APPLICATION OF CONTINUOUS FLOW

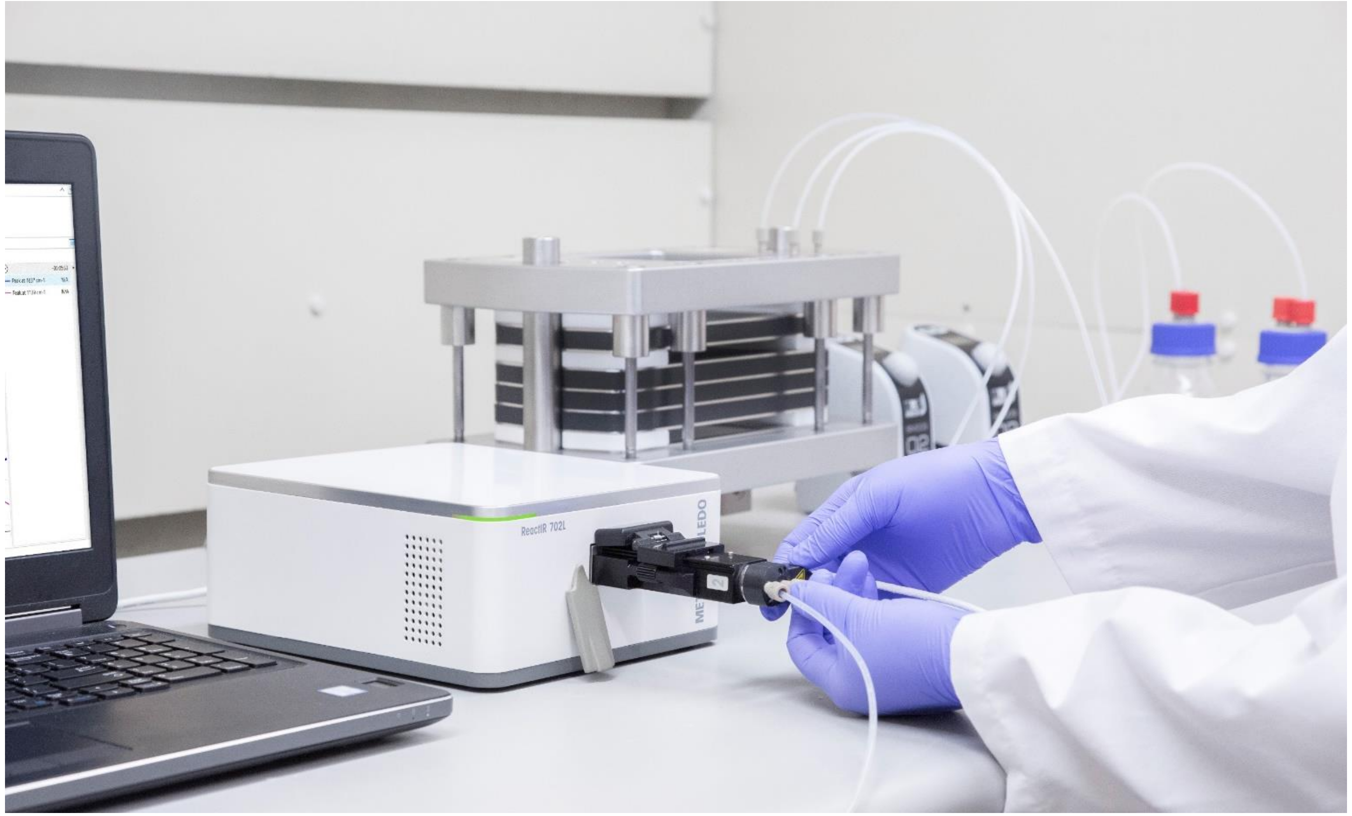
Controlling Hazardous Processes from R&D to Production

Dr Charlotte Wiles – June 2023

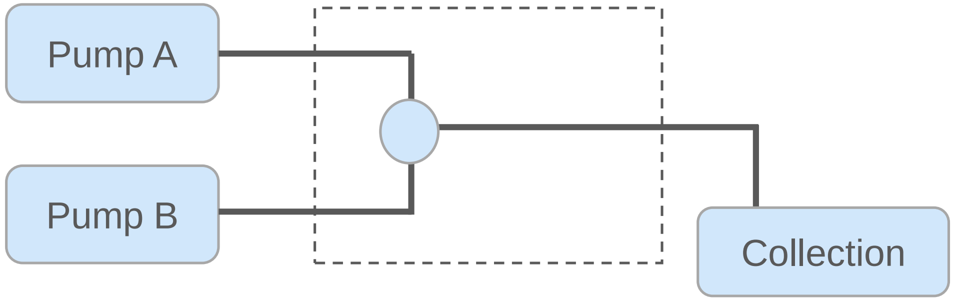
How are Flow Reactions Performed?

Solutions (typically) of reagents are pumped into a reactor, where they are;

- Mixed
- Heated or cooled
- Reacted for a specified period of time
- Collected for analysis or product isolation



Conceptually, a basic flow reactor comprises of;



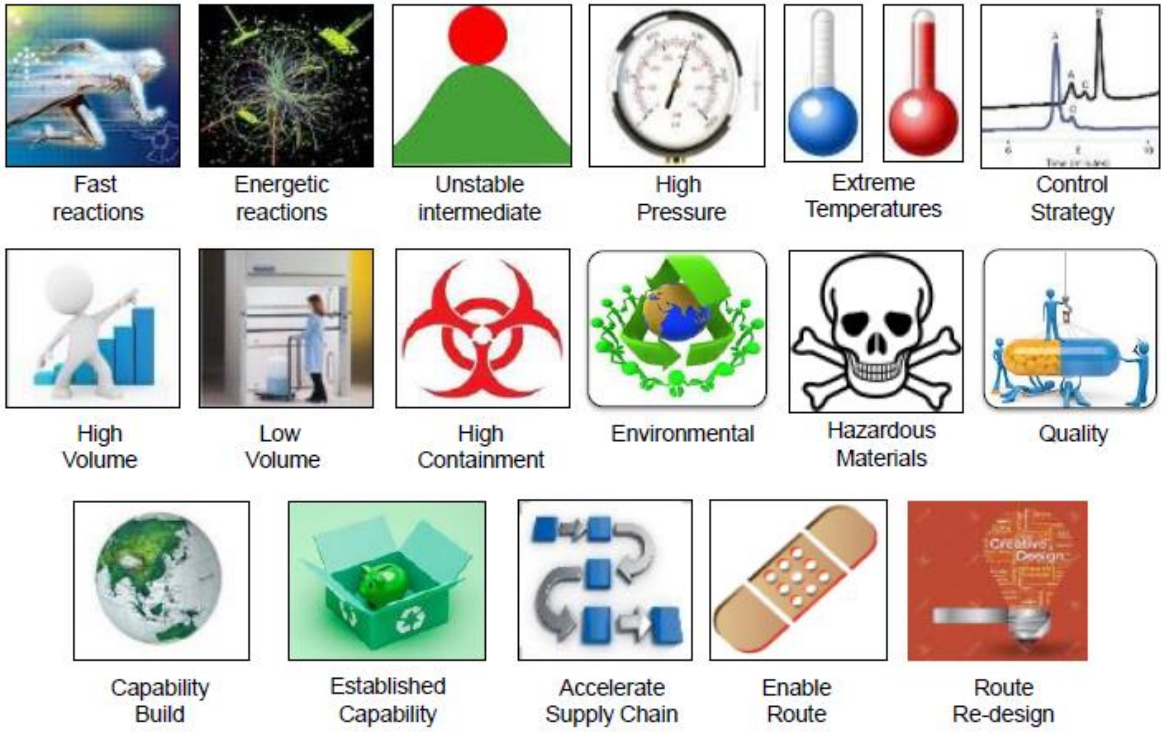
Key is to understand the requirements of your process & design the reaction set-up accordingly

- This contrasts with batch practices where you typically adapt the process to suit the available vessel(s)!

When to Consider Flow Chemistry?

A significant aspect of flow chemistry relates to performance versus scale. Reducing the reactor size can have a beneficial impact on;

- Heat transfer
- Mixing speed & mixing shear
- Repeatability
- Safety



Addressing priority areas of;

- Reduced energy costs & waste generation

  → *Process sustainability*
- Increased reaction efficiency & process safety

  → *Process intensification*

You must understand how these parameters influence your process before attempting scaling-up!

[1] McManus *et al.*, Eli Lilly, 2016.

