Formulation 4.0 - Digitalisation for formulated product design and manufacture

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RSC, London, 13 December 2018

Overview

- Process Systems Enterprise (PSE) and Formulated Products
- Digitalisation, Digital Manufacture, Digital Design, Digital Operation, Digital Twins
- Digital Design and Digital Operation of Drug Products and their Manufacturing Processes
  - Virtual DoEs: A rethink of QbD
  - Case studies
- ADDoPT project
- In conclusion

Process Systems Enterprise (PSE)

PSE HISTORY: FROM RESEARCH TO INDUSTRY

1989 – 1997

Imperial College London

Centre for Process Systems Engineering

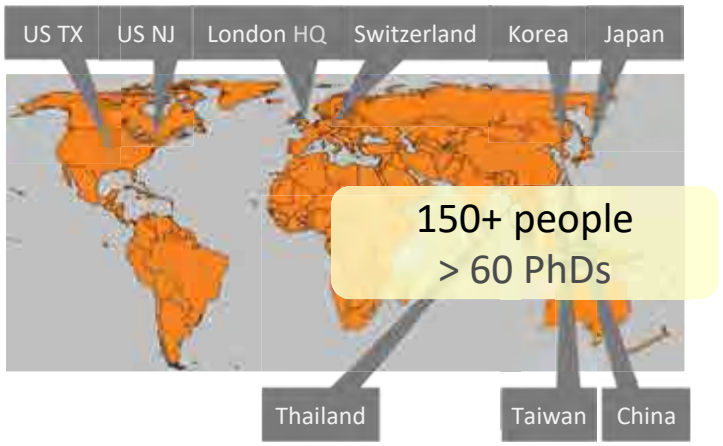
Simulation & modelling, optimisation, numerical solutions techniques, supply chain

1997

PSE gPROMS

Company 'spun out'
Acquires technology
Private, independent company incorporated in UK

Now



Advanced Process Modelling

Software, services and solutions
Process industry focus
Strong R&D

MISSION

"define, develop and drive the adoption of next-generation modelling technology, methodologies and workflows throughout the process industries"

gPROMS

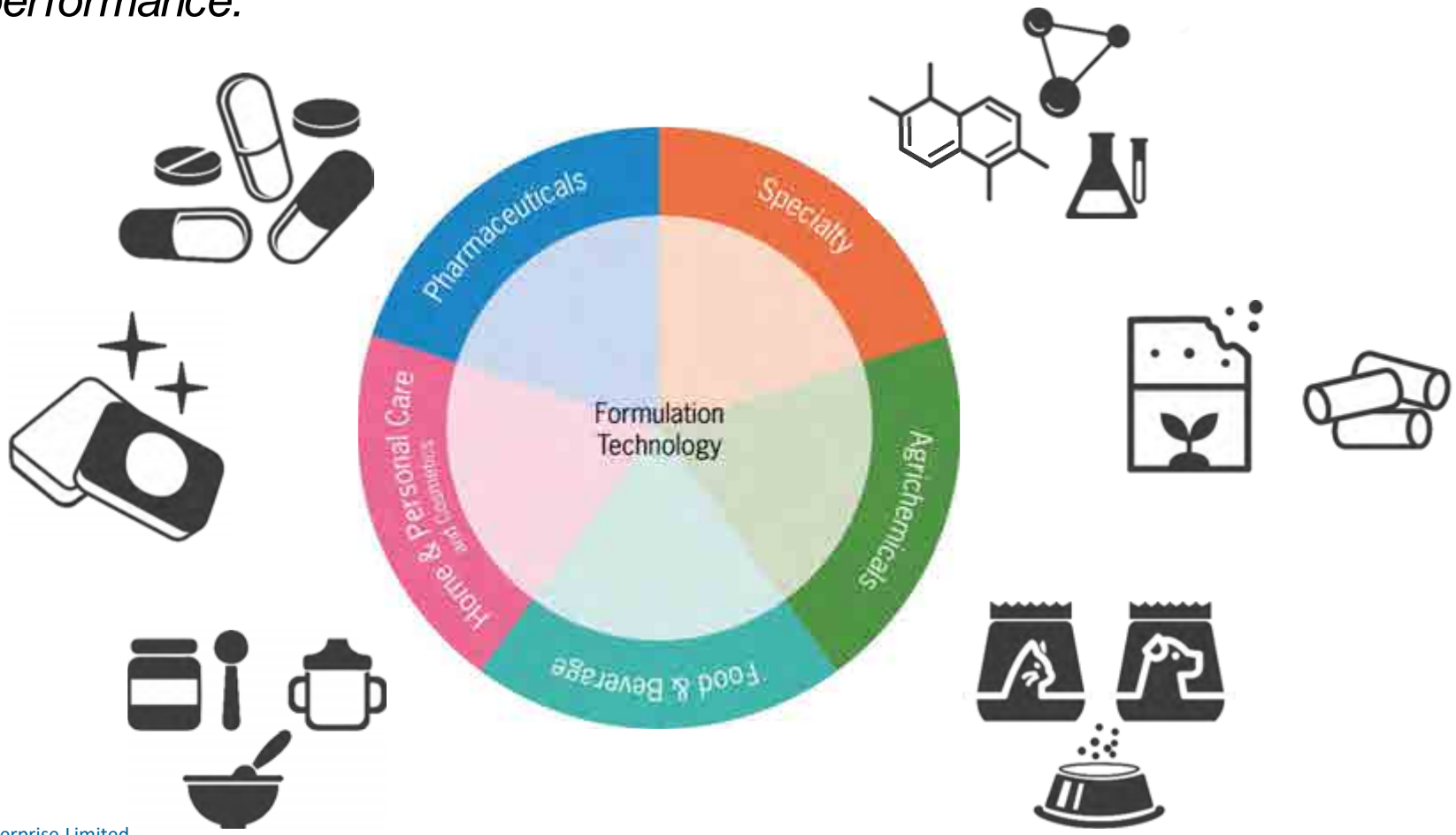
Advanced Process Modelling® technology

PSE Formulated Products

Mission & Industries

Mission

"Enable formulated products and their manufacturing processes to be optimally designed and operated with fewer resources, reduced risk and for better end-use performance."



PSE Formulated Products

A diverse user base

Digitalisation, Digital Manufacture, Digital Design, Digital Operation, Digital Twins, etc.

In the context of PSE's existing and evolving mechanistic models for drug products and their manufacturing processes

Digitalisation …

… is the use of digital technologies
to change a business model
and provide new revenue and value-producing opportunities;
it is the process of moving to a digital business

https://www.gartner.com/it-glossary/digitalization/

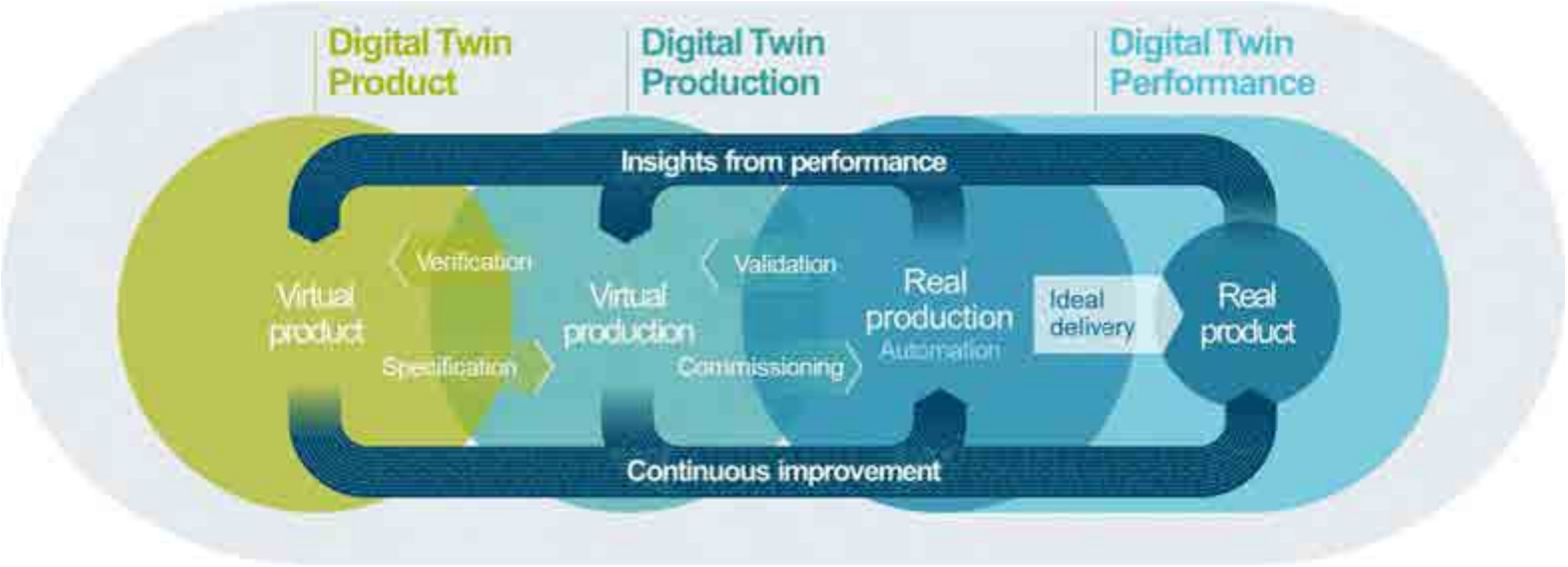
… is *not* the process of converting information
from a physical format into a digital one

https://workingmouse.com.au/innovation/digitisation-digitalisation-digital-transformation

Digital manufacture (Industry 4.0) …

… is the use of an integrated, computer-based system comprised of simulation, 3D visualization, analytics and collaboration tools to create product and manufacturing process definitions simultaneously

https://www.plm.automation.siemens.com/global/en/our-story/glossary/digital-manufacturing/13157



https://www.siemens.com/press/pool/de/events/2018/digitalfactory/2018-04-hannovermesse/presentation-press-conference-prior-to-hm18-e.pdf

Digital manufacture (Industry 4.0) …

A practical definition (Pantelides, APMF 2018, London)

Exploitation of a set of IT technologies

Data	Computation	Algorithms
▪ Bigger volume	▪ More power	▪ Machine Learning
▪ Wider range	▪ Lower cost	▪ Artificial Intelligence
▪ Higher quality	▪ Lower threshold	▪ Meta-modelling
▪ More accessible		▪ Data Mining
		▪ …….

…that have matured over the last couple of decades

…to the point where they can now usefully be applied to practical problems

Digital Design and Digital Operation

Modelling as a central evolving knowledge repository across product & process lifecycle

R&D

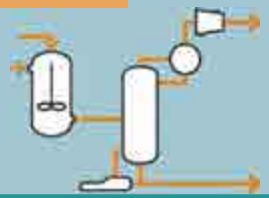
Engineering Design

Operations

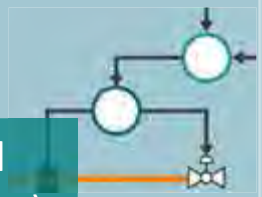
Digital Design

Digital Operation

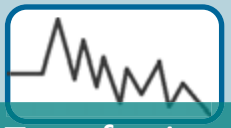
Data analysis, experiment design



Front-end engineering design (FEED)



Control design & verification



Troubleshooting

Model-based automation

Catalyst design and analysis

Detailed equipment design

Process optimisation

Design of operating policy

A single, evolving mechanistic model is used throughout R&D and Engineering (Tech Transfer).

