Improving Manufacturing in the Pharmaceutical Industry through the Implementation of Continuous Processing

Sarah Hunter, Process Engineer, R&D

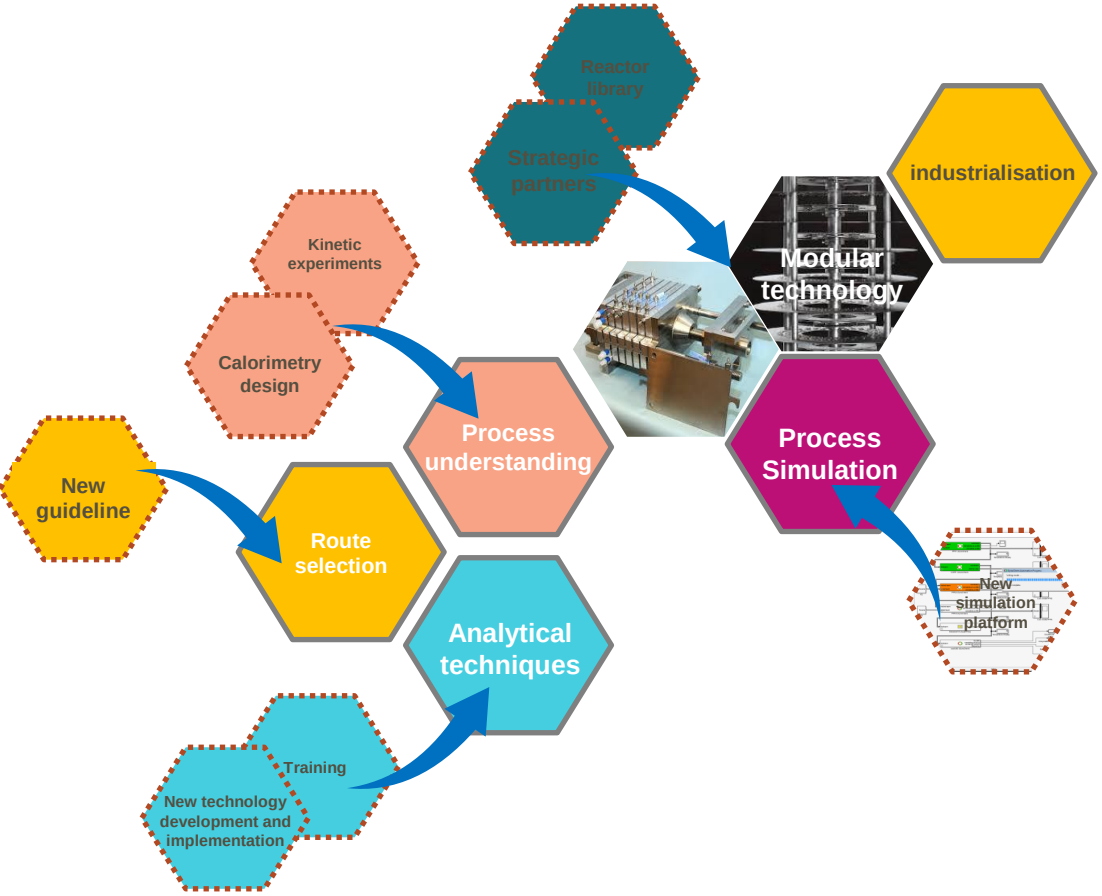
Batch Processes have and will continue to fulfill an important role in the manufacture of Active Drug Substance; they allow multiple recipes to be executed in the same core equipment. However, the compromise is, batch fails to deliver the precision, speed of manufacture and intensification of a flow process.

Here I present how, at GSK, we are developing flow processes for organometallic chemistry. Using process understanding generated using batch methods, and a combination of insilico simulation and physical demonstration we are able to redefine conventional operating parameters for this type of chemistry and industrialise processes which are not feasible in batch due to risk of scale.

We believe this will allow us to deliver more medicines of value to patients, both in affordability and function

Flow Chemistry at GSK

Where We Are



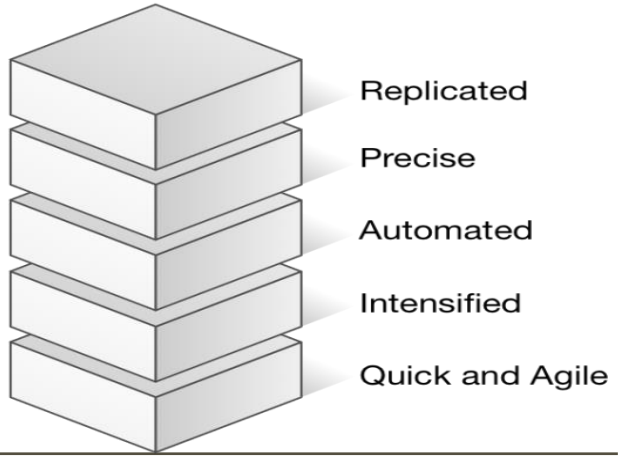
2003 Started Programme

2016 Gain First Commercial Credibility for 3 Stage Process.

Clinical Campaign of Organometallic Flow Process Case Study.

2017-2021 Design/Build the Space to house the next Phase of Projects

We want a Manufacturing solution with these attributes...



Flow Chemistry at GSK

Where We Aim to Be

Pharma has been working on a knowledge and trial and error principal. Development has been governed by statistical models and small scale increment changes until manufacturing scale.

GSK is partially converting its API batch portfolio to continuous with a great ambition to reach up to 50% by 2020.

To support this strategy, simulation has to be integrated at the centre of process development to;

- Accelerate process development
- Provide more robustness in the development phase
- Ensure and understanding from scale to scale

Batch is following the transition and integrate simulation as part of the workflow.

Organometallic Chemistry

Batch Process

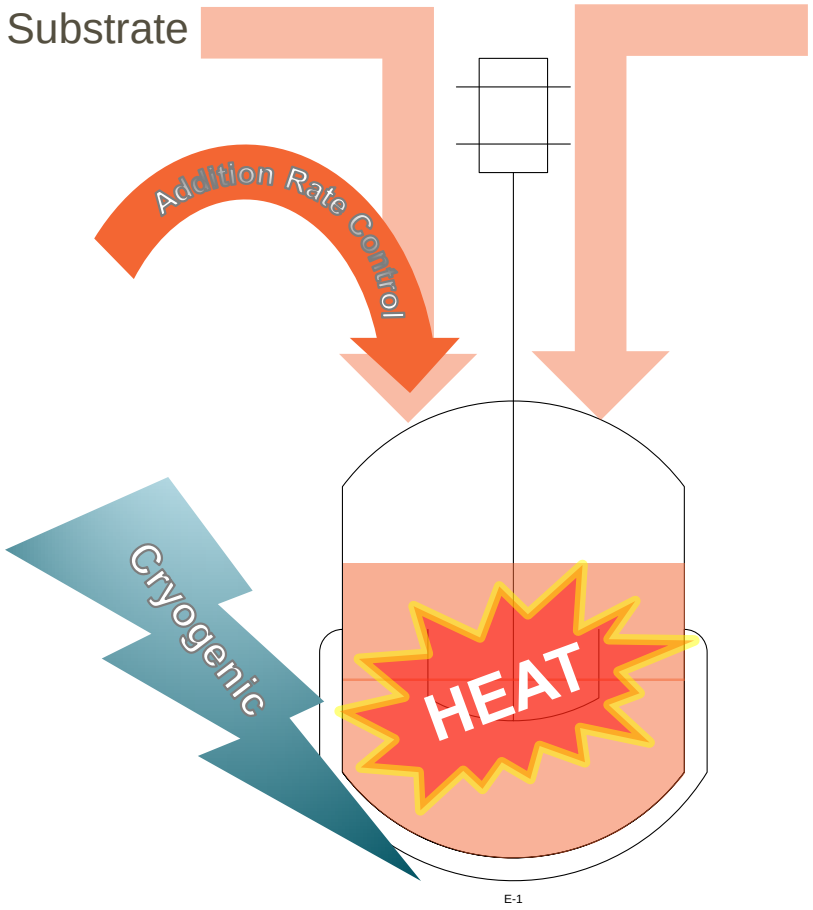
Organometallic chemistry is common place in pharmaceutical synthesis and often presents a challenging process to execute in batch.

