

Rudi Oliveira¹, Marianna Katz^{1,2}, Ana Cruz³, Filipe Ataíde¹, Carlos Afonso², Nuno Matos¹

1: Continuous Manufacturing R&D, Hovione FarmaCiencia SA, Sete Casas, 2674-506 Loures, Portugal

2: Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal

3: Process Chemistry Development R&D, Hovione FarmaCiencia SA, Sete Casas, 2674-506 Loures, Portugal

Introduction

Hovione builds upon its long experience in process chemistry development by incorporating new technologies and tools that are more efficient and provide economic and environmental benefits. Statistical and mechanistic approaches are current standards in batch process development at Hovione. Herein we present the use of the same approaches but in continuous manufacturing projects with the aim to gain deeper process understanding in a shorter development time.

Systematic workflow with gate reviews



Idea screening

Technical evaluation

Development

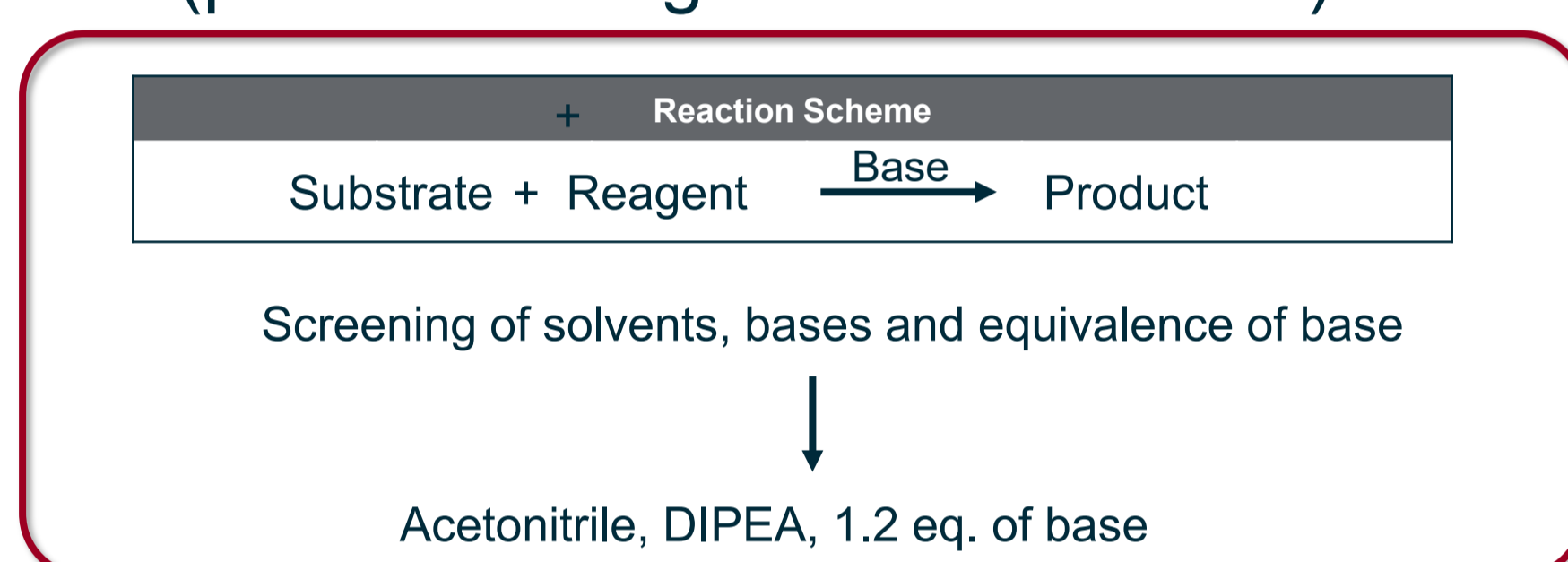
Identify drivers & objectives



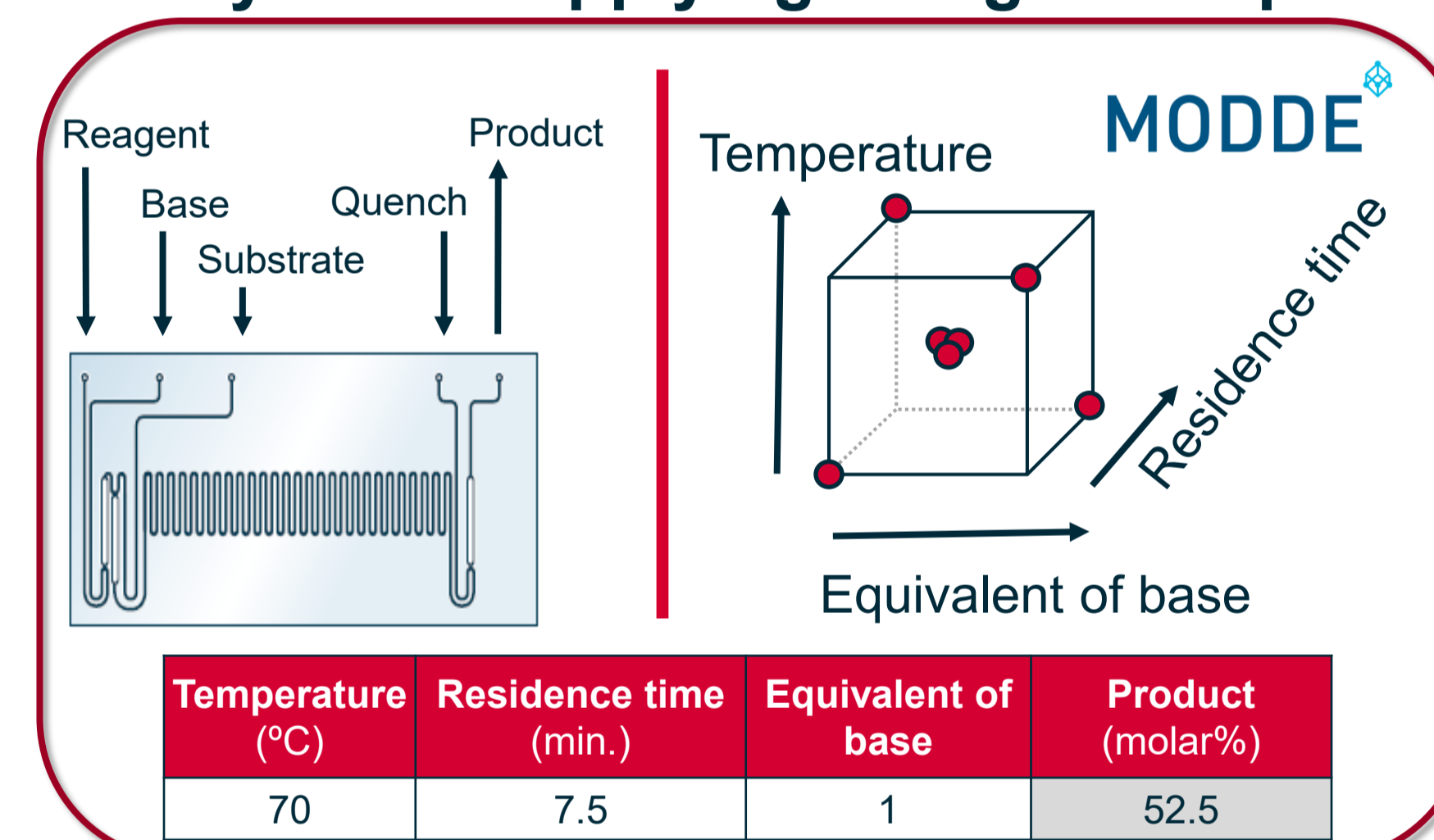
Identify constraints & risks
Select appropriate equipment

