Taking mechanistic models from R&D and Engineering into Operations

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Andy Mitchell (Perceptive Engineering)

Niall Mitchell (Process Systems Enterprise)

Introductions

PERCEPTIVE ENGINEERING

Who we are:
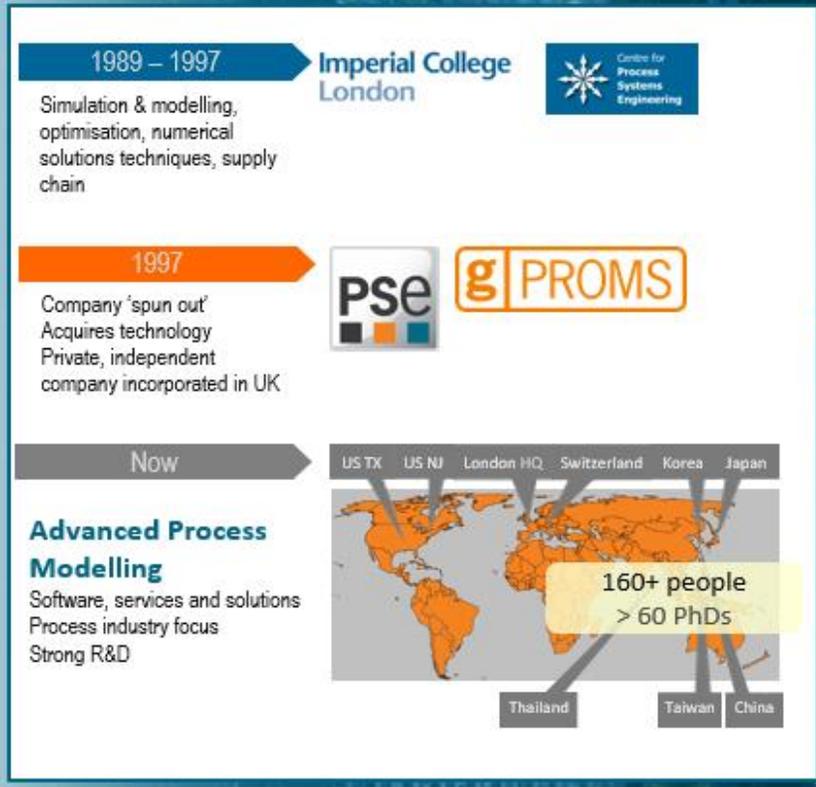- 30 Employees
- Offices in the UK, Singapore, Ireland

What We Do:
- We develop software for the automation industries:
  - PAT, Advanced Process Control, Monitoring and Optimisation.

Academic and Innovation Alliances
- Universities of Cambridge, Manchester, Newcastle, Rutgers, Limerick, Strathclyde, Leeds, Surrey
- Centre for Process Innovation (CPI), Centre for Continuous Manufacturing and Crystallisation (CMAC), Institute of Chemical and Engineering Sciences (ICES Singapore), Synthesis & Solid State Pharmaceutical Centre (SSPC)
- Industrial partnerships with Siemens and GEA

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

Now — US TX   US NJ   London HQ   Switzerland   Korea   Japan

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

160+ people
> 60 PhDs

Thailand   Taiwan   China

MISSION
"define, develop and drive the adoption of next-generation modelling technology, methodologies and workflows throughout the process industries"
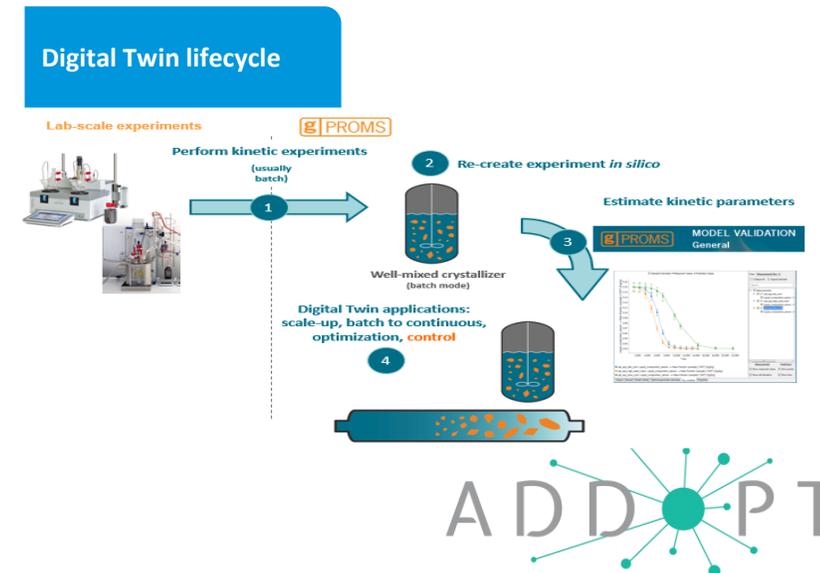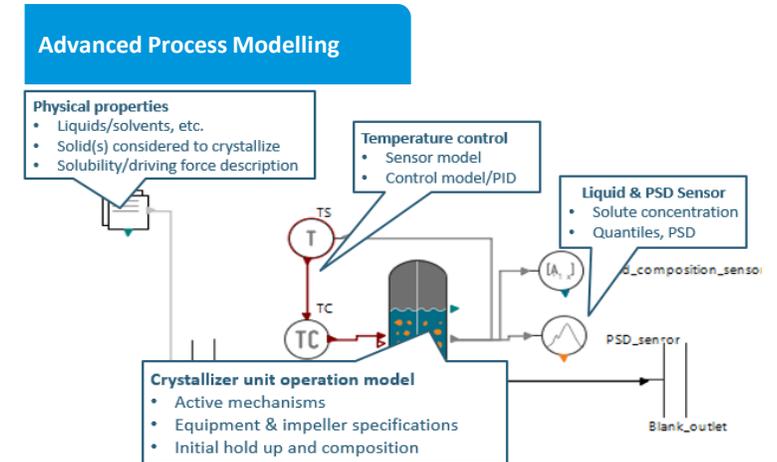
g PROMS
Advanced Process Modelling® technology

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Introductions

PERCEPTIVE ENGINEERING

- Advanced Process Control
- Process Modelling
- Data Visualisation
- Multi-Variate Statistical Process Control

