Gernaey K.V. (2012) Development of continuous pharmaceutical production processes supported by PSE methods and tools. The Scale-Up of Chemical Processes Conference, Baveno, Italy, July 9-11, 2012.

Gernaey, Krist V.

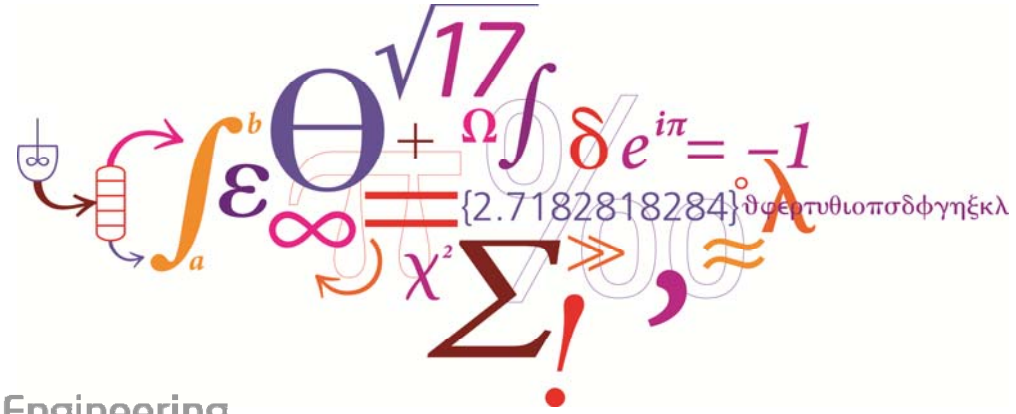
Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

Development of continuous pharmaceutical production processes supported by PSE methods and tools

Krist V. Gernaey

The Scale-Up of Pharmaceutical Processes
8-11 July 2012, Grand Hotel Dino, Lago Maggiore, Italy



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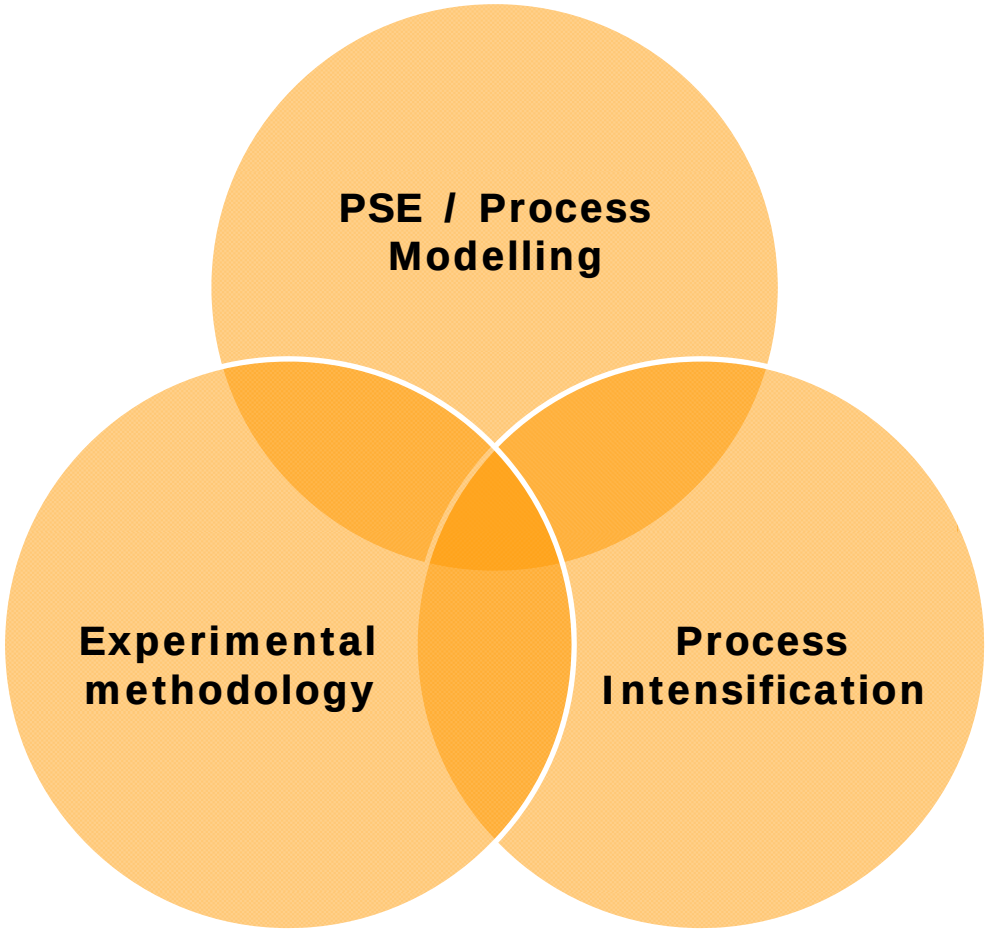
Department of Chemical and Biochemical Engineering

Outline

- Introduction
- Process Analytical Technology - pharmaceutical production
- PSE methods and tools in a PAT context
- Case study examples
- Conclusions and perspectives

Research focus



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A now well-known comment about conventional pharmaceutical manufacturing

- "The pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers.“

  The Wall Street Journal, Sept. 3, 2003

Conventional pharmaceutical manufacturing

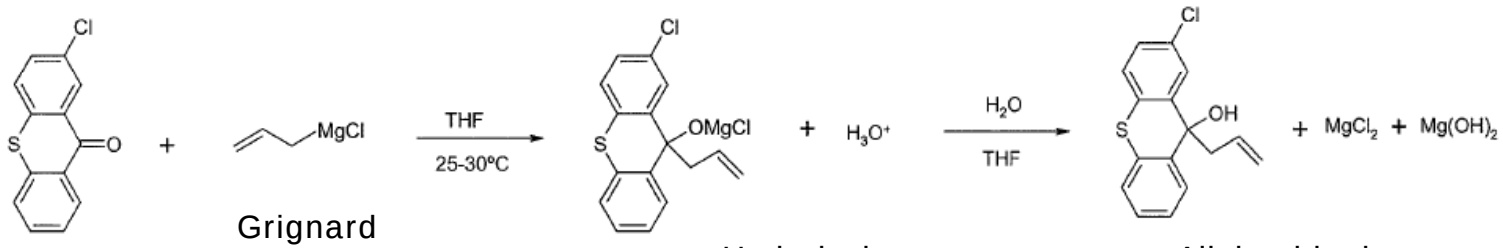
- **Conventional pharmaceutical manufacturing** relies on:
  - Batch processes, 'frozen processes'
  - Processing often based on time-defined endpoints (e.g. mix 2 hours)
  - Extensive laboratory testing on collected samples to evaluate quality of each batch (**'labcentric' approach**)

- As a consequence:
  - Limited on-line analysis
  - Limited process control

- Strengths:
  - Successful (safe medicines to the public)

- Weaknesses
  - Labor intensive
  - No reaction on disturbances
  - Not very efficient

An example of traditional production: Production of zuclopenthixol



CTX

Grignard reagent

Hydrolysis

Allylcarbinol

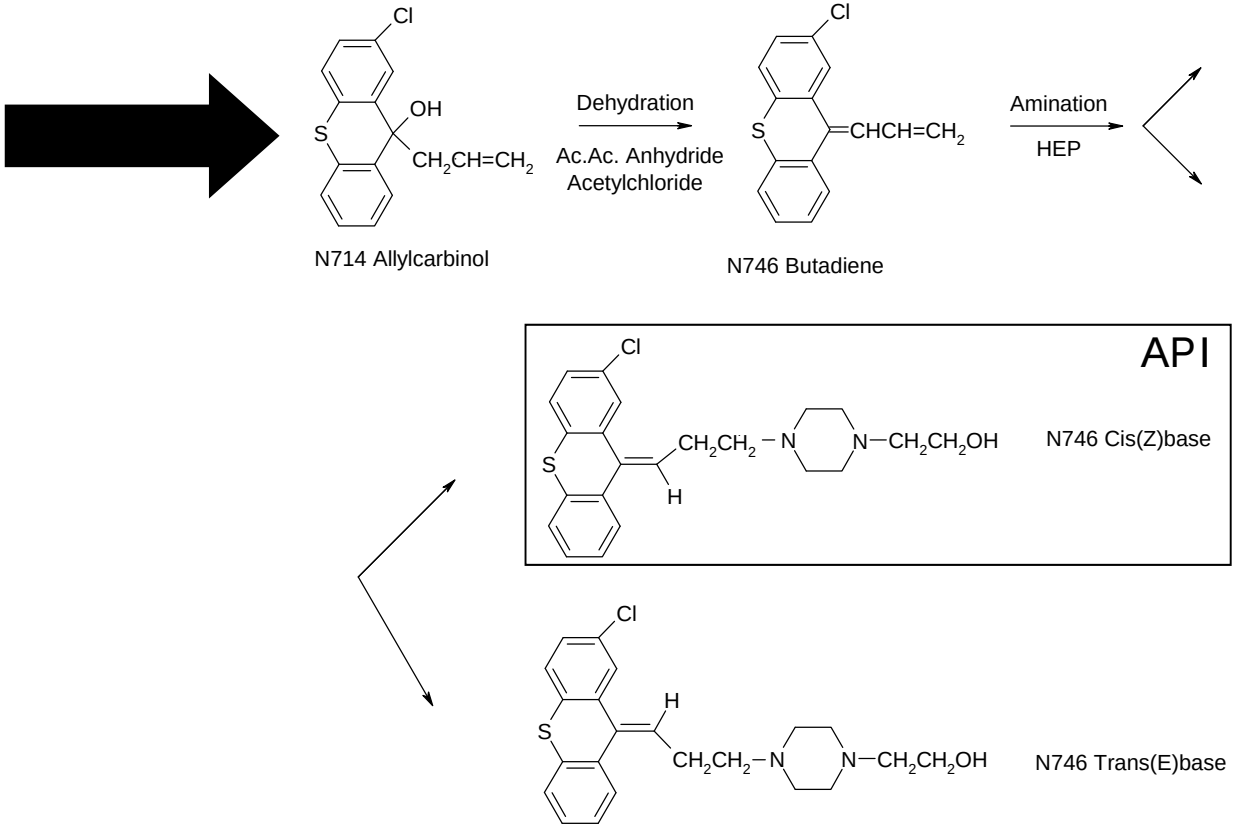
Batch process 1

Allylcarbinol (intermediate)

sent to storage

An example of traditional production: Production of zuclopenthixol

Batch process 2



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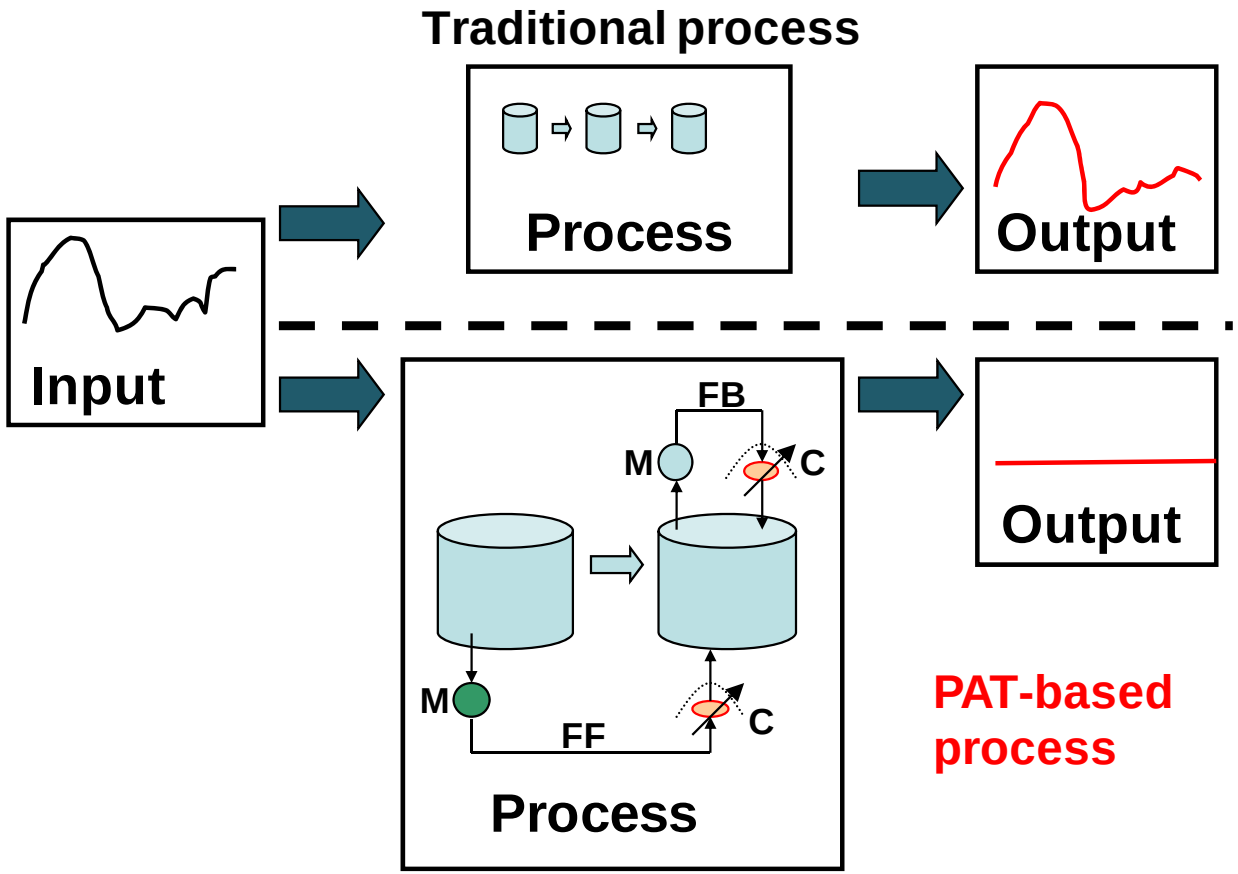
Process Analytical Technology – impact on production processes