Statistical Approach

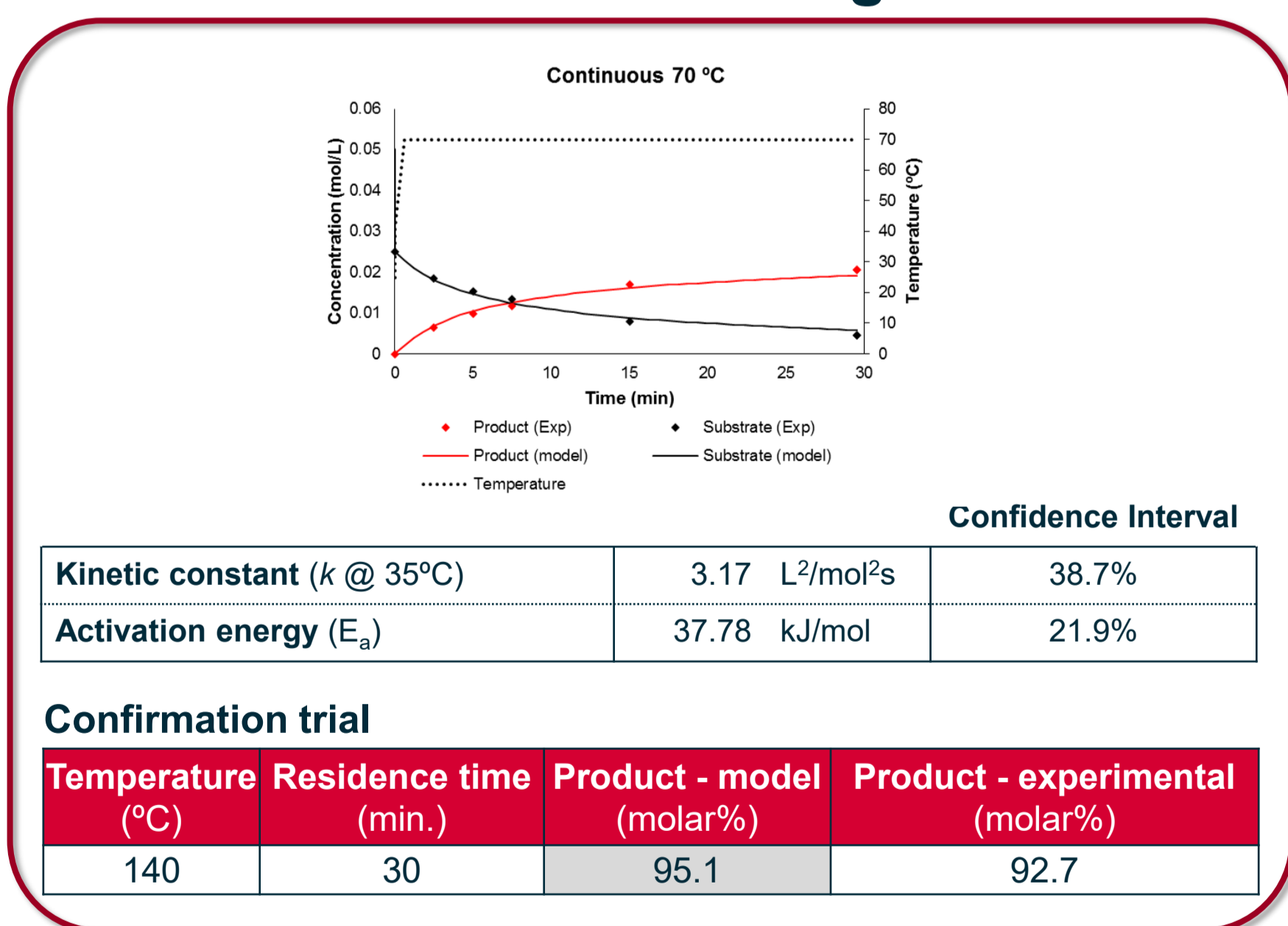
Feasibility study in batch
(predict starting conditions in flow)



