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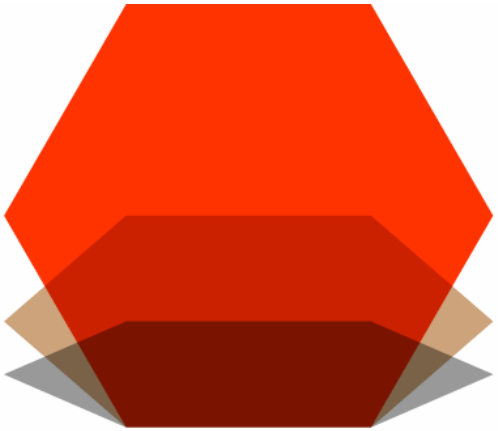
Your Specialist for Hazardous Reactions.

RSC Symposium - Continuous Flow Technology
Palexpo, Geneva, 15 -16 June 2011

Continuous Processes of Hazardous Reactions from Lab to Commercial Scale



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SYNTHESIS

Your Specialist for Hazardous Reactions.

Continuous Processing at DOTTIKON EXCLUSIVE SYNTHESIS

Introduction

Batch vs. Continuous

Development and Realization of Continuous Processes

Case study I

Case study II

Summary

DOTTIKON EXCLUSIVE SYNTHESIS,
Your Specialist for Hazardous Reactions.

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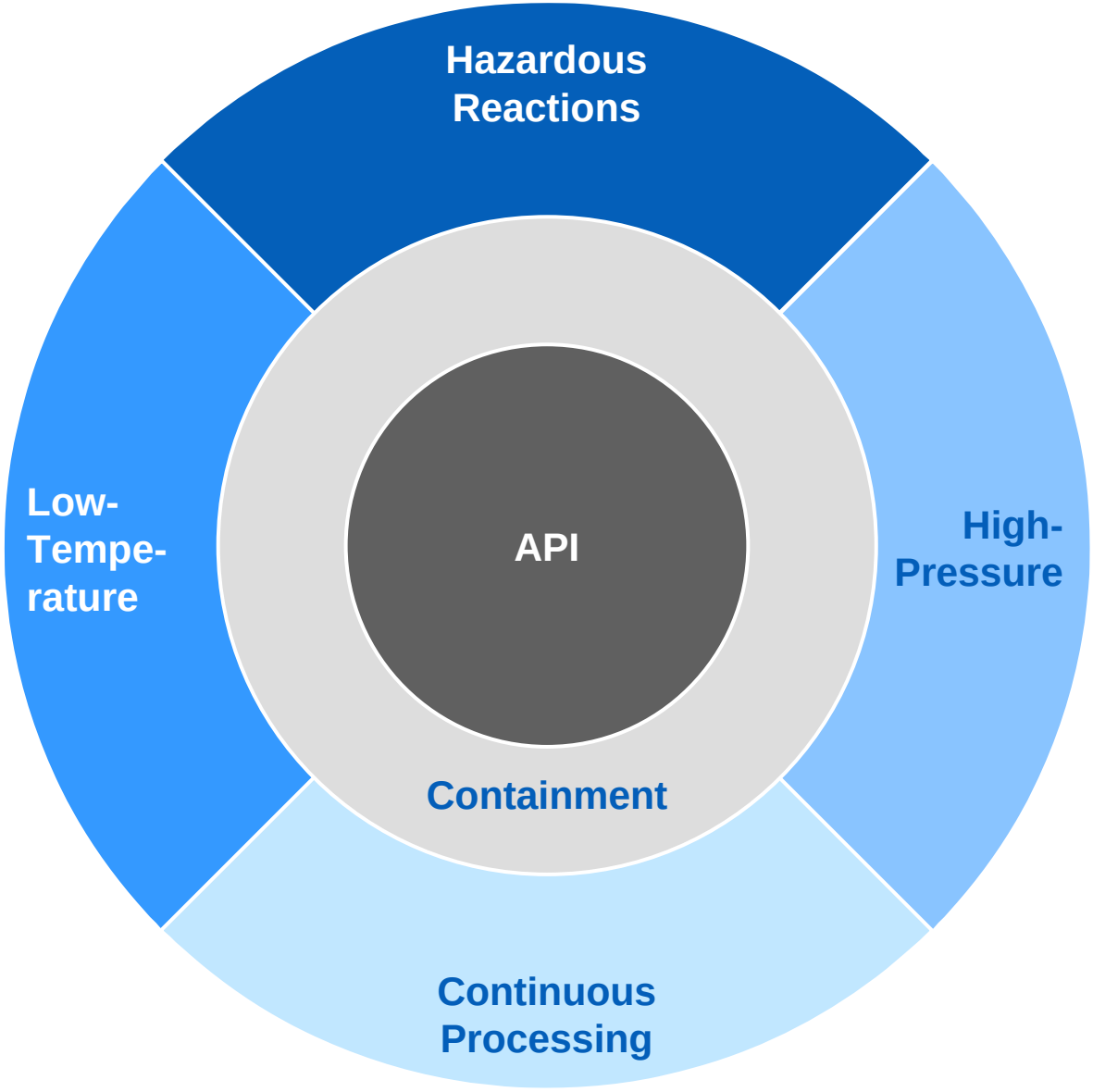
DOTTIKON ES' Technology Platform



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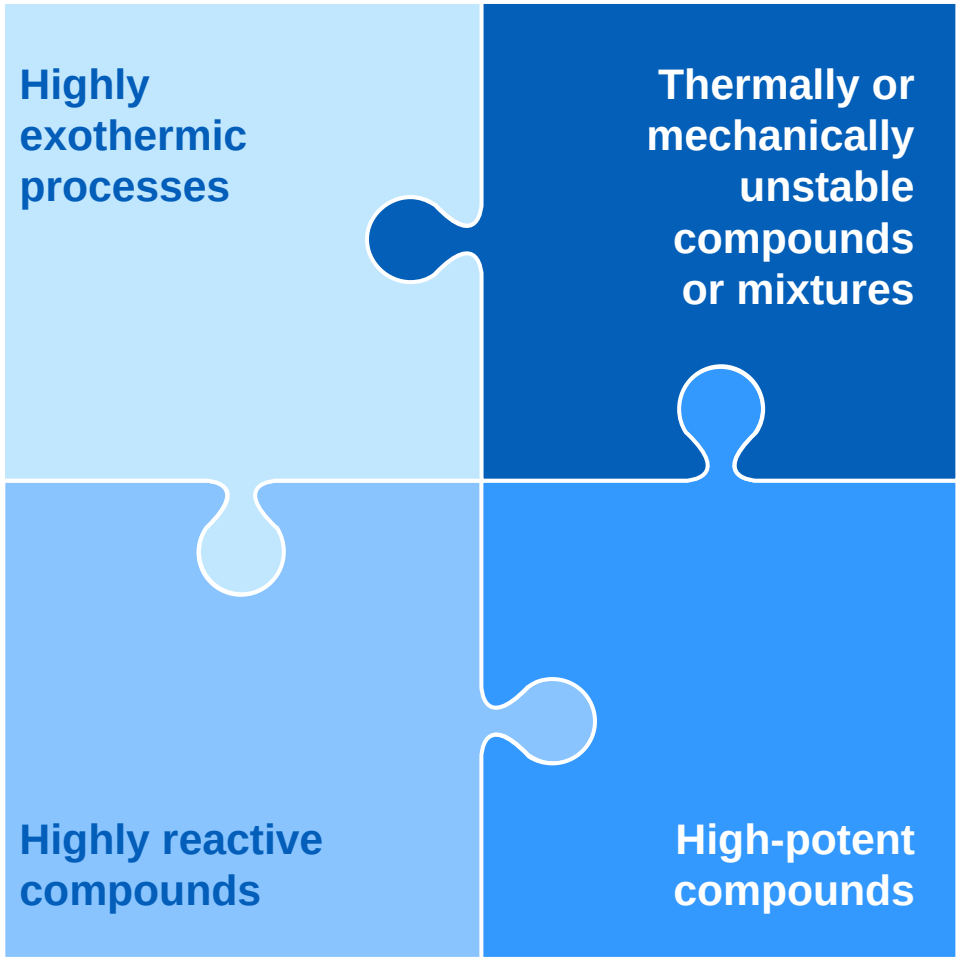
Hazardous Reactions

