APM 2013

The Advanced Process Modelling Forum

17-18 April 2013, London

Systems-based Pharmaceutics (SbP)
An update

Sean Bermingham, PSE Life Sciences, Consumer Goods & Fine Chemicals

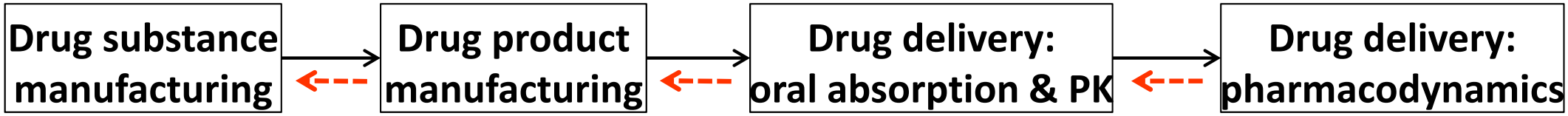
Overview

- A brief recap of the SbP vision
- Realising the SbP vision
  - How far have PSE and our clients come?
  - What's next?
- Concluding remarks

A brief recap of the SbP vision

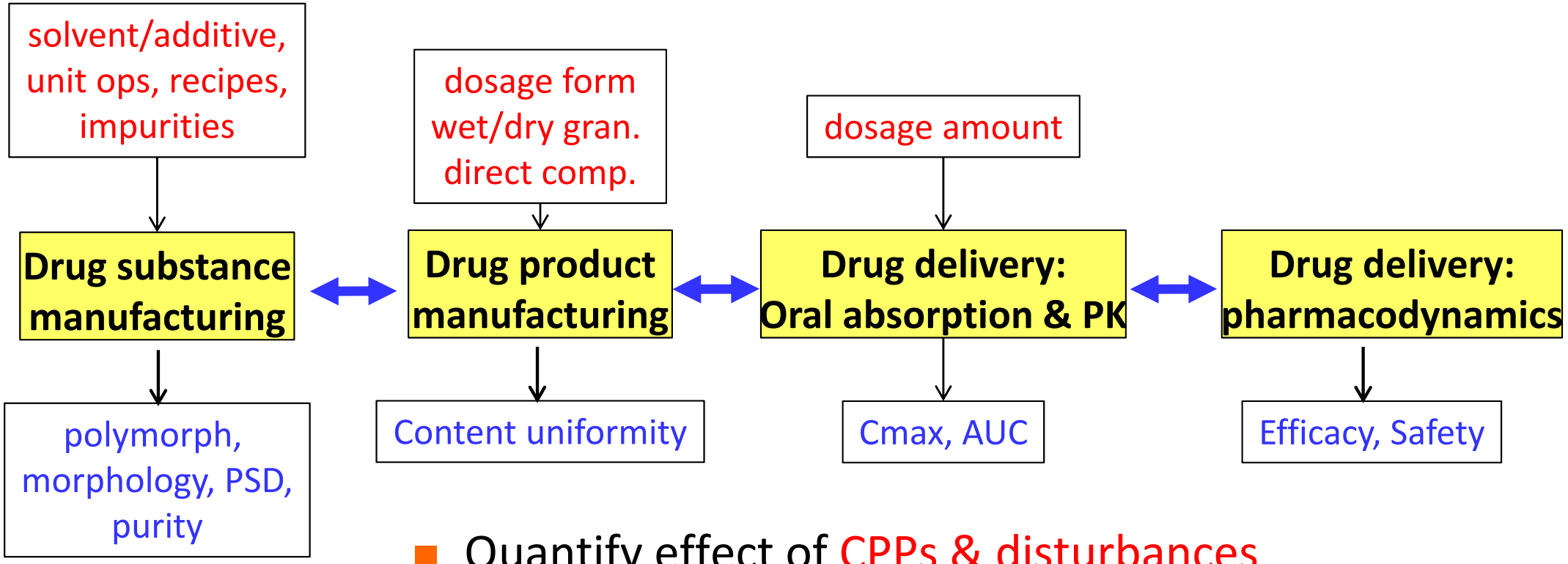
Why SBP?

