Industrial fine-chemical and pharmaceutical production with microreactor technology (MRT)
Lonza Ltd., Visp (Switzerland)

- **Life sciences-driven chemical and biotechnology company**
- sales ca 3 billion € in 2006
- 26 production and R&D sites worldwide
- 7100 employees

**Our divisions:**
- Exclusive Synthesis & Biopharmaceuticals (Custom Manufacturing)
- Organic Fine & Bioscience
Microreactor Technology

- It enables **Continuous Processes** based on plug flow reactors using a **minimal volume** of reagents, with **excellent temperature control**, **efficient mixing**, rapid dynamic responses and robustness, etc.
Batch vs Continuous Processing

- Advantages of batch processes:
  - Versatility (can deal with various phases: solid-liquid-gas, and downstream operations: distillation, extraction…)
  - Flexibility (can accommodate various reaction kinetics)

- Advantages of continuous processes:
  - Efficiency (e.g. bulk chemical industry)
  - Safety
  - Better process control in terms of residence time / mixing / temperature management
MRT in Lonza - Brief History

- Started February 2003
- 2 Dedicated laboratories
  - Connected with the kg-lab to produce kg-quantities
- 2 Integrated production units (c-SSP, R01)
- MRT team and own reactor development
- Collaborations with Corning, Siemens, and others

- 5 Chemical patent applications (wide-ranging)
  - 1 Process, Nitration and Organometallic reactions
- 3 Technical patent applications
  - 2 Microreactors, 1 lab system
- 3 Publications (CET, Angewandte Chemie, PharmaChem)
  - Citations in Nature, Chemical & Engineering News…
Lonza’s Context: Product Life Cycle in Pharmaceutical Industry

Success rate:

<table>
<thead>
<tr>
<th>DISCOV.</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
<th>FILING</th>
<th>PROD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>10-50%</td>
<td>50%</td>
<td>&gt; 90%</td>
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</tbody>
</table>

Tasks:
- sequence selection
- process development
- validation
- 2nd generation process

Process changes allowed:
- Process changes with change request!
- Process changes allowed

2-50 to, highly functionalized compounds

50-100 to, simple compounds

增加MR技术的吸引力
Key drivers for MRT Market Growth in Pharma

- **Controlled reaction conditions** leading to new synthetic routes that are not scalable in batch-mode
- **Enhanced safety conditions** enabling to work with hazardous reactions and unstable intermediates
- **Higher yield** and/or **selectivity** in production
- **Time-to-market:**
  - Powerful tool for process development
  - High Data Throughput (rapid parameter screening);
  - Rapid technology transfer “without” scale-up issues.
- **Constant product quality** (less QC/QA, less OOS)
- **PAT-ready**

MRT could push the paradigm shift from batch to continuous processing!
Field of Application – 5 Key Questions

- Mixing-sensitive reaction?
  Selectivity, yield, undesired by-products
- Temperature-sensitive reaction?
- Unstable intermediates?
- Need for highly diluted conditions?
- Hazardous educts, reactions, or products?

For reactions where one of the 5 key questions is answered by YES, continuous processing with MRT will play, most likely, a crucial role

Not every reaction is feasible or beneficial in microreactors, but microreactors enlarge the process window
Laboratory observations

Observations indicating MRT-feasibility

- Fast kinetics (<10 min)

- Mixing-sensitiveness:
  - Need long dosing time
  - Need for high stirrer speed, selectivity depends on stirrer speed

- Temperature-sensitiveness:
  - Highly exothermic / autocatalytic
  - Lower selectivity in larger vessels (heat transfer)

- Undesired by-product formation by overreaction
Reaction Classification & Advantages

- **Type A reaction:**
  - very fast (< 1s)
  - controlled by the mixing process
  - MR: **Yield increase** by optimum reaction conditions

- **Type B reaction:**
  - rapid reaction (1 s to 10 min)
  - predominantly kinetically controlled
  - MR: **Yield increase** by improved temperature control

- **Type C reaction:**
  - slow reaction (> 10 min)
  - would suit batch processes; but potential thermal or autocatalytic hazard
  - MR: **Safe operation** by improved temperature control
Microreactor-specific benefits

- **Mixing-Controlled Reactions:**
  - Higher pressure drop ⇒ more energy in the mixing zone
  - Scale a process using energy input in the mixing zone

- **Temperature-sensitive reactions:**
  - avoid hot spots by high heat transfer
  - higher process temperatures/concentrations are possible

- **Volume minimization:**
  - autocatalytic reactions are controllable
  - nitrations give better yield and selectivity
  - unstable intermediates can be intercepted
Shifting syntheses to suit Microreactors

- A, B, C loose classes: kinetics can be changed to fit MRT by:
  - Increased concentration
  - Increased temperature
  - More effective solvent and catalysts

- Processes can be changed to use
  - Unstable/hazardous reagents and intermediates (e.g. nitro- or labile organometallic compounds)
Example: Phenol Nitration (Type C)

- Phenol nitration autocatalytic, with large heat release
- Semi-batch operation forbidden: explosion risk!
- Safe reaction in microreactor
  - Set harsh conditions to start immediately the autocatalysis (Type C → B shift)
  - Temperature is under control
- Superior heat-exchange features allow making solvent-free reaction

