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ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Project overview: Vision, scope and deliverables

Sean Bermingham
Project Director ADDoPT
VP Formulated Products, Process Systems Enterprise

ADDoPT (2015-2019)

A £20.4m UK Government-Industry-Academia collaboration

Part-funded under the Advanced Manufacturing Supply Chain Initiative (AMSCI*)

Department for Business, Energy & Industrial Strategy

*A BEIS initiative delivered by Finance Birmingham and Birmingham City Council

Instigated by the Medicines Manufacturing Industry Partnership (MMIP)

abpi Bringing medicines to life

BIA UK BioIndustry Association

"This project has the potential to propel the UK to the forefront of medicinal product design and manufacture"
ABPI & BIA

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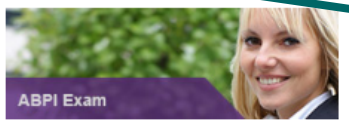
ADDoPT vision

Ian McCubbin, chair of MMIP 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.

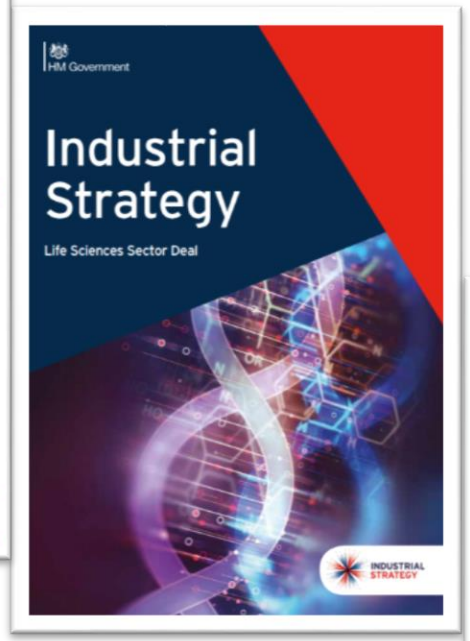
As I reflect on our contribution, it's clear we have progressed significantly with a number of important topics, not least the Advanced Therapy Manufacturing Taskforce (ATMT).

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,

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.

A digitalisation vision supported by key reports

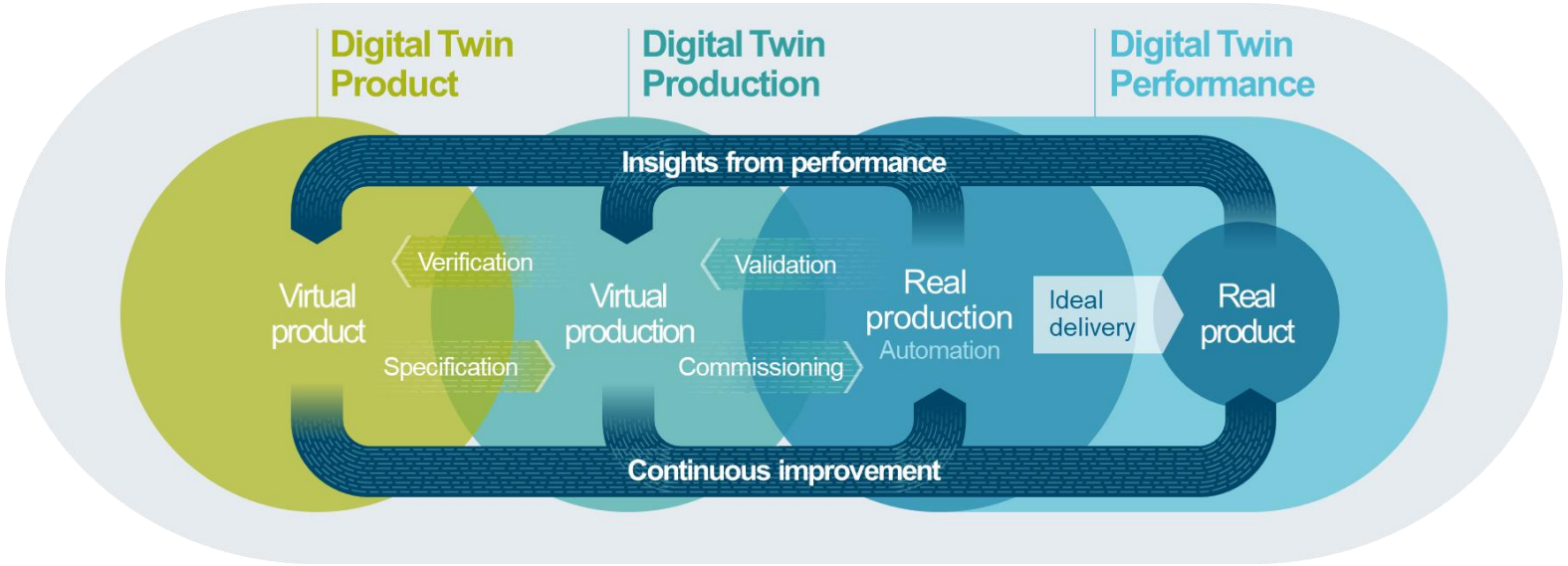


ADDoPT started two years before publication of these reports recognising / confirming the need for development and deployment of Digital Design and Digital Operation solutions