What we have heard from industry about **current state**



- Silo thinking
  - reflected in both available tools and organizational structures
- Results in too many iterations …
  - between product design and manufacturing process design
  - between subsequent manufacturing steps
  - between bioavailability targets and drug product/process development
  - between R&D and manufacturing (Tech Transfer)
- … and other inefficiencies
  - no central repository of consistent knowledge
  - many, long learning curves

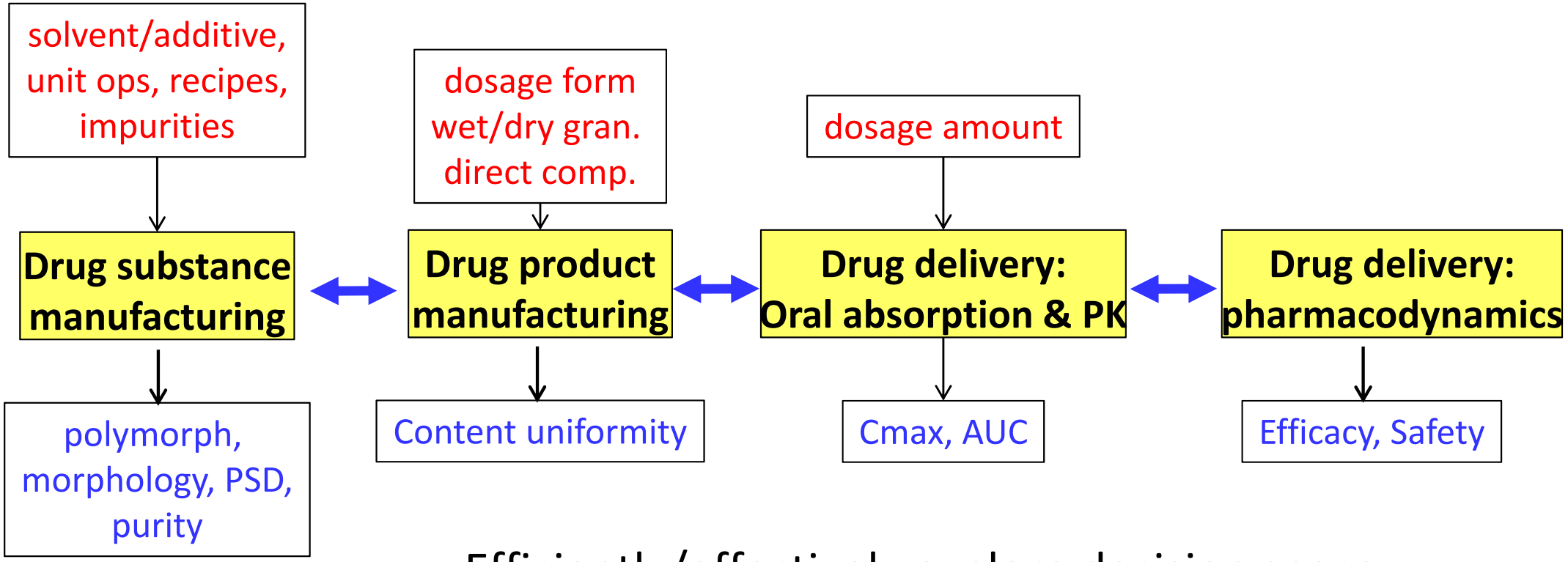
End-to-end decision support for pharma R&D



- Quantify effect of CPPs & disturbances
  - uncertainty in process knowledge
  - common cause variability

  on Key Performance Indicators
  - Critical Quality Attributes
  - process economics, operability, safety
- **From surrogate objectives to true KPIs**

End-to-end decision support for pharma R&D



- Efficiently/effectively explore decision space
  - use advanced mathematics to reduce trial-and-error approaches
- Manage risk by quantifying impact of uncertainty
  - model uncertainties
  - external disturbances, e.g. excipient characteristics

A repository for current & future knowledge

- Provide a formal framework for the **capture and generation of knowledge** - both current and future
  - support pharma eco-system
    - companies, universities, research organizations, suppliers
  - facilitate consistency, quality assurance
  - different stages of product/process lifecycle: R&D, Manufacturing, …
- …and the **effective deployment and exploitation** of this knowledge in a sustainable and secure manner
  - make benefits of models available to all stakeholders
  - ensure traceability/auditability of model-based decisions
- **Share what's common** across the industry, while supporting the development of **competitive advantage** where appropriate
  - common "language" for effective, industry-wide transfer of knowledge & ideas
  - facilitate regulatory approval

Initial feedback from the pharmaceutical industry

- Fairly unanimous agreement with objectives
  - increase R&D efficiency
  - manage risk associated with tech transfer
  - reduce silo mentality

- Mixed feelings whether the quality of available mechanistic models allows for the vision to be turned into reality

How far have PSE and our clients come?