- Nitrations
- Grignard reactions
- Hydrogenations
- Oxidations



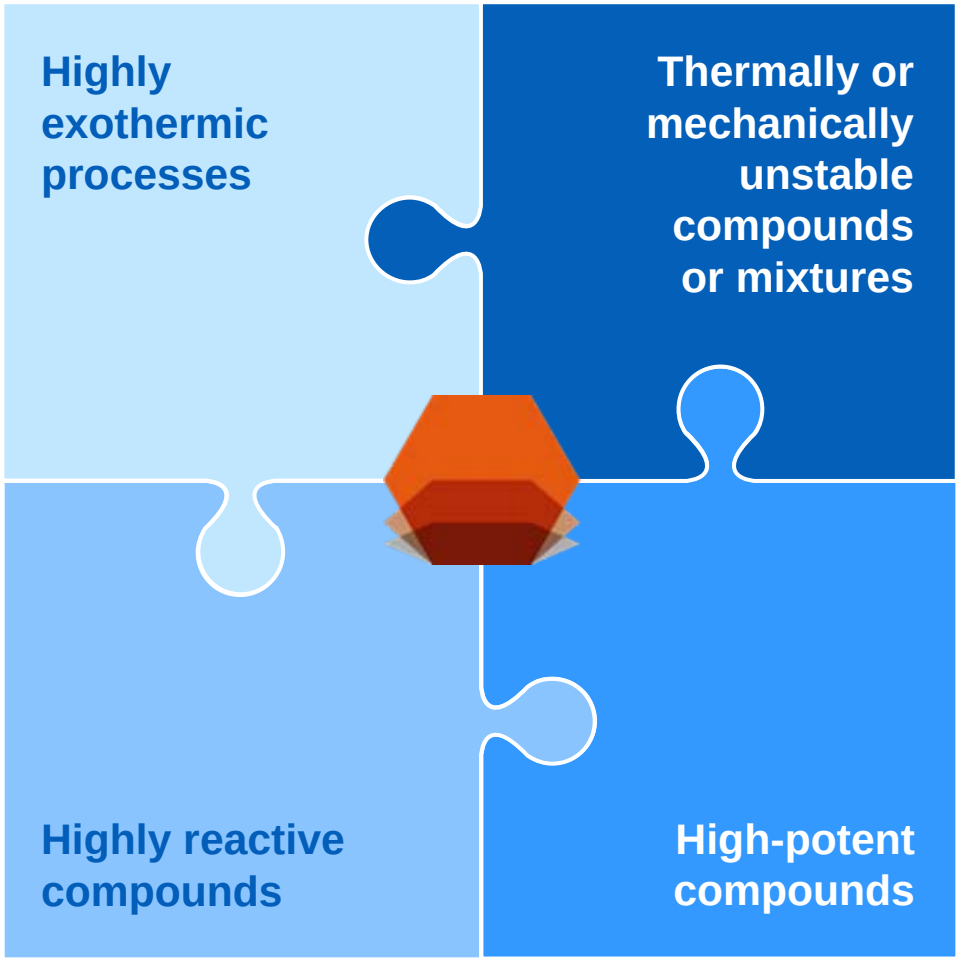
- Nitro compounds
- Azides
- Nitrate esters
- Peroxides
- Diazo compounds

- Hydrides
- Dimethyl sulfate
- Nitric acid
- $POCl_3$, PCl_5, $POBr_3$, PBr_3
- $SOCl_2$, SO_2Cl_2

- HAPIs
  - 20–100 µg/m^3
  - 1–20 µg/m^3
  - <1 µg/m^3

Hazardous Reactions at DOTTIKON ES

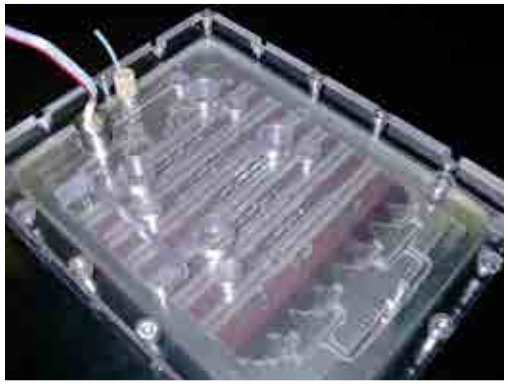
Prerequisites for Development and Production

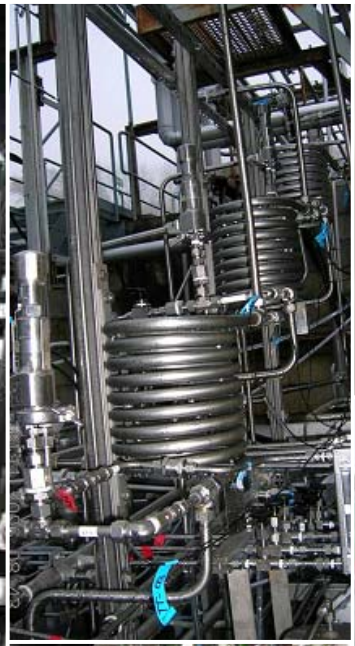


- Profound knowledge of critical process and engineering parameters
- Dedicated equipment on all scales
- Strongly developed safety culture

Over 40 Years of Experience in Continuous Processing

Micro reactors	Flow reactors	
	Kg's per hour	Multi-tons per hour





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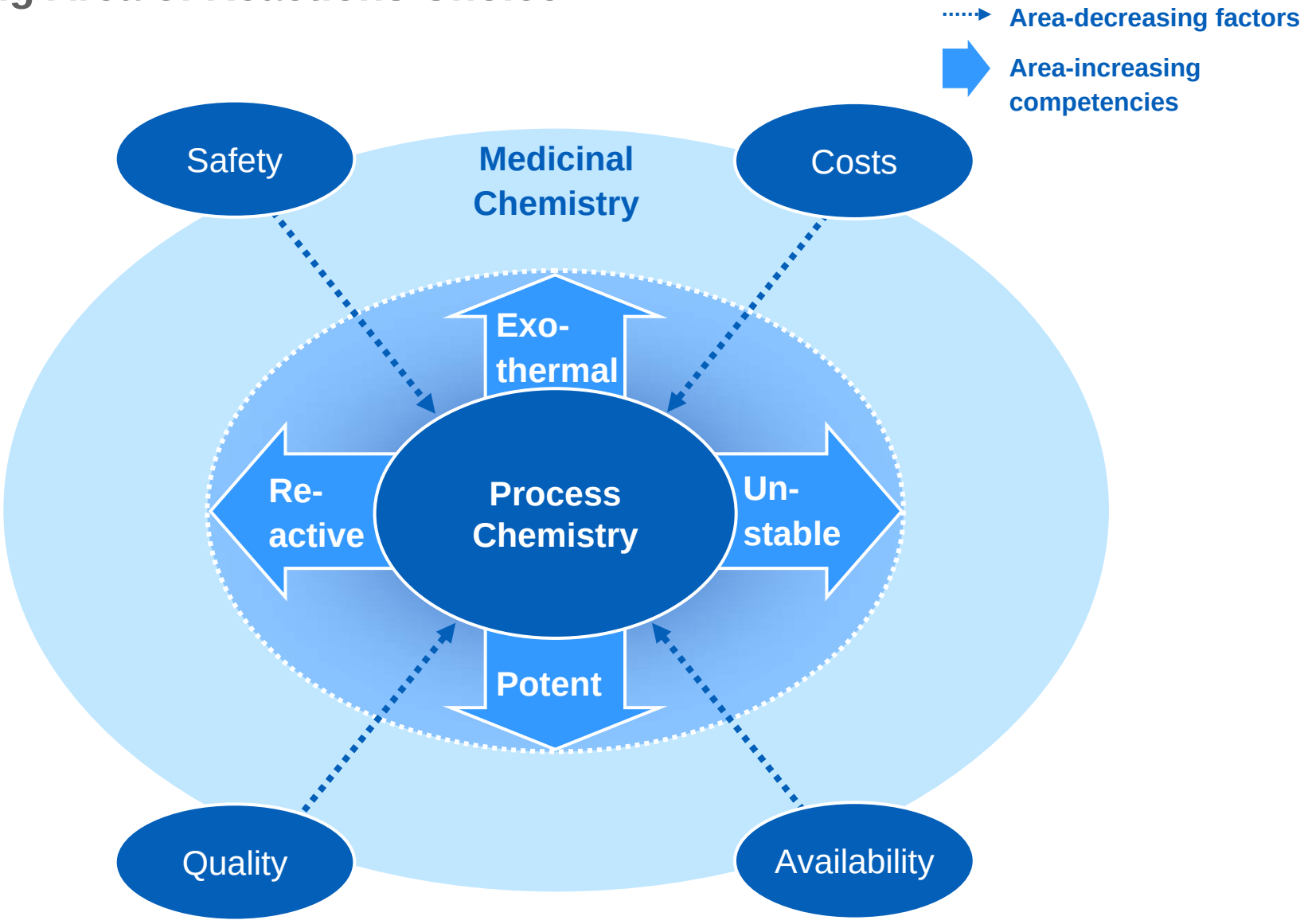
Competence in Innovative Technology Platform Allows Expanding Area of Reactions Choice