Advanced Process Control

Statistical Process Control Dashboard
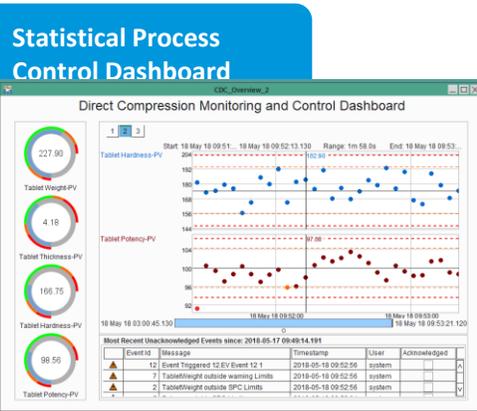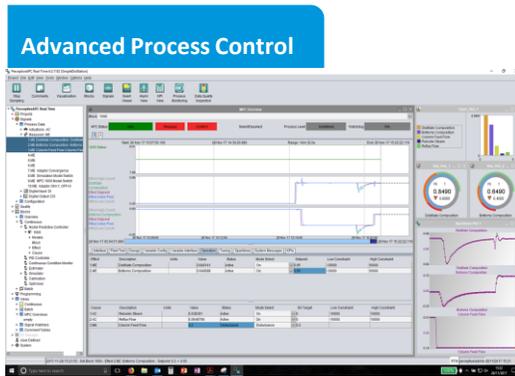
Process Systems Enterprise

pse

- Advanced Process Modelling
- Process Modelling and optimisation
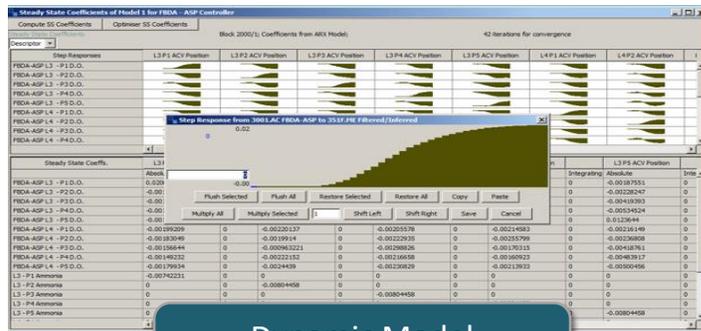- Process model validation
- Global system analysis

Advanced Process Modelling

Physical properties
- Liquids/solvents, etc.
- Solid(s) considered to crystallize
- Solubility/driving force description

Temperature control
- Sensor model
- Control model/PID

Liquid & PSD Sensor
- Solute concentration
- Quantiles, PSD

Crystallizer unit operation model
- Active mechanisms
- Equipment & impeller specifications
- Initial hold up and composition

Digital Twin lifecycle

Models

PERCEPTIVE ENGINEERING

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Statistical, Empirical or Data Driven Models

- Control: Dynamic Models
- Calibration: Static Models

Created from

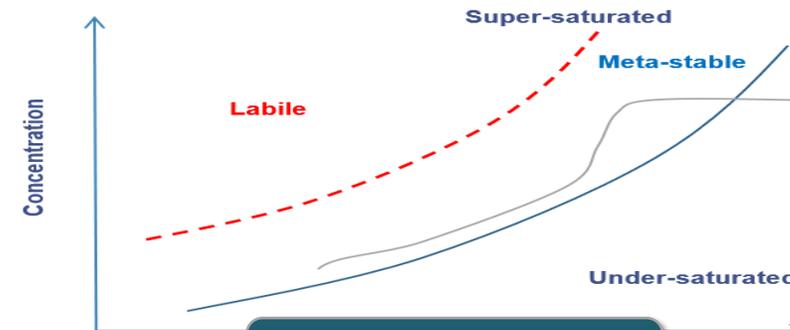- Designed Plant Tests
- Historical Process Data

Mechanistic & Empirical Models

- Dynamic & steady-state Models
- Calibration: Data rich lab-scale experiments

Created from

- Science-based understanding of key phenomena
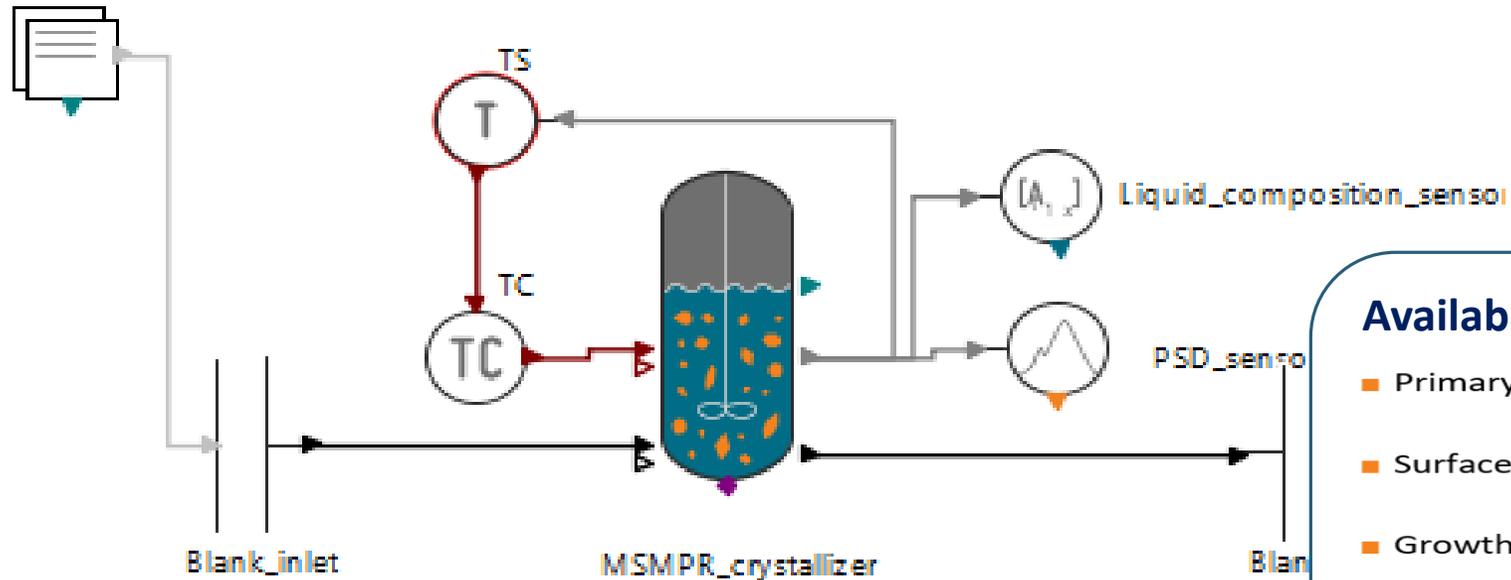- Rate expressions for kinetic phenomena