Modelling is augmented by targeted small scale experiments (physical properties, material properties and kinetics) to configure and calibrate the model.

Any large scale experimentation is used for blind testing and model refinement.

Transferring knowledge captured in mechanistic models developed and calibrated in R&D and Engineering to Operations for better monitoring and control solutions that are also less costly to develop and maintain

Impact of Digitalisation

1. Perform *individual* tasks better, faster, cheaper
2. *Combine* tasks ➔ better solutions, fewer iterations

Digital Design and Digital Operation of Drug Products and their Manufacturing Processes

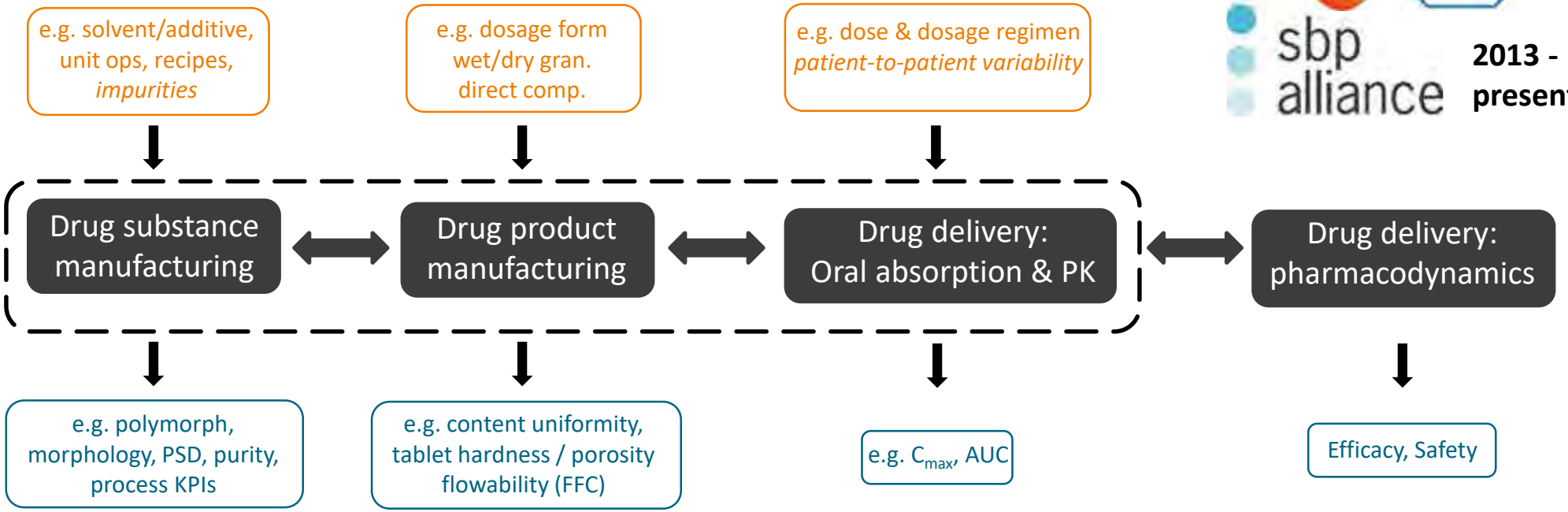
Tools and methodologies used in following cases are applicable to a wide range of formulated products

PSE's vision for the life sciences industries

Systems-based Pharmaceutics

Enable formulated products and their manufacturing processes to be optimally designed and operated with fewer resources, reduced risk and for better end-use performance

through the rapid configuration, calibration and deployment of mechanistic models using systems approaches

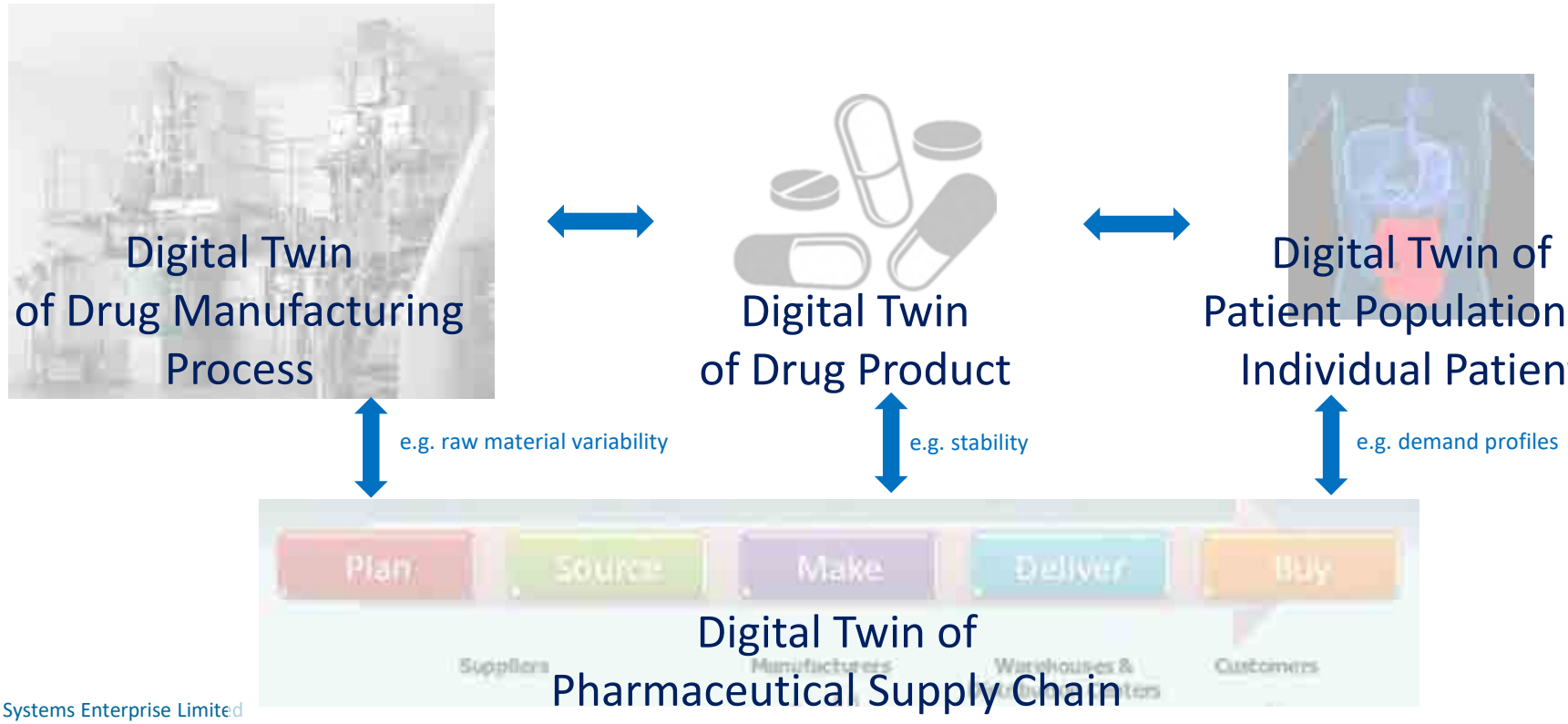


PSE's vision for the life sciences industries

In the context of *Digitalisation*

Enable drug products and their manufacturing processes to be optimally designed and operated with fewer resources, reduced risk and for better end-use performance

through the rapid configuration, calibration and deployment of *digital twins based on predictive sciences and data analytics*



Digital Design (and Digital Operation)

Vision as summarised by Ian McCubbin (MMIP chair) when ADDoPT proposal was submitted and approved for funding

www.abpi.org.uk/our-work/news/2017/Pages/Handing-over-the-helm-of-MMIP.aspx#

- UK EU Life Sciences Transition Programme
- Industrial Strategy
- ABPi blogs
- 2017
- 2016
- 2015
- 2014
- 2013
- 2012
- 2011
- Cancer Drugs Fund (CDF)
- Careers in the pharmaceutical industry
- Commercial
- Disclosure UK
- Falsified Medicines Directive (FMD)
- International Women's Day
- Resources for schools
- Strategy

Posted in category Opinion by Medicines Manufacturing Industry Partnership on 15/02/2017

Handing over the helm of MMIP

Ian McCubbin, Chair of the Medicines Manufacturing Industry Partnership, is stepping down from the role and reflects on the work achieved by MMIP over the past two years.

After two years of chairing the Medicines Manufacturing Industry Partnership (MMIP) I am now in the process of handing over to Andy Evans, the Head of AstraZeneca's manufacturing site in Macclesfield. Andy has already thrown himself into the role during what is a very interesting time, for two main reasons.

Firstly, MMIP has really established credibility in the medicines manufacturing community, and with Government and associated organisations. In many ways I know that MMIP is seen as a role model for how we should work with government in the Life Sciences sector. It is also very timely following the vote to leave the EU and as Government starts to design the Industrial Strategy and the Life Sciences Industrial Strategy within that.

As I reflect on our contribution, it's clear we have progressed significantly with a number of important topics, not least the Advanced Therapy Manufacturing Taskforce (ATMT)

environment. ADDoPT is the Advanced Digital Design of Pharmaceutical Therapeutics, it creates virtual medicine manufacturing systems to make sure they are effective and efficient before creating them in the real world.

and ultimately commercialisation and the sector's contribution to the UK economy. The Medicines Manufacturing Innovation Centre will provide an open-access hub where medicines manufacturing stakeholders can collaborate, research and pull through emerging technologies and manufacturing processes into a commercial manufacturing environment. ADDoPT is the Advanced Digital Design of Pharmaceutical Therapeutics, it creates virtual medicine manufacturing systems to make sure they are effective and efficient before creating them in the real world.

