micro innova

efficient processing

Continuous Manufacturing:
Process Intensification Strategies
in Synthesis, Workup and Formulation
with a special focus on solids

Dr. Dirk Kirschneck, Microinnova Engineering GmbH

Content

- **Microinnova** Overview
- **Development** Strategy for **Flow** Processes
- Characteristics of **Flow Plant Design**
- Case Study: **Propoxylation**
- Case Study: **Crystallization**
- Case Study: **API-Plant**

Microinnova

Overview

7 Differentiators of Microinnova

1 Chemist and Engineer Interaction

2 Regulated Environment Experts for Continuous Manufacturing

3 End-to-End Continuous Manufacturing Competence

- Synthesis
- Work-up
- Formulation

4 Multi Process Intensification Technologies

6 Tons per hour Competence

5 200+ Projects/WPs Experience

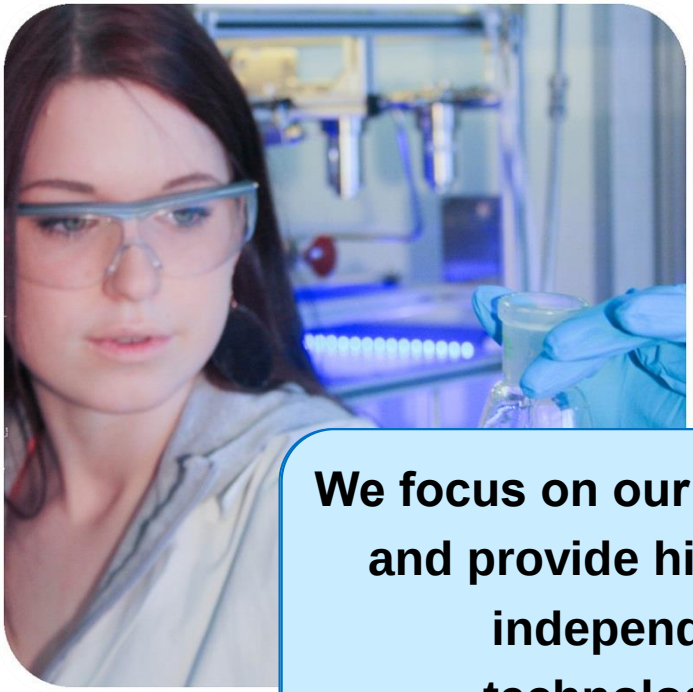
Flow Processing of Solids 7

Quelle: Google

specialists in process intensification

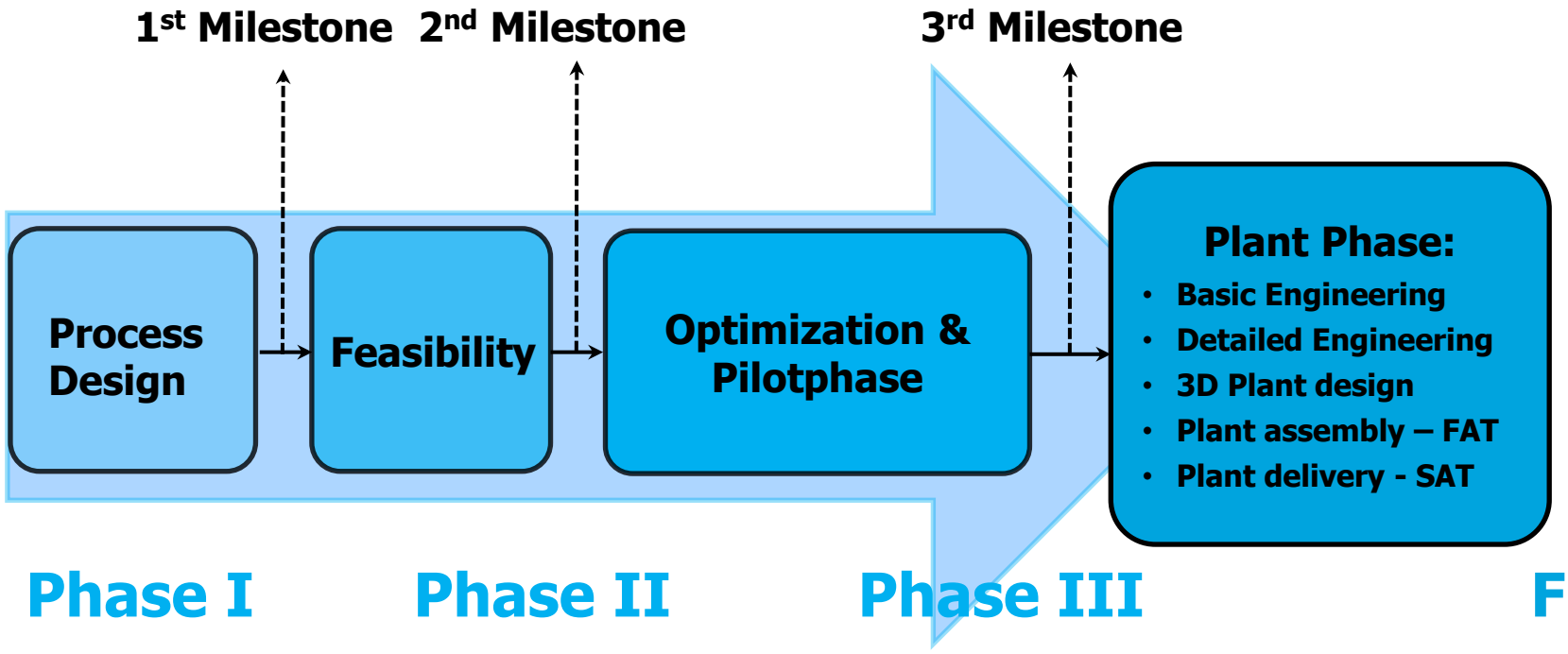
process development

engineering & plant



We focus on our customer's process and provide high level solutions independent from any technology or supplier

Microinnova`s Approach to Success



The entire **process design** and **development work** until the final **turnkey plant** comprises of consecutive phases that enable a stepwise transfer of the existing process to a continuously realized process. A first plant sketch and cost estimation will be given after **Phase I**.

Phase I – Process Design

A successful **business case study** for a specific product requires

- Theoretical data of the process to rate the overall process performance
- Estimations of investment costs

These informations will be available **after the Process Design Phase I.**

Theoretical Evaluation

Basic Lab Tests

Process Flow Diagram

Risk Assessment

Plant Cost Estimation

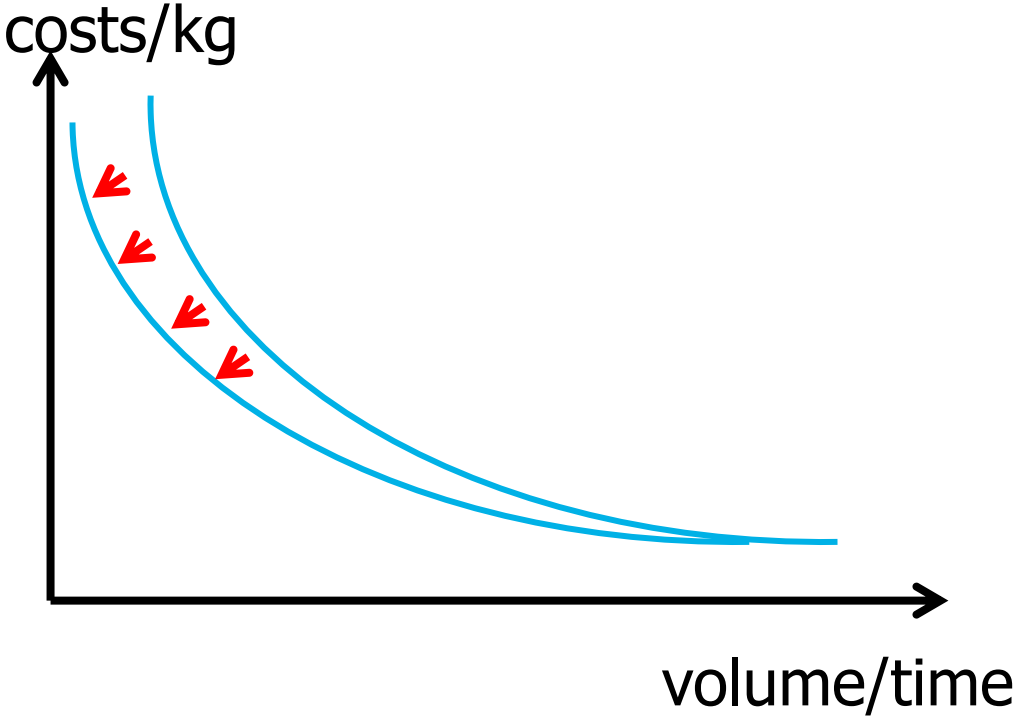
Phase II Feasibility

Focus on costs

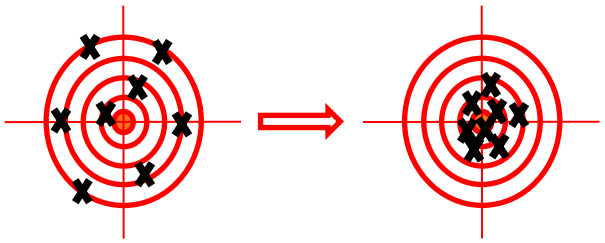
Getting Costs down

Statement from BASF

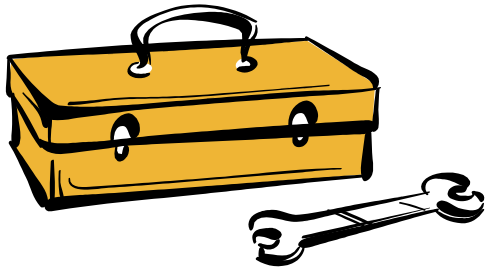
1. Intensified Processes
2. Universal Engineering Designs



Better Control



New Strategies



T. Stammer (BASF) et al, CHISA 2014, Prague

Development Strategy
for Flow Processes

How to design a flow process?