Dynamic Model for Control

Mechanistic Model for Digital Design

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Digital Design Vision

- Lab scale – In-silico/virtually

- Construct the flow sheet to represent the manufacturing process within **gPROMS FormulatedProducts**

Available crystallization mechanisms

- Primary nucleation
- Surface breeding
- Growth & dissolution
- Agglomeration
- Attrition
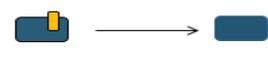
Digital Design Workflow
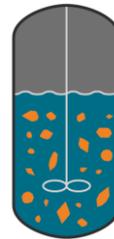
Lab-scale experiments

g|PROMS

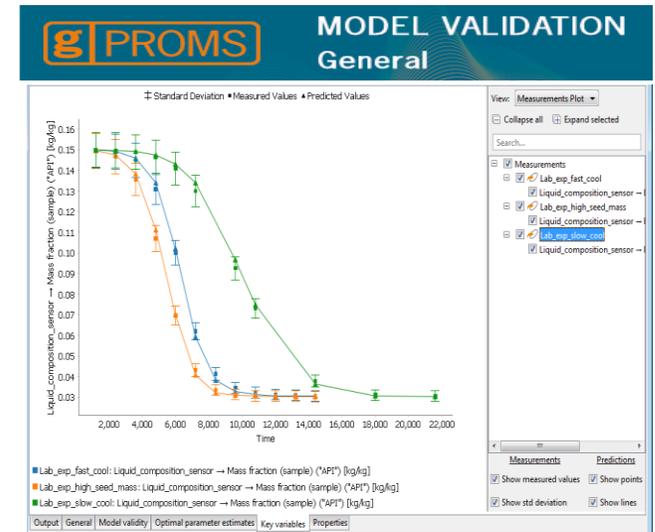**Perform kinetic experiments**

Re-create experiment *in silico*

1

2

Well-mixed crystallizer (batch mode)

Estimate kinetic parameters

3

g|PROMS MODEL VALIDATION General

Digital Twin applications: Scale-up, Tech transfer, optimisation, control

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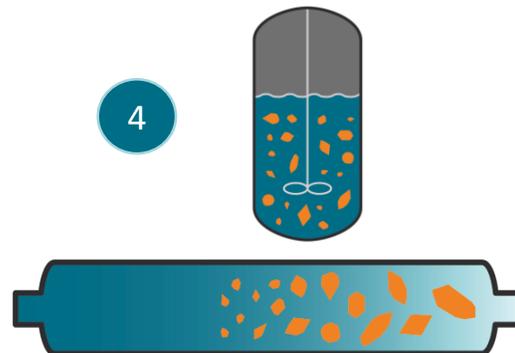
A "validated" environment

- Manufacturing process must achieve the requirements of the regulatory body and 'GAMP' (Good Automated Manufacturing Practice)
- Adherence to 21CFR Part 11 mandatory for data integrity & traceability

- Due to the validation requirements, material produced during commissioning must be destroyed.
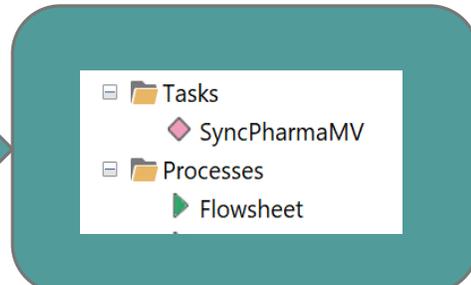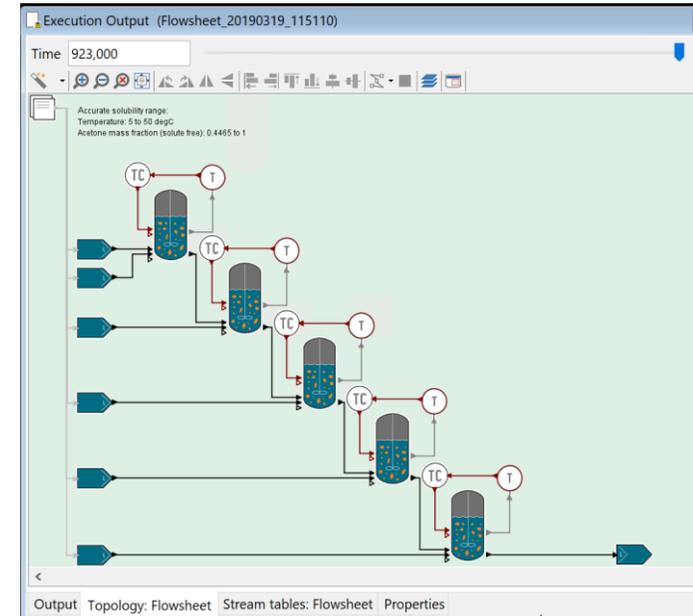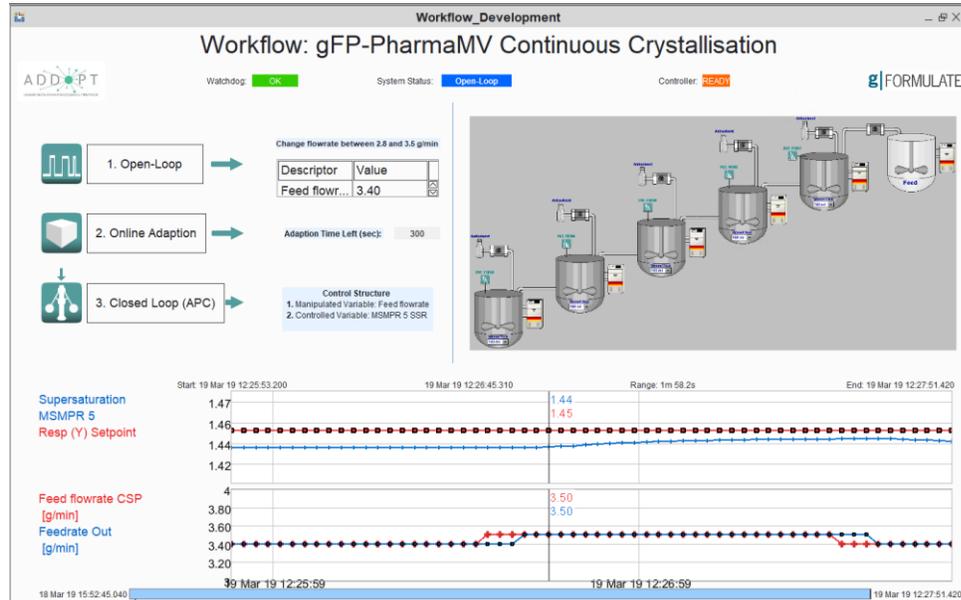- Places an emphasis on identifying models with minimal process data.