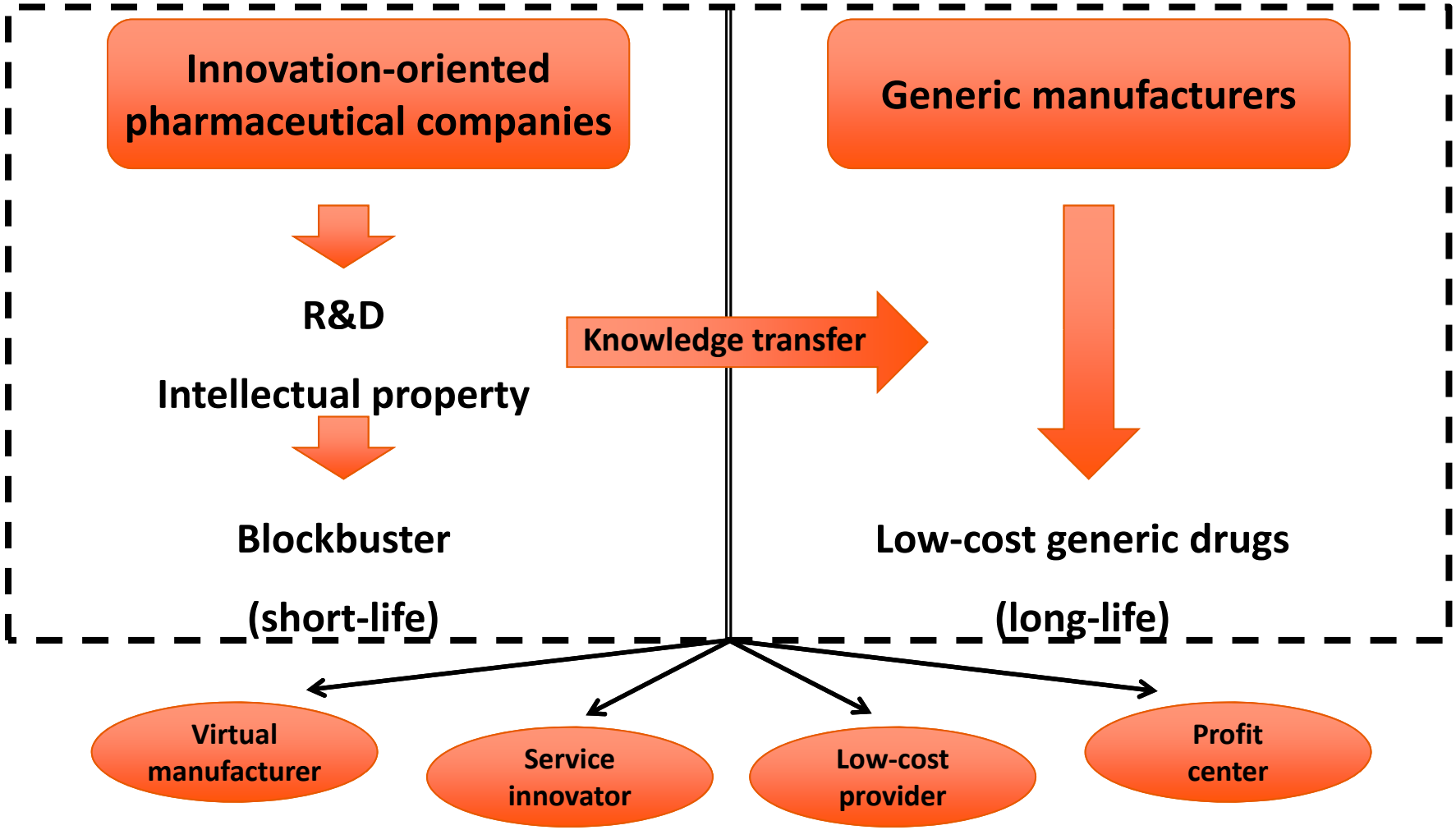


PAT-based pharmaceutical manufacturing

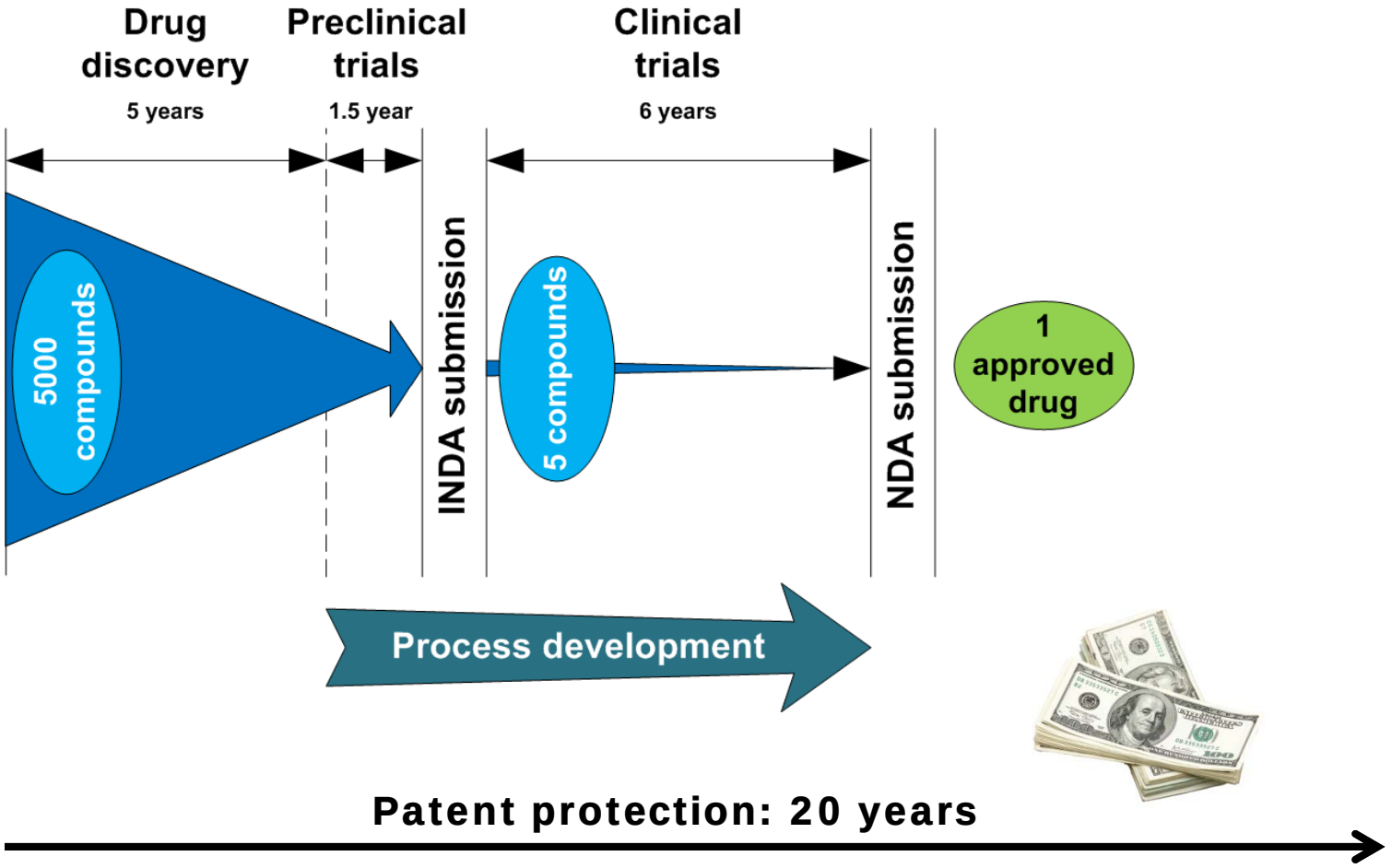
- **PAT-based pharmaceutical manufacturing** relies on:
  - Continuous processes replacing batch processing where possible (exploit full potential of PAT)
  - Limited off-line laboratory analysis
  - On-line / at-line analysis to guarantee product quality (design space)
  - The fact that the process endpoint is not a fixed point in time
- As a consequence:
  - Considerable on-line analysis
  - Significant contribution from process control
- Strengths:
  - Cheaper production (less rejected product)
  - Reduced human errors through automation
  - Smaller scale of operation if continuous processing
- Weaknesses
  - Knowledge intensive (time-consuming)
  - Necessitates multi-disciplinary production teams

Pharmaceutical business models

(PwC, 2011. *Pharma 2020*)



Innovation-oriented pharmaceutical industry



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What is Process Systems Engineering (PSE)?

- **PSE** is concerned mainly with the **use of systematic approaches to solve engineering problems**

- PSE areas:
  - PSE core methodologies (numerical analysis, optimization methods, etc)
  - PSE core domains (modelling, synthesis/design, control, operation, monitoring, etc)
  - PSE emerging methodologies (cyberinfrastructure, informatics and intelligent systems, integrated approaches to design, control and data analysis, systematic techniques for managing complexity, etc)
  - PSE emerging domains (product-process design, enterprise-wide optimization, energy and sustainability, biological engineering, pharmaceutical engineering, etc)

What is Process Systems Engineering (PSE)?

- PSE products:
  - Mainly models, techniques, algorithms, computer-aided systems (such as specialized software) that help to understand, analyze and solve a wide range of engineering problems

- PSE aims at providing the means to **manage the complexity** of a wide range of systems or problems

- **Strong dependence on models** (including data and/or knowledge based systems)!
  - The application range of the products of PSE depends on the applicability of the models used to develop and/or use them.

- **Advantage of using PSE**: significant reduction of resources (material, time, money, etc.) can be achieved, potential to satisfy the demands for "faster to market at reduced cost"

PAT tools (from PAT guidance document)

- Multivariate tools for design, data acquisition and analysis
  - Statistical DoE, chemometrics, pattern recognition methods

- Process analyzers
  - Traditionally univariate (pH, pressure, T, flow rate)
  - Now more and more multivariate (spectroscopy, size distribution)
  - Software sensors or softsensors
  - Measurements do not need to be expressed as absolute values, relative differences are sufficient as input to process control systems
  - Essential for process control

PAT tools (from PAT guidance document)

- Process control tools
  - Monitor process state, and actively manipulate it to maintain a desired state

- Continuous improvement and knowledge management tools
  - Learn from new experiments / production batches, e.g. via data mining, mechanistic models, uncertainty and sensitivity analysis, etc.

- **An appropriate combination of some, or all, of these tools may be applicable to a single- unit operation, or to an entire manufacturing process and its quality assurance**

PAT tools (from PAT guidance document)

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PSE methods and tools

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PSE methods and tools

- **For a more detailed overview of PSE methods and tools applied to pharmaceutical production process development:**
  - Gernaey et al. (2012) A perspective on PSE in pharmaceutical process development and innovation. Computers and Chemical Engineering, 42, 15-29.

Our approach to PAT

- **Process knowledge** is the key to developing successful PAT applications

- **Mechanistic modelling** = collection of process knowledge
  - Well-structured (model matrix)
  - Analysis
  - **Link to experiments** via
    - Parameter estimation (confidence intervals, correlations)
    - Uncertainty and sensitivity analysis (local, global)

- Models and Process Systems Engineering (PSE):
  - **Systematic approaches**, generic methodologies

    Gernaey and Gani (2010) Chemical Engineering Science, 65, 5757-5769.
    Samad et al. (2011) Computers and Chemical Engineering, 35, 828-843.
    Gernaey et al. (2012) Computers and Chemical Engineering, 42, 15-29.

Mechanistic model - development

- Model development – equations are structured in a matrix
  - Example: matrix description of Monod-Herbert aerobic growth model

Component, *i*	C_1	C_2	C_3	**Rates, r_j**
Symbols	S_S	S_O	X	
Units	C-mol/L	mol/L	C-mol/L	C-mol X/(L.h)
Process, *j*				
1. Growth	$-1/Y_{X,S}$	$-1/Y_{X,O}$	1	$\mu_{max}\frac{S_S}{S_S+K_S}X$
2. Decay	0	$-1/\gamma_X$	-1	$k_d X$

