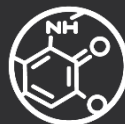# APM

ADVANCED PROCESS MODELLING FORUM **2014**

PSe

Systems-based Pharmaceutics
Progress update on turning the vision into reality
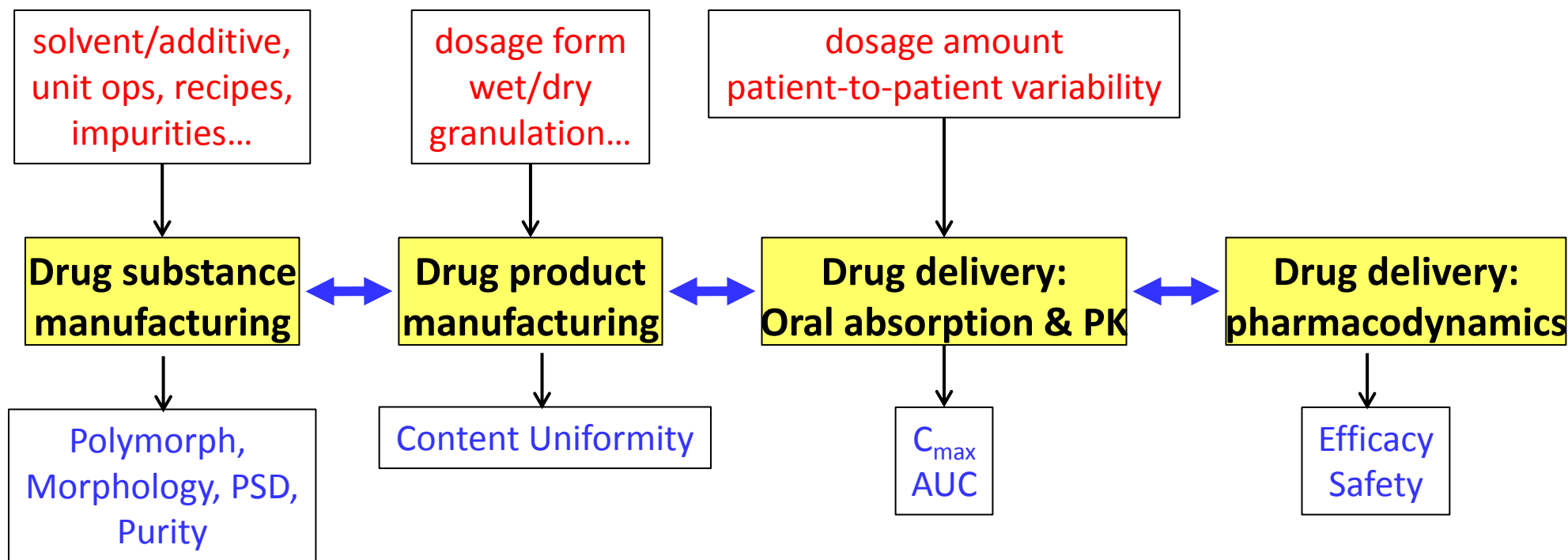
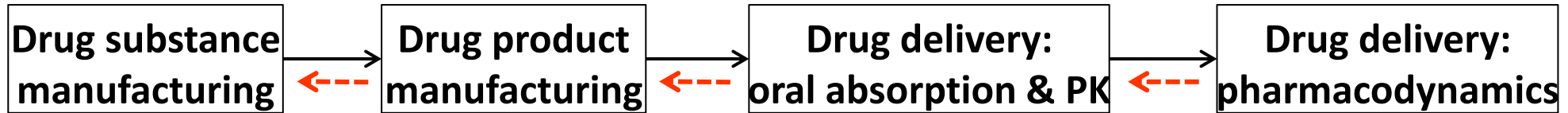### Sean Bermingham – VP Life Sciences, Consumer Goods and Specialty & Agrochemicals

gPROMS

Systems-based Pharmaceutics

*A holistic approach to the
development and optimisation of
drug manufacture and drug delivery*

ADVANCED PROCESS
MODELLING FORUM **2014**

CPPs & Disturbances

| solvent/additive, unit ops, recipes, impurities... | dosage form wet/dry granulation... | dosage amount patient-to-patient variability | |

Drug substance manufacturing ↔ **Drug product manufacturing** ↔ **Drug delivery: Oral absorption & PK** ↔ **Drug delivery: pharmacodynamics**