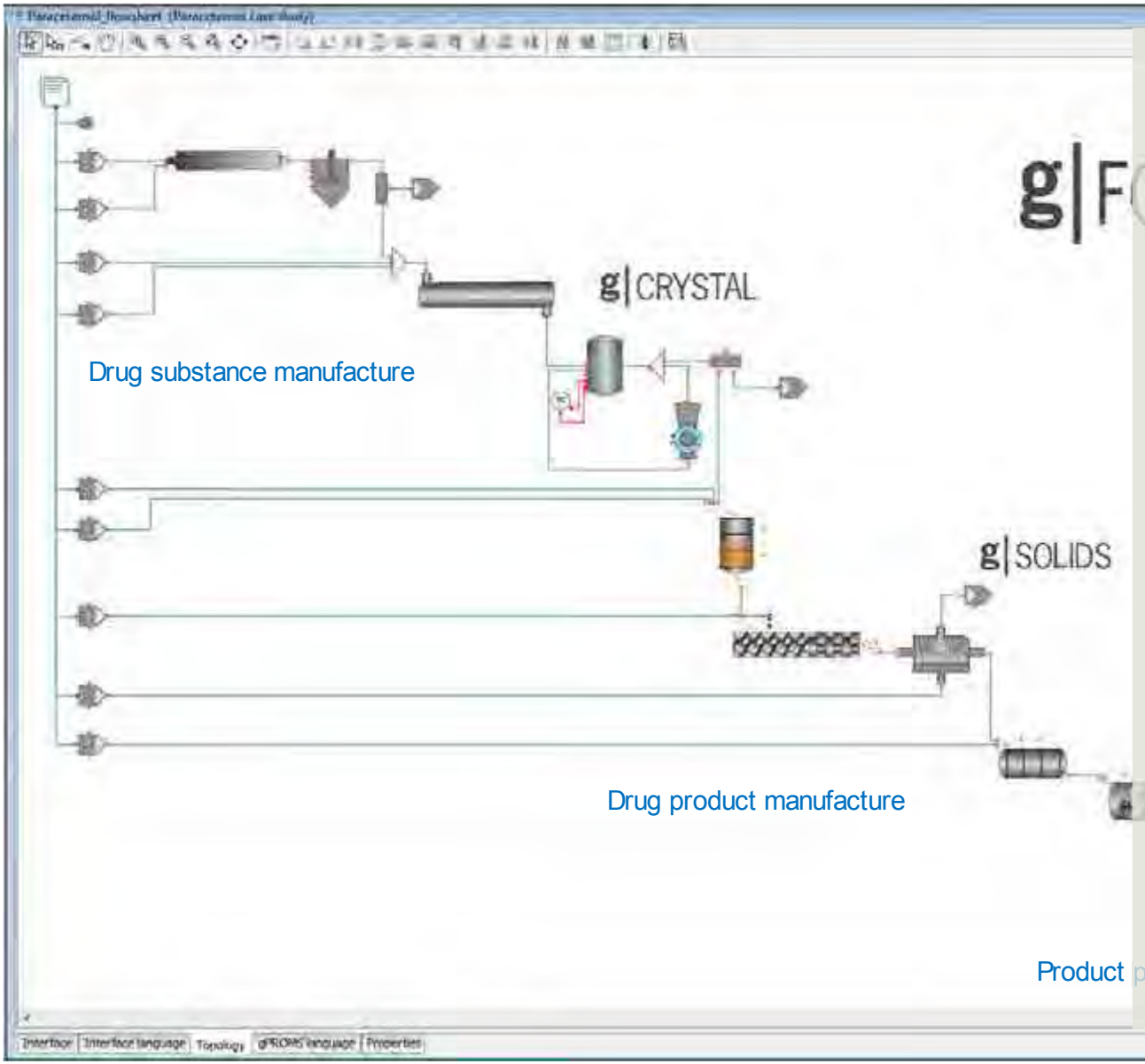
With the support of The Association of the British Pharmaceutical Industry, BioIndustry Association, Innovate UK Knowledge Transfer Network and of course all the companies who have committed their valuable time and energy, MMIP has been able to create momentum at exactly the right time. Some may say luck, but to paraphrase Gary Player,

ADDOPT

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

2015 – 2019

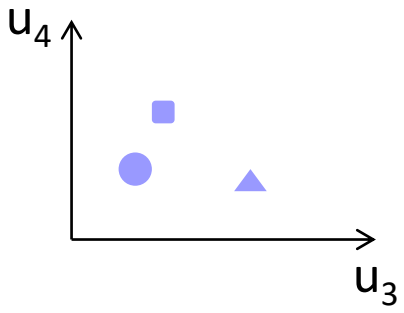
Digital Twins for Integrated Design and Optimisation of Drug Products and their Manufacturing Processes



- **Mechanistic** unit operation models
- Typically **calibrated** on a per unit operation basis
- Calibrated unit operation models can be used to construct **integrated system / flowsheet models**
- Calibrated unit op and flowsheet models can be used for
  - **Optimal** design and operation
  - Sensitivity analysis to identify and mitigate **robustness** issues
  - Monitoring (e.g. **soft sensing**) and advanced control applications (e.g. **MPC**)

Digital Twin based DoEs for comprehensive robustness approach

What we currently do: point calculations

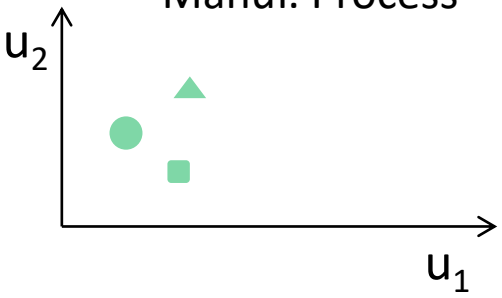


Environmental inputs

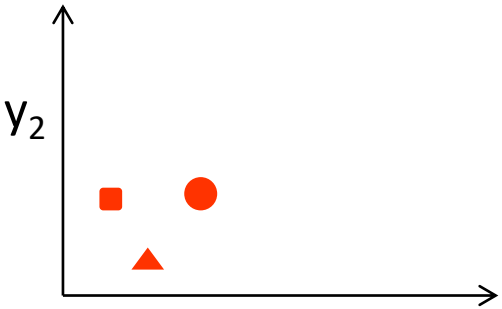
- Raw material variability (API & excipients)
- Patient-to-patient variability

Decisions / Parameters

- Formulation
- Device
- Manuf. Process



Calibrated science-based Digital Twin

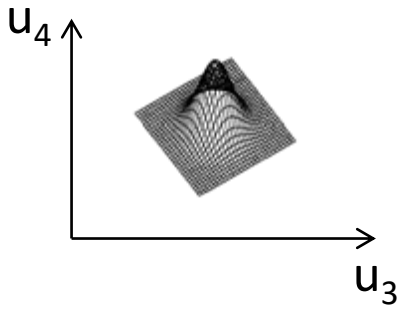


KPIs

- Bioavailability (e.g. Cmax, AUC)
- Manufacturability (e.g. FFC, CU)
- Yield
- Safety, Environmental
- Economic performance

Digital Twin based DoEs for comprehensive robustness approach

What we are really looking for: global system behaviour



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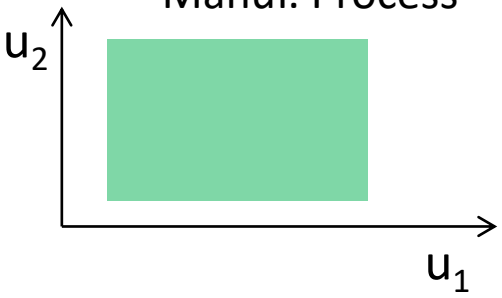
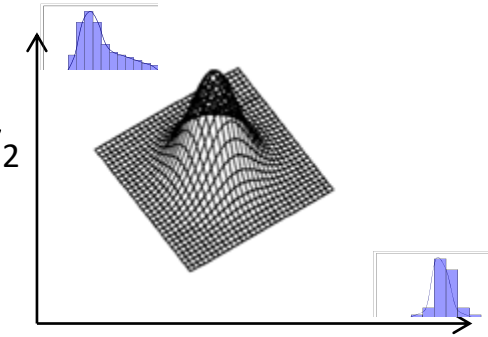


Calibrated science-based Digital Twin



KPIs

- Bioavailability (e.g. Cmax, AUC)
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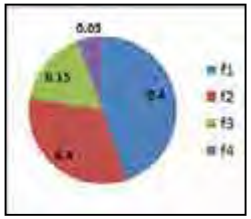
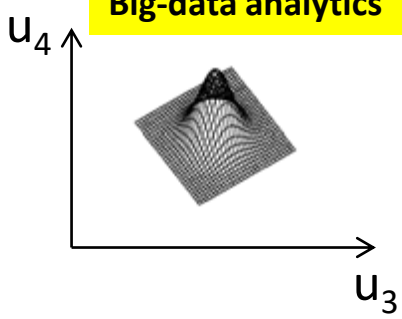


Global sensitivity indices of output response(s) with respect to input factors

Digital Twin based DoEs for comprehensive robustness approach

Determine combination of parameters that has minimal/acceptable sensitivity to variability

Big-data analytics



Environmental inputs

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Decisions / Parameters

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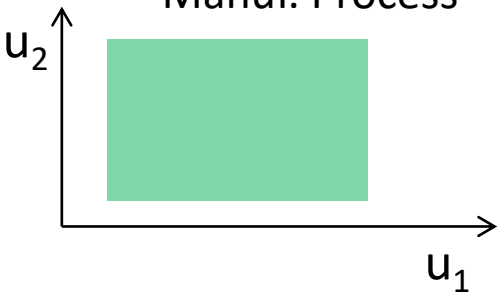
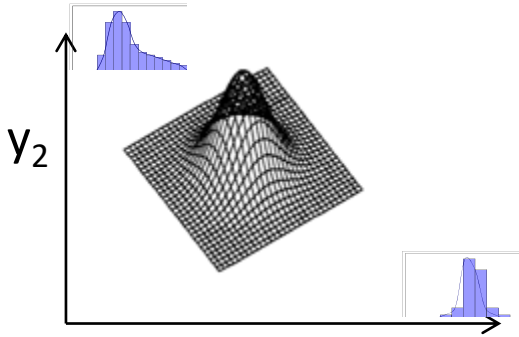


Calibrated science-based Digital Twin

High-performance computing

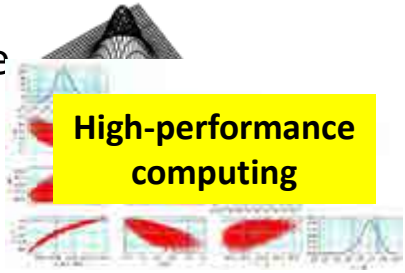


KPIs

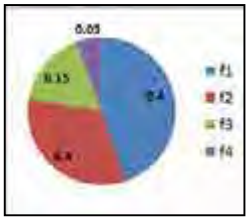
- Bioavailability (e.g. Cmax, AUC)
- Manufacturability (e.g. FFC, CU)
- Yield
- Safety, Environmental
- Economic performance

