ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

How Process Simulation can Influence the Process Development and Control Strategy of a Drug Substance Asset

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Background

Up to recently, process development and process control in the pharmaceutical industry have been dominated by experimentation. The definition of the process optimum and the control strategy was supported by Design of Experiments (DoE) feeding into statistical models.

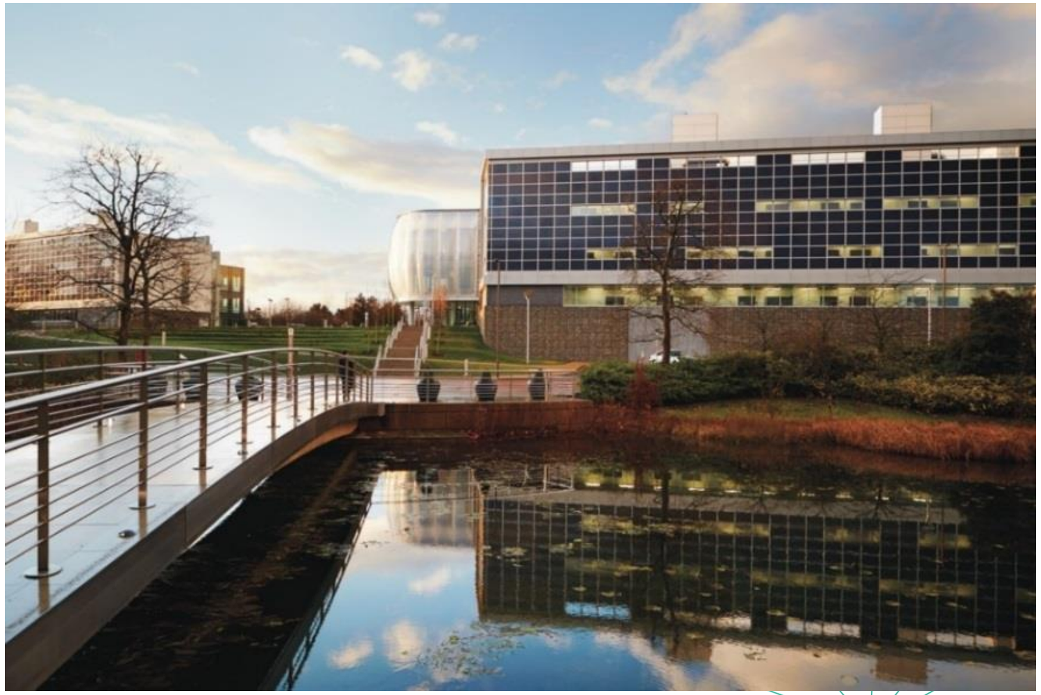
Despite the great value of such models, they are not always the most suitable solution to provide answers to complex and non-linear problems. This work aims to supply a more efficient solution to the process development phase and the control strategy for first principal models raised in pharma R&D.

At GSK, supported by a new modelling strategy, we are now embedding mechanistic and first principal models as part of our routine work from the laboratory to manufacture

Outline

1. Introduction

2. Change of strategy: Process development and control supported by modelling
   - Workflow / Milestones
   - Simulation strategy / Program



3. Case Study – Execution
   - Process design
   - Process implementation

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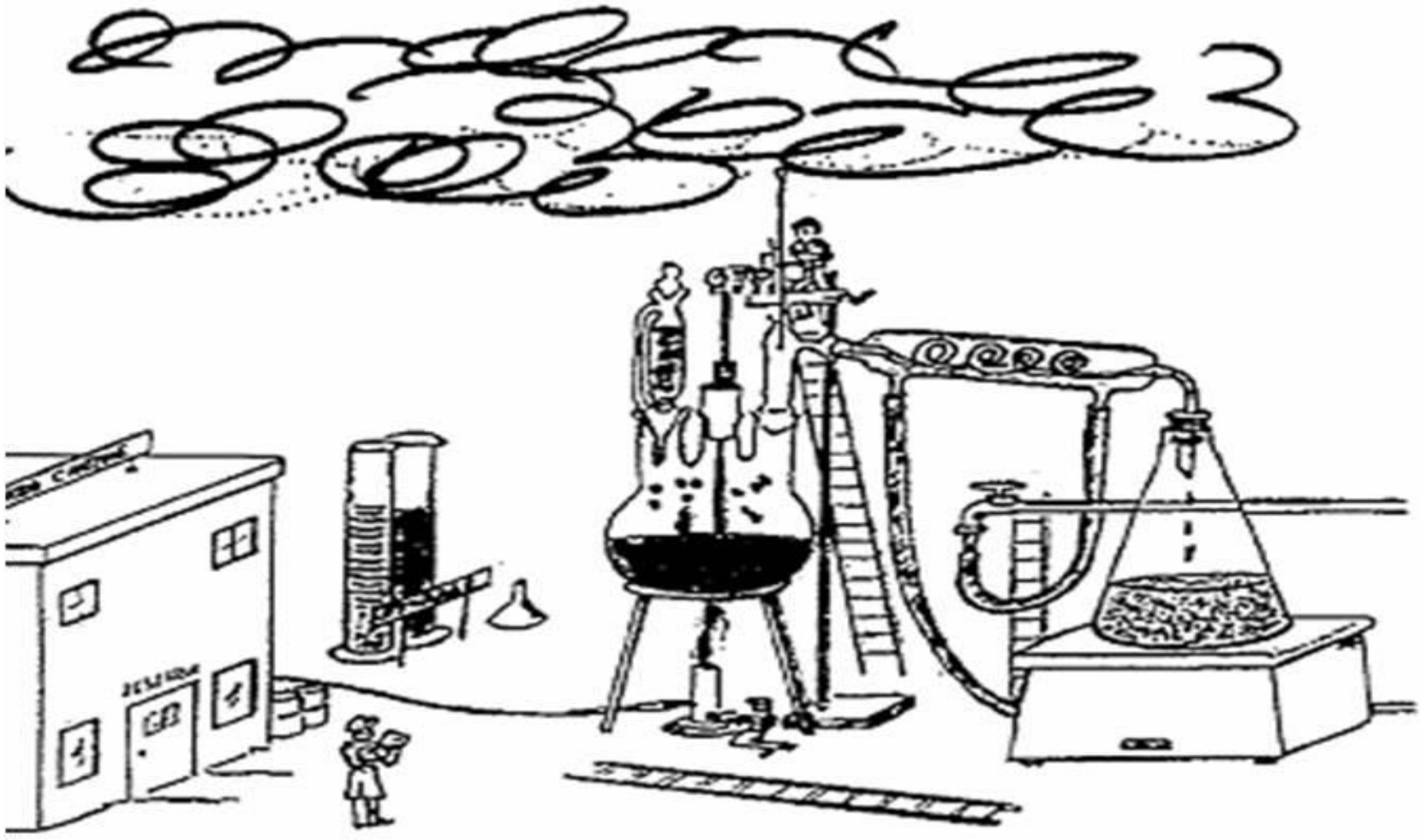
GSK

