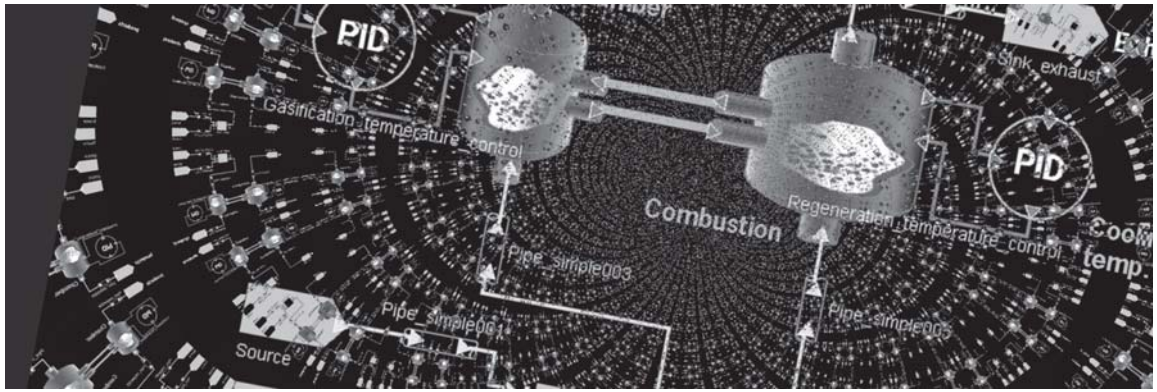


Continuous Flow Technology: Is the Batch Process Dead?

Lonza

Growth of Continuous Flow Technologies in Pharma

Dominique M. Roberge / Lonza AG / 16 June 2011

Our extensive know-how and offering have evolved to meet customer needs

Financially Stable / Global Footprint

- CHF 2.7 billion (2009 sales)
- 27 facilities; 8,300 employees

Focused on Life Sciences

- Bioresearch
- Pharma & Biotech
- Nutrition
- Personal Care
- Microbial Control
- Agriculture
- Materials Science

Global leader in custom manufacturing

- Chemical and biological APIs, cell therapy
- Lead optimization through market supply

Our Visp, Switzerland site is home to numerous cutting-edge technologies

Location

- 150km east of Geneva
- Footprint: 90 hectares

Fine Chemistry in Visp

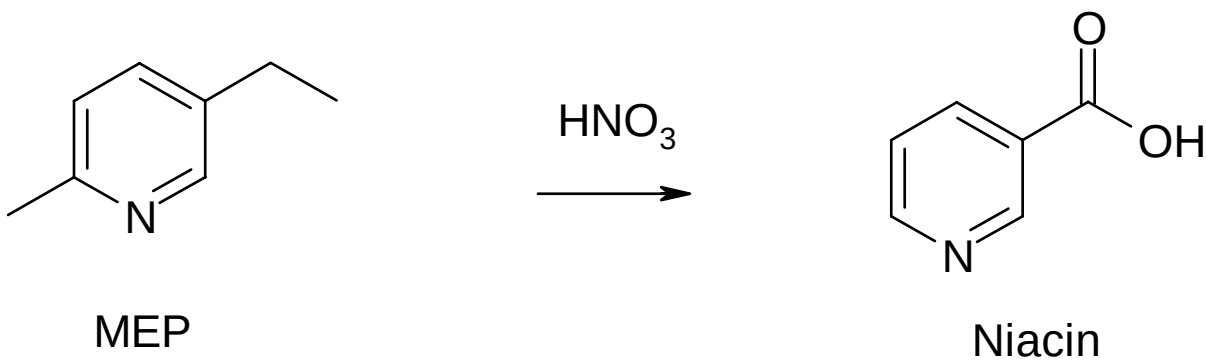
- Cracker for C2 supply
- Continuously operating production (e.g. Niacin)
- R&D, process development, small-scale production, and fine chemical complex FCC for pharma production
- Large fermentation units

Some key technologies

- Large-Scale (10m^3; total over 400m^3)
- cGMP phosgene plant
- cGMP Continuous Ozonolysis

Lonza Niacin

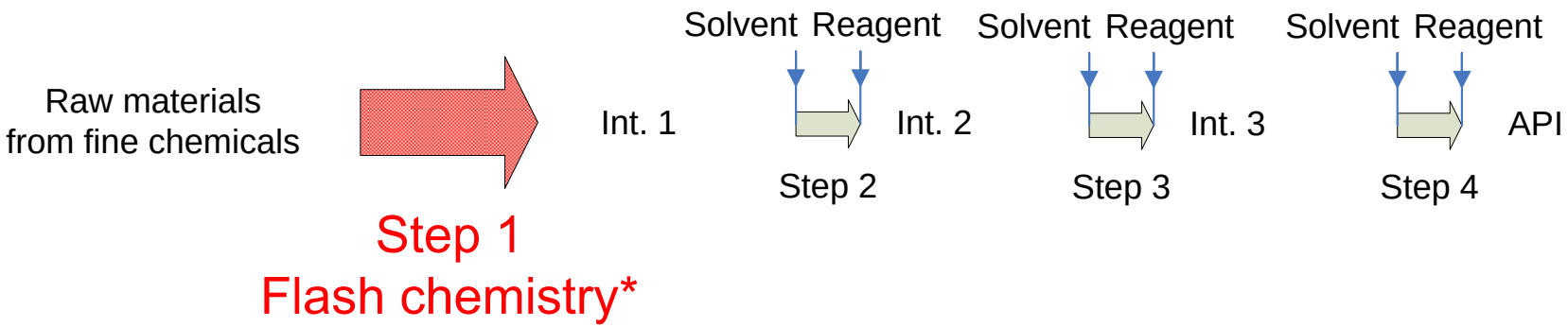
- Continuous process from feed preparation to packaging
- Manufactured under **cGMP conditions**
- One dedicated facility in Visp, Switzerland



MEP

Niacin

Re-design the Chemical Routes with the Concept of Flash Chemistry in Flow



- Flow Processes / Microreactors lead to drastic improvements
  - Excellent heat transfer & mixing
  - Exact control of residence time
  - Segregation of feeds, small volume, robust (pressure) etc.