Batch is….

Versatile.

Available across scales.

Familiar to chemists



Batch is also….

Imprecise.

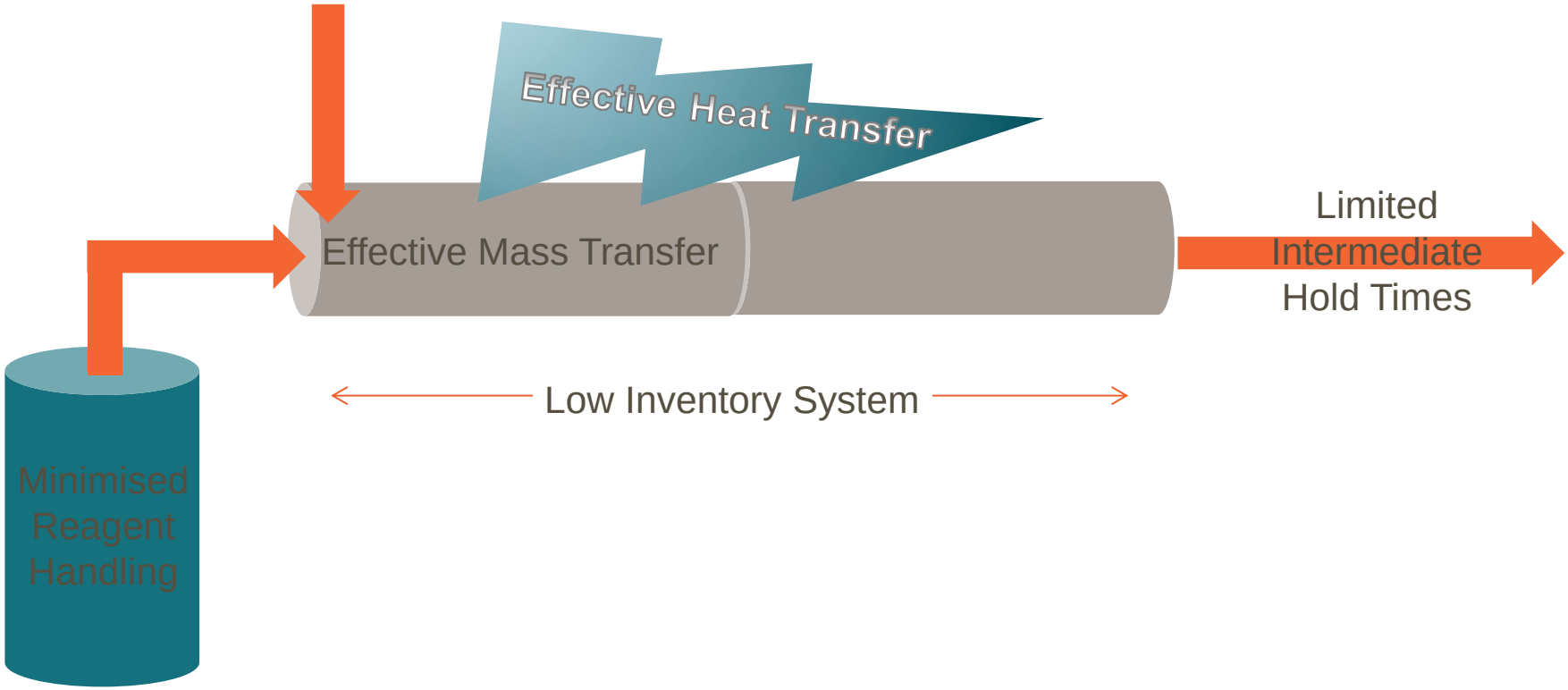
Hard to scale up.

Labour intensive and Slow.

Organometallic Chemistry

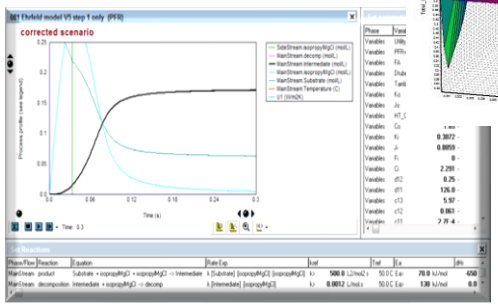
Flow Process

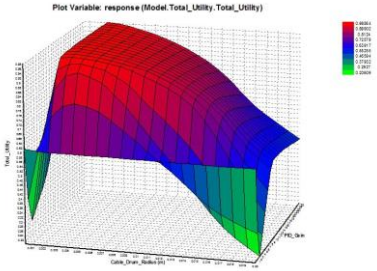
A team at GSK have been developing process workflow for effective design and scale up of continuous organometallic processes which is currently being applied to a number of processes in active development.