Drivers

- Operation Reduction
- Selectivity
- Labor Efficiency

Critical Parameters

- Micro Mix: < 1s
- Plug Flow: > BS 100

Tools

- Micro Mix
- Plug Flow
- Micro Heat Exchange

Drivers for Flow and/or Microreactors

Yield

Selectivity

Operation Reduction

Labor Efficiency

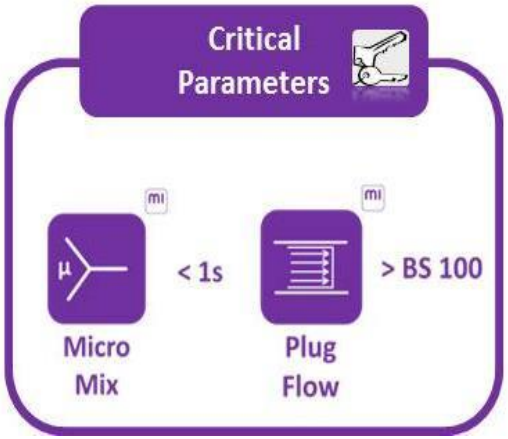
Safety

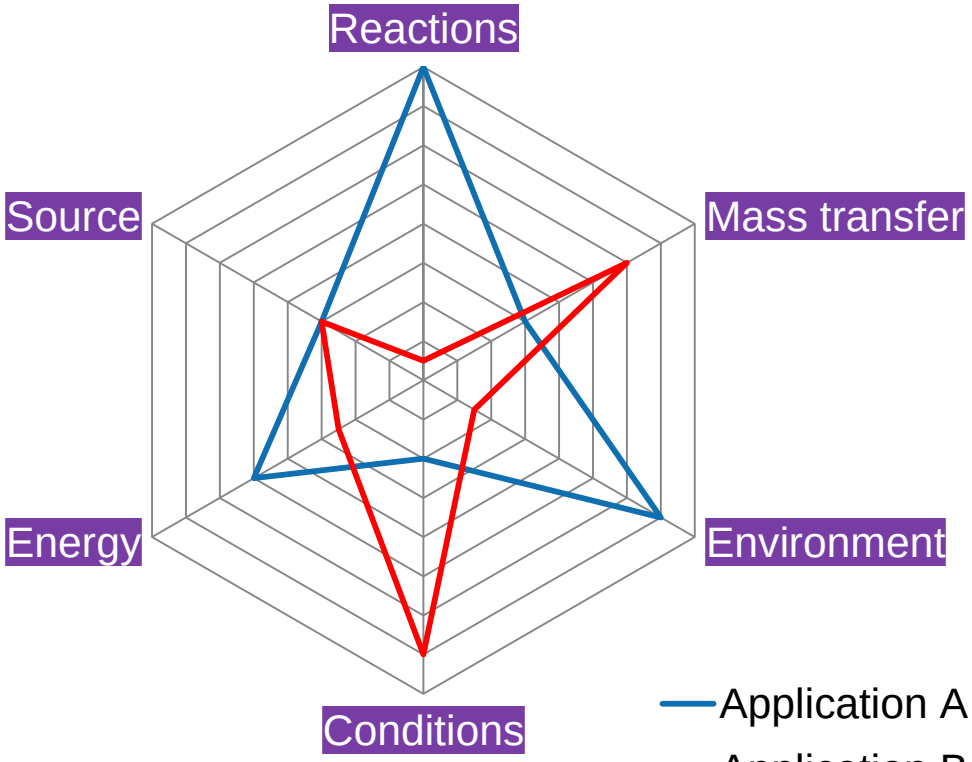
Space-Time Yield

Energy

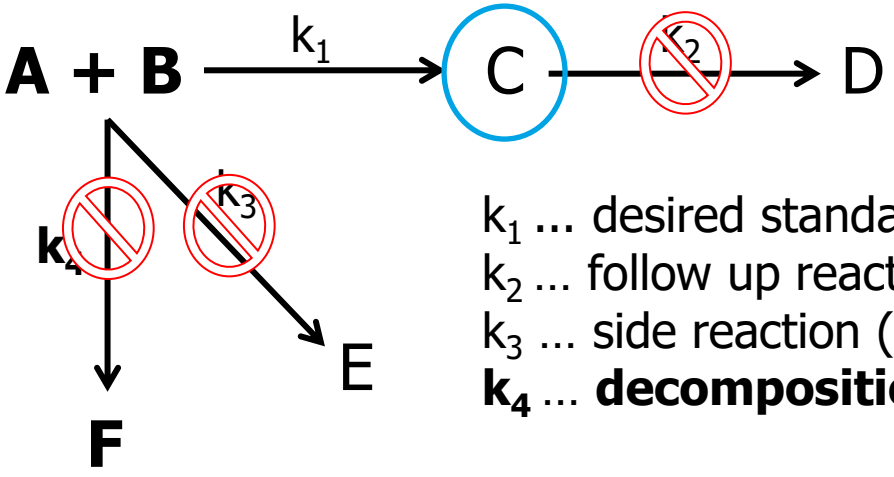
Development Speed

Application Profile

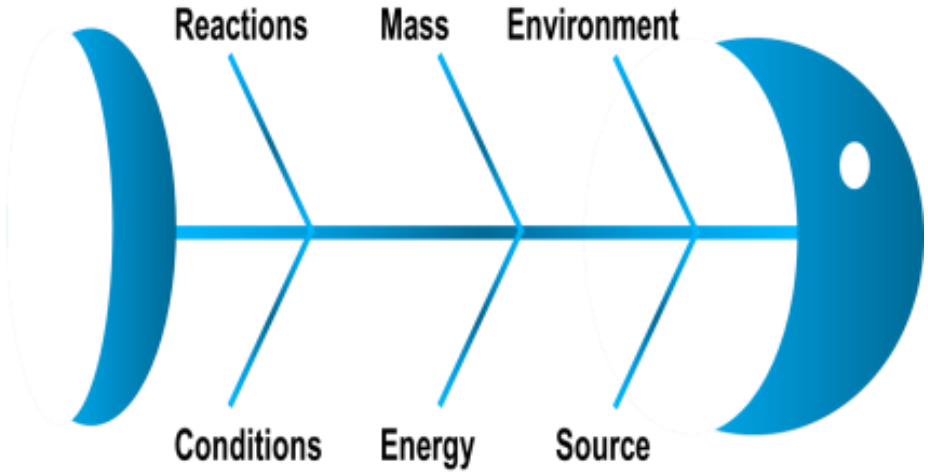




MIC Fish Methodology

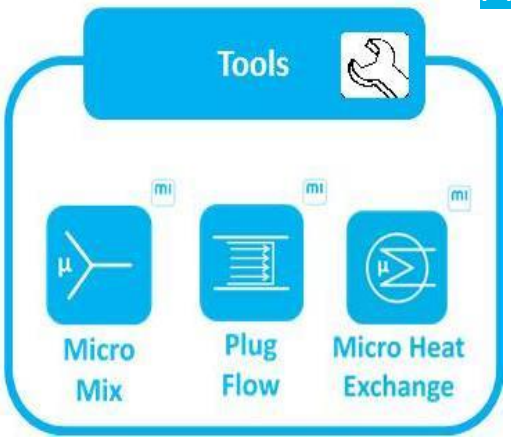


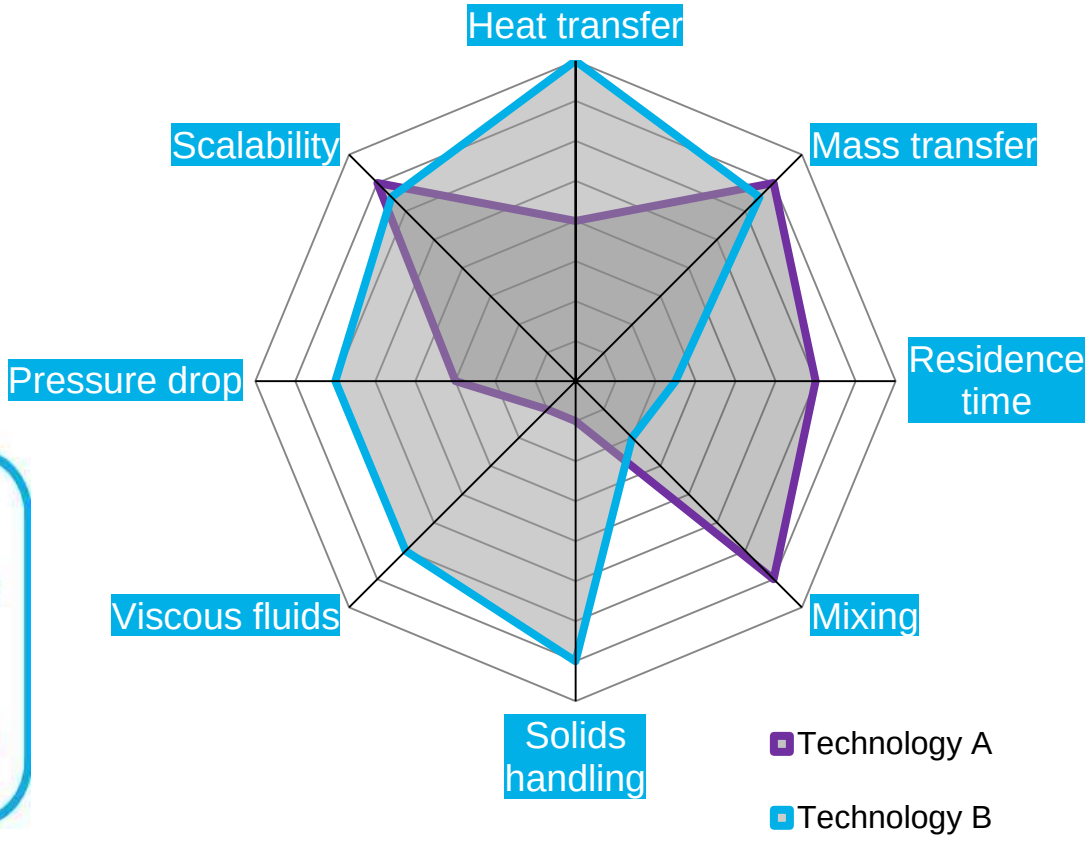
k_1 ... desired standard reaction (solvent effect)
k_2 ... follow up reaction (if late quench)
k_3 ... side reaction (if $C_A \neq C_B$)
k_4 ... decomposition (if high T)