Continuous Processing at DOTTIKON EXCLUSIVE SYNTHESIS

Batch vs. Continuous

Key Characteristics

Is continuous processing in pharmaceutical chemical production useful?

	Commodity products	Specialized products
Volumes	100's – 1'000's mt/year	1 – 100's mt/year
Demand	Steady	Variable
Quality	Standard quality	Customized
Production mode	Ongoing	Campaign wise
Plant type	Mono	Specialized multipurpose

Continuous

- High productivity
  - Full automation
  - High utilization

Batch wise

- High flexibility
  - Semi automation
  - Low product change effort

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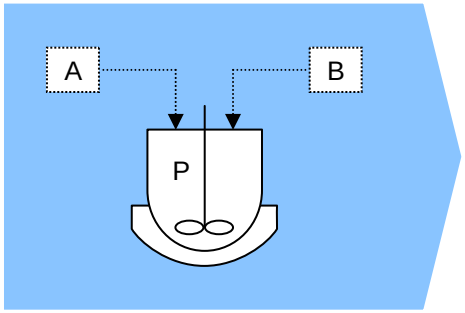
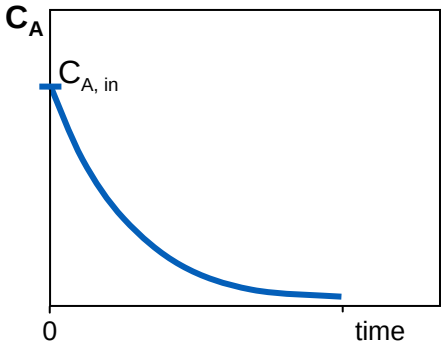
From Batch to Continuous

CONCEPTUAL

Different Reactor Concepts for Ideal Conditions

Batch

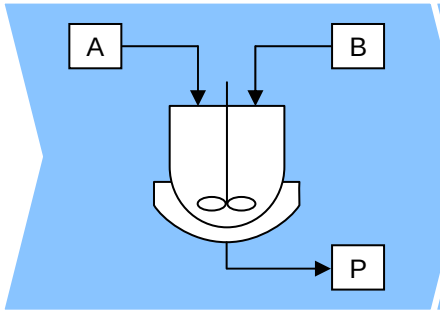


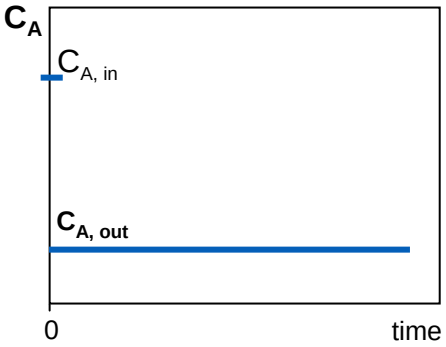


Composition change over time

- Suitable for most reactions
- Simple, flexible multipurpose equipment
- Batch
- Batch wise quality control
- High critical volume
- Low heat exchange capacity

CSTR*

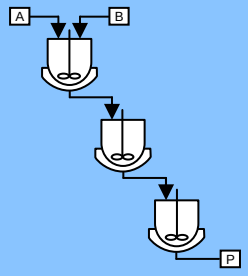


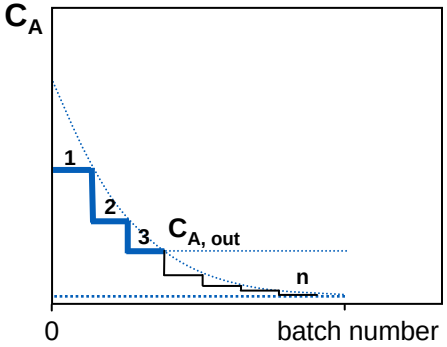


Composition constant over time

- Fast reactions
- Simple, flexible multi-purpose equipment

Cascade

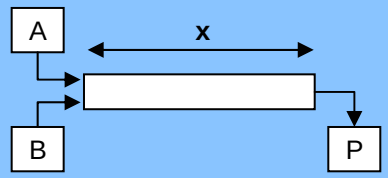


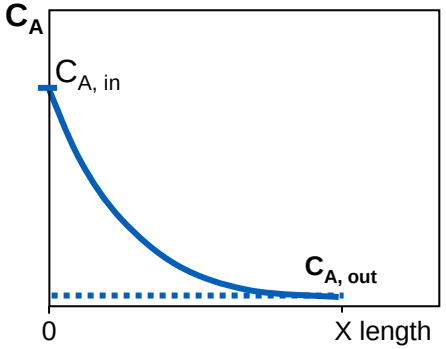


Composition different, but constant in each reactor over time

- Fast and exothermic reactions
- Expensive and complex equipment

Plug Flow





Composition change along reactor length

- Fast and exothermic reactions
- Inexpensive, dedicated equipment

- Online quality control
- Low critical volume
- High heat exchange capacity

* Continuous Stirred Tank Reactor

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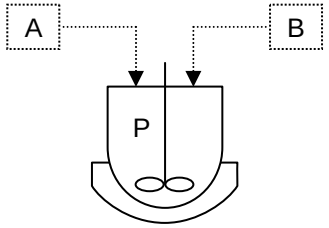
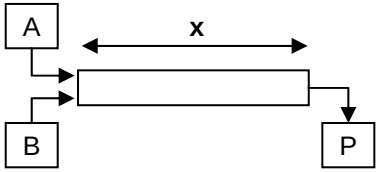
Comparison of Batch and Flow Reactor

Key Characteristics

	Batch reactor	Flow reactor
		

Basic require-ments for reaction mixture	▪ Homogeneous and heterogenous
	  ▪ Solid
	  ▪ Fluid
	  ▪ Gaseous
	▪ Up to high viscosity (stirrer power)
		▪ Mainly homogeneous
		  ▪ Fluid
		  ▪ Gaseous
		▪ Up to medium viscosity (pressure drops)