How do We Allow the Transition to Happen

From Laboratories to Manufacture



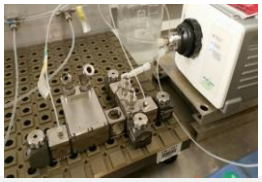


Simulation

Industrialisation

Demonstration

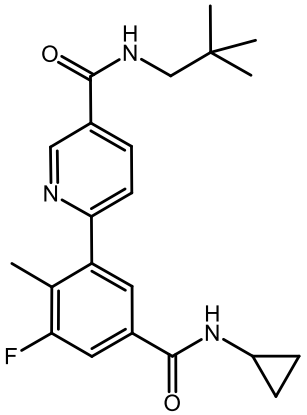
Process Understanding



Case Study

P38 Kinase Inhibition of Inflammatory Pathways

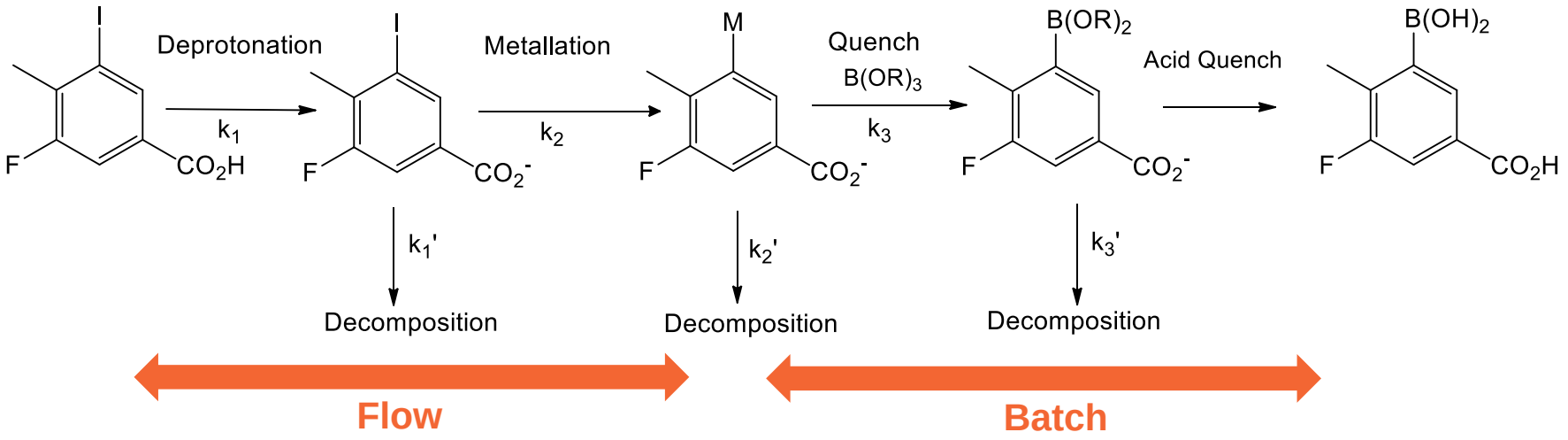
- Rheumatoid Arthritis – **Candidate selected 2003**
- Atherosclerosis
- Depression
- Neuropathic pain
- Acute Coronary Syndrome - **PhIII**
- COPD
- Focal Segmental Glomerular Sclerosis
- Stage 1 – Flow Synthesis



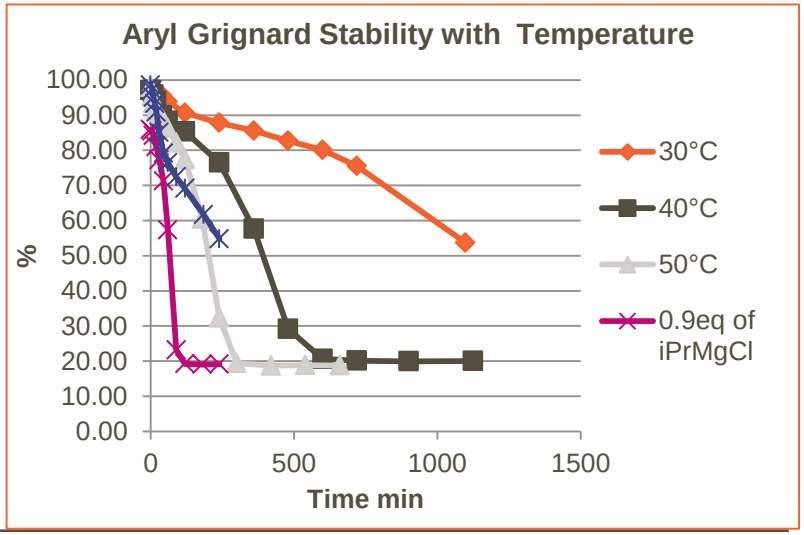
Losmapimod (GW856553X) (Oral)

Case Study

Flow Stage Development



- **Evaluation of solubilities, rates and stabilities required**
- **Kinetic model to define reactor characteristics**

