Particle Engineering and Pipeline Needs: Towards a Crystallisation Classification System (CCS)

CMAC, University of Strathclyde

MCERSI Co-Processed API Workshop

Alastair J. Florence, 13/07/22

Drivers for Particle Engᵍ Research at CMAC:

Bridging DS & DP

Understanding and control over material attributes

Minimise material use, Minimise experimental effort, Maximise understanding

Molecular structure and properties

Cryst / Particle Engineering / Excipient

Formulation Processes/ Transformation

Extrusion (melt/wet)

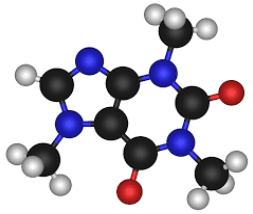
Wet granulation
Batch/Cont/TS

Direct compression
(batch/cont blend)

Roller Compaction

Dose Form Tablets/Capsules/Pills/structured doses

Compression, moulding, 3D printing, capsule etc.



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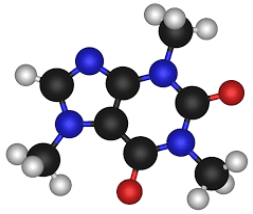

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Can we selectively control API attributes (e.g. size; shape; form; purity) and bulk properties (e.g. wettability; flow; compaction) for optimal *manufacturability, stability and performance ?*