**Phenol nitration: RC-1 run**

- Explosive-like autocatalysis
- Set harsh conditions to start immediately the autocatalysis (Type C → B shift)
- Temperature is under control
- Superior heat-exchange features allow making solvent-free reaction
Application domain from Lonza statistic

- Big circle based on kinetics only
- Inner circle based on kinetics and phases

- Organometallic reactions: 21%
- Diketene reactions: 50%
- Autocatalytic nitrations: 23%
- Type A reactions: 8%
- Type B reactions: 9%
- Type C reactions: 2%
- Remaining: 6%

Batch vs Continuous Processes

- Batch processing: versatile and flexible, various phases and reaction kinetics
- Continuous processing: efficient and safe with high throughput, better mixing, heat transfer and residence time control
- *Toolbox concept* for multipurpose continuous plant
  = Unit Operations (batch) = Modules (continuous):

<table>
<thead>
<tr>
<th>Batch unit operation</th>
<th>Continuous module</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charging</td>
<td>Dosage system</td>
</tr>
<tr>
<td>Heating/cooling</td>
<td>Heat exchanger</td>
</tr>
<tr>
<td>Reaction (batch/semibatch)</td>
<td>Reactor and manifold</td>
</tr>
<tr>
<td>Aging</td>
<td>Residence time</td>
</tr>
<tr>
<td>IPC/QC</td>
<td>On-line analytics</td>
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</tbody>
</table>
Toolbox Concept

**Toolbox**

- Dosing
- Heat exchange
- Reaction
- Residence time

`work-up`
The Toolbox Concept: Modular Approach

- This is a **fundamental change** in production strategy for the pharma and fine chemical industries.

- The toolbox concept enables to adapt a production unit to a chemical system within a multi-purpose system:
  - Integrate of mixing and heat exchange capabilities
  - Avoid dead volumes

- The ‘**toolbox’ modules** must be based on physical-chemical characteristics of the reaction such as:
  - Various kinetics / residence times
  - Reaction phases (liquid–solid–gas)
Toolbox example

- 2 Step synthesis: metatlation and coupling
  - Different kinetics:
    
    1) $\text{R'}-\text{H} + \text{Li} \rightarrow \text{R'}-\text{Li} + \text{LiH}$
    
    2) $\text{R'}-\text{Li} + \text{R''}-\text{W}_1-\text{X} \rightarrow \text{R''}-\text{W}_2-\text{R'} + \text{LiX}$

- Several ~600 kg-campaigns (3-4 weeks)

![Diagram showing the flow of reactions and modules](image)
Online Analytics in Toolbox: UV-VIS Nitration Monitoring

- Autocatalytic reaction: must occur entirely in the MR
- Just-in-time observation of the conversion

Produced ~5 kg in 24 h
Type A Reactions – Heat Exchange

- Heat exchange time ~ 200 ms under reasonable assumptions:
  - Nusselt number ~3.7 (laminar flow resistance, constant $T_{\text{wall}}$)
  - Average cross-diameter ~ 0.5 mm
  - Fluid properties as THF
- Mixing time in efficient micromixers ~ 100 ms

- Thus, temperature gradients are present in the mixing zone: **hot spot**
- Solution: **multi-injection principle and design.**
Type A Multi-Injection Principle

Corning Module

- Material: glass
- Enhanced mixing properties
- Multiple injection
- Low pressure drop

- Modular approach
- Transparent design
- Flexibility for production

Corning S.A.S. - Fontainebleau Research Center

Pictures copyright to Corning
Lonza Module (Self-developed)

- Aimed at maximizing heat transfer and mixing but allowing a residence unit
- Material: Hastelloy C, SiC
- Minimize pressure drop
- Modular, ease of adaptation

- Excellent mixing performance, can be used also for Type A
- Modular residence time up to 1 min.
- Pressure up to 100 bar
- Various partners for the reaction plates

D.M. Roberge et al, WO2007112945, to Lonza AG
Modules for Type C Reactions

- Conventional modules based on standard heat exchangers and static mixers with high flexibility example are from BHR (Flex reactor), Sulzer (SMR reactor), or Fluitec.

- Engineer and construct appropriate residence time modules (RT-module).
Gas-Liquid Modules

- Kg-scale lab system with Sulzer SMV mixing elements.
- Ton-scale system with Sulzer SMV in the launch plant for industrial production.
- Only for gases with low solubility and large volume fraction such as ozonolysis:
  - Gas-liquid mass transfer intensification.
- Scale-up: predictable mass and heat transfer ($K_{la}$).
- Fully automated system.
Scale-up in microreactor production

- Common target scale: ~1 ton/campaign (~100 days)
- Lonza concept
  - laboratory equipment in EX environm.
  - kg-runs, SSP, and ton-runs
- Typical flow rates and production rates