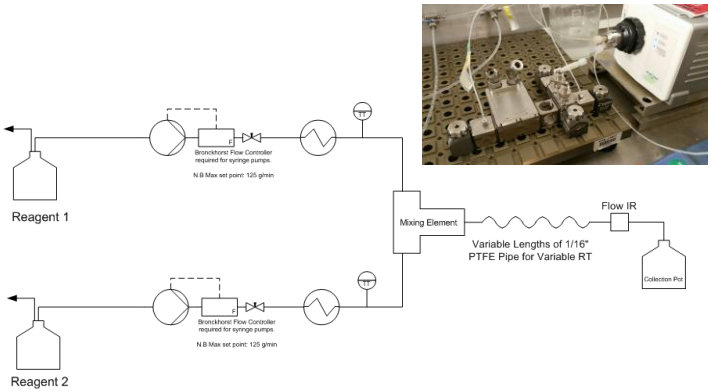


Process Understanding

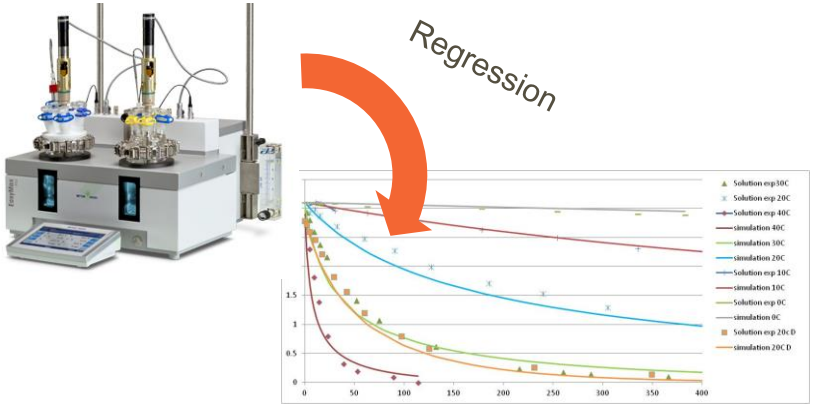
Kinetics & Calorimetry

Kinetics

Main Reaction

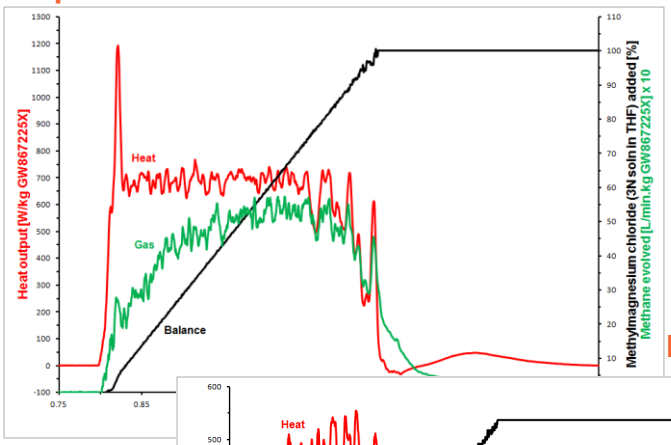


Degradation – Batch Time Course

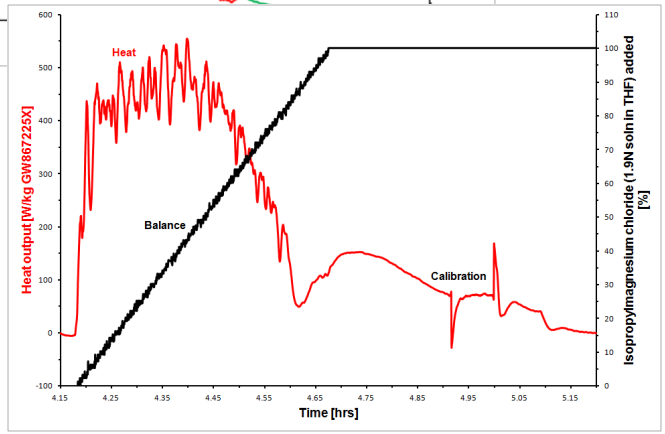


Calorimetry

Deprotonation

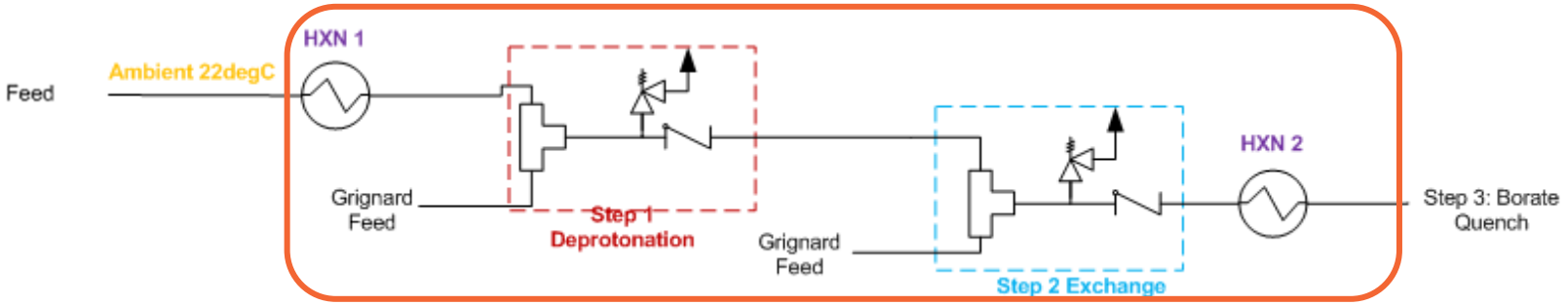


Exchange



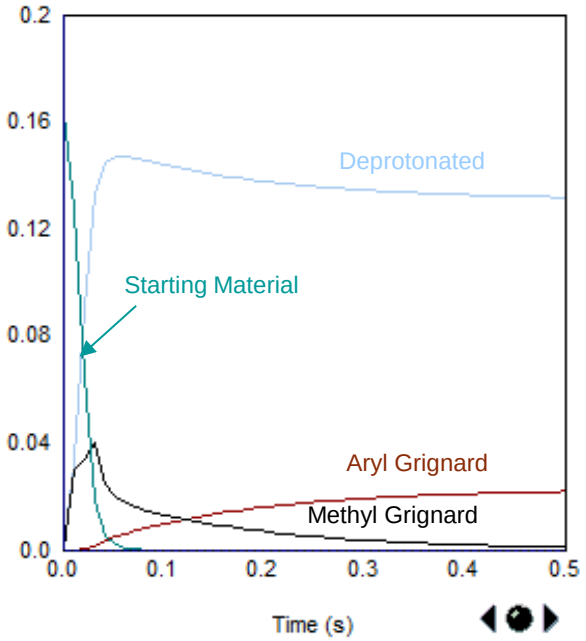
Simulation

PFR Model



Matching ;
- Temperature profile
- Residence times
- Reagent concentrations & flow rates

Define process parameter ranges and the equipment performance;
- Heat Transfer Coefficient
- Surface Area to Volume Ratio
- Micro mixing
- Bodenstein Number

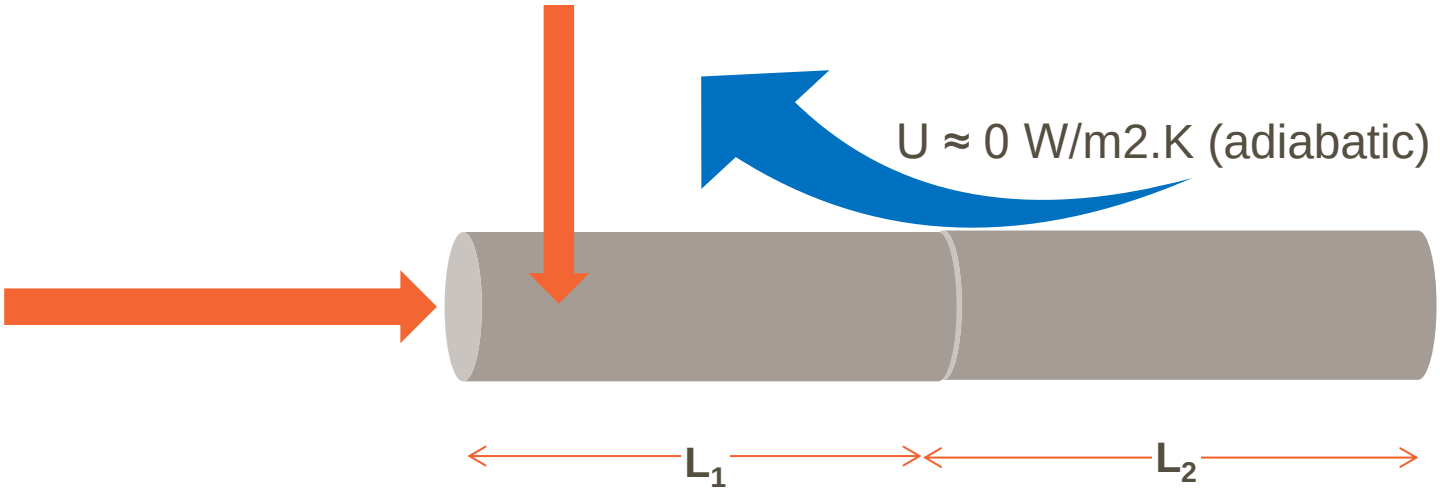


User Requirement Specification

Continuous Process

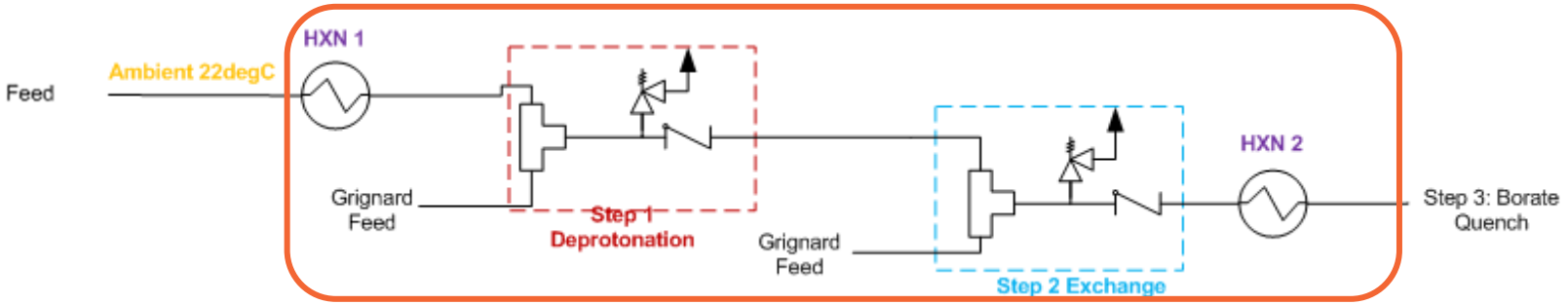
The simulation demonstrates process robustness low sensitivity to parameter inputs allowing the simplest design concept.