Polymorph, Morphology, PSD, Purity

Content Uniformity

C_{max} AUC

Efficacy Safety

CQAs & Process KPIs

The "Pragmatic" Approach – and its pitfalls

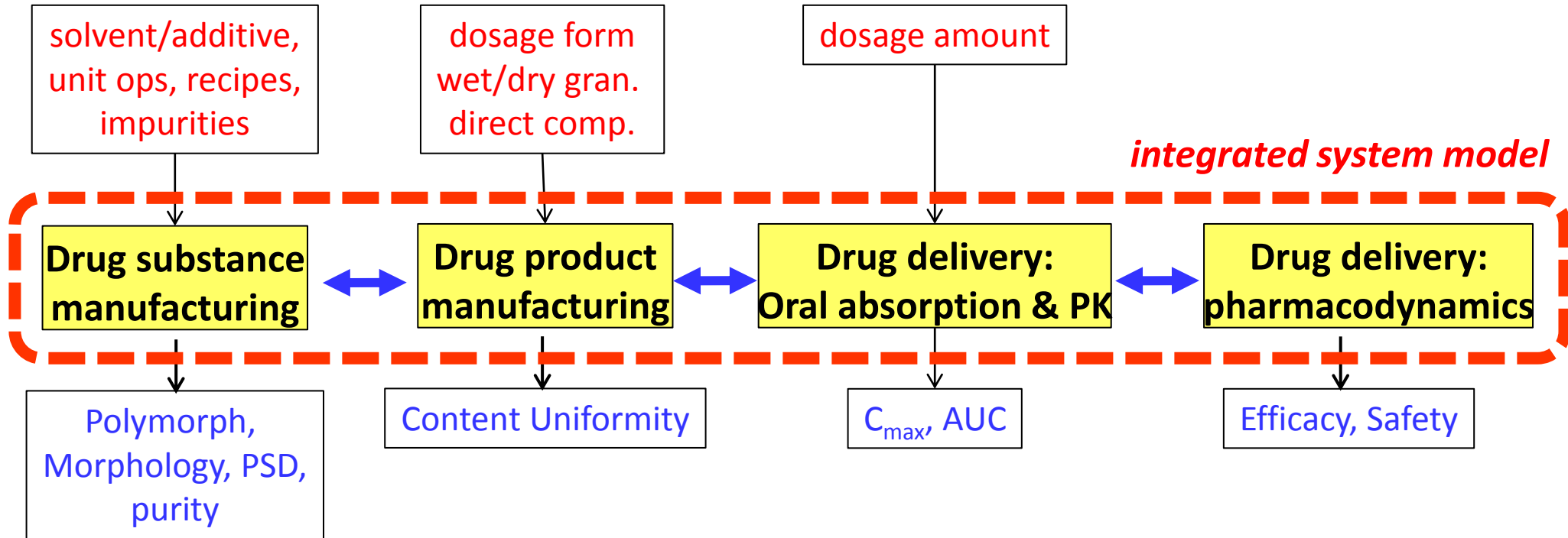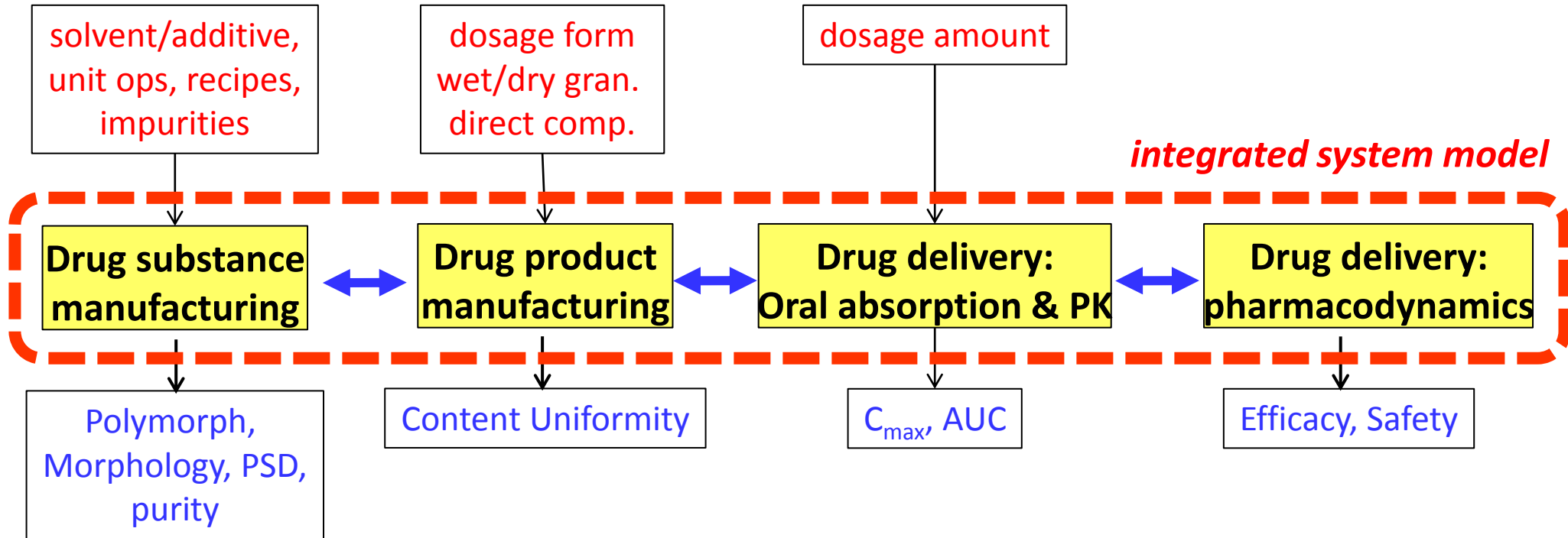| Drug substance manufacturing | → | Drug product manufacturing | → | Drug delivery: oral absorption & PK | → | Drug delivery: pharmacodynamics |

- **Essentially, a sequential approach**
  - "silo thinking" reflected in organisational structures, tools, …
- **Too many iterations between …**
  - consecutive manufacturing steps
  - product design (formulation) and manufacturing process design
    - bioavailability targets and drug product/process development
  - R&D and manufacturing (Tech Transfer)
- **… and other inefficiencies**
  - no central repository of consistent knowledge
  - many, long learning curves

