ADVANCED PROCESS MODELLING FORUM
22–23 APRIL 2015

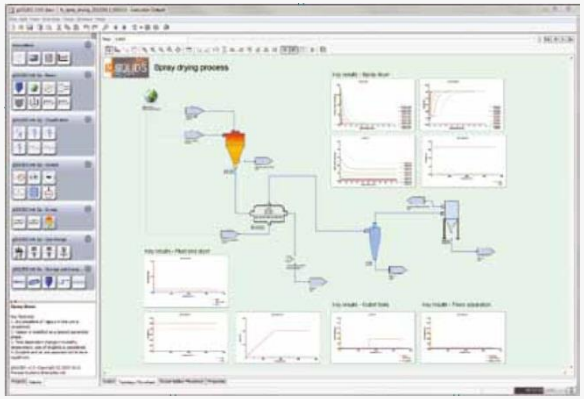
Integrated mechanistic modelling for design and optimisation of formulated products and their manufacturing processes

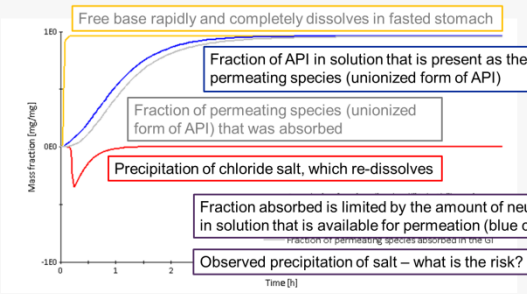
Frances Pereira
Head of Product Development
Life Sciences, Food, Consumer Goods and Specialty & Agrochemicals

Typical formulated product applications

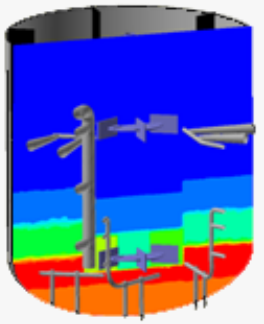
In the Life sciences, food, consumer good, specialty and agrochemicals industries

Integrated design of spray dryer and fluid bed dryer system





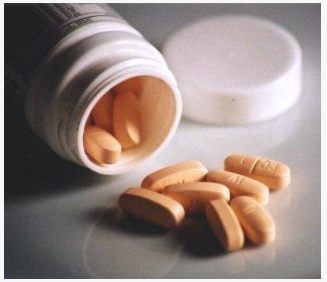
Risk assessment for Oral Solid Dosage forms [Pfizer]



Crystalliser scale-up for a **new process**

Optimisation of the batch recipe for pharma-grade lactose to reduce cycle time by 44% [FrieslandCampina]

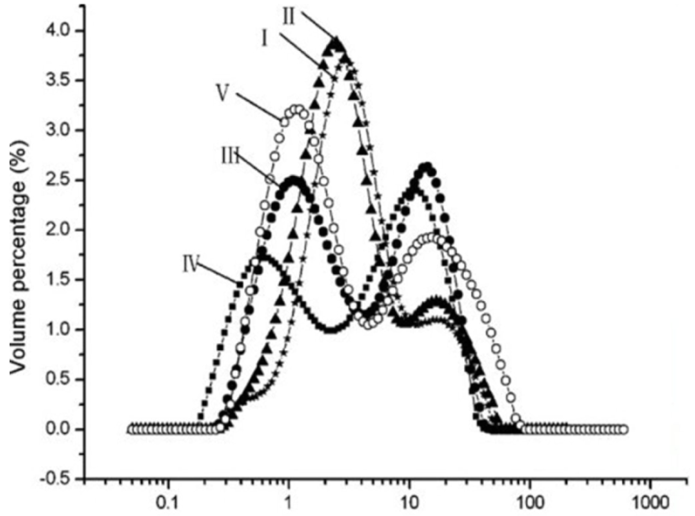
Optimisation of a pharmaceutical reactor to minimise impurity production [GSK]



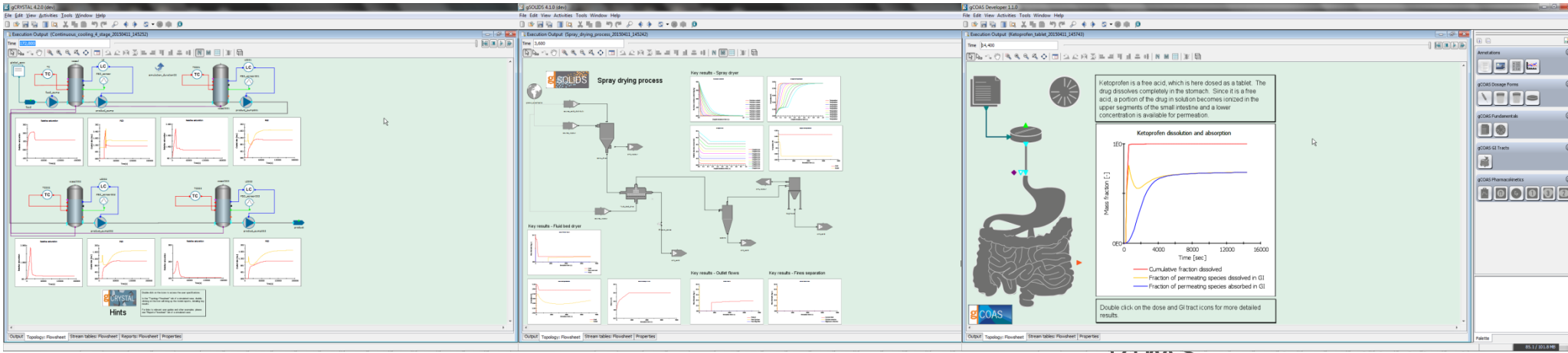
Optimising a pill coating process [Pfizer]

Scale-up of milling [P&G]

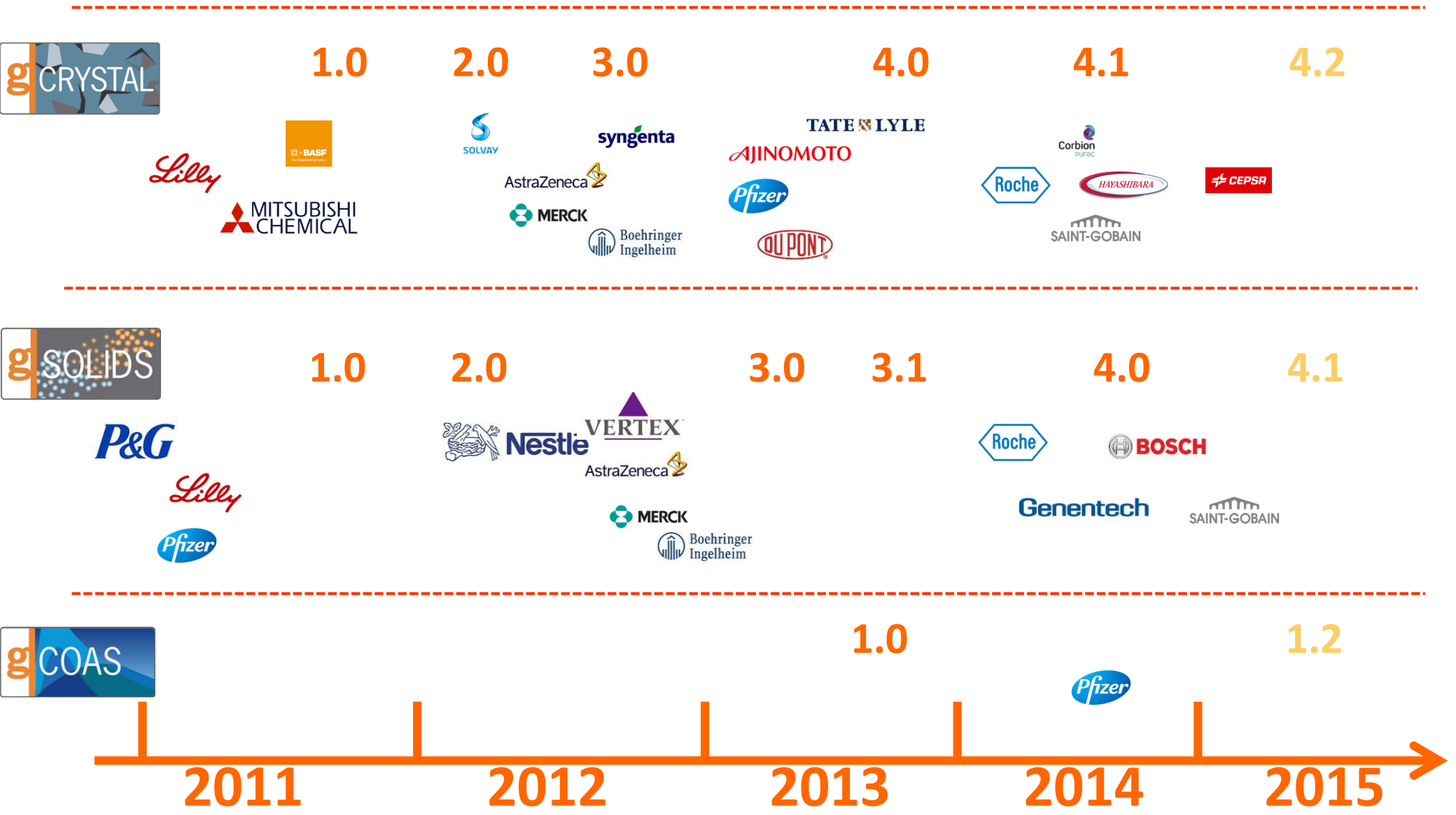
PSE tools that support decision making in the design of formulated products and their manufacturing processes