Virtual System Assurance

- Measurement variance
- Sampling variance
- Model parameters
- Model structure



High-performance computing

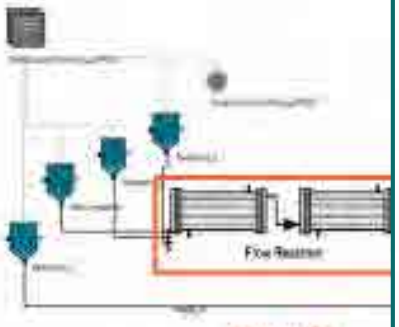


Global sensitivity indices of output response(s) with respect to input factors

Drug synthesis – Continuous

gPROMS Flowsheet – What Users See

Stages 2a - 2c

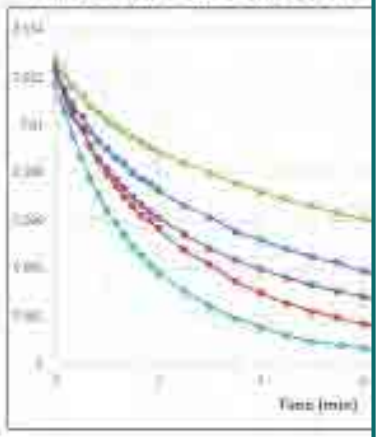


Stage 2a
Library model

Stage 2b Kinetic Model Development

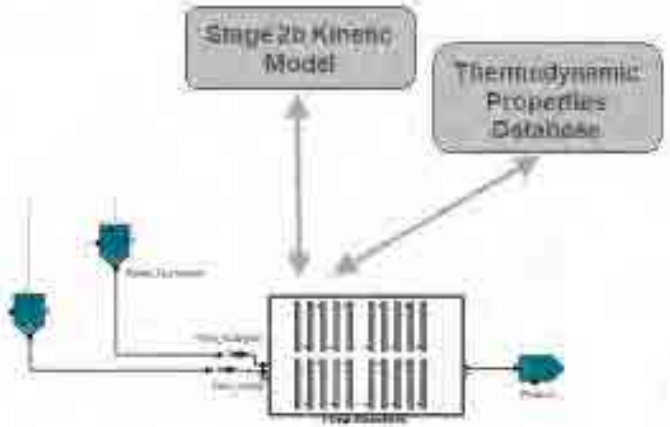
Single Phase (Dilute) Exp

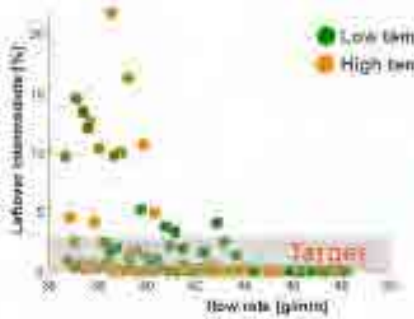
Varied temperature and reactan

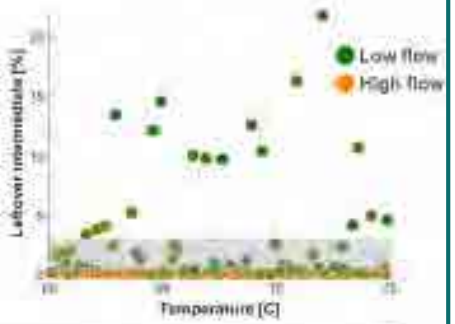


Stage 2b Sensitivity Analysis

Intermediate attributes vs process parameters







Process inputs:
All Stage 2a inputs
Reactant flowrate
Reactant concentration
Reactor temperature

Sensitivity indices (rank):
Reactant flowrate (0.33)
Reactant molarity (0.1850)
Reactant 2 temperature (0)
Stage 2a inputs (0)

Digital Twin based DoE applications

Drug synthesis – Batch

gPROMS Formulated Products

Enabling understanding of interoperable batch processes through digital design

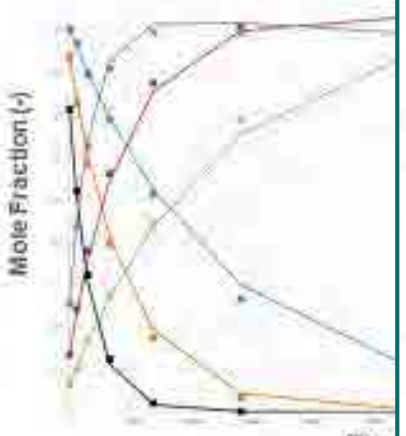
- Enabler for the modelling
  drug synthesis processe
- Multiple unit operation ty
  are available
- Enable modelling of vari
  phenomena, with an opti
  include custom expressi
- Models can be used in b
  and continuous mode, fo
  - Parameter estimatio
    (validating experime
  - Sensitivity analysis
  - Optimisation
  - Scheduling of
    interoperable flowsh
    (see opposite)

Reaction

Kinetic study

Reaction Kinetics Scheme

Example of effect of tempe
reactant conversion and m
product formation



GSA: Sensitivity analysis applied to reaction model

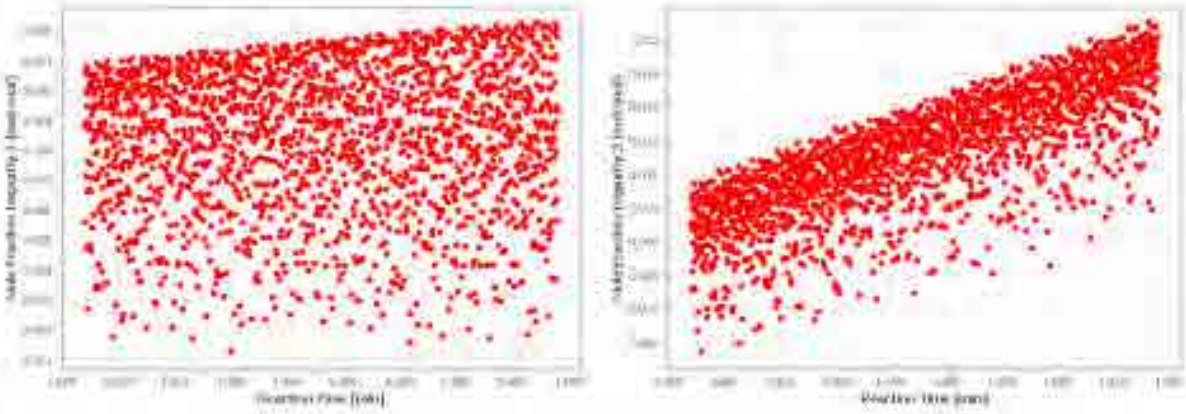
Impact of reaction time on impurity formation

Input changed:

Reaction time

Response:

(left) Mole fraction impurity 1 formed
(right) Mole fraction impurity 2 formed

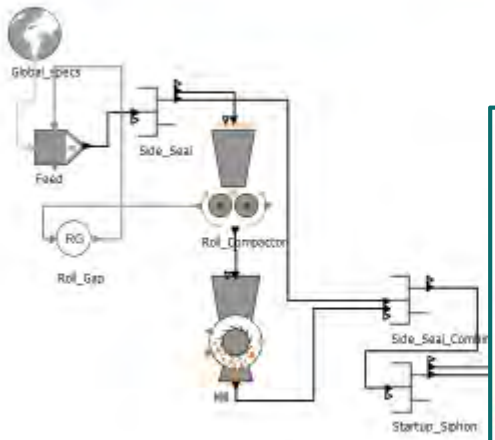


Greater sensitivity seen for the effect of reaction time on impurity 2 production – suggesting to limit the reaction time

Digital Twin based DoE applications

Drug product manufacture

gSOLIDS implementation



'Virtual Experimental Design': Factors to investigate

FACTORS

Roller Compactor
- Roll Force
- Roll Gap
- Side Seal Leakage

Mill
- Screen Size

Lubrication

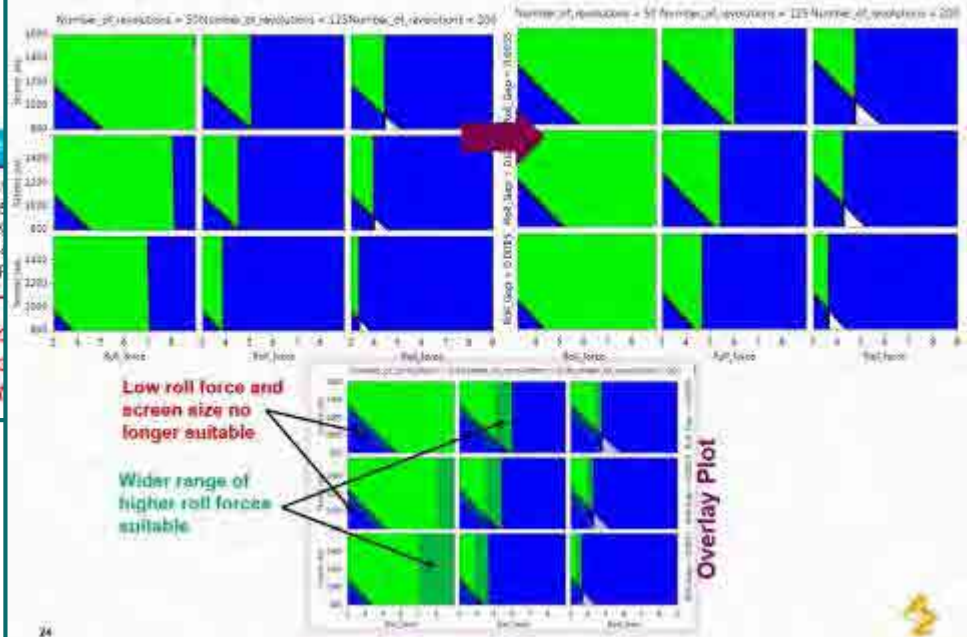
Tablet Press

RESPONSES

Ribbon
- Porosity

The results presented in the fo
over 3000 automated simulatio
fac

Risk Assessing: Change in grade of excipient

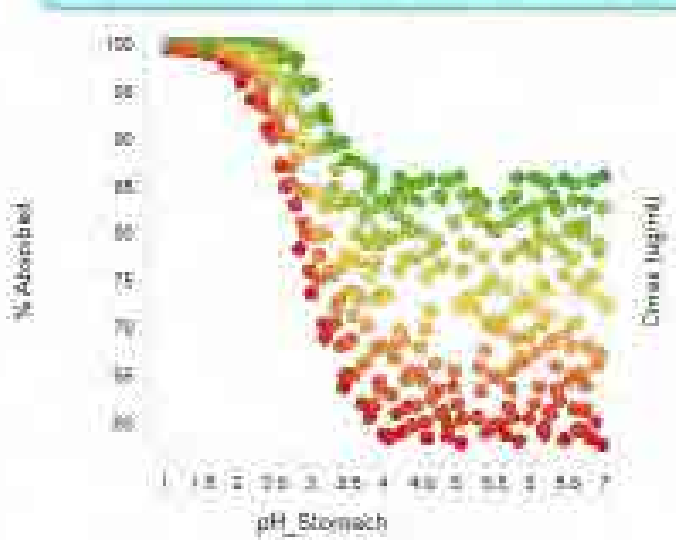


Product performance for OSD

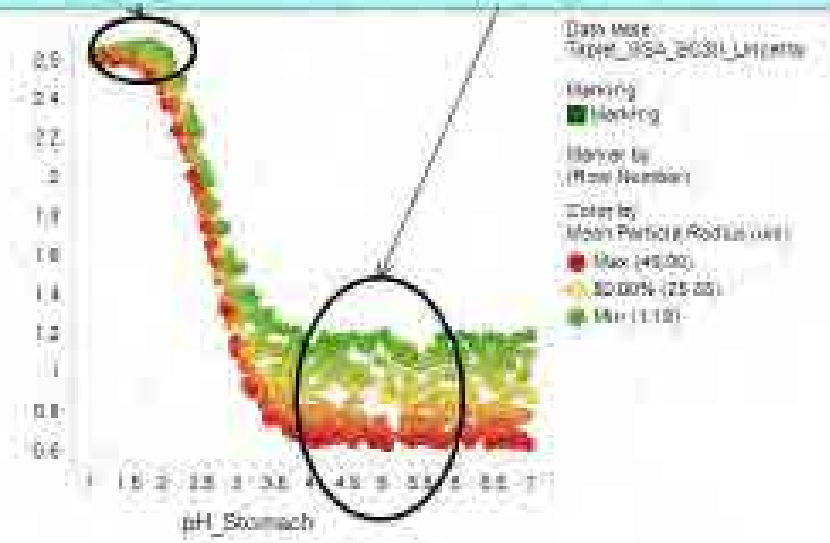
Uncertainty Analysis:
Influence of Particle Size and Gastric pH