Sin et al. (2008). Biotechnol. Bioeng., 101:153-171

Matrix, model of *S. coelicolor* fermentation

		Liquid phase													Gas phase				
	Components →i	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Rates
	Name	Glucose	Oxygen	Ammonia	Phosphate	Biomass	Antibiotic 1	Antibiotic 2	Carbon dioxide	Hydrogen ion	Ammonium	Phosphate	Bicarbonate	Hydroxyl ion	Nitrogen	Oxygen	Carbon dioxide	Nitrogen	Ammonia	
	Symbol	S_g	S_O	S_{NH}	S_{PO}	X	S_{P1}	S_{P2}	S_{CO2}	S_H	S_{NH4}	S_{HPO4}	S_{HCO3}	S_{OH}	S_{N2}	G_O	G_{CO2}	G_{N2}	G_{NH3}	
	Chemical composition	$C_6H_{12}O_6$	O_2	NH_3	$H_2PO_4^-$	$CH_{1.8}O_{0.5}N_{0.2}P_{0.015}$	$C_{32}H_{36}O_{14}$	$C_{25}H_{35}N_3O$	CO_2	H^+	NH_4^+	HPO_4^{-2}	HCO_3^-	OH^-	N_2	O_2	CO_2	N_2	NH_3	
j	Processes↓ (Units)	C-mmol/l	O-mmol/l	N-mmol/l	P-mmol/l	C-mmol/l	C-mmol/l	C-mmol/l	C-mmol/l	H-mmol/l	N-mmol/l	P-mmol/l	C-mmol/l	H-mmol/l	N-mmol/l	O-mmol/l	C-mmol/l	N-mmol/l	N-mmol/l	mmol/l-d
1	Biomass growth	$-1/Y_{SX}$	$\gamma_X/4.0 - \gamma_S/(Y_{SX}*4.0)$	$-i_{NX}$	$-i_{PX}$	1			$1/Y_{SX}-1$	$-i_{PX}$										$\mu^{max}\frac{1}{1+e^{t_s-t}}\frac{S_g}{S_g+K_g}\frac{S_O}{S_O+K_O}\frac{S_{NH3}}{S_{NH3}+K_{NH3}}\frac{S_{PO}}{S_{PO}+K_{PO}}X$
2	Actinorhodin production	$-1/Y_{SACT}$	$\gamma_{ACT}/4.0 - \gamma S/(Y_{SACT}*4.0)$				1		$1/Y_{SACT}-1$											$q_{ACT}\ r_X+\beta_{ACT}\left(1-\frac{S_{ACT}}{S_{ACT}^{max}}\right)\left(\frac{S_g}{K_g+S_g}\frac{K_{IP}}{K_{IP}+S_{PO}}\right)X$
3	Undecylprodigiosin production	$-1/Y_{SRED}$	$\gamma_{RED}/4.0 - \gamma S/(Y_{SRED}*4.0)$	$-i_{NRED}$					$-i_{CRED}$											$q_{RED}\ r_X+\beta_{RED}\left(1-\frac{S_{RED}}{S_{RED}^{max}}\right)\left(\frac{S_g}{K_g+S_g}\frac{K_{IP}}{K_{IP}+S_{PO}}\right)X$
4	Biomass maintenance	-1	$-\gamma_S/4.0$						1											$m_S\frac{S_g}{S_g+K_g}\frac{S_O}{S_O+K_O}X$
5			$-\gamma_X/4$	i_{NX}	i_{PX}	-1			1	i_{PX}										$k_d\frac{S_O}{S_O+K_O}\frac{K_g}{S_g+K_g}X$
6	Ammonium dissociation			1						1	-1									$k_{f,NH}S_{NH4}-\frac{k_{f,NH}}{K_{NH}}S_{NH3}\cdot S_H$
7	Dihydrogen phosphate dissociation				-1					1		-1								$k_{f,H2PO4}S_{H2PO4}-\frac{k_{f,H2PO4}}{K_{H2PO4}}S_{HPO4}\cdot S_H$
8	Carbon dioxide dissociation								-1	1			-1							$k_{f,CO2}S_{CO2}-\frac{k_{f,CO2}}{K_{HCO3}}S_{HCO3}\cdot S_H$
9	Water dissociation									1				-1						$1-\frac{k_{f,W}}{K_W}S_H\cdot S_{OH}$
10	Aeration (Oxygen)		1													-1				$K_La_{O2}\cdot(S_O^*-S_O)$
11	CO_2 stripping																-1			$K_La_{CO2}\cdot(S_{CO2}^*-S_{CO_2})$
12	Nitrogen stripping														1			-1		$K_La_{N2}\cdot(S_{N2}^*-S_{N2})$
13	Ammonia stripping			1															-1	$K_La_{NH3}\cdot(S_{NH3}^*-S_{NH3})$
Conservation matrix																				
Elements	Units																			
MW	g/C-mmol ; g/N-mmol ; g/P-mmol	30.00	32.00	14.00	31.00	25.07	19.81	15.72	12.00	1.00	14.00	31.00	14	1	14	32.00	12.00	14.00	14.00	
C	C-mmol/mmol	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	
N	N-mmol/N-mmol	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	
P	P-mmol/P-mmol	0.00	0.00	0.00	1.00	0.02	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
γ	mmol e/ C-mmol	4.00	-4.00	0.00	0.00	4.13	3.94	4.96	0.00	0.00	0.00	0.00	0	0.00	0	0.00	0.00	0.00	0.00	
Charge	mmol /mmol	0.00	0.00	0.00	-1.00	0.00	0.00	0.00	0.00	1.00	1.00	-2.00	-1.00	-1.00	0	0.00	0.00	0.00	0.00	

Equations biological processes

Equations chemical equilibria

Equations mass transfer

Conservative properties

Sin et al. (2008). Biotechnol. Bioeng., 101:153-171

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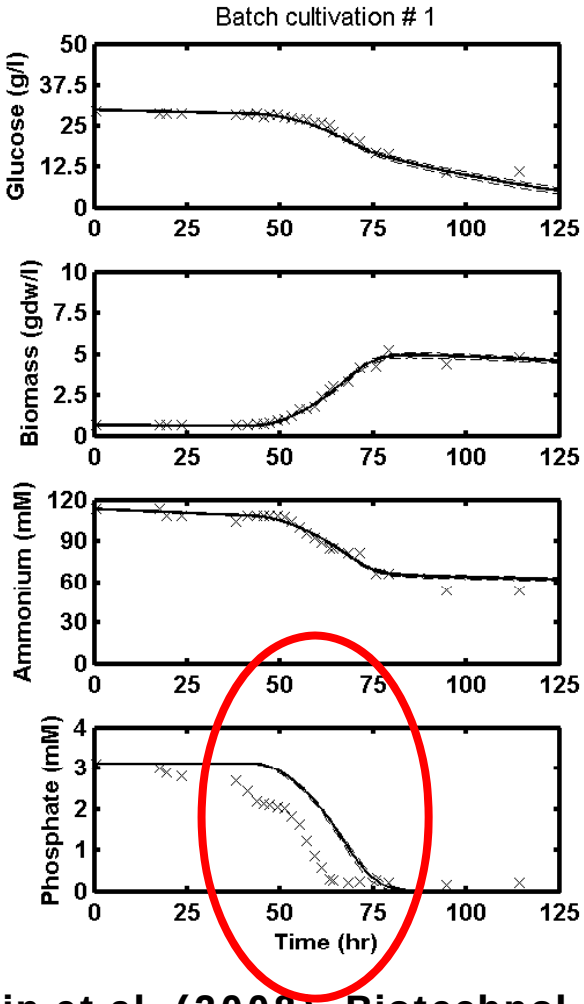
Mechanistic modelling



Mismatch between model and data indicates a lack of process knowledge

Confidence intervals on estimated parameters informs about quality of the data and the resulting model

Sin et al. (2008), Biotechnol. Bioeng., 101:153-171

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Case study 1: Switching from batch to continuous production – organic synthesis

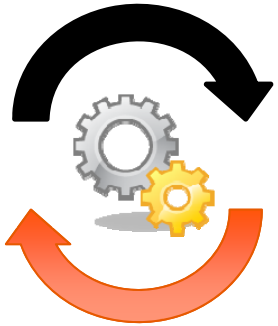
Objectives:

- **Obtain the continuous synthesis of clopenthixol (H. Lundbeck A/S)**
- **Develop a toolbox of continuous API synthesis and separation operations**

Solution approach:

- Experimentation with continuous flow technologies (micro- and mini-scale)
- Active use of PAT
- Use Process Systems Engineering (PSE) methods and tools

PROCESS SYSTEMS ENGINEERING



EXPERIMENTATION CONTINUOUS FLOW TECHNOLOGIES

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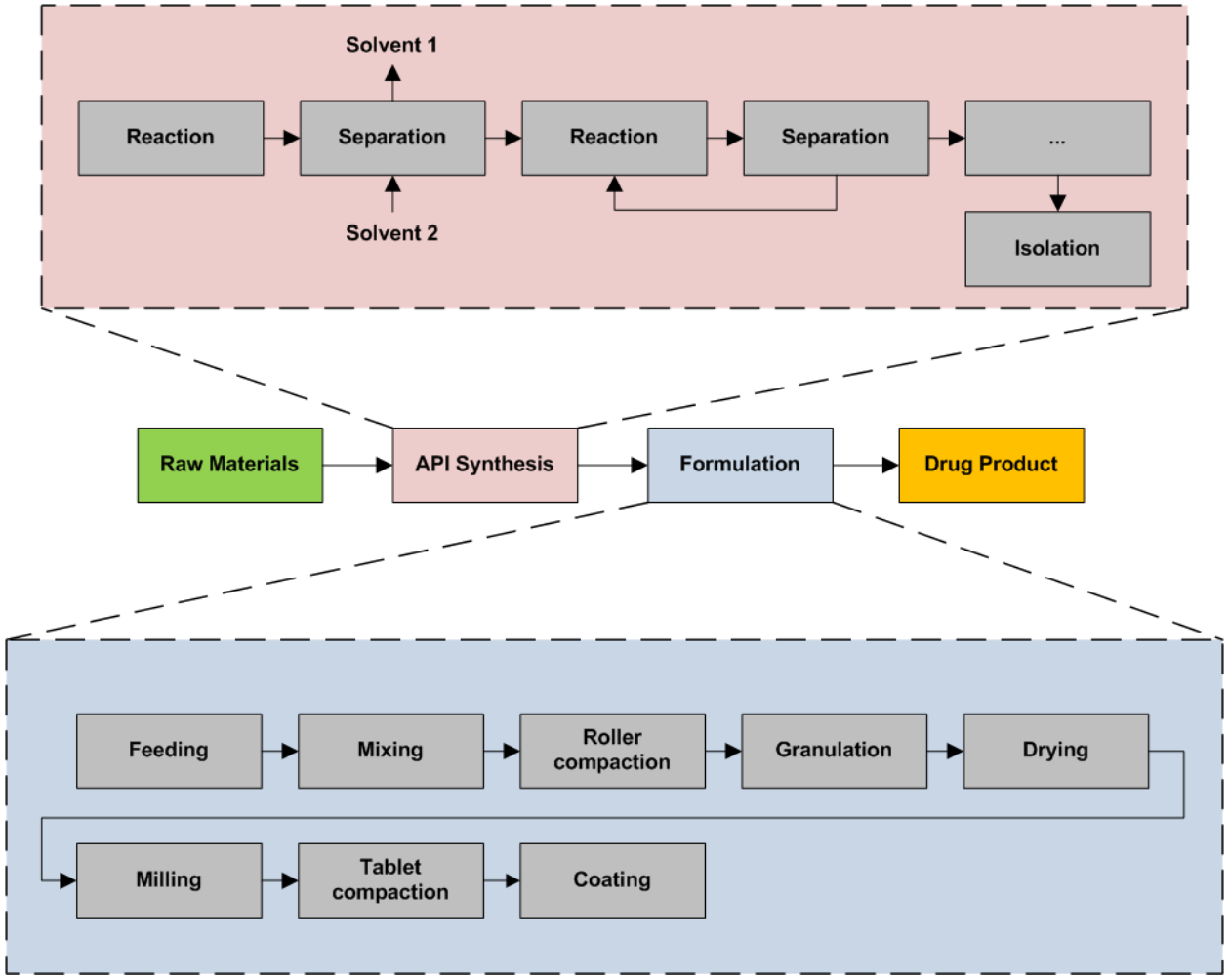
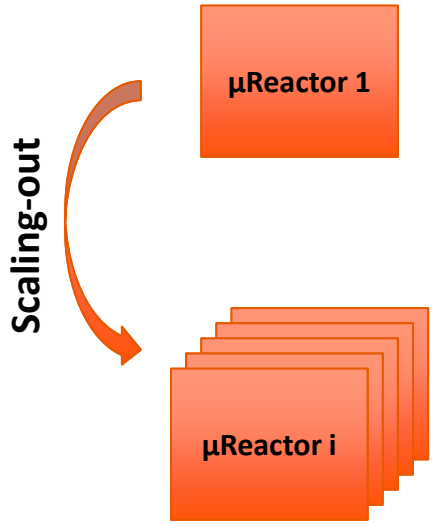
Transforming the supply chain



Novel pharmaceutical plants

- **Continuous processing**
- **Miniplants – microreactors**
- **Scaling-out**
- **Modular construction**
- **Standardization**
- **On-line monitoring - automation**



Improved heat & mass transfer
Dedicated equipment
Extreme conditions
Higher yield, higher selectivity
Low footprint, less waste
Increased safety

Lab-scale

No scale-up risk
Greater flexibility
Short time to market

Industrial-scale

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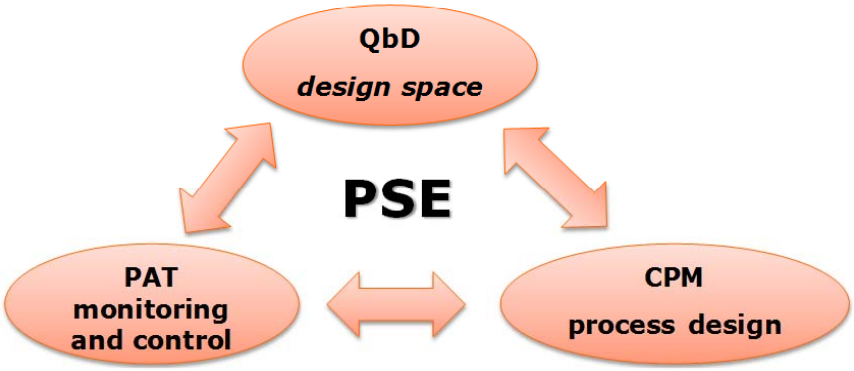
Methodology