Digital Design is an integral part of Digital manufacture (Industry 4.0) …

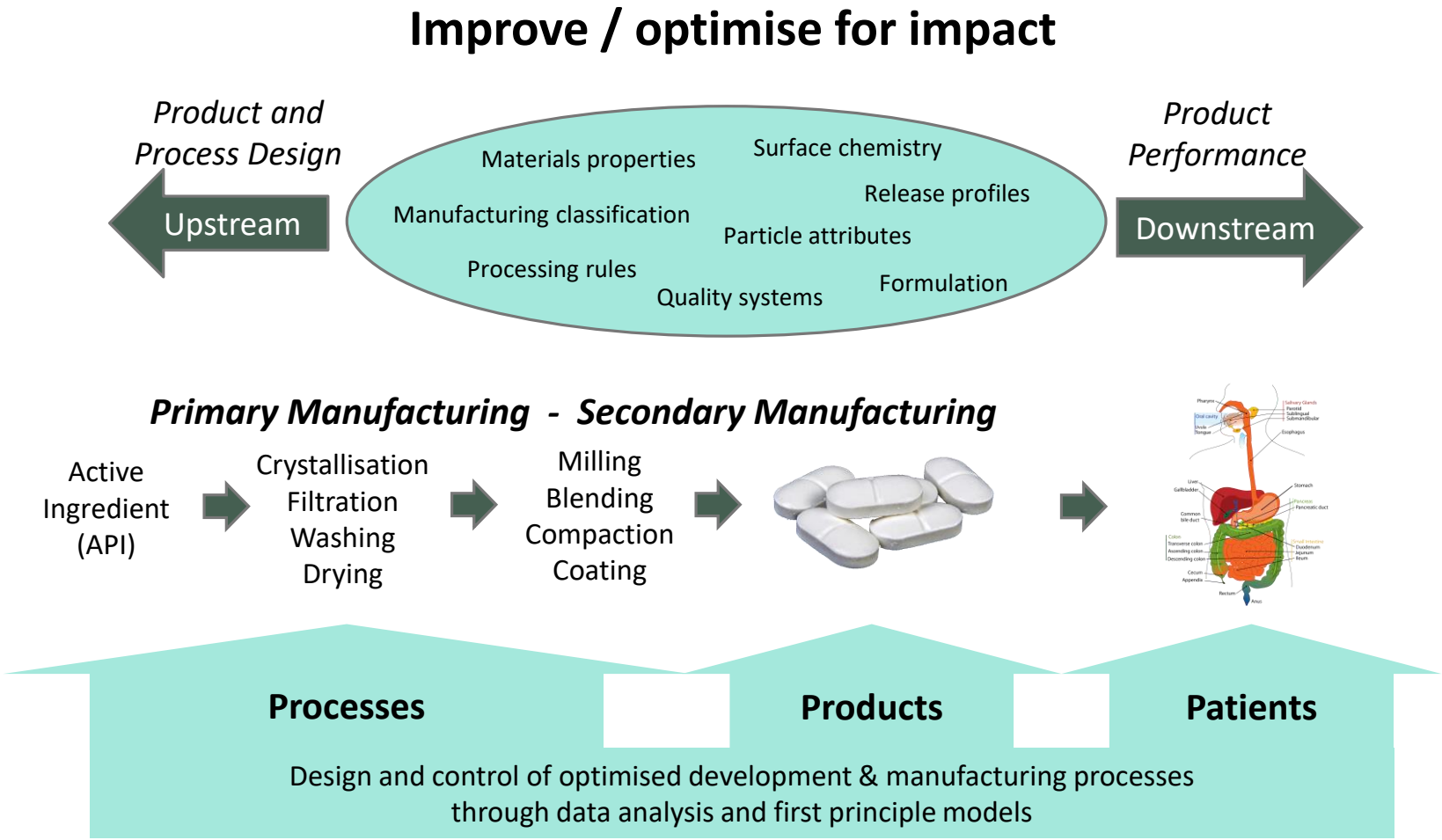
… is the use of an integrated, computer-based system
comprised of simulation, 3D visualization, analytics and collaboration tools
to create product and manufacturing process definitions simultaneously

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

ADDoPT scope



- A systems-based approach to pharmaceutics
- Horizontal integration: Manufacture → Product Performance (breaking down silos)
- Vertical integration: Length Scales & Design → Operation

See **delegate pack** for a more detailed description of the vision and benefits for patients and the pharmaceutical industry

Digital Design, Virtual Systems and Digital Twins

Creating virtual medicines and medicines manufacturing systems to ensure they are effective and efficient before creating them in the real world

The ADDoPT project has developed and implemented advanced digital design techniques that streamline drug design, development and manufacturing processes

The ADDoPT Vision

The ADDoPT vision is the creation of virtual medicines and medicines manufacturing systems - products and processes - to make sure that they are effective and efficient before creating them in the real world. The key element in the digital design workflow is the creation of a virtual representation or "Digital Twin" of a product or process based upon a mathematical model that predicts its performance. This allows a vastly more efficient and effective design process.