Feasibility in flow applying Design of Experiments



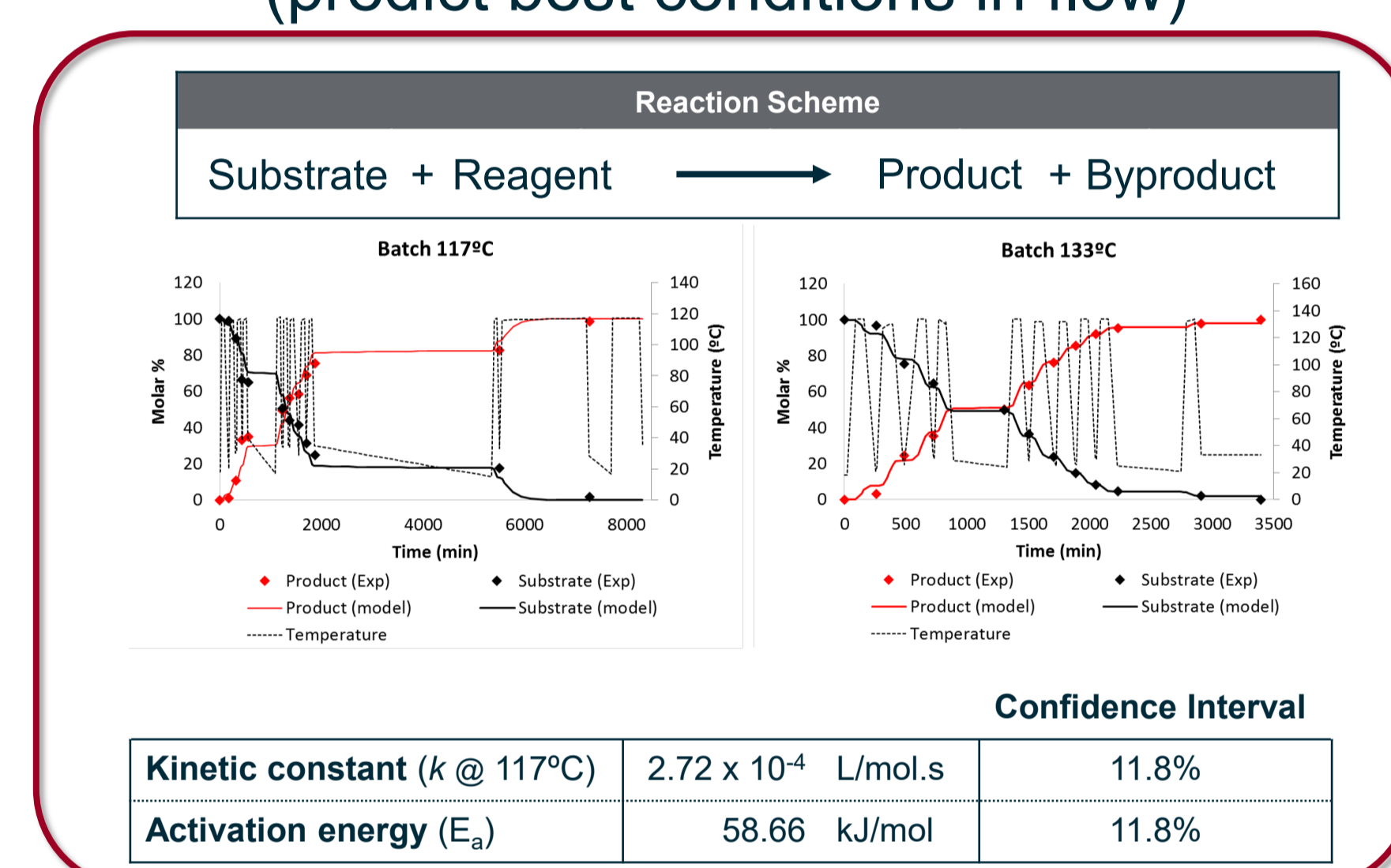
Build kinetic model using flow data



Process Drivers					
Safety	Efficiency	Quality	Environmental Impact	Time to market	Costs
Main features					
High efficiency in mass transfer		High efficiency in heat transfer		High control over processes extent by flow rate or reactor length	