API production involving continuous processes

PSE-assisted design framework



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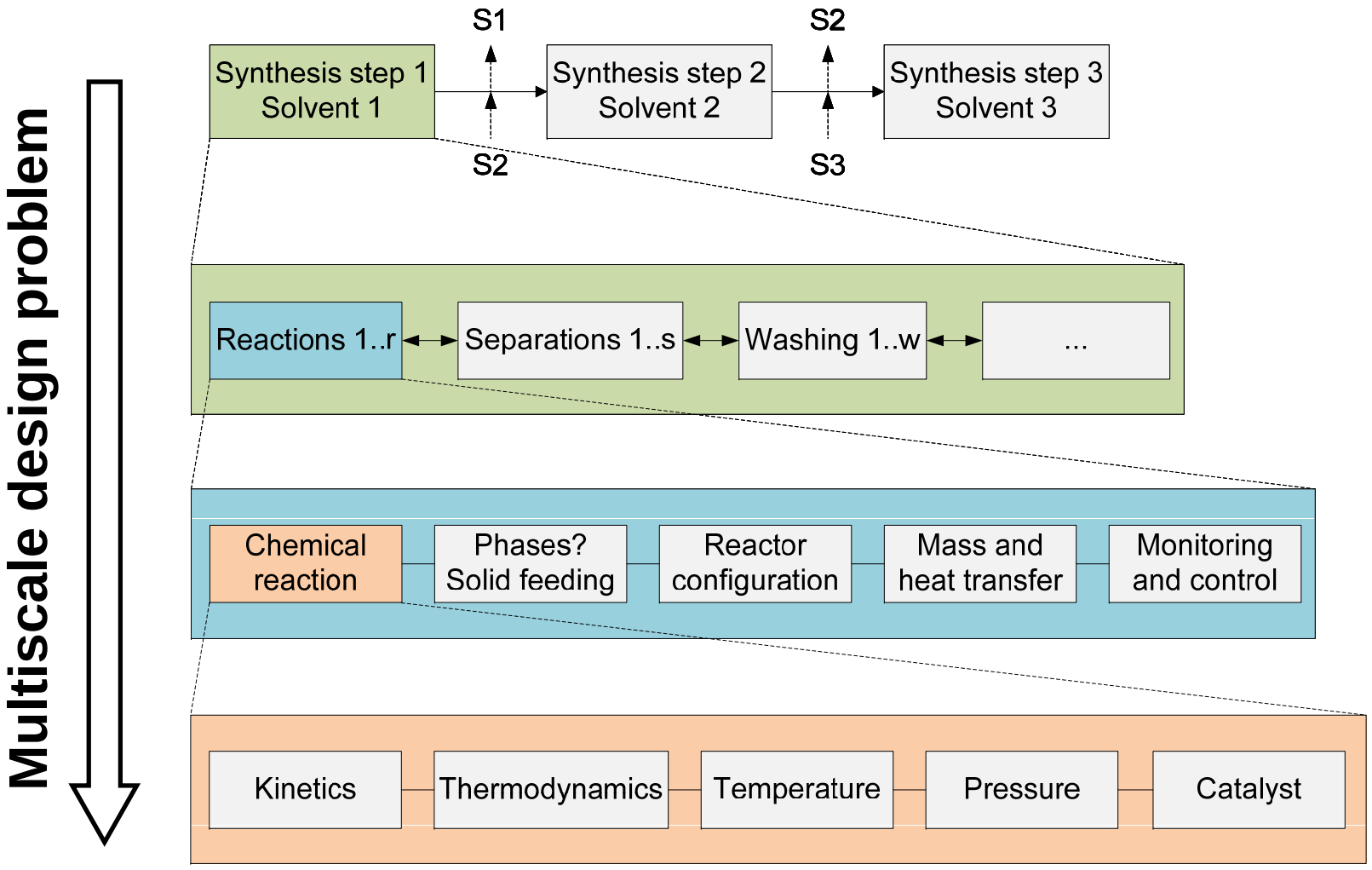
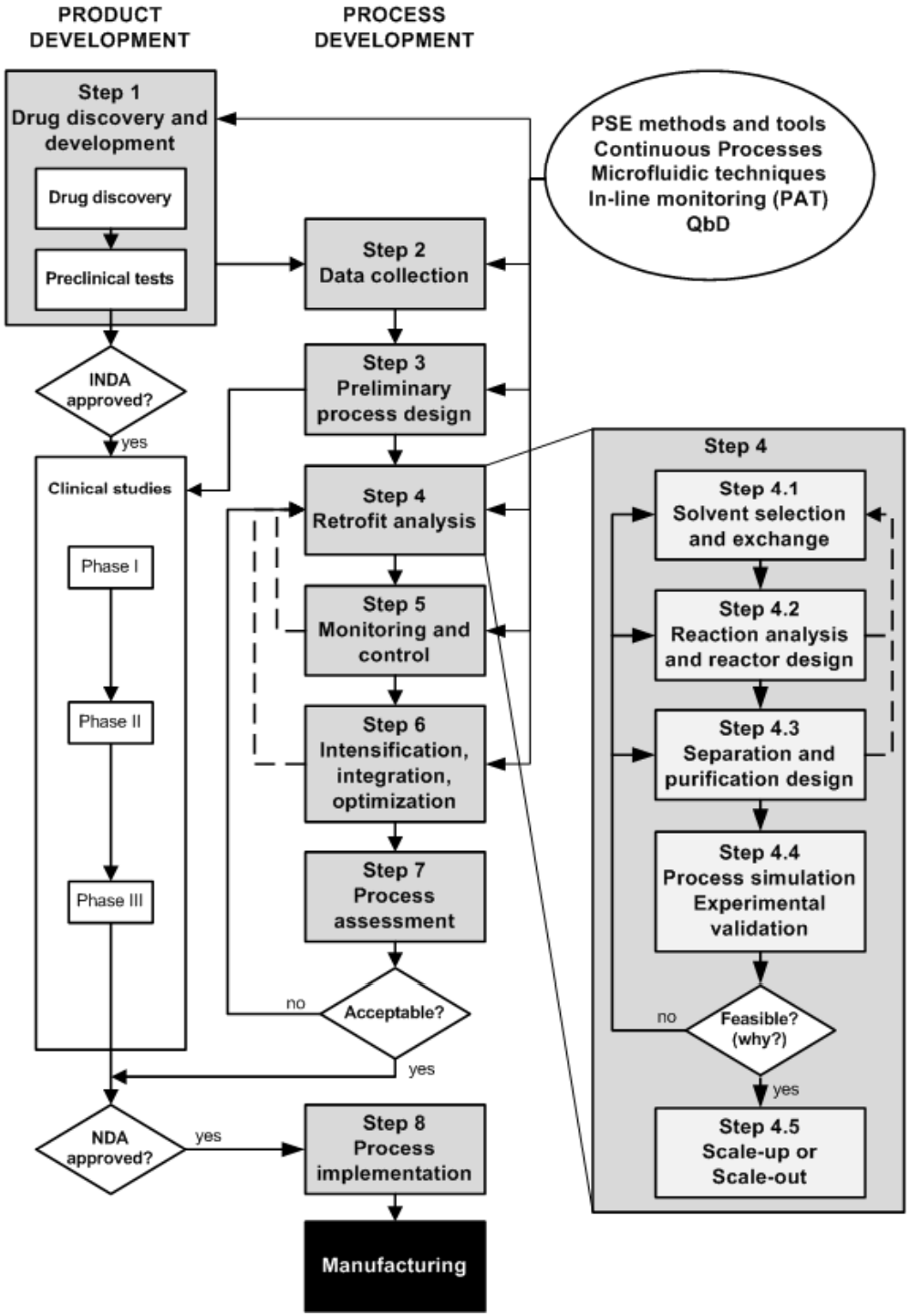
Multistep reaction systems





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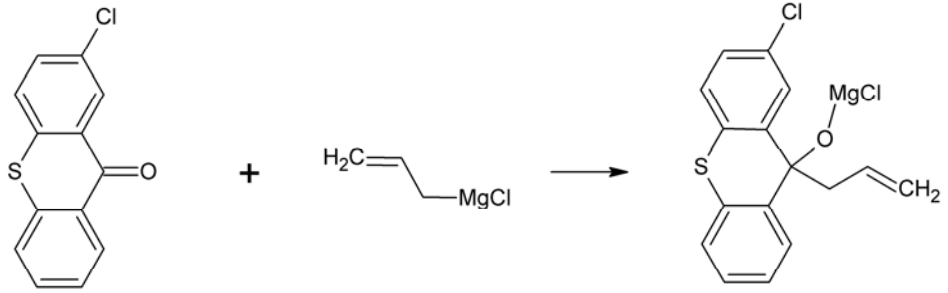
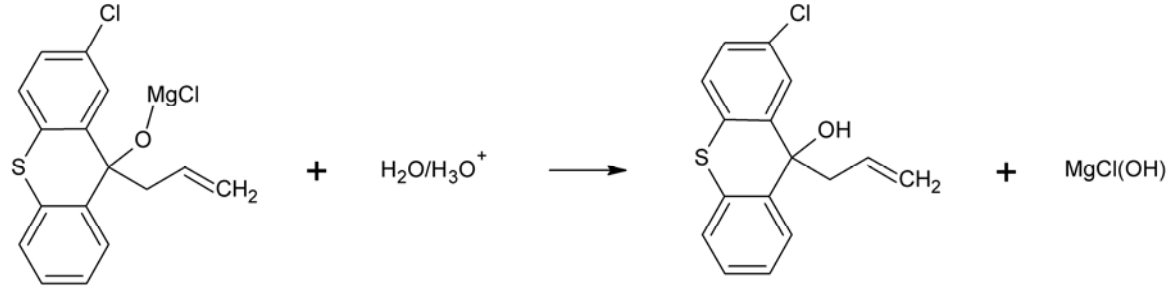
1. Alkylation



CTX AllylMgCl Alkoxide

THF

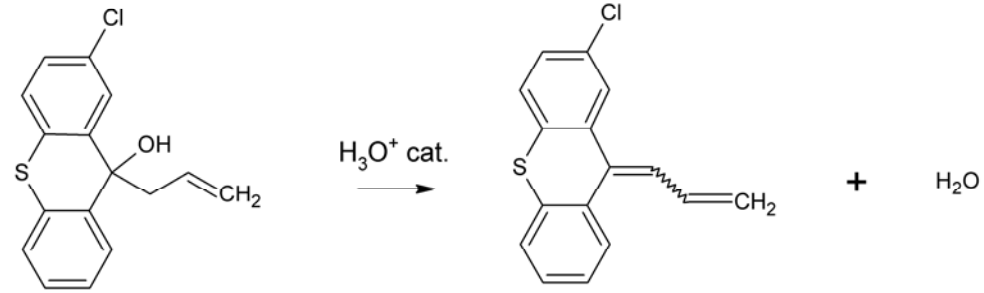
2. Hydrolysis



Alkoxide ’Allylcarbinol’

THF

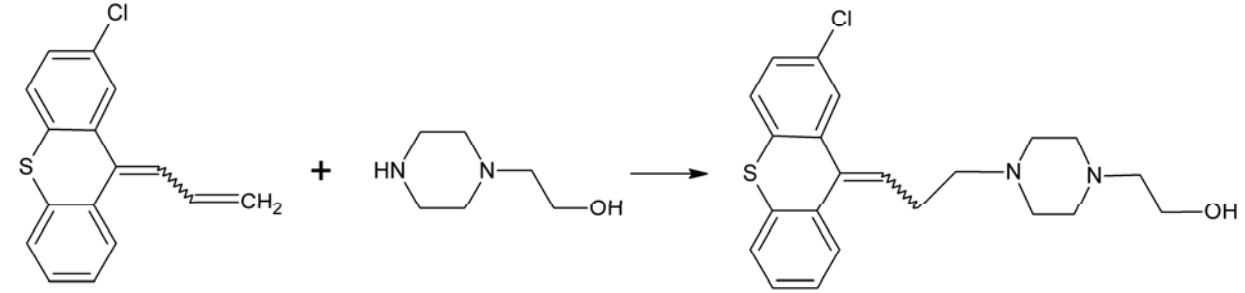
3. Dehydration



’Allylcarbinol’ ’Butadiene’

Toluene/THF

4. Hydroamination



’Butadiene’ HEP Clopenthixol

Solvent free

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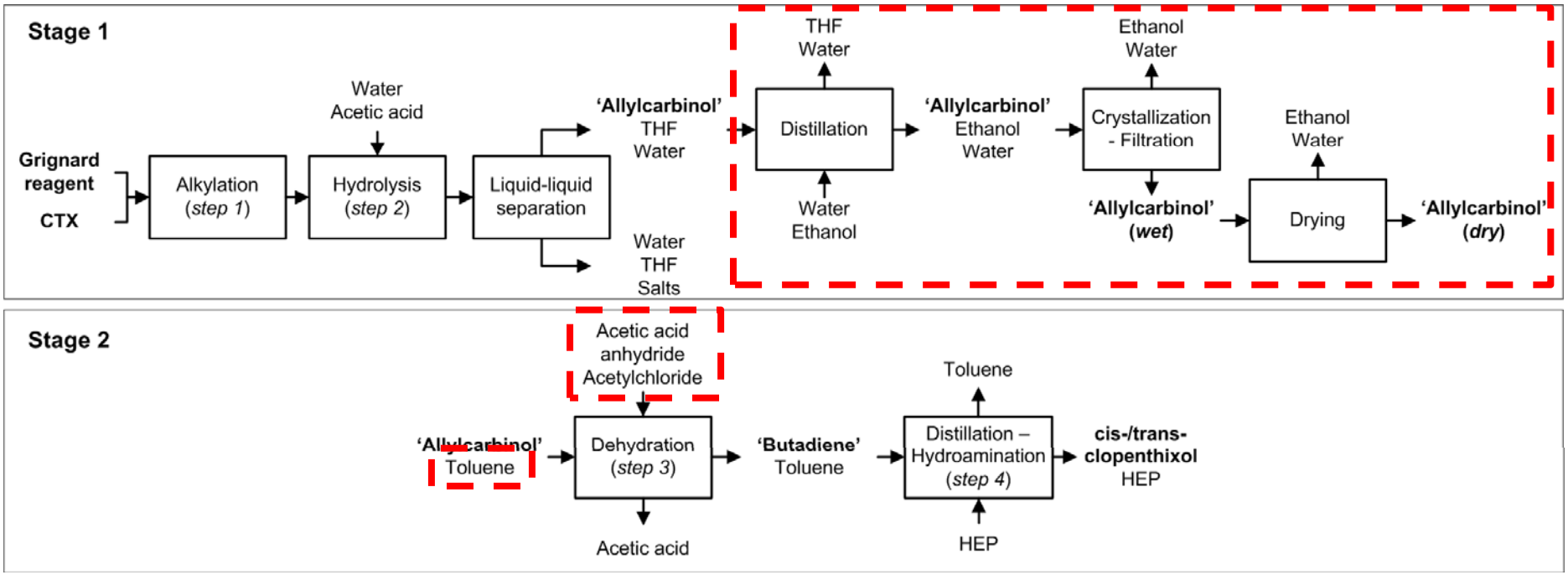
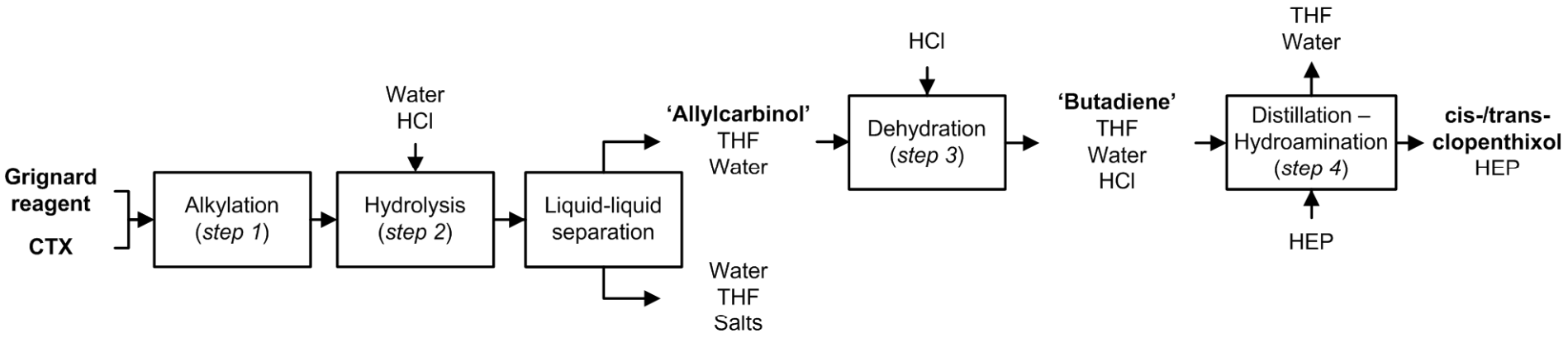
s Engineering and Technology