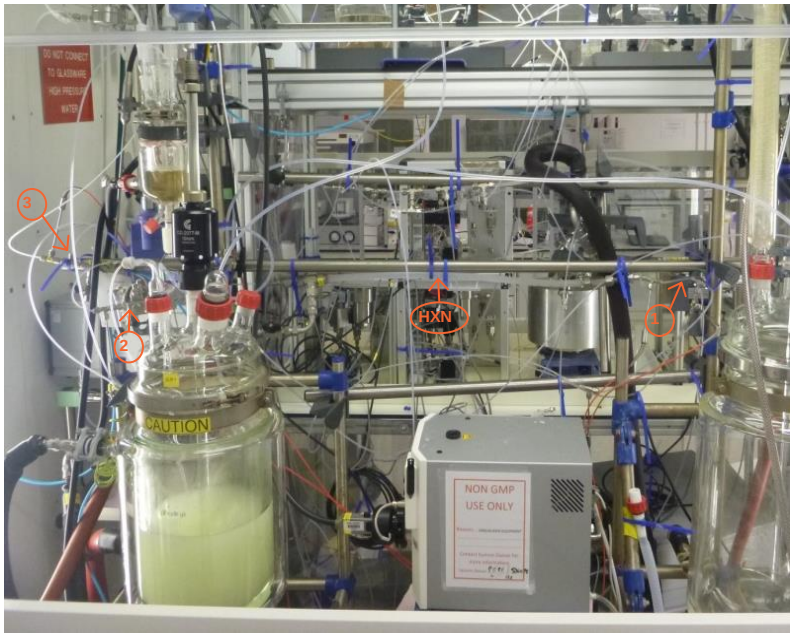
Plug flow reactor with static mixer;