plug flow ?
high T, p ?
process liquid A ?
process gaseous A ?

Technology Comparison





Process Intensification Toolbox

Micro Mix

Micro Heat Exchange

Unstable Reagents

Plug Flow

Cascade

Small Volume

Mass Transfer

Precise Processing

Novel Process Windows

Rotor Stator

Quench

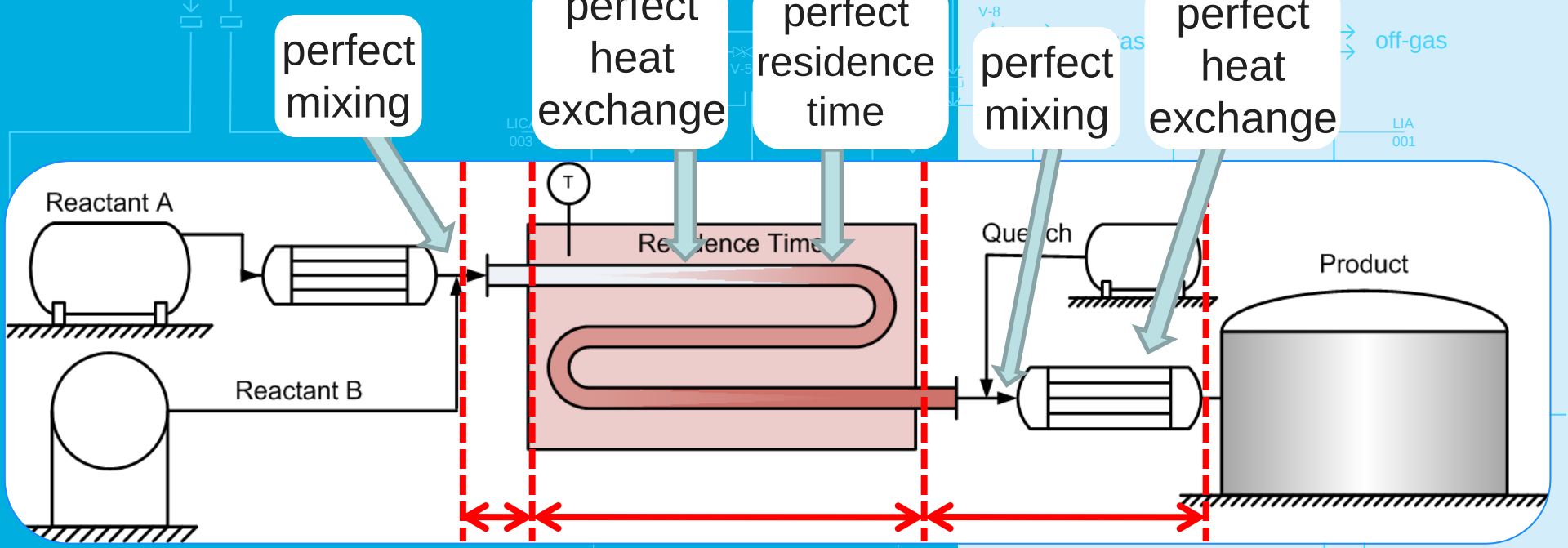
Microwave

Ultrasound

Membrane

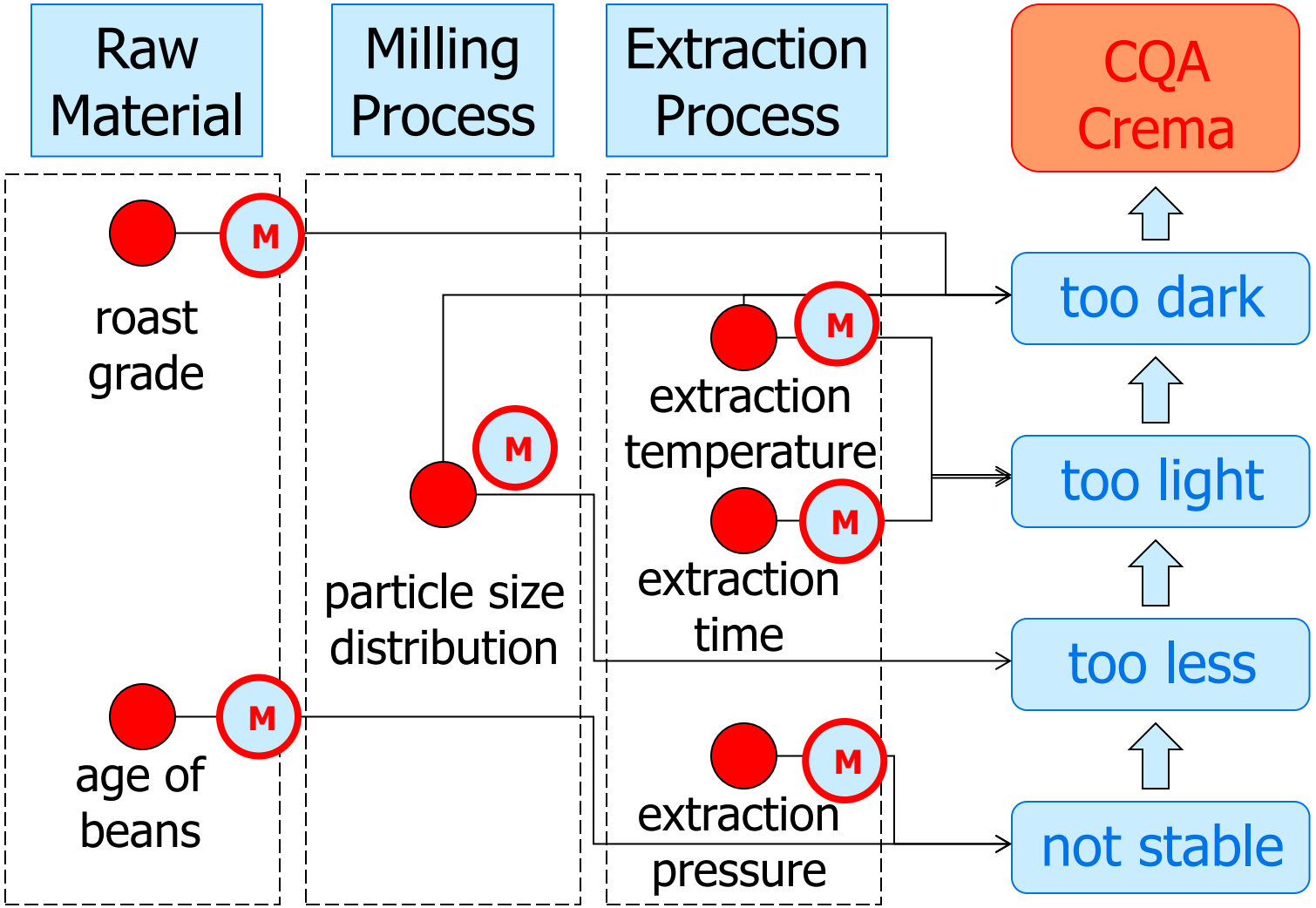
Extrusion

Towards perfect processing



- narrow residence time distribution
- no backmixing
- no hot spots
- ideal stoichiometry
- no high concentration spots
- no dead zones

QbD: Critical process parameter map



Out of the Box

Liquid-Liquid Processes

- up to 400 °C
- Selfignition by O_2
- Cryogenic Reactions
- High Viscosity
- High Corrosivity
- High exothermic reaction