A Demand-Led Roadmap

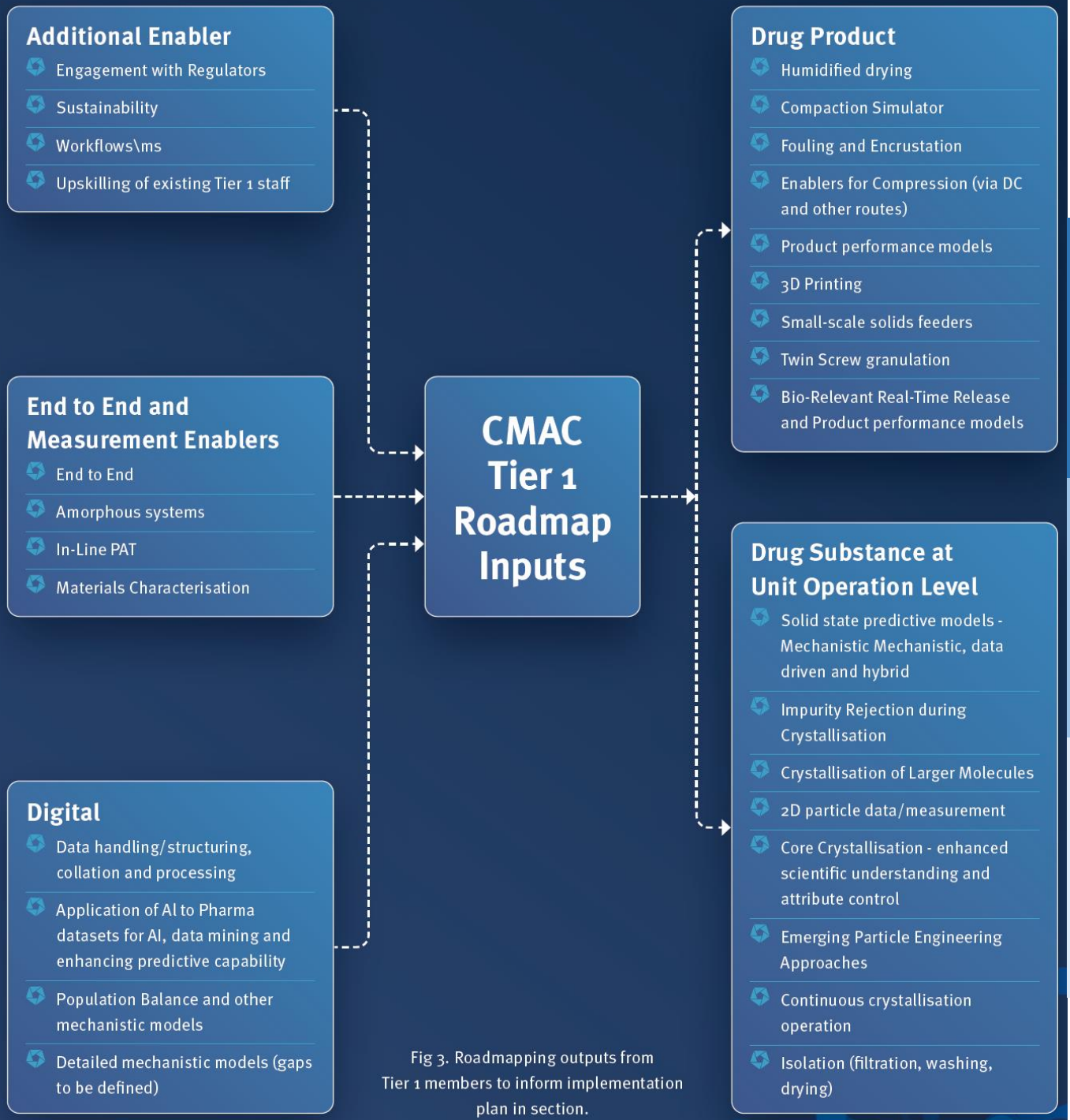

Fig 3. Roadmapping outputs from Tier 1 members to inform implementation plan in section.

Consolidate e.g.

- Particle design, formation and control
- Continuous processing
- Materials characterisation
- Population balance modelling

Grow e.g.

- Emerging particle engineering approaches
- Application of AI to pharma datasets
- Amorphous systems
- In line PAT

New e.g.

- Crystallisation of large molecules
- Product performance models
- Bio-relevant performance and design

Engage – Co-create – Co-deliver – Train – Disseminate - Translate

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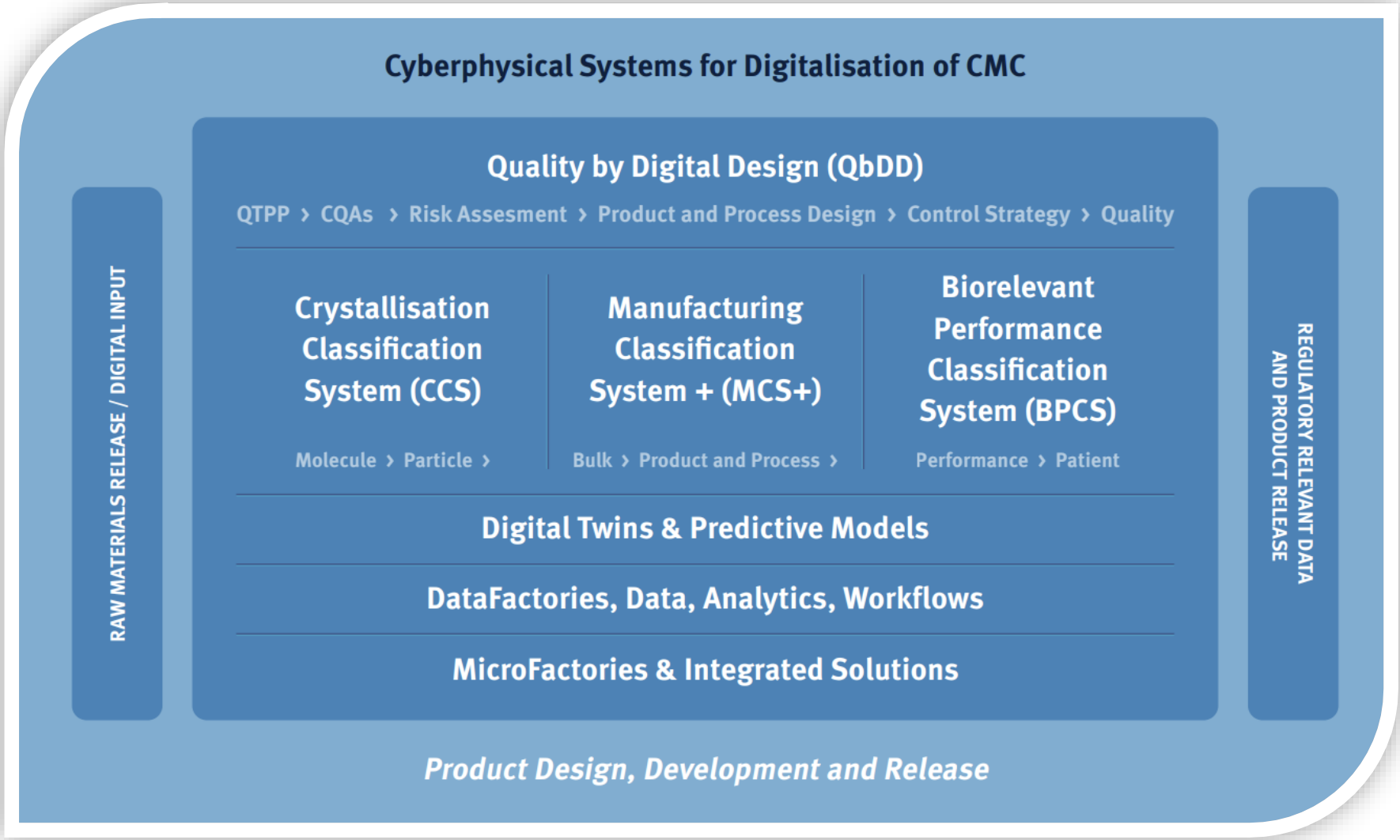
An Integrated Digital Toolbox