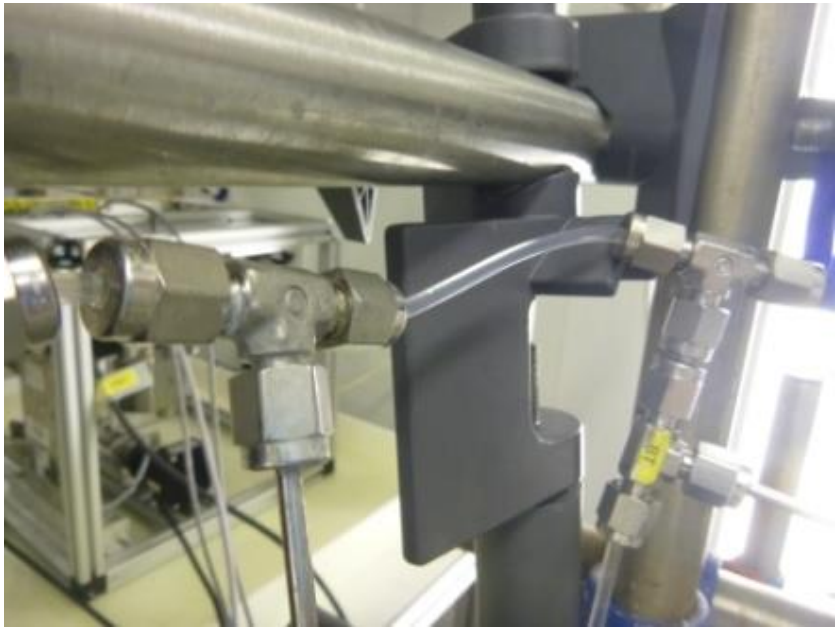


Demonstration

PFR Model

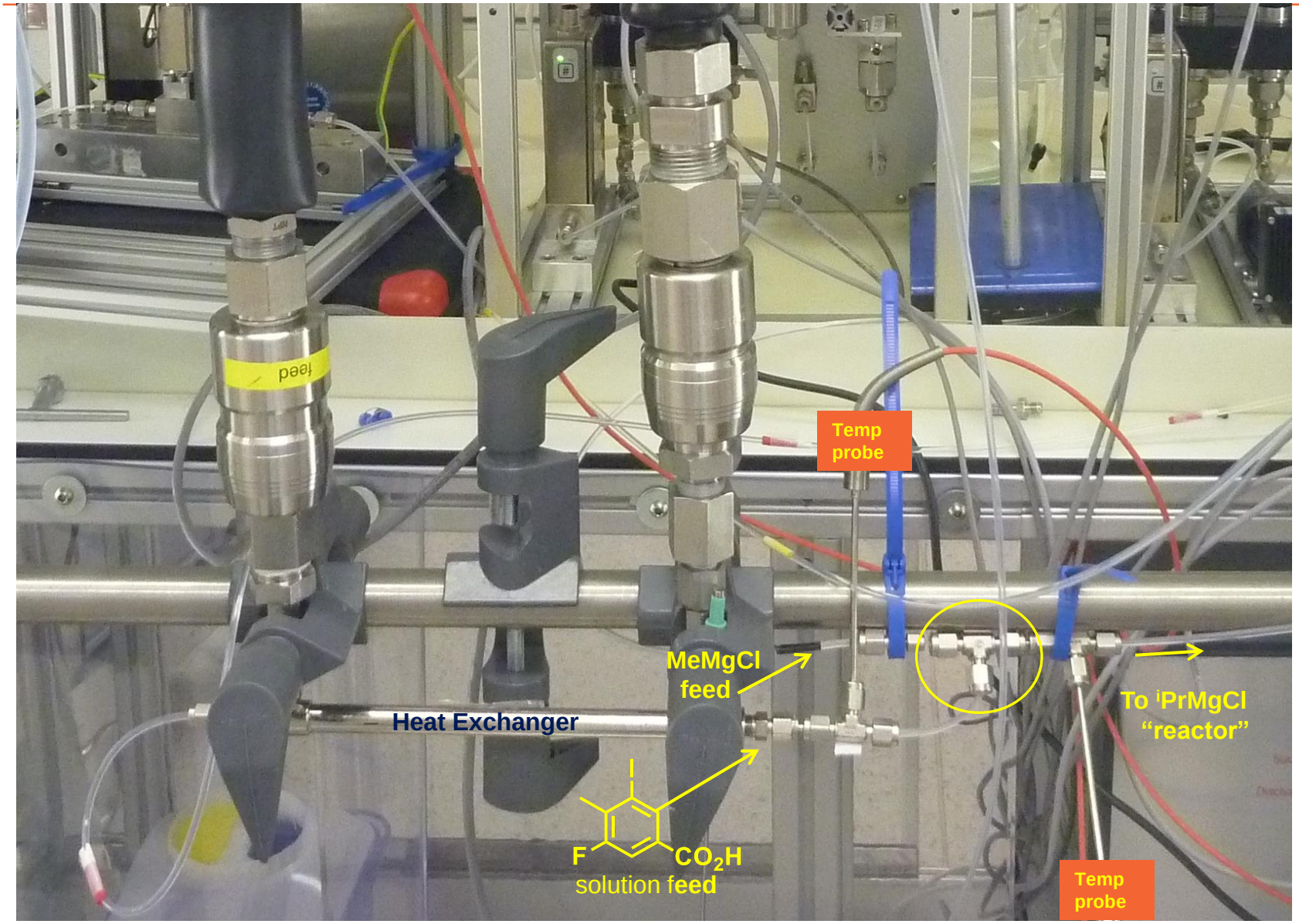






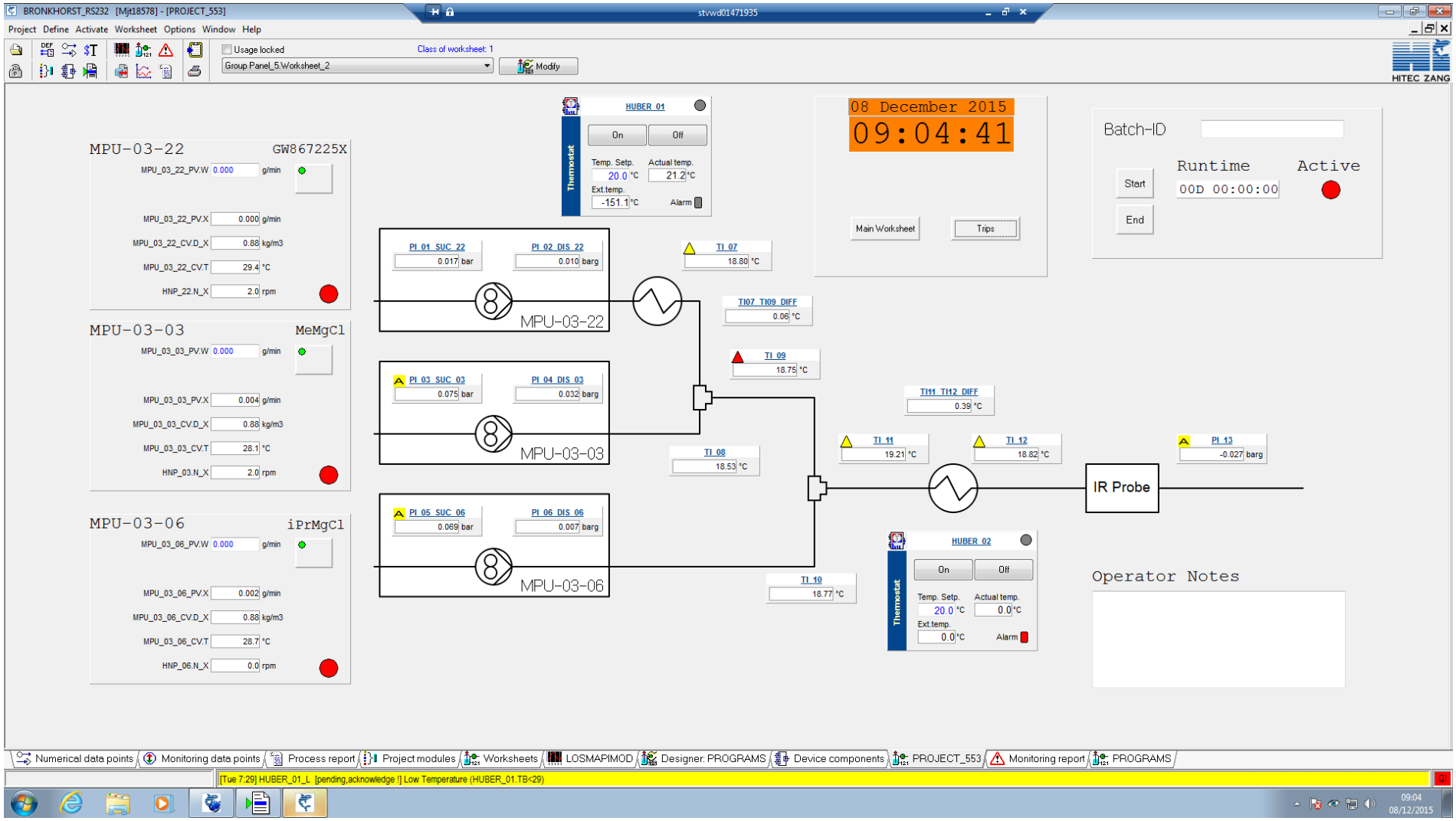
Demonstration

Continuous Process



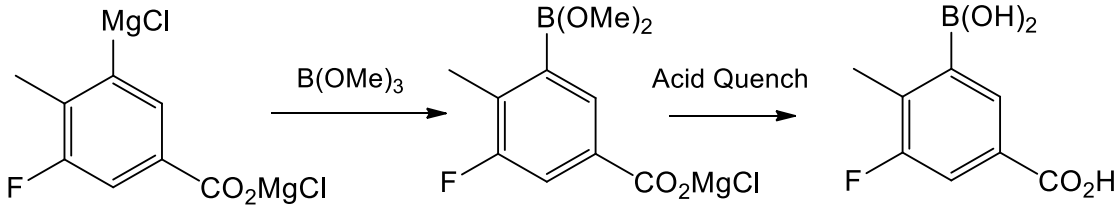
Demonstration

Process Control



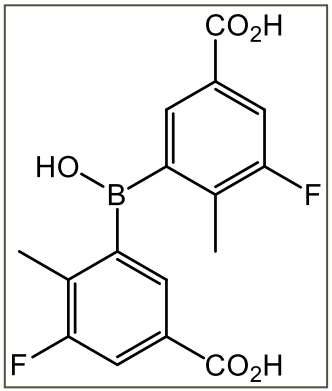
Demonstration

Work Up



– Initial intent: to flow directly into a quench pot containing the trimethyl borate