Traditional practice involves an iterative design cycle consisting of building a physical prototype and its real-world testing. Through repetition of the cycle, a workable solution is reached and the product is developed, without knowing whether more robust and/or more efficient solutions exist. In ADDoPT, Digital Twins have been developed on the basis of predictive science (mechanistic models) with data analytics used to address gaps in the mechanistic understanding. Once calibrated, using greatly reduced physical experimentation, these Digital Twins can predict the performance of products or processes across a far greater design space than was used in calibration and with respect to a much wider range of material attributes and process parameters to identify those which are truly critical. Consequently, performance of the Digital Twin can be evaluated without the continual need for the production and testing of a physical prototype (efficiency gains) and robustness can be more comprehensively evaluated and optimised with respect to raw material and physiological variability. Rapid iteration of the digital design test cycle then leads to an optimum virtual product that can be replicated with confidence in the real world. Eliminating the physical make-test cycle is inherently much more efficient in material, time and cost. Our ability to model physical and biophysical properties of tablets such as hardness or bioavailability without making prototype formulations demonstrates the potential of digital approaches to vastly improve the efficiency of drug development.

Benefits to Patients and Industry

Digital design has the potential to significantly improve the speed and efficiency of Pharmaceutical product and process development. This is important given current industry trends.

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Our ability to model physical and biophysical properties of tablets without making prototype formulations demonstrates the potential of digital approaches to vastly improve the efficiency of drug development

Until now clinical trials have typically been lengthy and are often unsuccessful. The advent of more targeted precision medicines allows for smaller trials and improved chances of success. Whilst in the past clinical development was almost always on the critical path to launch and commercialisation, we are now seeing more examples where development of the commercial product and its manufacturing process are the rate limiting steps on the path to market. The efficiency of Digital Design offers pharmaceutical product and process development groups a way of addressing this emerging challenge.

An implication of Precision Medicines is that more products will need to be developed: better targeted medicines will improve efficacy for specific patient populations but will reduce the size of population that each medicine will serve. In order to meet the needs of the overall population more products will have to be developed overall, and the demands on product and process development groups will increase in an already resource and cost constrained environment. Digital Design offers these groups the opportunity to achieve a step change increase in productivity in order to address this challenge.

The primary benefits of Digital Design are increased speed and efficiency of development however other benefits are apparent over traditional heuristic and purely data driven techniques currently widely used in development to underpin Quality by Design. Digital Design techniques generally need fewer experiments as the scientific knowledge captured in mechanistic models acts as *a priori* information. This leads to experimental and material efficiencies. Additionally, mechanistic modelling techniques allow for a more rigorous assessment of robustness and key sources and quality variability, enabling a more holistic approach to addressing raw material variability: Typically process optimisation work is done with input materials of fixed quality or limited material variability. The use of Digital Design and process modelling allows for an evaluation of the impacts of input product variability on product performance as part of the modelling process.

The benefits of Digital Design to industry flow through to patients in the form of faster access to and enhanced availability of new medicines and better assured supply

From Digital Design to Digital Operations

The fruits of Digital Design will be most fully reaped through an integrated Digital Operations approach to manufacture. Having a calibrated digital twin of the manufacturing system and equipment that identifies and predicts the key relationships between material characteristics, process parameters and product performance allows medicines manufacturers to readily identify the manufacturing and control systems that are needed to assure product quality. Subsequently, the digital twin can streamline process optimisation, accelerate technology transfer and underpin both advanced process monitoring (inferred measurements for quality attributes that cannot be reliably measured in-line or at-line) and model predictive control to ensure the robustness of ongoing manufacture.

The case studies outlined in this brochure demonstrate that a shared ambition to achieve step-change improvement in pharmaceutical product and process development has led to real examples of improvement that are already bringing real benefits to industry and patients today