- Establish cyberphysical design & production systems for medicines
- Build on current capabilities e.g. BCS, DCS, MCS
- ***In silico prediction across materials, processes & products***
- ***Decision support tools for rapid development***
- ***Towards unified data model, ontologies and semantics for CMC***
- ***Quantitative risk and uncertainty understanding***
- QbDD to accelerate from performance target (QTPP) to production of on spec product
- Accelerate development; enhance sustainability

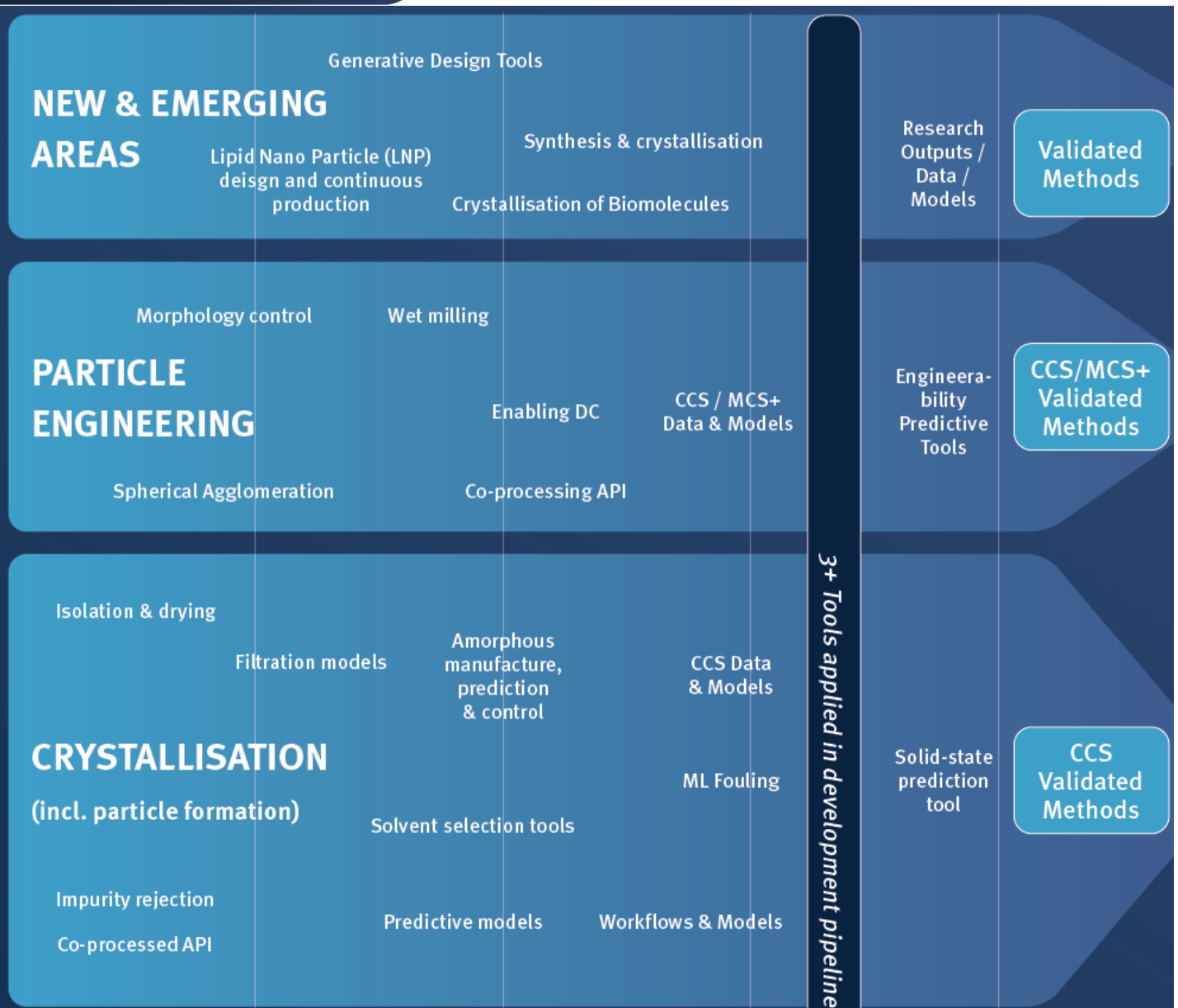
Working Definitions for a Crystallisation Classification System (CCS)