Gas-Catalytic Processes

- up to 50 bar
  up to 300 °C

Liquid-Solid Processes

- Precipitation
  Crystallization
- Particle Surface Modification
- Continuous Suspensions
  (cat/solid educt)
- Melted Educt

Liquid-Gas Processes

- Reactions with Cl_2/HCL
- Reactions with O_2/H_2
- Ozone (plant)
- Reactions with NH_3 (liq)

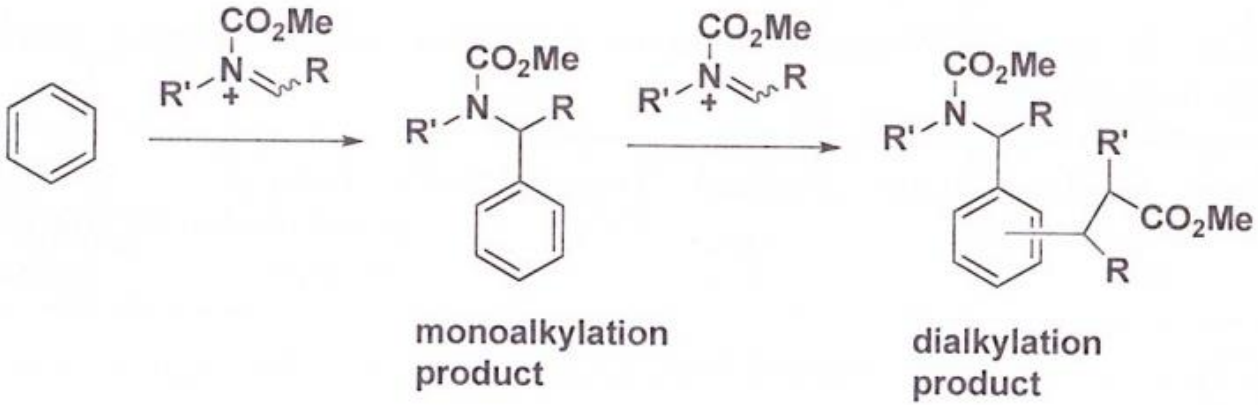
Customer examples
5 out of Pharma TOP 10
4 out of Generic TOP 10
Chemical Global Players
Polymer Companies
Crop Protection