Advanced Process Control (APC)

Compared to batch reactions, whereby changes evolve over hours, continuous processes can have reaction times in sec's to min's & operate under a state of control

- Analytical feedback therefore needs to be faster for continuous processes than batch
- Techniques that accurately reflect the process state need to be used
- After start-up, in flow you are typically monitoring for no process change

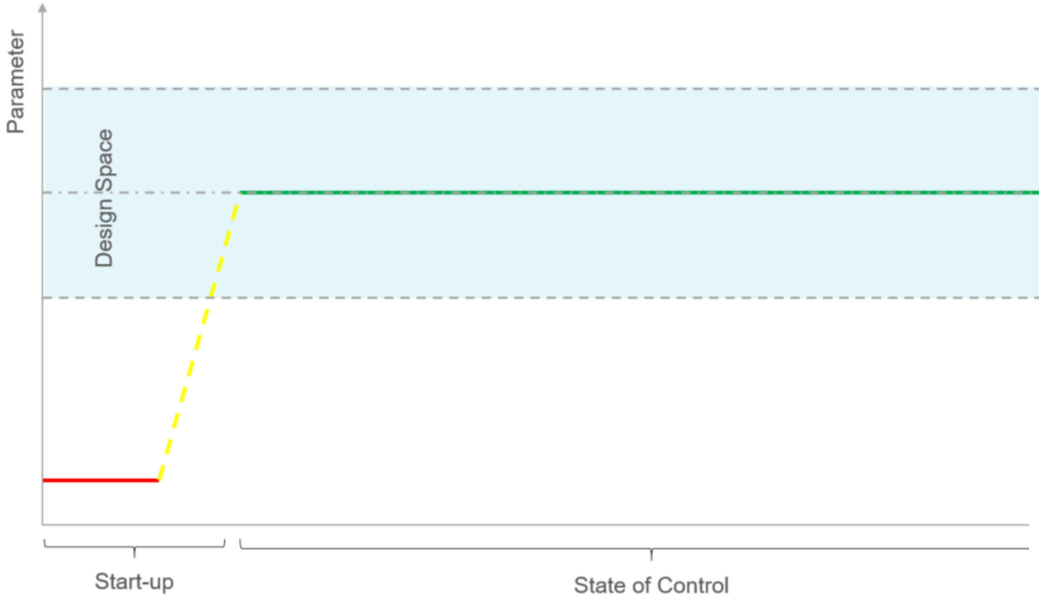
1. Design a manufacturing process to meet target(s)
    - Identify & control critical quality attributes
    - Understand impact of process parameter variability
    - Select hardware to ensure target conditions are met
2. Monitor the process parameters to ensure consistent quality
    - Dramatic reduction in operating costs
    - Reduced reliance on man-power for plant operation

Replication of the unit & controls = same output quality

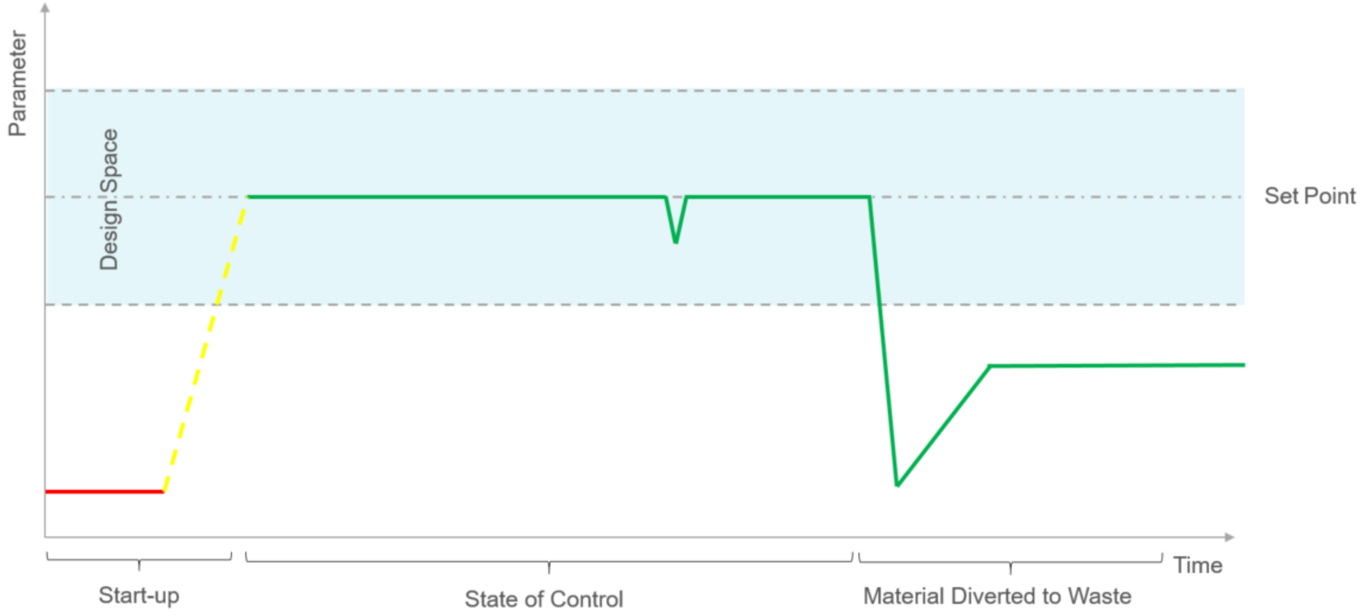
- Enabling decentralised manufacturing to be realised

PROCESS CONTROL \ PROCESS UNDERSTANDING	LOW	HIGH
LOW	High Potential for Failures	Problems are Detected (after they occur) *via* Testing/Inspection
HIGH	Reproducible Process within Narrow Operating Ranges	Robust & Reproducible Process

Process Control - Operating Under a State of Control



Many different PAT tools are used, ranging from T / P / flow / conductivity to FTIR, Raman, UV, MS & NMR

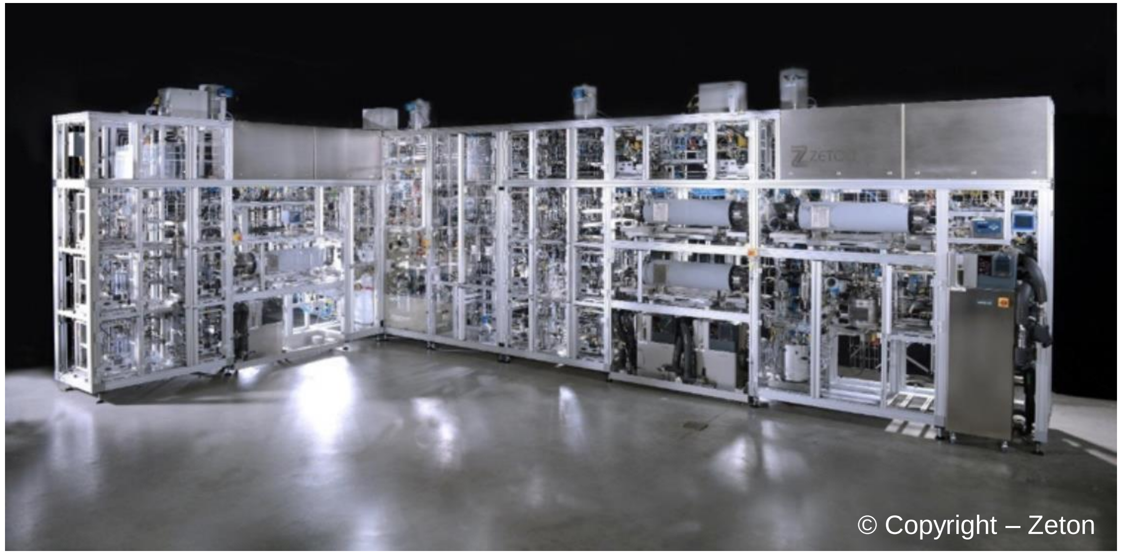


- If you only analyse the collected material you can miss these disturbances!