CCS: To classify molecular types in terms of their predicted crystallisation outcomes.

Purpose	Develop integrated platform/s to support efficient and science driven development from molecule to particle
Scope	• Probabilistic predictions on how molecular structure impacts particle formation • AI/ML tools integrated to inform process selection and design
Benefits	• Support rapid translation • Inform screening & form selection • Data driven, mechanistic and hybrid predictive tools for: solvent selection, rapid estimation of crystallisation model kinetic parameters; impurity rejection; in silico process design • In silico process and particle design tools

- Provide predictions that inform/support decisions
- *E.g. Solvent selection; Fouling; Achievable Outcomes/Engineerability; Rapid PBM Development; Particle Engineering route selection…..*

Research Implementation Planning Across CMAC Portfolio



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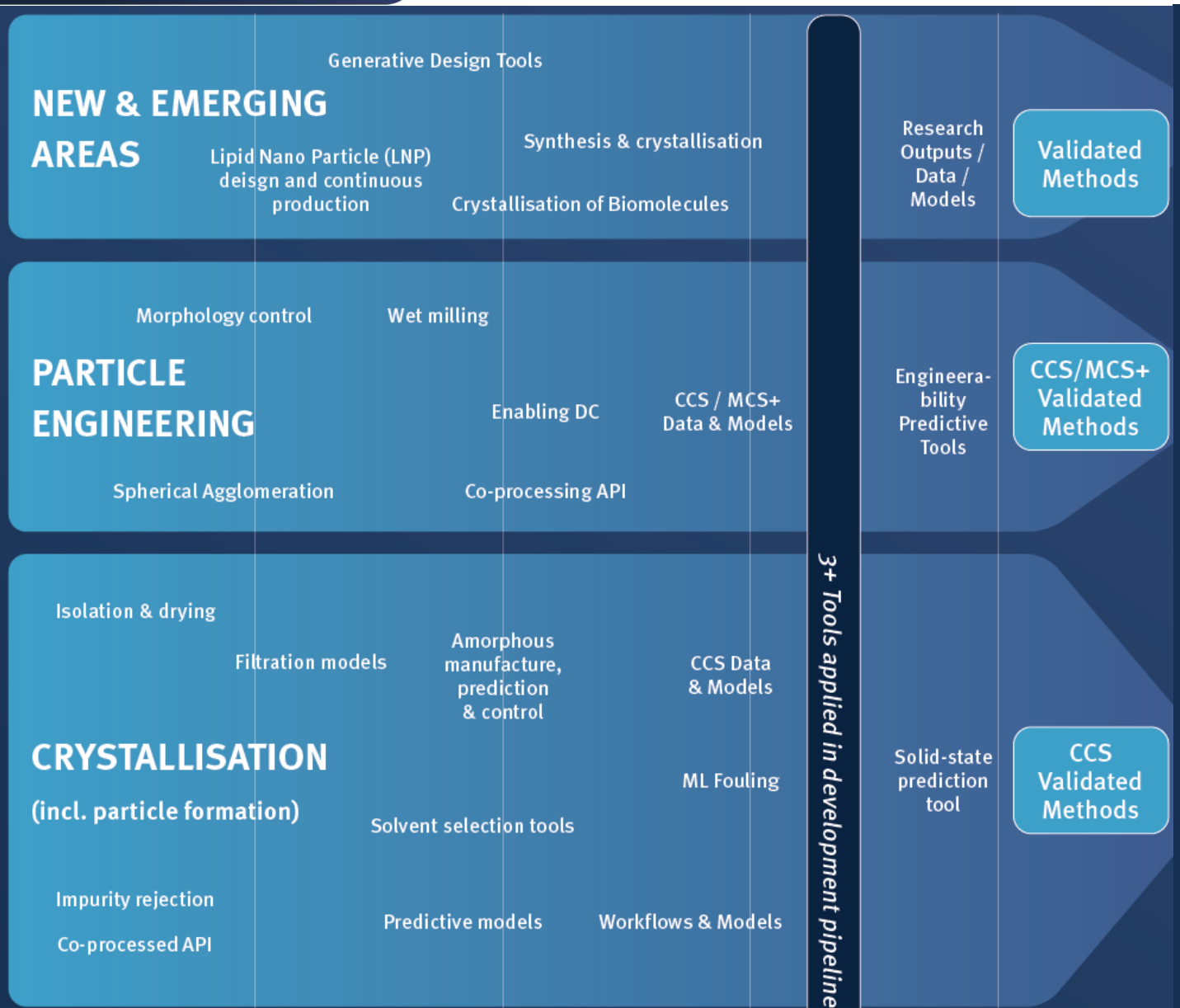