gCRYSTAL gSOLIDS gCOAS



Product timelines and adoption

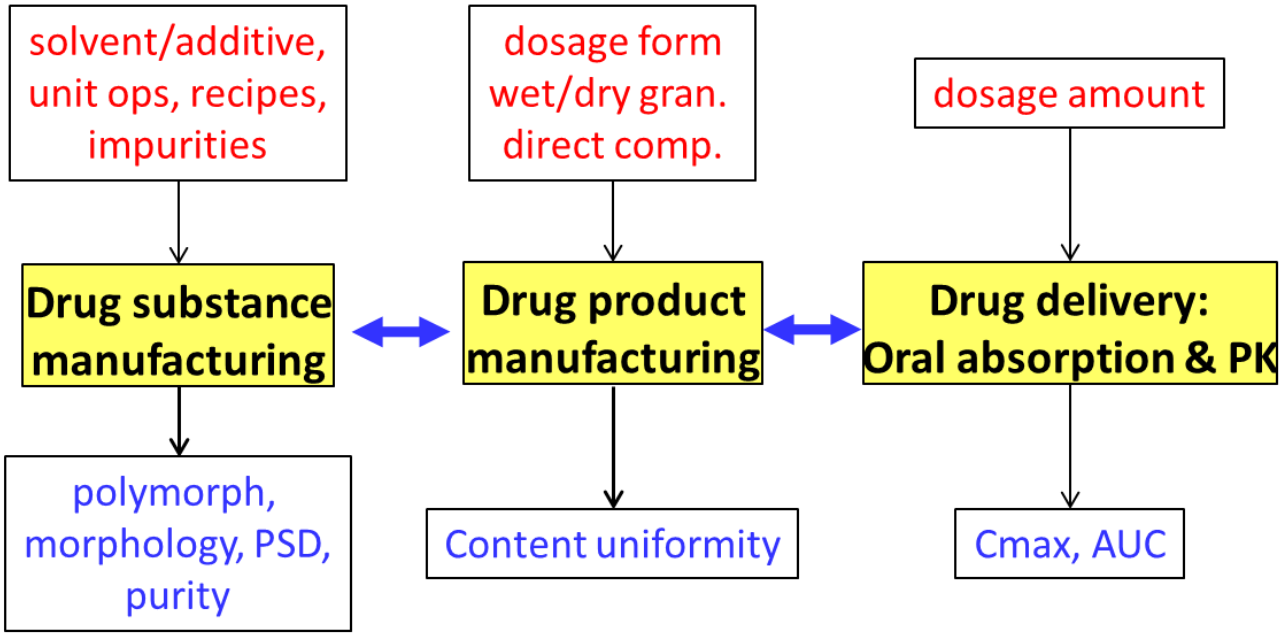


Interoperability

gCRYSTAL+gSOLIDS+gCOAS

Drivers for interoperability

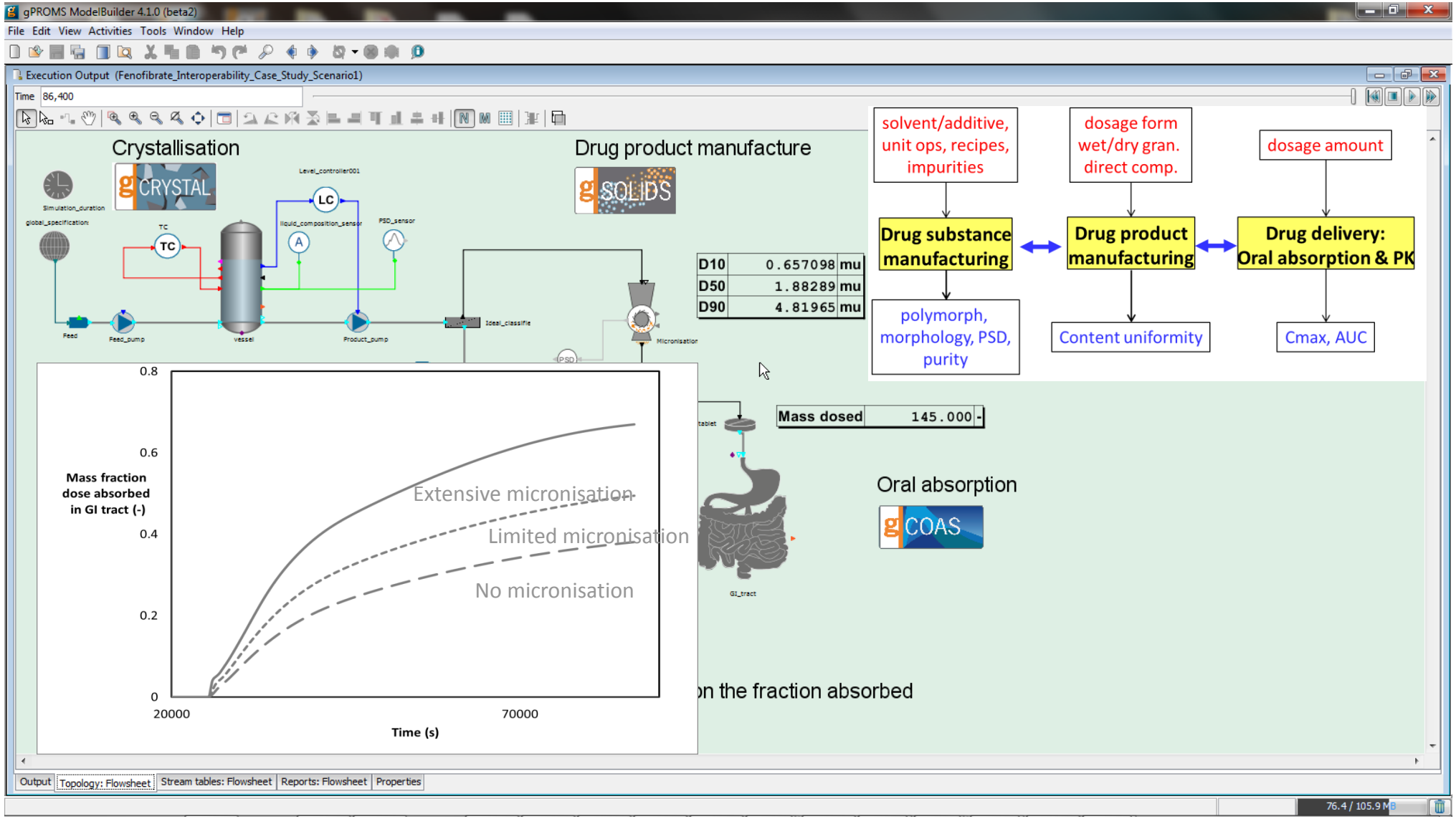
- PSE customers increasingly using multiple products
- Enable holistic view, e.g. Systems-based Pharmaceutics
- Consistency in con



Drivers for interoperability

- PSE customers increasingly using multiple products
- Enable holistic view, e.g. Systems-based Pharmaceutics
- Consistency in content, look and feel and terminology

Interoperability illustrated



A single modelling framework

Integrated mechanistic modelling for design and optimisation of formulated products and their manufacturing processes

The challenges of interoperability

Challenges? *What* challenges?