Realising the Systems-based Pharmaceutics vision

Product development

gCRYSTAL v3

- Multiple kinetic model options per phenomenon
- Enhanced solubility models, mainly aimed at AS crystallization
- Temperature and composition sensor
- Fluid mixing analyzer
- Solubility analyzer and regression tool
- PSD comparison tool

gSOLIDS v3

- Electrostatic precipitator
- Steady state & dynamic screen
- Fluid bed agglomerator
- Improvements to dryer models
- Agglomerator with breakage
- Tablet press
- Tablet coater
- Tablet dissolver
- Sensors
- Roll gap control

How far have PSE and our clients come?

Life Sciences session at APMF 2012

Life Sciences Keynote: A new vision for Systems-based Pharmaceutics	
Pfizer Ravi Shanker	Systems-based Pharmaceutics is a revolutionary model-based approach for optimising drug manufacture and delivery by taking a holistic view that encompasses both biological effects in the human body and drug substance and product engineering. Ravi Shanker explains the vision, developed by PSE and leading pharma companies, that has the potential to change the way that pharmaceutical companies design manufacturing and delivery processes.
Using gCRYSTAL to optimise a batch crystallisation process	
Eli Lilly Christopher Burcham	A typical use of gCRYSTAL is to analyse and optimise batch crystallisation processes. Chris Burcham describes how experimental data are used to estimate accurate kinetic parameters for growth, attrition and other phenomena; the validated model is then used to optimise the recipe subject to quality constraints.
Dynamic flowsheet simulation of continuous pharmaceutical manufacturing processes with gSOLIDS	
Rutgers University ERC-SOPS Rohit Ramachandran	Regulatory authorities recognise the benefit of model-based design and control in a Quality by Design (QbD) approach to continuous pharmaceutical manufacturing. Dynamic flowsheet modelling is a pre-requisite for the design, analysis, control and optimisation of an integrated process. The ERC-SOPS consortium is developing high-fidelity models implemented within gPROMS and gSOLIDS to study the effect of upstream material properties and process parameters on downstream pharmaceutical critical quality attributes (CQAs). The dynamic simulation is used to better optimise and design processes, reducing experimentation and enhancing product quality, profitability and sustainability.
Using gSOLIDS to manage risk in organic and aqueous tablet film coating processes	
Pfizer Salvador Garcia Muñoz **PSE** Mark Pinto Simon Leyland	Tablet coating, in which tablets are coated with an aqueous or organic film coating, is an important processing step in the pharmaceutical industry. Pfizer uses rigorous gSOLIDS models to aid in design of experiments, scale-up and determining optimal process conditions as formulations change. This provides process engineers with a means of predicting target operating conditions for optimisation, scale-up and robustness studies. For ease of use, models are delivered to technicians via an EASA web interface.
Using gSOLIDS to optimise spray drying operations	
GSK Thoralf Hartwig	GSK uses spray drying as a particle forming strategy for making drug substances. The correct selection and adjustment of spray drying process parameters is crucial to ensure that dried powder of the desired quality and physical characteristics is consistently produced across scales. This presentation describes the approach used to model the spray chamber and the cyclone in gSOLIDS in order to identify optimal conditions for spray drying active pharmaceutical ingredients.
Systems-Based Pharmaceutics – transforming drug manufacturing in the pharmaceutical industry	
PSE Costas Pantelides Sean Bermingham	APM techniques make it possible to consider a systems-based approach to pharmaceutical processes, where the manufacturing steps are optimised to ensure optimal delivery of the drug in the human intestine. Two of the leading innovators in this area, PSE MD Costas Pantelides and Sean Bermingham, VP of PSE's Solids business, explain the underlying concepts behind the vision presented by Ravi Shanker earlier.