Scale-effects & PAT

- Extract process knowledge & understanding
- Models Need to Handle Changes in Scale…
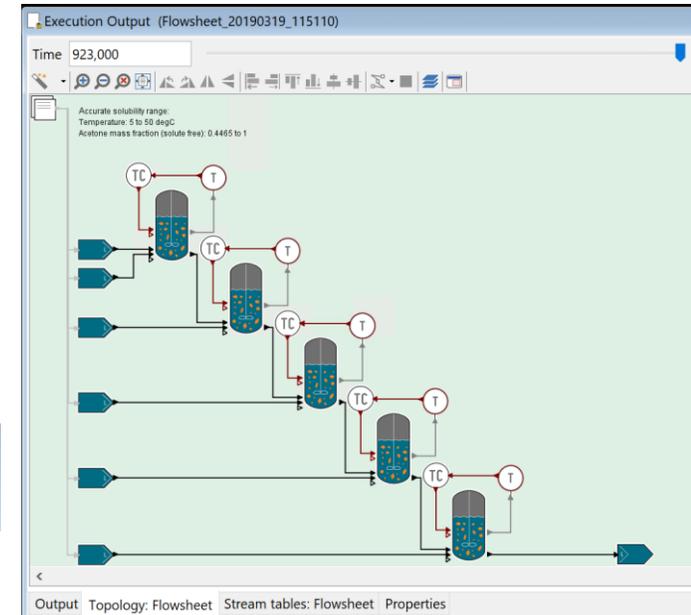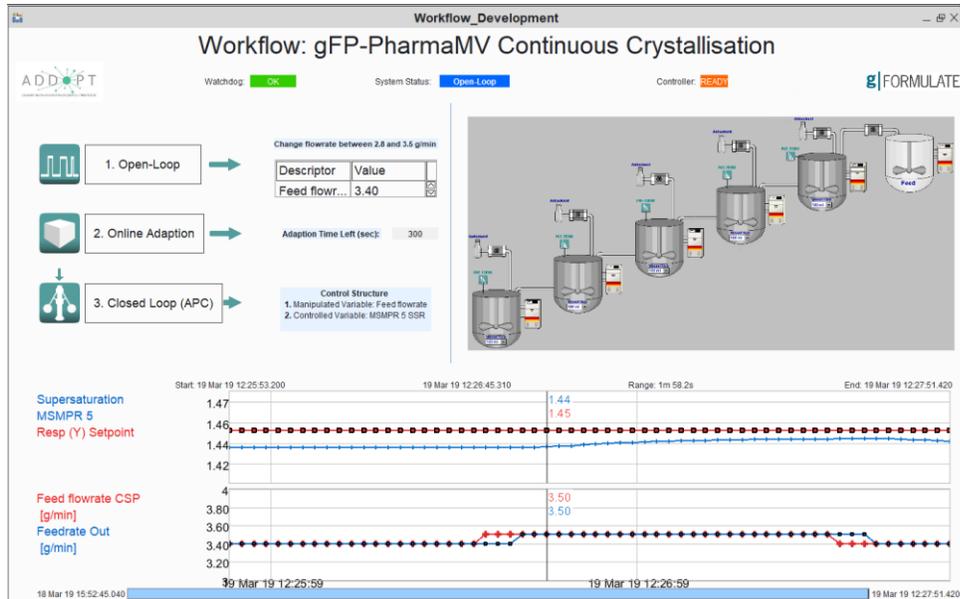- Models developed in the lab may need refinement to describe full-scale operation

Use of PAT (Process Analytical Technology)

- Spectroscopic sensors such as NIR & Raman.
- Integrate spectral calibration models, mixed mode process/spectral models, and MPC in one package

Digital Twin

ADDOPT DIGITAL DESIGN SHOWCASE, LONDON

Foreign Object Interface

Tasks
- SyncPharmaMV

Processes
- Flowsheet

Virtual Step Test / What If

Virtual
Design of Experiments

Virtual Soft Sensor

Integrated Digital Twin, Case Studies and Examples

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Continuous Crystallisation Digital Twin