API particle size has no impact on tablet performance in healthy volunteers but significant impact on % absorbed in patient population

Use of GSA highlights the need for setting particle size specifications to ensure right exposure / profile obtained in the patient population



% absorbed



C_{max}

WORLDWIDE RESEARCH & DEVELOPMENT

Digital Twin based DoE applications

SbP example: Drug Manufacture and Product Performance

M7077

Solid Drug Product and Process Design using Multi-Scale Interconnected Flowsheet Modelling and Global System Analysis

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[a]Worldwide Research and Development, Pfizer Inc., Sandwich, United Kingdom, [b]Worldwide Research and Development, Pfizer Inc., Groton, CT, US, [c]Process Systems Enterprise Inc., Cedar Knolls, NJ, US

CONTACT INFORMATION: Marta.MorenoBenito@pfizer.com

2017 AAPS ANNUAL MEETING & EXPOSITION

PURPOSE

- Combine mechanistic models of standard unit operations at multiple scales to predict the impact of design decisions on quality attributes.
- Capture all relevant interactions between multiple stages and scales of product and process design.
- Use Global Systems Analysis (GSA) to identify the design space around the process to deliver quality drug product performance.

METHODS

A comprehensive flowsheet (Figure 1) using multi-scale population balance models of unit operations is implemented in gPROMS FormulatedProducts.

A GSA approach evaluates the key performance indicators for a range of values of the input variables to the model of each individual operation (Figure 2). Monte Carlo simulation scenarios are generated, and statistical measures and Sobol indices are calculated to quantify the impact on the model outputs.

To analyse the holistic system, a hierarchical approach (Figure 3) is used. Following the analysis of individual units, the whole system is evaluated simultaneously with a reduced set of factors based on the learnings of the individual investigations.

Figure 3. Methodology for analyzing interconnected flowsheets via GSA

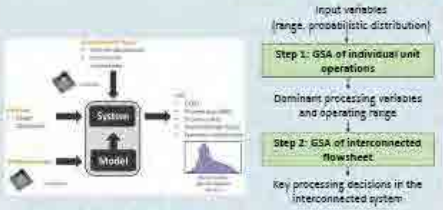


Figure 2: Schematic of GSA approach

RESULTS

Each unit operation is initially calibrated and tested separately or in smaller process trains for verification.

The plots in Figure 4 show the effect of the dominant processing variables on the key product attribute for each unit operation. The dots are coloured according to the secondary conditions. The lines indicate the quality targets.

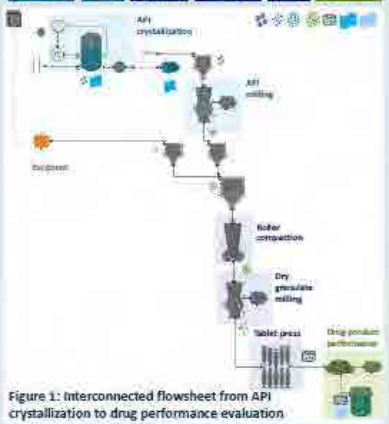
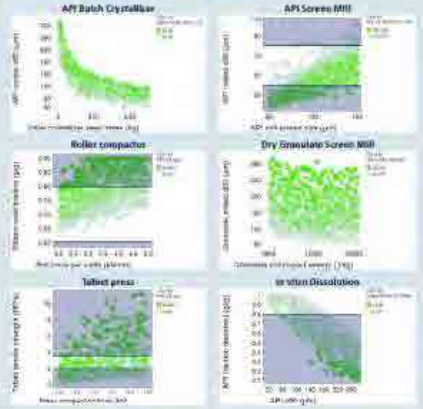


Figure 1: Interconnected flowsheet from API crystallization to drug performance evaluation

Figure 4: GSA results of individual unit operations



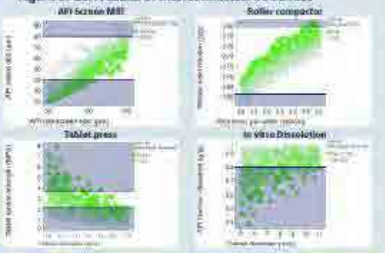
The results of the GSA investigations of individual unit operations gives a qualitative insight into which of the material properties generated in the preceding steps are likely to have the most impact on the complete process and final product properties.

The insights from analyses of the individual unit operations are used along with practical estimates of equipment and material variability to drive the investigation space for the complete process model.

Table 1: Sensitivity indices of interconnected flowsheet

Attributes / Processing decisions	Units	Min	Max	API crystal d50	API milled d50	Ribbon solid fraction	Granulate d50	Tablet tensile strength	API fraction dissolved
Initial crystalliser temp.	°C	30	90	0.197	0.011	0.000	0.000	0.001	0.000
Initial crystalliser seed mass	g	0.1	25	0.195	0.068	0.004	0.000	0.006	0.013
API mill screen size	µm	50	150		0.858	0.021	0.000	0.007	0.214
API mill impact energy	J/kg	2,000	20,000		0.228	0.013	0.000	0.017	0.250
Roll force per width	kN/cm	2	5			0.722	0.000	0.158	0.215
Roller speed	RPM	2	8			0.228	0.000	0.003	0.040
Granulate mill screen size	µm	200	500				1.042	0.000	0.000
Granulate mill impact energy	J/kg	5,000	25,000				0.258	0.000	0.000
Tablet diameter	mm	5	11					0.441	0.345
Press compaction force	kN	2	12					0.430	0.322
Dissolution impeller speed	RPM	10	200						0.014

Figure 5: GSA results of interconnected flowsheet



The Sensitivity Indices (Table 1) quantify the effect of upstream processing decisions on key quality attributes obtained in subsequent drug manufacturing stages.

For instance, API dissolution depends most on tablet diameter, compression force, screen size in API mill and roll force.

By using GSA to analyse the system holistically (Figure 5), a more complete picture of the factors affecting the final product performance and how to achieve the desired design space is gained. Some factors which influence individual unit operations are dissipated as a result of downstream stages.

CONCLUSIONS

- Global Systems Analysis of holistic process models is used to identify the critical process parameters from API crystallization to tablet compaction affecting critical quality attributes and performance of solid drug product.
- The results obtained can help to reduce the time required in product development and improve the quality of medicines through detailed design space exploration, indicating areas of missing knowledge, and identifying critical process parameters affecting quality attributes and performance.
- There is still a need to address some challenges associated with interconnected unit operations. The main challenges are related to linking intermediate variables like material properties obtained in one unit operation, which could affect downstream processes. It is our goal to leverage statistical models and experimental data to fill the remaining gaps in the mechanistic models and material properties of complex phases.
- Using this methodology it may be possible to optimise the process globally and select the most suitable unit operations to satisfy key product attributes and enhance process robustness (Figure 6).

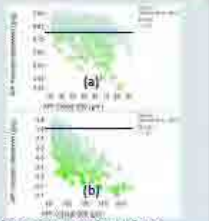


Figure 6: Comparison of GSA prediction with (a) and without (b) API milling after crystallization

ACKNOWLEDGEMENTS

The authors would like to thank Ravi Shanker, Mary am Ende, Martyn Ticehurst, Bob Docherty, and Sean Bermingham and SbP Alliance for Systems-based Pharmaceutics vision, as well as Susan Ewing, Kevin Girard, Bill Ketterhagen, Hugh Verrier for fruitful discussions and Dana Barrasso, David Slade and Maria Fuentes-Gari for their support of gPROMS FormulatedProducts.

ADDoPT

Further development of tools discussed so far

Development of a wide range of complementary digitalisation tools

ADDOPT

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Instigated and supported by

Medicines Manufacturing Industry Partnership

abpi BIA Innovate UK Knowledge Transfer Network

Vision

Creating virtual medicine manufacturing systems to make sure they are effective and efficient before creating them in the real world

Ian McCubbin, MMIP chair 2015-2017

Product and Process Design

Upstream

Materials properties
Surface chemistry
Release profiles
Manufacturing classification
Particle attributes
Processing rules
Quality systems
Formulation

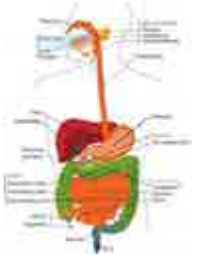
Downstream

Product Performance

batch and continuous

Drug Substance Manufacture - Drug Product Manufacture

API synthesis & solvent recovery → Crystallisation Filtration Washing Drying → Milling Blending Compaction Coating



Processes **Products** **Patients**

Rapid, efficient and effective design and control of manufacturing processes through mechanistic models and data analysis

AstraZeneca · Bristol-Myers Squibb · GSK · Pfizer · PSE · PERCEPTIVE ENGINEERING LTD · UNIVERSITY OF CAMBRIDGE · UNIVERSITY OF LEEDS · University of Strathclyde Glasgow · The Cambridge Crystallographic Data Centre · Hartree Centre

Development of digital design and digital operation tools using

DIGITAL MANUFACTURE

Digital Design

Digital Operation

Engineering / R&D

Operations

Mechanistic understanding

Big data

Select / screen / assess **Molecule**

Solid form assessment – CSD-Materials (WP5)

Solubility prediction – gSAFT (WP5)

Stabi /P5)

Solubility prediction (WP3&5)

Particle

Particle surface visualisation and analysis (WP4&5)

Dissolution

Lattice energ

l absorption

diction (WP3)

Morphology prediction - VisualHabit (WP4?)