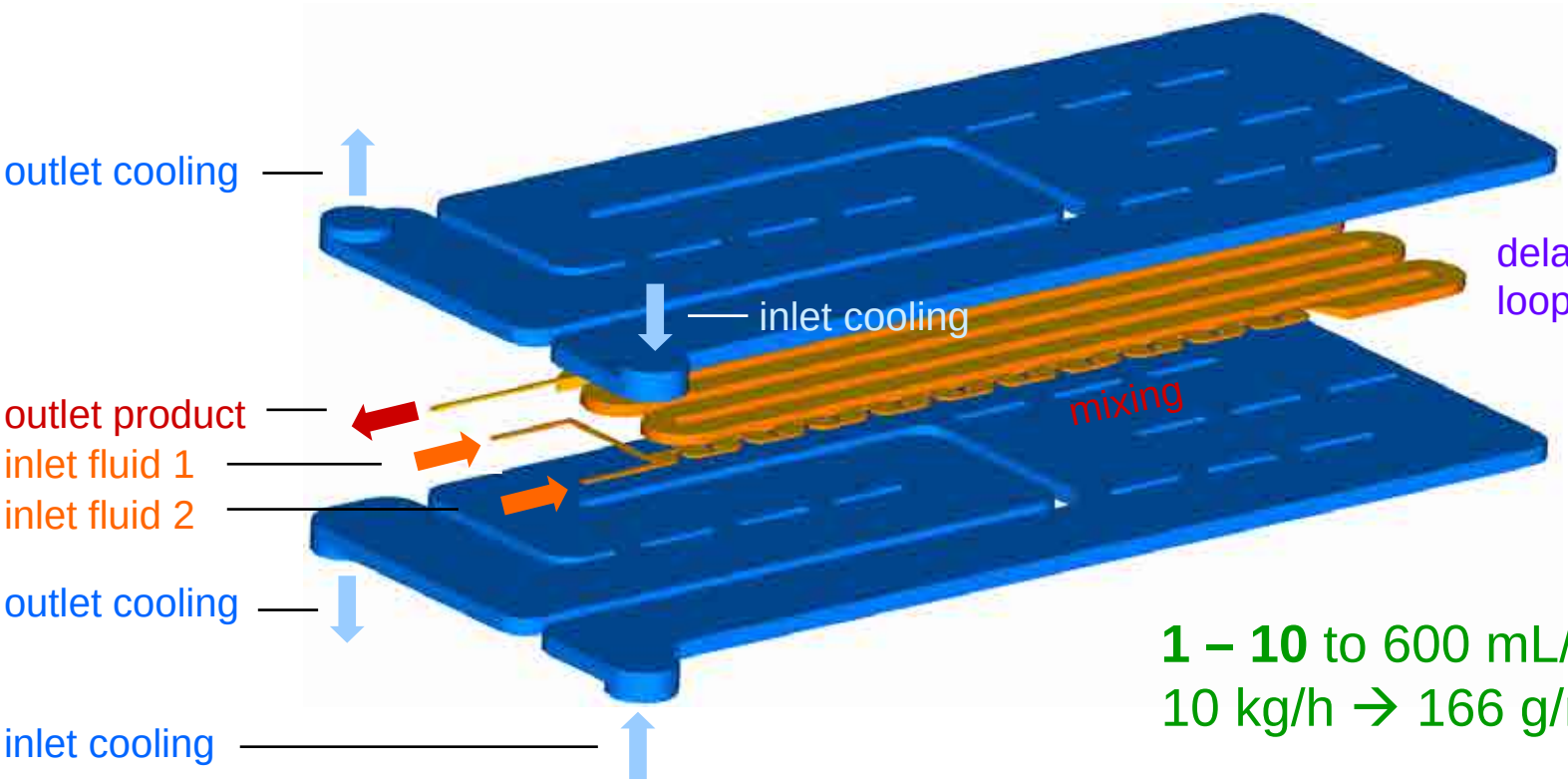
- **Inherently Safer Design** from the high level of confinement

= Intensified Mini-Plant Concept

* flash chemistry concept see: Yoshida, J.-I. et al., *Chemistry - A European Journal* **2008** (14) 7450

Microreactors are at the heart of a dramatic shift in API production

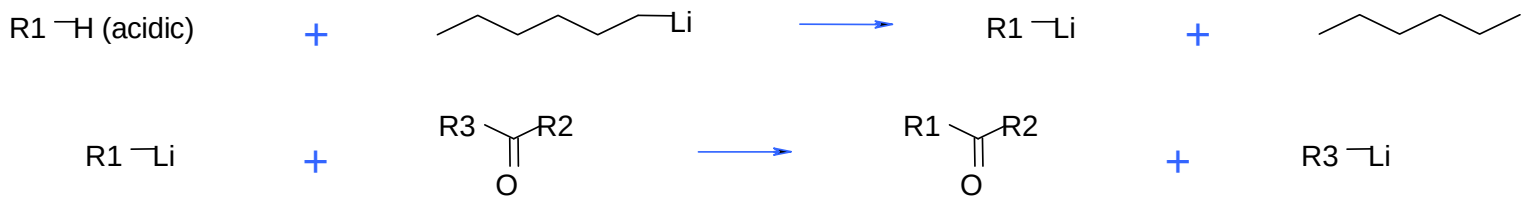
It enables **continuous processes** based on plug flow reactors with **minimal volume** of reagents, **rapid dynamic responses** and robustness, **good temperature control**, **efficient mixing**, etc.



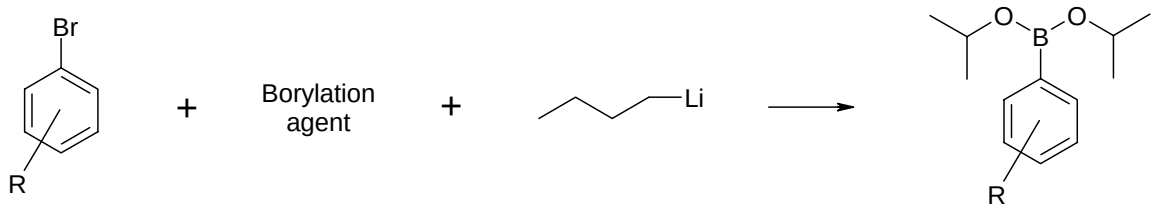
1 – 10 to 600 mL/min
10 kg/h → 166 g/min

Example 1: Control of Organometallic Reactions based on HexLi/BuLi

3-Feeds setup via 2 reactions in series



2-Feeds setup via 1 single reaction (In Situ Quench Method)