Process Development and NCEs Manufacture

Introduction



The lab results were so good
we bypassed Process Development

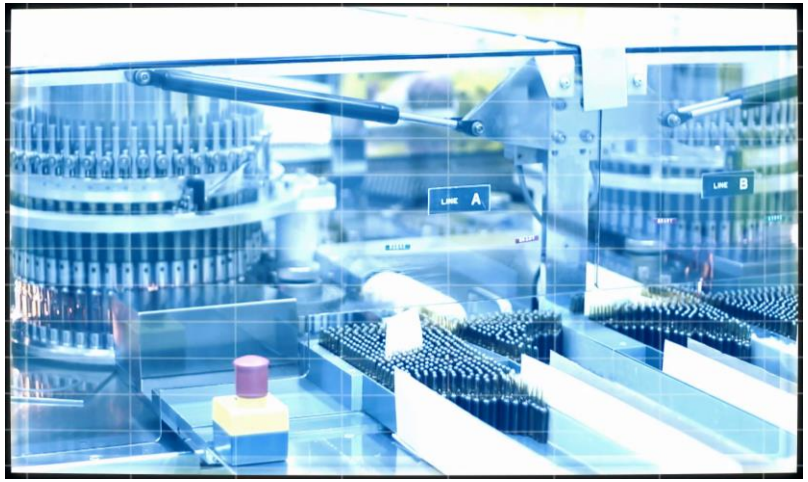
Application of Process Simulation

Objectives

R&D

Small & Large Molecule Process Development
- Process Design and Optimisation
- Selection / Design of equipment platform
- Design of System Models for Control Strategy

Manufacture



API & Drug Product continuous
•Quality control using modelling soft sensor
•Process control using MPC/APC

Objectives

Deploy process modelling across Small molecule DS and DP and BioPharmaceutical

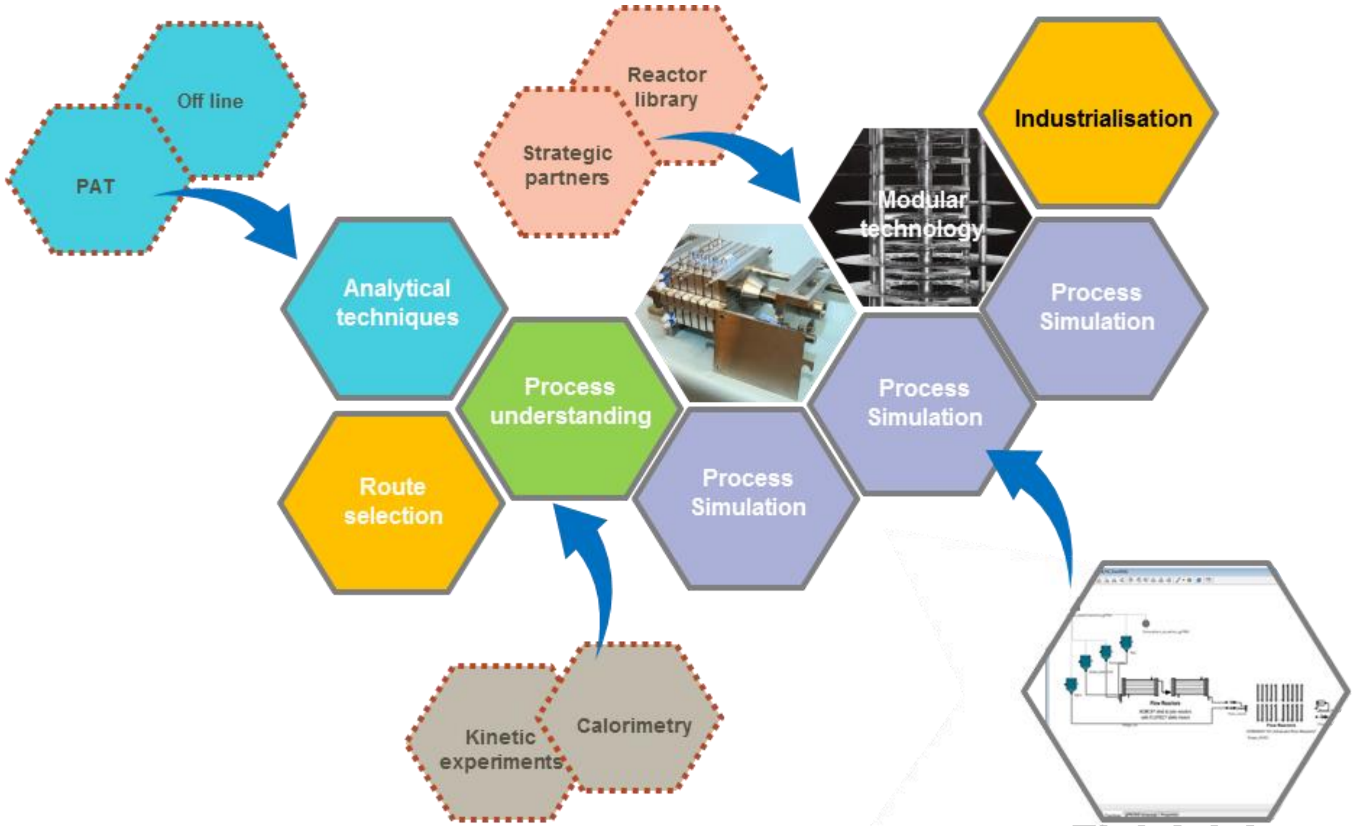
- Support process development through deployment of modelling
  - Development and optimization of the process
  - Scalability assessment and enhancement of robustness
  - TRA, Tech. transfer and process verification