Stabi /P5)

Flowability prediction (WP3)

Process design, optimisation & tech transfer

Drug substance manufacture unit operations (WP5)

Drug product manufacture unit operations (WP4)

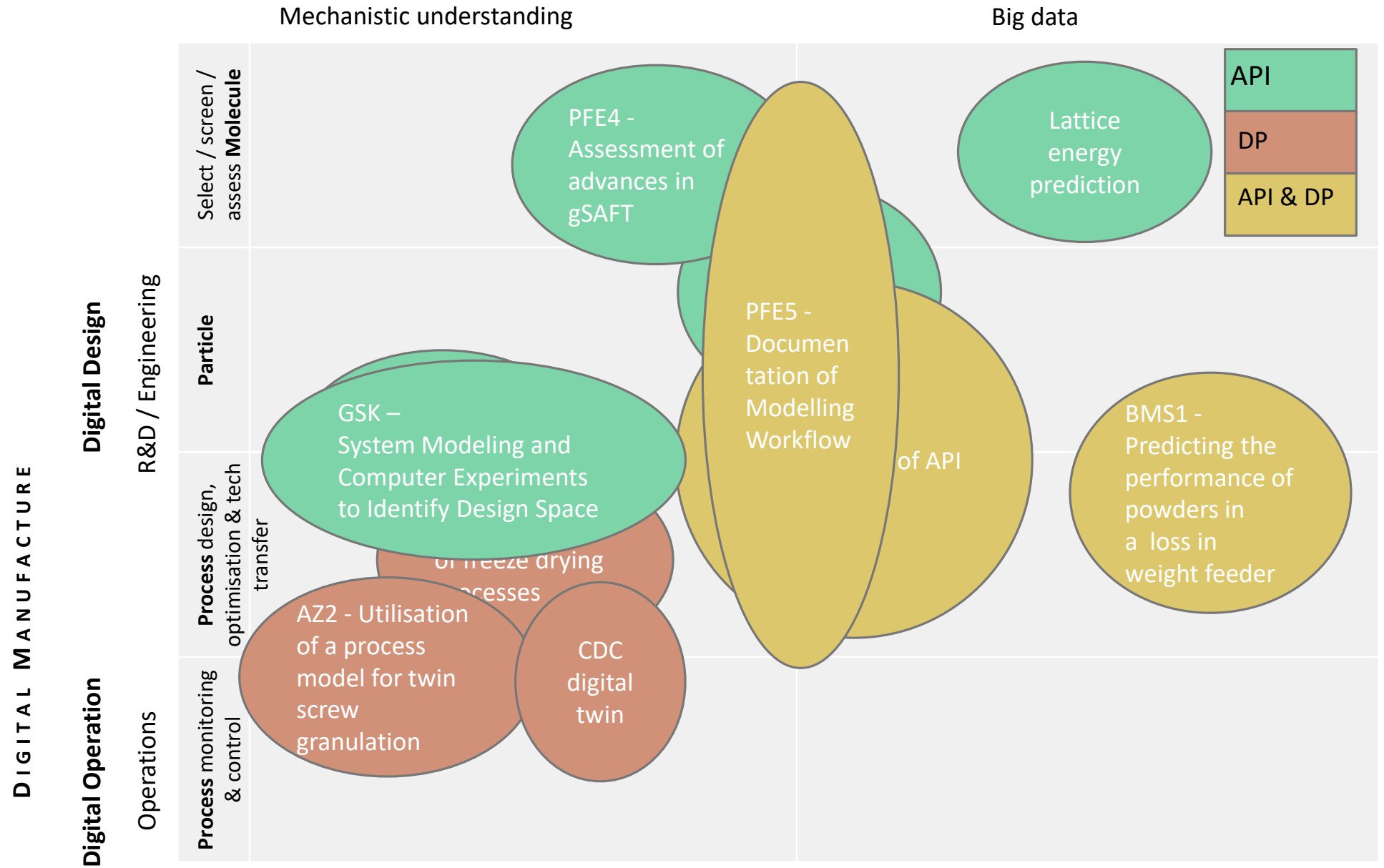
Leveraging Mechanistic models for Design & Operation. (WP6)

Aggregating data from a mixture of sources to develop, design, and operate processes. (WP6)

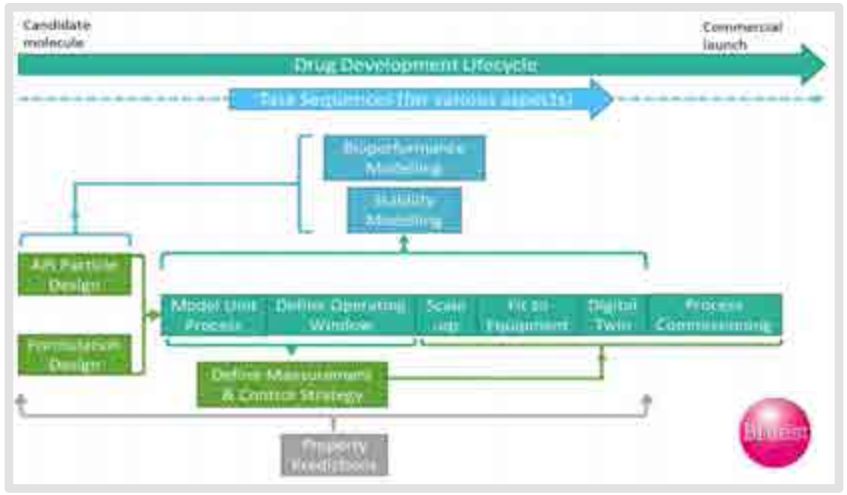
Process monitoring & control

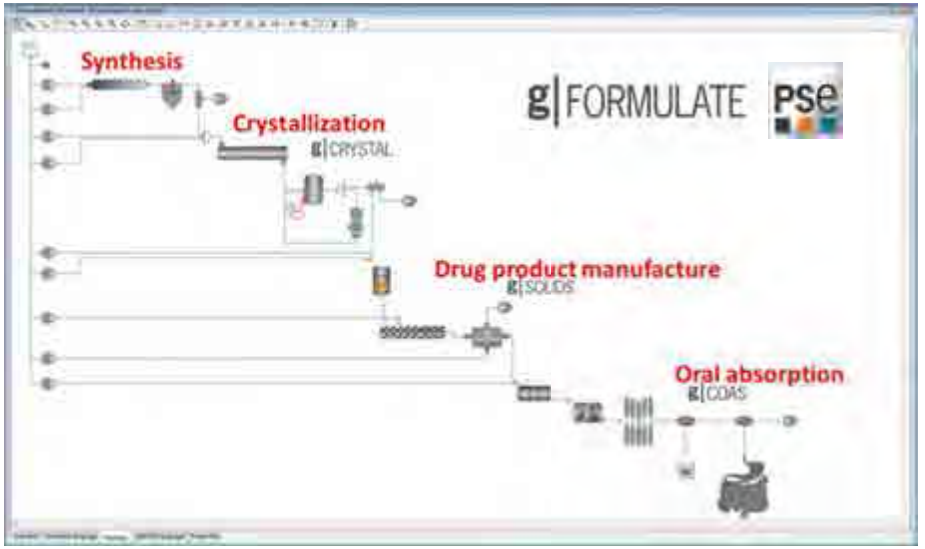
Workflows & Integrated system modelling platform (WP1)

Application of digital design and digital operation tools - 15 pharma led case studies



ADDoPT outcomes relevant to digital design and digital operation of continuous manufacturing processes are available as enhancements to existing tools …





… and it's not over yet

ADDoPT 2015-2019

Showcase event

Thursday 28 March 2019

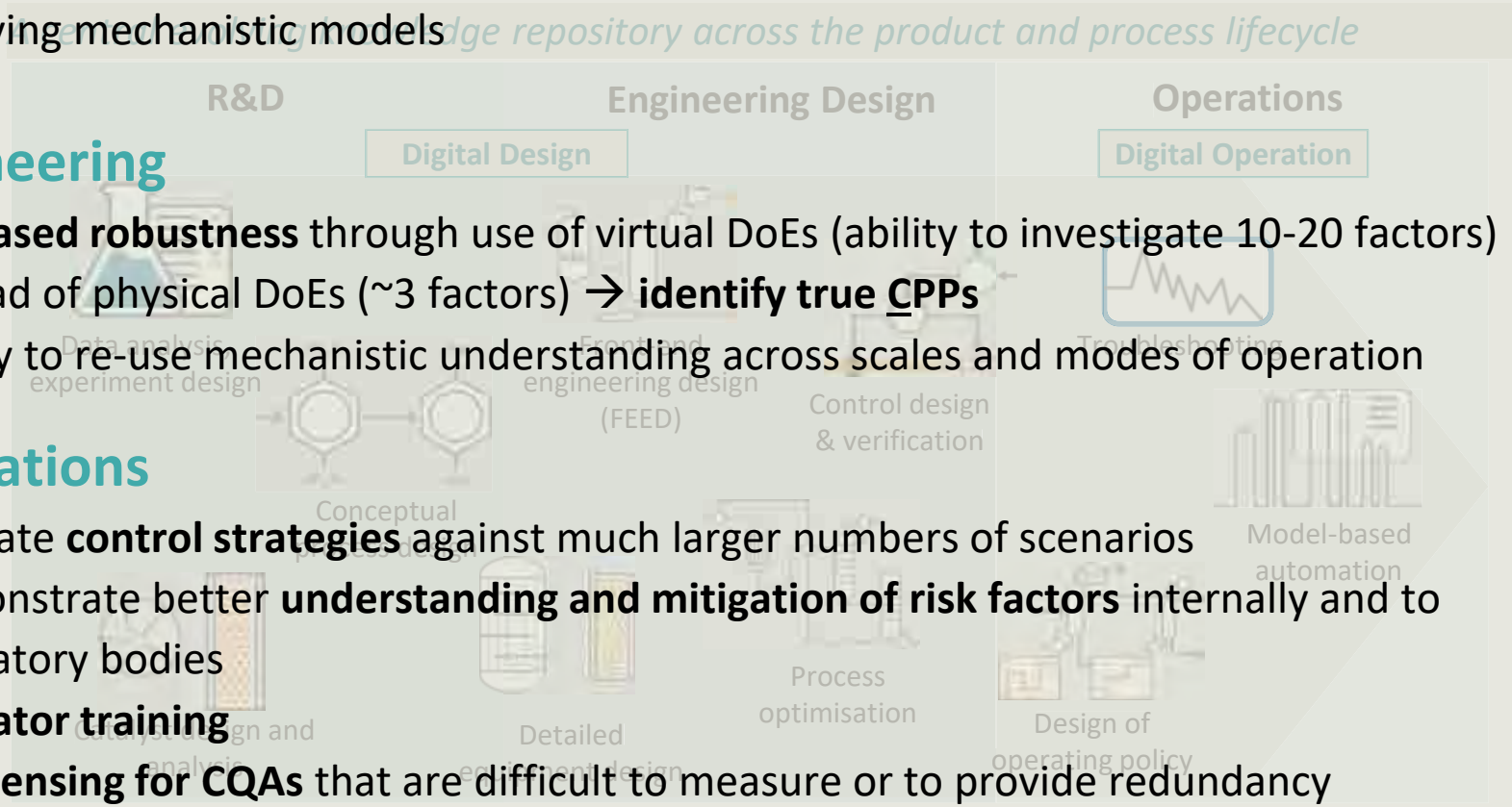
Clayton Hotel Chiswick, London W4 5RY

Also a cross-industry networking event for ISCF wave 3

In conclusion …

Value derived from Application of Mechanistic Model-based Digital Twins

- **R&D**
  - **Increased efficiency** by moving from purely data driven approaches to approaches involving mechanistic models
- **Engineering**
  - **Increased robustness** through use of virtual DoEs (ability to investigate 10-20 factors) instead of physical DoEs (~3 factors) → **identify true CPPs**
  - Ability to re-use mechanistic understanding across scales and modes of operation
- **Operations**
  - Evaluate **control strategies** against much larger numbers of scenarios
  - Demonstrate better **understanding and mitigation of risk factors** internally and to regulatory bodies
  - **Operator training**
  - **Soft sensing for CQAs** that are difficult to measure or to provide redundancy
- **Overall**
  - Faster time to market – process development is increasingly on the critical path