ADVANCED PROCESS MODELLING FORUM **2014**

Systems-based Pharmaceutics – I

solvent/additive, unit ops, recipes, impurities	dosage form wet/dry gran. direct comp.	dosage amount	

integrated system model

Drug substance manufacturing	↔	**Drug product manufacturing**	↔	**Drug delivery: Oral absorption & PK**	↔	**Drug delivery: pharmacodynamics**

Polymorph, Morphology, PSD, purity	Content Uniformity	C_{max}, AUC	Efficacy, Safety

- Use an integrated system model to quantify effects of CPPs & disturbances on CQAs, process economics, operability, safety

solvent/additive, unit ops, recipes, impurities

dosage form wet/dry gran. direct comp.

dosage amount

integrated system model

Drug substance manufacturing ⟷ **Drug product manufacturing** ⟷ **Drug delivery: Oral absorption & PK** ⟷ **Drug delivery: pharmacodynamics**

Polymorph, Morphology, PSD, purity

Content Uniformity

C_{max}, AUC

Efficacy, Safety

- **Efficiently/effectively explore decision space**
  - formal optimisation to eliminate trial-and-error
- **Manage risk by quantifying impact of uncertainty**
  - model uncertainties / gaps in process knowledge
  - external disturbances, e.g. excipient quality

- A formal framework for the **capture and generation of knowledge** - both current and future
  - support pharma eco-system
    - companies, universities, research organisations, suppliers
  - facilitate consistency, quality assurance
  - ...across 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

ADVANCED PROCESS
MODELLING FORUM **2014**

An ambitious vision shared by major pharma companies

Systems-based Pharmaceutics Alliance

A single model-based framework
for drug substance manufacturing,
drug product manufacturing,
oral abs...

Systems-based Pharmaceutics Alliance formed

Process Systems Enterprise Ltd, Pfizer, Inc., and another major pharmaceutical company have formed the Systems-based Pharmaceutics Alliance.

The SbP Alliance aims to develop a single model-based framework for drug substance manufacturing, drug product manufacturing, oral absorption and pharmacokinetics.

It will seek to establish best practices in the application of model-based techniques which will be incorporated in validated commercial quality computer software for the solution of industrially important problems.

To more rapidly meet the Alliance's objectives, we are further exploring opportunities to partner with additional, interested companies.

23 March 2014

sbp

Linking Process Engineering to Product Performance
A roll compaction case study

Gavin Reynolds
Emmanuela Gavi

Pharmaceutical Development, Macclesfield, UK

AstraZeneca

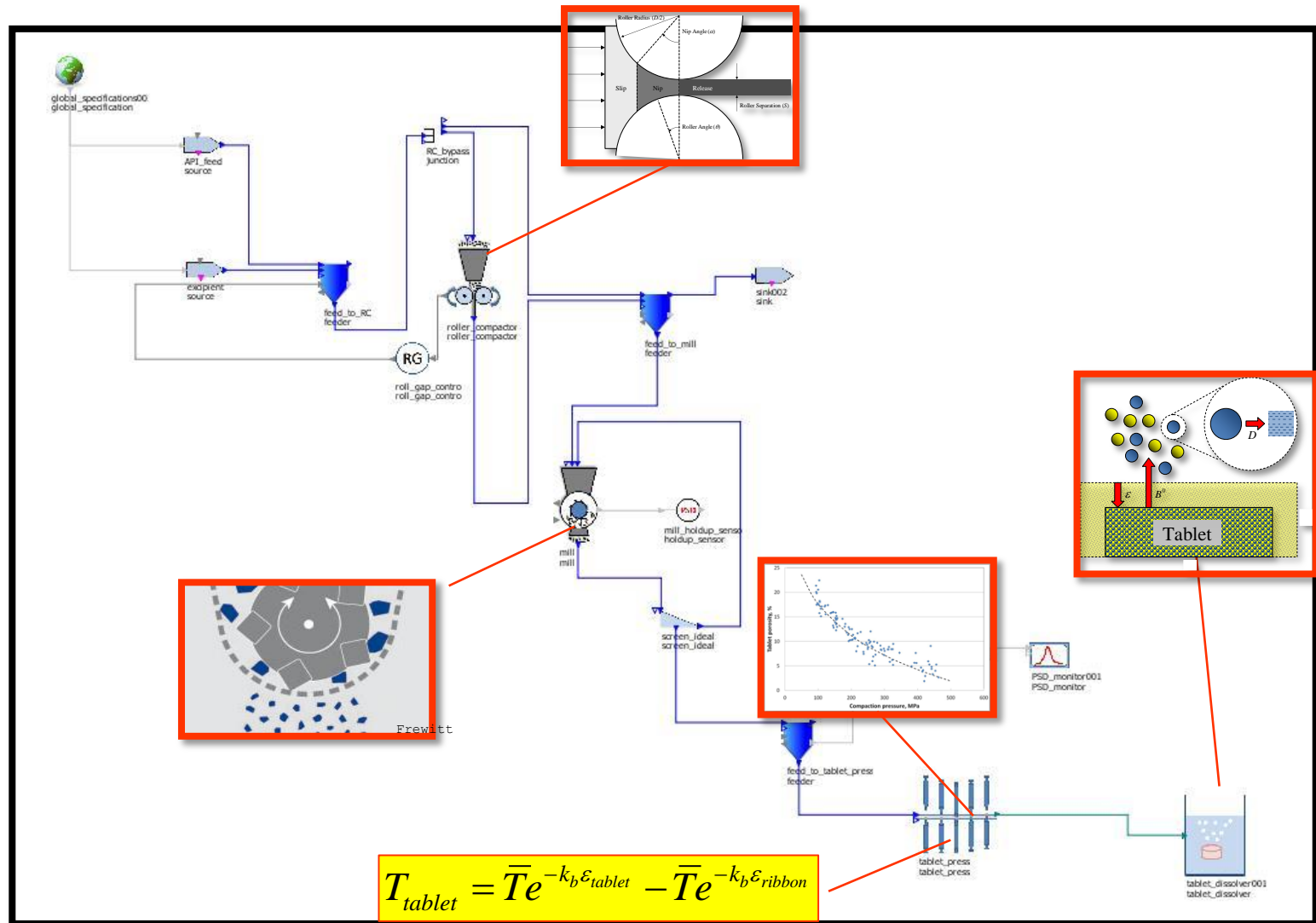1   Global Medicines Development | Pharmaceutical Development