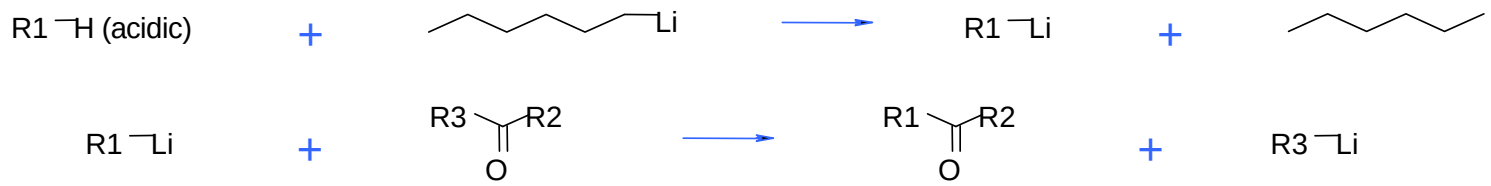


in collaboration with AstraZeneca

- **Exact control of residence time**: Li intermediates are short-living = s to m reactions
- **Perfect control of micro-mixing**: Bromo compound reacts faster than the quench reagent (borylation agent) = ms reactions

Lonza FlowPlate™ Reactor to Control Reaction Heat

2-Step Synthesis: Lithiation and Coupling



Some Disadvantages

- **Plugging** = Lonza patent applied Ultrasonic De-plugging System

First reaction: Type A, highly exothermic (ΔT_{ad} > 75°C)

- Microreactor

Second reaction: Type B, exothermic (ΔT_{ad} < 25°C)

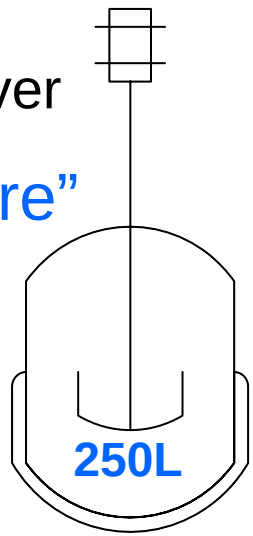
- Use of a static mixer under adiabatic conditions

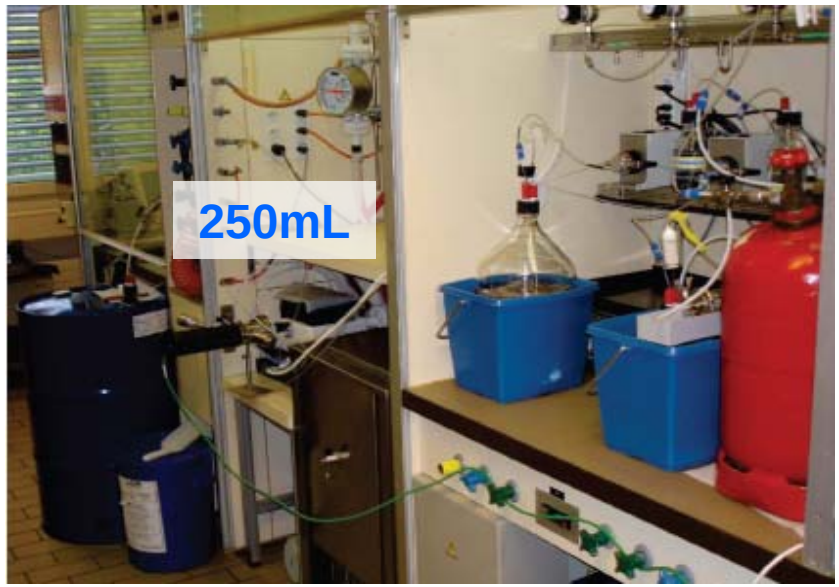
Microreactor Technology Leads to Dramatic Process Intensifications

Process intensification to enable inherently safer processes leading to a production paradigm

- Lower reactor investment
- Less manpower
- Higher flexibility
- Enhance safety
- Faster change-over

"Factory of the Future"

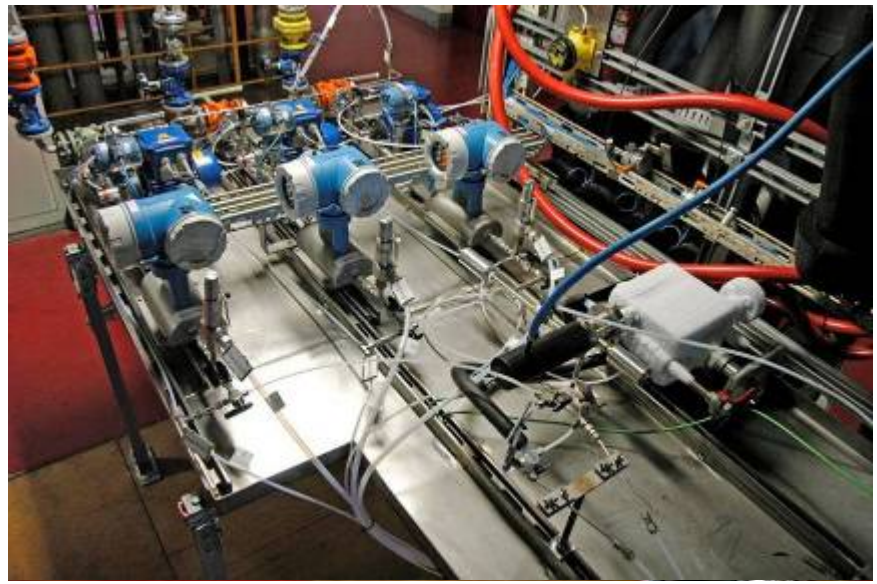




Pilot Plant Microreactor Technology

Key Features

- Multi-purpose system
  - Modular
  - Hastelloy
  - T = -80 to +180°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