Slurry Feeder Setpoint

Measured Signals
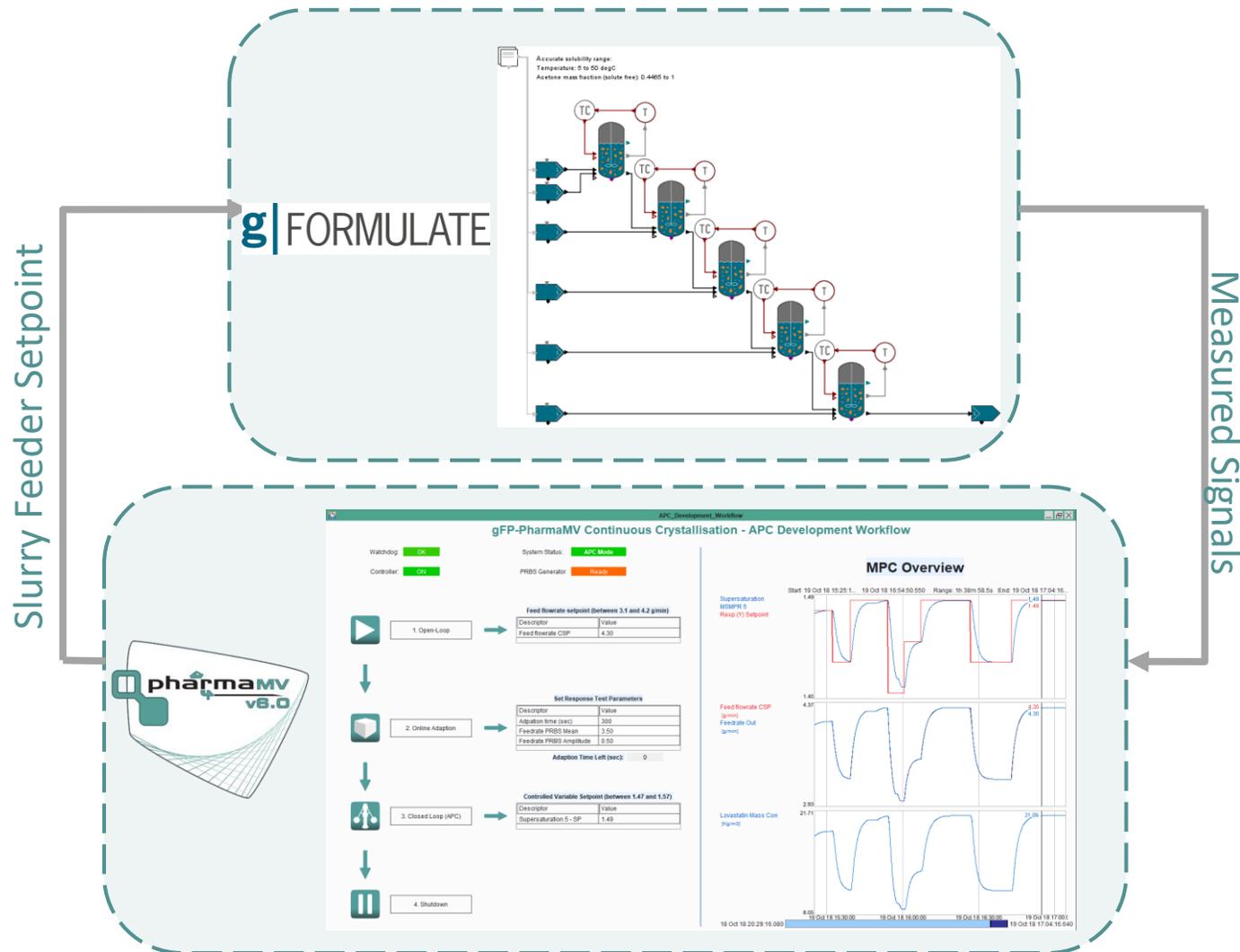
- Through the ADDoPT project, a Digital Twin was developed for the Continuous Crystallisation process as part of the CMAC Open day 2018.

- The flowsheet consists of 5 MSMPRs each with its own temperature controller as well as an anti-solvent pump.

  - A slurry of Lovastatin and Acetone is fed into the first MSMPR

  - The antisolvent (Water) is pumped into each of the MSMPRs

- The platform includes options for open-loop testing, online model adaption as well as APC.

Twin Screw Granulator

Virtual Process

Controller

Manipulated Signals

Measured Signals
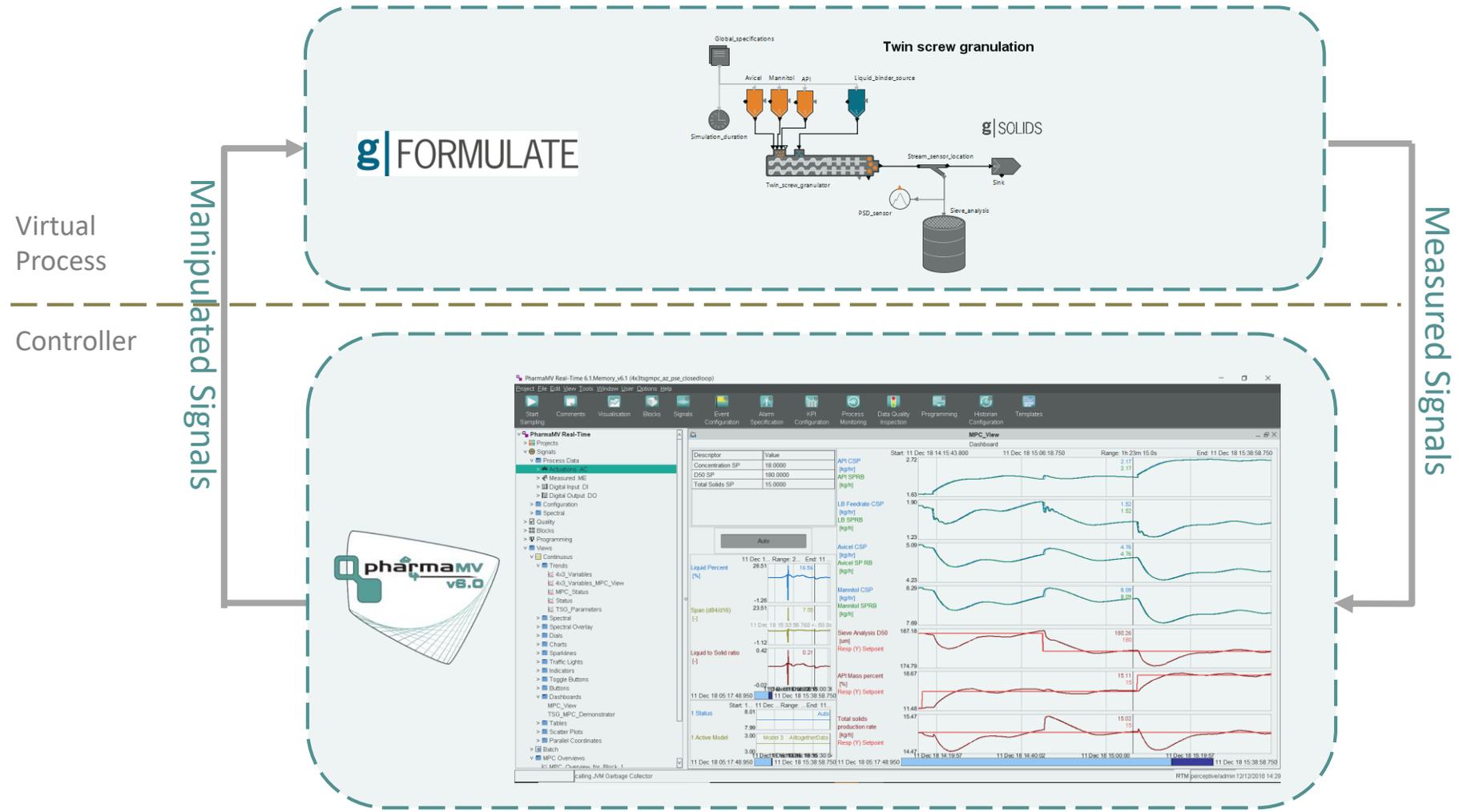
- ADDoPT Case Study to integrate a Twin Screw Granulator gPROMS FormulatedProducts model with PharmaMV.