Small, Agile Production Units

Flexibility is often requested when looking at small-scale manufacturing units. Flexibility can be towards;

- Raw material & product type, production location & production capacity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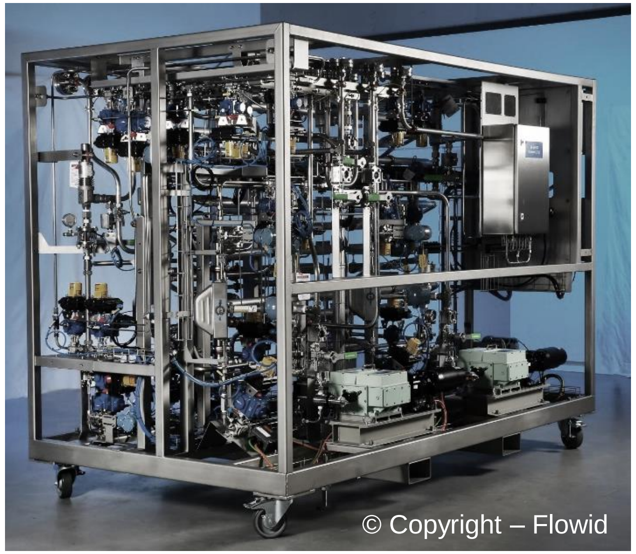
© Copyright – Flowid

By adopting a modular approach, small flow production units can accommodate these needs & be replicated at different sites

- Whilst there is no ‘one-size fits all’ flow process
  - Similar reaction types can use a common platform (dosing, reactor etc.)
- Build in redundancy to enable a faster response to surges in material demand
  - Rapid, local ramp-up of manufacturing output

REALISING PROCESS INTENSIFICATION

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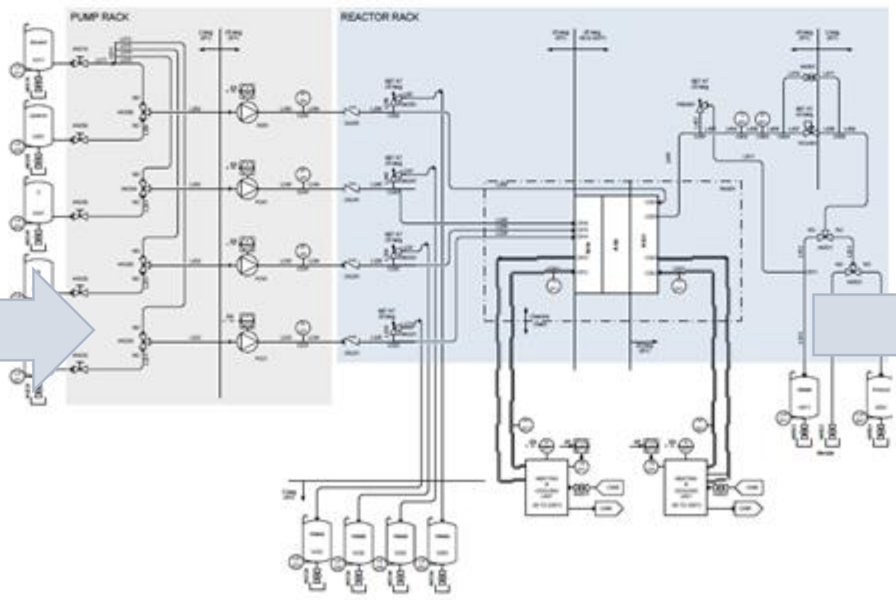
Scalable Flow Chemistry

From Lab to Manufacturing



1. Theoretical Evaluation

- Definition of process targets
- Identification of the ‘problem’
- Theoretical opportunities for process improvement

2. Basic Feasibility Study

- Lab-scale trial(s)
- Deliver proof of concept
- Outline milestones for process optimisation

3. Parameter Optimisation

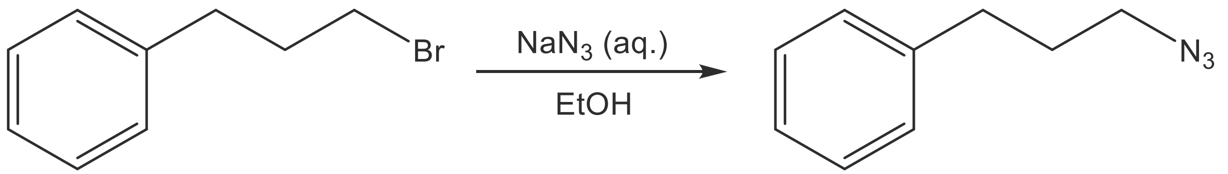
- Evaluate suitable hardware
- Demonstrate hardware feasibility
- Define process parameters for engineering design

4. Realisation

- Design pilot / production plant
- Build & test
- Commission

CHEMTRIX Scalable Flow Chemistry

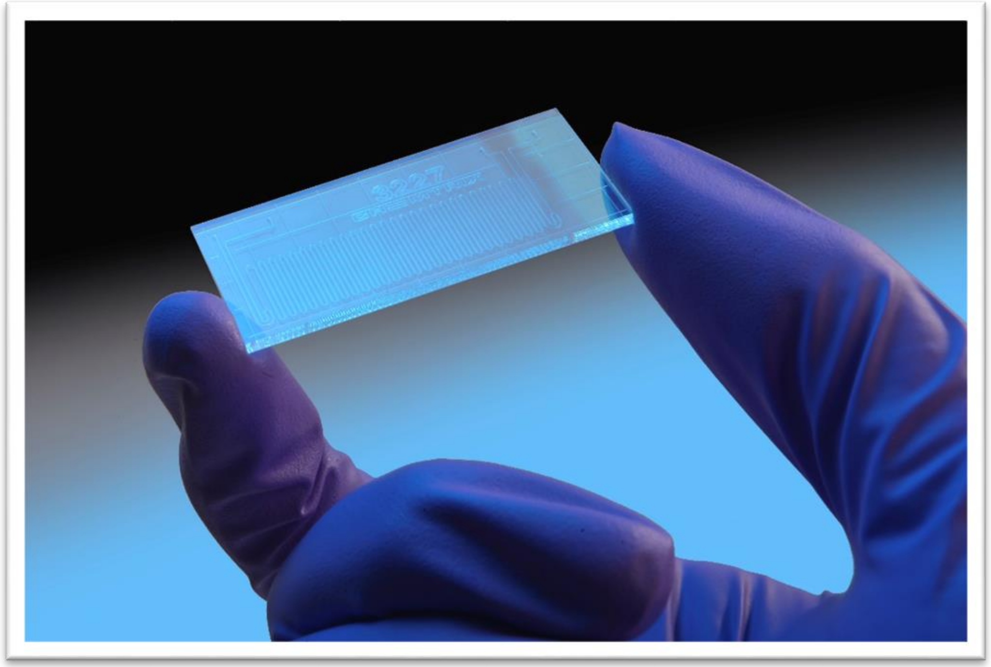
A Safe & Efficient Method for the Preparation of Organic Azides



- No headspace – no HN_3 build-up
- Safe access to ‘Novel Operating Windows’
- Short reaction times, no decomposition

Demonstrating the rapid development of continuous flow protocols, using mg’s of materials

Labtrix® Start – glass flow reactor(s)



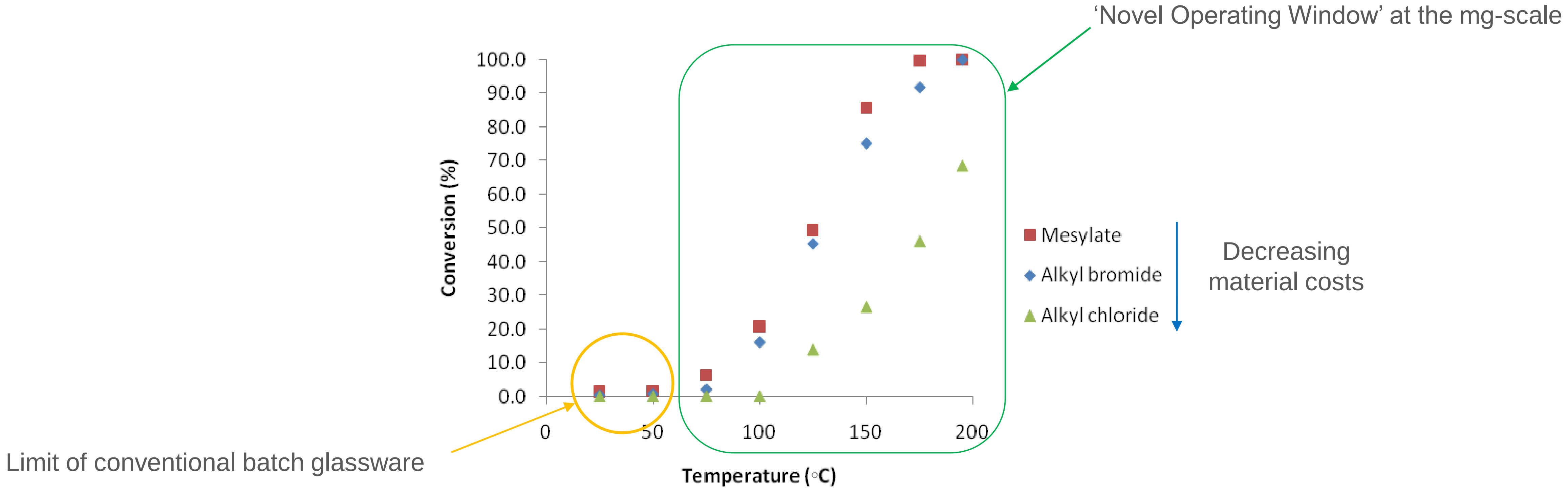
- -20 to +195 ºC at 20 bar

CHEMTRIX Scalable Flow Chemistry

A Safe & Efficient Method for the Preparation of Organic Azides

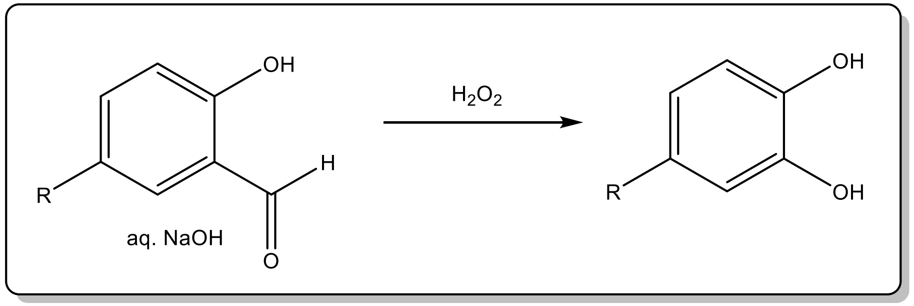
Advantages:

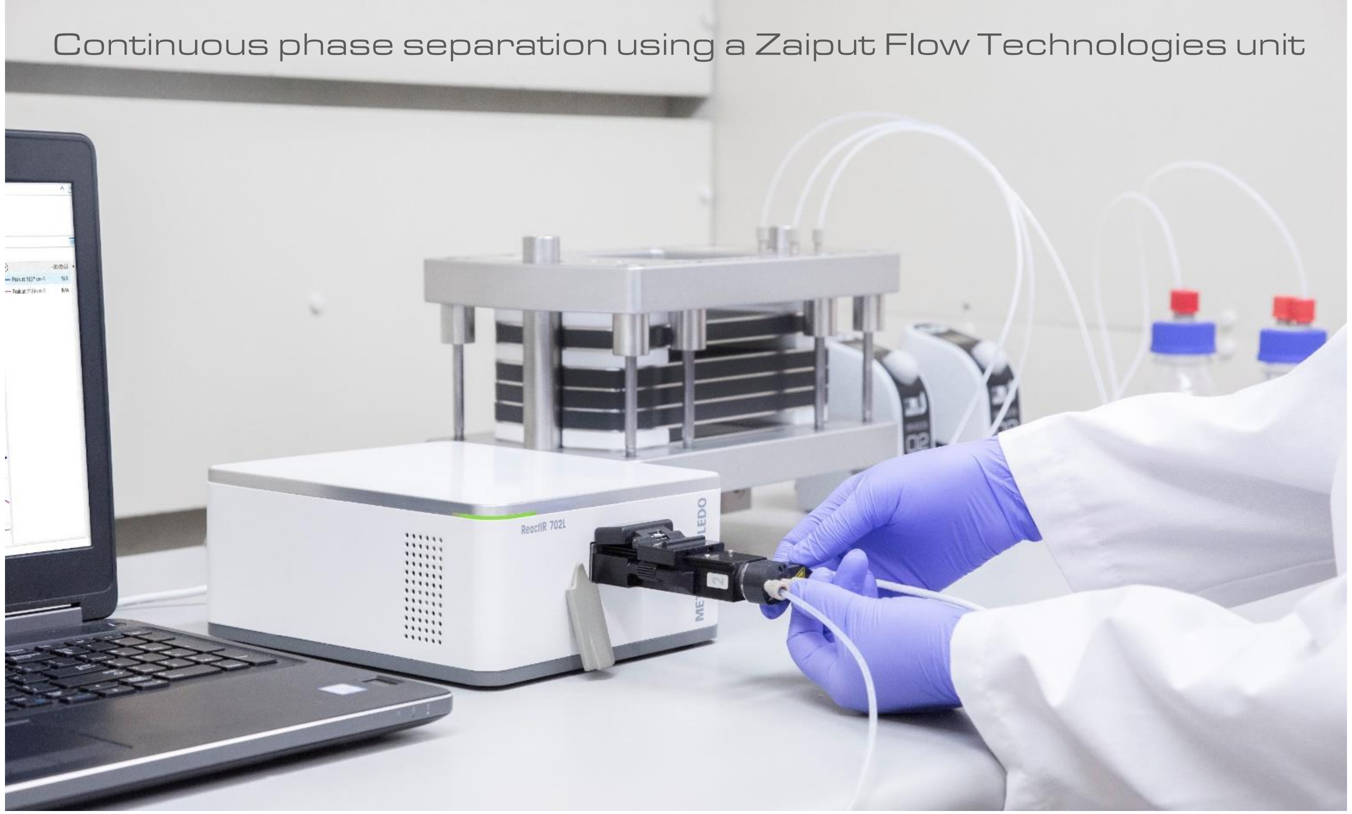
- Low consumption of material (mg's)
- Fast data generation
- Insight into key influences on product / by-product formations
- Early indication of viability of manufacture



CHEMTRIX Scalable Flow Chemistry

Customer Case – Biphasic, Dakin Oxidation





Drivers for flow method development;

- Safe use of H_2O_2 at scale
- Shorter synthetic route
- Reduced reagent use
- Increased production rate

Protrix® Flow Reactor:

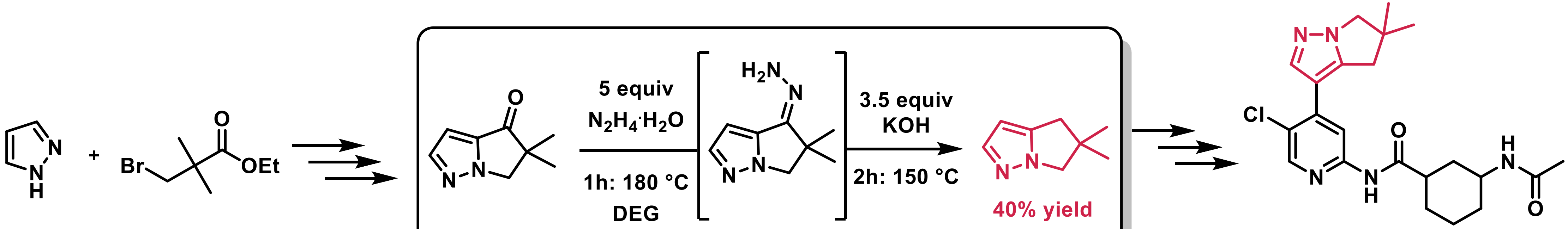
- Metal & glass-free reactor
- Integrated thermal control

→ 30 s reaction cf. 6 h in batch affording quant. catechol (4.8 kg 8 h^{-1})

Partners: METTLER TOLEDO, ZAIPUT

Customer Case - Wolff-Kishner Reduction

CDK9 Inhibitor, potential treatment of haematological malignancies (in Phase 1 clinical trials)



AZD4573

<u>Reasons for Flow:</u>

- Safety risk as scale – hot N_2H_4 in excess
- Challenging corrosivity
- Increased throughput / decreased reaction time

<u>Protrix® for Development:</u>

- Metal & glass-free reactor with integrated thermal control
- Reduced N_2H_4 excess due to no losses (3.5 eq. reduction)
- Time reduced from 2 h to 20 min
- Yield increased by 40 % (80 % with >99 % purity)

CCFLOW Partners: GOFLOW AstraZeneca

CHEMTRIX Scalable Flow Chemistry

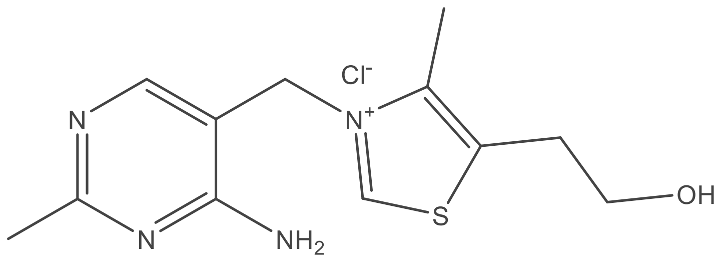
Customer Case – Securing a Key Intermediate used in Vitamin B_1 Synthesis

3-Chloro-4-oxopentyl acetate is a key intermediate used in the synthetic preparation of Vitamin B_1 (Thiamine)