- Presentation of SbP concept
- Unit operations
  - crystallization
  - spray drying
  - tablet coating
- Flowsheet modelling

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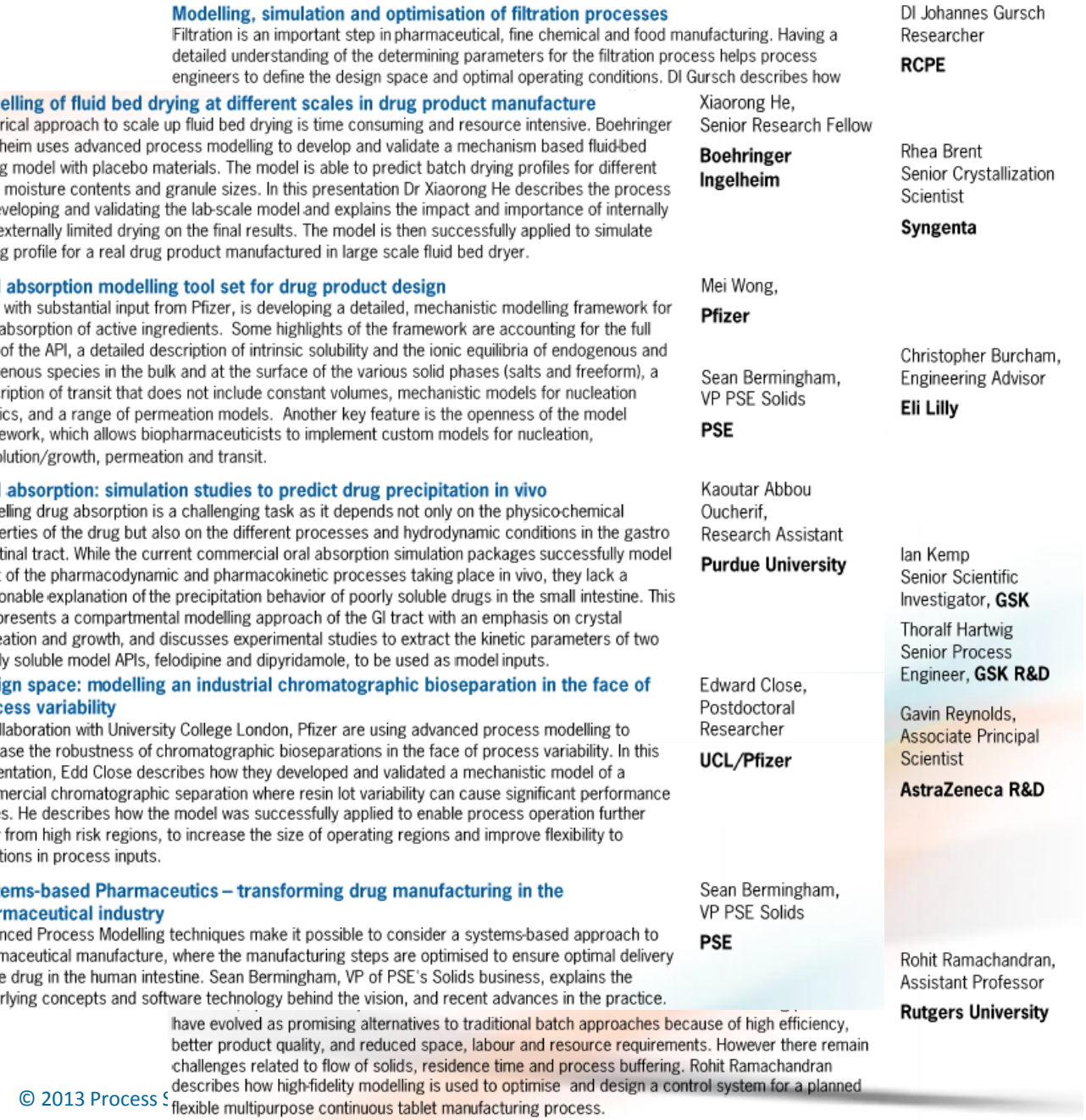
How far have PSE and our clients come?

Life Sciences & Fine Chemicals session at APMF 2013



Modelling, simulation and optimisation of filtration processes
Filtration is an important step in pharmaceutical, fine chemical and food manufacturing. Having a detailed understanding of the determining parameters for the filtration process helps process engineers to define the design space and optimal operating conditions. DI Gursch describes how

DI Johannes Gursch
Researcher
RCPE

elling of fluid bed drying at different scales in drug product manufacture
rical approach to scale up fluid bed drying is time consuming and resource intensive. Boehringer heim uses advanced process modelling to develop and validate a mechanism based fluid-bed g model with placebo materials. The model is able to predict batch drying profiles for different moisture contents and granule sizes. In this presentation Dr Xiaorong He describes the process veloping and validating the lab-scale model and explains the impact and importance of internally externally limited drying on the final results. The model is then successfully applied to simulate g profile for a real drug product manufactured in large scale fluid bed dryer.