Core Crystallisation

- Solvent selection
- Co-processed API e.g. addition of functional excipient during crystallisation/isolation
- Impurity rejection
- Continuous isolation & drying
- Workflows, Modelling & Simulation

Particle Engineering

- Spherical agglomeration
- Morphology control
- Wet milling
- Enabling direct compression

New & Emerging Priorities

- Crystallisation of peptides and proteins
- Coupling synthesis & crystallisation

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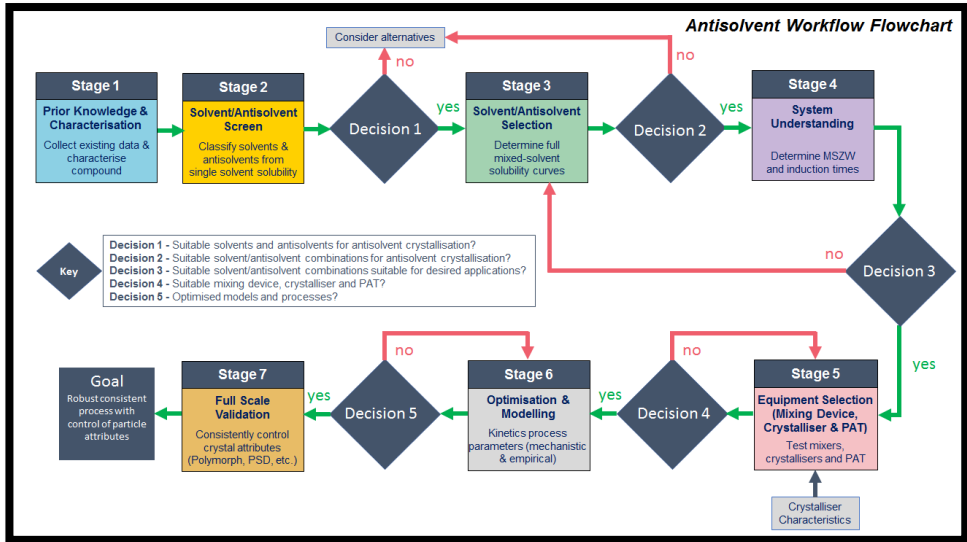
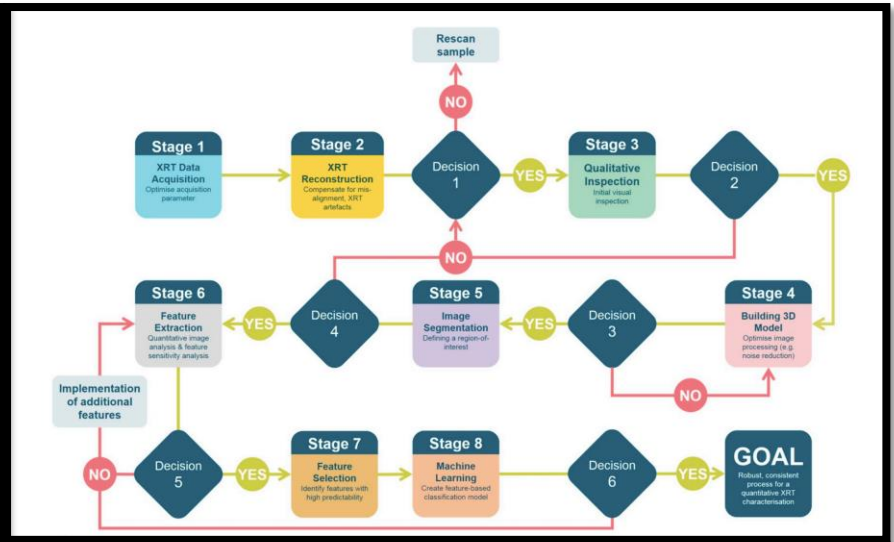
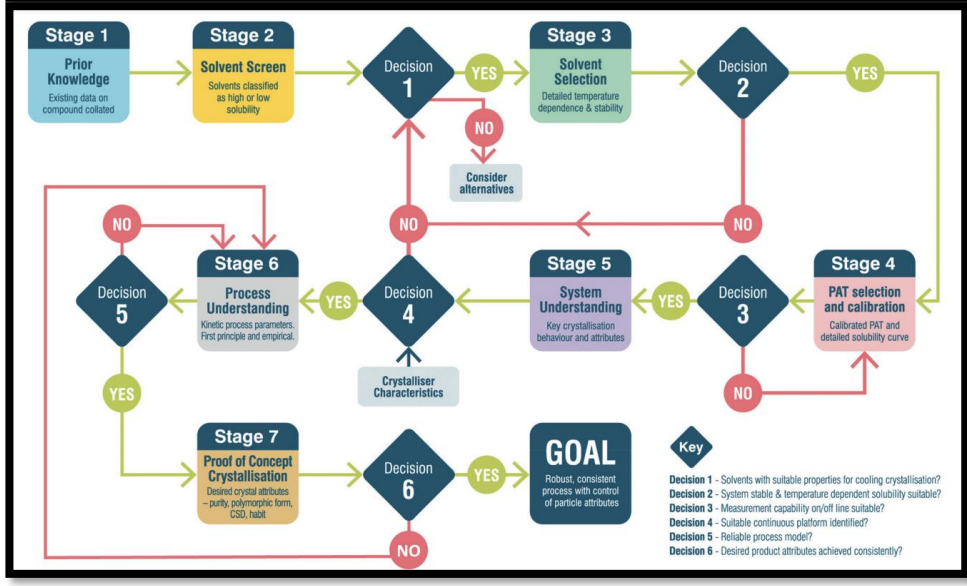
Research Excellence & Intensity