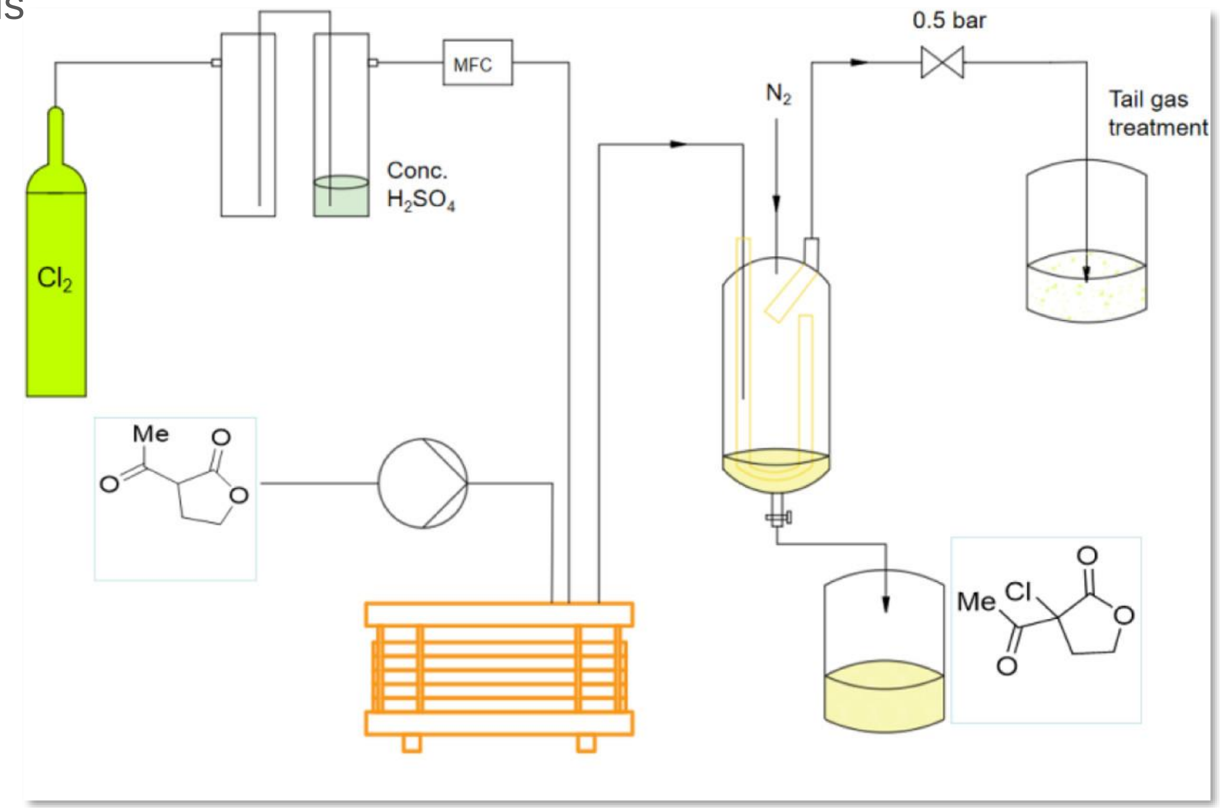
→ Vitamin B_1 is an antineuritic vitamin used in humans & animals

Drivers for flow process development;

- Improved yield of the chlorination step
- Reduced isolation costs
- Reduced waste generation



Vitamin B_1 (Thiamine)



Using Protrix® Prof. Chen demonstrated the synthesis of 3-acetyl-3-chlorodihydrofuran-2(*3H*)-one;

- Reporting a 93 % yield (98 % purity), with a reaction time of 30 s (at 25 ºC)
- Subsequent decarboxylative acylation afforded the target in 90 % yield (96 % purity)

Partner: Fudan University 1905

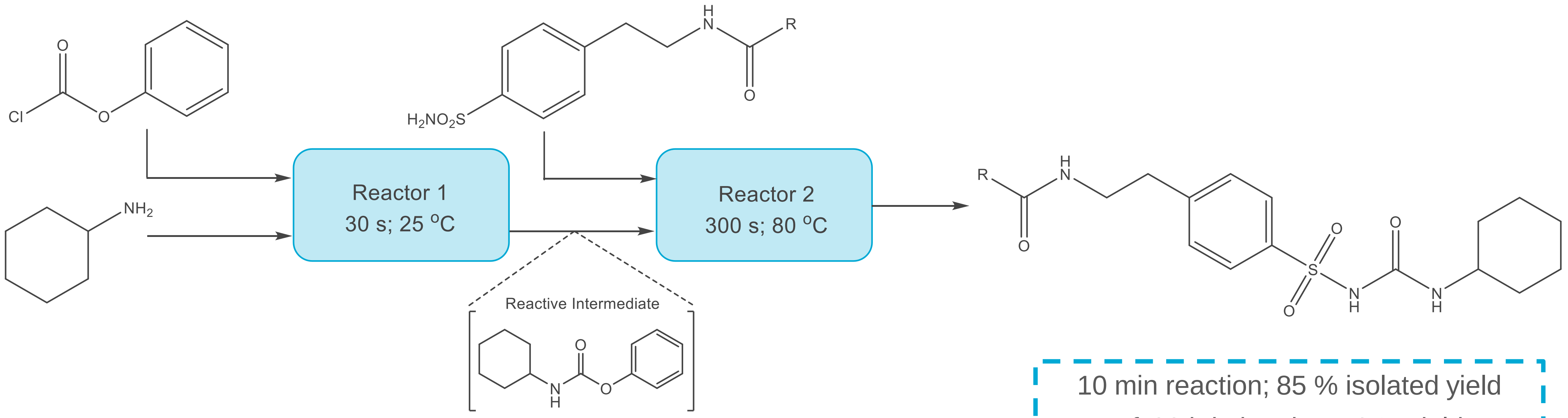
Chen *et al.*, OPRD, 2021, **25**, 2020-2028.

CHEMTRIX Scalable Flow Chemistry

Customer Case – Local Manufacture of Diabetes API's

Diabetes mellitus (DM) is a global health concern, with Type 2 DM most prevalent & managed with oral anti-diabetic drugs

→ Incidences of DM are growing in low- & middle-income countries resulting in increasing costs for its management



10 min reaction; 85 % isolated yield
cf. 32 h in batch & 46 % yield

Drivers for flow method development;

- Control of API costs by manufacturing locally (currently API formulation only)
- Shorter, more efficient synthetic routes
- Increased production rate within a small footprint

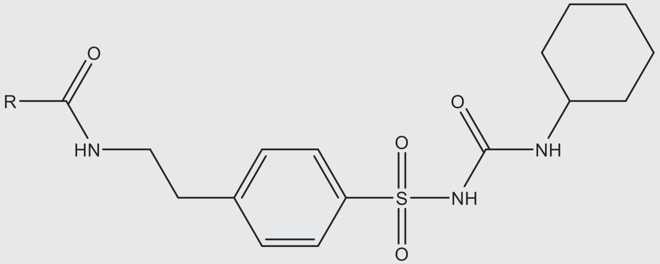
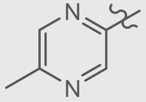
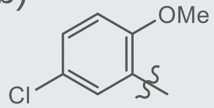
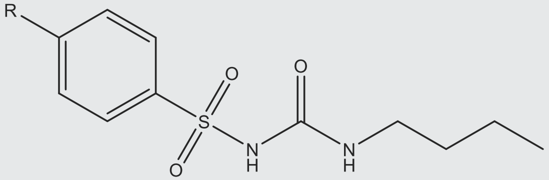
Partner: NELSON MANDELA UNIVERSITY

CHEMTRIX Scalable Flow Chemistry

Customer Case – Local Manufacture of Diabetes API's

Using KiloFlow® glass flow reactors, Researchers at NMU (ZA) demonstrated the development & scale-up of four DM API's

→ Realising productivities ranging from 3.5 to 31.5 kg/week from a laboratory fume cupboard

Anti-diabetic Drug (API)	R Group	Day^{-1}
 R = (a) Glipizide; (b) Glibenclamide	(a) 	0.6 kg
	(b) 	0.5 kg
 R = (c) Tolubutamide; (d) Chlorpropamide	(c) CH_3	4.4 kg
	(d) Cl	4.5 kg

- Significant steps towards local API manufacture in South Africa!

Partner: NELSON MANDELA UNIVERSITY

Watts *et al.*, 'Feasibility of Africa-based Manufacturing of API's', CFRT Virtual 2021

CHEMTRIX Scalable Flow Chemistry

Customer Case – Manufacturing using a Lachrymator

Buchem BV identified an opportunity to improve their productivity for an existing product - combining batch & flow

Heart of the system was a 170 ml Plantrix® flow reactor containing SiC reactors, selected for chemical compatibility towards the challenging process & continuous mixing required, a 20 L Buchi rotavapor & a 50 L glass reactor followed

Cooperation: Buchem, Flowid & Chemtrix

Buchem – process & chemistry

Flowid – system design & engineering

Chemtrix – proof of concept & reactor design

Advantages:

- Higher productivity & robust process
- Smaller equipment
- Reduced material inventory
- Improved process control

→ Annual production requirements were met from a fume hood

Partners: BUCHEM BV FLOWID

FLOW PROCESS COMMERCIALISATION

CHEMTRIX Scalable Flow Chemistry

Customer Case – Multi-step API & Intermediate Production

Fast process scale-up from R&D to production drove the innovation in this project!