Please visit the reactors at booth H.18

EHRFELD Mikrotechnik BTS
A Bayer Technology Services Company

Lonza

Lonza FlowPlate™ Reactors

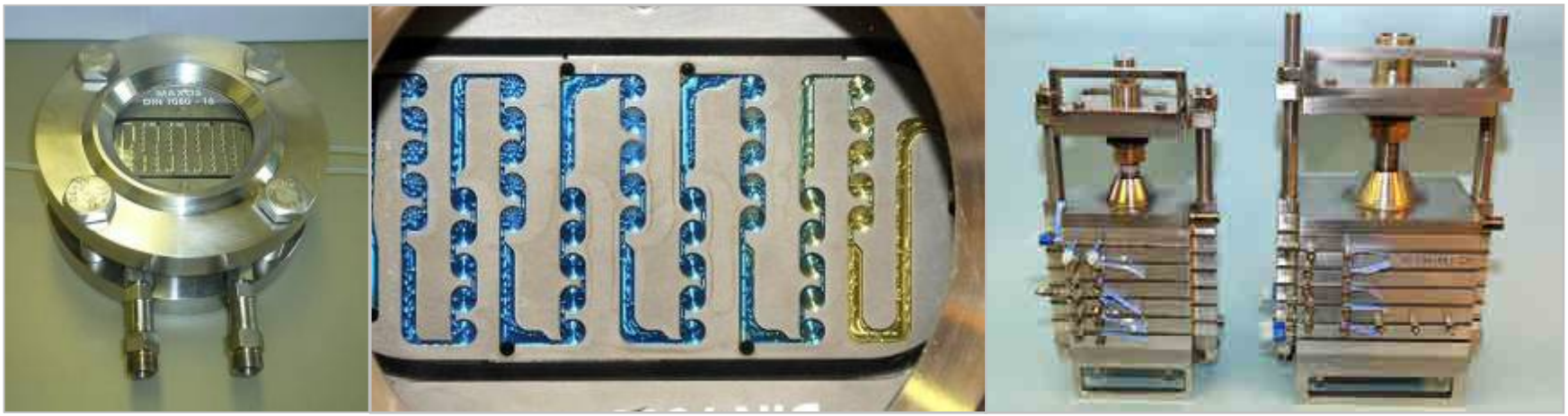
Development Reactor

- View the chemistry
- Reaction at tiny flow rates
- Test different channel geometries

Production Reactor

- Design as key ingredient to scale-up
- Avoids total parallelization
- Multi-purpose and modular