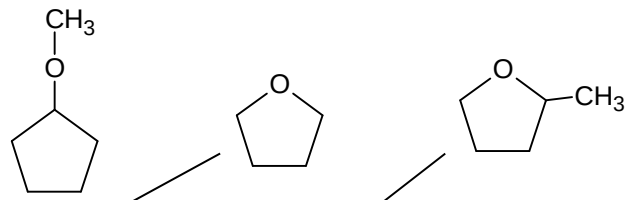
Original batch-wise process



Simplified continuous process



Alternative solvents



	CPME[a]	THF	2-MeTHF[a]	MTBE[a]	Et_2O	dioxane
density (20 °C)[g/cm^3]	0.86	0.89	0.85	0.74	0.71	1.03
vapor specific gravity (air = 1)	3.45	2.49	2.97	3.1	2.56	3.3
boiling point[°C]	106	65	80	55	34.6	101
melting point[°C]	<−140	−108.5	−136	−110	−116.3	11.8
viscosity (20 °C) [cP]	0.55	0.55	0.6(25 °C)	0.35	0.2448	1.31
surface tension (20 °C) [mN/m]	25.17	26.4	unknown	19.8	17.3	33.74
vaporization energy (bp) [kcal/kg]	69.2	98.1	89.7	81.7	86.08	98.6
specific heat (20 °C) [kcal/kg·K]	0.4346	0.469	unknown	0.51	0.5385	0.41
refractive index (20 °C)	1.4189	1.407	1.406	1.369	1.353	1.422
solubility parameter [cal/mL]	8.4	9.5	8.52	unknown	7.4	unknown
dielectric constant (25 °C)	4.76	7.58	7	2.6	4.197	2.227
dipole moment [*D*]	1.27 (calcd)	1.7	unknown	1.4	1.12	0.45
azeotropic point with water [°C]	83[b]	64	71[c]	52.9[d]	34.2	87.8
solubility in water [g/100 g]	1.1 (23 °C)	∞	14	4.8	6.5	∞
solubility of water in the solvent [g/100 g]	0.3 (23 °C)	∞	4.4	1.4	1.2	∞
flash point [°C]	−1	−14.5	−11	−28	−45	12
ignition point [°C]	180	205	270	224	180~90	180
Log Pow	1.59	0.47	unknown	0.94	0.89	−0.42
explosion range [vol %]	1.1−9.9	1.84−11.8	1.5−8.9	1.6−8.4	1.85−48	2−22

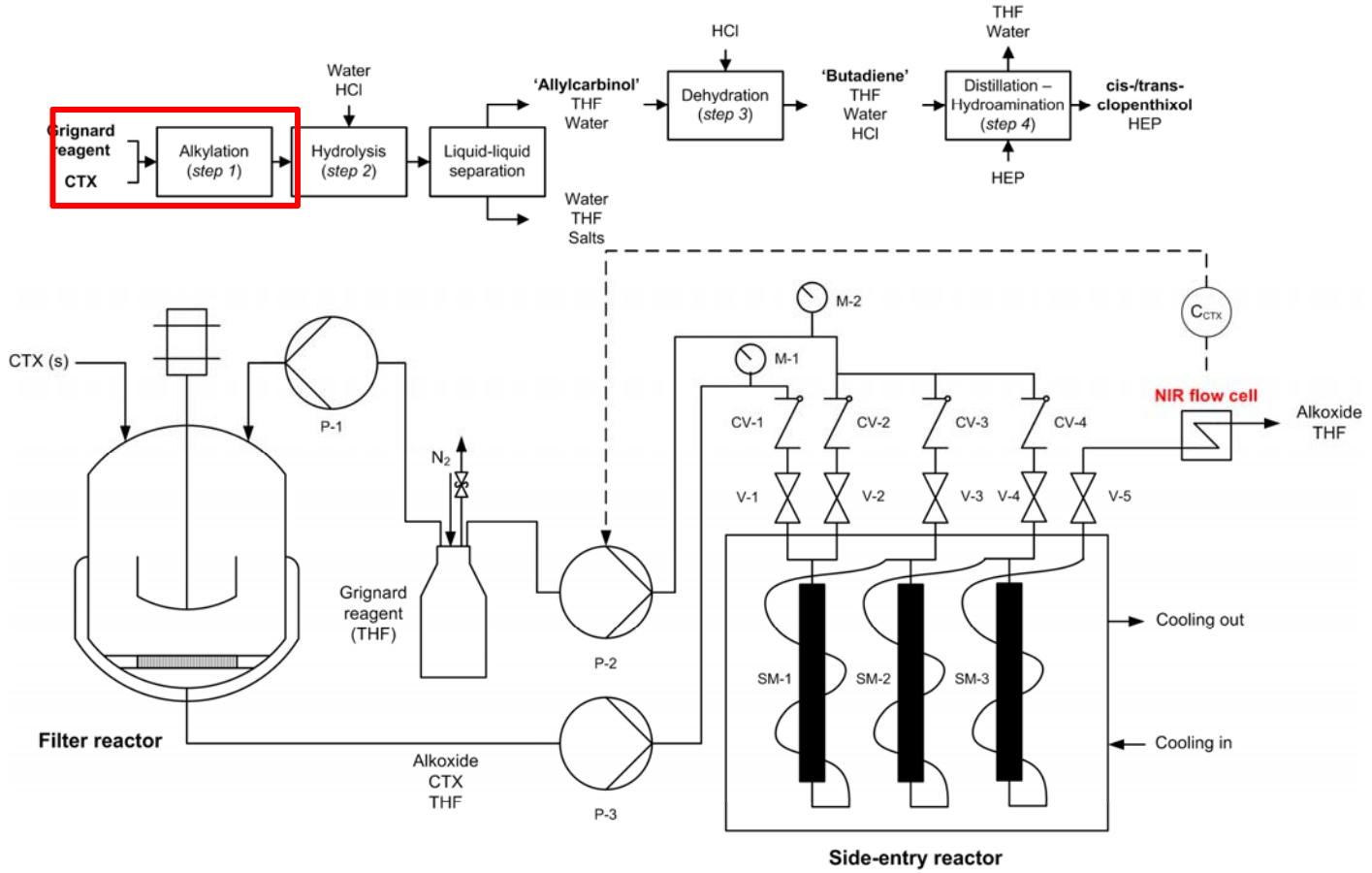
[a] Azeotrope (wt %). [b] Composition = CPME: 83.7, H_2O: 16.3. [c] Composition = MeTHF: 89.4, H_2O: 10.6. [d] Composition = MTBE: 96.5%, H_2O: 3.5.

(Watanabe et al., 2007)

Simplifying the process using continuous flow

1. **Continuous alkylation reaction with low impurity formation and low solvent use**

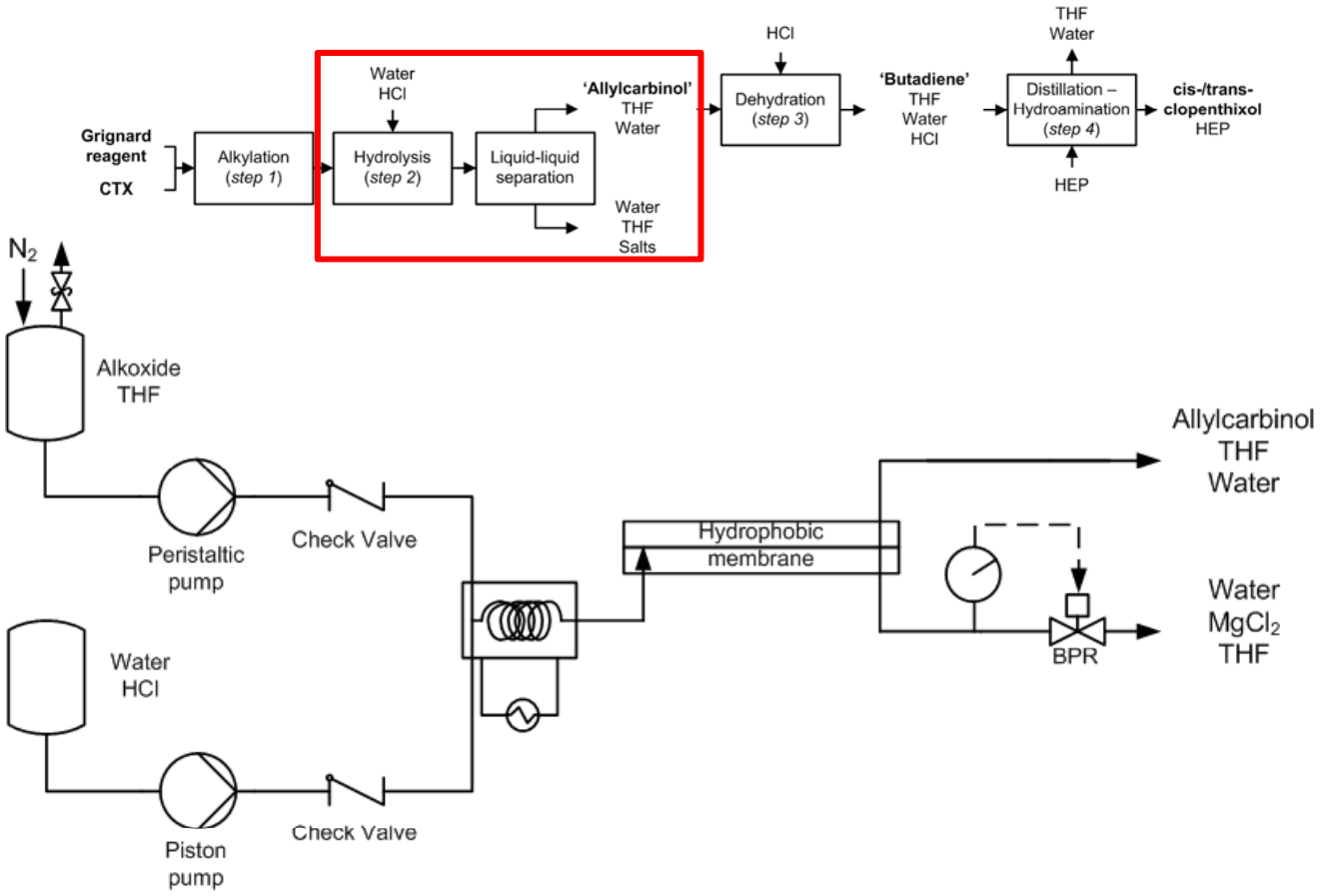
   Cervera-Padrell et al. (2012) Organic Process Research and Development, 16, 901-914.



Simplifying the process using continuous flow

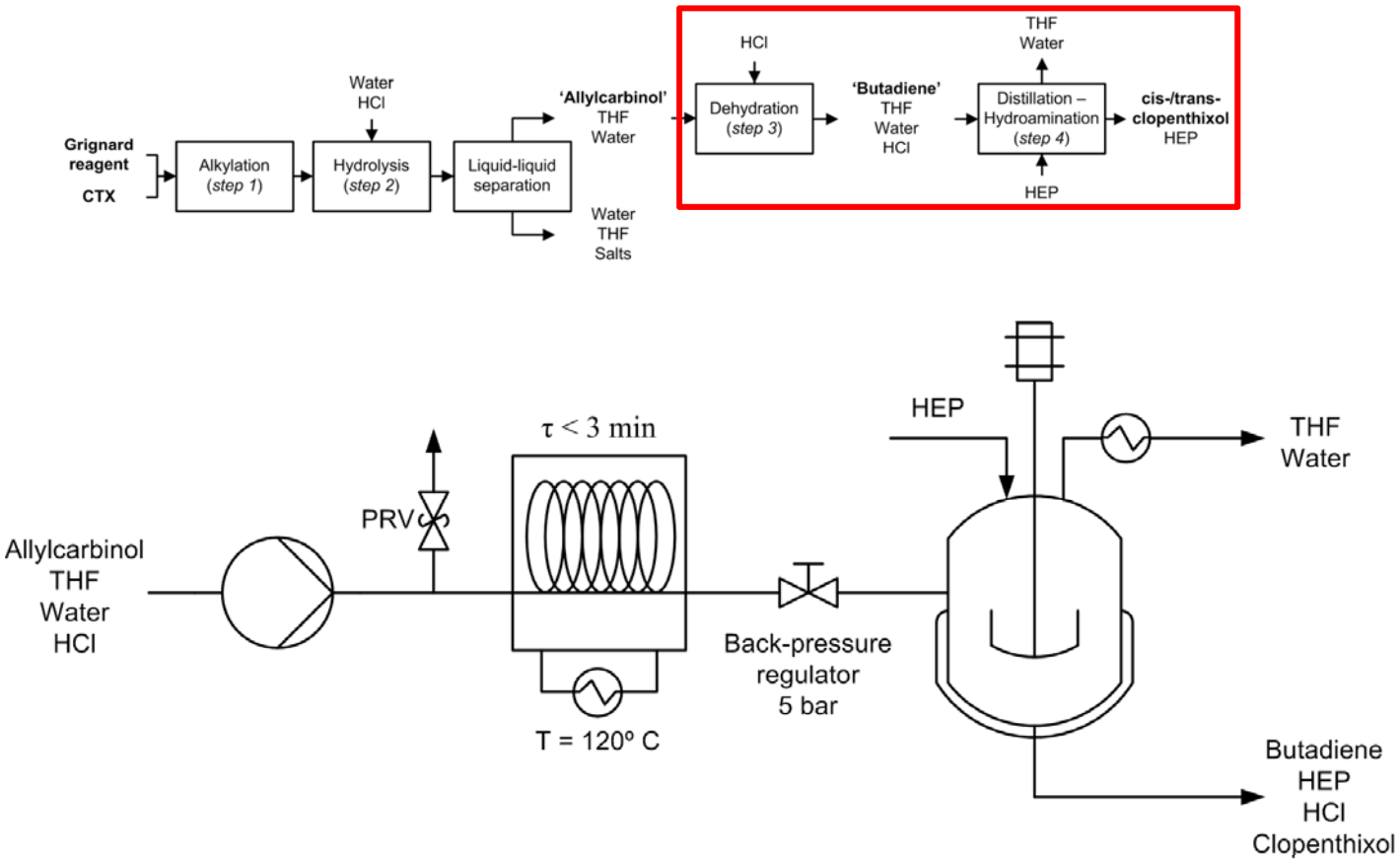
2. Demonstrate continuous hydrolysis and L-L separation

Cervera-Padrell et al. (2012) Organic Process Research and Development, 16, 888-900.