All three products are built on the same gPROMS Platform

BUT…

- Material streams carry very different physical properties information
- Multiple versions of similar models

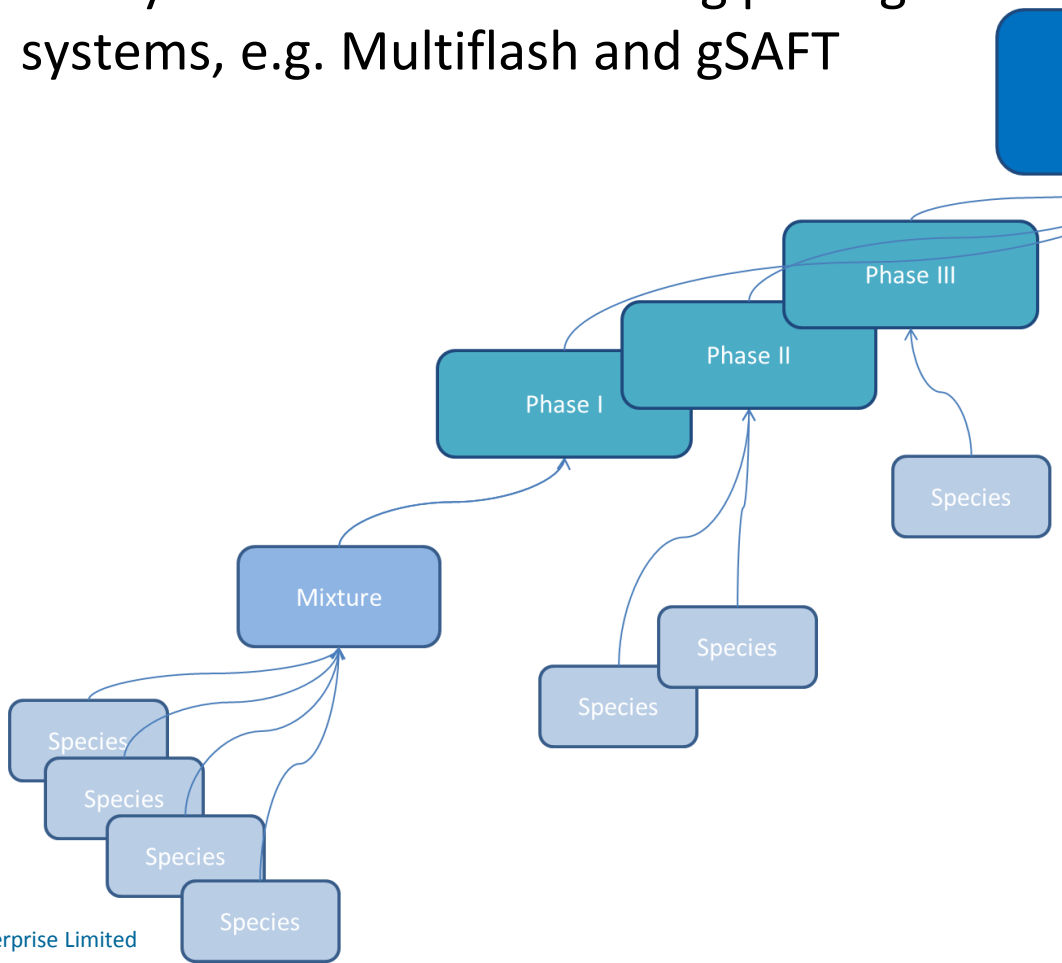
gPROMS

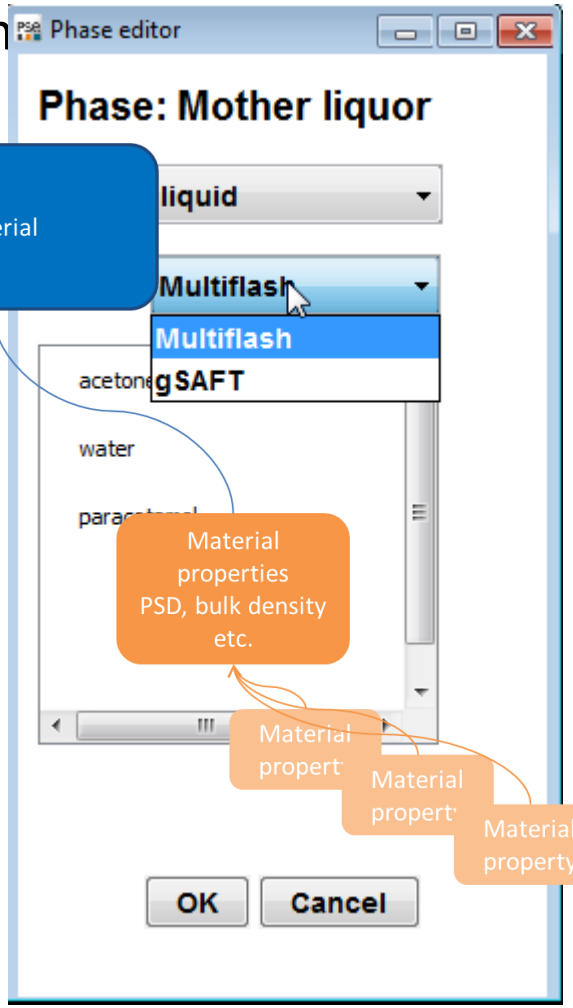
The gPROMS platform

Equation-oriented modelling & solution engine

A unified description of materials & their behaviour

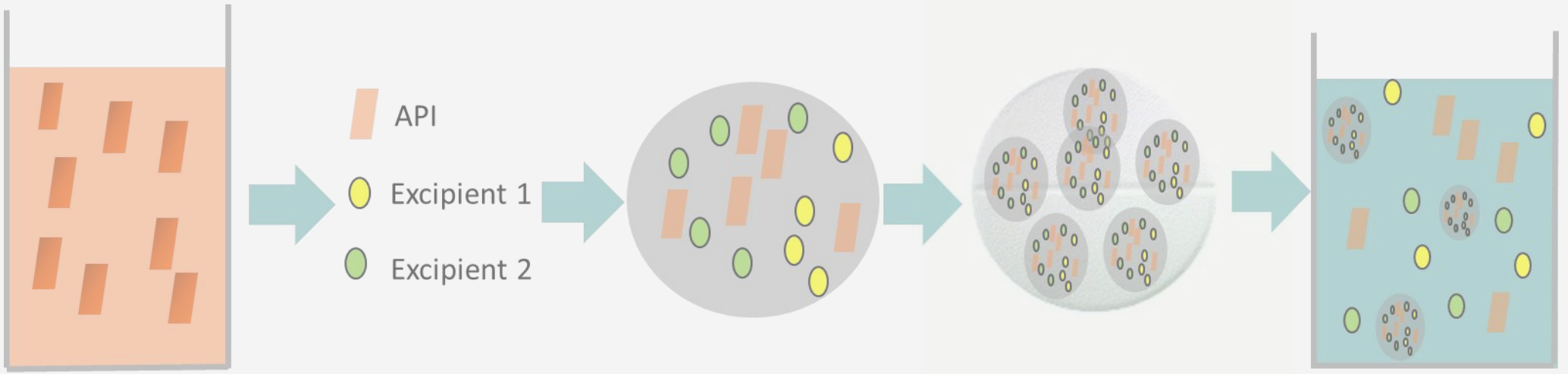
- Suitable for complex materials (*and* simple ones too)
  - representation of material in terms of species, m
  - ability to make use of existing packages for fluid systems, e.g. Multiflash and gSAFT



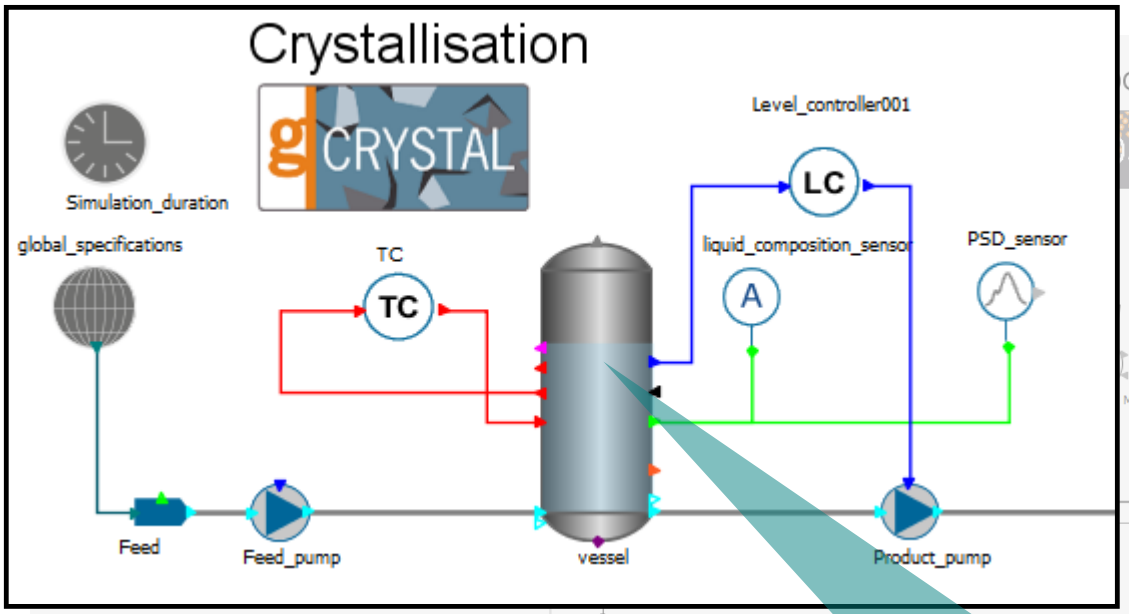


A unified material connection

- Development of an architecture to describe,
  - evolution of distributed phases
  - existence of composite phases