- Support the control strategy by implementation of System based Model
  - The integration of appropriate models, statistical and mechanistic
  - The deployment of strategic model for prediction of CQAs

New Work Flow Application

Simulation at the Centre of Process Development and Implementation

- System modelling approach defines data requirement and drives experimental plans
- Quantitative input to CPP identification and design space boundaries
- Transfer model from R&D to commercial manufacturing



Simulation Platforms

Mapping out of platforms and deliverables

Support of portfolio acceleration **Process Development**

Objectives

Provide models to support acceleration of process development.

Support commercial design **Control Strategy**

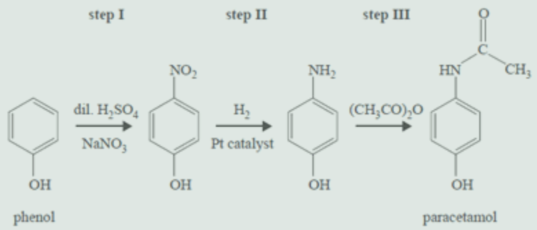
Objectives

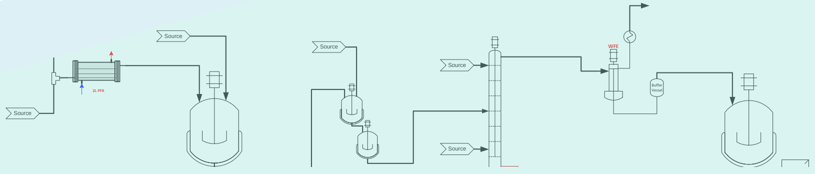
Provide models to support control strategy and continuous process improvement.