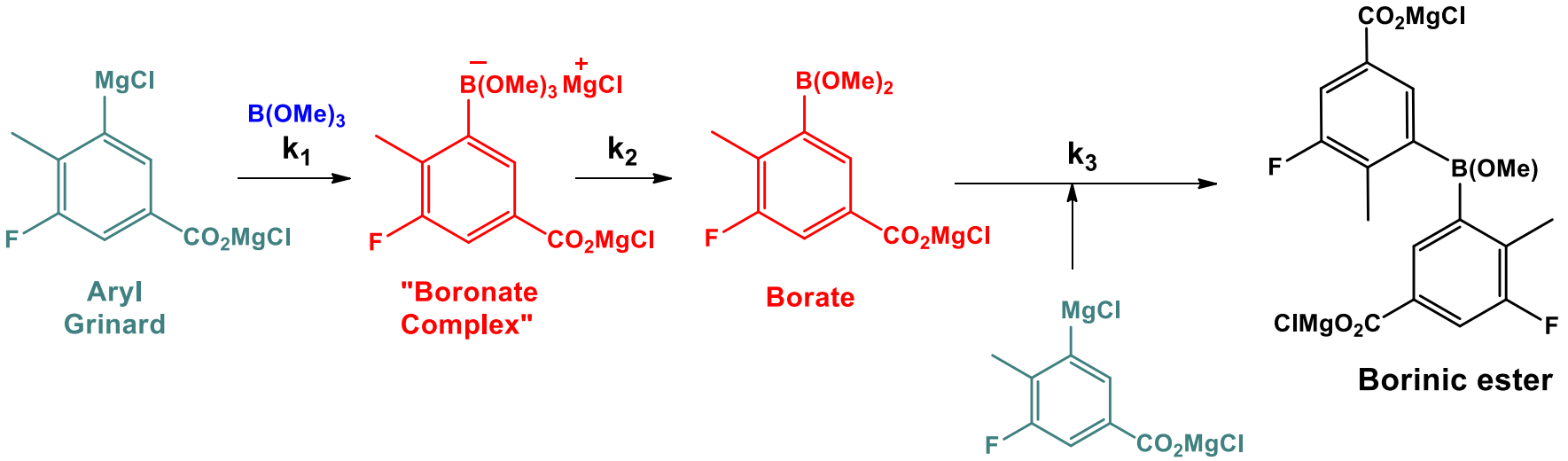
– Extended addition time gave higher levels of the borinic acid



Addition time (min)	Borinic acid level HPLC (%a/a)
0.5	1.3
3.5	4.2
8	7.9

Demonstration

Work Up



- **If k_1 and k_3 fast but k_2 slow?…..**

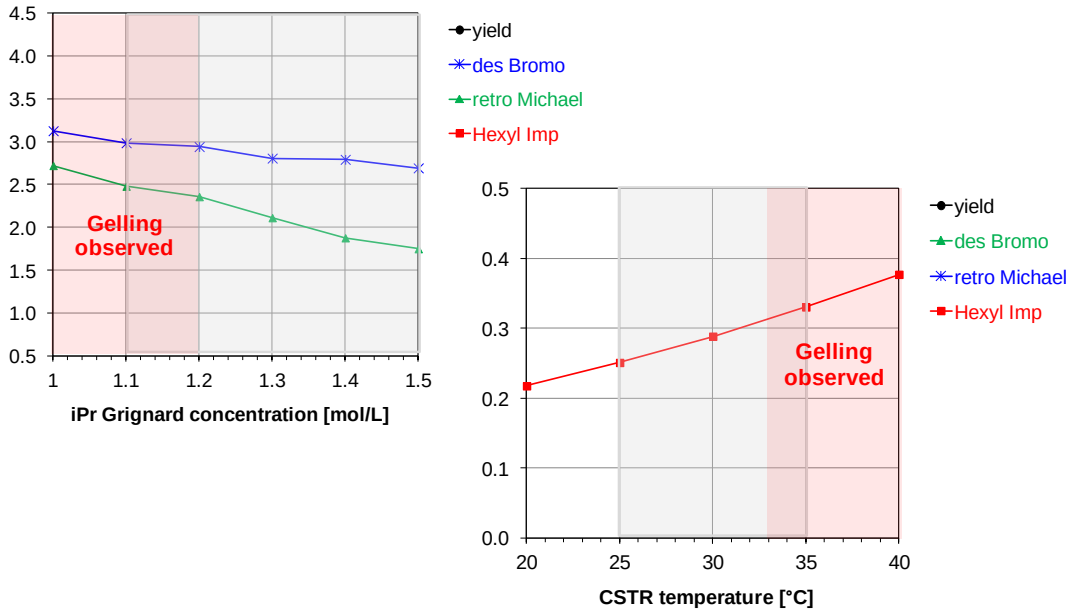
- Rate of addition relative to progression of the “ate” complex controls borinic levels
- Rapid trimethyl borate addition to the Grignard solution preferable

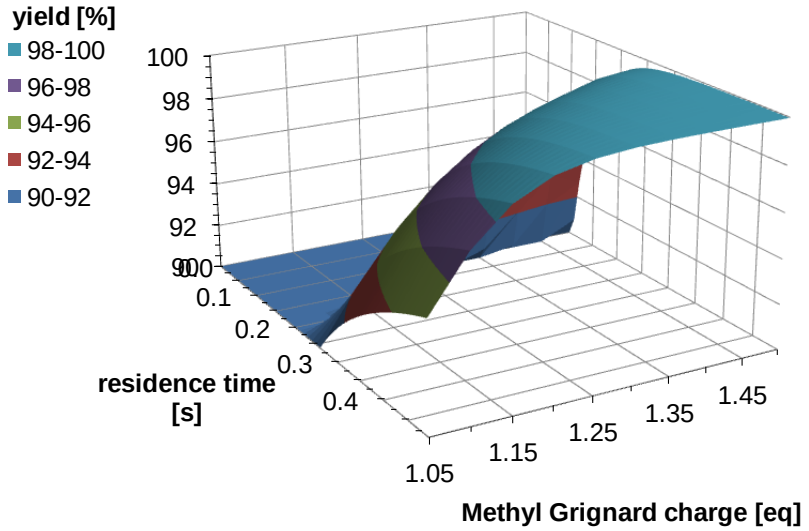
Simulation

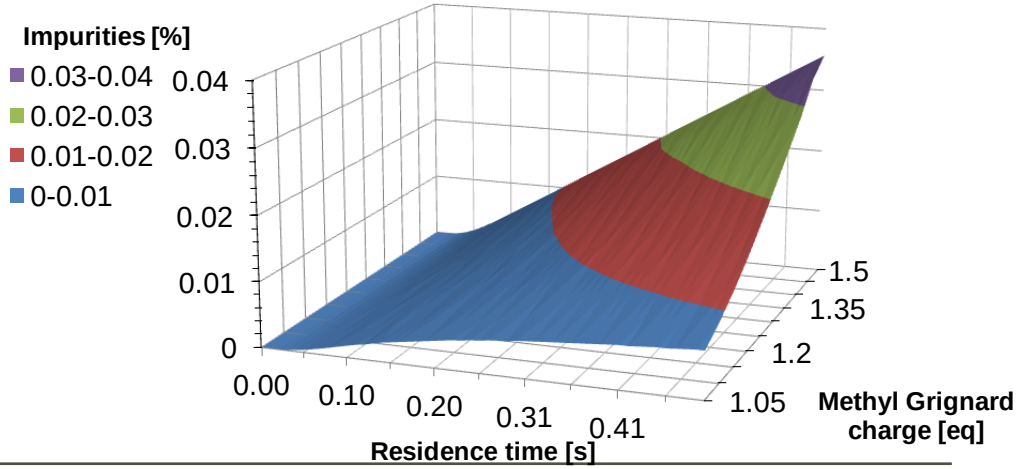
Design Space and QbD

The simulation is a critical part of development facilitating;