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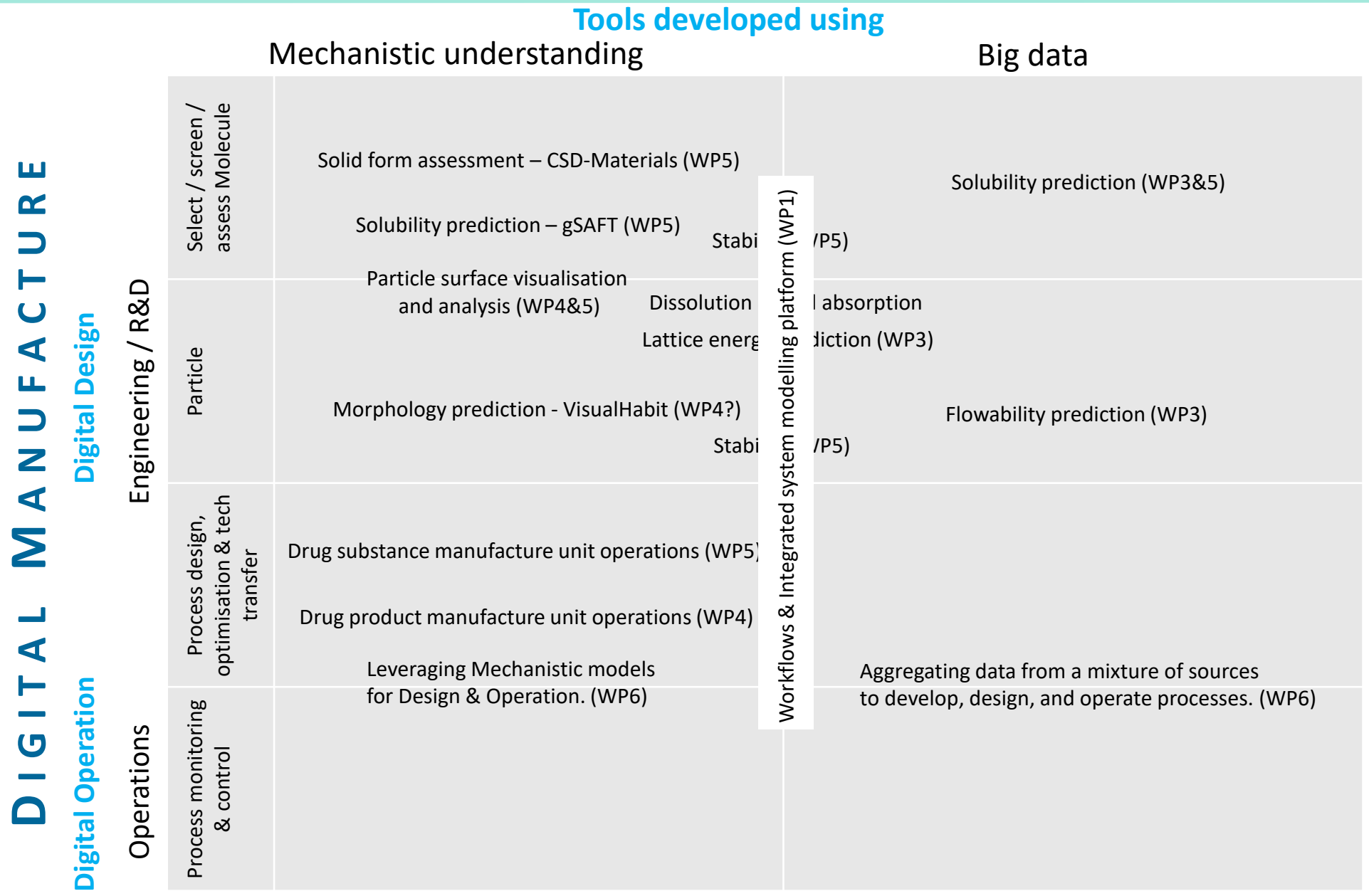
Development of digital design and digital operation tools using mechanistic understanding, big data and hybrid approaches



- Data is typically not ubiquitous nor cheap to generate at the R&D and Engineering stages
- → Use targeted data driven approaches to fill gaps in mechanistic understanding
  - E.g. flowability, compressibility, bulk density
- → Hybrid models