Adequate chemical reaction types	▪ Most chemical reactions, however limited in the case of hazardous reactions	▪ Preferred fast kinetic
		▪ Hazardous reactions
		  ▪ Highly exothermic reactions
		  ▪ Highly reactive compounds
		  ▪ Toxic and high-potent compounds
		  ▪ Unstable compounds (explosives)
		▪ Kinetic controlled reactions (selectivity)

Scale-up and economics	▪ Standard equipment from small to large scale with well-known characteristics	▪ Customized equipment engineered for specific throughput

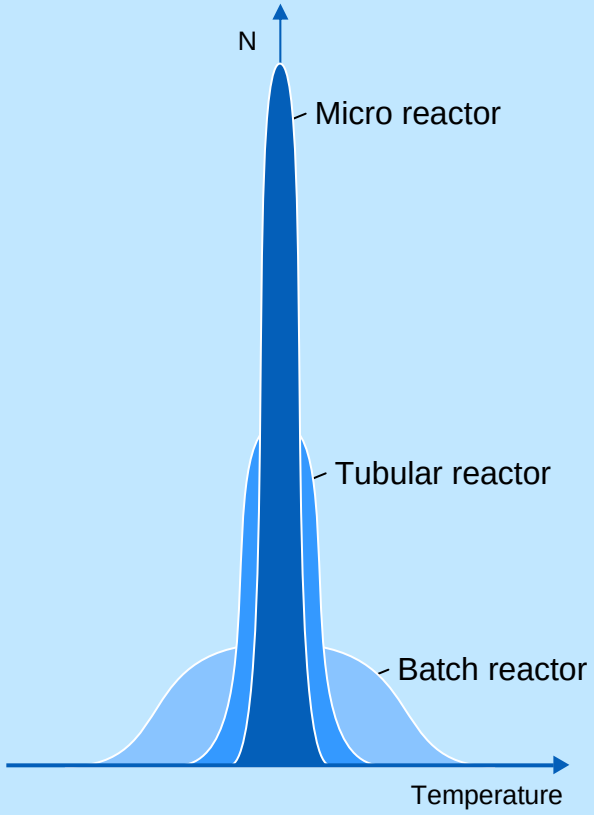
Continuous production for pharmaceuticals is useful whenever hazardous reactions are involved

Precise Temperature Profile Allows Kinetic Control

ILLUSTRATIVE

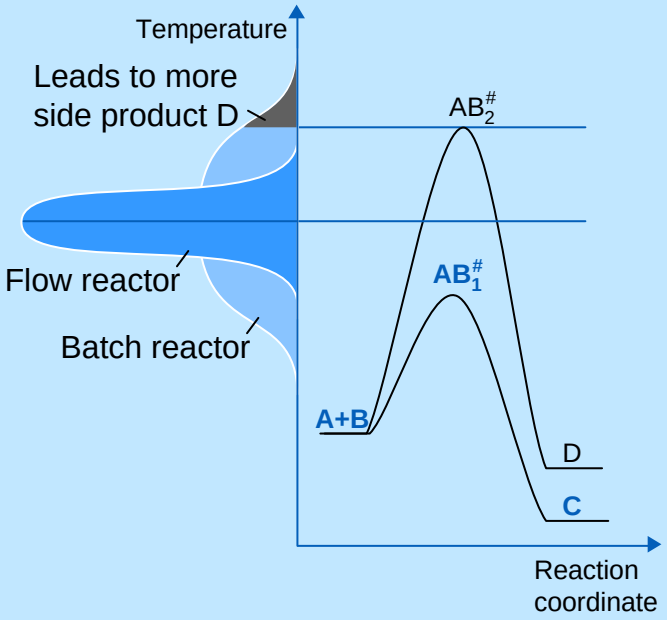
Reaction Selectivity

Temperature profiles



- Flow reactors have a sharper temperature profile than batch reactors

Improved selectivity through narrow temperature distribution



Improved selectivity in flow reactor

- High heat transfer
- Efficient mixing (no hot spots)
- Micro reactors allow best selectivity

Side reaction

$A+B \rightarrow AB_2^{\#} \rightarrow D$

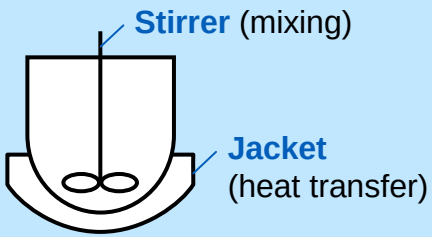
$A+B \rightarrow AB_1^{\#} \rightarrow C$

Preferred reaction

Source: Chemical Micro Process Engineering, V. Hessel, S. Hardt, H. Löwe, Wiley-VCH, 2004.

Engineering Parameters of Batch and Flow Reactors

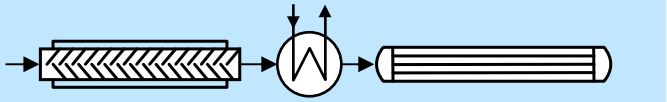
Batch reactors

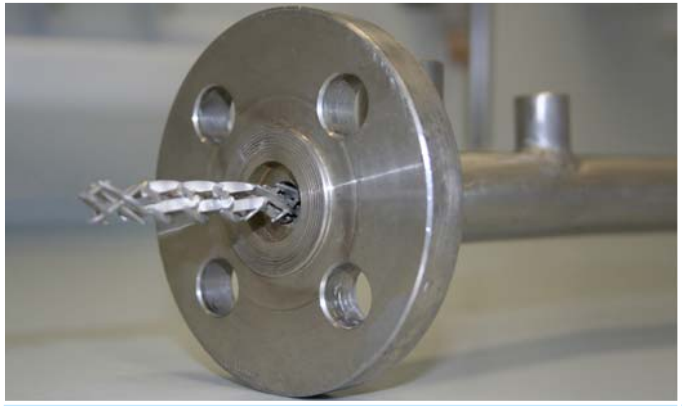


- Reactor volume
  - dm^3 – m^3
- Reactor geometry
  - Spherical / Cylindrical
- Stirrer type
- Scale up

Flow reactors

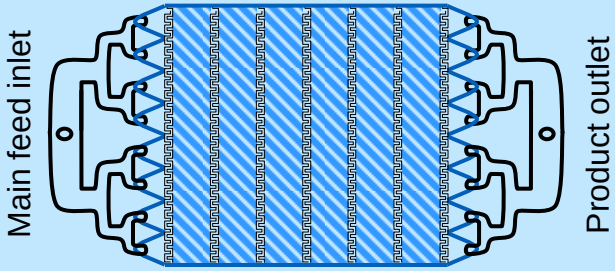
Tubular reactor

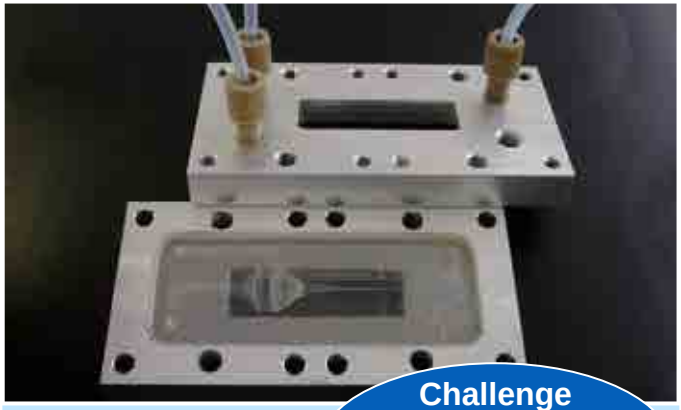




- Tube diameter
  - mm – dm
- Tube length
- Number of tubes and type of mixers
- Flow distribution system
- Scale up and parallelization

Micro reactor





Challenge
Clogging of channels with insoluble side products

- Channel diameter
  - µm – mm
- Channel length
- Channel wall dimension and structure
- Flow distribution system
- Number of channels / numbering up