Usage

Aspen

DynoChem



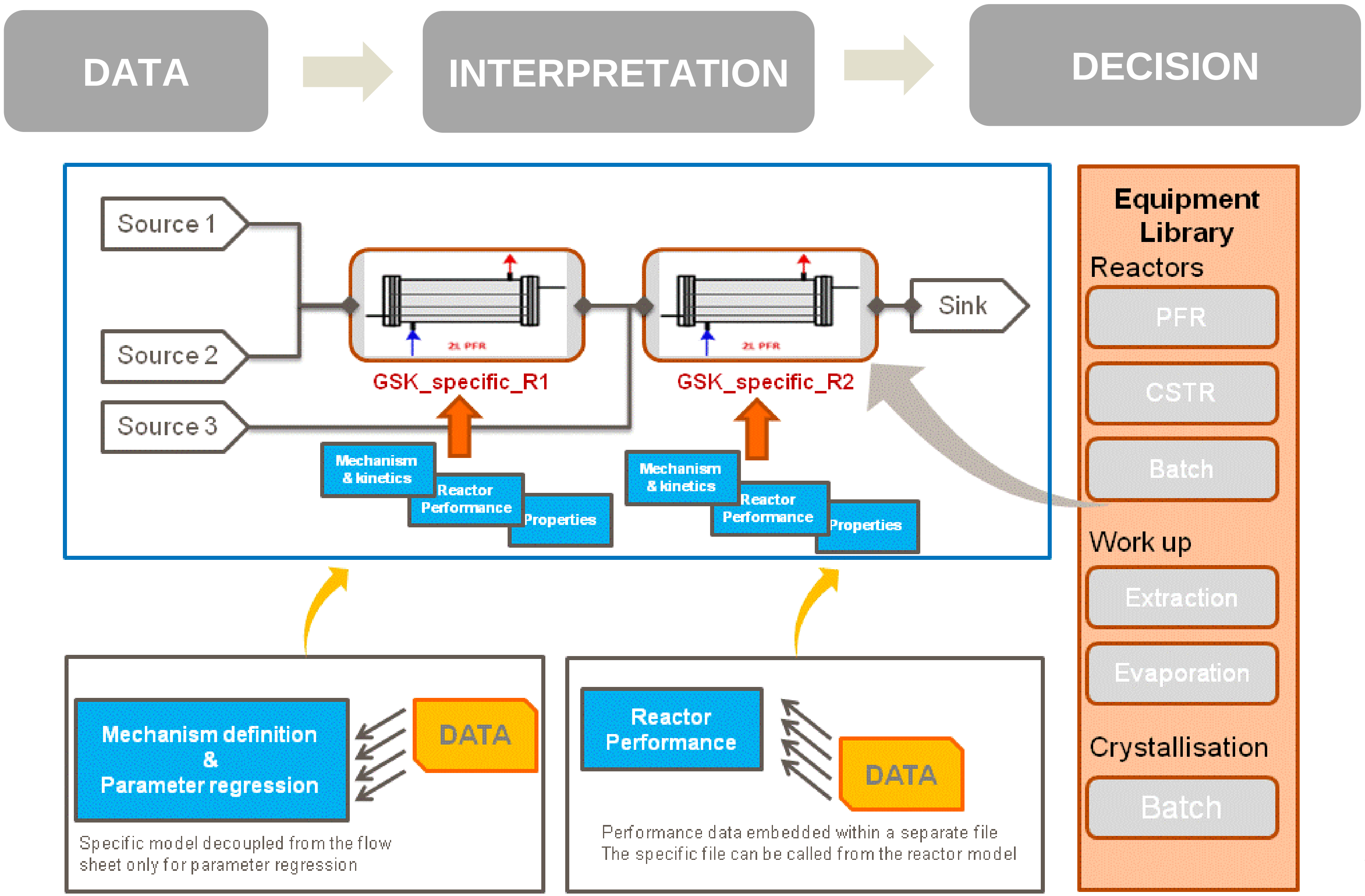


gPROMS

T

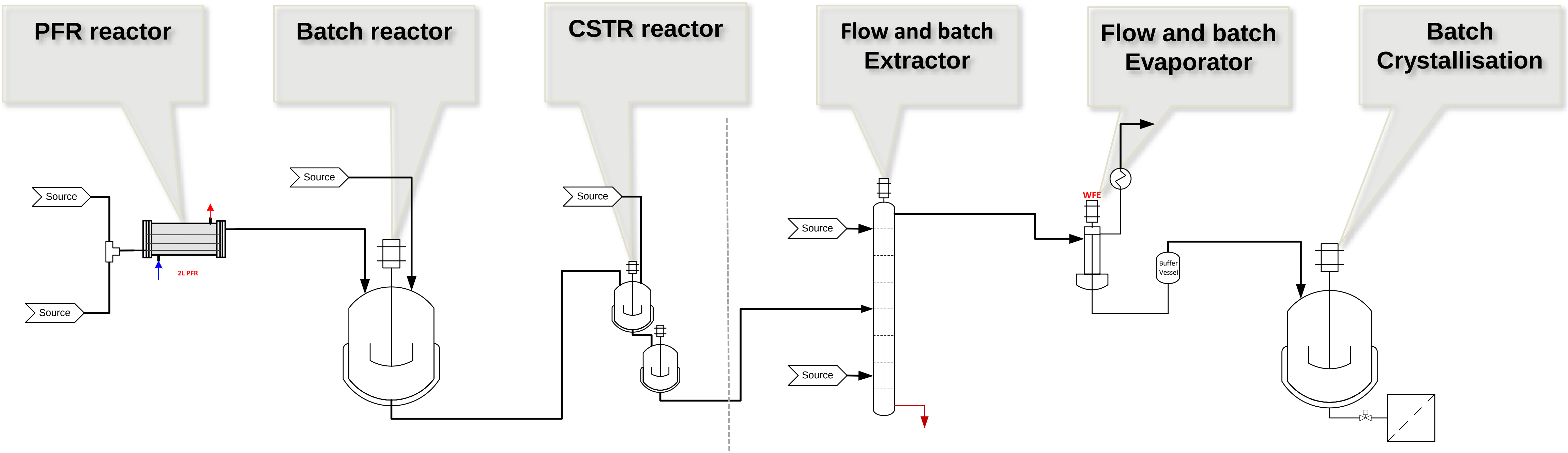
Candidate Selection **Commit to Medicine** **Commit to Phase III** **Commit to File**