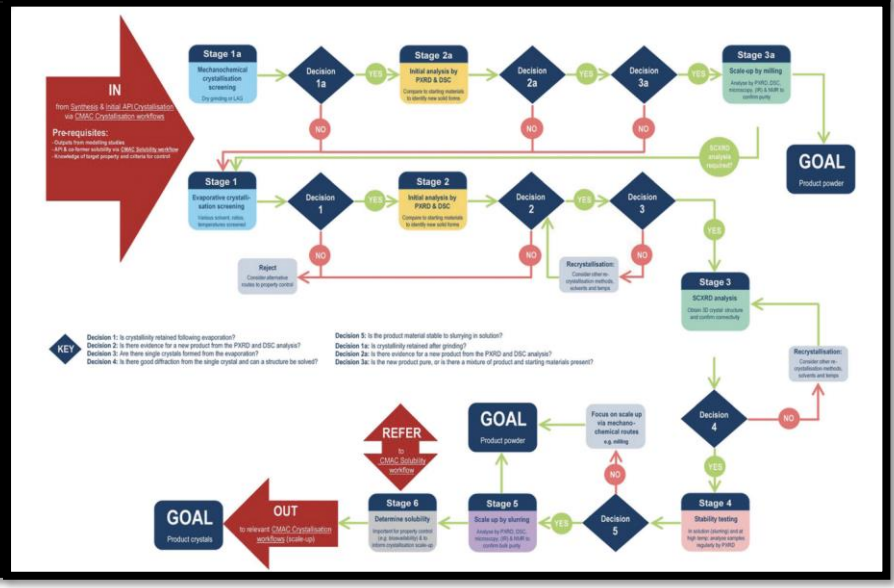
User-Centric Workflows

Standardised, model driven, rational experimental design methodologies and data generation