- Process design
- Risk evaluation
- Specification of deign space

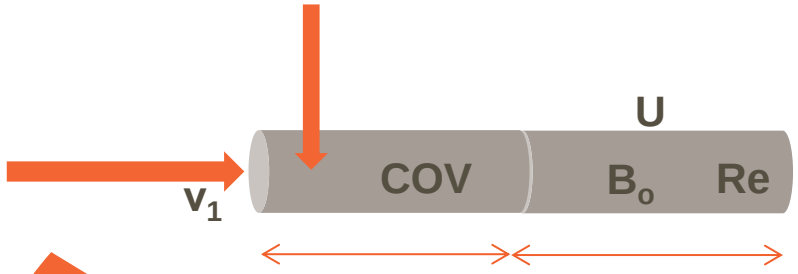


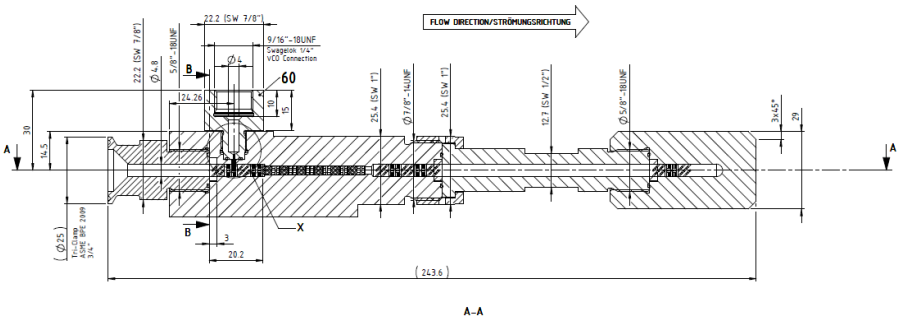




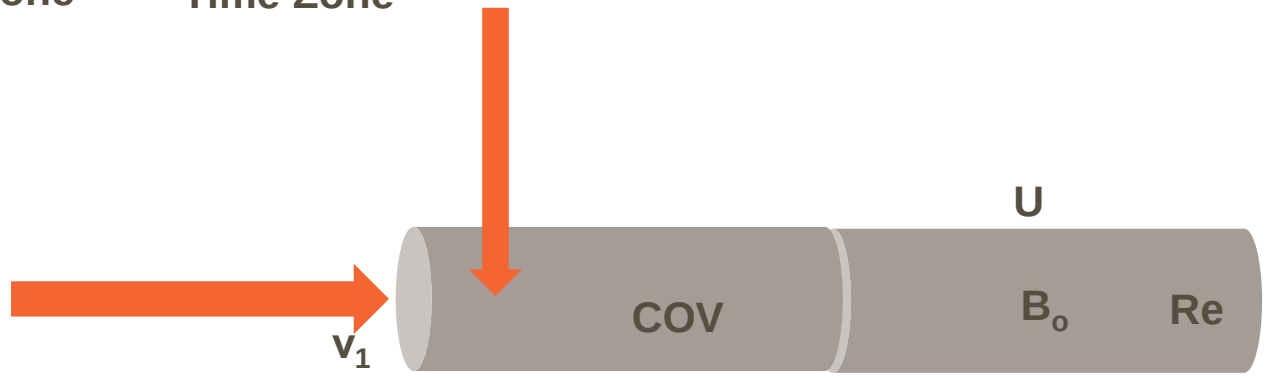
Industrialisation

Scale Independent Design

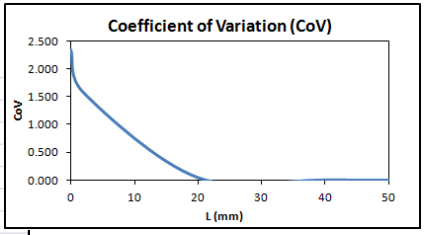




Scale Up



Mixer 1	SMX	
Length	200	mm
Diameter	3.9	mm
Process fluid	THF	
Main stream flow	220	mL/min
Side stream flow	40	mL/min
Volume of internals	1.2	mL
Temperature	80	C



Mixing Zone

Residence Time Zone

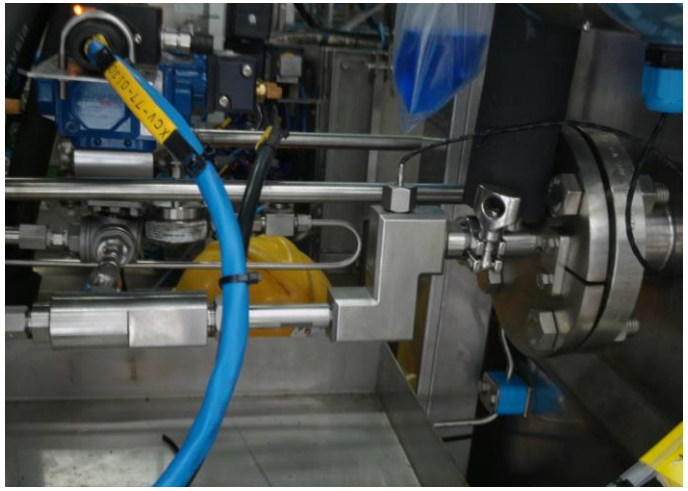
Industrialisation

In Practice

Processes have been demonstrated at production rates of;

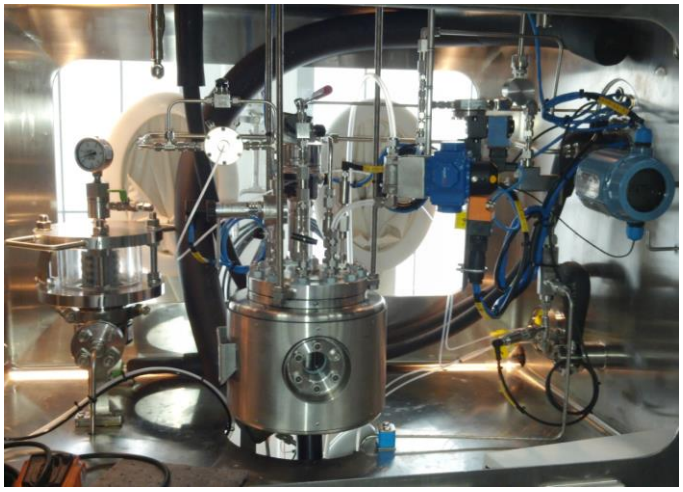
- Lab scale ~100g/hr

  Isolated Yield 70% th
  Isolated Quality 99.7% a/a
- Pilot plant scale ~500g/hr.



Operating as a flow process

- Enabling operating conditions which are not feasible as a batch operation.
- Eliminating a potential critical quality attribute.



A recent pilot plant campaign produced 88.2 kg of clinical material.

Yields averaged 84.95% th.

Acknowledgements

Continuous Primary Team

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