Process Simulation Platform



System-based Modeling: Our Vision

Model development for support



Reaction in PFR

Reaction in batch

Reaction in CSTR

Component extraction in batch vessel or flow equipment e.g. RDC

Evaporation in batch vessel or flow equipment e.g. WFE

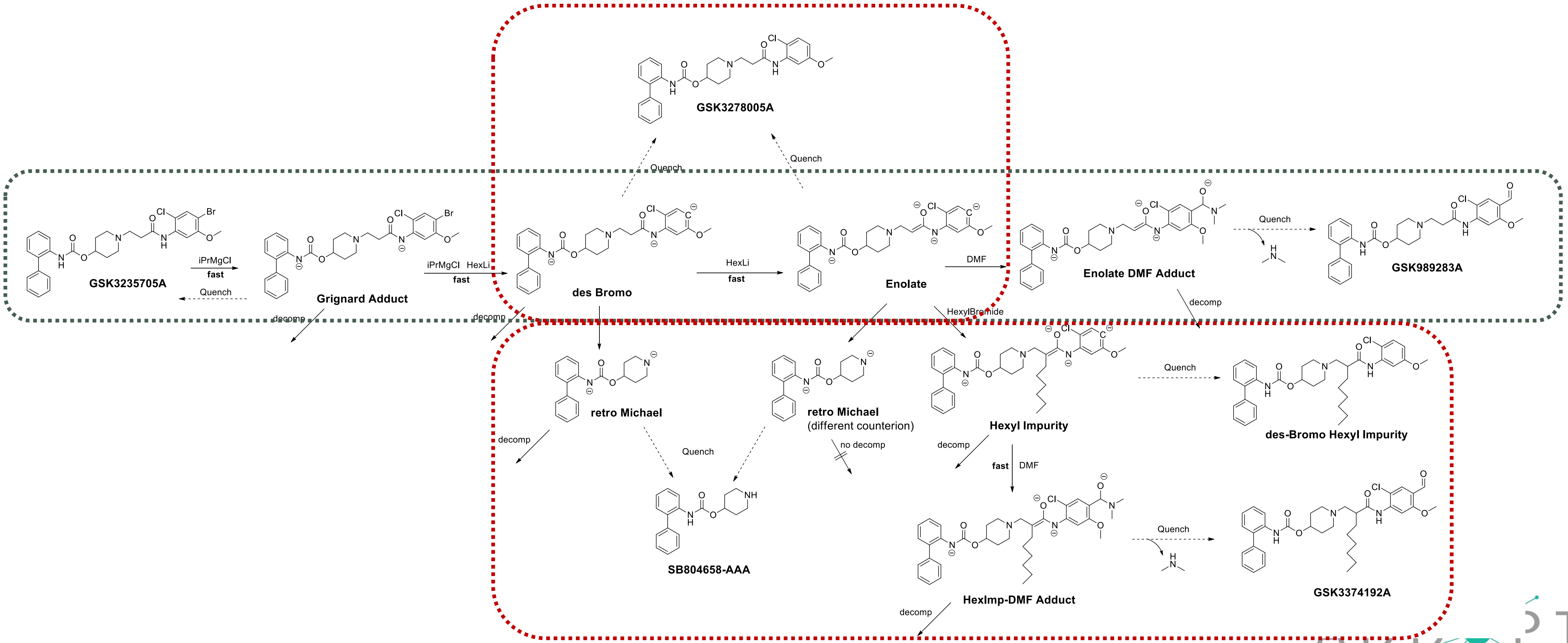
Impurity absorption

EXECUTION

Reaction Scheme

Understanding of the Process Mechanism and rates

Mapping out the main transformation and the side product formation is critical



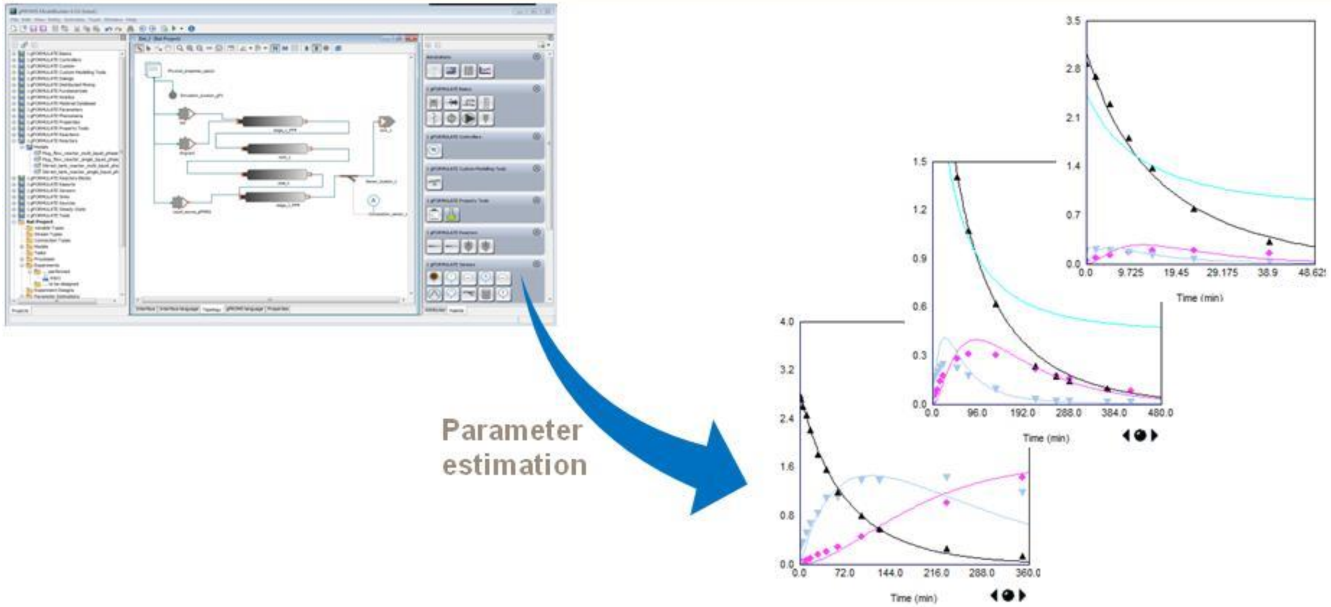
Simulation Application: Process Understanding

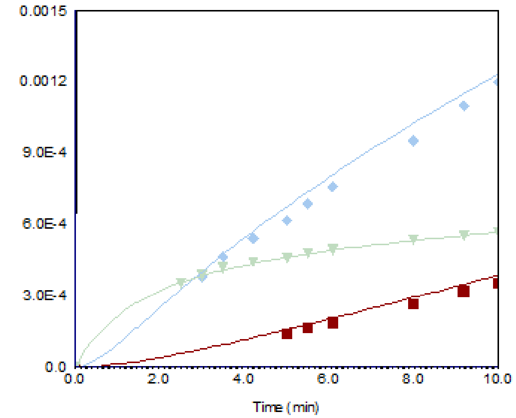
Mechanism definition & Parameter regression

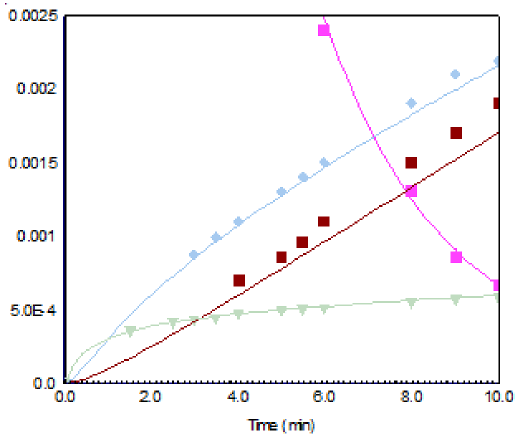
DATA

Kinetic orientated exps
- Calorimetry
- Concentration time course at various temperature, concentration, mixing time