Realised by combining Plantrix® flow reactors & an Agitated Tube Reactor (ATR) as a reactor/extractor. Smooth operation was ensured using super metering pumps.

Cooperation: Cipla, Pi Process Intensification, AM Technology, Fuji Techno & Chemtrix

Result:

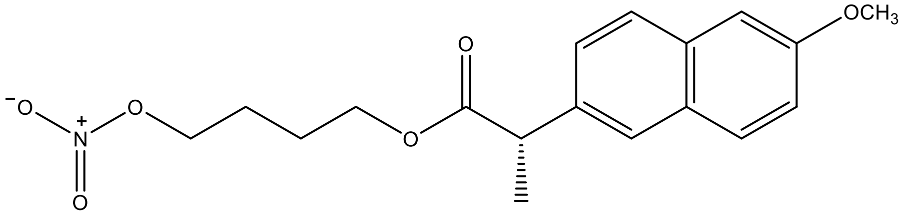
- Multi-product, multi-step flow chemistry production plant
- Compact, retrofitted into an existing asset base

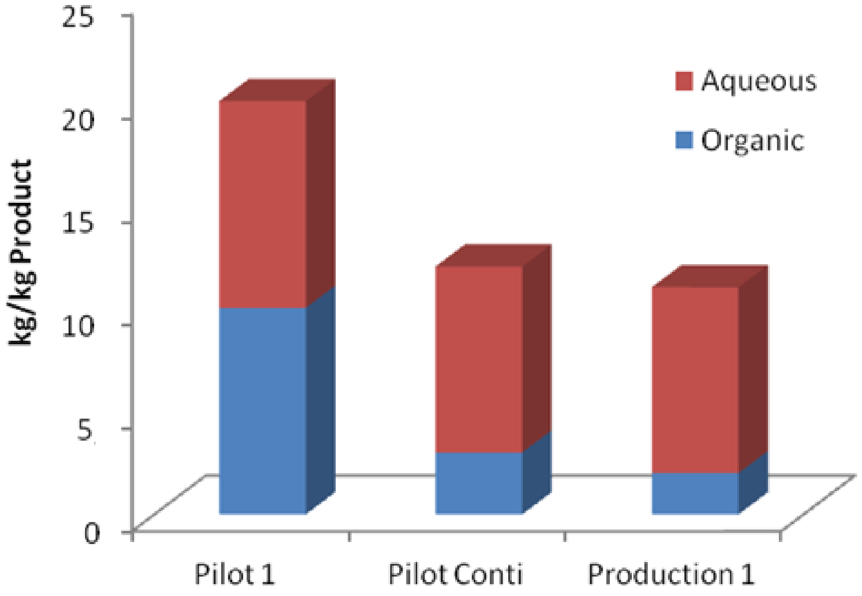
Advantages:

- Process flexibility & safety
- Speed of scale-up & enhanced process control via automation
- Reduced inventory of hazardous reagents
- Reduced 'batch to batch' variation

Partners: Cipla, AMTechnology, Fuji Techno (Fuji Techno Industries Corporation), processintensification

Customer Case – Selective Nitration





Partner: patheon by Thermo Fisher Scientific

- Patheon uses flow reactors made of 3M^{TM} SiC in a pharmaceutical production plant

FLOW PROCESS COMMERCIALISATION

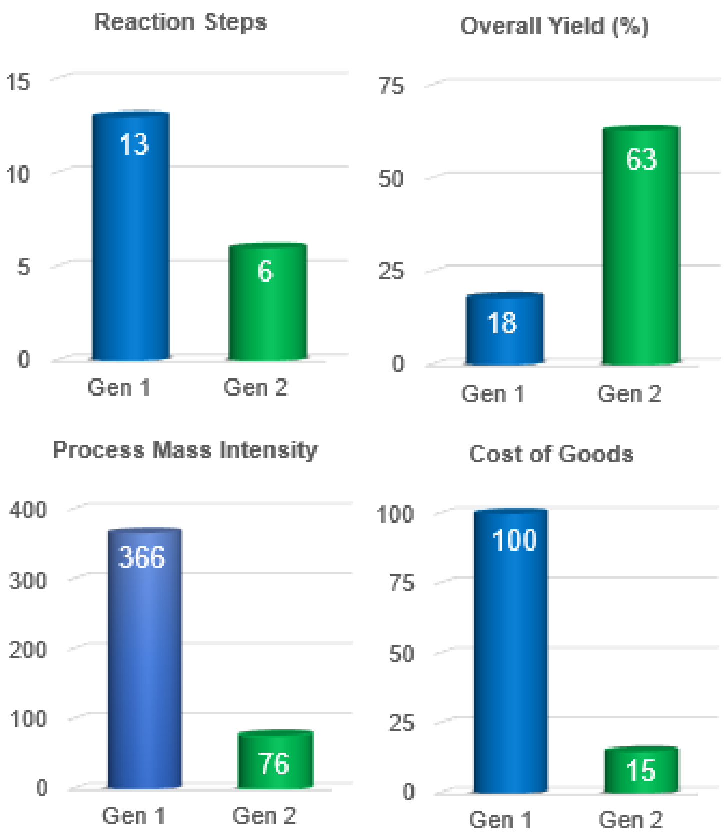
CHEMTRIX Scalable Flow Chemistry

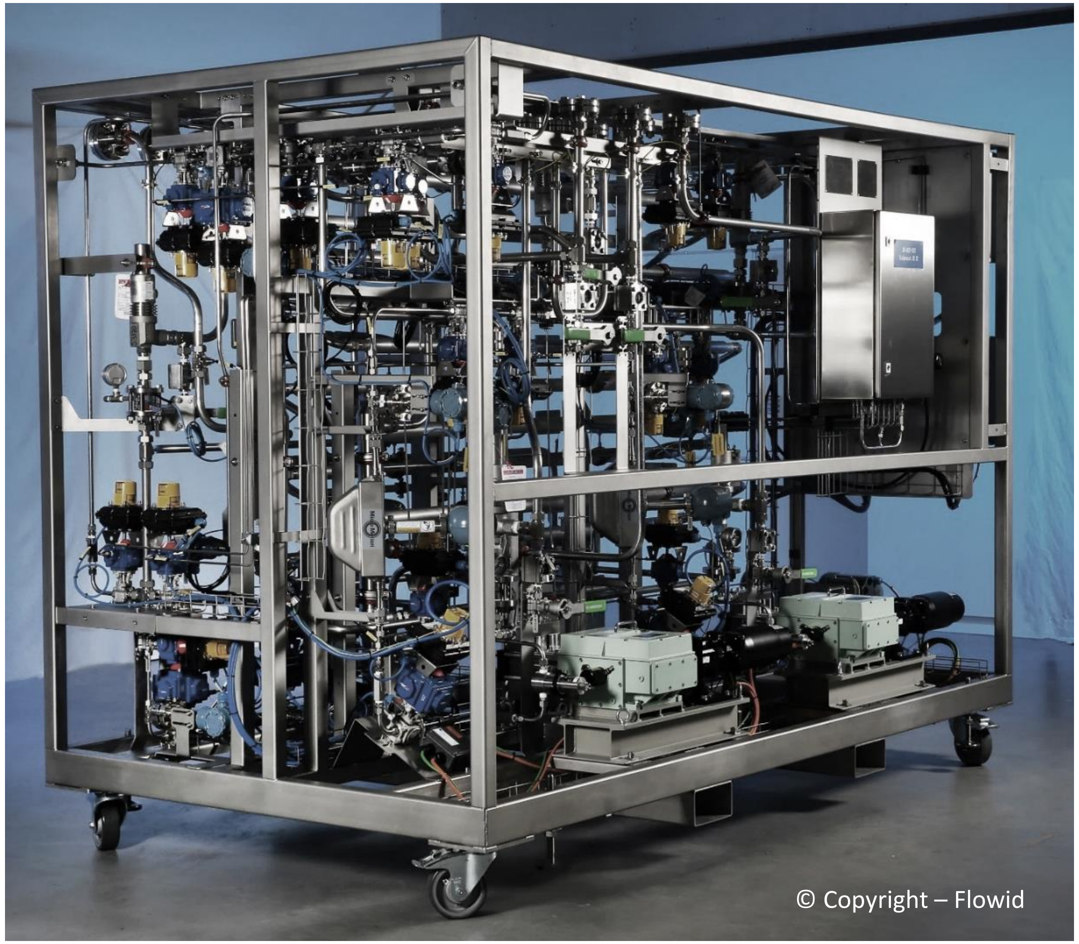
Customer Case – Merck Sharpe Dohme (Gefapixant)

FLOWID

Standalone synthetic unit with monitoring of CPP utilising pressure, temperature & spectroscopy

- Operating at litres/min





- Consistent product quality from continuous systems reduces the reliance on batch release & therefore work in progress

FLOW PROCESS COMMERCIALISATION

CHEMTRIX Scalable Flow Chemistry

Customer Case – Ajinomoto Bio-Pharma Services (CDMO)

Targeting a reduction in unit operations & increased productivity, Ajinomoto Bio-Pharma Services (BE) switched to flow!