Simplifying the process using continuous flow

3. **Study the dehydration kinetics and demonstrate continuous reaction in THF/other**



Cervera-Padrell (2012) PhD thesis. Technical University of Denmark (DTU)

Benefits of simplified continuous process

Task	THF	CTX (s)	AllylMgCl (1 M in THF)	Water	HCl (37% aq)	Toluene	HEP	E/Z clopenthixol	Comments	Reactor
S1. Alkylation		ref (1 kg)	4.1						(1)	Reactors C1 and C2
S2. Hydrolysis				10.9	0.34				(2)	Reactor C3
S3. L-L separation	-2.4			-11.23	consumed to $MgCl_2$				(3)	Separator C1
S4. Dehydration					0.03				(4)	Reactor C4
S5. Solvent exchange and hydroamination	-1.4			-0.08			3.5*		(5)	Reactor B5
S6. Solvent exchange to toluene & aqueous extraction of HEP										Reactor B5
S6.1 Add toluene						5.9*				Reactor B5
S6.2 Add water				3*						Reactor B5
S6.3 L-L separation				-3*			-2.9*		(6)	Reactor B5
S6.4 First wash				2.3*						Reactor B5
S6.5 L-L separation				-2.3*					(7)	Reactor B5
S6.6 Second wash				2.3*						Reactor B5
S6.7 L-L separation				-2.3*					(7)	Reactor B5
TOTALS in (kg)			4.1	18.7*	0.37	5.9*	3.5*			
PRODUCT								1.1	(8)	
PMI (kg/kg)	29*								(9)	

Process Mass Intensity reduced to half of its original value

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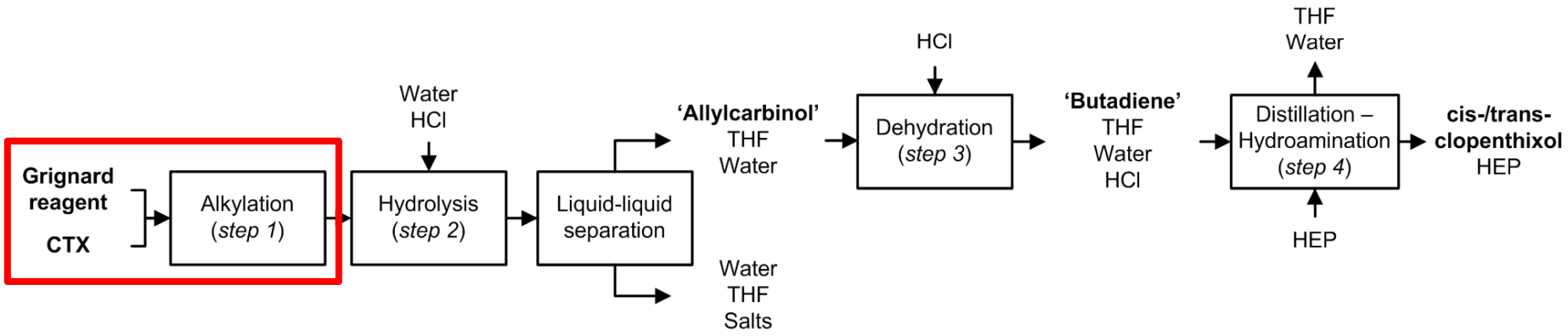
Monitoring and control of a continuous alkylation reaction using in-situ NIR spectroscopy measurements

Cervera-Padrell et al. (2012) Organic Process Research and Development, 16, 901-914.



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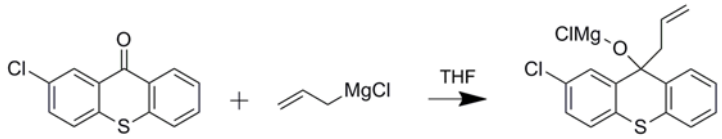
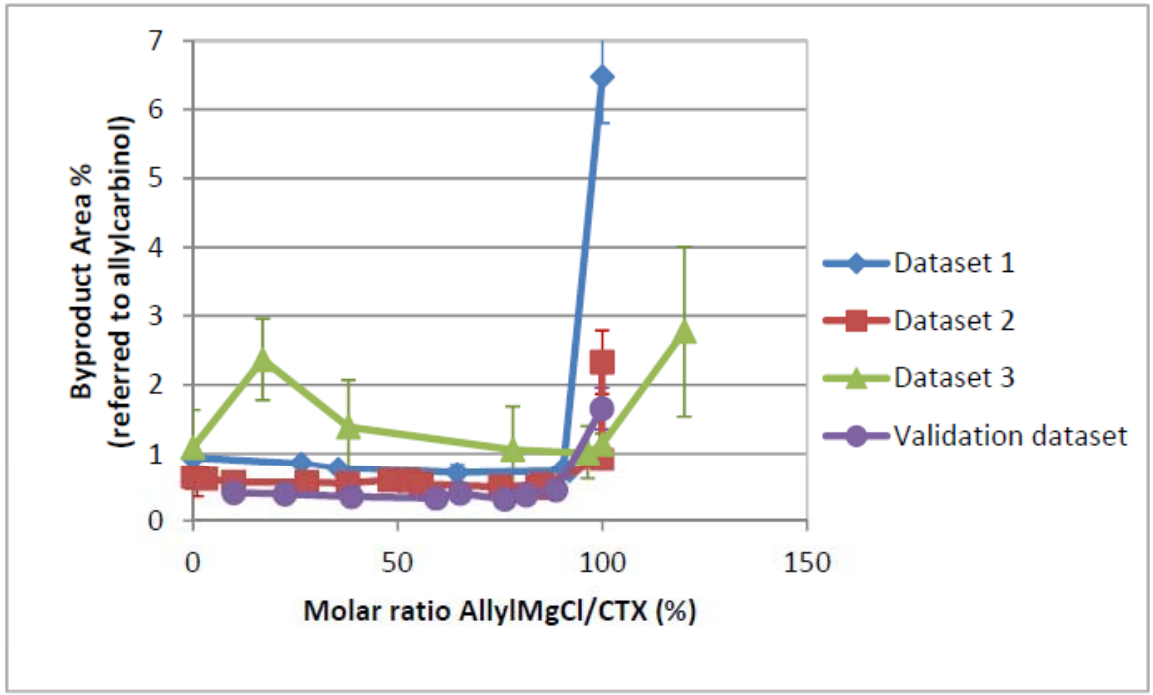
Impurity formation

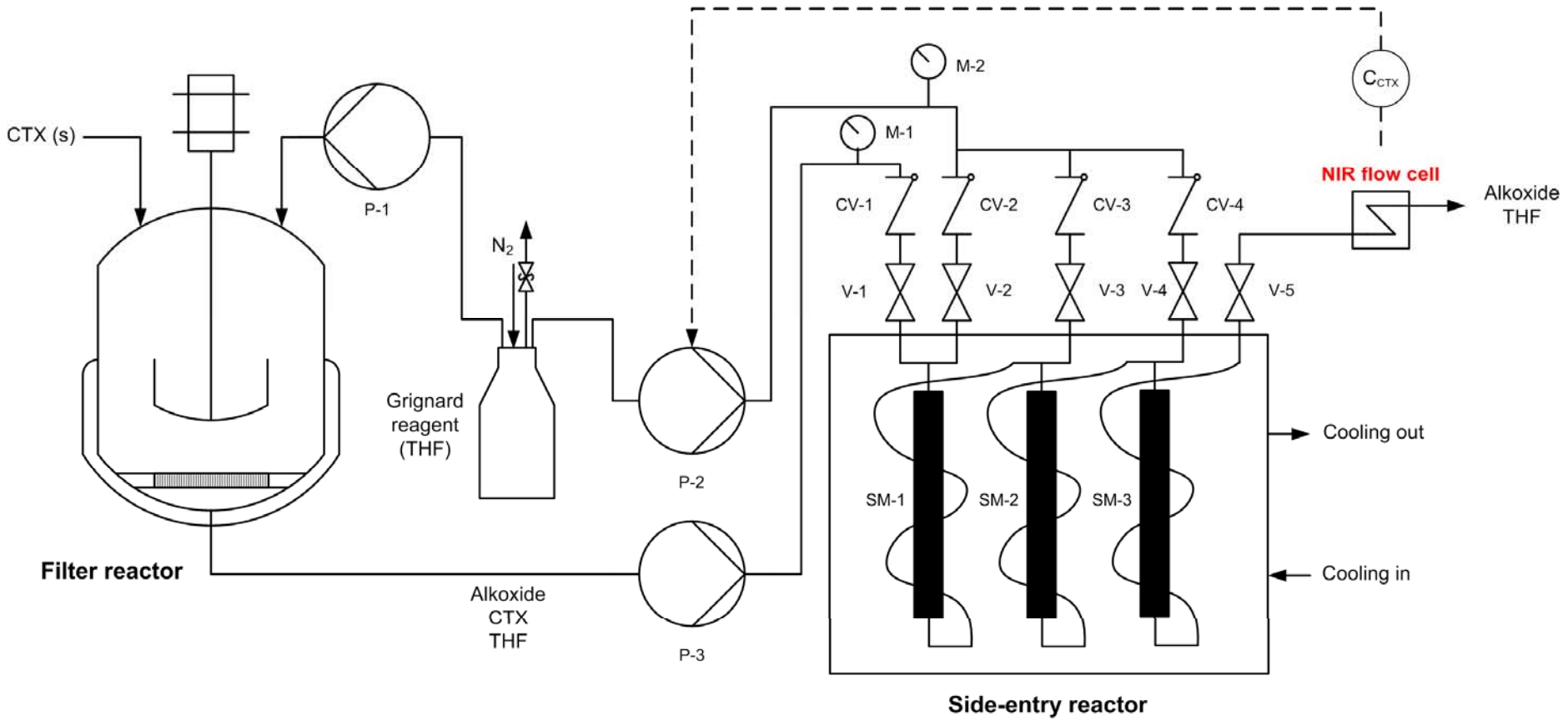
- **Excess of Grignard reagent produces impurities**



CTX Alkoxide

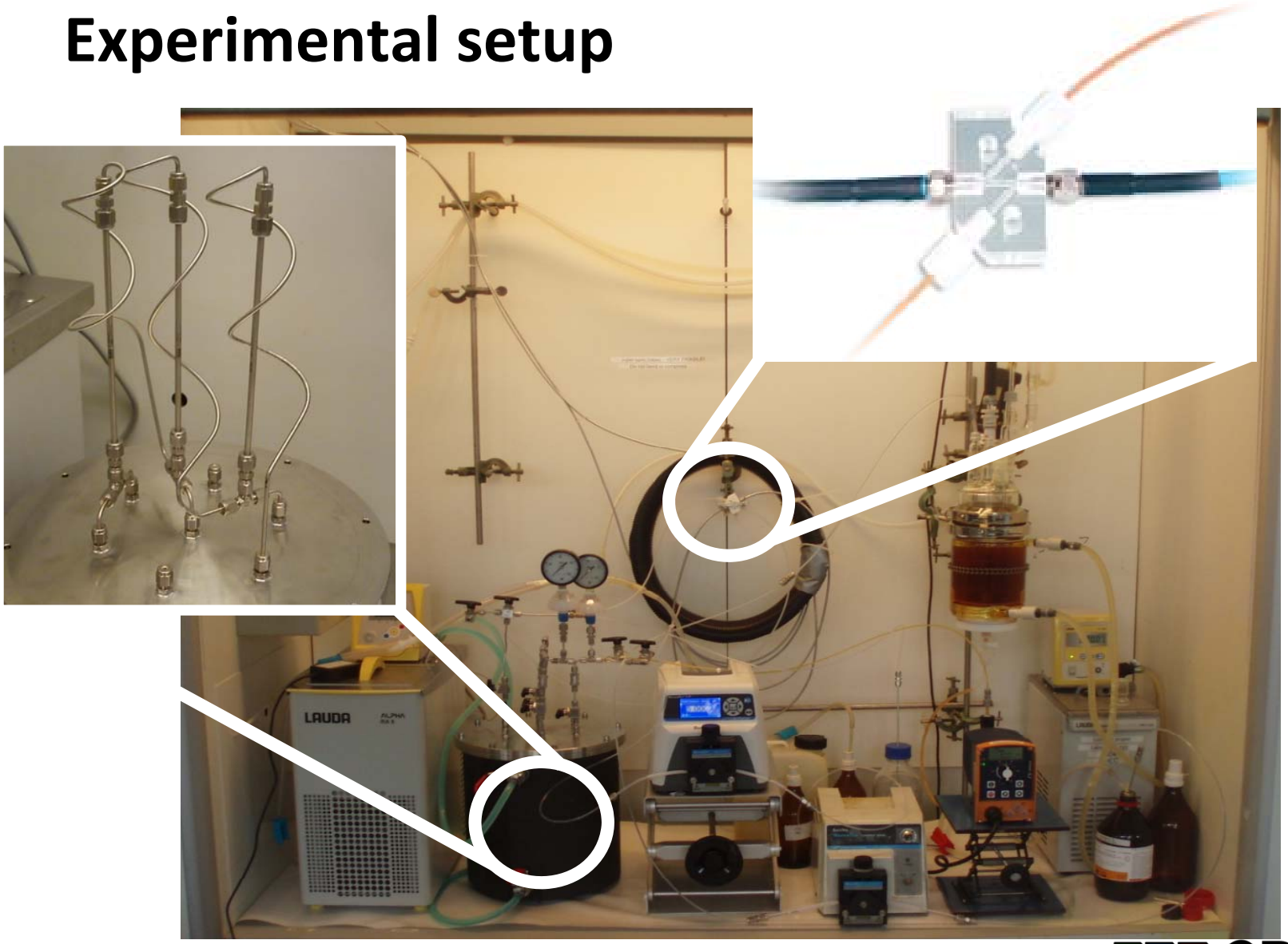


Continuous alkylation reactor

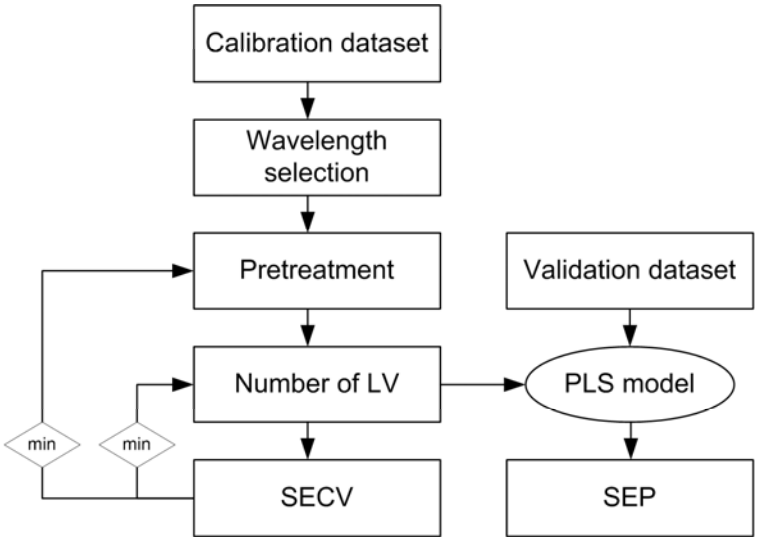


(Müller et al., 2011)