Specific model decoupled from the flow sheet only for parameter estimation







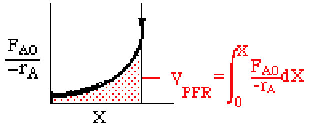
Process Assessment and Selection

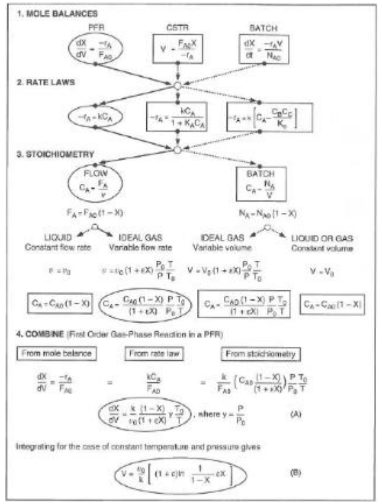
Kinetic of the reaction

Batch operation

$$t_1 = \int_{N_{A1}}^{N_{A0}} \frac{dN_A}{-r_A V}$$

Continuous Operation



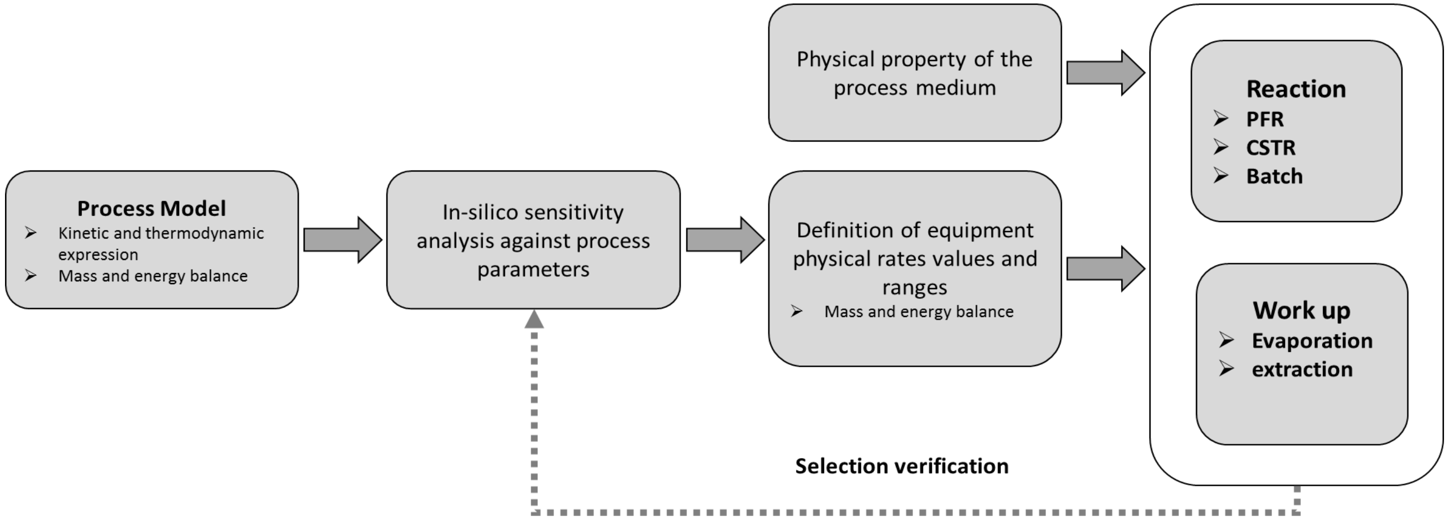


Reaction / Operation

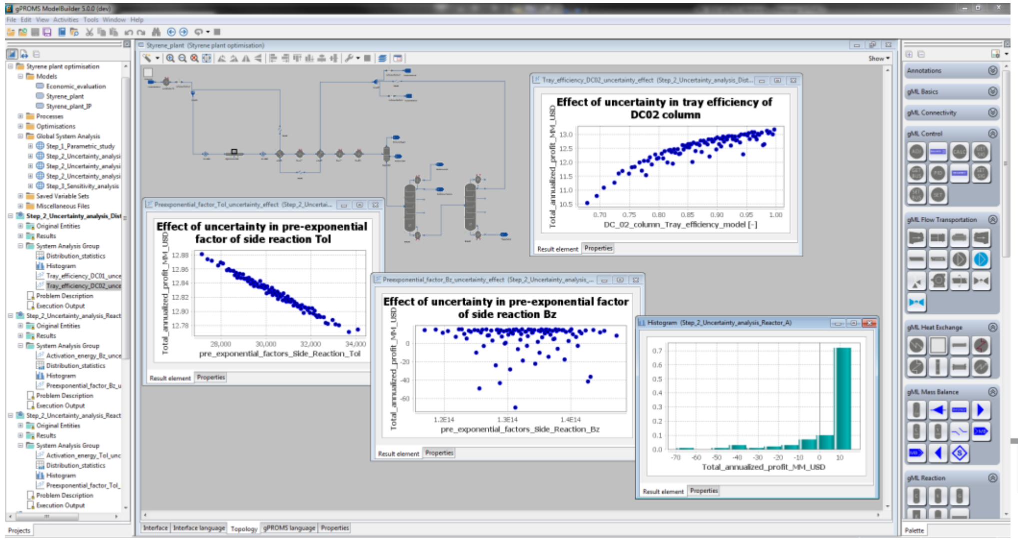
time, yield, impurity

Global Systems Analysis

CPP identification



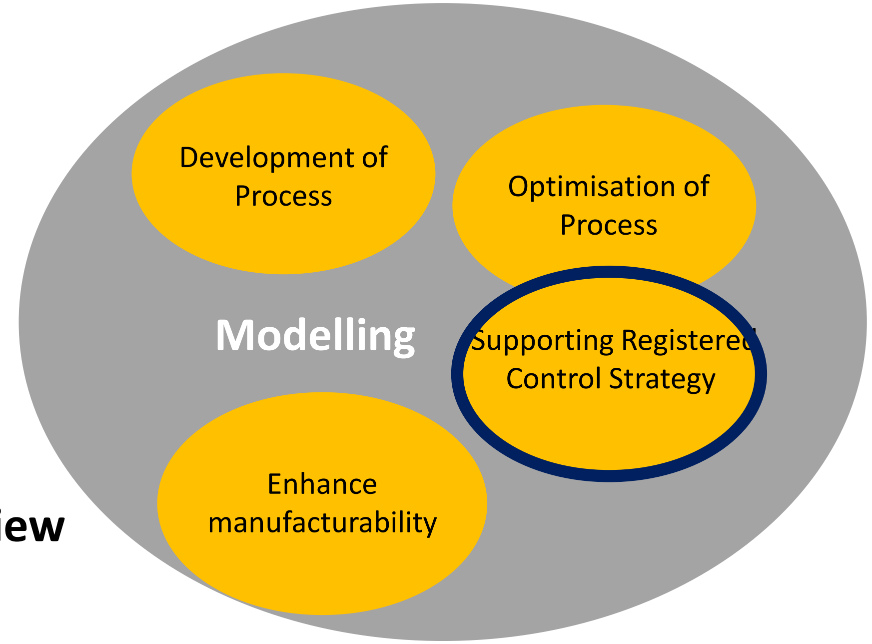
"Global systems analysis (GSA) allows the comprehensive exploration of the behaviour of a system over domains of any user-selected subset of its input variables ('factors'), and output variables ('responses')"



