Industrial Applications of Microreactor Technology
Microreactors are at the heart of a dramatic shift in API production

Microreactor (MR) technology enables continuous processes based on plug flow reactors with minimal volume of reagents, rapid dynamic responses and robustness, good temperature control, efficient mixing, etc.
Lonza Reactor Technology

Multi-scale design to maximize heat transfer and optimize mixing

but allowing variable residence time modules ⇒ gain volume

- Up to several hundreds of milliliters (seconds to minutes)
- Plates with different widths
- To limit pressure drop

Can be coupled with coils

- Several liters (5-20 minutes)

Flow rate from 50 to 600 mL/min
No internal parallelization
Micro dimension = ca 500 µm
Larger dimension = 2 mm
Lonza Microreactor as Universal Modules

Equipment Features
- Modular, robust, over 100 bar
- Hastelloy plates: process fluid
- Aluminum plates: thermal fluid
- Compactness, easy to adapt
- Each plate = one specific design

1) Plate for multi-injection
2) Reactor system with 6 plates
3) A6 and A5 reactor systems
All Lonza Microreactors

Development Reactor
- View the chemistry
- Reaction at tiny flow rates
- Test different

Production Reactor
- Design as key ingredient to scale-up
- Avoids total parallelization
- Multi-purpose

Lab-Plate | Channel structure | Plate Size: A6 | Plate Size: A5
Pilot Plant Microreactor Technology

Key Features

- Multi-purpose system
  - Modular
  - Hastelloy
  - $T = -80$ to $+180^\circ$ C
- ATEX standards
- Qualifiable for cGMP production
- 3 dosage lines
  - 1 - 6 bar
  - 5 - 300 g/min (per line)

Track record
- Organolithium exchange
- Organolithium coupling
- Nitration reactions
Continuous Production in Launch Plant

Key Features

- Multi-purpose system
- Capacity in the range of 150 kg/h
- Campaigns were performed with in-between cleaning
- Based on conventional technology
  - Static mixers
  - Mini-heat exchangers
  - Etc.

Track record
- Simmons-Smith reaction
- Organolithium coupling
Continuous Ozonolysis (Gas-liquid)

Key Features

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

Track record
- Several ozonolysis projects
Commercial Manufacturing: Track Record

Chlorination
- Falling film reactor.
- Highly exothermic reaction ($\Delta T_{\text{adiabatic}} > 250^\circ\text{C}$).

Dehydrogenation
- Heterogeneous catalyst filled in a tubular packed bed;
- High temperatures $> 500^\circ\text{C}$.

Organolithium coupling reaction
- Small CSTR reactor:
  - For an exothermic reaction
  - To avoid reactor plugging.

All dedicated reactors
Mini-Plant Technology at the Center of Flow Processes

Mini-Plant concept to enable inherently safer processes from the huge impact of process intensification on the continuous process

Key Features
- Microreactor for flash reactions
- Mixers-settlers/acid neutralization
- Distillation
- Reactor cascade (CSTR)
- Liquid-liquid extraction
- Fully automated system

Throughput
- More than 10 kg/day of active compound
Lonza Niacin

- Continuous process from feed preparation to packaging
- Manufactured under cGMP conditions
- One dedicated factory in Switzerland

\[ \text{MEP} \xrightarrow{\text{HNO}_3} \text{Niacin} \]
Conclusions

Flow technologies are the heart of a quantum leap in pharmaceutical manufacturing leading to greener processes at lower costs

- Design new chemical routes

Lonza is a leading manufacturer of chemicals using flow processes and advanced technologies

- The central part of the lab development is the microreactor

Acknowledgments

- N. Kockmann, M. Gottsponer, M. Eyholzer, W. Quittmann, N. Bieler, R. Forbert, and L. Ducry
- J. Pont, D. Oehlers, B. Zimmermann, and A. Brunner
Thank you. Questions?
Lonza Proposal

Phase 1: Proof of Concept (2 wks) – milestone go/no-go

Phase 2: Optimization Study (2-4 wks) – milestone go/no-go
- Design of experiments (DOE) or complete kinetic analysis

Phase 3: Long Run Study (3 wks) – milestone go/no-go
- kg-Lab production from 1–20 kg

Phase 4: Pilot Production & Commercial Manufacturing
- From 20 kg to 2.5 tons of product for pilot production
- Ton quantities for commercial manufacturing
  - CAPEX assessment