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Continuous Processing at DOTTIKON EXCLUSIVE SYNTHESIS

Continuous Processing

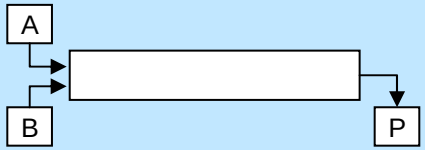
Chemistry

- Possible improvement of
  - Reaction rate
  - Selectivity
  - Yield
  - Quality
- Process intensification

Engineering

- Equipment fitted to chemistry
- High mass and heat transfer
  - Safety
  - Low critical volume
- Throughput
- Process control
- Automation

Continuous production



- Investment in dedicated continuous equipment

Economy

- Low production costs
  - High throughput/ volumes
  - Automation
- High and constant product quality

Product

Development and Realization of Continuous Processes

Process development

Reaction parameter and ranges

- Determination of relevant reaction parameters and ranges
  - Chemical reactivity and selectivity
  - Kinetics
  - Thermo-dynamics
  - Physical properties

Process layout and optimization

- Process layout based on optimal reaction parameters
- Lab simulation experiments to optimize process parameters and modules

Engineering

Design

Conceptional design

- Process flow diagram (PFD)
- Concept of process measuring and control technology

Basic design

- Engineering parameters
- Equipment list
- Cost estimates
- HAZOP analysis

Detail design

- Detailed PFD
- Equipment specifications
- Costs
- Execution plan

Construction

- Final bidding round and equipment ordering
- Build-up of equipment modules and assembling
- Configuration of measuring and control systems
- Commissioning

Production

Qualification

- Design qualification (DQ)
- Installation qualification (IQ)
- Operation qualification (OQ)
- Performance qualification (PQ)
  - Test runs

Manufacturing

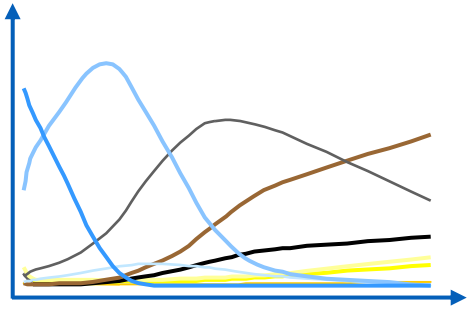
- Training of staff
- Leveling to steady state
- Standard production
- Shut down cleaning and maintenance

Process Development of Continuous Processes

Determination of reaction parameters and ranges

One shot

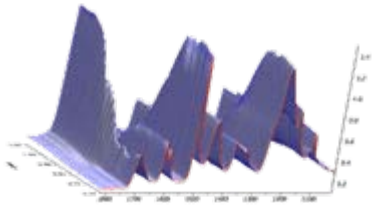
Kinetics



DSC

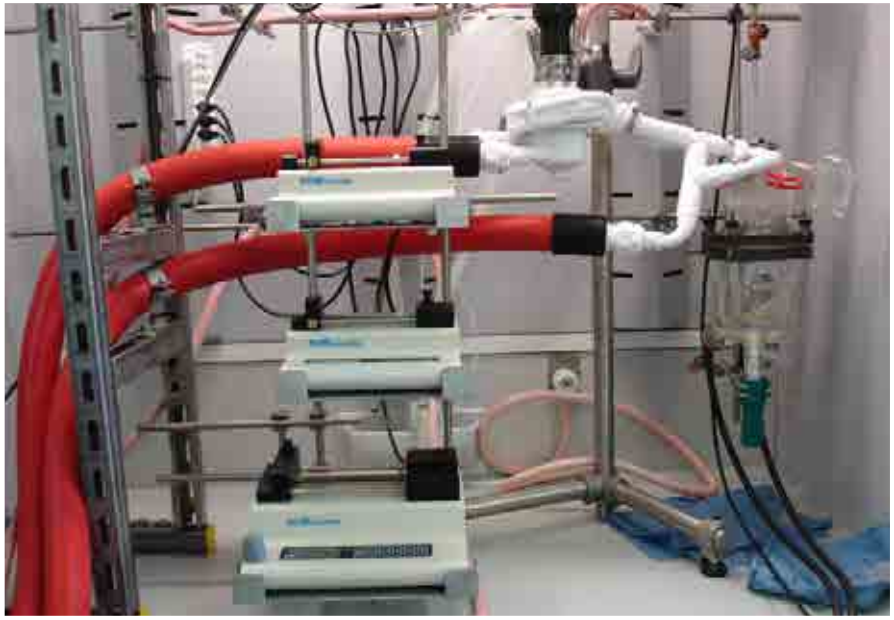
Reaction calorimetry

PAT



Process layout and optimization

Low-temperature CSTR



Micro reactor set up

Pumps

Cooling bath with microreaction unit, incl. reactor, residence time unit, quench, analytics

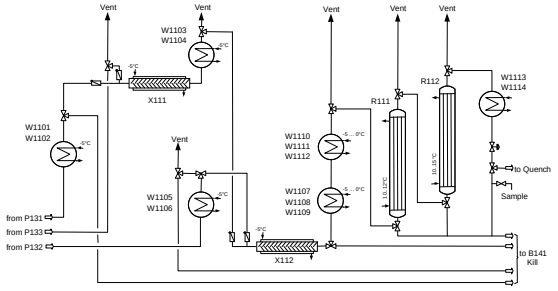
Separating funnel

Feed solution

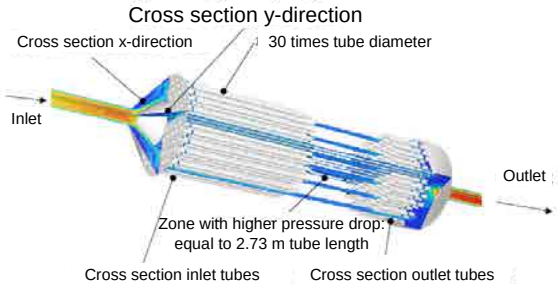
Product stream, analysis

Engineering – Design and Construction of Continuous Plant

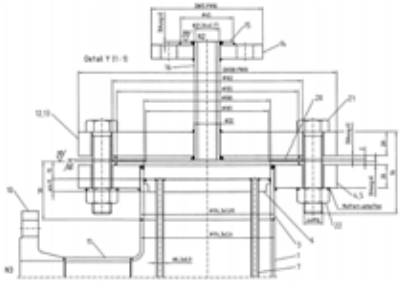
Conceptual



Basic



Detail



Construction and Commissioning

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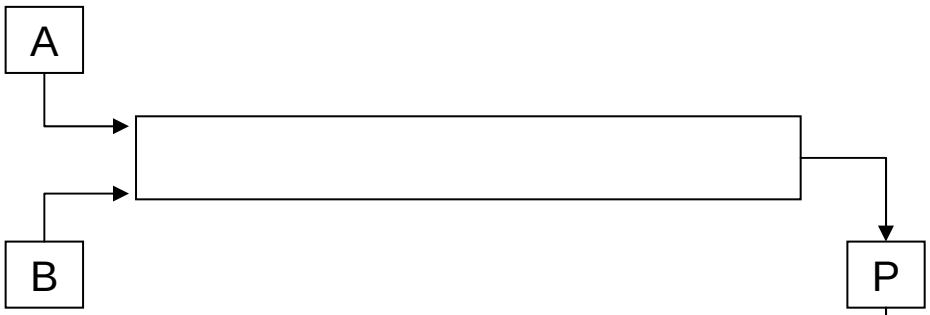
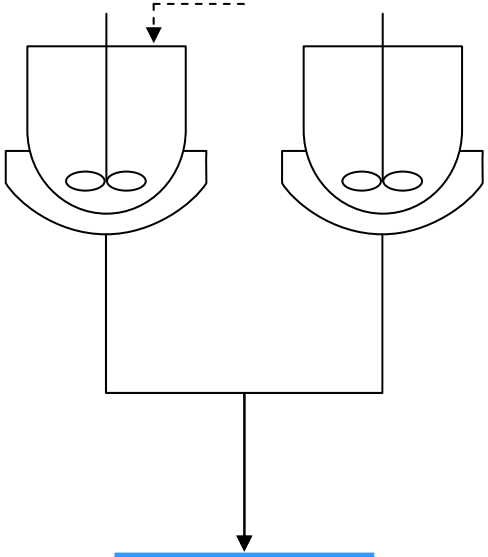
From Flow Reaction to Full Continuous Production