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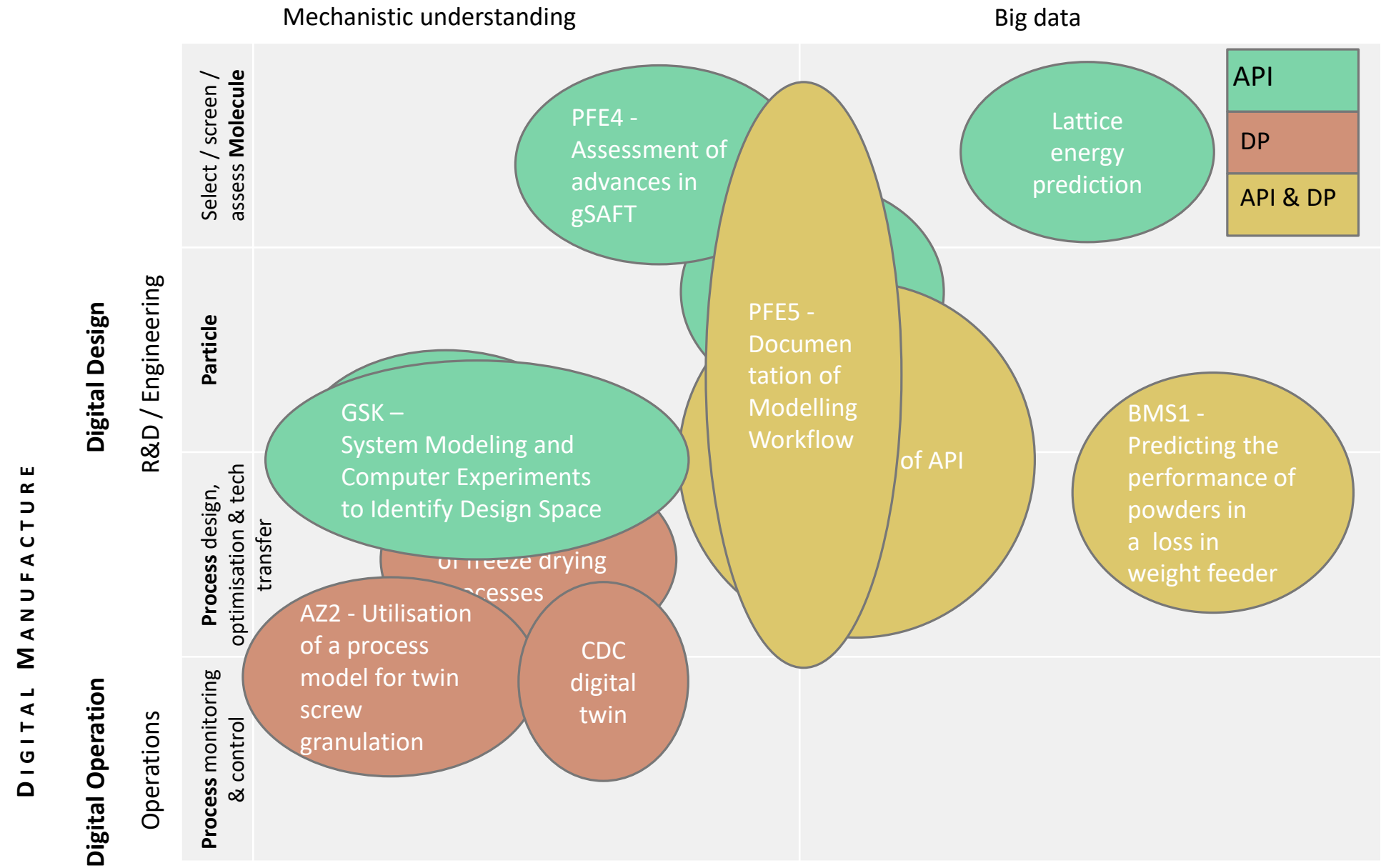
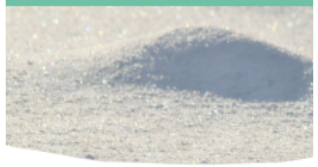
Application of digital design and digital operation tools > 15 pharma led case studies



See **delegate pack** for summaries of six case studies

Understanding Powde Continuous Processin

Earlier and better decision making



Drivers

The manufacture of solid oral dose pharmaceutical forms is underpinned by need for good powder flow. Most Active Pharmaceutical Ingredients (APIs) are fo very fine solids and do not inherently flo and so additional treatment by wet or dr granulation is frequently needed to rend flowing blends.

Industry trends towards more complex A continuous processing further increase th for a better grasp of the links between measurable particle properties and result behaviour, and the means to predict one other as early as possible in the developm workflow.

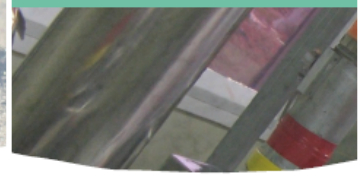
Approach

This work has taken place in parallel with the context of the development of a Manufacturing Classification System[1], mo on the FDA Biopharmaceutics Classificat System. This will allow materials to be cl for processability according to the API pc properties and the level of drug loading. material's position in the classification th informs the choice of processing route, o whether further particle engineering is re

1. MCS Working Group (2018): *Manufacturing classificat real world*, Pharmaceutical Development and Technolog 10.1080/10837450.2018.1534863

Mechanistic Modelling o Powder Feeding

Predicting flow performance and miti



Drivers

Powder feeders are an integral part of many pharmaceutical industry solid dosage form processing trains and are particularly critical continuous processing equipment, where an fluctuation in the rate of delivery risks being propagated into downstream blending. Mana feeder performance is often less than straightforward when dealing with active pharmaceutical ingredients (APIs) in particul due to their challenging flow properties.

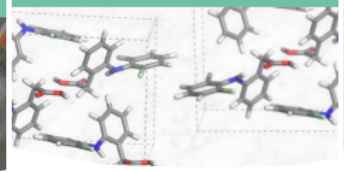
An accessible predictive model of feeder performance would enhance both drug prod development and manufacture, increasing th speed of development, reducing the associat costs, and improving process robustness.

Approach

A model based upon the best currently availa the public domain literature for powder flow been incorporated into a user-friendly interfa suitable for use by "super-users" (scientists primarily focused on pharmaceutical materia with some degree of comfort in the use of modelling tools), and by subject matter expe modelling specialists.

Lattice Energy Predicti Data Approaches

Understanding and predicting API so



Drivers

The sophistication of modern therapies has driven drug discovery towards higher mole weight, lower solubility compounds. Understanding and predicting solubility ea the development cycle using lattice energy indicator property can provide business advantage by streamlining candidate select and linking up thinking between medicinal chemistry and drug development.