Lab | **Channel structure** | **Plate Size: A6** | **Plate Size: A5**



Please visit the reactors at booth H.18

EHRFELD Mikrotechnik BTS
A Bayer Technology Services Company

Lonza

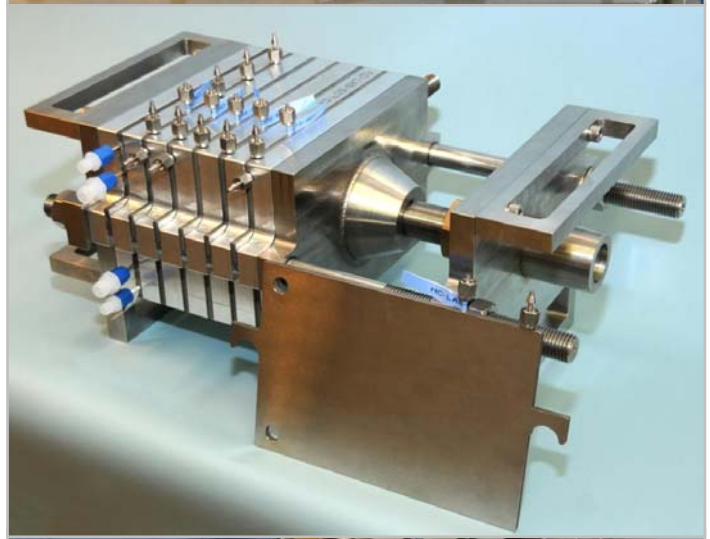
Lonza MicroReactor as Universal Modules

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

2



3

1 Plate for multi-injection

2 Reactor system with 6 plates

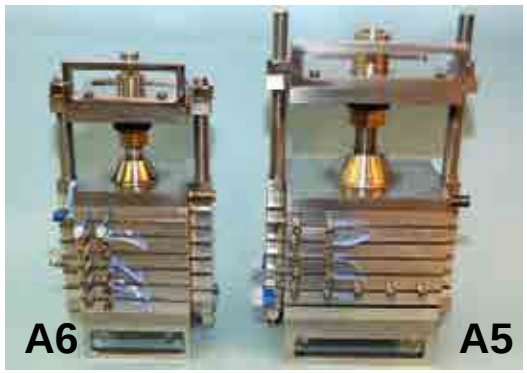
3 A6 and A5 reactor systems

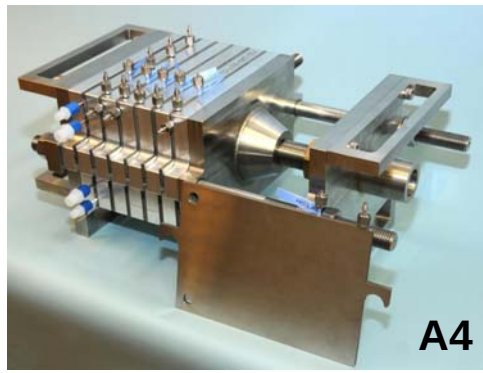
Please visit the reactors at booth H.18

EHRFELD Mikrotechnik BTS
A Bayer Technology Services Company

Lonza

Scale-up Concept with MicroReactor in Plant

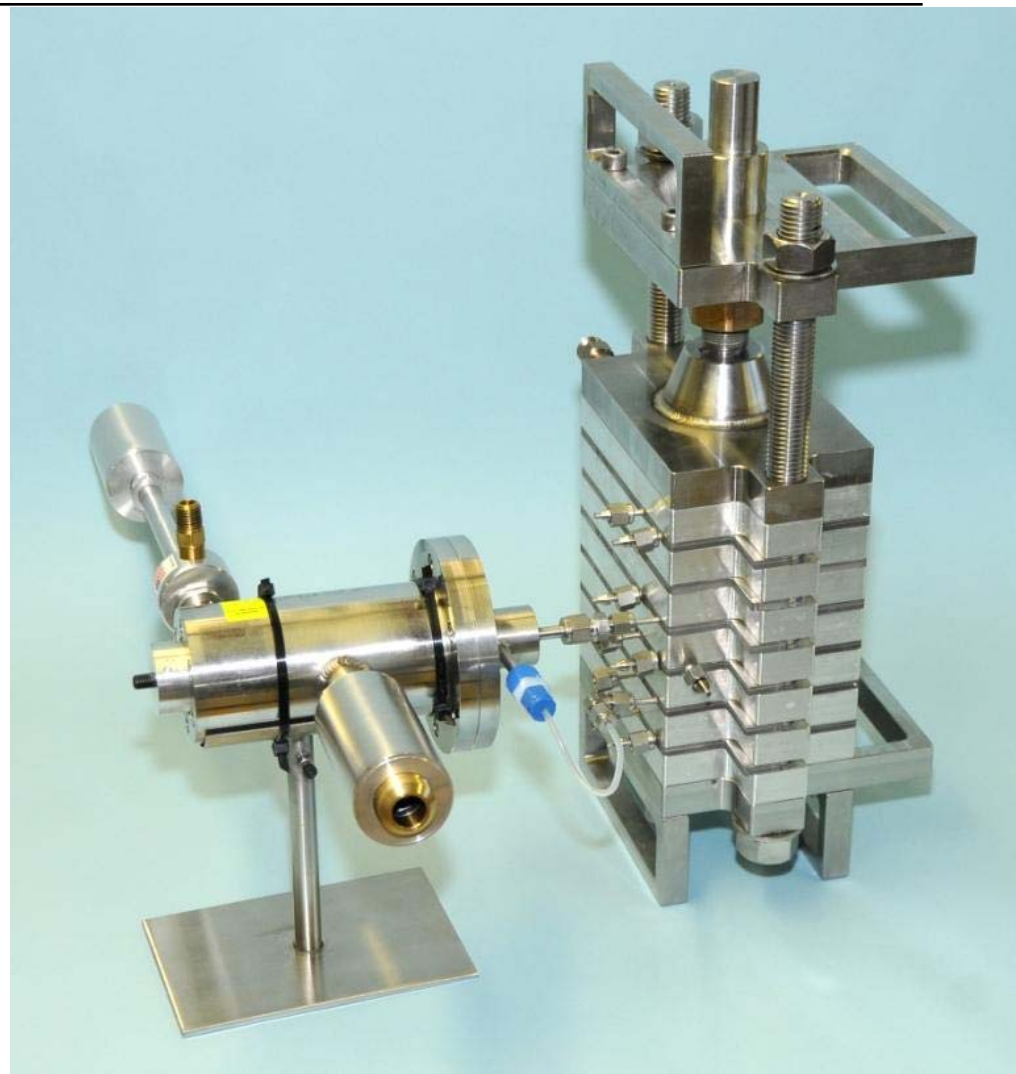




Laboratory System	Small-Scale	Large-Scale
MicroReactors & conventional technology	MicroReactors & conventional technology, cGMP, EX environment	MicroReactors & conventional technology, cGMP, EX environment
1-30 g/min sample production	**15-300 g/min** 2-10 kg campaigns **300-600 g/min** 0.1-2 t campaigns	**0.6- 5 kg/min** 50 t + campaigns
Pre-clinical phase Process research Process development	Phase 1, 2, 3	Commercial Products

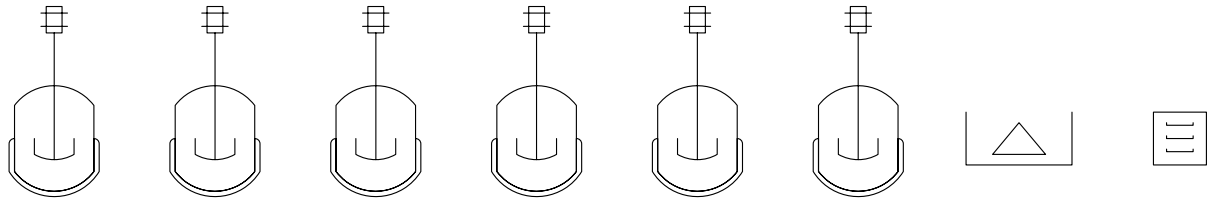
Lonza Ultrasonic De-plugging System

- Optimize to use with Lonza MicroReactors
- Ultrasonic System to enable stable operations over days / weeks
- Imperative when working with organometallic like BuLi / Grignard
- Ultrasound is generated in the liquid → to create true cavitation
- Optimal for spot plugging like in the mixing zone or exit

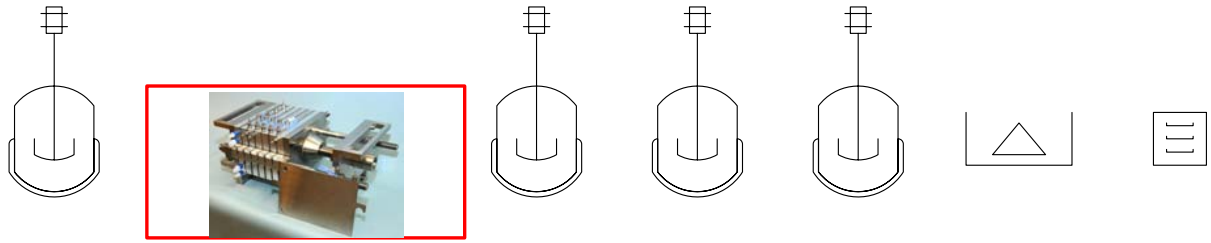


The Future of Flow Processes: Full Integration of MRT in Production Units

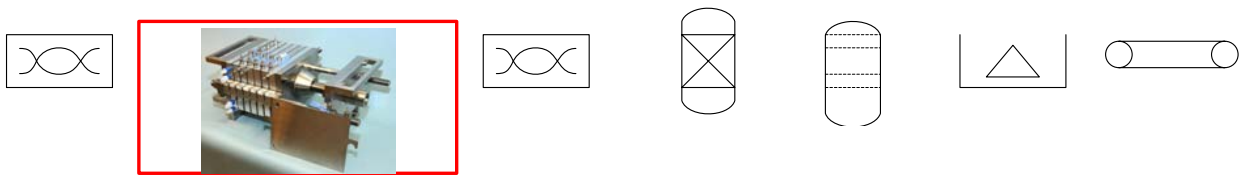
In the past conventional means all batch processes