Very difficult Processes

Process Design Strategies

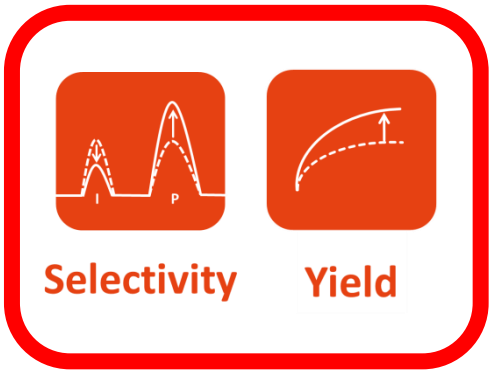
Example: **selectivity increase**

Friedl-Crafts-Alkylation

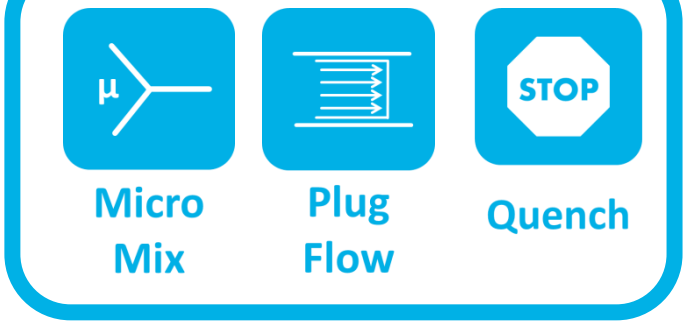


J. Yoshida, “Flash Chemsitry”, Wiley, 2008

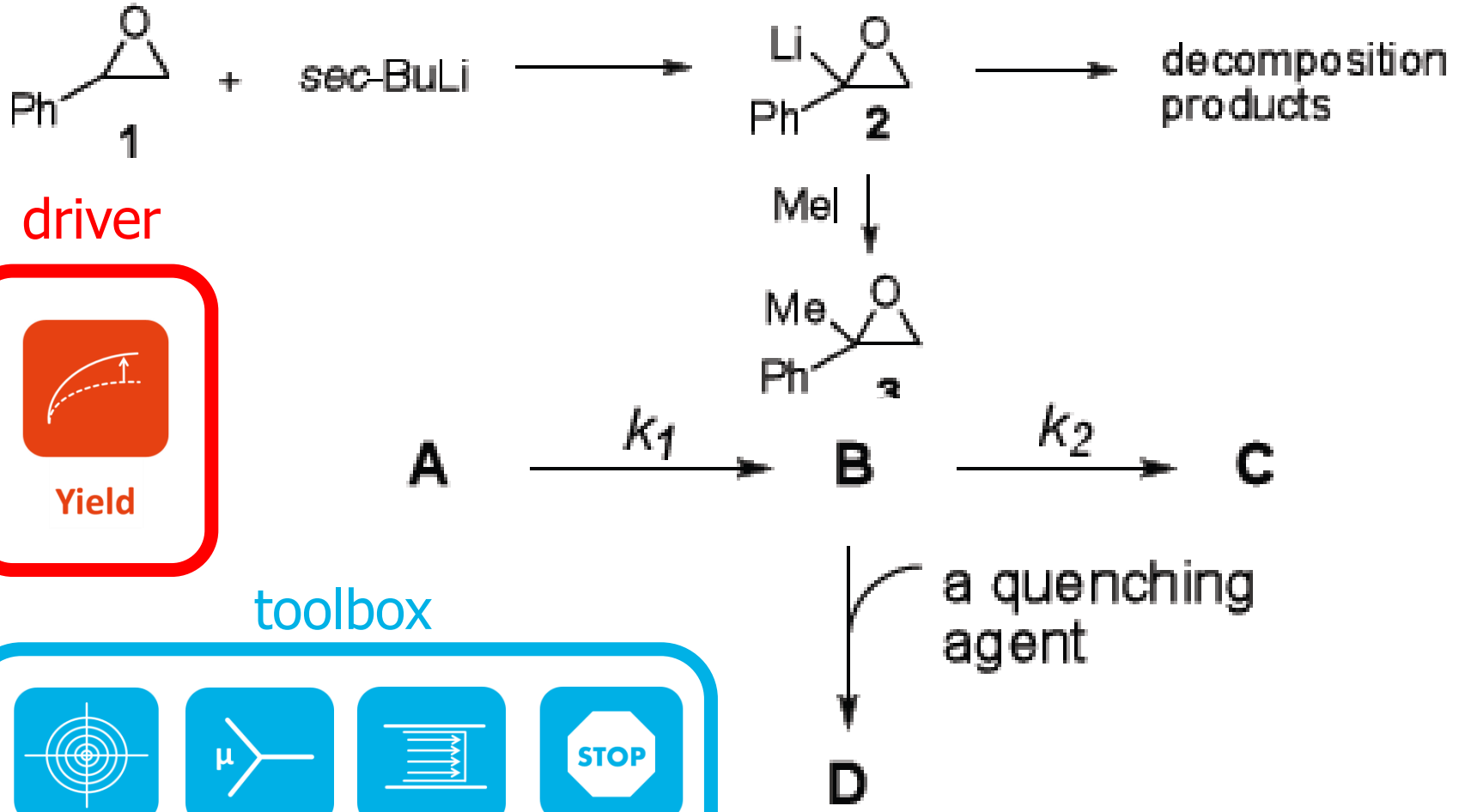
driver



toolbox



Example: **Unstable reagents**



driver

Yield

toolbox

Precise Processing

Micro Mix

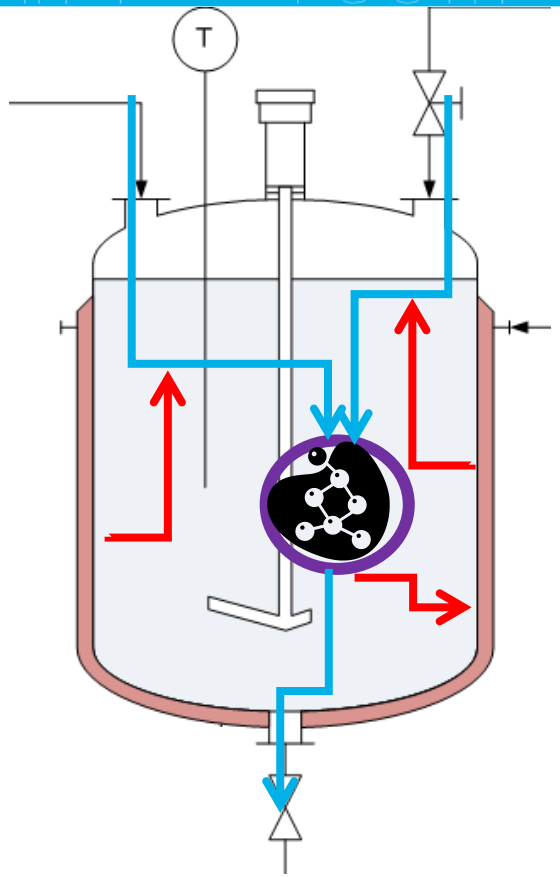
Plug Flow

Quench

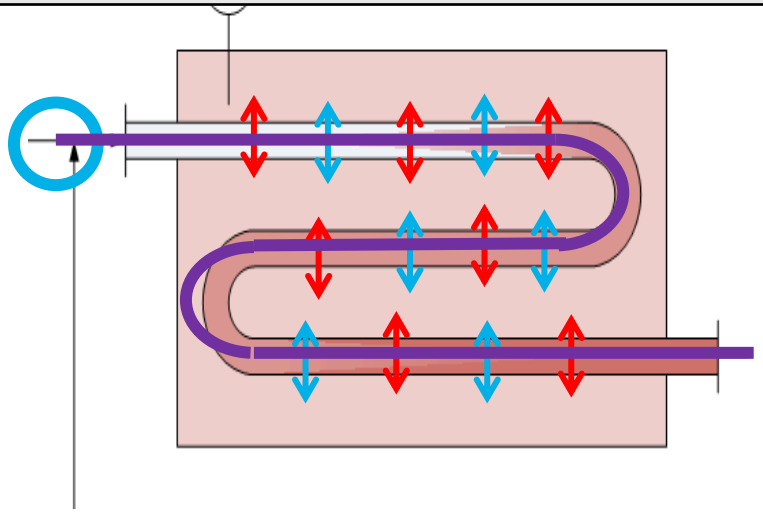
Heejin Kim, Aiichiro Nagaki & Jun-ichi Yoshida

Nature Communications **2**, Article number: 264

Value by optimizing mass & heat transfer



Operation	Batch	Flow	Factor
Reaction	20 min	20 min	1
Mass Transfer	50 min 1 m	0,5 min 1 cm	100
Heat Transfer	25 min 0,5 m	0,5 min 1 cm	50



Technology Example: **Extrusion**

Continuous generation of one substream of a Healthcare formulation

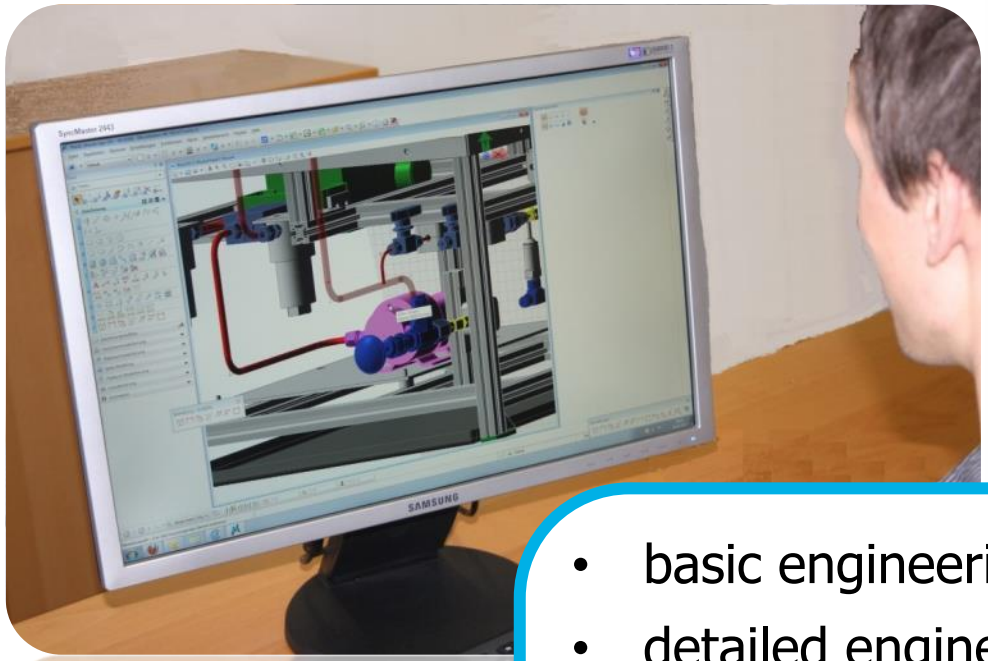
Pharma Top10 Company

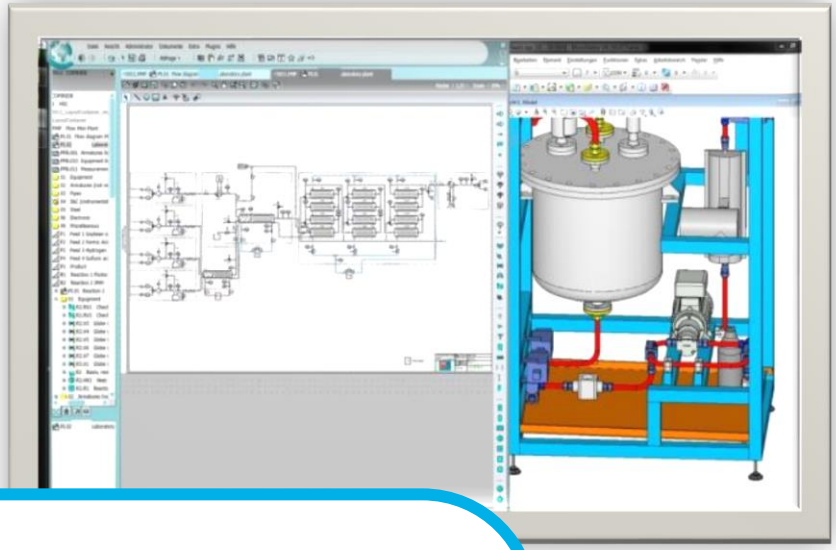
Polymer Projects

- Free Radical Polymerisation
- Modification of Functional Groups
- Cross Linking
- Endcapping
- Oligomer Synthesis
- Formulation (e.g. Gel Structure)
- Encapsulation (Interfacial area Polymerization)

Engineering

Engineering Competence Microinnova





- basic engineering
- detailed engineering
- 3D design
- automation solutions
- plant construction
- commissioning
- CE, ATEX, UL, UL-Ex, cGMP