Crystallisation



duct manufacture

D10	–	mu
D50	–	mu
D90	–	mu

Micronisation

tablet

Mass dosed – -

Oral absorption

gCOAS

The impact of changes in the crystallization and milling operations on the fraction absorbed

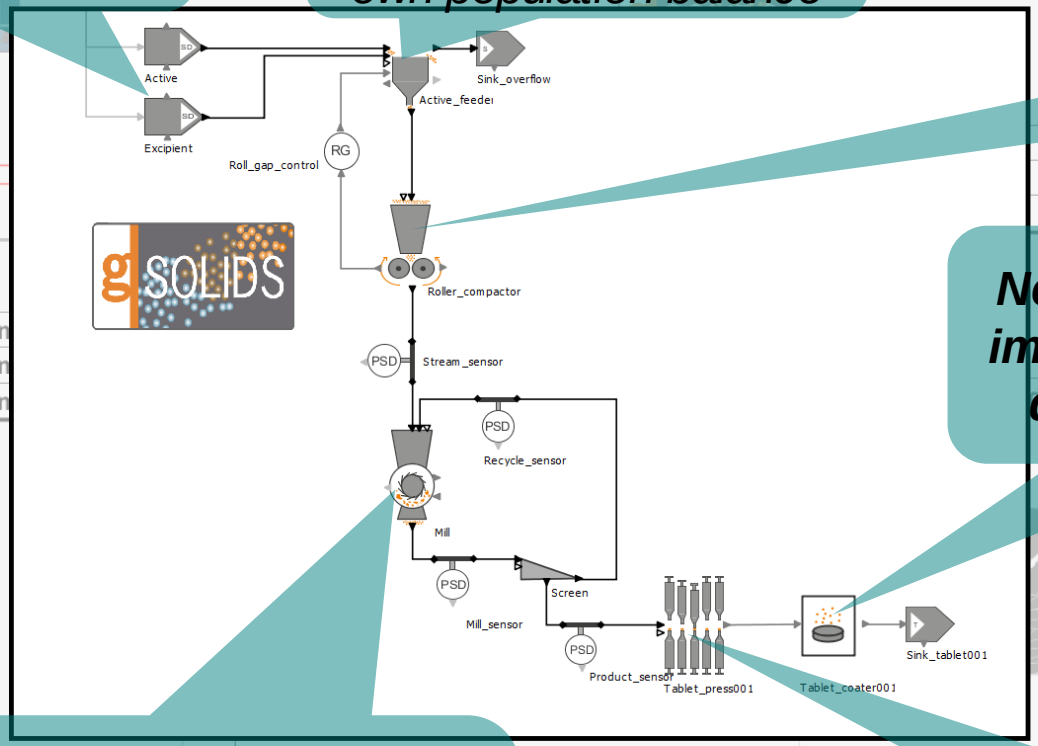
Complex phase behaviour:
Multiple precipitating / dissolving
Liquid-liquid immiscibility
Vapour-liquid equilibrium
Ionic speciation and equilibria

Property package and phase structure to handle the following complex phenomena

Solids processing

Multiple species per solid phase

Multiple solid phases, each described by its own population balance



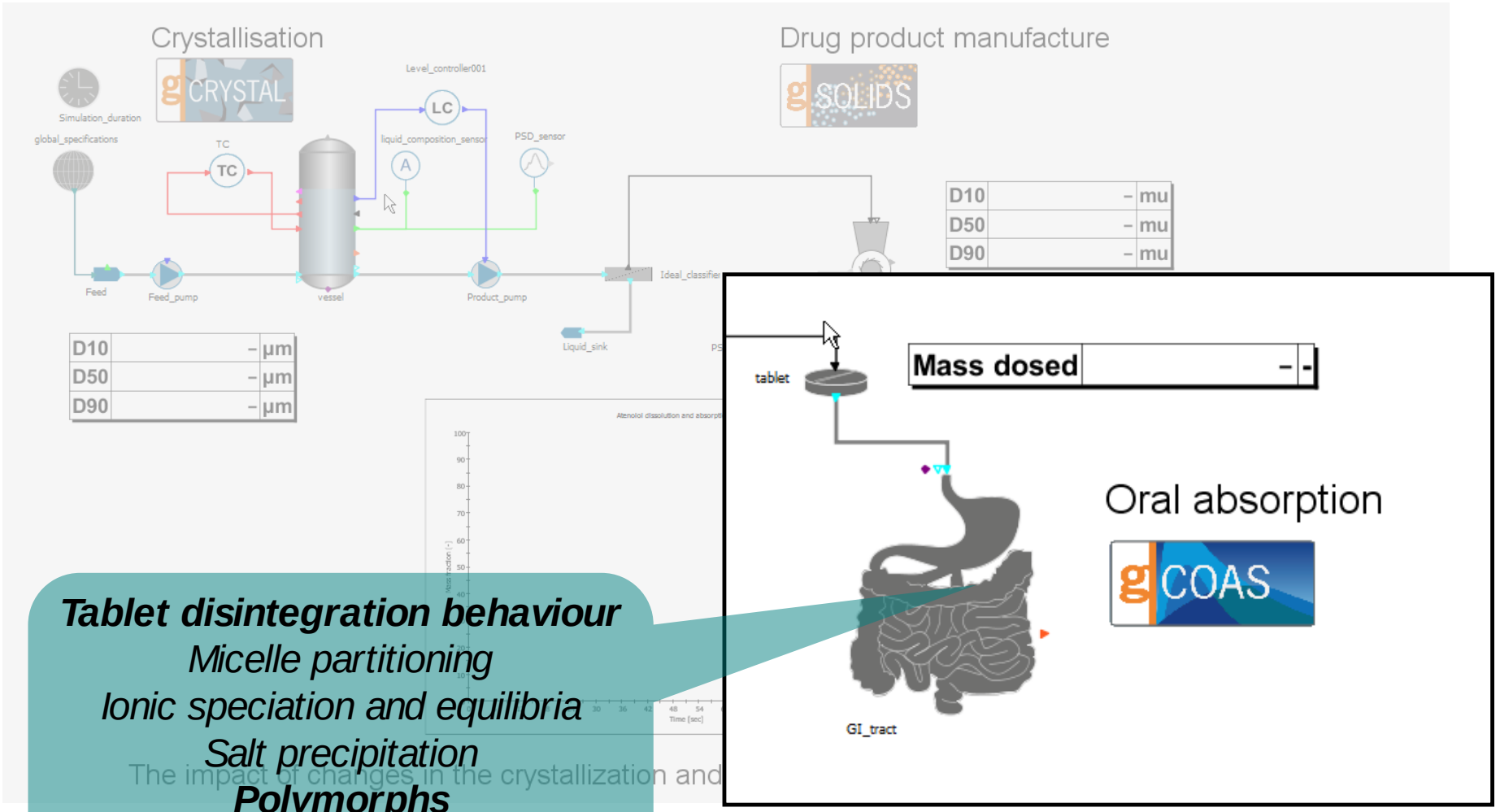
Primary particles combined into granules

Nested phase structure impacts disintegration / dissolution behaviour

Granules and roll compaction bypass are being milled. Preserve relevant properties of nested phases

Granules combined into tablets. Preserve relevant properties of granules

Oral absorption



Opportunities

Increasing usability

The new physical property infrastructure has enabled more general database feature

- Flexible database structure compatible with
  - PSE provided databases
  - 3rd party databases
  - corporate databases, etc.