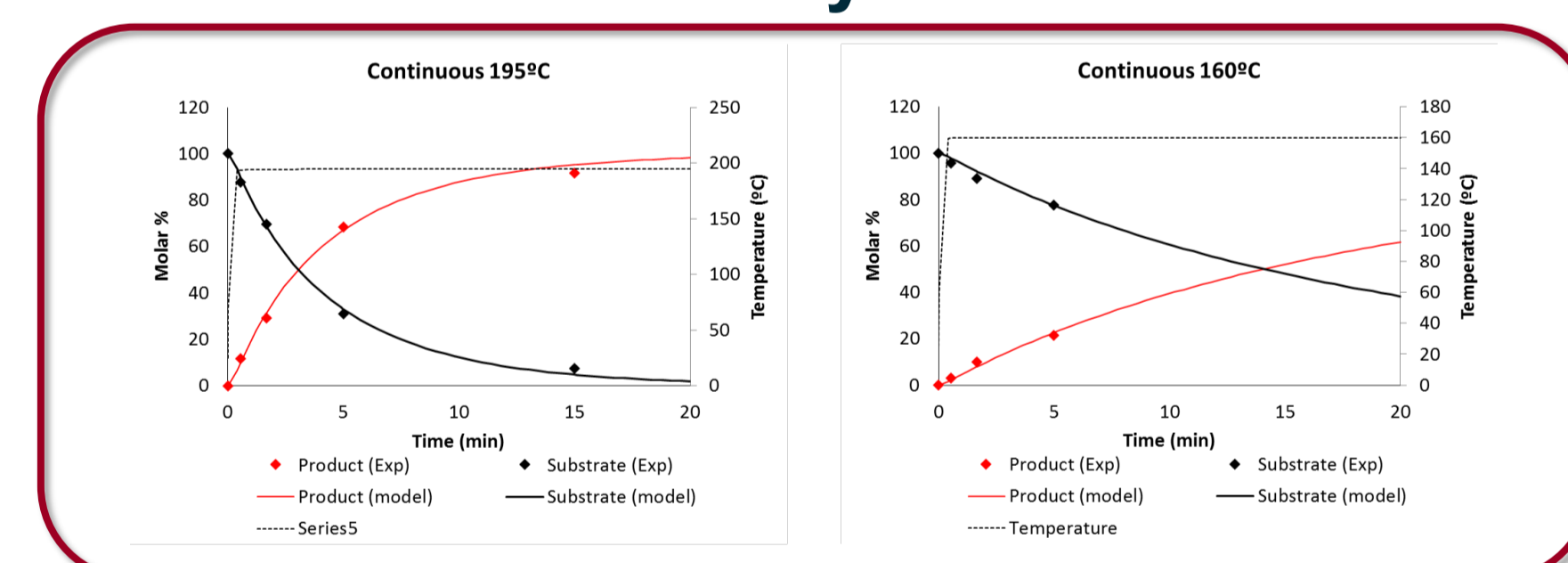
Mechanistic Approach

Build kinetic model using available batch data
(predict best conditions in flow)