Optimal mix of predictive science and data analytics

- Dependent on the stage of the development life cycle
  - R&D and Engineering
    - Little data available, data generation costly
    - Design and operation space still large
  - Operations
    - Data generated on a continual basis
    - Design fixed, reduced operation space

- Dependent on availability of mechanistic knowledge
  - Equipment failure hard to predict based on laws of physics and chemistry
  - Variability in raw material attributes, in particular from external suppliers, simply needs to be characterised

QbD using mechanistic model-based Digital Twins: Paradigm shift for design of robust products and processes

	pre-QbD	"QbD 1.0"	"QbD 2.0"
Models used	Typically none	Statistical models (MVDA) **Data driven Digital Twin**	Mechanistic models - **Science driven, Data calibrated Digital Twin**
Aim of experimental programme	Attain improve-ments in the system	Determine combined effect of CPPs on CQAs	Estimate physics / chemistry / biology related parameters to calibrate Digital Twin
Identify robust formulation / process operation / control strategy	Not possible	Perform **physical DoE** with respect to 3-4 factors **deemed to be Critical Formulation and Process Parameters**	Using calibrated Digital Twin to perform a **virtual DoE** with respect to 10-20 factors → **ability to identify true Critical Formulation and Process Parameters**
Limitations / challenges of the approach	Combined effect of changes in CPPs unknown, so difficult to predict robustness	Very resource intensive experimental programme **Limited ability to transfer knowledge to other equipment / scales** Regulatory acceptance / understanding	Selecting appropriate mechanistic model (model discrimination) **Not widely applied yet → training and culture change required** Regulatory acceptance / understanding

Thank you

Development of Digitalisation Tools undertaken in and supported by a wide ecosystem

SbP: Vision

SbPA: coordination, industry adoption & regulatory acceptance

gsk Lilly Pfizer Roche

PSE experience in, and developments for, other industry sectors

Tools & Workflows

g|FORMULATE

gPROMS gSAFT

ADDOPT D3P ReMediES

Collaborative R&D

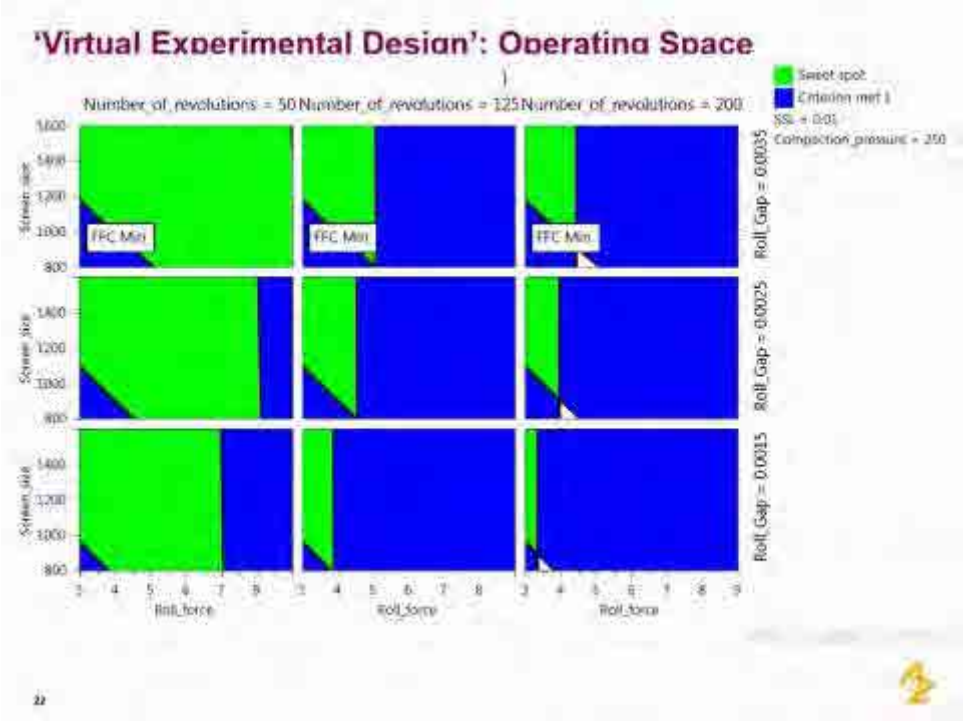
Developments undertaken in and supported by a wide ecosystem

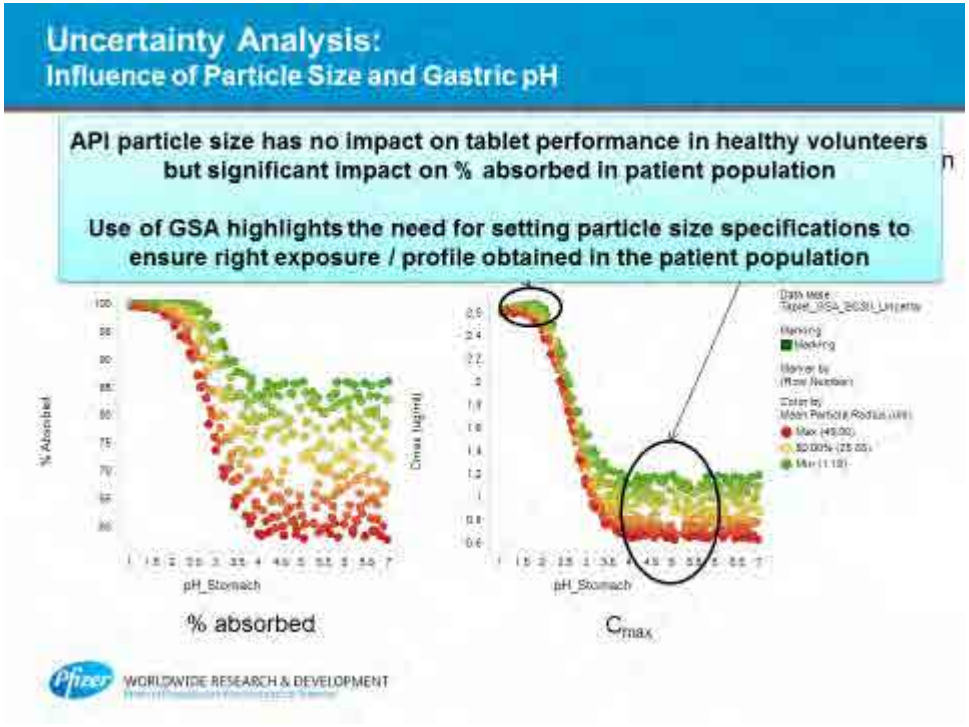
Systems-based Pharmaceutics Alliance

- Pre-competitive alliance founded by Eli Lilly, Pfizer and PSE in 2013
  - Accelerating development, adoption and regulatory acceptance of SbP tools
  - Phase I completed Oct ‘15; Phase II kicked off Dec ’15; GSK and Roche Dec ’16
  - Phase III kicked off Apr’ 18
- Benefits
  - close interaction between scientific liaisons from each pharma company in a pre-competitive environment, incl. two 1-week in-person meetings per year
  - accelerate and direct development of solutions (tools and workflows) with input from 30-40 SMEs from industry: requirements, feedback & network
- Deliverables
  - architecture for gPROMS FormulatedProducts to realise of SbP vision
  - several new models (more later)
  - extensions to capabilities for model calibration and external model validation

Digital Design of Drug Products (D3P; 2014-2016)

- Innovate UK project with AstraZeneca, Britest, GSK and Pfizer
- PSE funding: £444k
- Deliverables for PSE
  - Global System Analysis (part of gPROMS 5.0)
  - Industrial case studies presented at conferences and as a webinar





ReMediES (2014-2018)

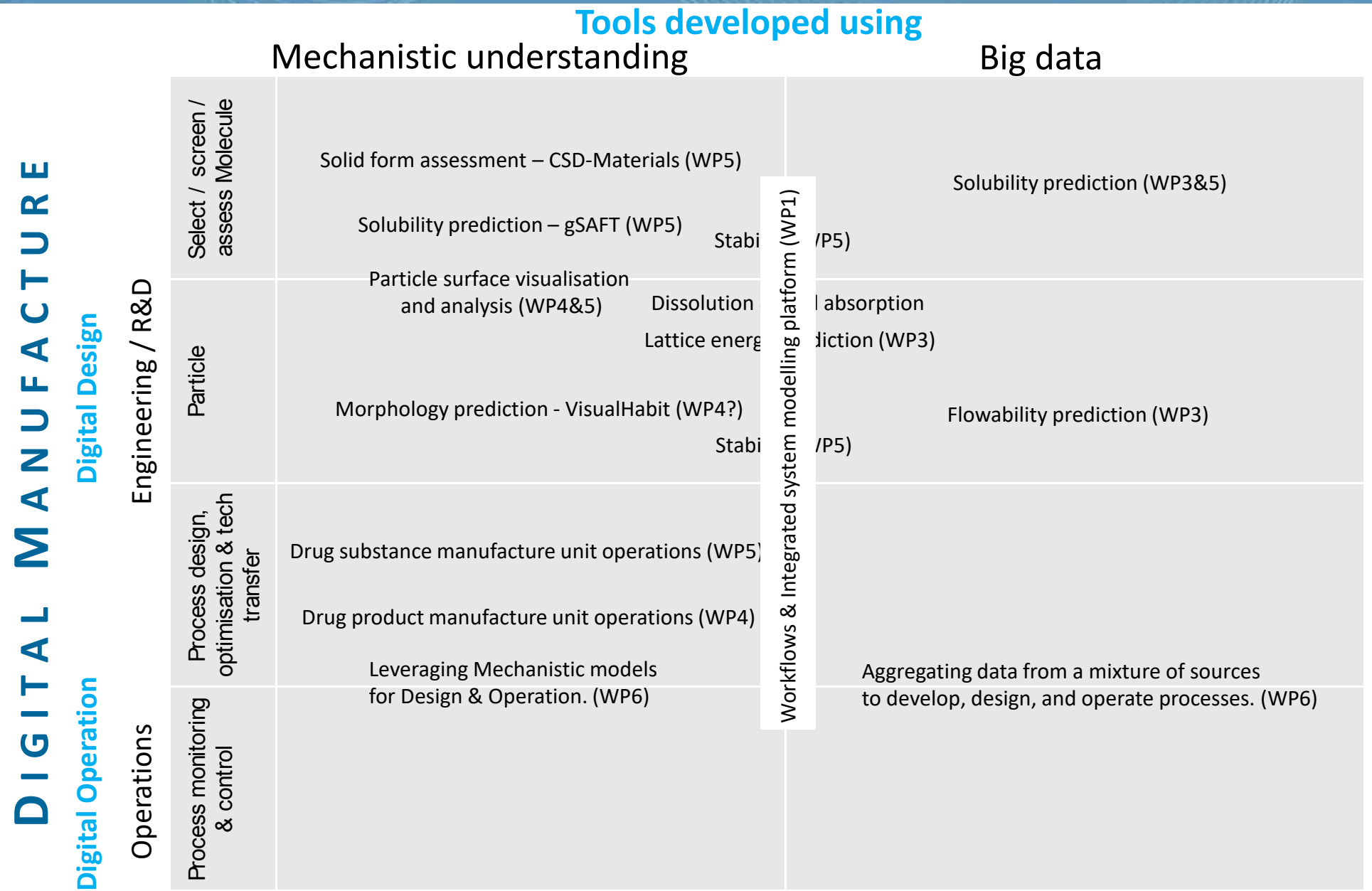
- £22M AMSCI project (partner)
- AstraZeneca, GSK, GEA, Britest, PEL, U. Strathclyde, U. Cambridge (IfM) and ~20 others
- PSE funding: £400k; 1.6 FTE
- PSE a partner in App B from the start
  - Continuous drug product manufacture
  - Delivered several models within the gPROMS FormulatedProducts platform: Initial continuous filtration, feeder, blender, feed frame and HME models
  - Contributed to several case studies
- PSE a partner in App A for last year of the project
  - Continuous drug substance manufacture
  - Case study for Thomas Swan
  - CMAC Micro factory with PEL