Materials

Dosage forms

Equipment

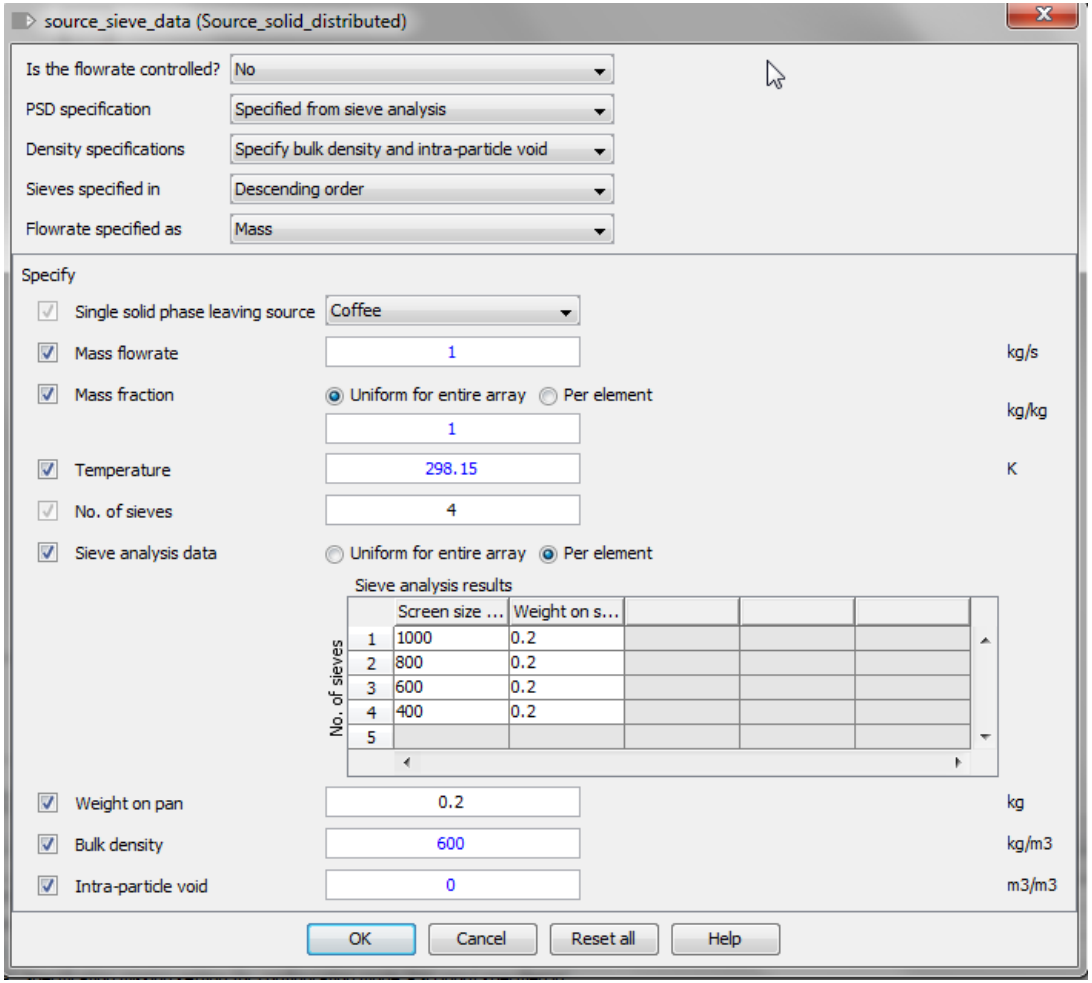
Physiology

- Significant increase in usability
  - single repository for validated data
  - less looking up of data
  - fewer transcription errors

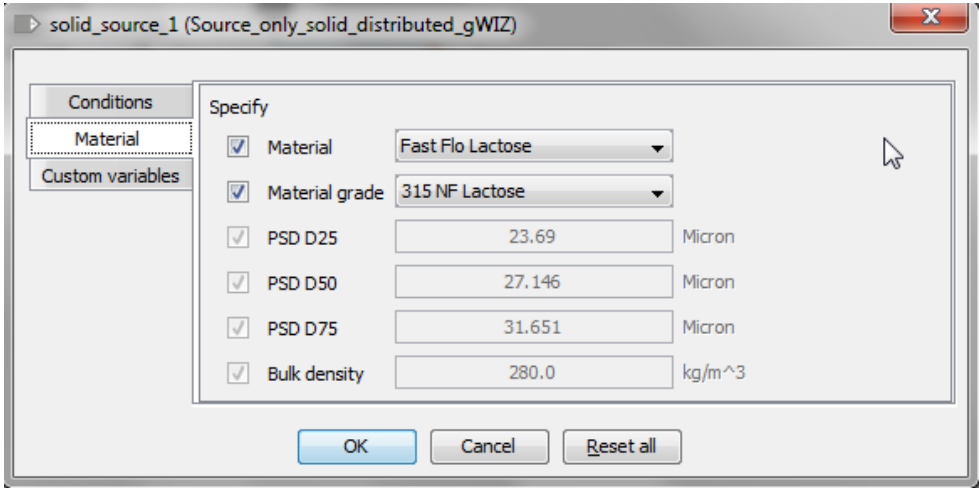
Significant increase in usability

Material database

Pre-database



Using database

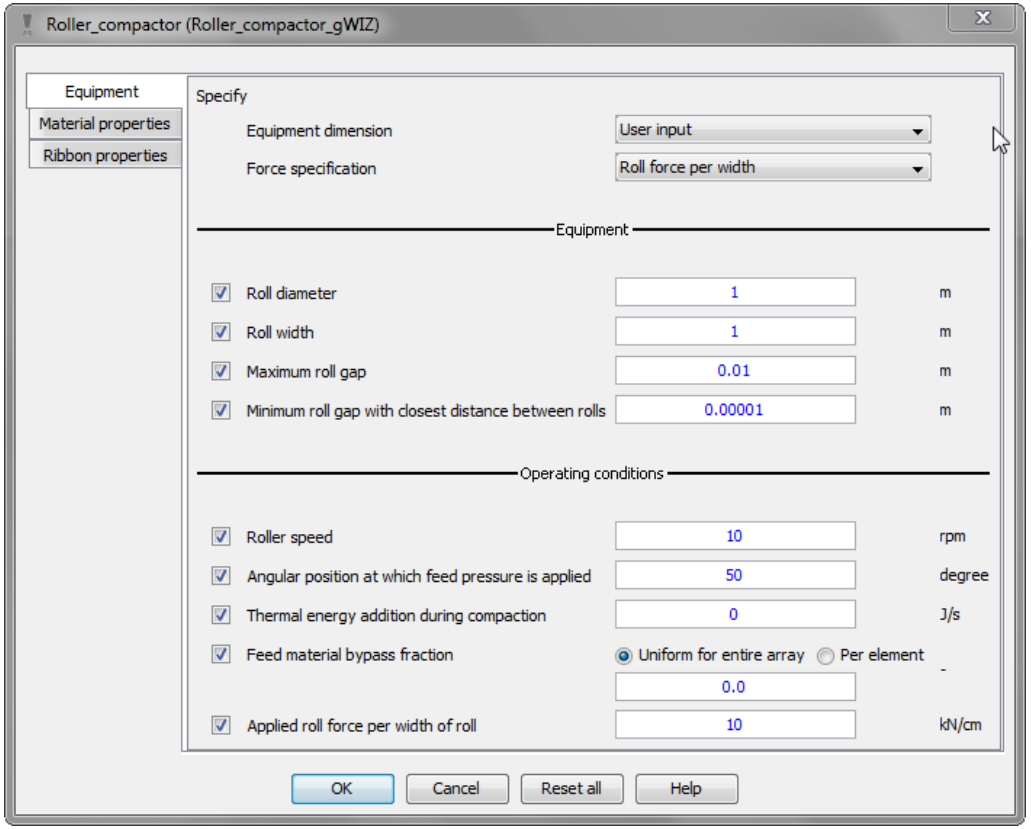


- Material list filtered by species available
- User now only needs to specify values for flowrate and temperature
- Custom material still a possibility: pre-database functionality