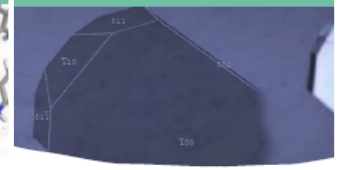
A new modelling tool allows lattice energie be predicted for the crystalline form of a r of molecular variants. This gives a measure likely solubility directly from 2D structure, allowing candidates to be ranked with no n for experimentation.

Approach

Solubility of any crystalline material is the r of a balance of solvation and solid state pac effects, so effective modelling needs to con solid-state as well as molecular properties. done under ADDoPT has affirmed the importance of the solid-state contribution solubility and provided a practical model to account for them.

Early Stage Prediction Morphology

Accelerating and de-risking drug de



Drivers

This case study addresses the need to acce and de-risk drug development pathways a reduce development costs by providing a r earlier indication of any potential issues associated with the expected crystal morpl of drug candidates. Early signalling of such will enable preventative work, including triggering more detailed modelling, to be out off the development critical path.

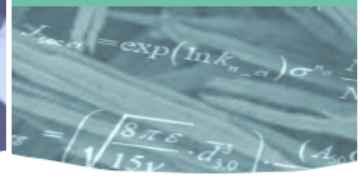
Longer term, linking the underlying predi capability developed with other crystallisa models will contribute to improved experi design. Taken together, these benefits wou effectively increase overall resource efficie and hence capacity to progress a pipeline product development projects.

Approach

With the aim of predicting crystal morpho properties (and limited mechanical proper from a single crystal structure, database ar visualization scripts have been developed CCDC to interface with and harness the morphological predictive ability of Leeds' Habit software, and bring these tools to be live drug candidates within Pfizer.

Optimising Crystallisatio Habit and Physical Prop

Designing processes to deal more effi



Drivers

Active Pharmaceutical Ingredients (APIs) of needle-like shape tend to impact powder flowability and, with industry trends towards more challenging APIs, higher drug loadings more continuous manufacture. are often considered as high risk and a source of difficu in the manufacture of a pharmaceutical dosa form. As a result, the technical challenge of designing upstream processes, notably crystallisation, is important to ensure that go flow is achieved for downstream processes su as formulation. A model-based approach offe the prospect of both a more efficient optimis workflow and improved plant utilisation by having better understood and optimised crystallisation processes.

Approach

This study addresses the challenge of dealing APIs which tend to crystallise as long needle during simple seeded cooling crystallisation. These form cohesive powders in bulk which extremely difficult to handle in downstream formulation processes.

Current practice involves a great deal of experimental work to develop crystallisation processes with wet milling temperature cycli

A Process Model for Twin Screw Granulation

Using models to optimise implementation of new technology platforms

A cutting-edge modelling approach can dramatically reduce experimental burden without sacrificing process understanding

Drivers

Twin screw granulation offers a flexible and effective continuous formulation route, but the near-infinite potential variations in screw elements and set-up that provide such useful configurability also make it highly challenging to cover all the options in a solely practically-based approach to platform optimisation.

The purpose of this case study was to see to what extent modelling could be used to reduce the number of practical trials needed without sacrificing the amount of process understanding obtainable across the full range of design space. A lower experimental burden (cost of materials and time in experimental design, execution and analysis) equates to increased efficiency in development and cost reduction.

Approach

An early version of an advanced mechanistic model using a population balance based approach to describe the complex set of simultaneous rate processes occurring within a twin screw granulator was implemented within a worksheet environment by PSE for evaluation to see how close it was to utility as part of a normal AZ development workflow.