Xiaorong He,
Senior Research Fellow
Boehringer Ingelheim

absorption modelling tool set for drug product design
with substantial input from Pfizer, is developing a detailed, mechanistic modelling framework for absorption of active ingredients. Some highlights of the framework are accounting for the full of the API, a detailed description of intrinsic solubility and the ionic equilibria of endogenous and enous species in the bulk and at the surface of the various solid phases (salts and freeform), a ription of transit that does not include constant volumes, mechanistic models for nucleation ics, and a range of permeation models. Another key feature is the openness of the model ework, which allows biopharmaceuticists to implement custom models for nucleation, olution/growth, permeation and transit.

Mei Wong,
Pfizer

Sean Bermingham,
VP PSE Solids
PSE

Rhea Brent
Senior Crystallization Scientist
Syngenta

Christopher Burcham,
Engineering Advisor
Eli Lilly

absorption: simulation studies to predict drug precipitation in vivo
elling drug absorption is a challenging task as it depends not only on the physico-chemical erties of the drug but also on the different processes and hydrodynamic conditions in the gastro tinal tract. While the current commercial oral absorption simulation packages successfully model of the pharmacodynamic and pharmacokinetic processes taking place in vivo, they lack a onable explanation of the precipitation behavior of poorly soluble drugs in the small intestine. This presents a compartmental modelling approach of the GI tract with an emphasis on crystal eation and growth, and discusses experimental studies to extract the kinetic parameters of two ly soluble model APIs, felodipine and dipyridamole, to be used as model inputs.

Kaoutar Abbou Oucherif,
Research Assistant
Purdue University

Ian Kemp
Senior Scientific Investigator, **GSK**

Thoralf Hartwig
Senior Process Engineer, **GSK R&D**

gn space: modelling an industrial chromatographic bioseparation in the face of cess variability
llaboration with University College London, Pfizer are using advanced process modelling to ase the robustness of chromatographic bioseparations in the face of process variability. In this entation, Edd Close describes how they developed and validated a mechanistic model of a nercial chromatographic separation where resin lot variability can cause significant performance s. He describes how the model was successfully applied to enable process operation further from high risk regions, to increase the size of operating regions and improve flexibility to tions in process inputs.

Edward Close,
Postdoctoral Researcher
UCL/Pfizer

Gavin Reynolds,
Associate Principal Scientist
AstraZeneca R&D

ems-based Pharmaceutics – transforming drug manufacturing in the rmaceutical industry
nced Process Modelling techniques make it possible to consider a systems-based approach to maceutical manufacture, where the manufacturing steps are optimised to ensure optimal delivery e drug in the human intestine. Sean Bermingham, VP of PSE's Solids business, explains the rlying concepts and software technology behind the vision, and recent advances in the practice.

Sean Bermingham,
VP PSE Solids
PSE

Rohit Ramachandran,
Assistant Professor
Rutgers University

have evolved as promising alternatives to traditional batch approaches because of high efficiency, better product quality, and reduced space, labour and resource requirements. However there remain challenges related to flow of solids, residence time and process buffering. Rohit Ramachandran describes how high-fidelity modelling is used to optimise and design a control system for a planned flexible multipurpose continuous tablet manufacturing process.

- Unit operations
  - crystallization (2)
  - filtration
  - spray drying
  - fluid bed drying
- Oral absorption (2)
- System modelling and control (2)
  - linking manufacturing behaviour to dissolution performance

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What's next?

Realising the Systems-based Pharmaceutics vision

What's next?