Currently the MR is used to increase reaction yield & safety

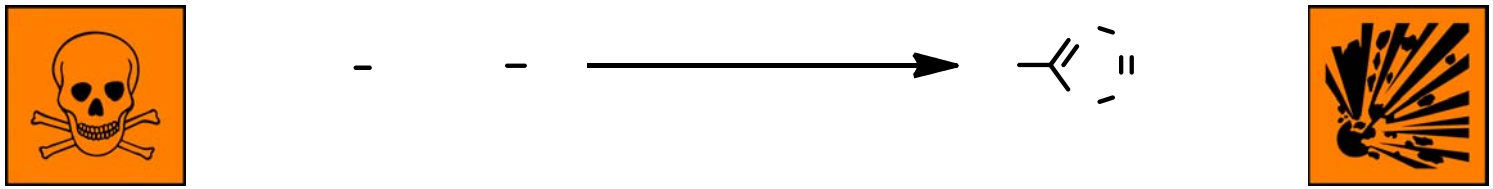


Future will lead to fully integrated flow processes: MR and more…



Example 2: Azide Chemistry In Microreactors

Azide-Nitrile Addition to make Tetrazole Derivatives



Typical Type C reaction requiring several hours

The mixture was heated under a N_2 atmosphere at **100-105°C for 50 h**

- **Segregation of Feeds**: NaN_3 prepared in a special containment and precisely mixed in the reactor avoiding batch bulk handling
- **Volume Minimization & Robustness**: Atmospheric batch process with 100% accumulation of heat → in a bunker

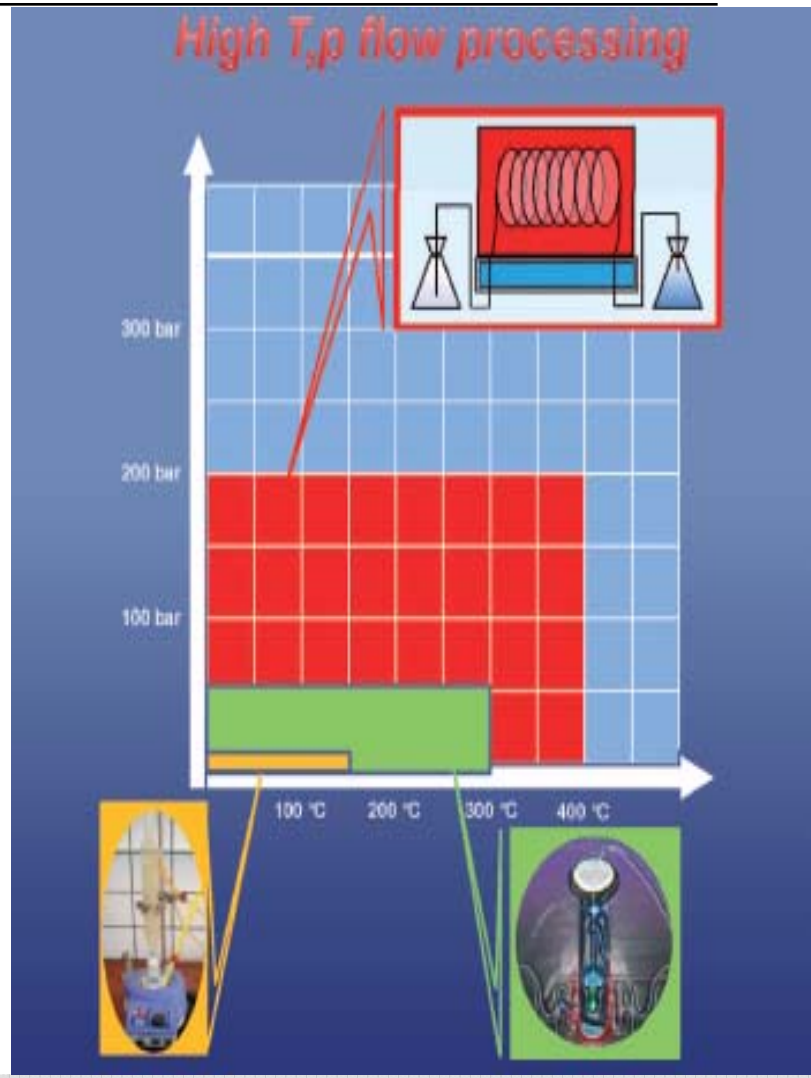
Development of Type C Reactions in MW

Advantages

- Small autoclave in glass of 2 mL that can sustain ca 20 bar
- Expeditious reaction mixture heat up
- Use extensively in the medicinal chemistry

Disadvantages

- Not scalable in bulk
  - Microwave penetration is a few mm only
- Larger cost of energy
- No magic MW effect