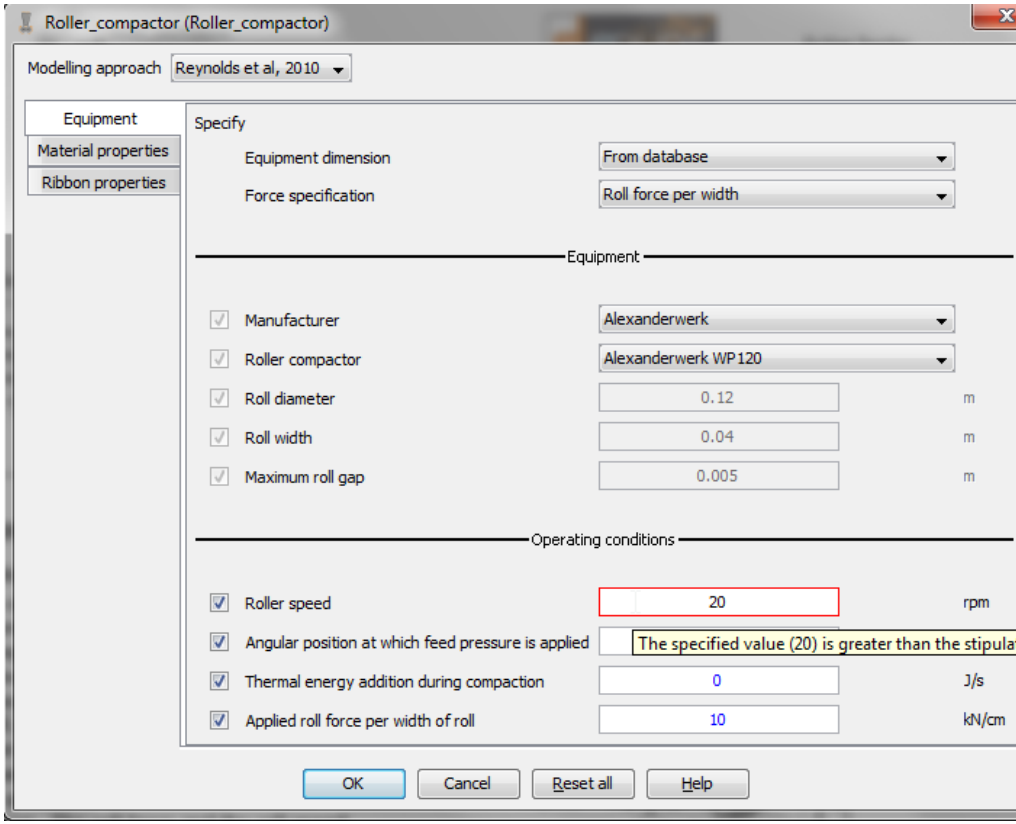
Significant increase in usability

Equipment database

Pre-database



Using database

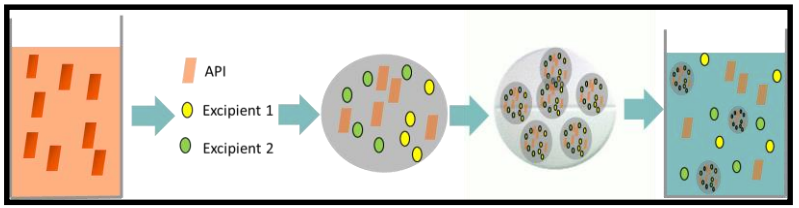


- User now only specifies operating conditions, which are verified against bounds also provided by the database
- Custom equipment still a possibility: pre-database functionality

Prototypes in action

Configure this flowsheet

Crystallisation, granulation and tablet compaction



gCRYSTAL

Liquid source
Active phases

Solid source 1
Active phases

Solid source 2
Active phases

gSOLIDS

Blender
Active phases

Crystalliser
Crystalliser D50 mu
Active phases

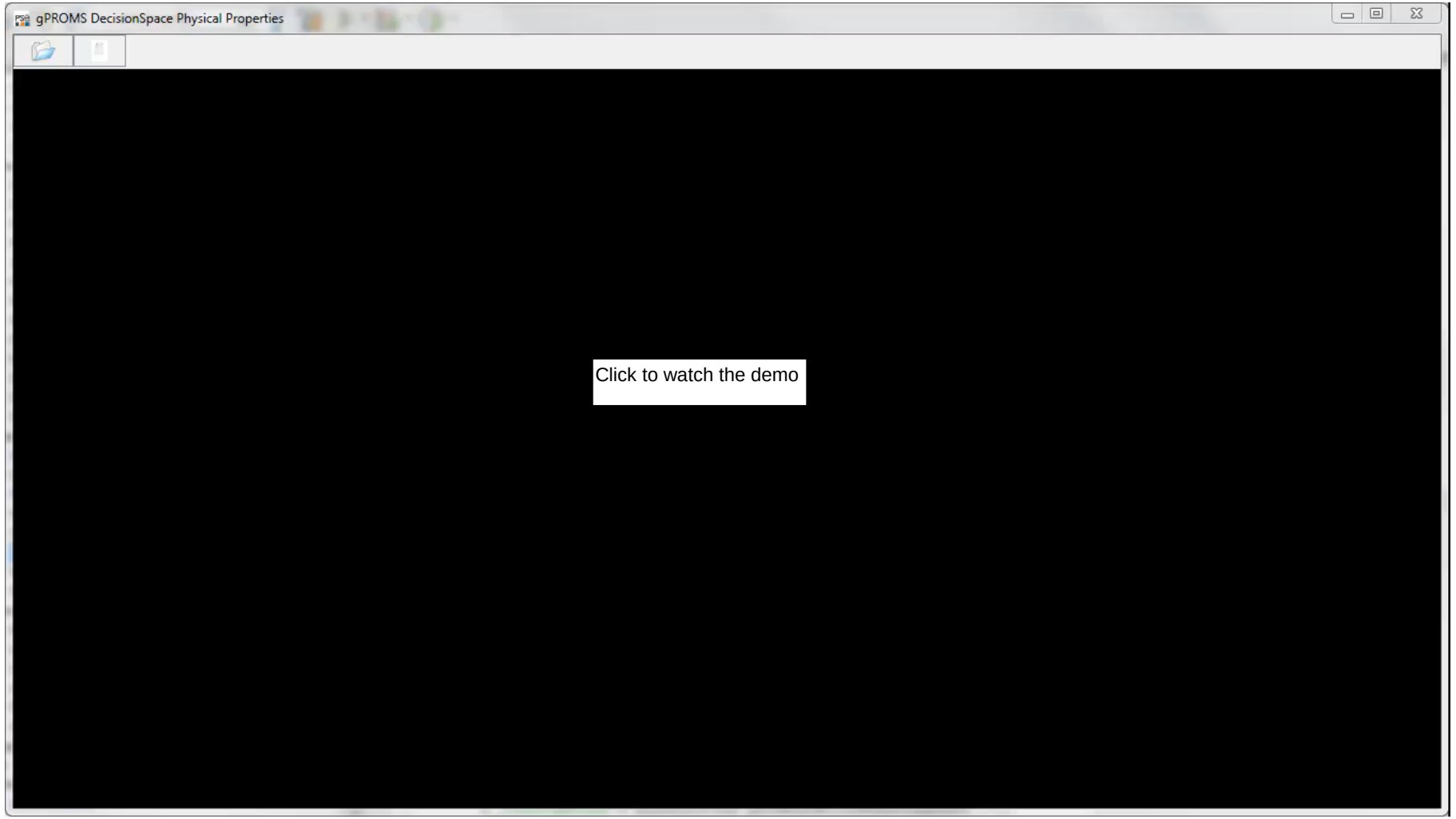
Roller compactor
Granule porosity m3/m3
Active phases
Phase hierarchy