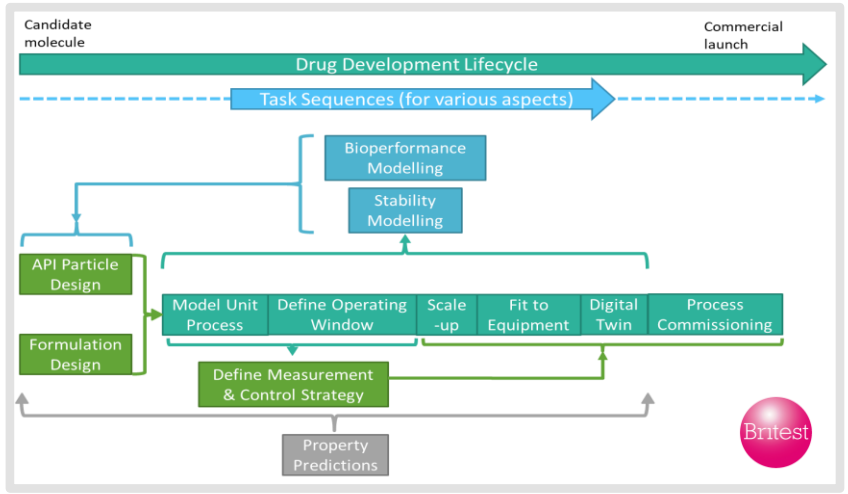
Key Features

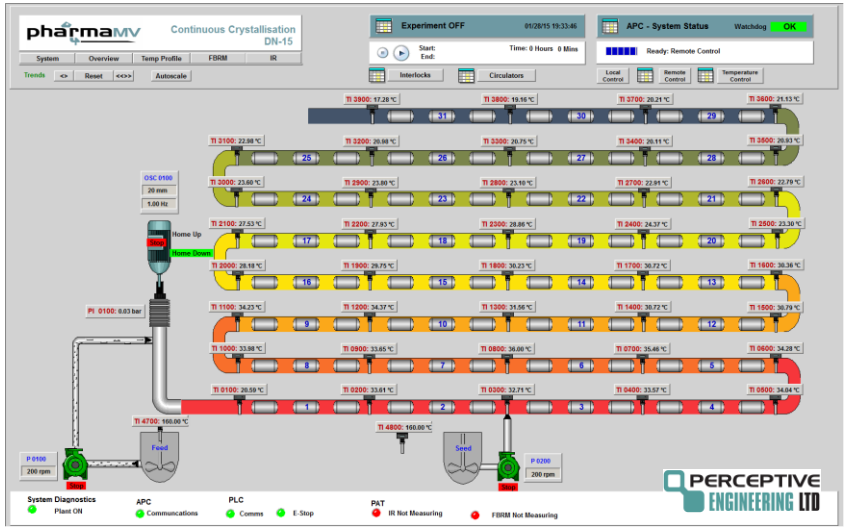
- An advanced mechanistic model has been evaluated in a flowsheet environment facilitating rapid, virtual experimentation in place of expensive and time-consuming practical experimentation
- A sufficiently predictive model was achieved using just 5 trials instead of 24
- The study demonstrates the potential for early, virtual process platform optimisation

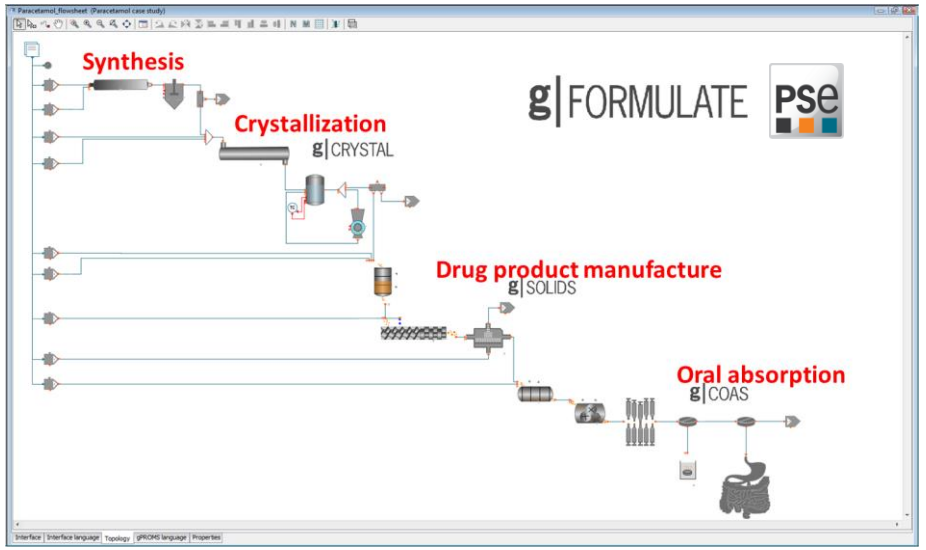
The tool was used on a retrospective example to assess the potential for reduced experimental requirements. Whilst the case study was fairly limited in scope - a practical design space including two screw configurations was used to predict behaviour in a third – a sufficiently successful demonstration would be a significant step forward and a good indicator of future utility in further process understanding work.

An ADDoPT Case Study featuring collaboration between PSE and AZ

ADDoPT outcomes relevant to digital design and digital operation are available as new software tools or enhancements to existing tools …







- Have also worked on integration of tools from various parties, e.g.
  - CCDC and U. Leeds
  - STFC and PSE
  - PSE and PEL

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See **delegate pack** for an overview of the project outcomes, many in the form of software tools, accessible by ADDoPT and non-ADDoPT partners

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ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

A UK-based knowledge value supply chain for the pharmaceutical sector and beyond

Building upon UK excellence in big data, mechanistic modelling, process optimisation and control, ADDoPT has been a catalyst for innovation across the specialist solution-providing businesses and knowledge-base partners at the heart of the project

PSE Building the gPROMS FormulatedProducts environment, for integrated system models covering active ingredient manufacture, formulation manufacture and product performance

- New unit operation models: CSTRs, PFRs, *n*D PBE crystalliser for predicting size and shape distributions, jet mill, HSWG & TSG
- Enhancements to unit operation models: dry mill, jet mill, film coating, pressure filter, agitated filter dryer, and tablet press
- Sensor models: New laser backscatter (CLD) and laser diffraction models
- New gPROMS platform capabilities: support for HPC clusters, OPC client interface, multi-start parameter estimation and optimisation, and ability to launch physical property packages from gPROMS FormulatedProducts
- Interface for development of hybrid models combining data driven (statistical) models and mechanistic models
- gSAFT thermodynamic property prediction: development of flash algorithms for SLE (solubility); extensions to databank
- Joint industrial case studies, interactive courses