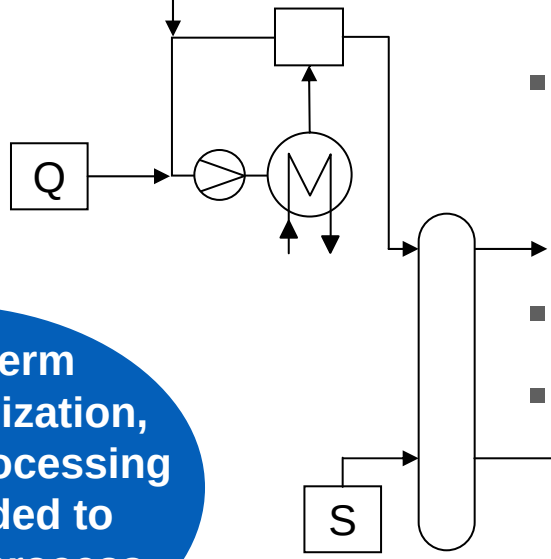
Batch quench and work up

- Quench
- Extraction
- Distillation



Separation and Isolation

Continuous quench and work up



- Quench
- Extraction
- Distillation

Separation and Isolation

For long-term economic utilization, continuous processing to be extended to subsequent process steps

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Introductionary Remarks to Continuous Process Case Studies

Case studies out of exclusive customer projects

- No disclosure of exclusive and proprietary know how
- No disclosure of process specific data

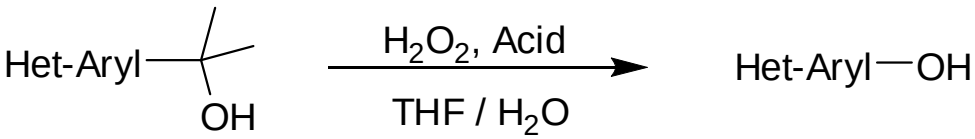
Case studies

- Two recent projects as examples for continuous processing
  - **I.** Know-how transfer from customer, engineering and fast realization (engineering, construction, installation, production) at DOTTIKON ES
  - **II.** Complete in-house process development/engineering/production of hazardous reaction

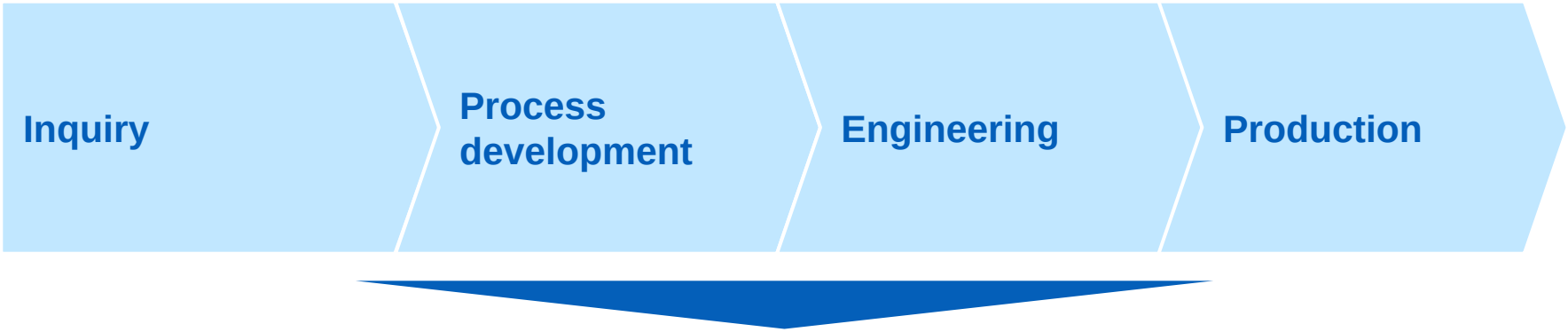
Continuous Processing at DOTTIKON EXCLUSIVE SYNTHESIS

Case Study I – Control of Hazards by Continuous Processing

Oxidation using H_2O_2 (50%) as reagent and rearrangement

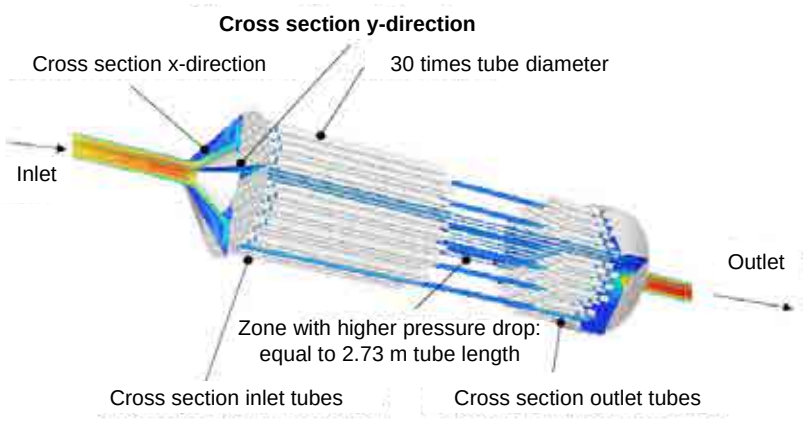


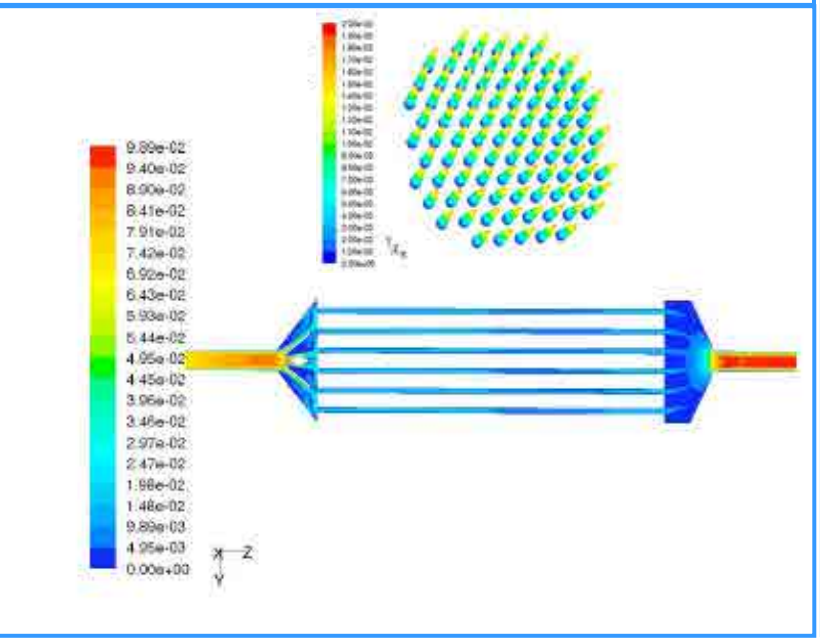
- Production of ca. 500–1'000 kg product as second step of a five step synthesis
- Continuous process developed by customer on lab scale (MRT) and small pilot scale
- Construction and installation of continuous equipment within 6 months
- All made in Hastelloy
- Design/engineering of new residence time unit