Modelling to Support the Registered Control Strategy

Model is used to

- Justify criticality of CPPs against CQAs
- Provide understanding of multivariate Interactions on individual unit operation and across the entire process
- Identify Established Conditions (Q12)
- Justify process ranges / Design Space
- Support scalability and tech. transfer

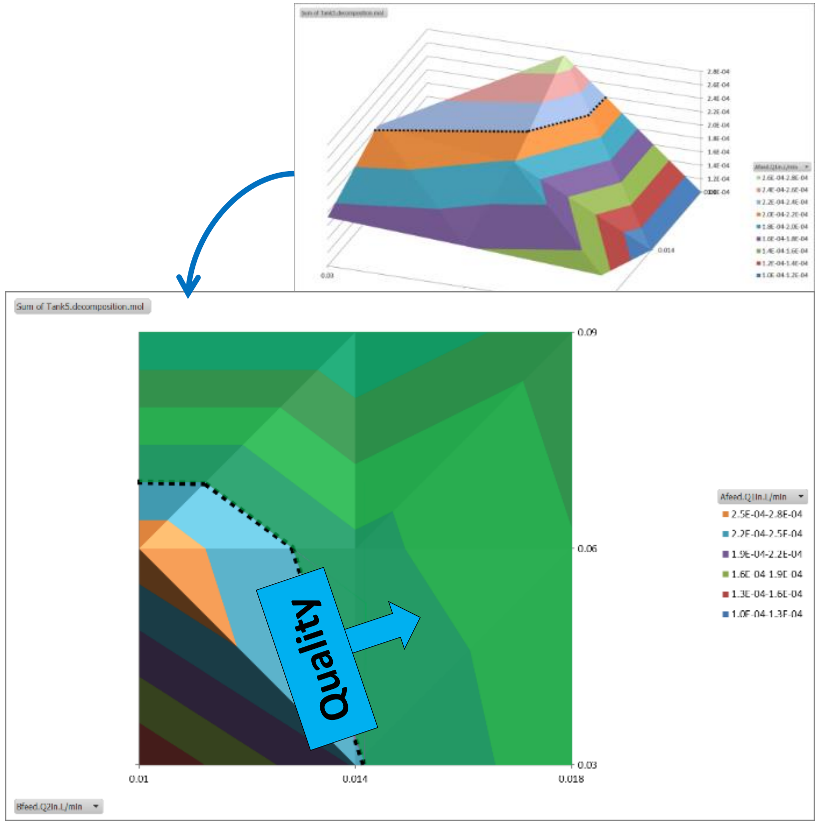


This forms part of the Control Strategy Intent and Experimental Plan review

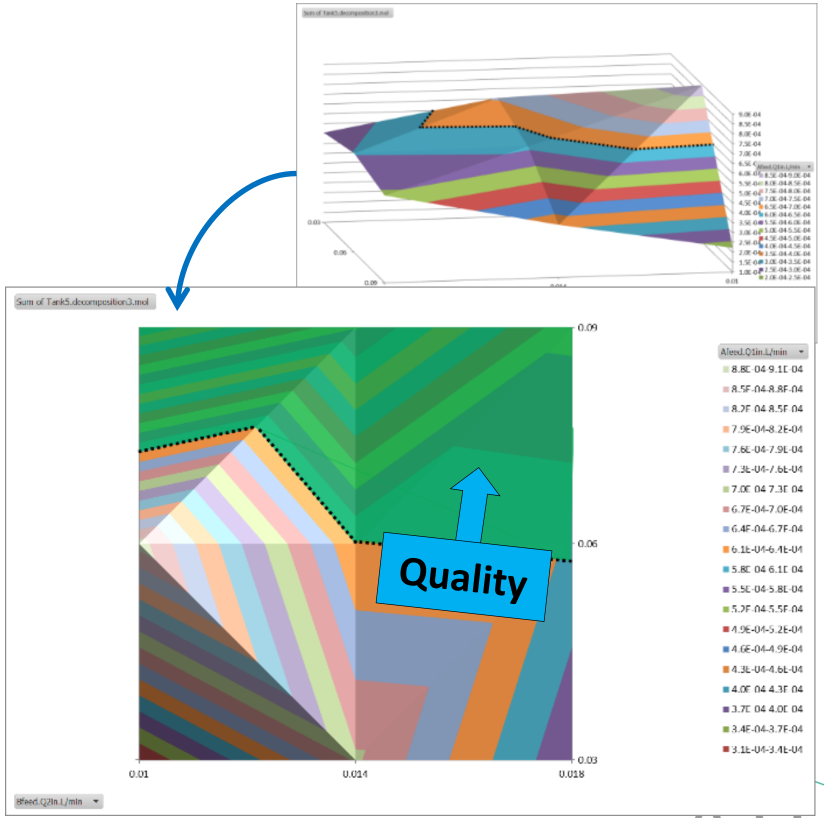
Design space and Operating Conditions

CQAs have been identified and process simulation is used to assess CPP sensitivity and impact on the process

