operations Intensification:
- Significant increase in process capability (from 0.67 to 2)
- Avoidance of non value added rework operations for out of spec batch
- Drastic reduction of Quality control costs

Process Intensification:
- Mass and Heat transfer Optimization through characteristic dimensions reduction of the reactor (from meter to few millimeters)
- Increased product quality, yields, safety and decreased environmental impact

Production Facility Intensification
- Decrease of the footprint associated with production facility more compact, safer and cheaper
Continuous Production of Pharmaceuticals & Fine Chemicals

### Intensification

<table>
<thead>
<tr>
<th>Facility</th>
<th>Operations</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimize risks</td>
<td>Eliminate variability sources</td>
<td>Improve Process performance</td>
</tr>
</tbody>
</table>

| Maintenance of Business   | +                                 | ++++                                 | ++        |
| New Products              | +                                 | +++                                 | +++       |
| New Markets               | ++++                              | ++                                  | ++++      |

**System Engineering**

**Reaction & Reactor Engineering**