- Goal to develop a controller that will maintain quality attributes when the process is adjusted with minimal physical process testing.
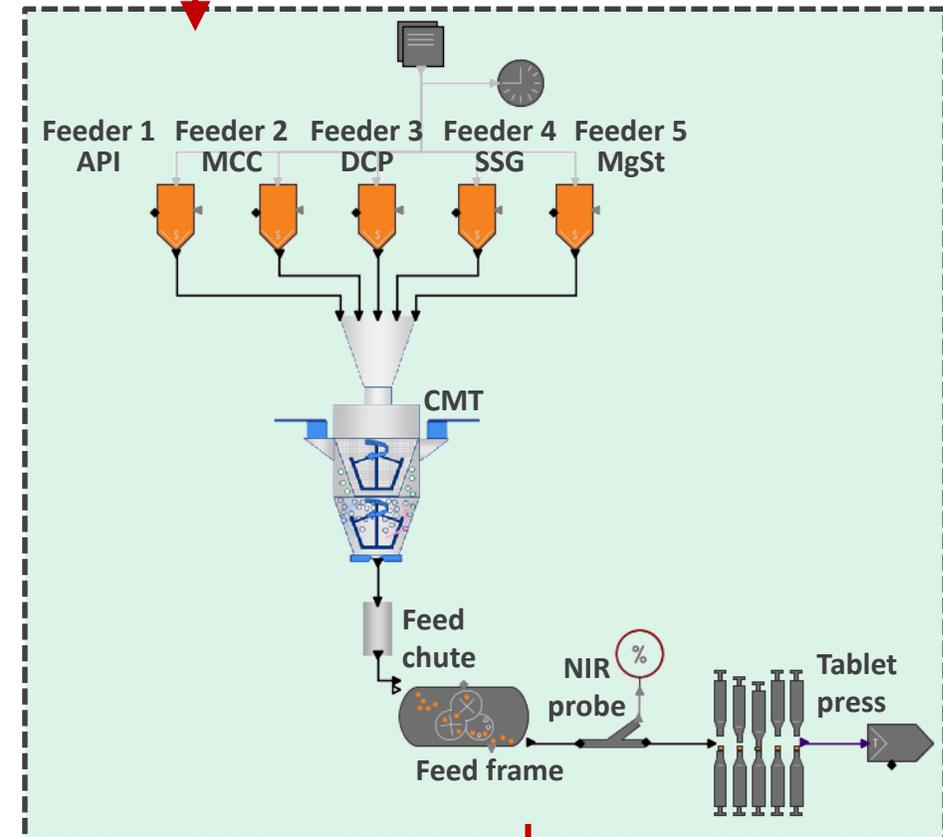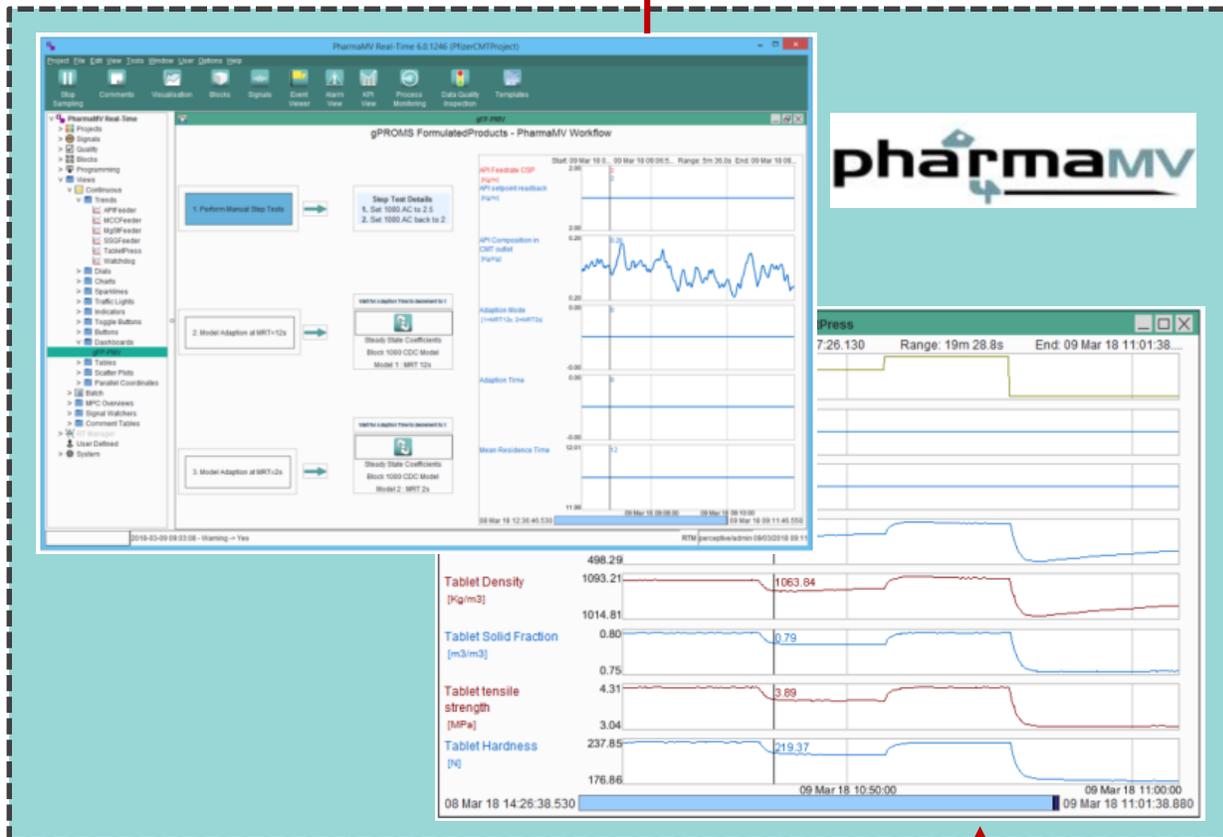
- Further details in Gavin Reynolds presentation.