<u>Customer Process:</u>

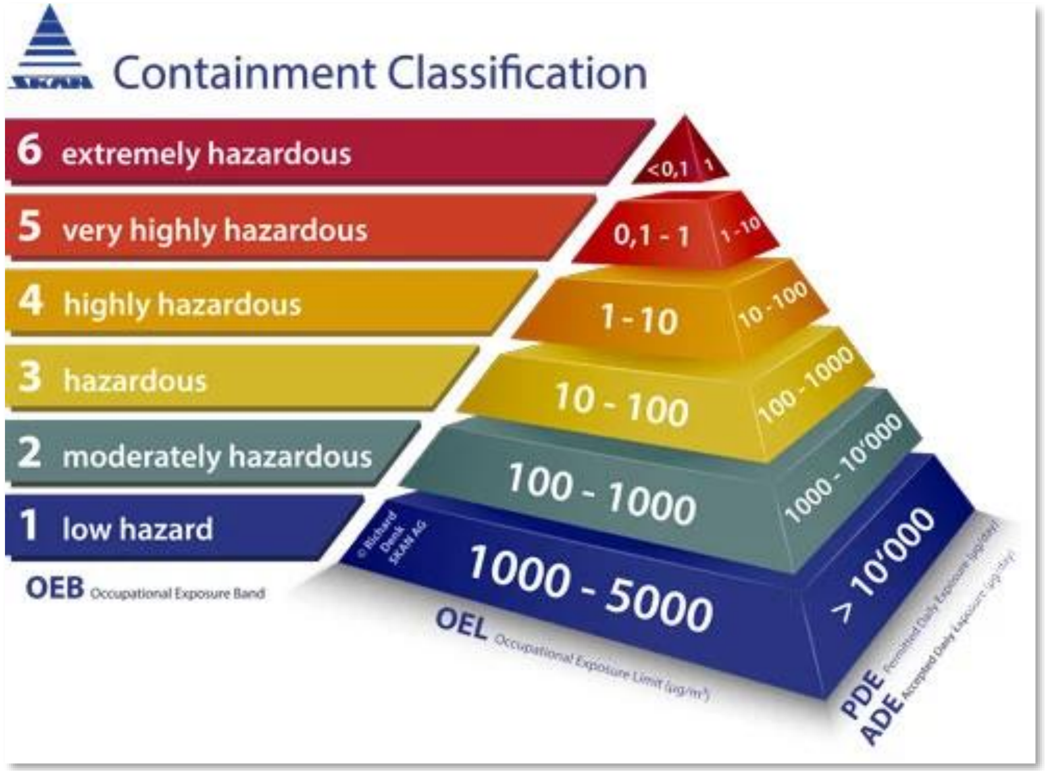
- Three exothermic steps, requiring slow reagent addition (8 h)
- Potent product (OEB-5; 0.1-1 $\mu g/m^3$)

Developing a multi-stage continuous process, at the end of 2017, gave:

- Increased process safety due to thermal control
- Minimised operator exposure
- Higher productivity *cf.* batch (x2)

<u>Technical Advantages:</u>

- Small, mobile equipment tested in the lab & moved to production
- Reduced material inventory
- Enhanced process robustness *via* automation



→ Converting 70 % of the process to continuous improved batch capacity utilisation

Partner: AJINOMOTO BIO•PHARMA SERVICES

CHEMTRIX Scalable Flow Chemistry

Customer Case – Ajinomoto Bio-Pharma Services (CDMO)

Targeting a reduction in unit operations & increased productivity, Ajinomoto Bio-Pharma Services (BE) switched to flow!

Scaled-up process commissioned 2020:

- Three chemical steps (2x continuous & 1x batch)
- >500 MT of active compound produced in the first year!

In addition to the advantages realised at the pilot-scale, the Industrial multi-stage continuous process enabled:

- Target price to be reached
- Increased annual output *cf.* dedicated synthesis unit (250 MT/y)
- Release of two 6000 L vessels for additional batch processes

Outlook:

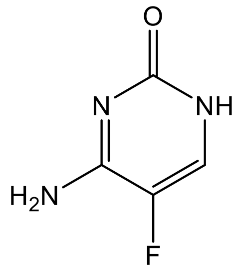
- Downstream batch improvements increase output to >500 MT/y
- Development work shows 3rd step is also feasible in flow

Partner: AJINOMOTO BIO•PHARMA SERVICES

Next Steps: Additional installation on a 2nd ABPS site in 2023 with all three steps continuous!

Customer Case – Manufacturing using F_2

Fluorine substitution in agrochemicals & pharmaceuticals is increasing in popularity however challenges with the safe & selective use of F_2 means using expensive alternative reagents. Sandford & Pichon [1] recently demonstrated synthesis of Flucytosine.



& similar compounds

Challenges in Batch:

- Hazardous reagent (F_2)
- Highly exothermic reactions (DT up to 180 °C)
- High dilution & long dosing times
- Challenges to perform at scale

Advantages in Flow:

- Thermal control = Intensification
- Metal-free reactors = Reduced corrosion risk
- Selective mono-fluorination = Increased product purity
- Single reaction step = Reduced isolation costs

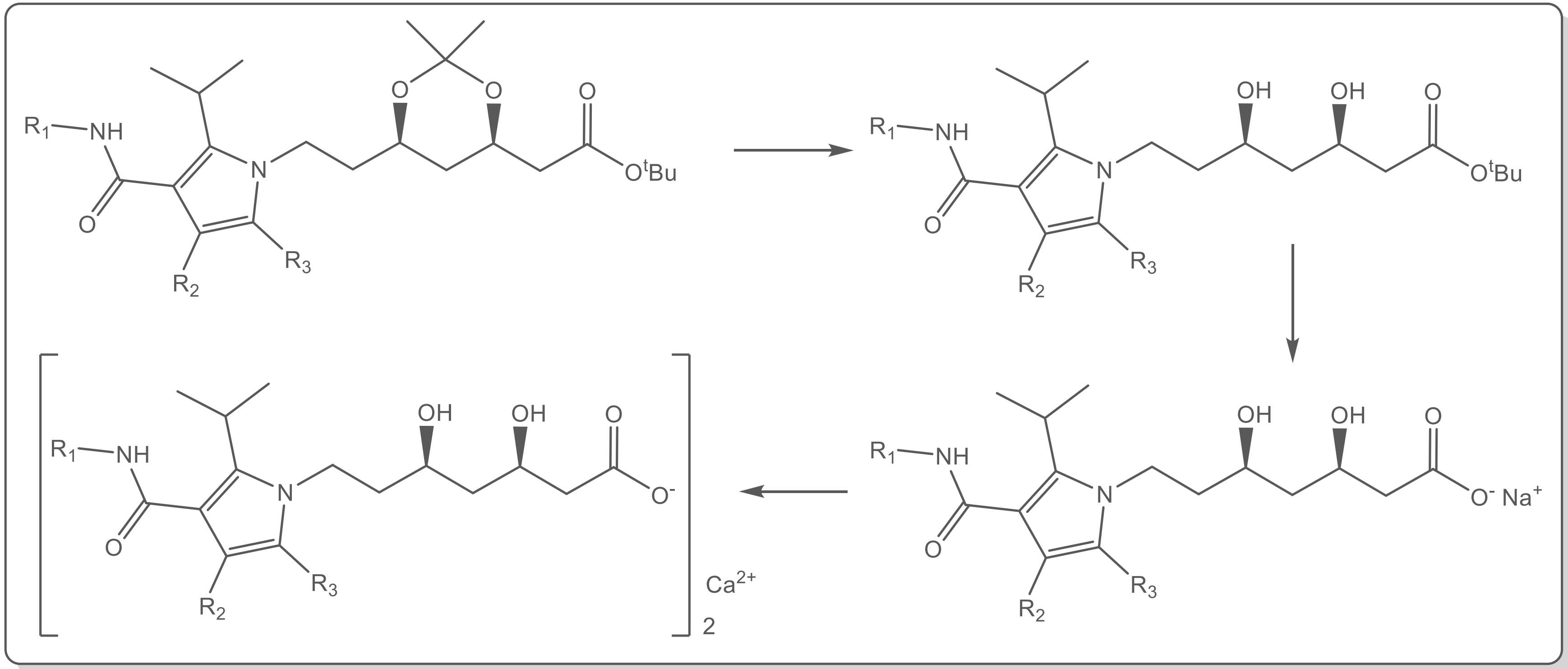
A range of products for various application spaces performed in Plantrix®;