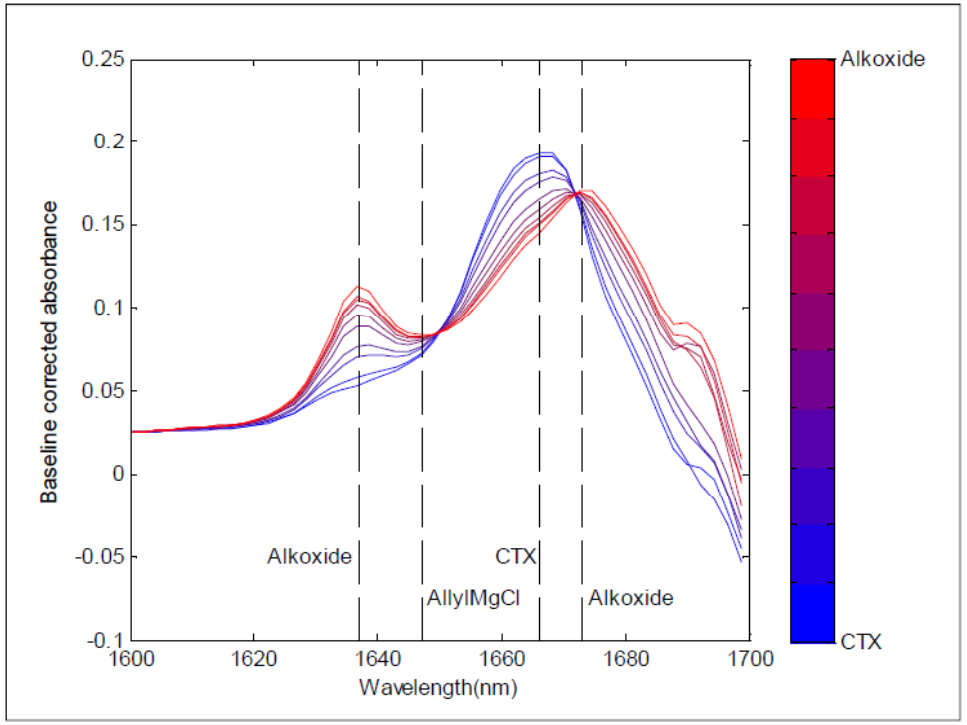
Experimental setup



Calibration procedure



Wavelength selection



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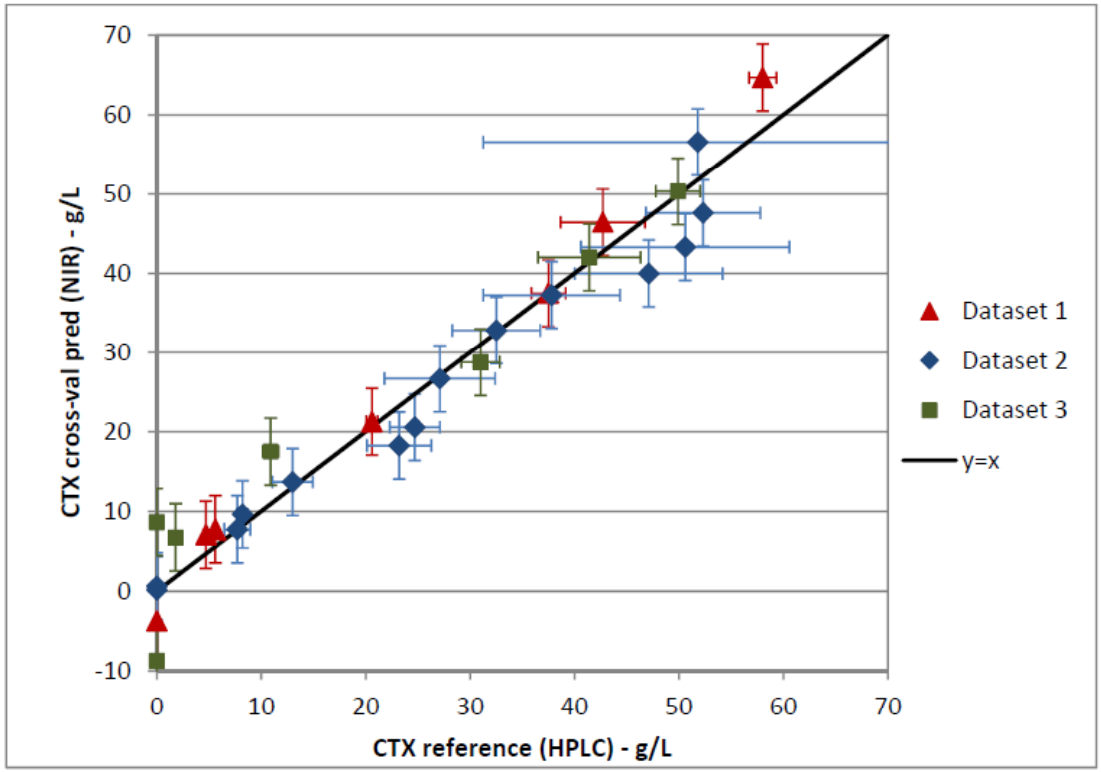
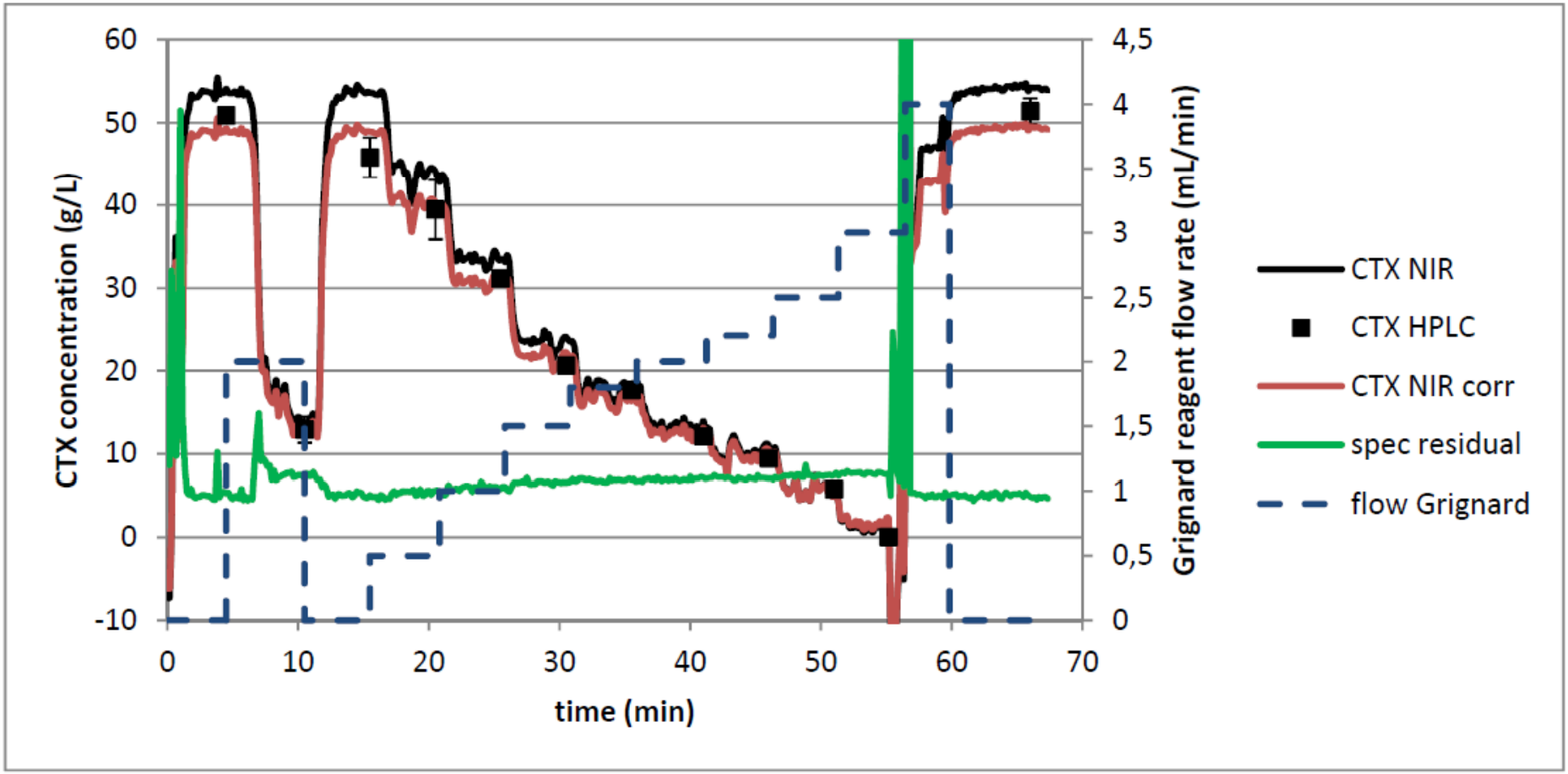
Calibration procedure

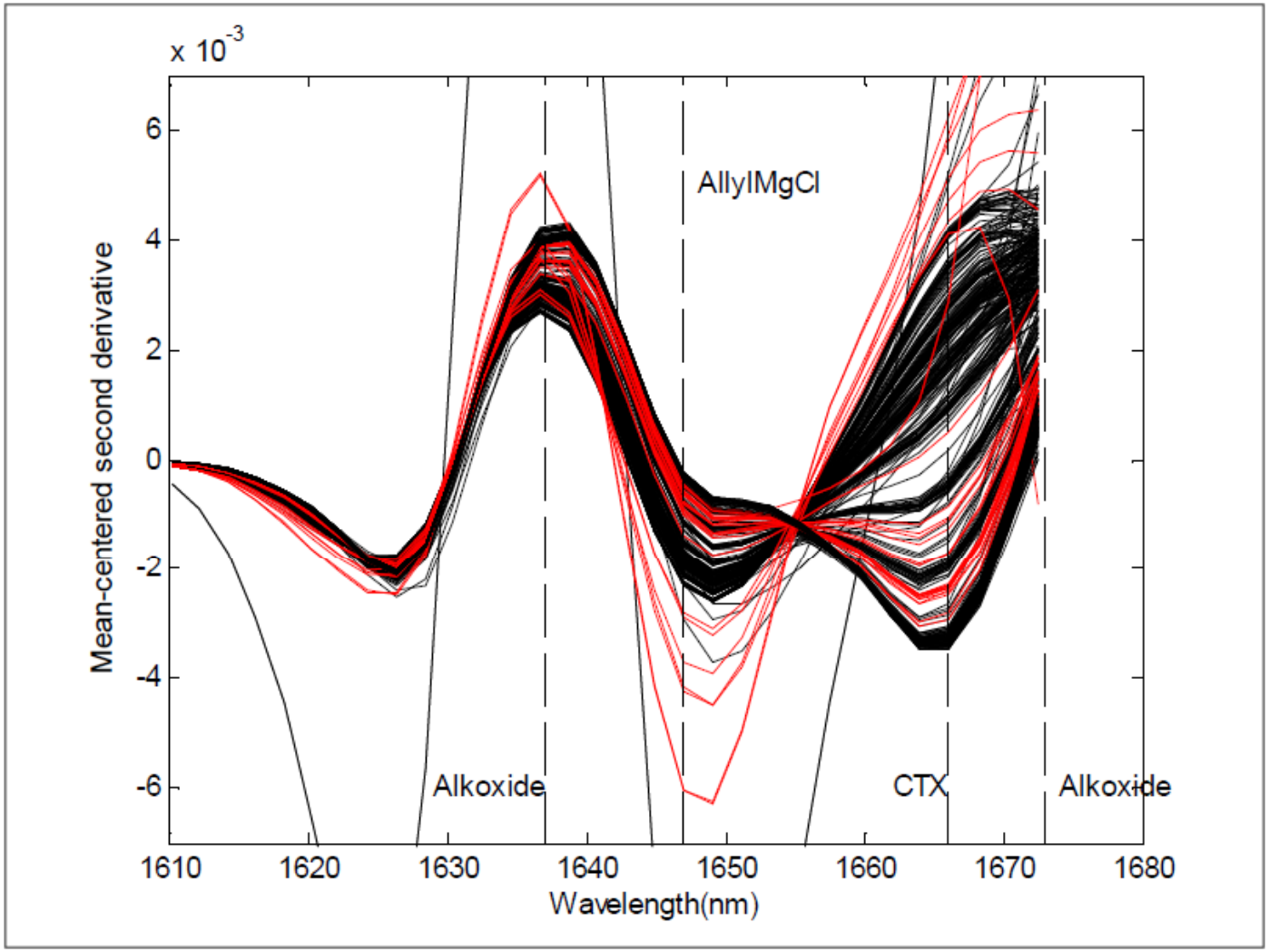
	Calibration dataset			Validation dataset
	Dataset 1	Dataset 2	Dataset 3	
Initial alkoxide concentration	135 g/L	225 g/L	290 g/L	180 g/L



Validation


CTX concentration (g/L)
Grignard reagent flow rate (mL/min)
time (min)
60
50
40
30
20
10
0
-10
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
0
10
20
30
40
50
60
70
CTX NIR
CTX HPLC
CTX NIR corr
spec residual
flow Grignard