Mill

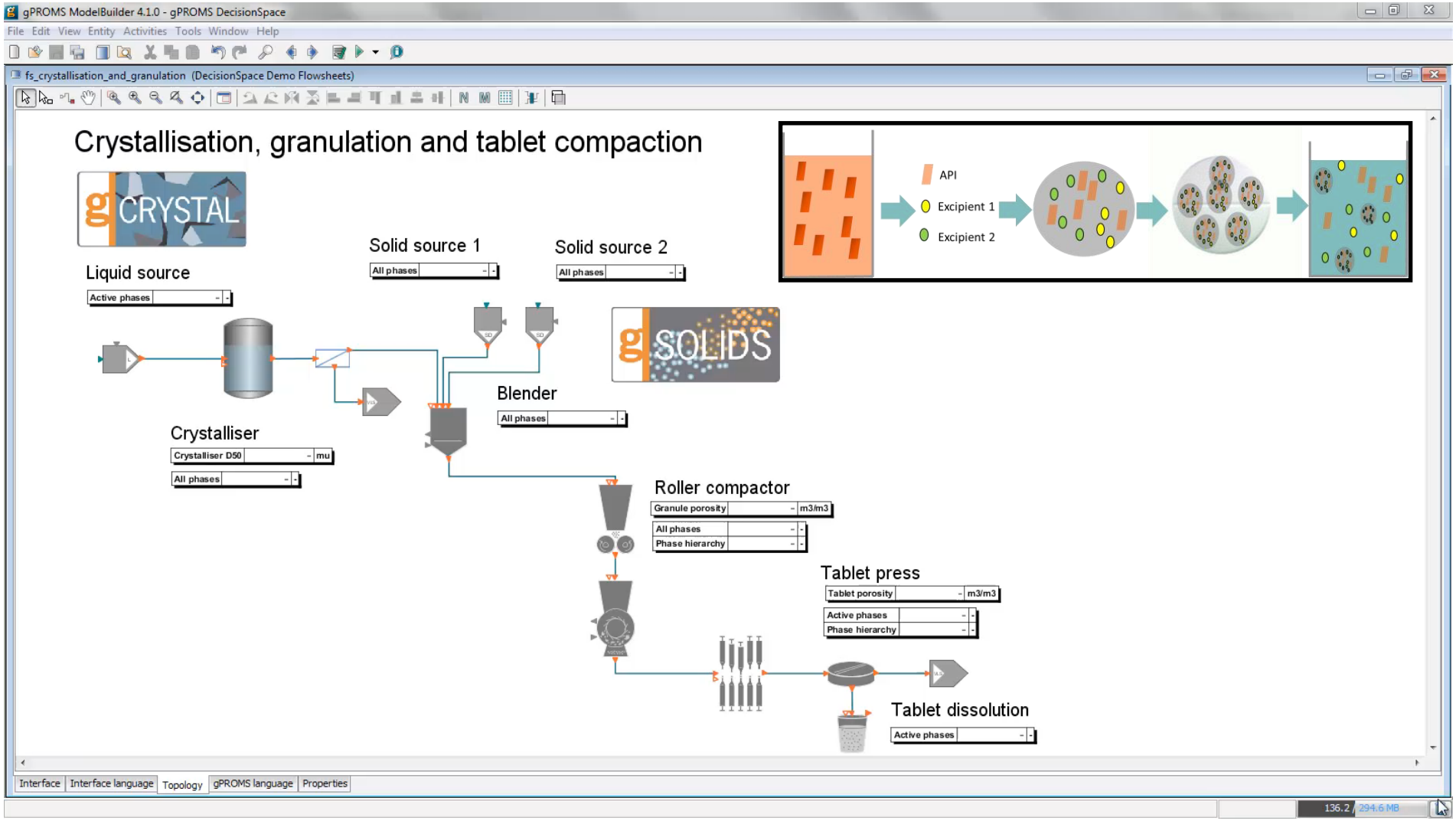
Tablet press
Tablet porosity m3/m3
Active phases
Phase hierarchy

Tablet dissolution
Active phases

Definition of physical properties



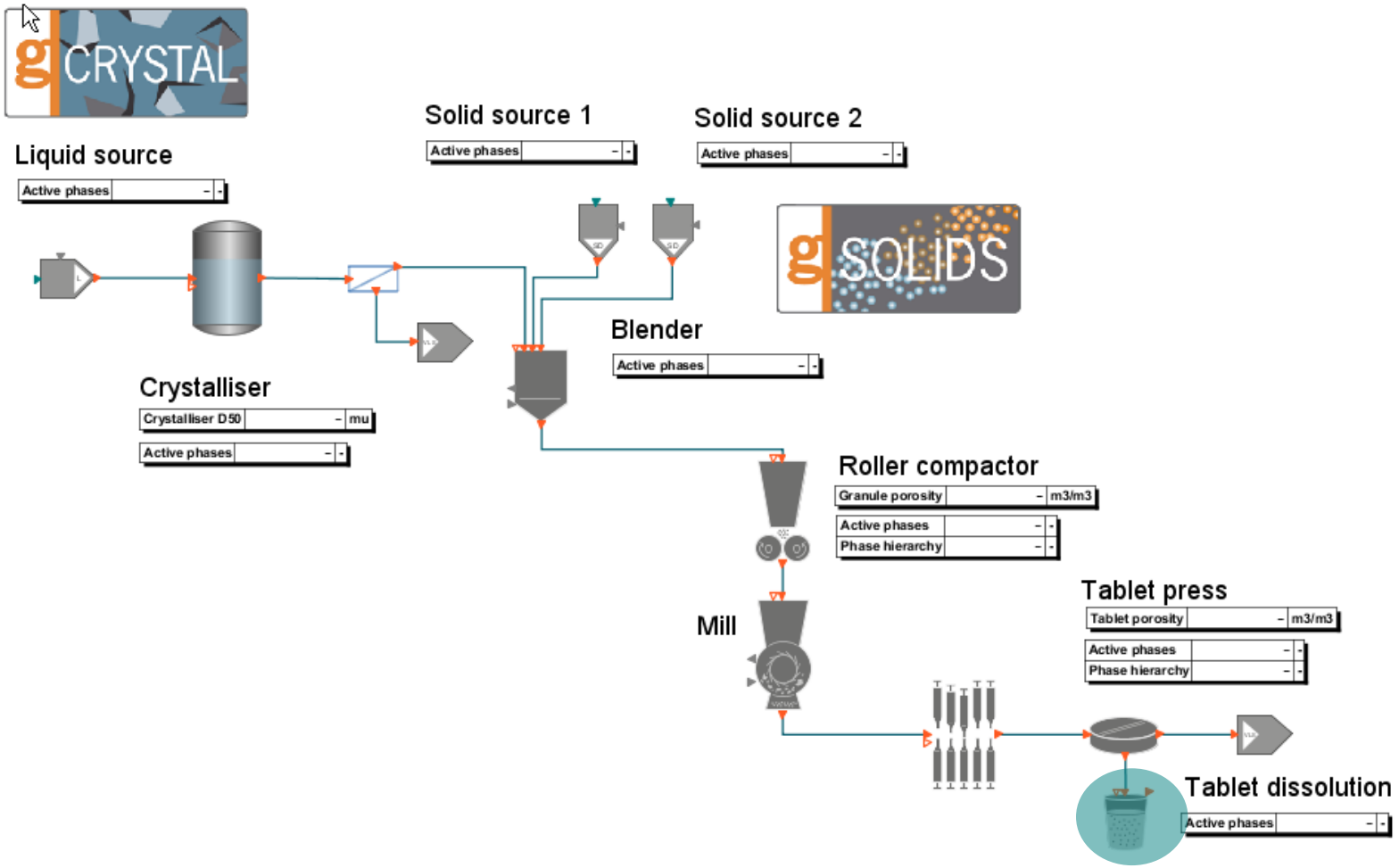
Structured phases and databases



Click on the above image to watch the demo

Let's look at some simulations…

Crystallisation, granulation and tablet compaction



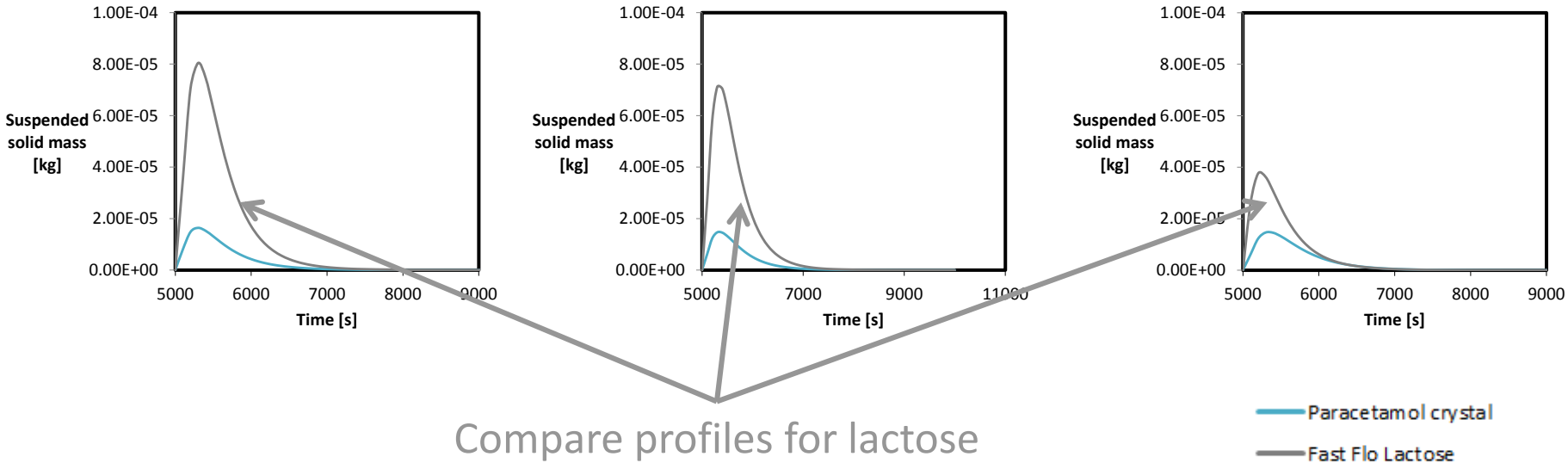
Impact of upstream processing on formulation properties