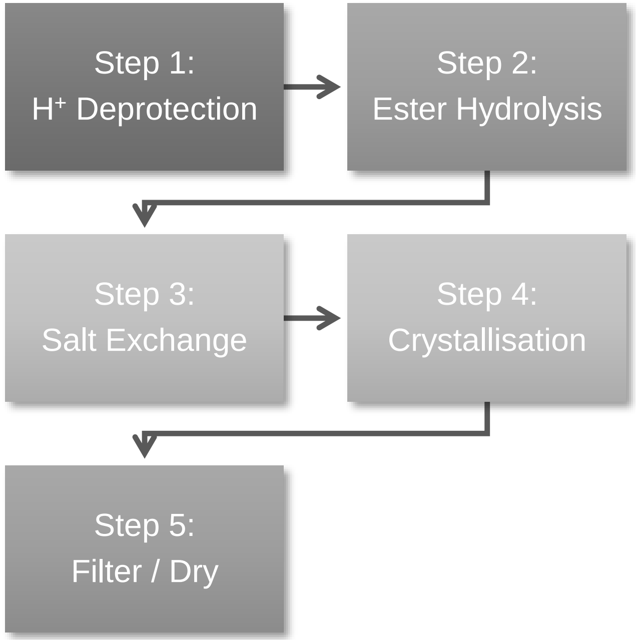
- Typically, 10 % F_2 in N_2 & active in polar solvent
- Throughput ranging from 3 to 30 kg/day isolated material (>90 % yield)

[1]. Sandford *et al. OPRD*, 2017, 21, 273-276.

Customer Case – Generic API Manufacturing

Development of a CM route for a marketed drug substance comprising of multiple reactions, crystallisation, filtration & drying!





Scaled-up from Protrix to Plantrix MR555 with ~100 MT/annum capabilities, achieving:

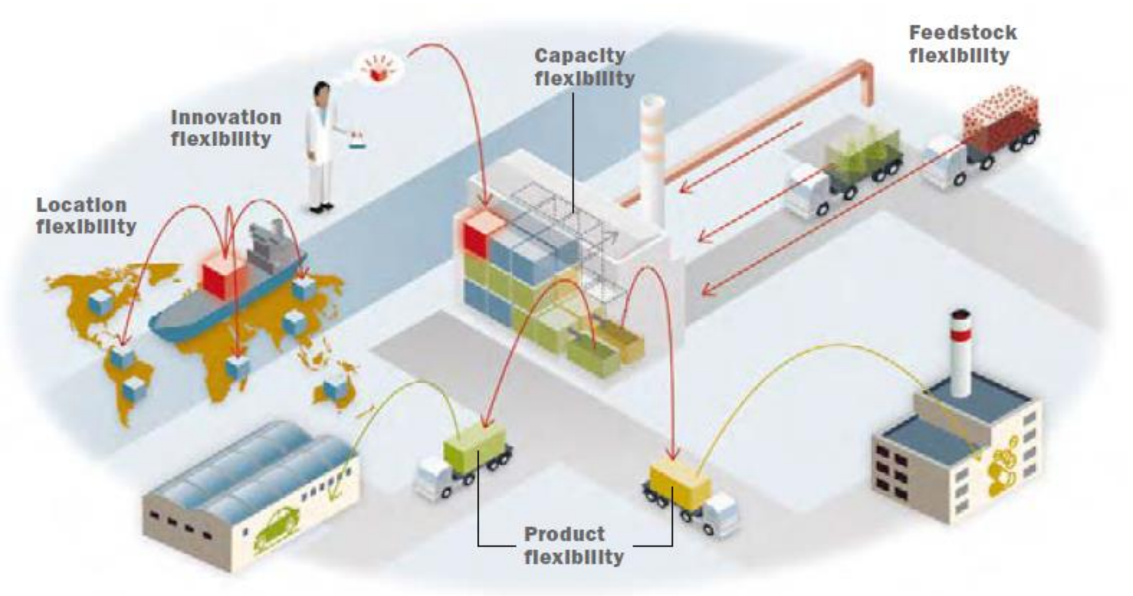
- Process simplification, reduced processing time (52 h to 14 h), improved robustness, reduced cost of goods, power consumption & space utilisation
  - → Illustrating that generic API's manufactured in Asia still have a lot to benefit from 'going flow'

[1] Patent: WO2021105934 A1

CHEMTRIX Scalable Flow Chemistry

Future of Flow Chemistry & Process Intensification

- Supply chain management is favouring in-house / local / distributed manufacturing models
  - Reducing the environmental burden caused by moving raw materials / intermediates / products between sites
- Continuous manufacturing brings an opportunity to further disrupt conventional supply chains, enabling;
  - On-demand manufacturing
  - Reduced ‘work in progress’ goods
  - Geographic diversification



- When combined with PAT/model-based predictive control, modular & flexible CM can robustly address the Industry needs!

CHEMTRIX
Scalable Flow Chemistry

Widely Accepted Benefits for Primary Processing

The rationale for a Company to 'Go Flow' is varied & depends on the sector, process type & scale of operation!

1 . Safe Use of Extreme Reaction Conditions

- Efficient mixing
- Excellent thermal control
- Process intensification of hazardous reactions

2. Reduced Development Time

- Small hold-up volume
- Rapid reaction optimisation
- Minimal scale-up steps

3. Improved Process Control

- High level of reaction control
- Process reproducibility
- Quality by Design

4. Reduced Production Costs

- Increased product quality
- Reduced safety investments
- Higher unit productivity

Engineering for efficiency, flexibility & sustainability bring opportunities to commercialise intensified processes!

- Dramatic reductions in plant size
- Access to reaction conditions previously unobtainable
- Flexibility towards different product types & production volumes

DISADVANTAGES OF CONTINUOUS FLOW

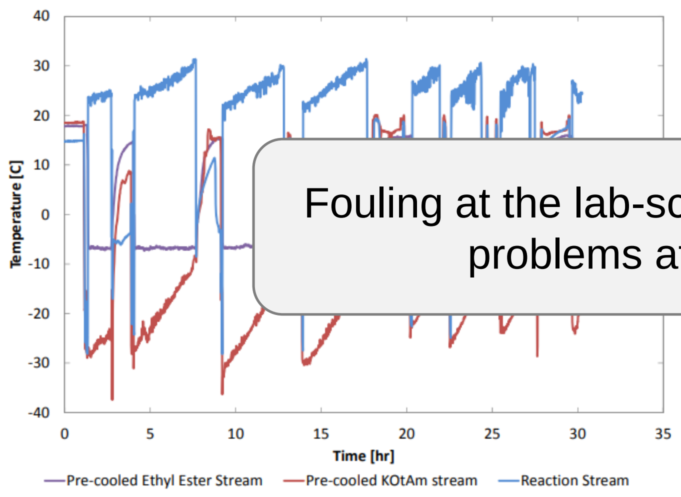
CHEMTRIX Scalable Flow Chemistry

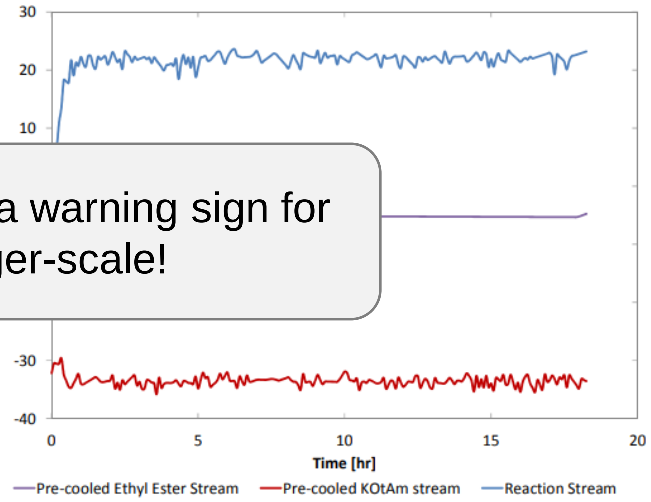
Where Chemists & Engineers Meet!

"….The only disadvantage of continuous processing, with its different skill & knowledge requirements, is that companies will need to change their ways of working to take full advantage of its benefits.

With typically, 90% of manufacturing costs locked in at the design stage, & the cost to change a process increasing exponentially the further down the development route it is implemented, good management of early process design & development are essential….."

'The Reality of Continuous Processing', Manufacturing Chemist, April 2005
Huw Thomas, Foster Wheeler





Fouling at the lab-scale is a warning sign for problems at a larger-scale!

[1]. McMullen *et al.*, *Org. Proc. Res. Dev.*, 2018, 22(9) 1208-1213.

CONTACT US

CHEMTRIX
Scalable Flow Chemistry

Partner to Accelerate Success!

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