<table>
<thead>
<tr>
<th>Product kg/d</th>
<th>lab</th>
<th>c-SSP</th>
<th>dedicated plant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>flowrate</td>
<td>mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>100</td>
<td>1000</td>
</tr>
<tr>
<td>5%</td>
<td>0.7</td>
<td>7.2</td>
<td>72</td>
</tr>
<tr>
<td>10%</td>
<td>1.4</td>
<td>14</td>
<td>144</td>
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<tr>
<td>20%</td>
<td>2.9</td>
<td>29</td>
<td>288</td>
</tr>
<tr>
<td>30%</td>
<td>4.3</td>
<td>43</td>
<td>432</td>
</tr>
<tr>
<td>50%</td>
<td>7.2</td>
<td>72</td>
<td>720</td>
</tr>
</tbody>
</table>
Scale-up for microreactor production

- Simple numbering-up in multipurpose plant is limited
  - Need for large stock of MR units
  - Process control issues
  - No economic advantage
- Toolbox concept is the solution

<table>
<thead>
<tr>
<th></th>
<th>Lab scale</th>
<th>Small-scale production</th>
<th>Large scale production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td>100 x</td>
</tr>
<tr>
<td>Pressure (flowrate)</td>
<td></td>
<td></td>
<td>4 x</td>
</tr>
<tr>
<td>Concentration</td>
<td></td>
<td></td>
<td>2-6 x</td>
</tr>
<tr>
<td>Cross section (flowrate)</td>
<td></td>
<td></td>
<td>4 x</td>
</tr>
<tr>
<td>More reactors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campaign size</td>
<td>1 kg</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 ton</td>
<td>100 ton</td>
</tr>
</tbody>
</table>
c-SSP: Pilot Plant with Microreactor Technology

- Multi-purpose system:
  - Modular
  - Hastalloy-made
  - Temperature: -80 to +180 °C
- ATEX standards
- Qualifiable for c-GMP production

- Dosage Lines:
  - 3 Lines
  - Pressure: 1 – 6 bar
  - Process flowrate: 5 – 300 g/min (per line)
c-SSP Track Record

- **Organolithium exchange reaction:**
  - Up to 1 ton of product; few weeks of operations
  - Corning multi-injection reactor and Lonza module

- At the end of the campaign the reactor was cleaned by standard procedure and used again for a new project.

- **Organolithium coupling reaction:**
  - Several kg of product; operation 7 consecutive days; 24 hours per day
  - Corning multi-injection reactor & Corning single-injection reactor for validation, Lonza module

- **Nitration reaction (kg-lab):**
  - Few kg of product; 24 hours operations;
  - Corning multi-injection reactor.
R01: Continuous Production in Launch Plant

Based on Conventional Technology

- Multi-purpose system
- Capacity in the range of 150 kg/h
- Use of conventional technology such as static mixers, mini-heat exchangers, etc.
- Campaigns were performed with in-between cleaning
R01 Track Record

- Simmons-Smith reaction:
  - Several campaigns
  - Tons of product; production over weeks
  - Static mixer with conventional mini-tube heat exchangers (as small as needed)

- Organolithium coupling reaction:
  - Several campaigns
  - Tons of product; production over weeks
  - Static mixer in an adiabatic regime
Other examples

- Organolithium/magnesium reactions (Type A/B)

\[
\begin{align*}
R_1 R_2^+ + R_3^{-M} & \rightarrow R_1 R_2^\text{OH} & M = \text{Li, MgX} \\
R_1 X^- + R_3^{-\text{MgX}} & \rightarrow R_1 R_3^\text{O}
\end{align*}
\]

- Nitrations (Type B/C)

\[
\begin{align*}
\text{Ar}^{-\text{H}} + \text{HO}^{-\text{NO}_2} & \rightarrow \text{Ar}^{-\text{N}_2^\text{O}} \\
\text{R}^{-\text{OH}} + \text{HO}^{-\text{NO}_2} & \rightarrow \text{R}^{-\text{NO}_2}
\end{align*}
\]

- Metalations and metal/halogen exchange (Type A/B)

\[
\begin{align*}
\text{R}^{-\text{H}} + \text{Li} & \rightarrow \text{R}^{-\text{Li}} \\
\text{Ar}^{-\text{X}} + \text{Li} & \rightarrow \text{Ar}^{-\text{Li}}
\end{align*}
\]
Potential Collaboration Modes

- Joint evaluation of microreactor opportunities

- Customer provides projects for feasibility studies of certain products or critical reaction steps

- Customer rents fixed capacity in Lonza’s labs for feasibility studies in process development or small scale production

- Development program with milestones for selected projects
  - feasibility study with process development
  - 24h runs in kg lab (e.g. preparation of kg samples)
  - production in c-SSP (>10kg)
Conclusions

- Lonza is a leading company in continuous manufacture of chemicals using microreactors or conventional technology:
  - The lab development is solely made in the microreactor

- Lonza can be your partner from sample to large scale production:
  - Can produce under c-GMP conditions

- Acknowledgment:
  - **Lonza team**: Norbert Kockmann, Fabio Rainone, Michael Gottsponer, Markus Eyholzer, Wilhelm Quittmann, Walter Brieden and Bertin Zimmermann
  - Dominique Roberge (now at University of Ottawa, Canada)