- Significant input to roadmap from Advisory Board
  - BASF, Eli Lilly, GSK, Nestle, Novozymes, P&G, Pfizer, Solvay Purdue University, Sheffield University & TU Delft

- Priorities for 2013/4
  - Enhancements to existing APM tools 

  - A new APM tool for oral absorption modelling 

  - Interoperability between those products and with PSE APM tools
  - Physical properties and material properties
  - Design space / Sensitivity analyses of CQAs with respect to
    - CPPs
    - uncertainty in process knowledge
    - process variability

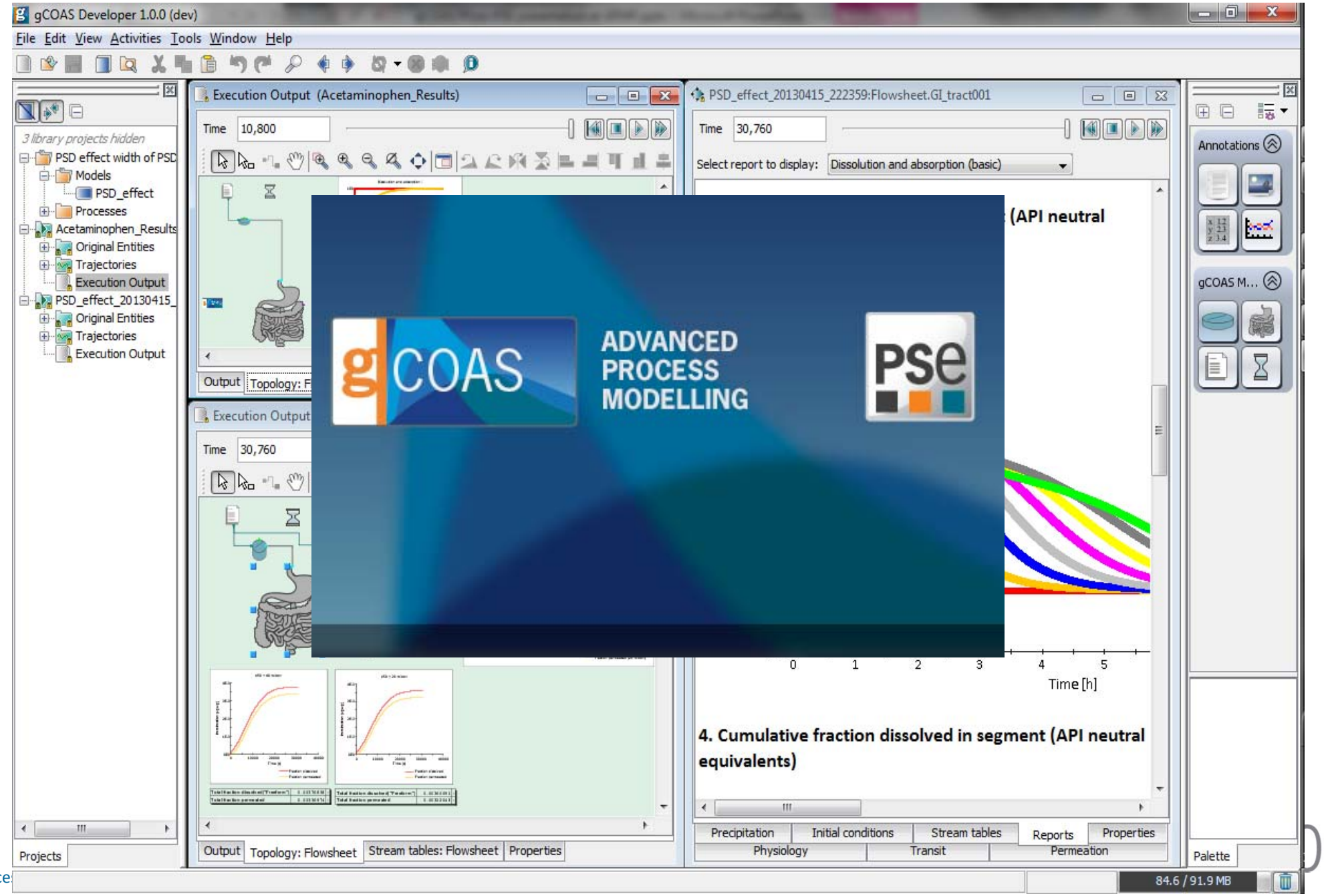
Enhancements to existing APM tools

- Additional unit operations
  - Seed pot
  - Wurster column
  - fluid bed granulation
  - HSWG
  - 1-2 screw granulators

- Significant usability enhancements to parameter estimation and optimisation
  - same naming as used for inputs and outputs of simulations
  - import dialog box values (simulation) as initial guesses (for PE)
  - option to update dialog box values with obtained parameter estimates

What's next?