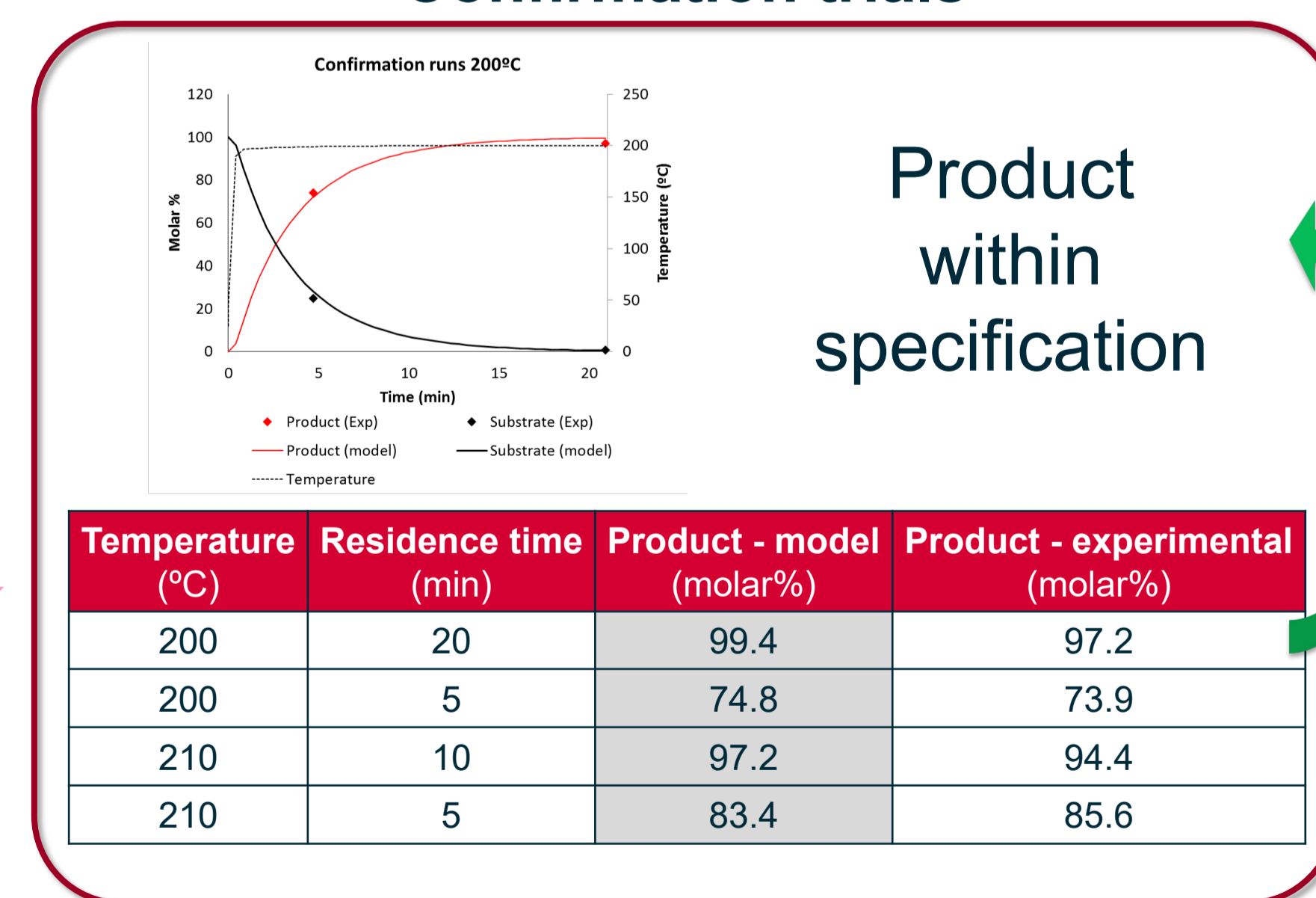
Step 1

Feasibility in flow



Step 2

Confirmation trials



Step 3

PROCESS UNDERSTANDING
SHORT DEVELOPMENT PERIOD
STRAIGHTFORWARD SCALE-UP

Conclusion

Quality by Design development of continuous processes is possible using statistical or mechanistic approaches, just like in batch processes.

We performed feasibility and kinetic experiments in a short period of time using small amounts of material, building deep process understanding in the initial phase of development. The results gathered will be used to compare statistical and mechanistic approaches by quantifying their benefits in order to establish the most advantageous route to process development and understanding.