CQA #1 below acceptance level

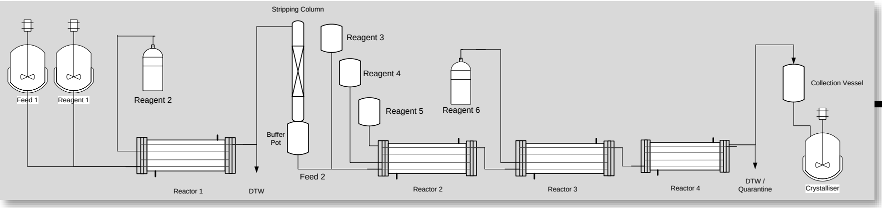


CQA #2 below acceptance level



Modelling Architecture Background

- Properties / composition
- Transport phenomena
- Kinetic model



HPLC online
16 process sensors

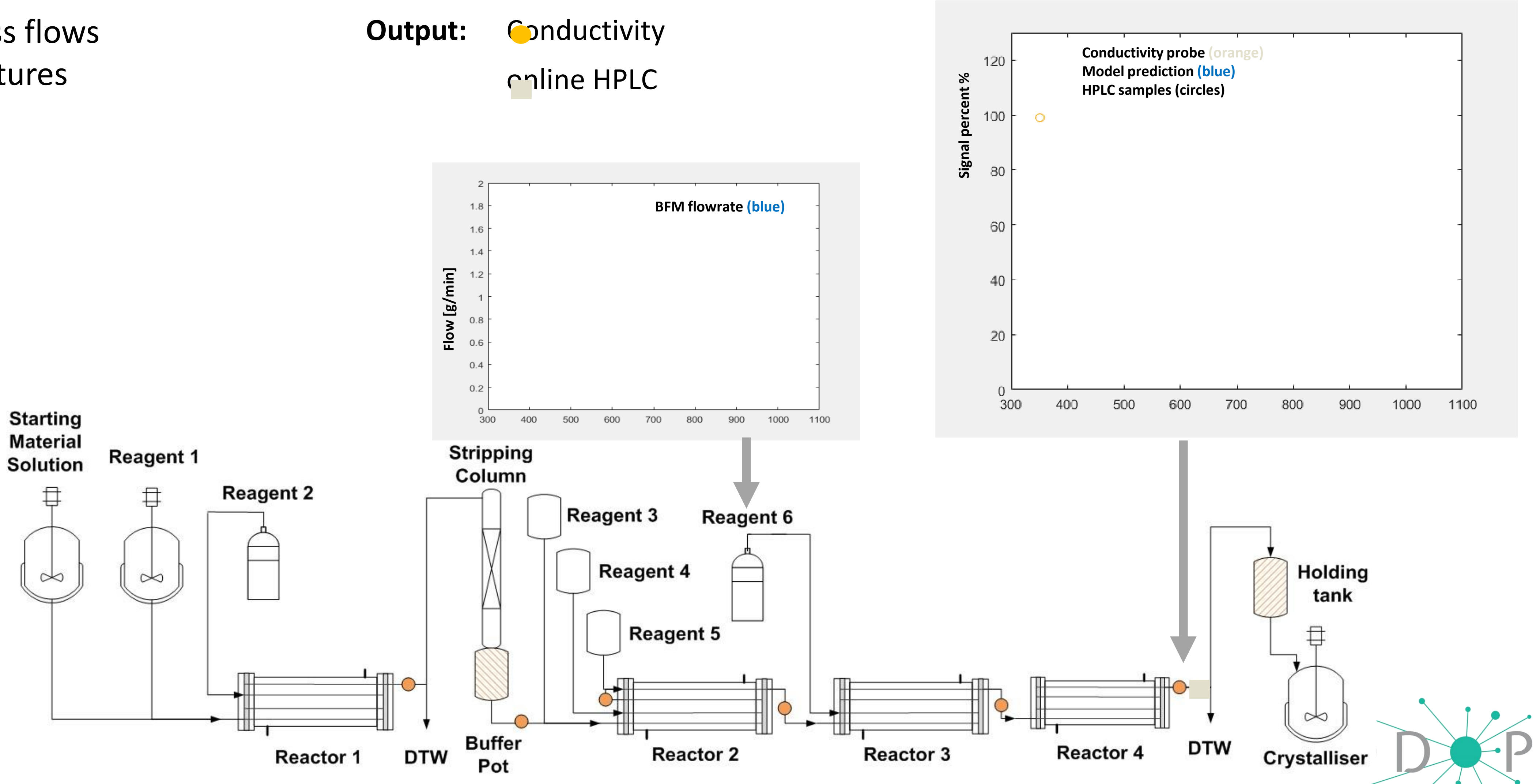
SiPAT

<u>LIVE PRODUCT QUALITY PREDICTION</u>

Model Implementation in Manufacturing Environment

Input: mass flows
temperatures

Output: Conductivity
online HPLC



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Conclusion

System Modeling Benefits Realized

- ❑ Replace experimentation during Process Design ✓
- ❑ Reduce rework during Process Design ✓
- ❑ **Use to identify CPPs and PARs/Design Space** ✓
- ❑ **Reduce plant Verification / Robustness runs** ✓
- ❑ **Increase process understanding** ✓
- ❑ Streamline Risk Assessment
- ❑ Use for advanced controls

Successful use of System Modeling

ADDOPT

THANKS