Continuous Direct Compression

Control & monitoring platform | **Virtual process**

Manipulated signals

Measured signals

Feeder 1 API · Feeder 2 MCC · Feeder 3 DCP · Feeder 4 SSG · Feeder 5 MgSt
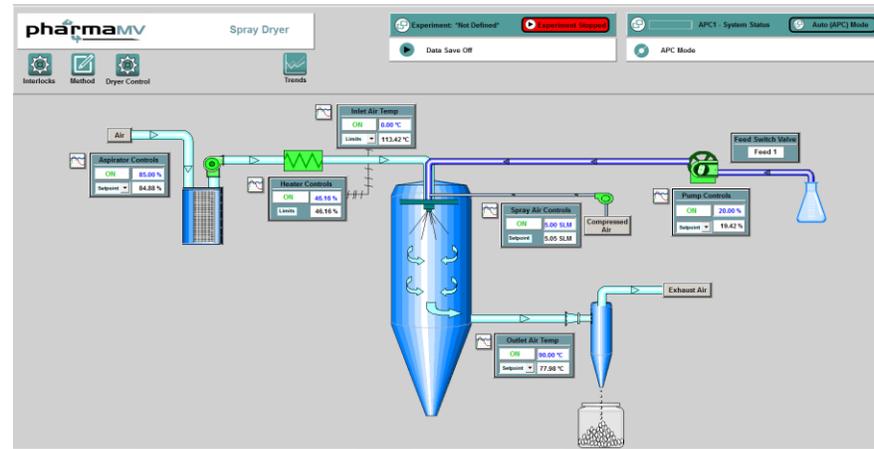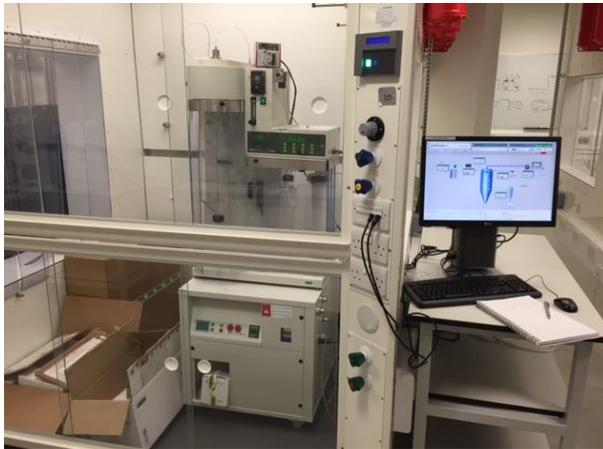
CMT

Feed chute

Feed frame

NIR probe

Tablet press

Pharmaceutical Spray Dryer

- Fully integrated into Dryer
- Operator User Interface and workflow
- Flexible inlet/outlet temperator control using heater, aspirator and feed pump.

From Digital Design to Operation

From Digital Design to Digital Operation

15:25	Taking mechanistic models from R&D and Engineering into Operations	Andy Mitchell - *Perceptive Engineering* Niall Mitchell - *Process Systems Enterprise*
15:45	How process simulation can influence the control strategy of a Drug Substance asset	Flavien Susanne - *GlaxoSmithKline*
16:05	Application of hybrid models for Advanced Process Control of a Twin-Screw Wet Granulation Process	Gavin Reynolds - *AstraZeneca*

A D D O P T

Integrated Digital Twin, Journey & Future

Enabling Advanced Digital Design of Pharmaceutical Therapeutics (ADDoPT)

- **And Digital Operations**

More than just a common vision!

ADDoPT Science Meeting
Theme: Work package interconnectivity and beyond
Fitzwilliam College, University of Cambridge

09:30 – 09:45 Links with REMEDIES App A "continuous drug substance manufacture" [Stewart Mitchell (U. Strathclyde)]

09:45 – 10:30 Links with REMEDIES App B "continuous drug product manufacture" illustrated through HME, spray drying & crystallisation applications [Andy Mitchell (PEL) and Niall Mitchell (PSE)]

Everyday example of communication gone wrong!

- Ordering a coffee

- Workflow

  - Place order

  - Ask for **name**

  - Wait for preparation

  - Receive and enjoy!

  - Reality is a little different
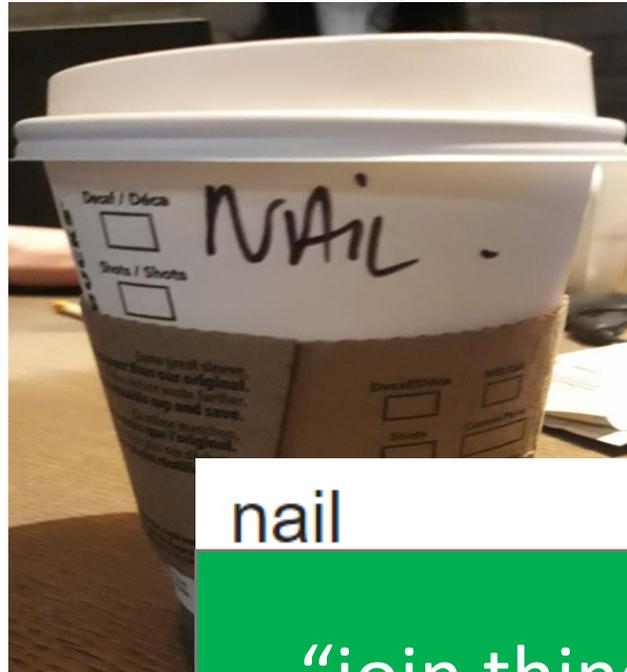
Definition

nail

"join things together"

...d to join things together or to

synonyms: pin, spike, tack, rivet; More

Ensured through demonstrators & application cases

Streamlined workflows & interfacing (1)

Integration of PharmaMV interface within gPROMS FormulatedProducts release (version 1.4 - April 2019)

Release notes & document

Contents

1.1.1.5 Integration with PharmaMV to enable Digital Operation

The required components to allow for integration of gPROMS FormulatedProducts to Perceptive Engineering's platform, namely PharmaMV have been included in this release. This will allow for the usage of the mechanistic models developed and validated within the gPROMS FormulatedProducts environment as Digital Twins or Virtual Plant. The interface can subsequently be utilised to develop data driven Model Predictive Controllers (MPC) or Soft Sensors for the process, by step-testing or performing Pseudo-Random Binary Steps (PRBS) on the Virtual Plant to mimic the real process. This was developed as part of the Advanced Digital Design of Pharmaceutical Therapeutics (ADDoPT) project.