Advanced Process Modelling Forum, London, April 2013

Tablet manufacturing (adapted from Reynolds & Gavi, 2013)

$$T_{tablet} = \overline{\overline{T}}e^{-k_b\varepsilon_{tablet}} - \overline{\overline{T}}e^{-k_b\varepsilon_{ribbon}}$$

Independent of SbP Alliance discussions …
Tablet manufacturing (adapted from Reynolds & Gavi, 2013)

Roll pressure (30-70 bar)
Screen size (1.25-2.00 mm)
Compaction force (5-20 kN)

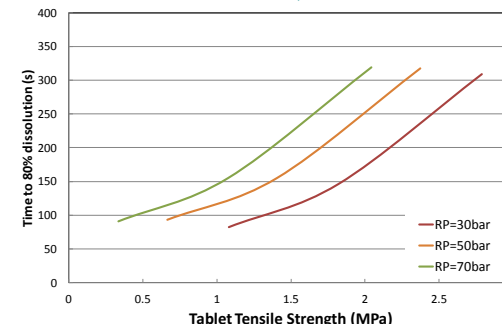Model of tablet manufacturing process
Roll Compacting → Milling → Mixing → Tableting
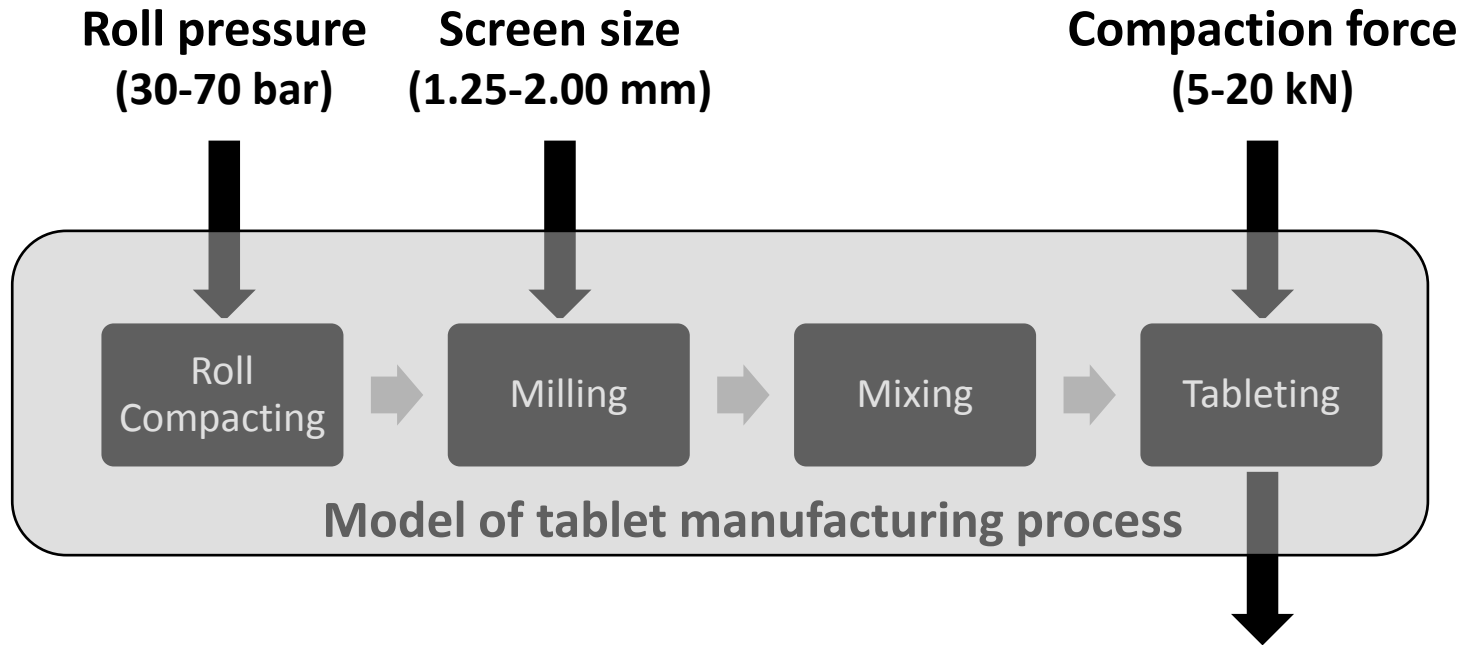
Tablet characteristics