Comparison batch versus conti / flow

advantage batch
- flexibility
- multipurpose

process is adjusted to the plant

advantage conti/flow
- process performance
- safety
- easy automation

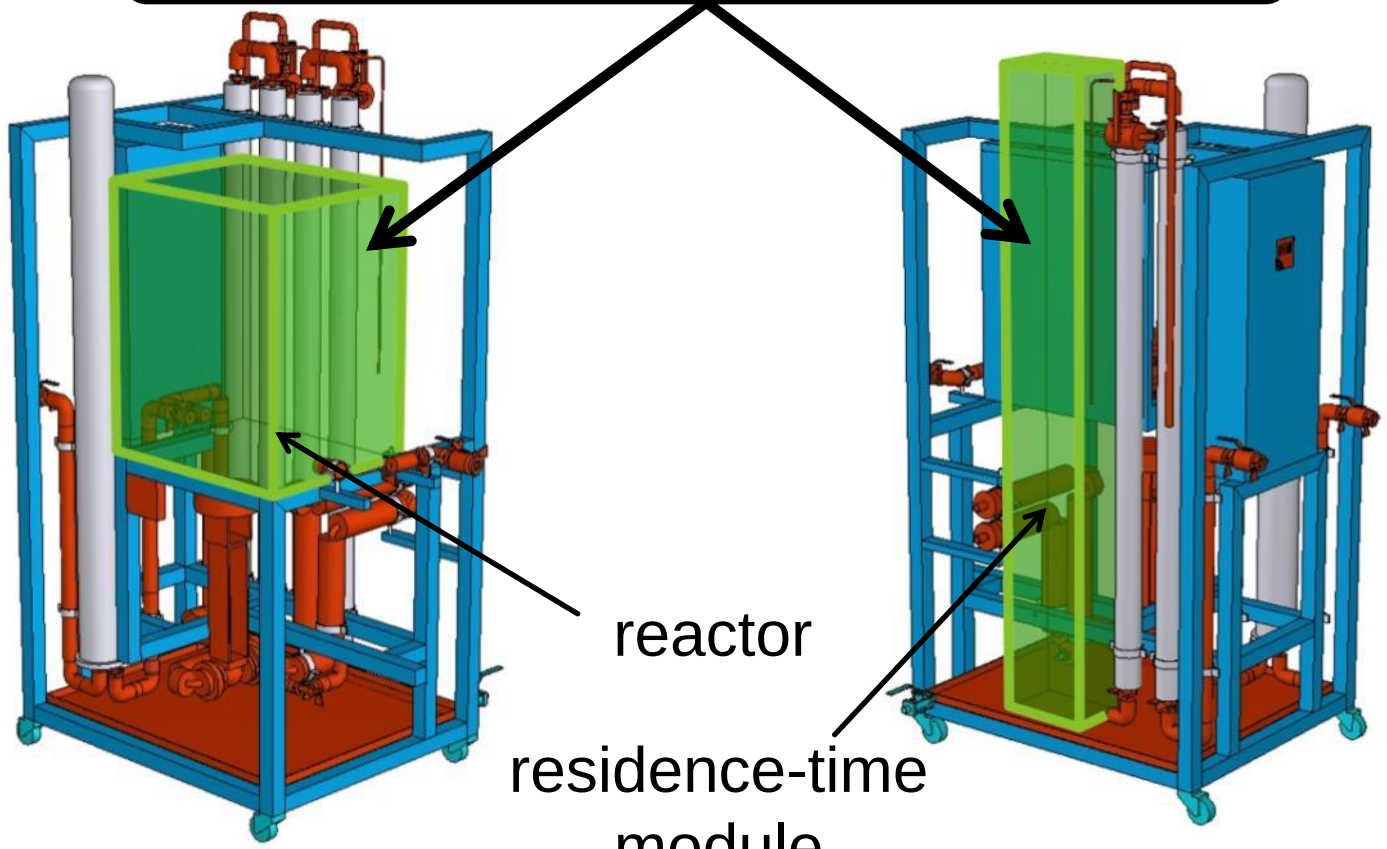
plant is adjusted to the process

concept necessary, which combines batch flexibility with continuous performance

On-module flexibility

on-module adaption by exchanging specific parts

engineered spaces for adaption



Modular plant design

tank farm

utilities

automation + supply

- bus /plc
- electricity
- control air
- nitrogen

heating + chilling

control room

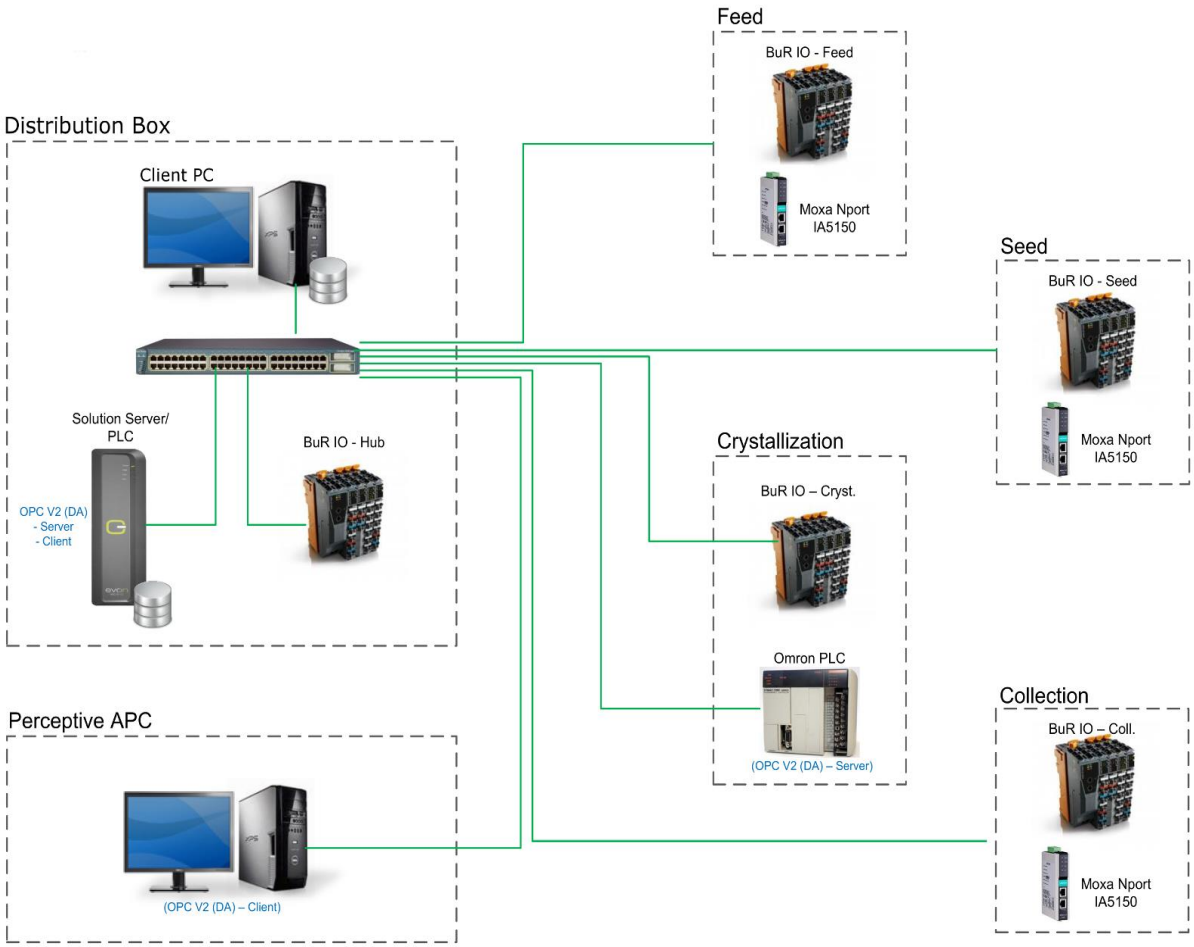
utilities-hub

production area

module storage

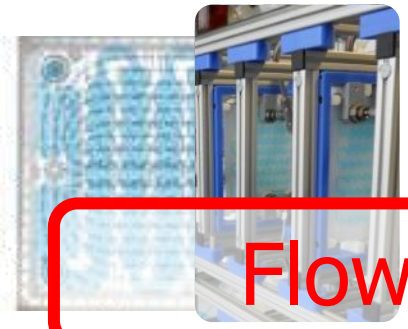
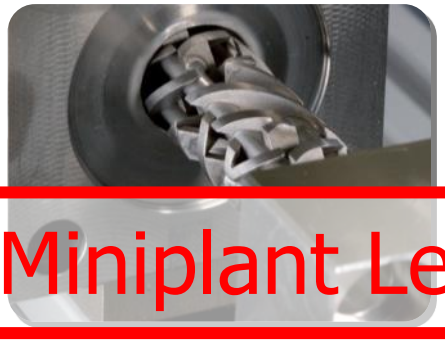
feed 1 | feed 2 | feed 3 | reactor 1 | reactor 2 | product

System Architecture Automation

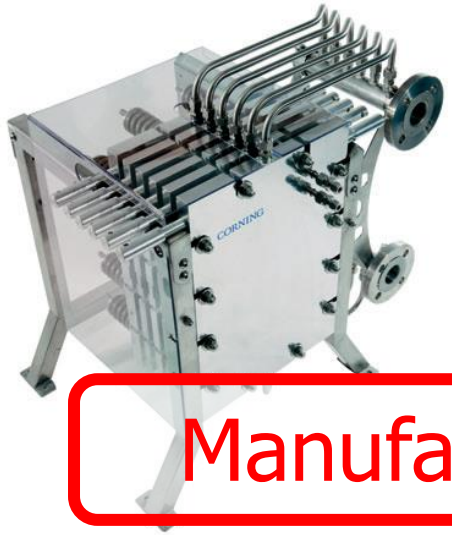


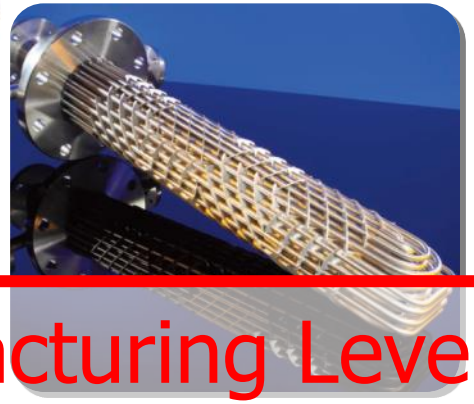
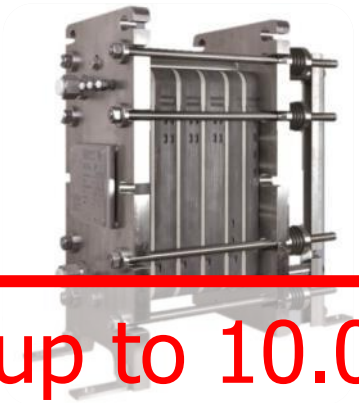
Scale up of flow processes