ADDoPT (2015-2019)

- £20.4M AMSCI project (lead)
- PSE funding: £3,600k; 10 FTEs
- AstraZeneca, BMS, GSK, Pfizer, Britest, Perceptive Engineering, CCDC, STFC, U. Leeds, U. Strathclyde, Cambridge U.
- PSE deliverables
  - gPROMS FormulatedProducts, which subsumes gCRYSTAL, gSOLIDS and gCOAS, for integrated modelling of drug products and their manufacturing processes
  - A large number of new unit operation models (more later)
  - Ability to include statistical models in mechanistic model framework → hybrid models with better predictions and extrapolability
  - Support for 9 industrial case studies across the 4 pharma companies
    - AZ: Crystallization, Lyophilisation and Twin Screw Granulation
- Other project deliverables
  - Ability for PharmaMV to directly interface gPROMS FormulatedProducts to generate models for process monitoring and control

Developments undertaken in and supported by a wide ecosystem

ADDoPT (2015-2019)



Developments undertaken in and supported by a wide ecosystem

Several bi-lateral collaborations, e.g. P&G (gSOLIDS 1.0), Pfizer (gCOAS 1.0), Lilly (distillation column), AstraZeneca (RC and CDC) & UCB (segmented FBD)

Other collaborations

- Centre of Excellence for Pharma with RCPE
  - FBG & HME
- CMAC – Continuous manufacture for pharma
  - Tier 2 member representative for CMAC board (2016-2018)
- CPI – National Formulation Centre
  - Particle modelling project – further development of TSG model from ADDoPT
- Rutgers University – C-SOPS & FDA continuous manufacture
- University Massachusetts Lowell – FDA continuous manufacture
- T-MAPPP – DEM interfacing – U. Edinburgh
- U. Sheffield – granulation

Roadmap for further development of PSE's Digitalisation Tools

Small molecule

- R&D and Engineering
  - Increasingly focussed on workflows→ training and documentation

- Operations
  - Work with lead customers to demonstrate feasibility and added value of mechanistic model-based process control and monitoring solutions

Accelerating deployment in commercial manufacture of Digital Twins capturing knowledge evolved during R&D and Engineering

- June 2018
- A preferred partnership

Biologics

- Create model libraries, initial focus on mAb and advanced therapeutics (e.g. CAR-T cells)

- Platform functionality is largely application agnostics, i.e. ability to perform parameter estimation, external model validation, optimisation, virtual DoEs and to link to online systems are all directly applicable

General

- Hybrid approaches combining predictive science and data analytics
- Model discrimination to enable generation of better Digital Twins more efficiently
- Create awareness in industry and regulatory bodies that virtual DoEs allow a more comprehensive assessment of robustness, how best to mitigate associated risks and how this links to enhanced safety and efficacy for the patient

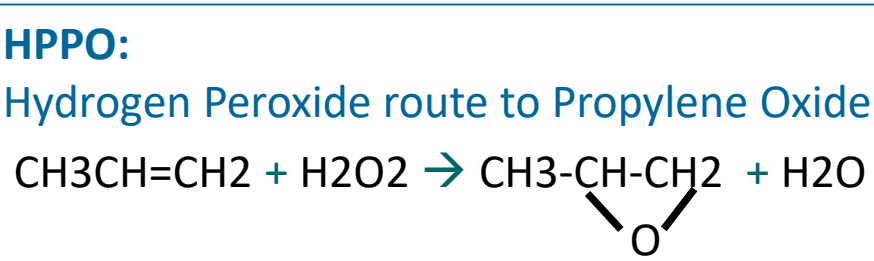
Motivation for virtual DoEs

Hydrogen Peroxide route to Propylene Oxide (HPPO)

The process

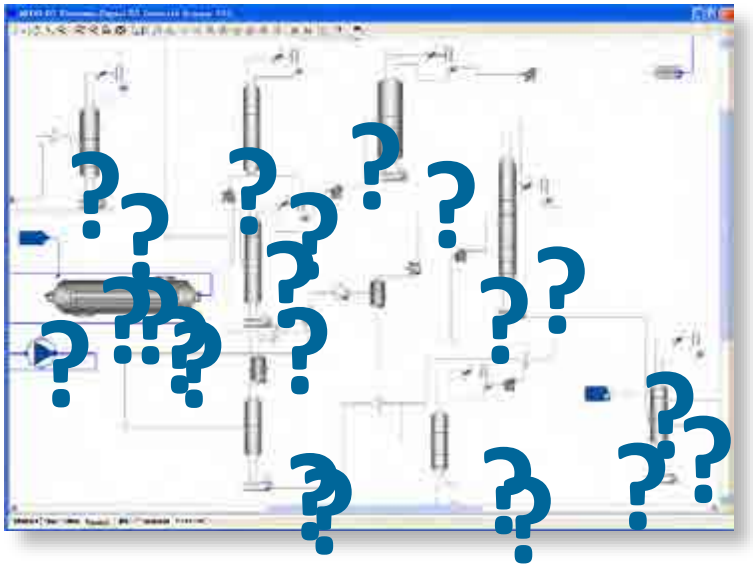
- Traditionally PO co-produced with styrene monomer (SM)
  - complex process
  - large capital investment
  - economics dependent on SM market
- New Repsol HPPO process
  - addresses all of above
  - minimal by-products
  - own process

HPPO:
Hydrogen Peroxide route to Propylene Oxide



The challenge

- Process ‘already optimised’ using traditional simulation software, but process economics looking poor



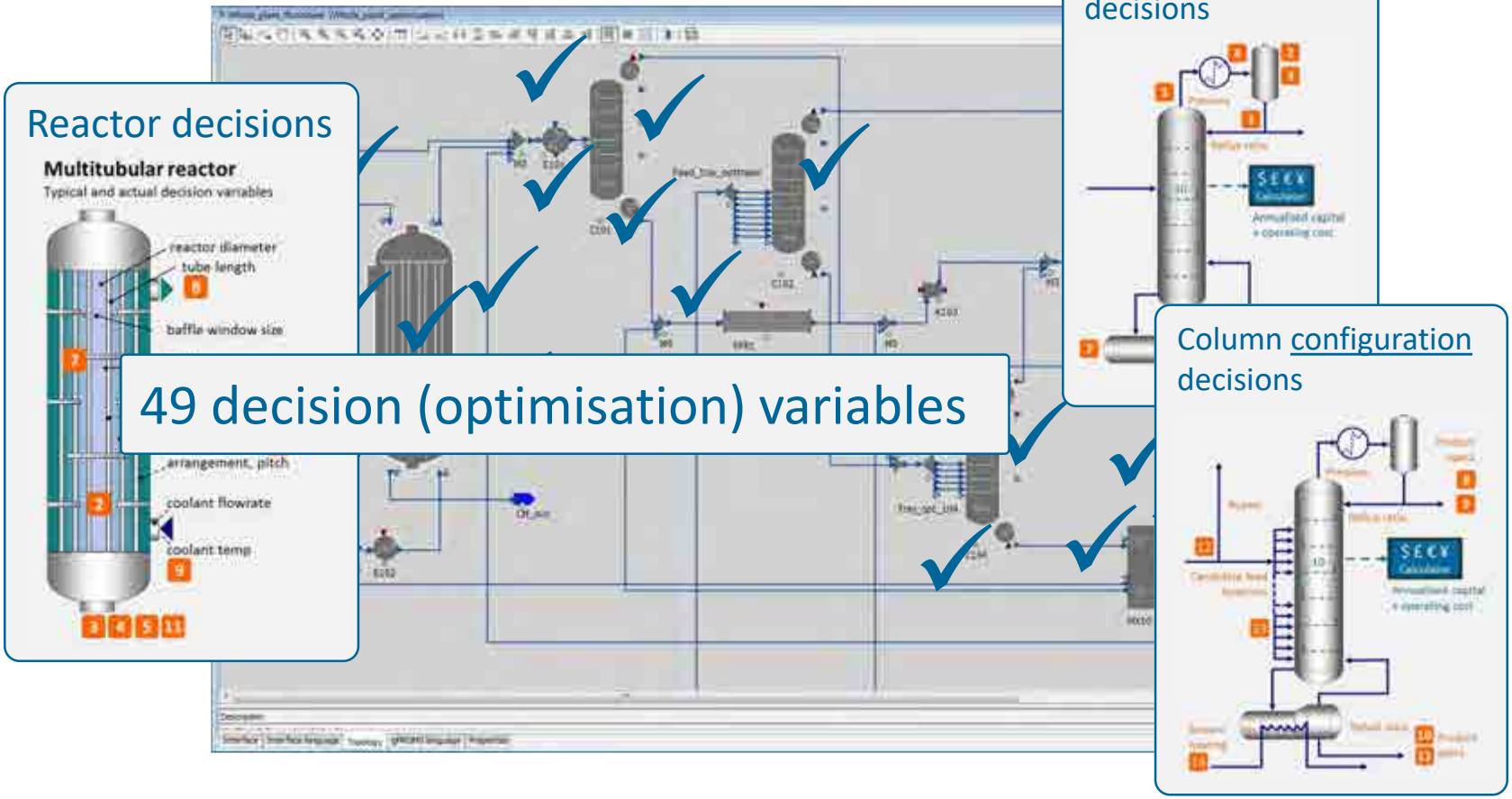
- Many decisions and trade-offs
  - complex multitubular reactor
  - complex separation system (> 10 columns)

How can we improve whole plant process economics?

Approach

- Construct and validate model of proposed process design
- Nominate process design variables, constraints, objective

  "Minimise total annualised cost"



Results

The result

- Large **savings in operating and capital cost** with respect to ‘optimal’ base case
- Two columns **eliminated entirely**
- Heat integration yielded significant **operating cost savings** with attractive ROI (payback < 4 months)

Improvement in process economics:
“10s of millions of Euros”

- Process is **feasible** (all constraints met)
- Rigorous and validated models – used for design – contain valuable knowledge for detailed engineering, and operation.