Tensile strength (MPa)
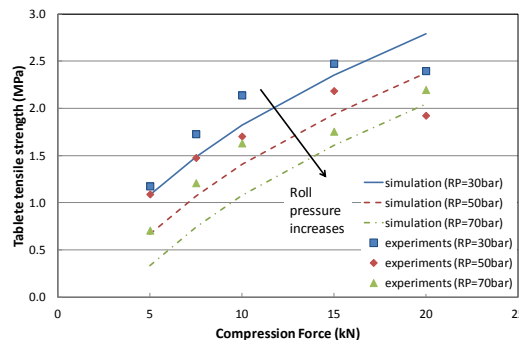
Time to 80% disintegration (s)

Systems-based Pharmaceutics = QbD ?

- QbD is a systematic approach to development that
    - begins with predefined objectives
    - emphasizes product and process understanding and process control
    - is based on sound science and quality risk management

- What we have heard from our pharma customers
    - QbD hasn't lived up to its hype
    - however, it can help design more robust manufacturing processes
    - albeit at a very high cost in terms of required resources

- Our assessment: QbD is very <u>effective</u>, but current methods leave a lot of room for <u>efficiency improvements</u>
    - efficiency can be improved through the "sound science" element of the QbD definition, appreciating we know more than the I/O structure

ICH Q8(R2) Pharmaceutical Development

Experiment design method

Aim of experimental programme

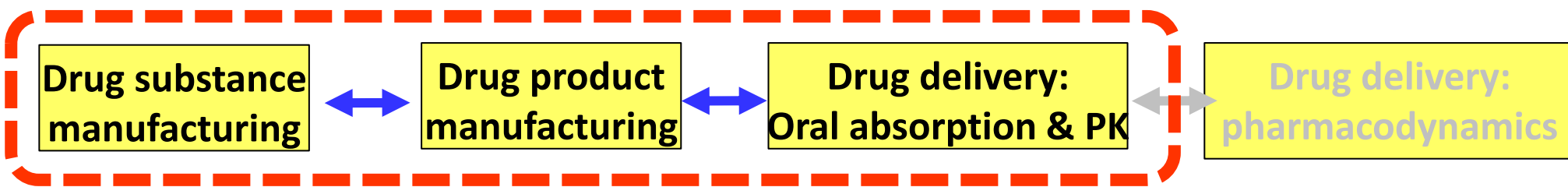**Models used**

Limitations / challenges of the approach

Progress on turning the vision into reality

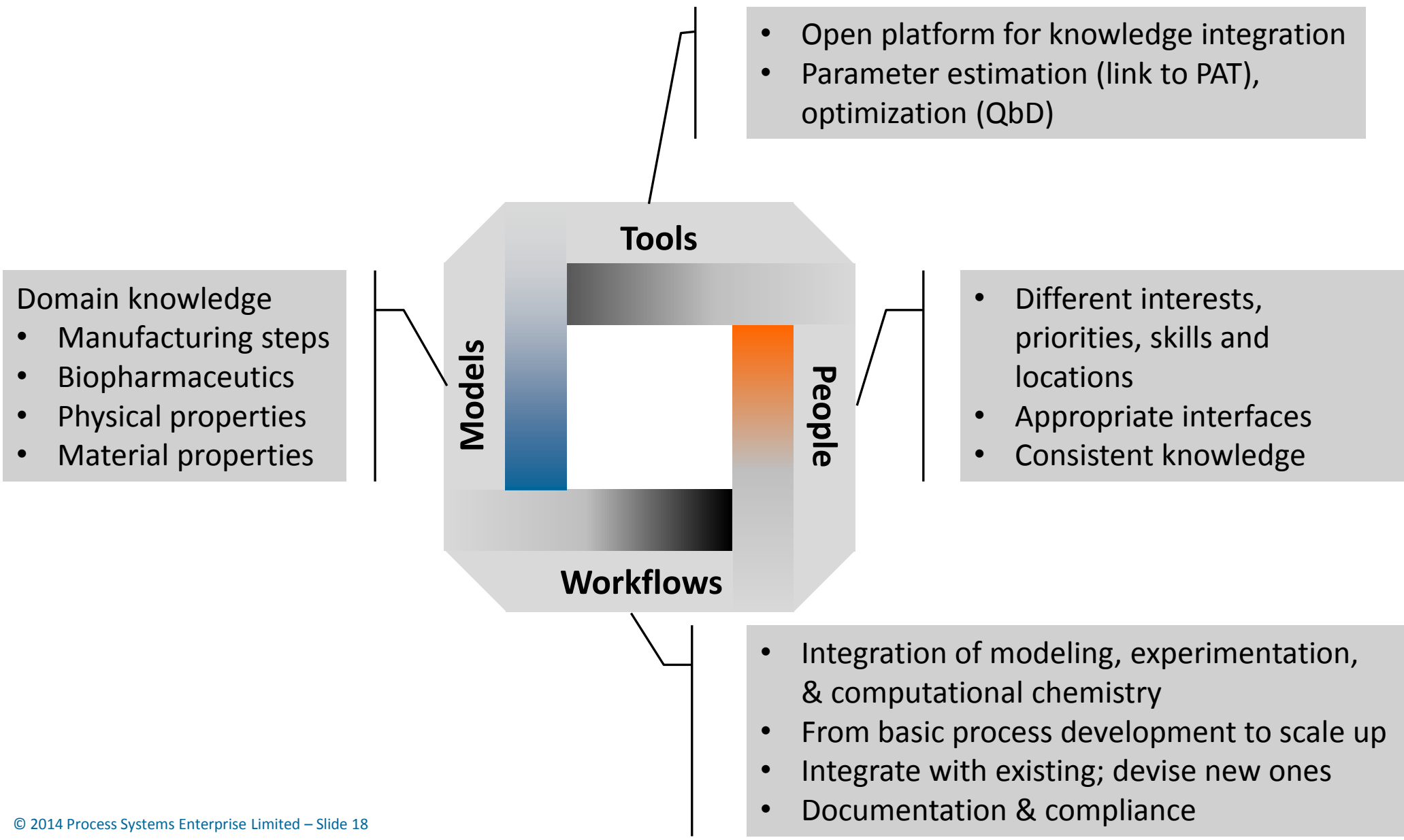# We are not starting from scratch

current focus of PSE Life Sciences

| **Drug substance manufacturing** | ⟷ | **Drug product manufacturing** | ⟷ | **Drug delivery: Oral absorption & PK** | ⟷ | **Drug delivery: pharmacodynamics** |

Process Builder

g CRYSTAL · g SOLIDS · g COAS

The gPROMS platform
Equation-oriented modelling & solution engine

ADVANCED PROCESS MODELLING FORUM **2014**

Several aspects are being addressed considered

Tools