Case Study I – Design/Engineering of Residence Time Unit

Computed Flow Distribution Simulation





Targets

- Good flow distribution at the inlet for homogenous velocity
- No vortexes (side products)
- Residence time of 12 minutes

Results

- Conical inlet with a special designed insert
- All requirements fulfilled

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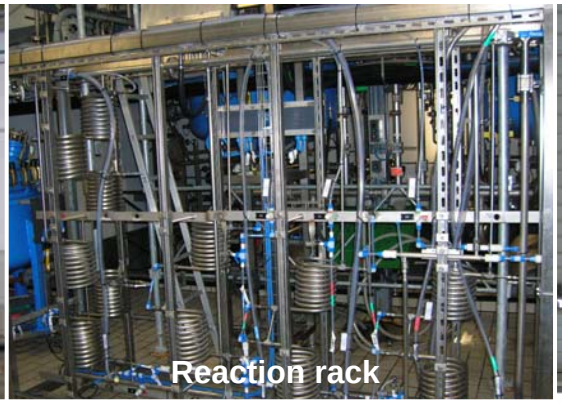
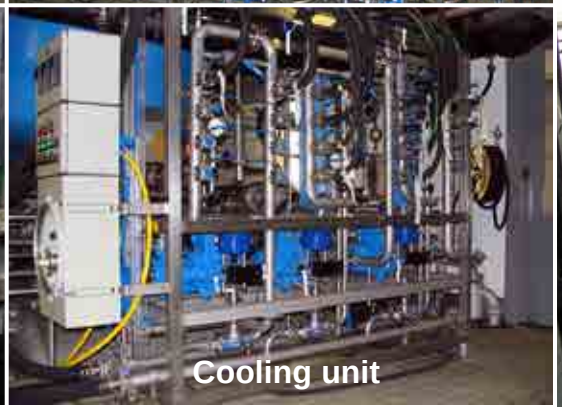
Case Study I – Production Equipment

- Batch wise quench and work up in plant (2 reactors in parallel, ca. 11 hour runs)
- Total flow: ca. 50 L/h
- Production of 500–1'000 kg isolated product per campaign


Feeding vessel


Reaction rack


Pumps/flow meter


Cooling unit


Residence time unit

Production using installed continuous equipment


Overview reaction rack and tank

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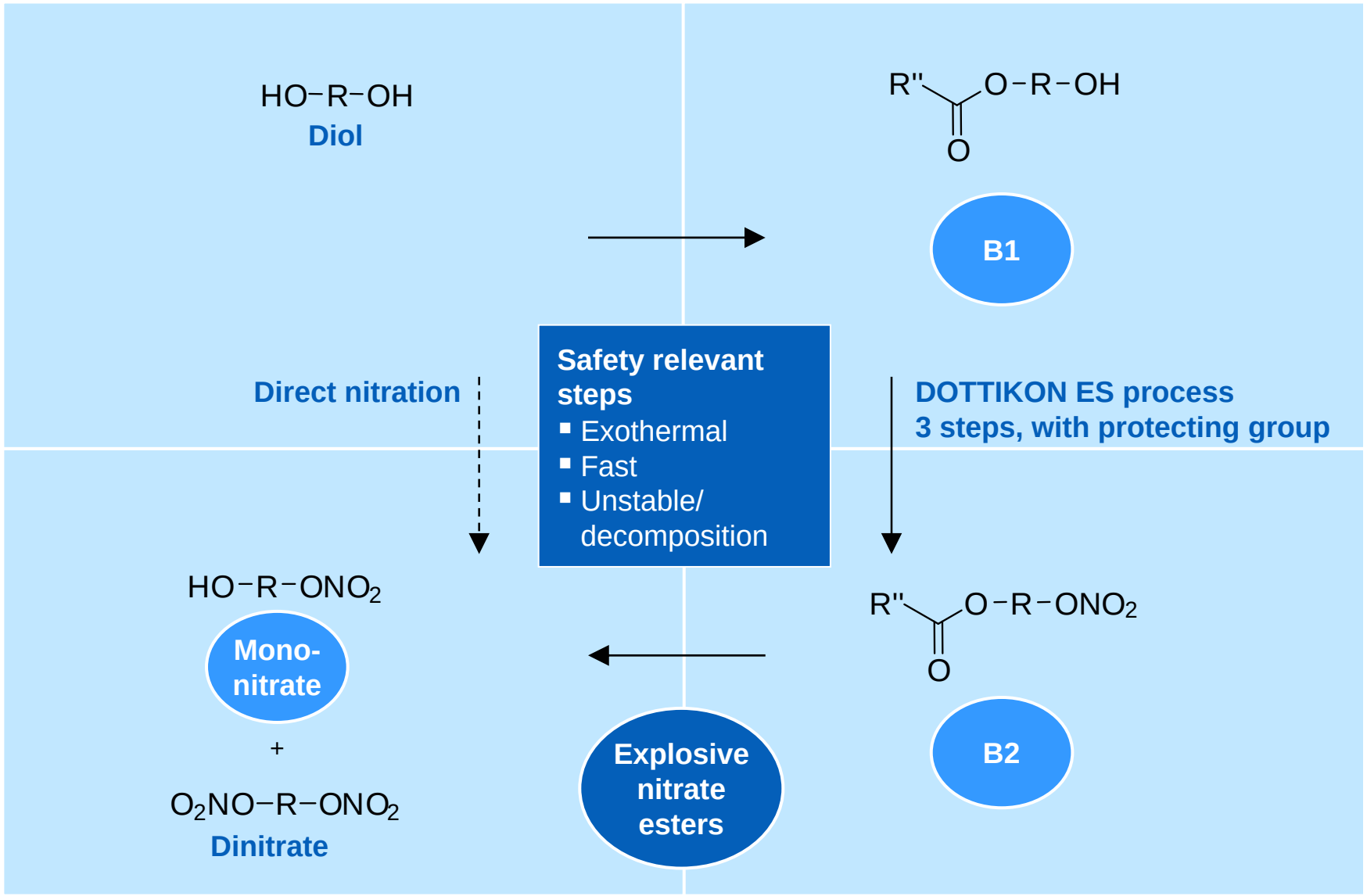
Continuous Processing at DOTTIKON EXCLUSIVE SYNTHESIS

Case Study II – Production of Mononitrate



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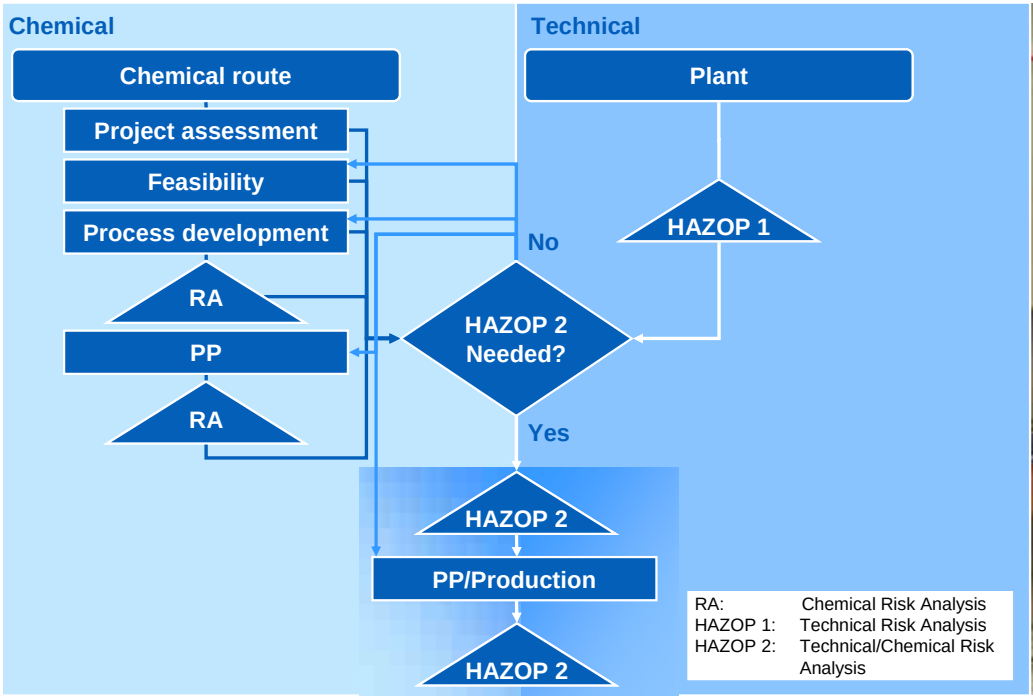
Case Study II – Risk Analysis and HAZOP