Utilising the knowledge from nearly one million crystal structures in the Cambridge Structural Database (CSD)

- Novel informatics-based methodologies including surface and particle property assessment, informing downstream behaviour and design of drug products
- Ability to systematically and routinely apply these new methodologies, enabling assessment over large datasets and landscapes of predicted crystal structures
- Enhanced interoperability of Visual HABIT and CCDC functionality through CSD programming interfaces
- New subsets of CSD data, including the CSD Drug Subset – a collection of all published crystal structures of approved small molecule drugs, providing an understanding of the chemical and crystallographic space of pharmaceuticals
- Interactive and intuitive access to all methods and approaches through the CSD-Materials software suite

PERCEPTIVE ENGINEERING Enhancing the capability of the PharmaMV software platform to provide process monitoring, diagnostics, analytics, control and optimisation through the use of leading-edge digital twin technologies

- New workflows integrating PharmaMV with gPROMS FP to enable the transfer from digital design to digital operation for monitoring, control and optimisation
- A DoE real time platform to generate (or import) and then automatically execute new experimentation plans directly connected to lab or pilot scale process units
- Improved usability of PharmaMV through dashboard tools, guided workflows and templates, providing the user with the information required at the point of need
- Digital twin training courses available to support the implementation of the new digital design workflow
- Created a platform for users to implement models and algorithms, via Python with secure traceable integration with PharmaMV
- Cloud-based connectivity to run PharmaMV on MS Azure, AWS and potential for Apps to be developed on Siemens MindSphere
- Case studies demonstrating digital workflow for crystallisation, twin screw wet-granulation and continuous direct compression processes

Contributing to job creation and safeguarding in the pharmaceutical supply chain, and enhancing UK skills and capabilities in new tools and methodologies for Digital Design and Operations

A highly competitive knowledge value supply chain: helping protect UK manufacturing and ready to support growth

Hartree Centre Providing access to world class high performance computing resources and expertise

- Advanced computing, big data analytics, and AI technologies and expertise: machine learning models built on bespoke data, *e.g.* particle image analysis; cheminformatics
- Advanced scientific computing, *e.g.* modelling and simulation of molecular structures and calculating fundamental properties for input into the digital design workflow
- Advanced expertise in optimising software and its applications for computing resources (in-house or the Hartree Centre's)
- Training in programming, software applications, and AI: using machine learning to extract maximum value from data
- A wide range of computational science and engineering expertise to produce solutions that drive innovation, reduce R&D costs and streamline prototyping

Britest Developing and delivering specialist structured facilitation services

- Development of a digital information flow for model -based pharmaceutical design, manufacture and performance, linking current models and identifying opportunities for new developments
- Generation of bespoke digital design information flows for industrial end-users, helping them to link their current models, share information on model status, and identify opportunities to use new tools
- Support to academic partners in generating industrially relevant workflows from innovative model developments
- Linkages between particle properties of the active molecule and wider drug product manufacturing, stability and performance, to help optimise particle design
- Process knowledge and understanding capture, providing information-rich visual summaries and qualitative mechanistic models against which to test the scope and assumptions of computational models

UNIVERSITY OF CAMBRIDGE Physical and mechanistic models to prototype and optimise new pharmaceutical materials and processes early in development

- Predictive models for powder flowability under low shear rate conditions, and associated response surfaces which can be deployed in production
- Workflows for translation of data on die compaction of pharmaceutical powders into constitutive models that can be used to simulate tableting
- A deeper understanding of tablet coating thickness variability in batch spray coaters, and associated production-deployable response surfaces
- Simplified analytical models to predict cap-to-band coating thickness ratios for tablet of different shape based on their orientation distribution during coating

UNIVERSITY OF LEEDS Working in collaboration to deliver extensive Digital Design capabilities

- Digital workflows through VisualHABIT/Mercury for the design of solid-form and particulate surface properties from molecular and crystallographic data
- A triaged grid-search and molecular dynamics tool set for predicting solvation and molecular structure within solutions and at crystal/solution interfaces
- Solubility prediction through machine learning linked with experimental big-data and molecular descriptors
- Morphological population balances for prediction of crystal size/shape evolution during processing
- An integrated CFD, population balance and multi-zonal modelling platform for prediction of batch crystallisation and spray drying processes at lab and pilot plant-scales
- Agitated filter drying simulation capability incorporating filtration/sedimentation integrated with contact/convective drying models
- Prediction and control of particle size through milling processes through new breakability assessment techniques and breakage functions
- Simulation-based design of operating conditions and material properties for continuous powder blenders
- Morphologically based powder flow models linked to X-ray tomography measurements for simulating the consolidation and processing of cohesive faceted particles in powder rheometers within screw feeders

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www.addopt.org

ADDoPT is a collaboration instigated by the Medicines Manufacturing Industry Partnership, and part funded under the Advanced Manufacturing Supply Chain Initiative, a BEIS initiative delivered by Finance Birmingham and Birmingham City Council.

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Questions?

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