- Open platform for knowledge integration
- Parameter estimation (link to PAT), optimization (QbD)

Models

Domain knowledge
- Manufacturing steps
- Biopharmaceutics
- Physical properties
- Material properties

People

- Different interests, priorities, skills and locations
- Appropriate interfaces
- Consistent knowledge

Workflows

- Integration of modeling, experimentation, & computational chemistry
- From basic process development to scale up
- Integrate with existing; devise new ones
- Documentation & compliance
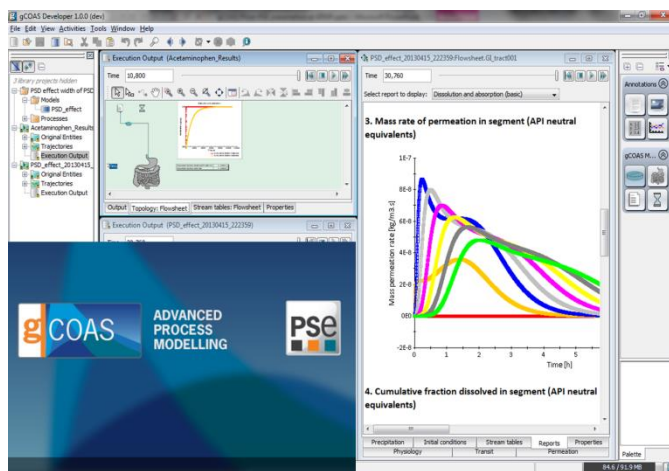
Several aspects are being addressed considered

Domain knowledge
- Manufacturing steps
- Biopharmaceutics
- Physical properties
- Material properties

Model implementation (existing science)
- robustness
- compatibility
- documentation
- maintenance

- **New oral absorption modelling tool**
- **Enhancements to gCRYSTAL & gSOLIDS**
- Physical property package
- Filtration, wet milling
- In-vitro models
  - USP-2
  - ASD
- More enhancements to gCRYSTAL, gSOLIDS & gCOAS

ADVANCED PROCESS MODELLING FORUM **2014**

Several aspects are being addressed considered

Model development (new science)

- Academia, e.g. CMAC, C-SOPS, RCPE, SSPC, …
- Pharma companies
- …

Domain knowledge

- Manufacturing steps
- Biopharmaceutics
- Physical properties
- Material properties

Tools

Models

People

Workflows
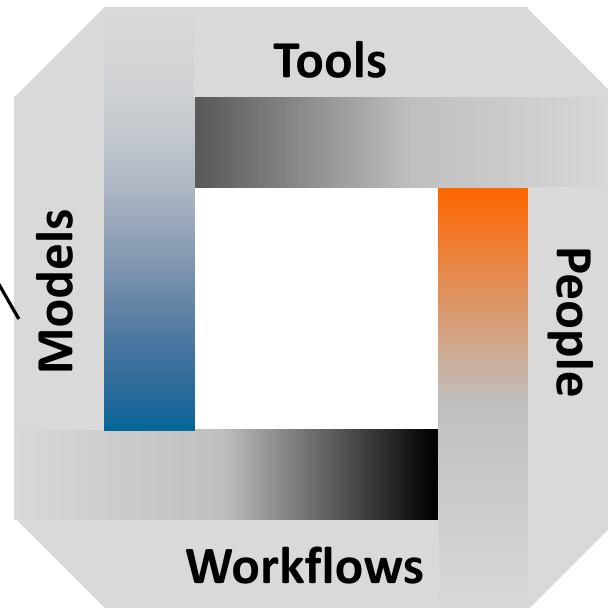
- **(Spray) drying modelling framework**
  - different droplet / particle drying models
  - agglomeration
  - TSB project (Hossein Ahmadian's talk earlier today)