Process development | **Engineering** | **Production**

Reaction parameter and ranges → Process layout and optimization → Design → Construction → Qualification → Manufacturing



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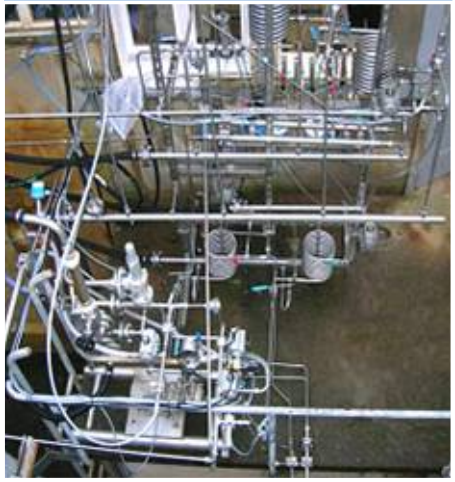
Case Study II – Production

Process development		Engineering		Production	
Reaction parameter and ranges	Process layout and optimization	Design	Construction	Qualification	Manufacturing

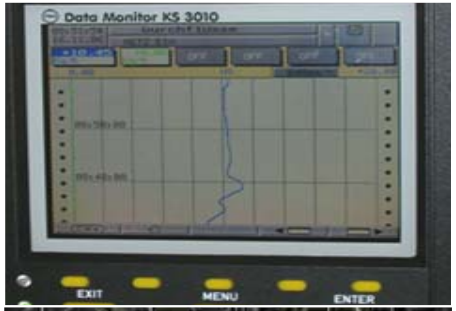
Feed tanks

Tubular reactor unit



Quench unit

Control units

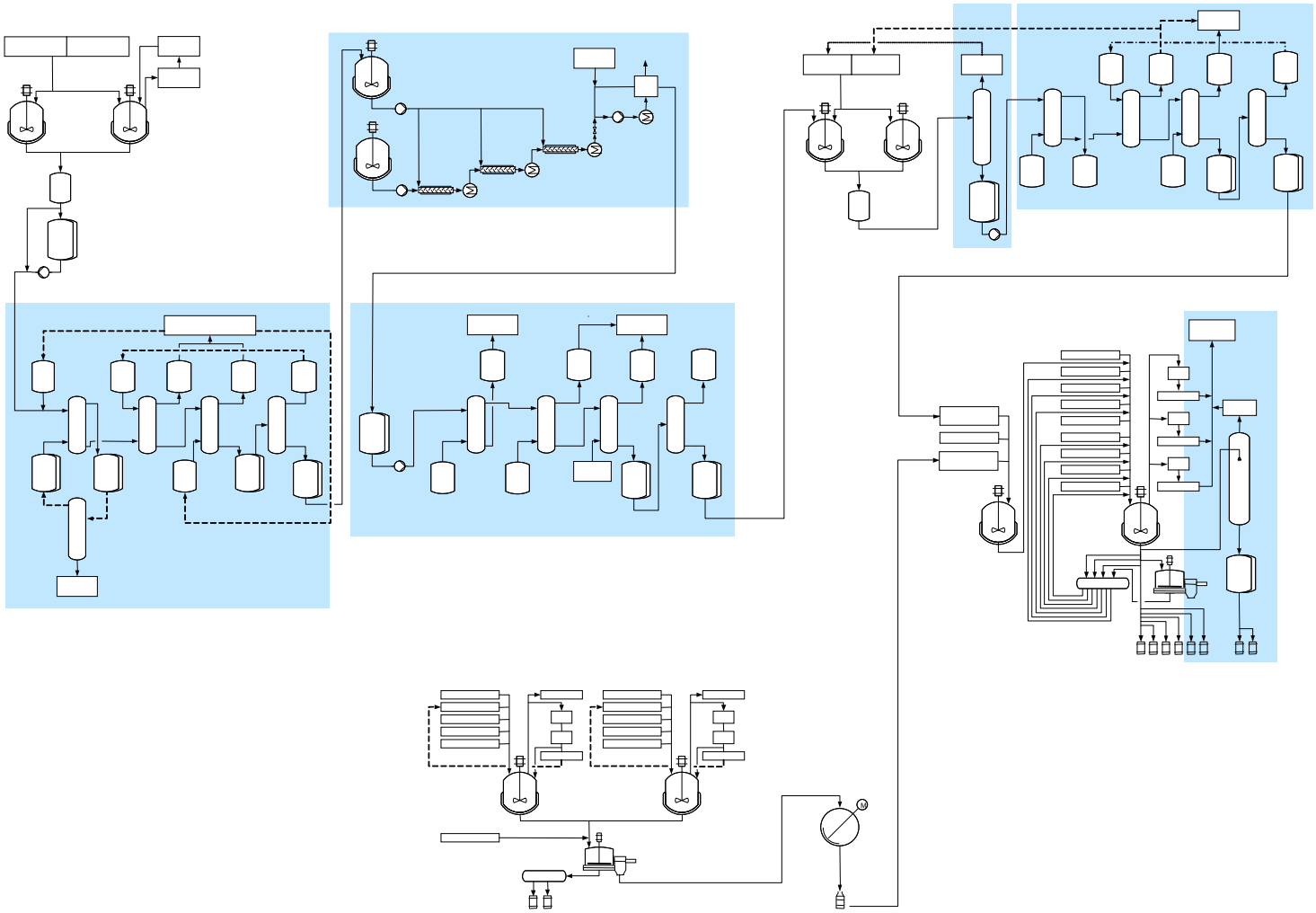


Cooling unit

Continuous extraction unit

Case Study II – Investment Phases for Scale-up

Continuous unit operation



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Continuous Processing at DOTTIKON EXCLUSIVE SYNTHESIS

Summary and Conclusion

Summary

- Continuous processing in pharmaceutical chemical production is useful when reactions have
  - Fast kinetics
  - Hazardous chemistry involved
  - Selectivity issues
- Engineer flow reactors always as small as needed, but never as small as possible
- In scale-up, volume increase (size) outnumbers equipment multiplication (number) economically

DOTTIKON ES, your partner in continuous processing

- Process development
- Engineering and manufacturing
- Process transfers and scale-up

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DOTTIKON's Continuous Specialists

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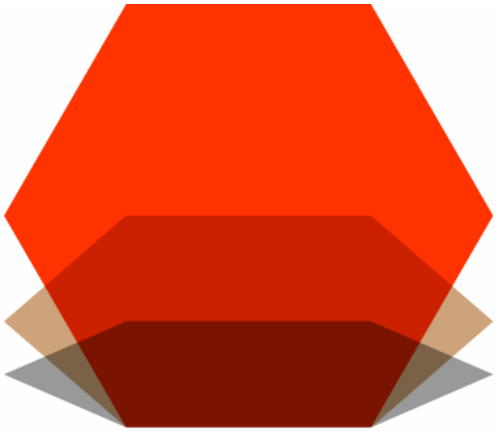

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SYNTHESIS

Your Specialist for Hazardous Reactions.