Corning AFR	**Fluitec** XR	**ESK** MR	**IMM** Star-Lam

Flow Miniplant Level up to 10 l/hour




Manufacturing Level up to 10.000 l/hour

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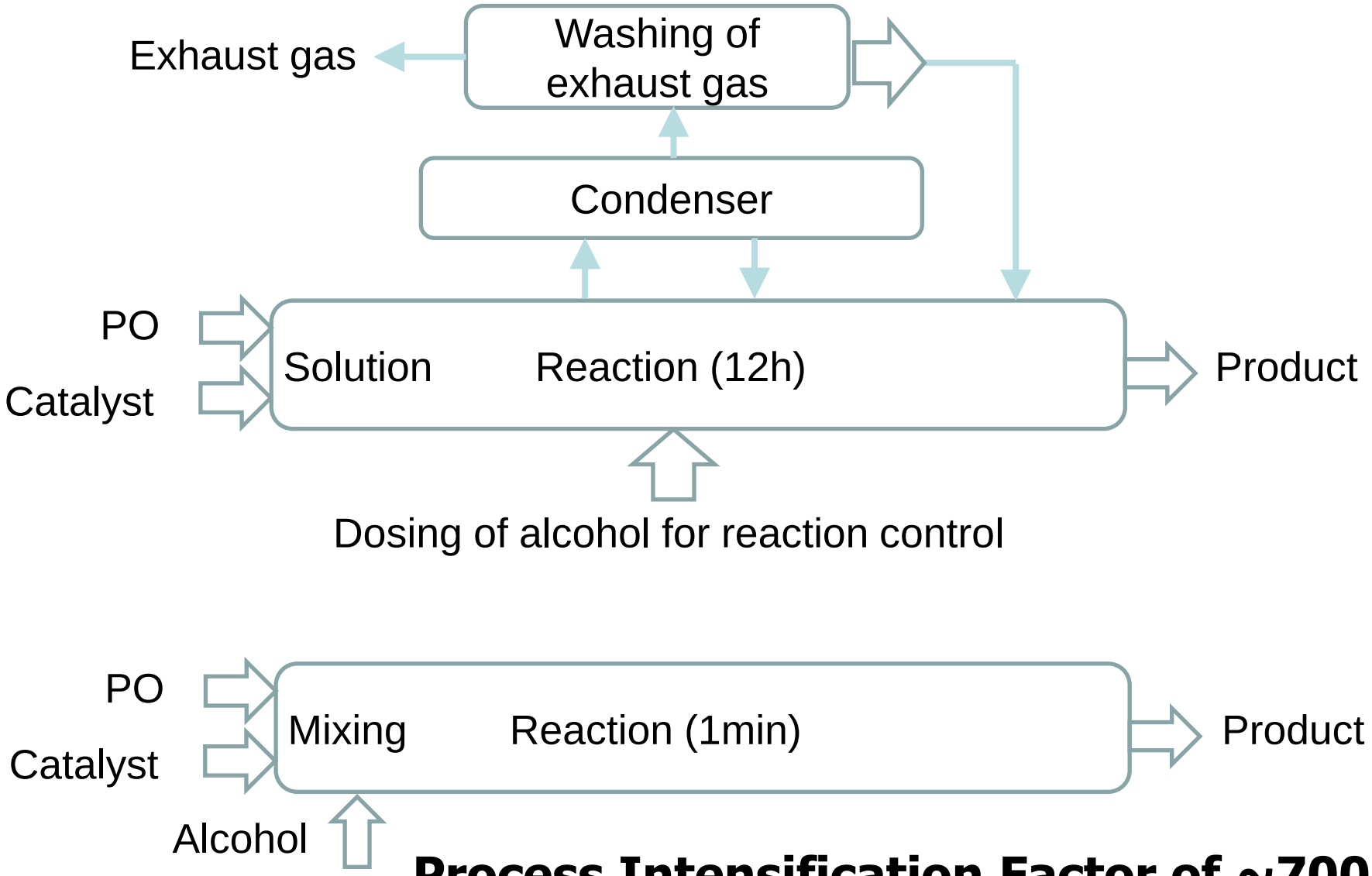
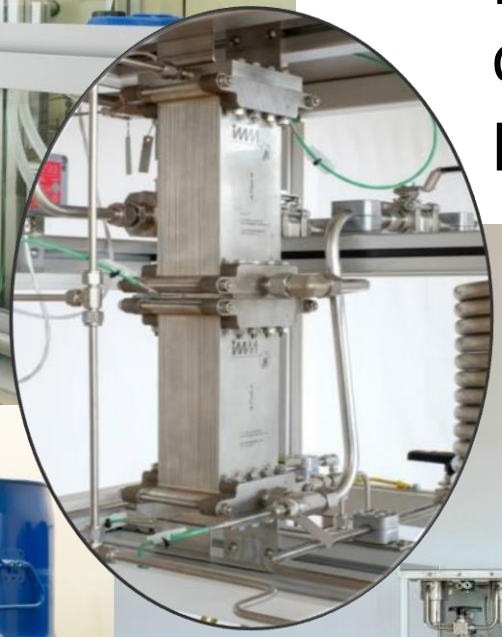
Case Study: **Propoxylation**

Case Study Propoxylation



Process Intensification Factor of ~700

Case study: Flow Miniplant



Flow Miniplant

Example of a 20 kg/h development or small scale production system

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Case Study: **Crystallization**

Preferred particle size

Flame retardant

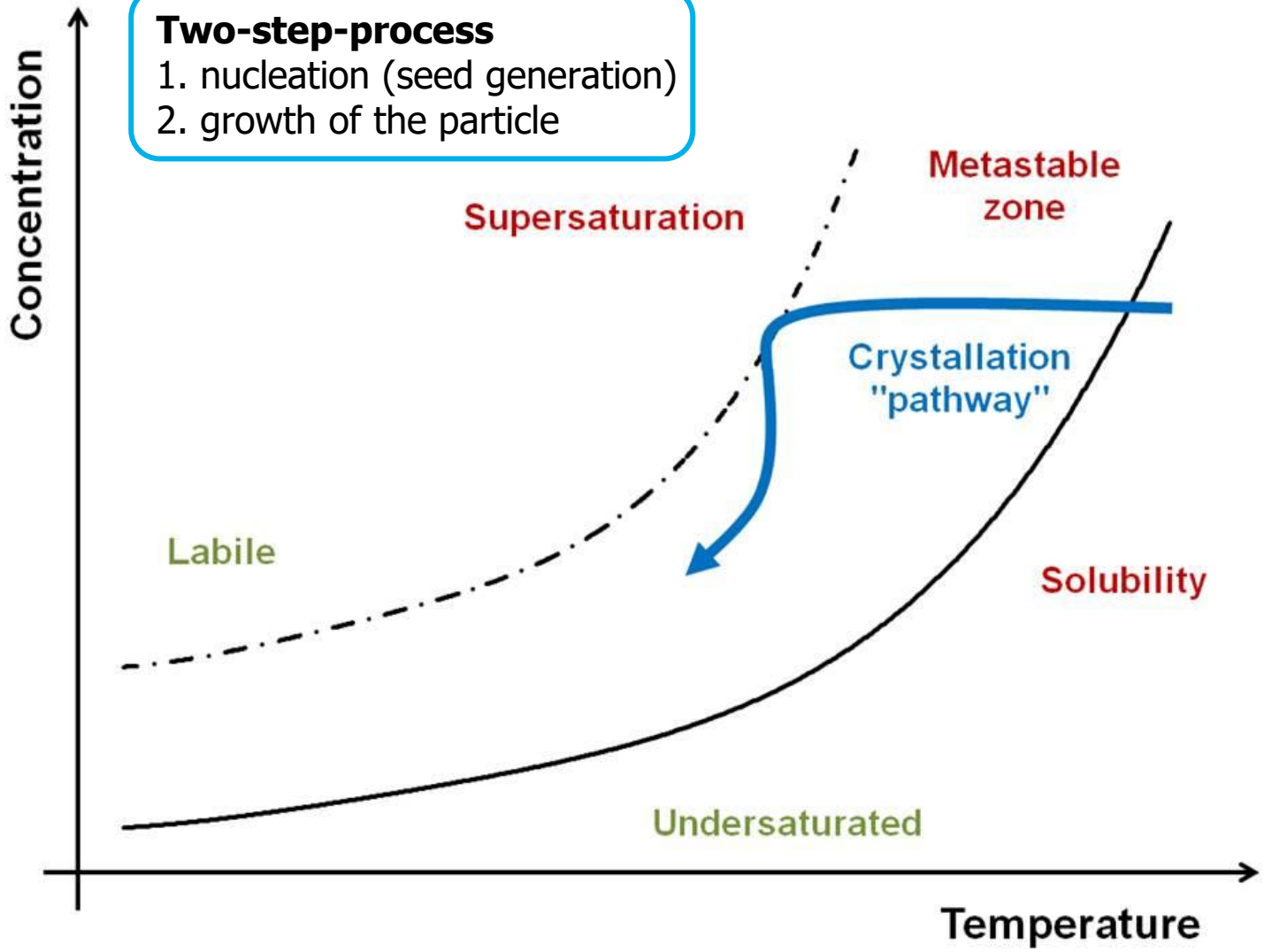
upper limit: mechanical properties of polymer
lower limit: retardant behaviour