Strategy

MicroWaves

www.biotage.com

- High throughput machine
- Higher degree of freedom than in CF

transpose

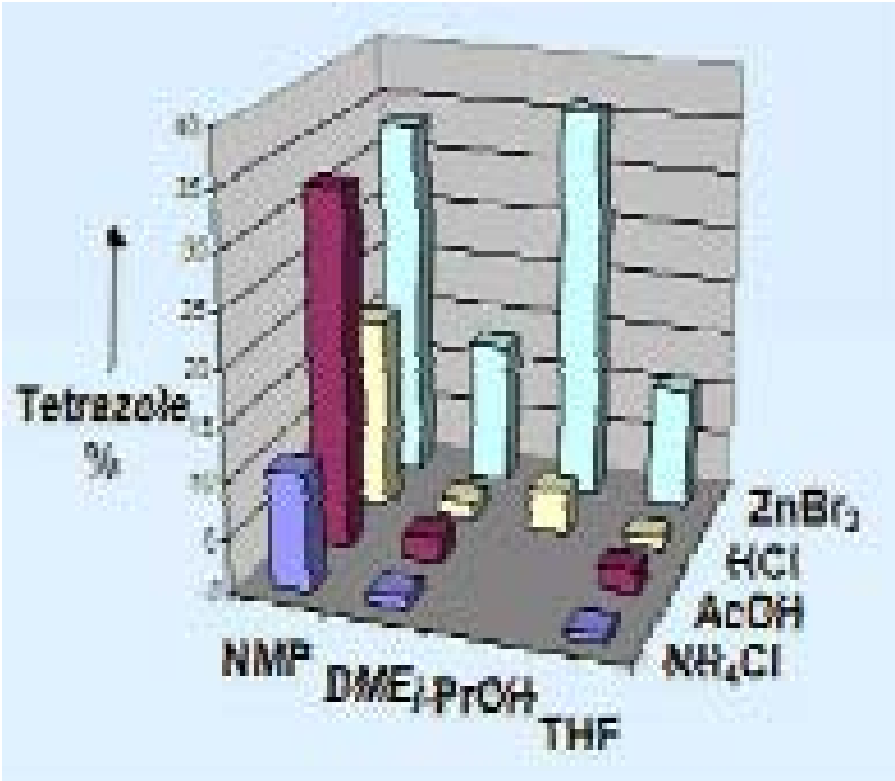
CF / MicroReactors

www.uniqsis.com

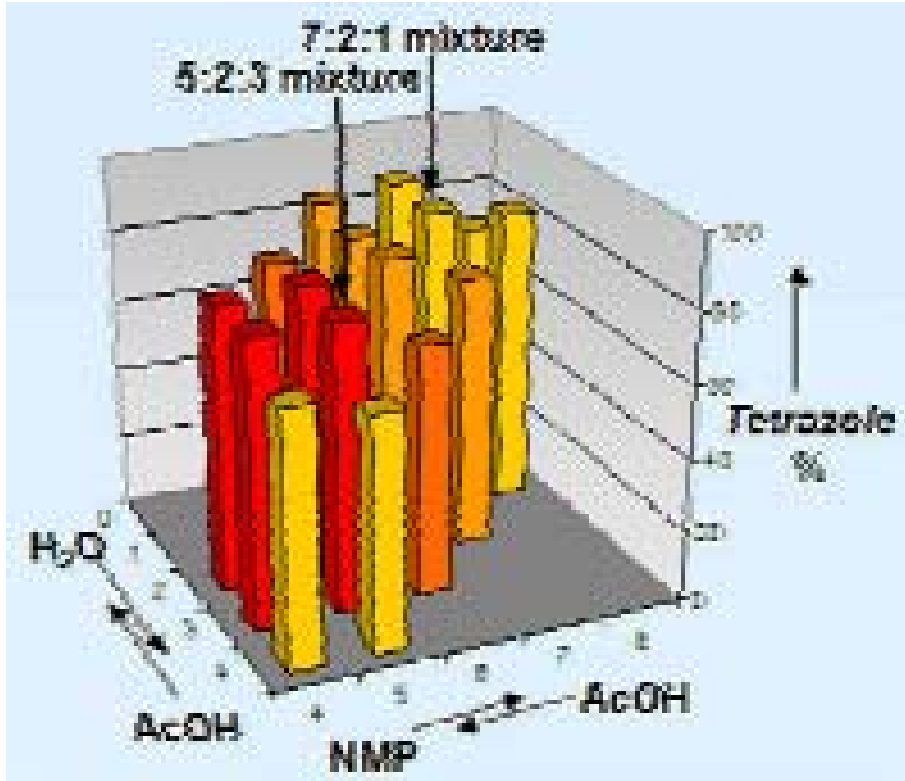
- High throughput machine as well
- Need homogeneity
- **Results are transposable**