- **Granulation modelling framework**
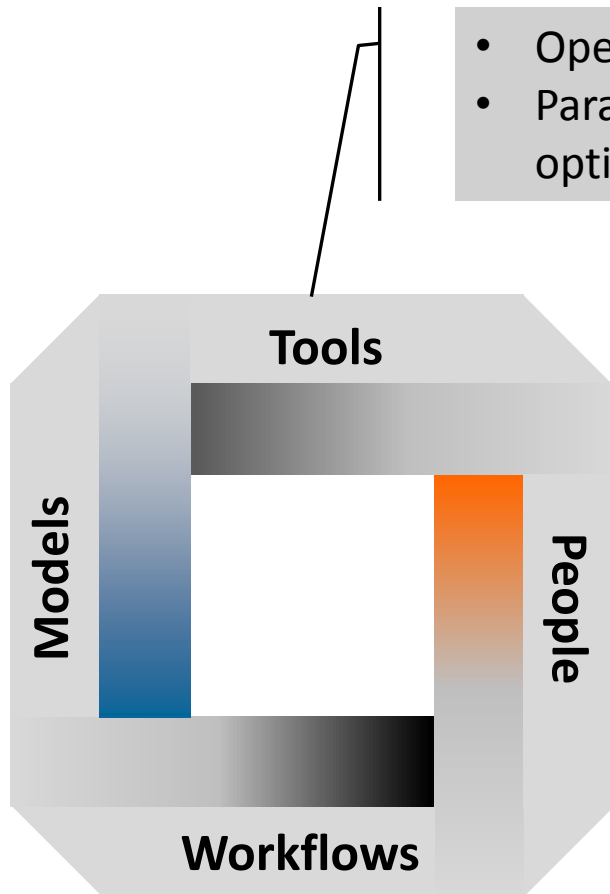 - HSWG, FBG, (screw granulation)

- **Fed-fasted-fed dynamics**
  - time varying pH and bile conc.

ADVANCED PROCESS MODELLING FORUM **2014**

Several aspects are being addressed considered

- Open platform for knowledge integration
- Parameter estimation (link to PAT), optimization (QbD)

Tools

Models

People

Workflows
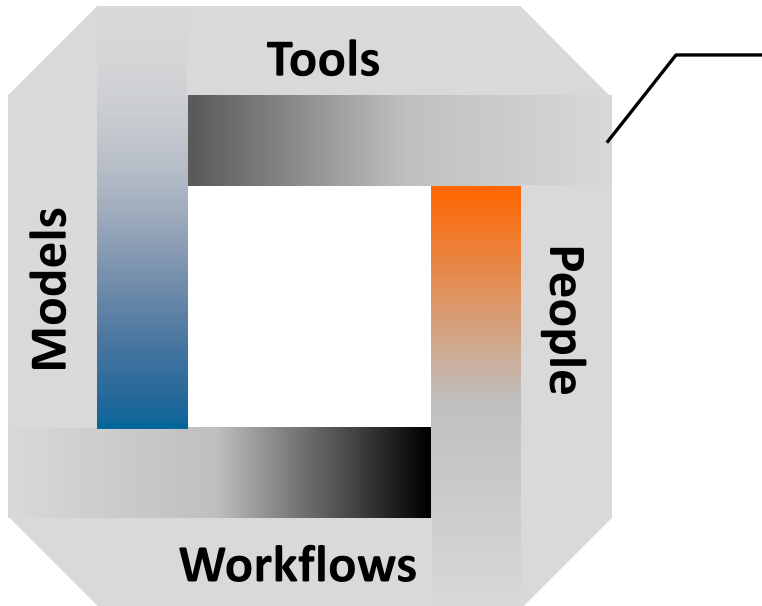
■ Global Sensitivity Analysis

  – Different sources of variability/uncertainty

      – Covariance of estimated parameters

      – Common cause variability

      – Patient-to-patient variability

  – TSB funded activity to start May/June 2014

■ Multizonal CFD:EL-gPROMS interface

  – TSB spray drying project (Hossein Ahmadian's talk earlier today)

■ Multizonal DEM-gPROMS interface

  – C-SOPS (Dana Barrasso's talk later today)

  – TMAPPP

ADVANCED PROCESS MODELLING FORUM **2014**

Several aspects are being addressed considered

Tools

Models

People

Workflows

- Different interests, priorities, skills and locations
- Appropriate interfaces
- Consistent knowledge

■ **Developer versions (Tier I users)**

gCOAS Developer

■ **Standard versions (Tier II users)**

gCOAS ADVANCED PROCESS MODELLING

■ **Deployment of models via corporate intranet**
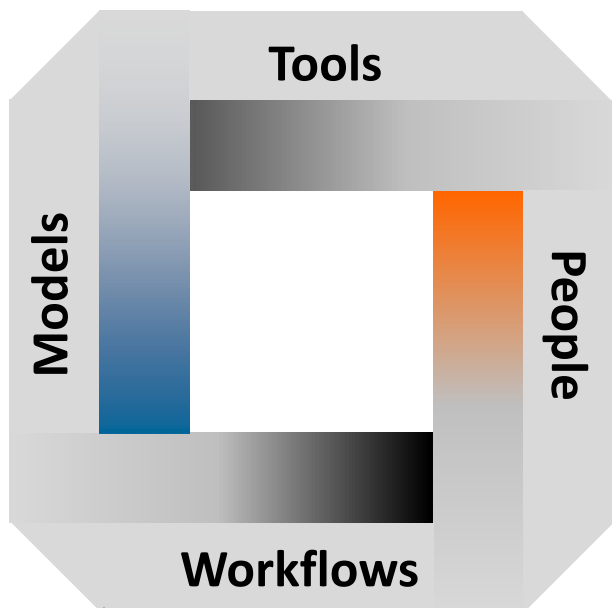
gE:Web – Enterprise Web Publishing Solution

Publish and deploy gPROMS models via the web or intranet

The gPROMS Enterprise Web Publishing Solution makes the power of gPROMS models developed in the gPROMS ModelBuilder and the other members of the gPROMS product family accessible across the enterprise.