Soluble salt

upper limit: speed of solubility
lower limit: dust formation

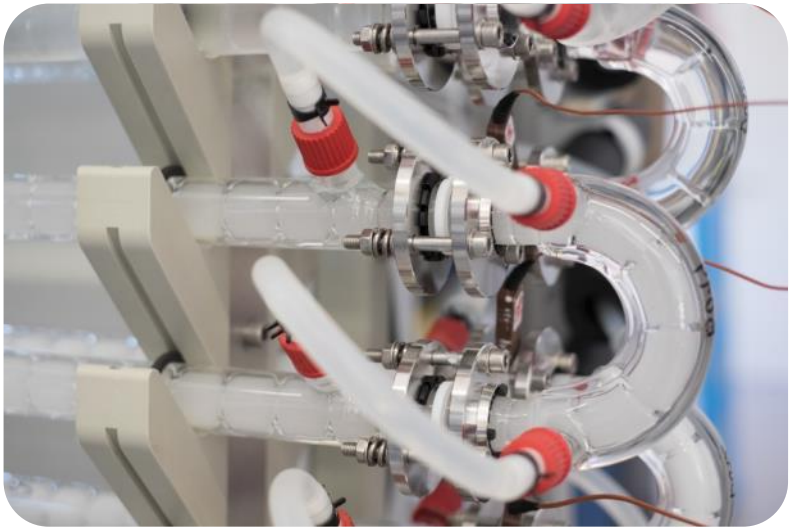
Cooling Crystallization

Two-step-process
1. nucleation (seed generation)
2. growth of the particle



Case Study Flow Miniplant

Continuous Crystallization



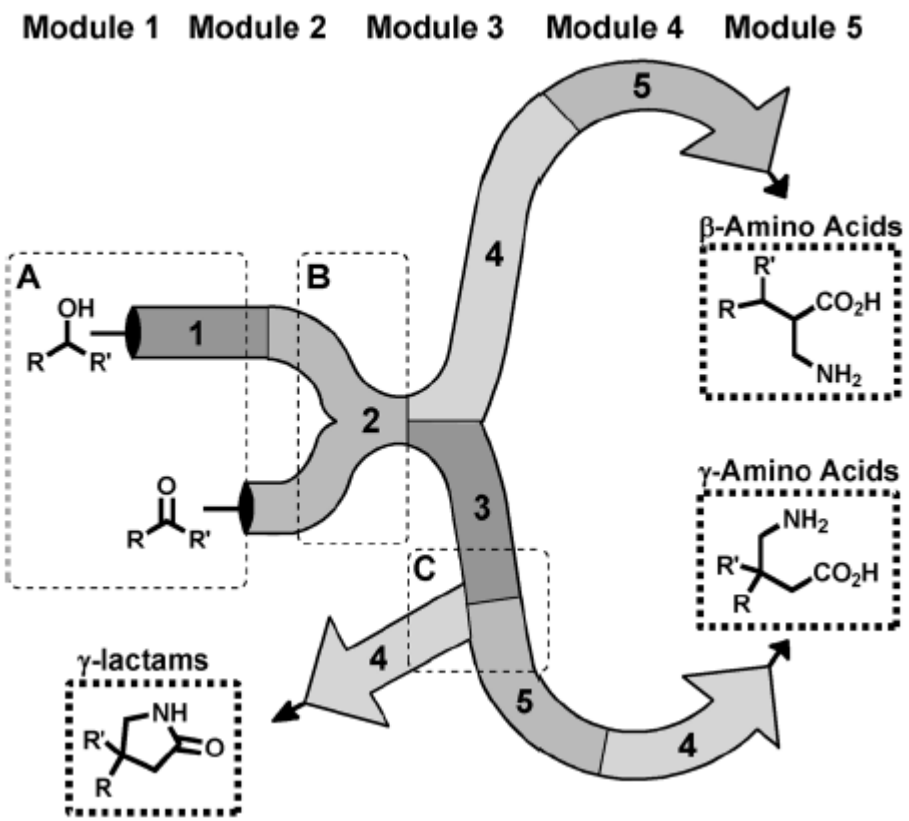
Continuous Crystallization

Model Predictive Control

DN-15 reactor predictive controller

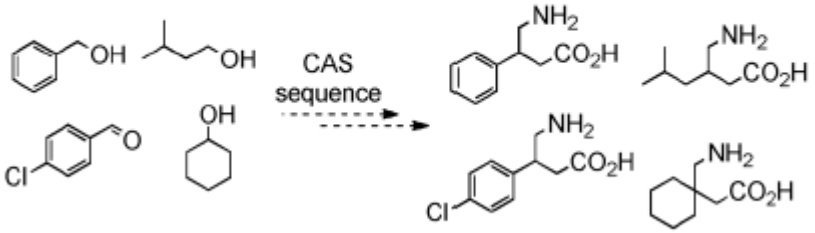
From Perseptive Engineering

Multi-API Approach by Modules



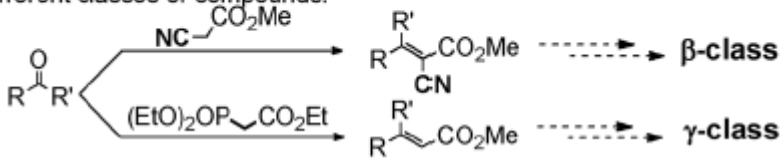
1. Starting Material

By changing starting material, different products with similar core structures can be obtained using the same modular sequence.



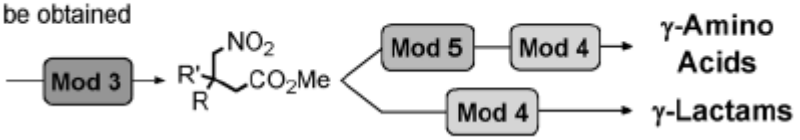
2. Reagent Choice

By changing the reagents within a module it is possible to access different classes of compounds.



3. Order of Modules

By changing the order of modules, different families of structures can be obtained



D. Ghislieri, K. Gilmore, P. Seeberger; Angew. Chem. Int. Ed. 2015, 54, 678-682

Continous Cryogenic API Plant

Reaction: Continuous Solid Dosing into corrosive liquid under cryogenic conditions

- **Residence time improved:**

  - from 7 hours to 15 min

- **Process safety increased**
- **Lossless scale-up**

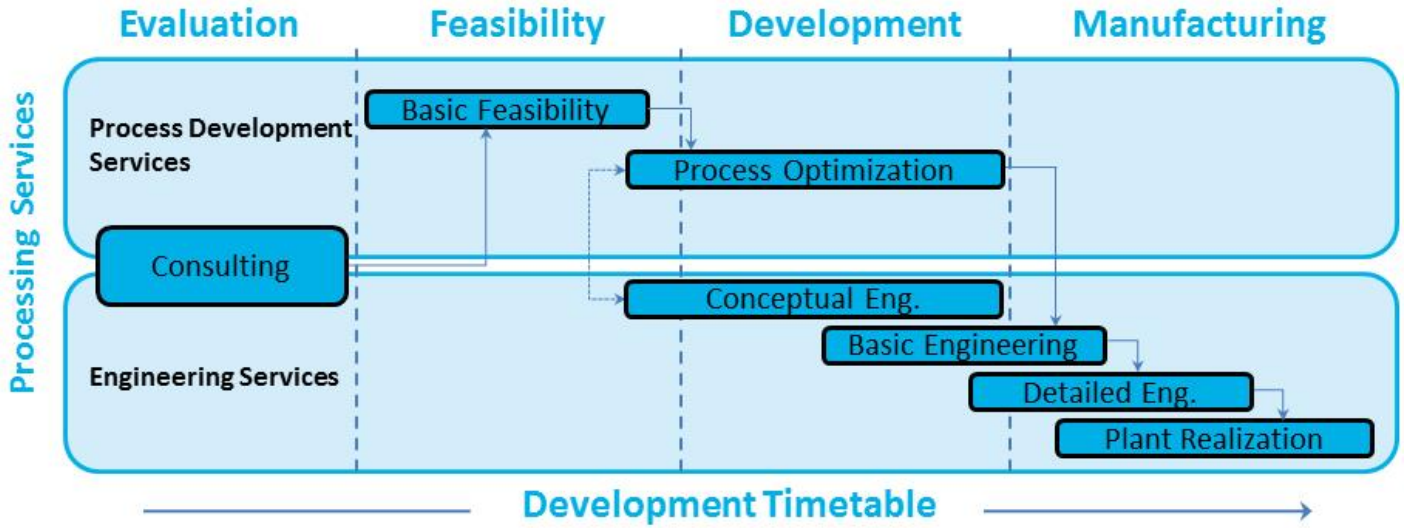
Unit operation: Filter-dryer

Continuous

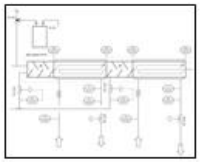
Filtering & Drying

Services & Results

Service Map & Results



Results



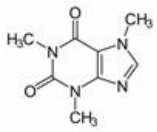
Documents
-conceptual engineering
-basic engineering
-detailed engineering

-unit operation

Turnkey Plants

-modular/multipurpose

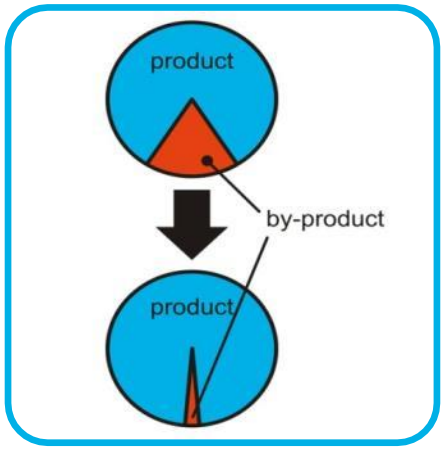
Reports
-consulting
-feasibility
-optimization



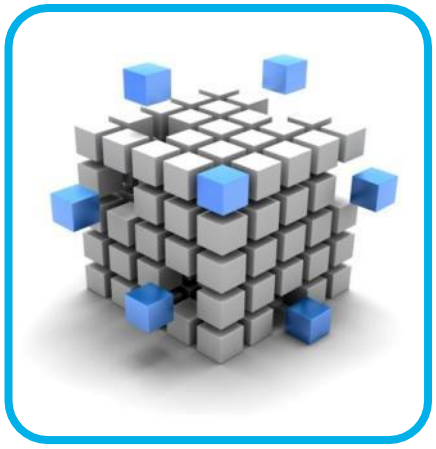
Lab experiments
-feasibility
-optimization

-redesigned

Summary



process performance



flexibility

safety

fast track realization

turning process performance into money

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