MW Screening Results

Solvents / Additives

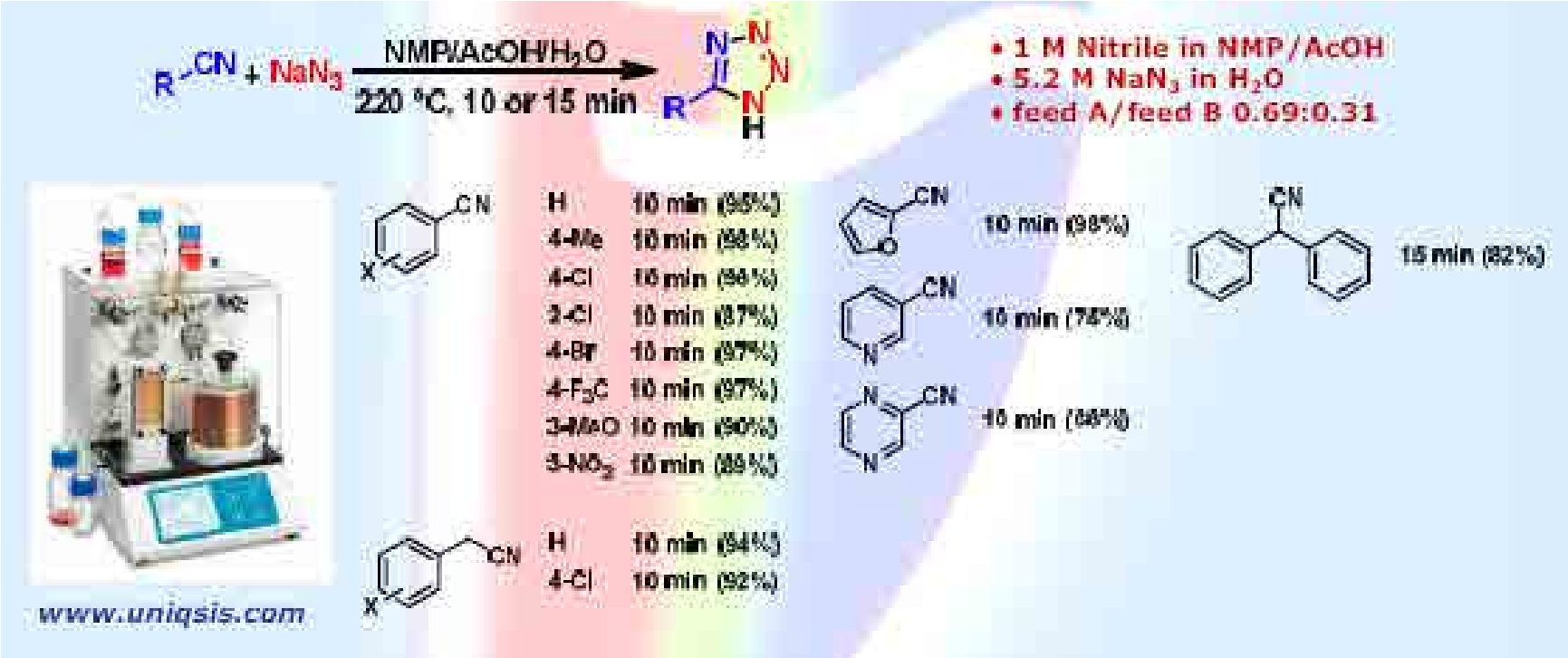


Solvent Composition



Solvents / Additives

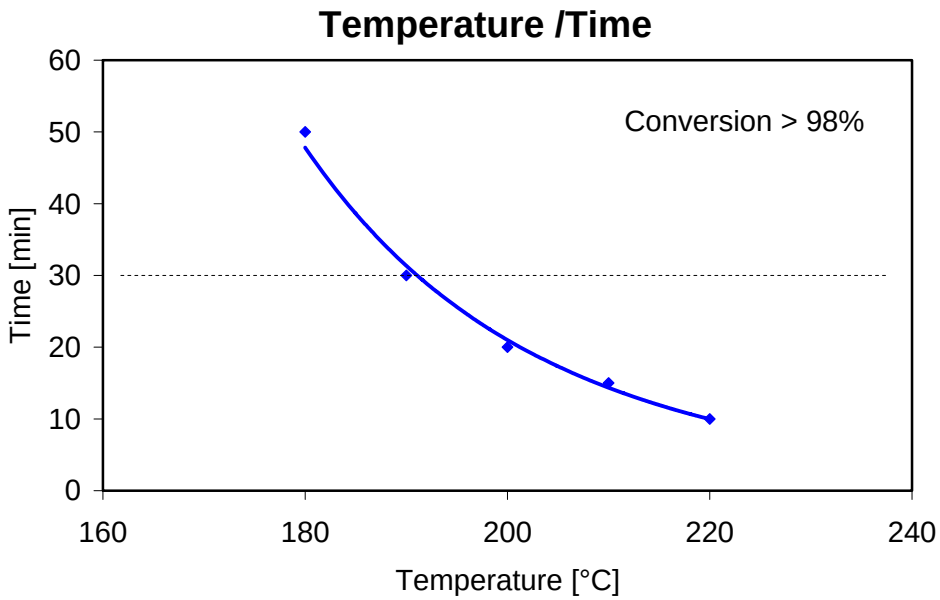
Optimization in CF



Optimized in CF

- NMP/AcOH/H2O = 5/2/3
- Slightly reduce reaction rate

Drastic Intensification via Flow

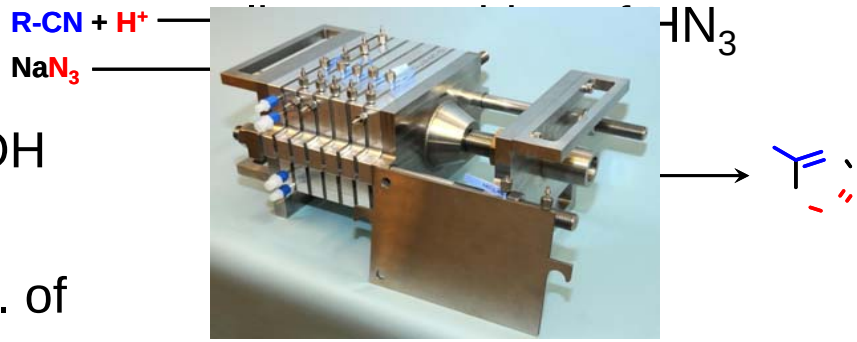


Optimized Conditions

- Acetic acid as proton donor = in situ formation of HN_3
- Water to allow solubility of NaN_3
- Micromixer at higher T = avoidance of precipitation
- No HN_3 headspace and in-

Segregation of Feeds

- Feed-1: 1 M nitrile in NMP / AcOH
- Feed-2: NaN_3 in water
- NMP/AcOH/H2O = 5/2/3, 2 equi. of NaN_3



Reaction and Work Up Integrated in One Flow Unit

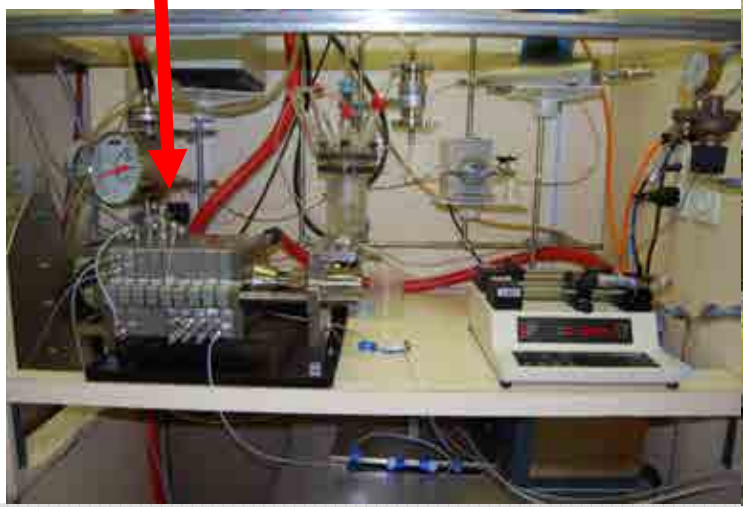
Mini-Plant concept to enable **New Processes** and extend the design space of how we perform chemistry

Key Features

- Microreactor for a **flash reaction**
- CSTR for precipitation
- High pressure valve
- Filter to removal salt
- Wiped film evaporator
- Fraction collector

Throughput

- More than 1 kg/day of product; distillation is limiting



Mini-Plant Technology at the Center of Flow Processes

Mini-Plant concept to enable **New Processes** and extend the design space of how we perform chemistry

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

Throughput

- 250 mL → 10 kg/day of product
- 1000 mL → 40 kg/day

Batch Versus Flow: Comparison at Various Scales

Example 1: Process development in clinical trials / kg scale	
Batch Process	**Flow Process**
Reactor volume = 250 L	Reactor volume = **250 mL**
	Faster change over & cleaning
	Manufacturing gain = **up to 30%**
Example 2: Commercial manufacturing / ton scale	
Batch Process	**Flow Process**
Reaction time = **10 - 14 h**	Reaction time = **0.2 h**
Reactor volume = **10 m^3**	Reactor volume = **0.03 m^3**
Cycle time = 21 h	Cycle time = 16 h
Productivity = **764 kg/d**	Productivity = **977 kg/d**
Need bunker to cover the 10 m^3 Investment = 4 MCHF for a bunker infrastructure	Lower assets usage; special confinement

Please visit the reactors at booth H.18

EHRFELD Mikrotechnik BTS
A Bayer Technology Services Company

Lonza

Conclusions

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

- Design new chemical routes

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

- The heart of the process is the microreactor

Acknowledgments

- N. Kockmann, M. Eyholzer, M. Gottsponer, J.-P. Roduit, C. Noti, B. Rittiner (Lonza)
- O. C. Kappe, B. Gutmann (University of Graz)