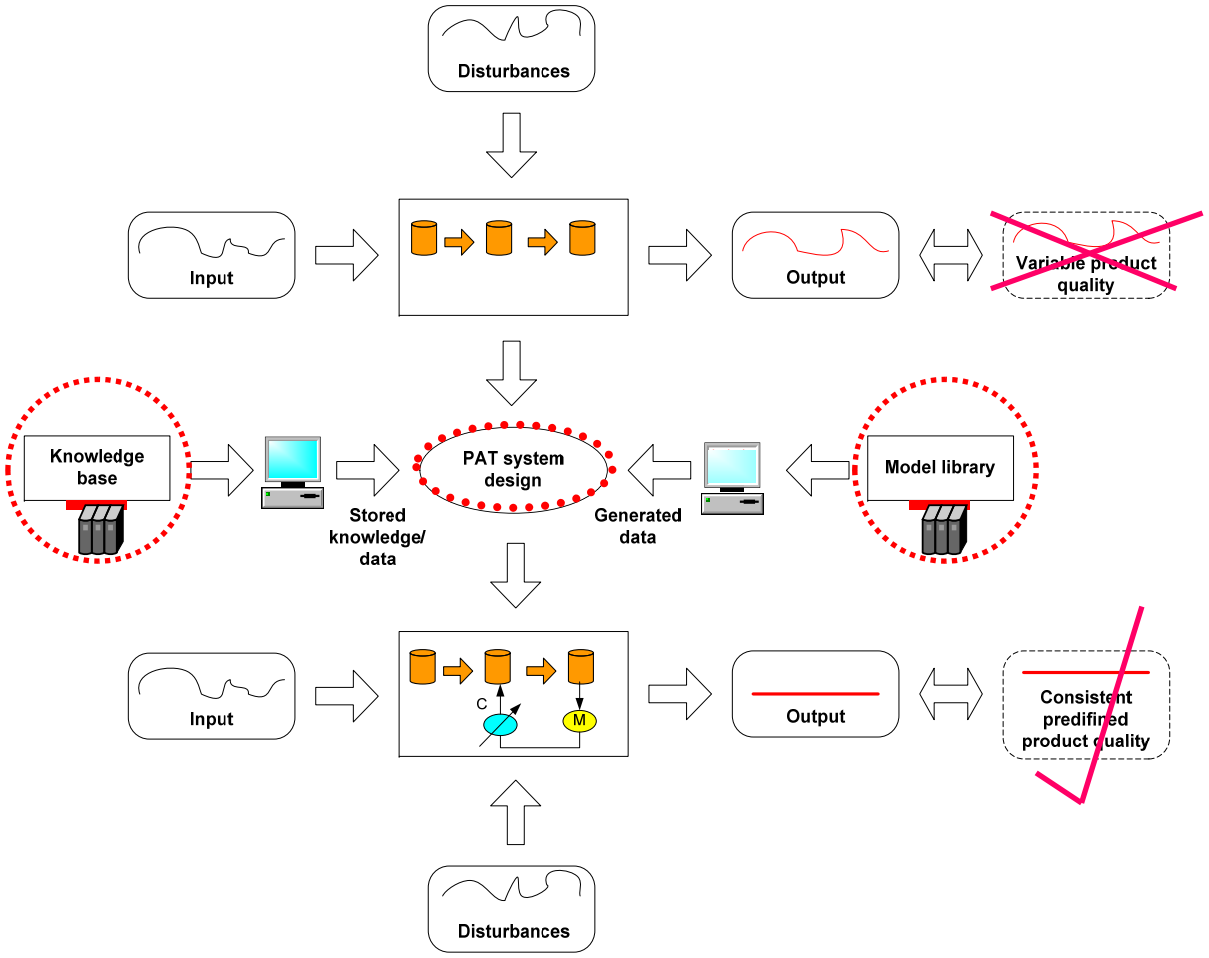
Detecting conditions of impurity formation

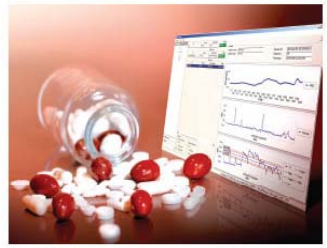


Conclusions – monitoring and control of continuous alkylation

- A filter reactor coupled with a side-entry reactor were used for the continuous alkylation of CTX with low solvent use and low impurity formation
- Real-time in-situ NIR spectroscopy measurements were used to determine CTX
- Pretreated spectra may be used to identify conditions of impurity formation
- High-frequency real-time data was used to investigate the reactor dynamics
- A feed-forward feed-back controller was validated by simulation based on this information

Case study 2: PAT system design





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PAT system design

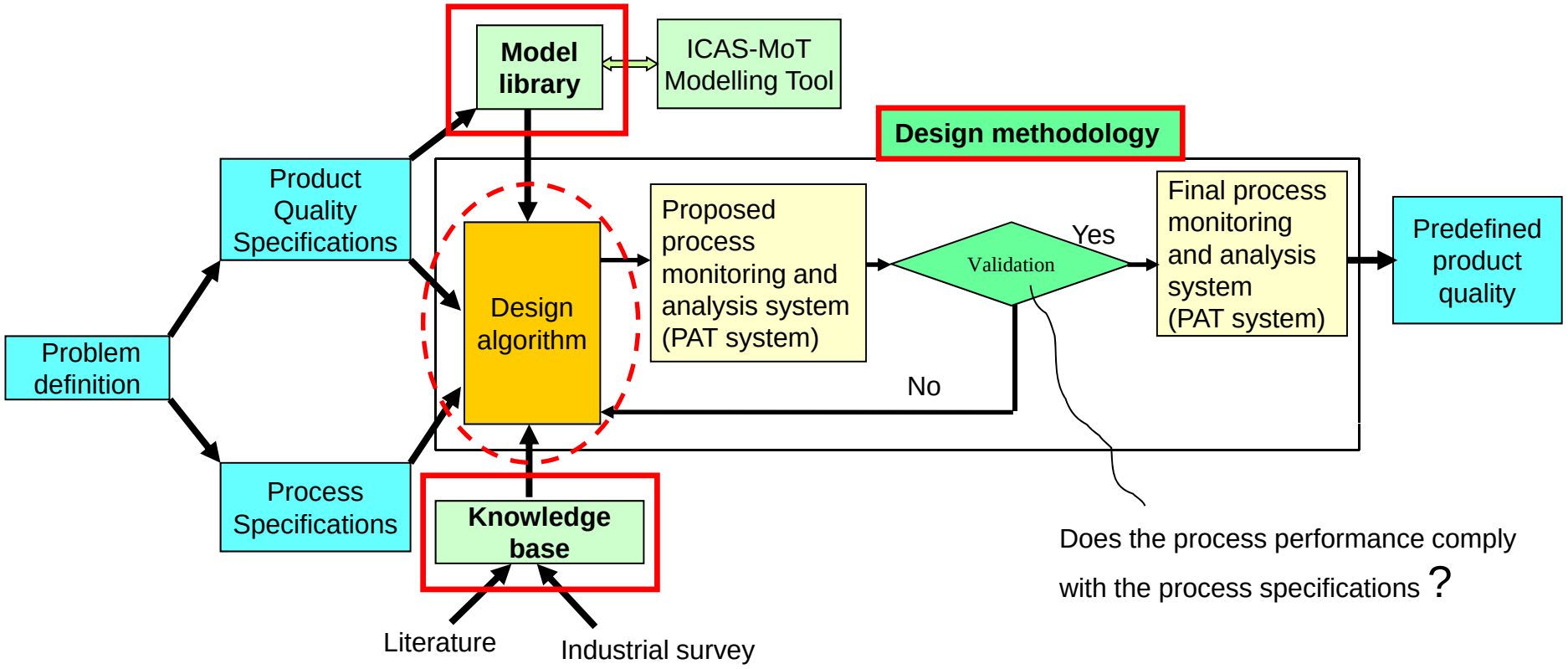
Design of a process monitoring and analysis system for a PAT process involves:

- Selection of critical process variables
- Selection and location of suitable measurement methods
- Selection of suitable actuators
- Implementation of a control system

- Collected data is supplemented with generated data from models to quickly design and/or analyze (configure) a PAT system – what to measure, what to analyze, which equipment to use, ….?

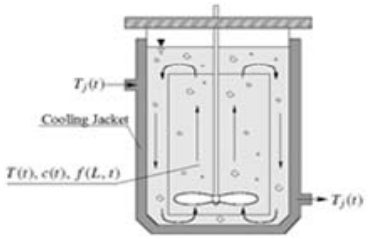
- Inherent assumption:
  - Implementing models – mechanistic models – is an excellent way to archive and later on exploit process knowledge in a structured way!

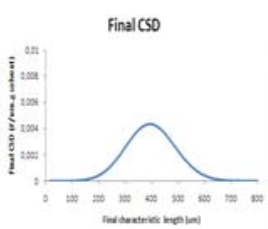
Systematic design framework, overview



Singh *et al*. (2009). Computers and Chemical Engineering, 33:22-42

A generic and systematic model-based framework for design of PAT systems for crystallization processes





"Crystallization Process"

"Target Product"

1. Problem Definition

2. Crystallization Model Development

3. Design of Set Point Profiles

Problem-System Specific Model

4. Design of Process Monitoring and Control (PAT) System

Data Handling and Model Identification

5. Uncertainty and Sensitivity Analysis of Process Monitoring and Control (PAT) System

6. Implementation of Process Monitoring and Control (PAT) System

Samad et al. (2012), Computers & Chemical Engineering (Submitted)

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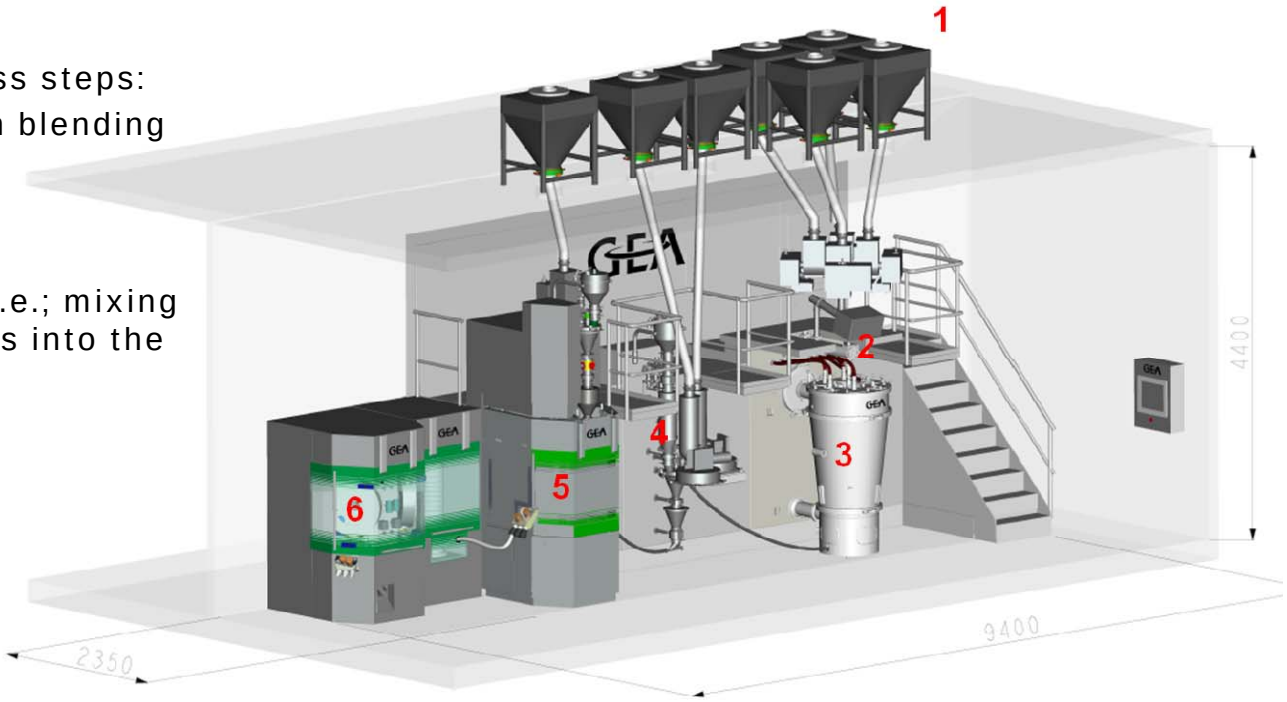
Case study 3: Formulation

- Formulation – continuous processing
  - Collaboration with University Ghent
    - Development of CFD-PBM models for a Consigma™ drying process
    - Development of CFD-PBM models for a continuous twin-screw granulation process

GEA Consigma, 6 successive process steps:

1. Feeding and pre-granulation blending of API and excipients;
2. Granulation;
3. Drying;
4. Post-granulation blending (i.e.; mixing desintegrants and lubricants into the dried granules);
5. Compression
6. Coating



Outline

- Introduction
- Process Analytical Technology - pharmaceutical production
- PSE methods and tools in a PAT context
- Case study examples
- **Conclusions and perspectives**

Conclusions and perspectives

- PSE methods and tools are essential for successful implementation of Process Analytical Technology (PAT) based processes

- PSE methods and tools play a key role in the development of continuous manufacturing processes as well as development of greener pharmaceutical production processes, two major trends in pharmaceutical manufacturing

- Achieving the full benefit from PSE methods and tools is only possible by applying them during the entire life cycle of a pharmaceutical product and its production process

- There are difficulties in transferring PSE methods from academia to industry

Conclusions and perspectives

- The regulatory bodies should be involved early on when adopting a new PSE tool in pharmaceutical production processes, in order to minimize potential problems with process validation

- The PSE methods and tools developed thus far are often focused on reaction-separation sequences. Similar developments are needed for downstream processing and formulation (e.g. granulation, drying, tablet press).

- Pharmaceutical companies require generic and systematic approaches to problem solving.

Acknowledgements

- Albert E. Cervera-Padrell
- Aleksandar Mitic
- Nanna Petersen Rønnest
- Gürkan Sin
- Peter Ödman
- Noor Asma Fazli Abdul Samad
- Kresten T. Meisler
- Asmus Mortensen
- Daniel Lewandowski
- Sophie Morthensen

- Financial support
  - H. Lundbeck A/S
  - Technical University of Denmark
  - Novozymes A/S
  - Danisco A/S

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