More details can be found in the help documentation on the integration which can be found in examples -> Model Deployment -> PharmaMV Integration within the installer.

Streamlined coupling of Digital Twin to control environment
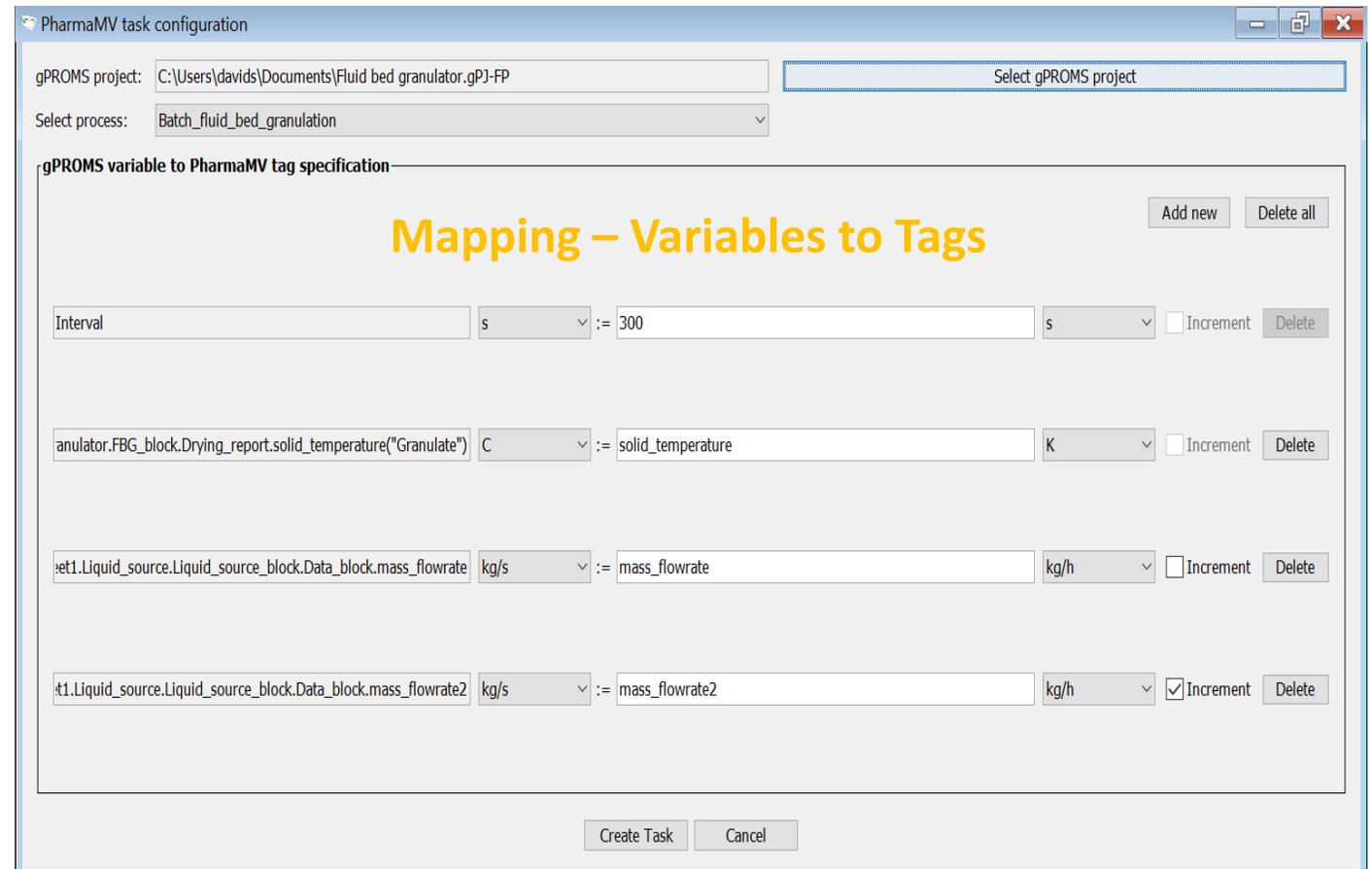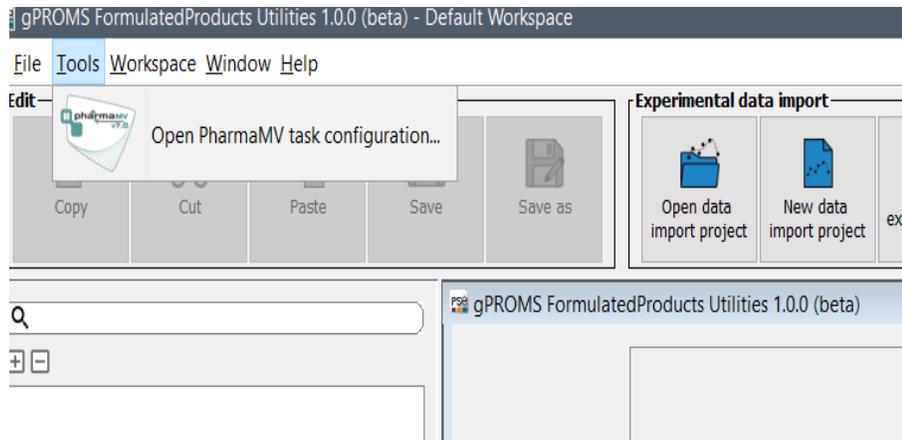
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