■ Model-based control

ADVANCED PROCESS MODELLING FORUM **2014**

Several aspects are being addressed considered

Tools

Models

People

Workflows

- Integration of modeling, experimentation, & computational chemistry
- From basic process development to scale up
- Integrate with existing; devise new ones
- Documentation & compliance

■ gCRYSTAL-gSOLIDS-xxx interoperability

■ Databases for
- physical properties
  - complex phase structures
- material properties
  - excipient and API lots; drug formulations
- equipment characteristics
  - dimensions and operating constraints
- physiology

hierarchy: personal > group > corporate > alliance > PSE
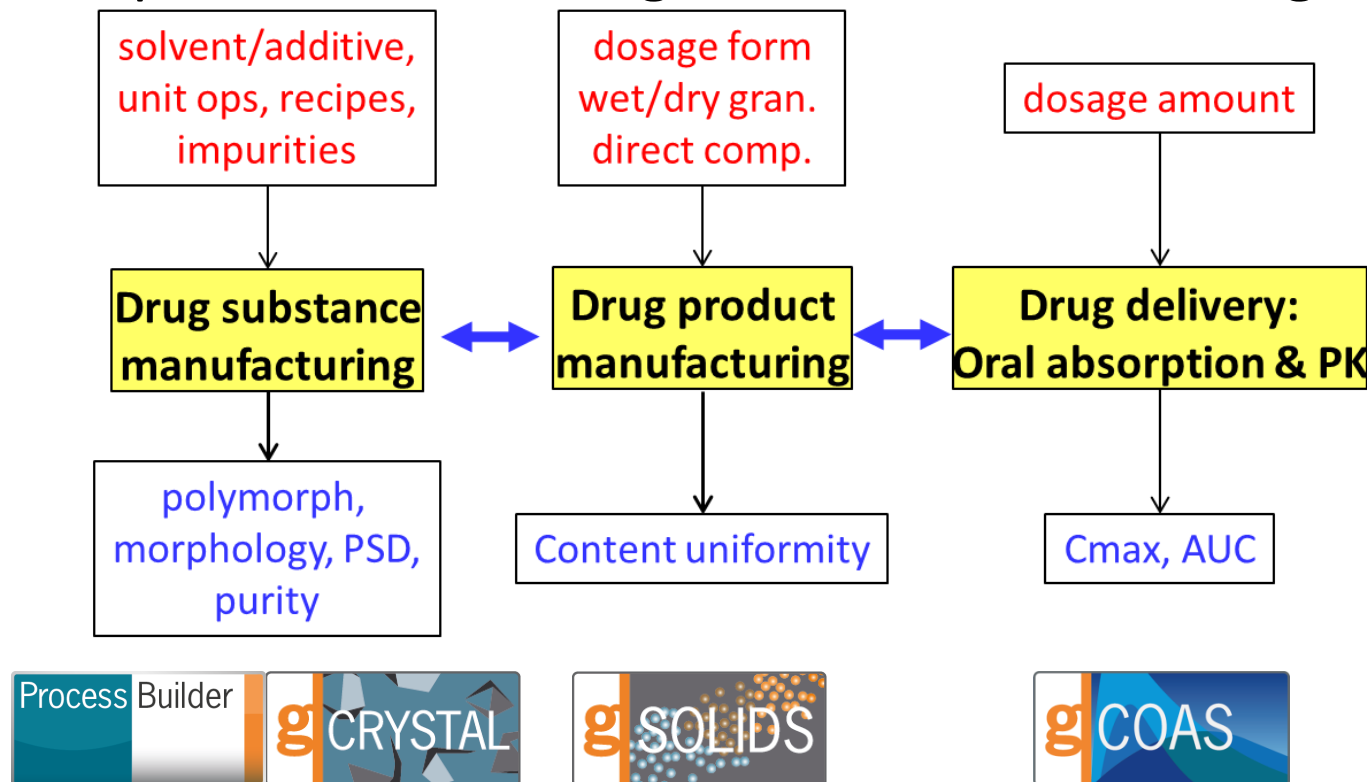
■ Use of experimental data for PE
- avoid copy-paste errors
- data processing
  - aligning time stamps
  - filtering high frequency data

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MODELLING FORUM **2014**

Concluding remarks

Concluding remarks

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

| solvent/additive, unit ops, recipes, impurities | dosage form wet/dry gran. direct comp. | dosage amount |

Drug substance manufacturing ↔ **Drug product manufacturing** ↔ **Drug delivery: Oral absorption & PK**

polymorph, morphology, PSD, purity   Content uniformity   Cmax, AUC

Process Builder   gCRYSTAL   gSOLIDS   gCOAS

   - supported by mechanistic APM tools and associated workflows
      - that are being enhanced on a continual basis
   - being adopted by a rapidly increasing number of companies

Thank you