Tablet dissolution profiles for lactose and paracetamol

Scenario 1
Base case

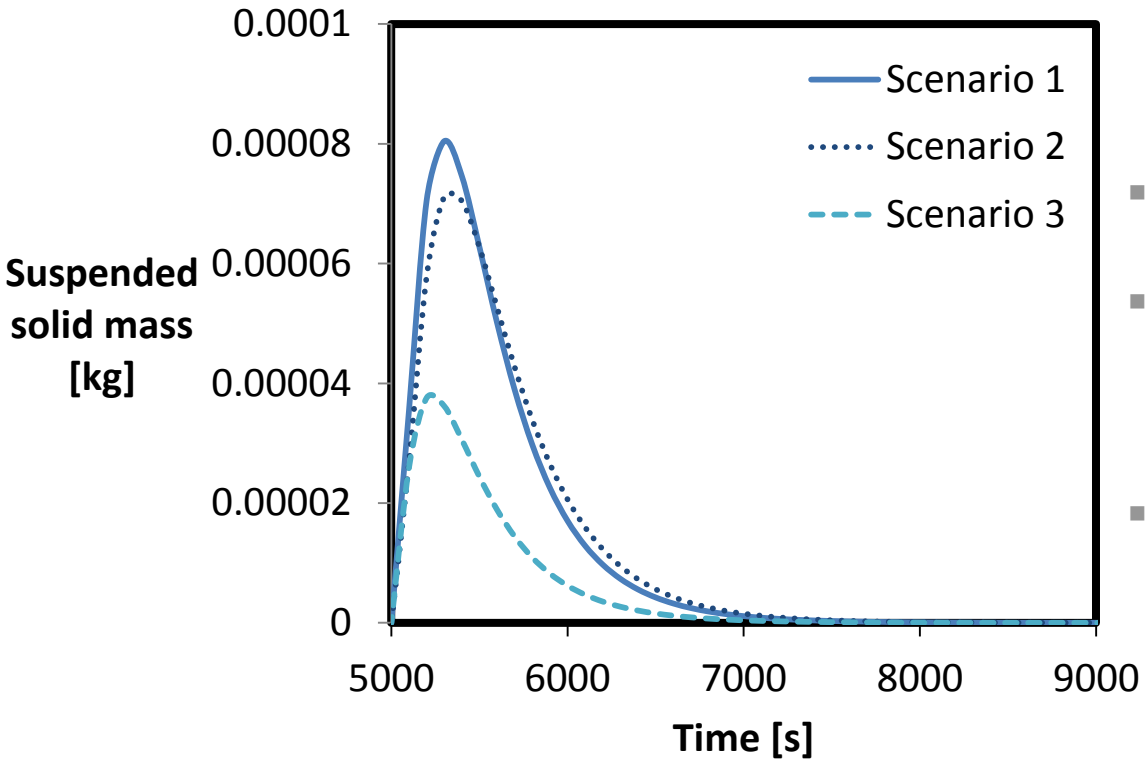
Scenario 2
Higher tablet compaction pressure

Scenario 3
Lower lactose D50



Compare profiles for lactose

Impact of upstream processing on formulation properties



Tablet dissolution profiles for lactose

- **Scenario 1:** Base case
- **Scenario 2**: Higher tablet compaction pressure -> slower tablet disintegration -> fewer suspended lactose particles
- **Scenario 3**: Lower lactose D50 -> faster lactose dissolution -> less suspended lactose

Practicalities and logistics

This interoperability stuff sounds great, but I'm only interested in one product. What will it do for me?

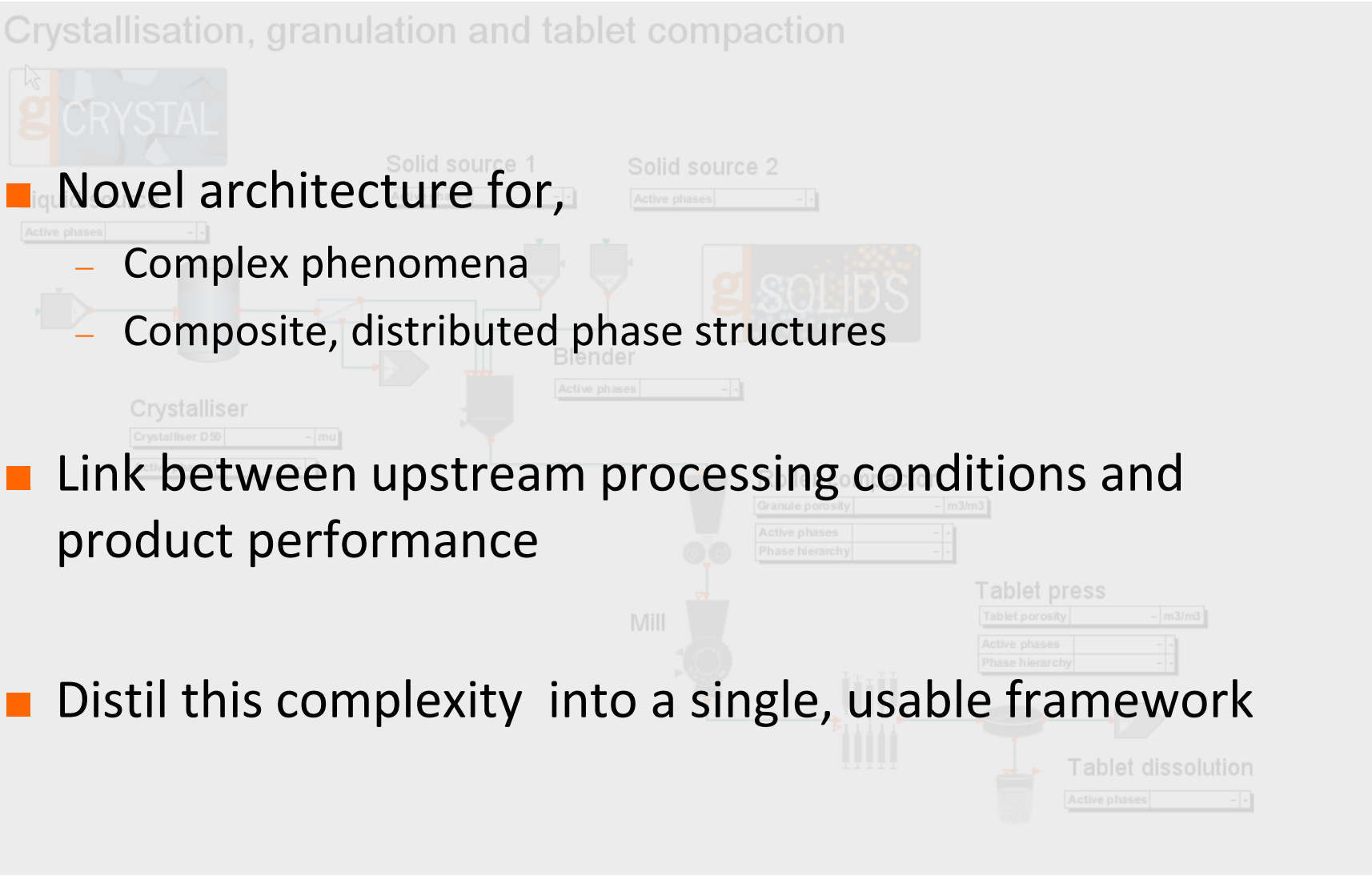
Shared functionality, e.g.,

- Databases
  - dosage forms, equipment, physiology, materials, etc.
- pH shift crystallisation
- Oiling out crystallisation
- Co-crystals
- ….

Release date and backward-compatibility

- Beta release in autumn 2015
  - on a beta of v4.2 of the gPROMS platform
- Integrated framework will be backward-compatible with gCRYSTAL, gSOLIDS and gCOAS
  - licences
  - flowsheets

Summary



- Novel architecture for,
  - Complex phenomena
  - Composite, distributed phase structures
- Link between upstream processing conditions and product performance
- Distil this complexity into a single, usable framework

Many thanks to…

- PSE Solids Advisory Board

- Costas Pantelides
- Sean Bermingham

PSE Product development team for Life Sciences, Food, Consumer Goods, Specialty and Agrochemicals,

- Niall Mitchell – London, gCRYSTAL
- David Slade – London, gSOLIDS
- Edd Close – London, gCOAS
- Jianfeng Li – New Jersey, gSOLIDS
- Dana Barrasso – New Jersey, gSOLIDS
- Dan Braido – New Jersey, gCOAS

- PSE Software Technology Group

Thank you