Release a new APM tool for oral absorption modelling



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Concluding remarks

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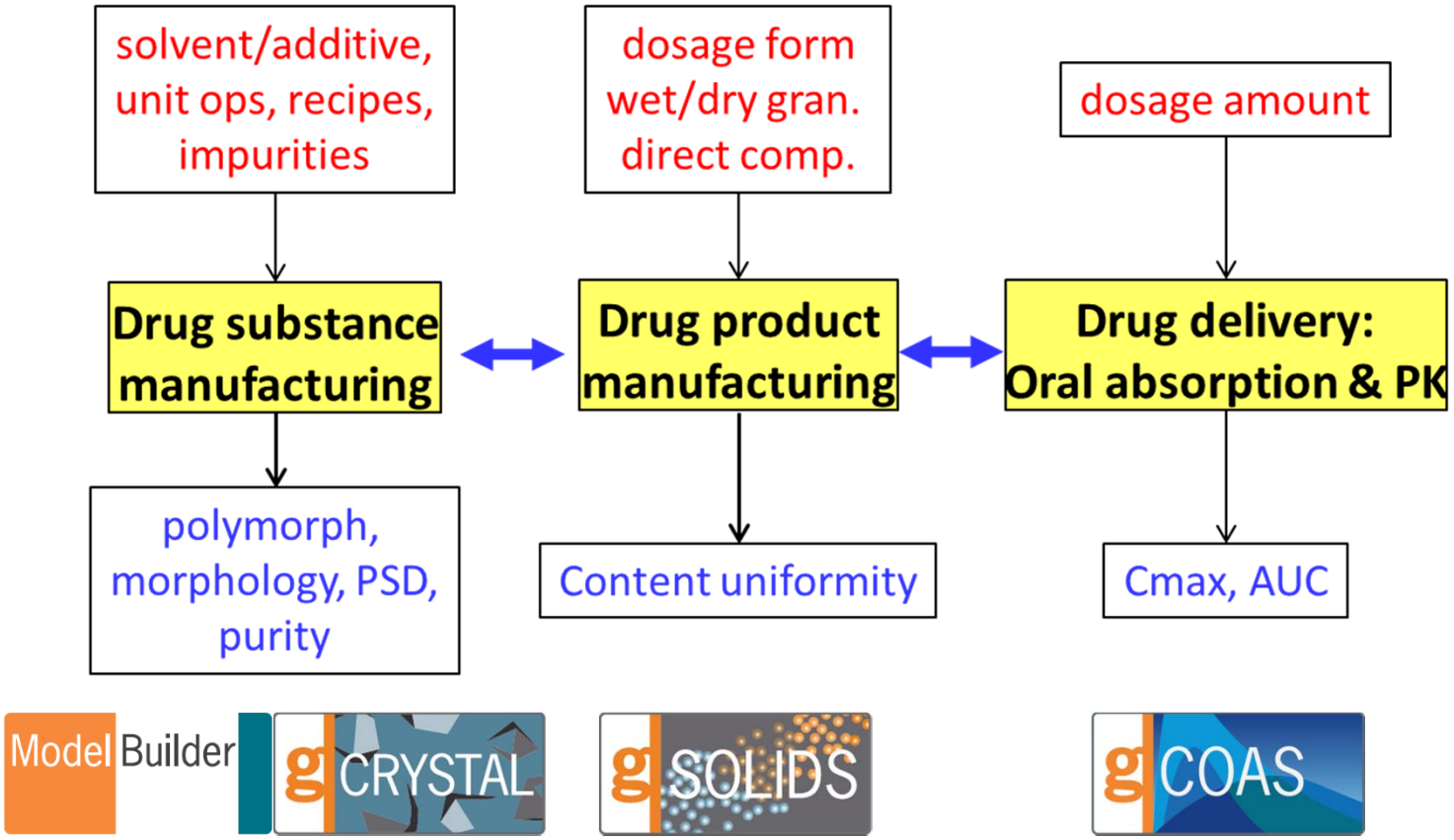
- SbP is a holistic approach to the development and optimization of drug manufacture and drug delivery systems



  - supported by mechanistic APM tools
  - being adopted by a rapidly increasing number of companies

Thank you!

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