Current CMAC Workflows include:

- Seeded, cooling crystallisation
- Antisolvent crystallisation
- Impurity rejection
- Additive mediated morphology control
- Spherical agglomeration
- Wash solvent selection
- Multicomponent structural informatics
- Micro-XRT analysis & ML for the characterisation of multi-particulate capsule formulations
- Direct compression formulation design
- Quality by Digital Design (QbDD)

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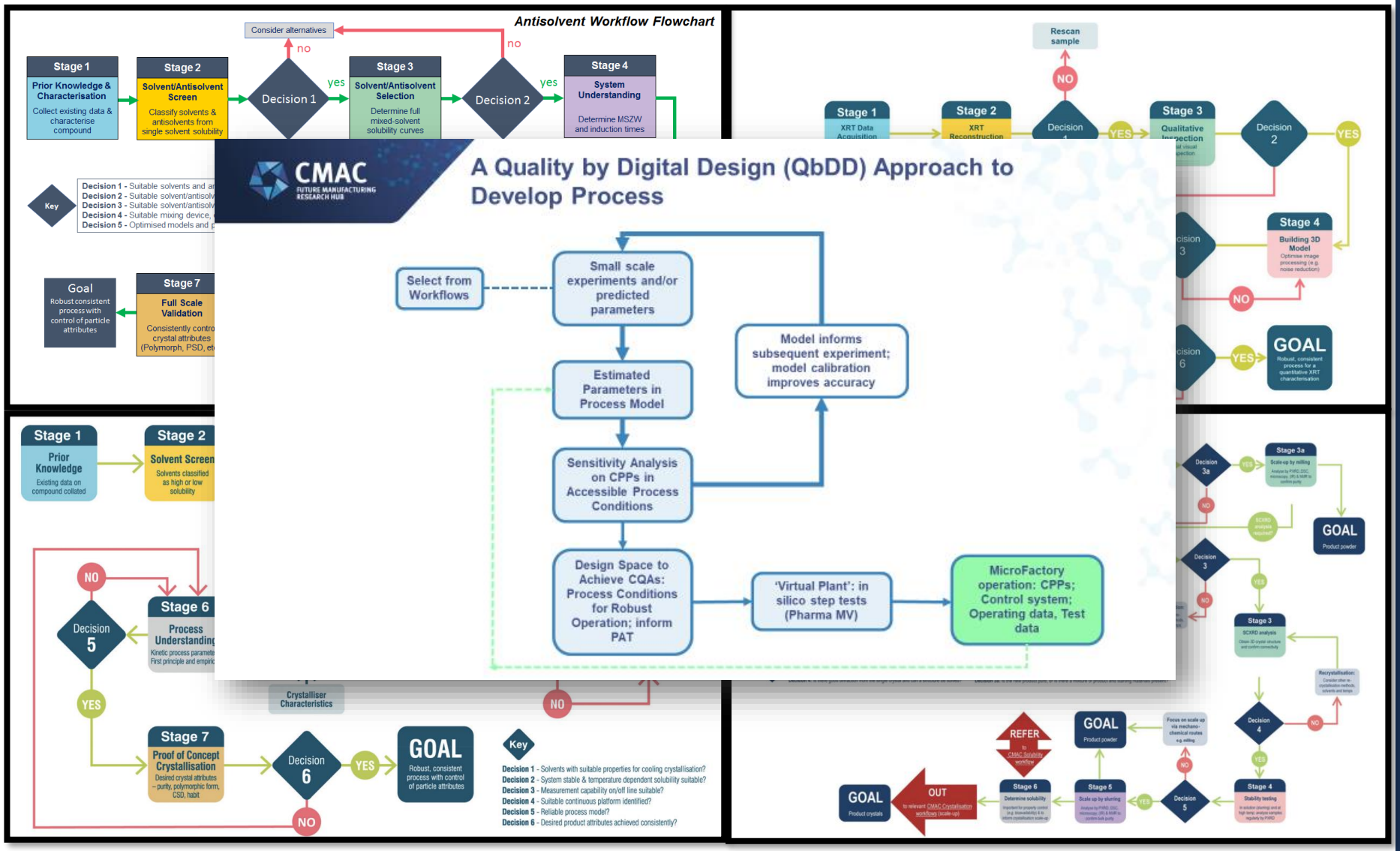

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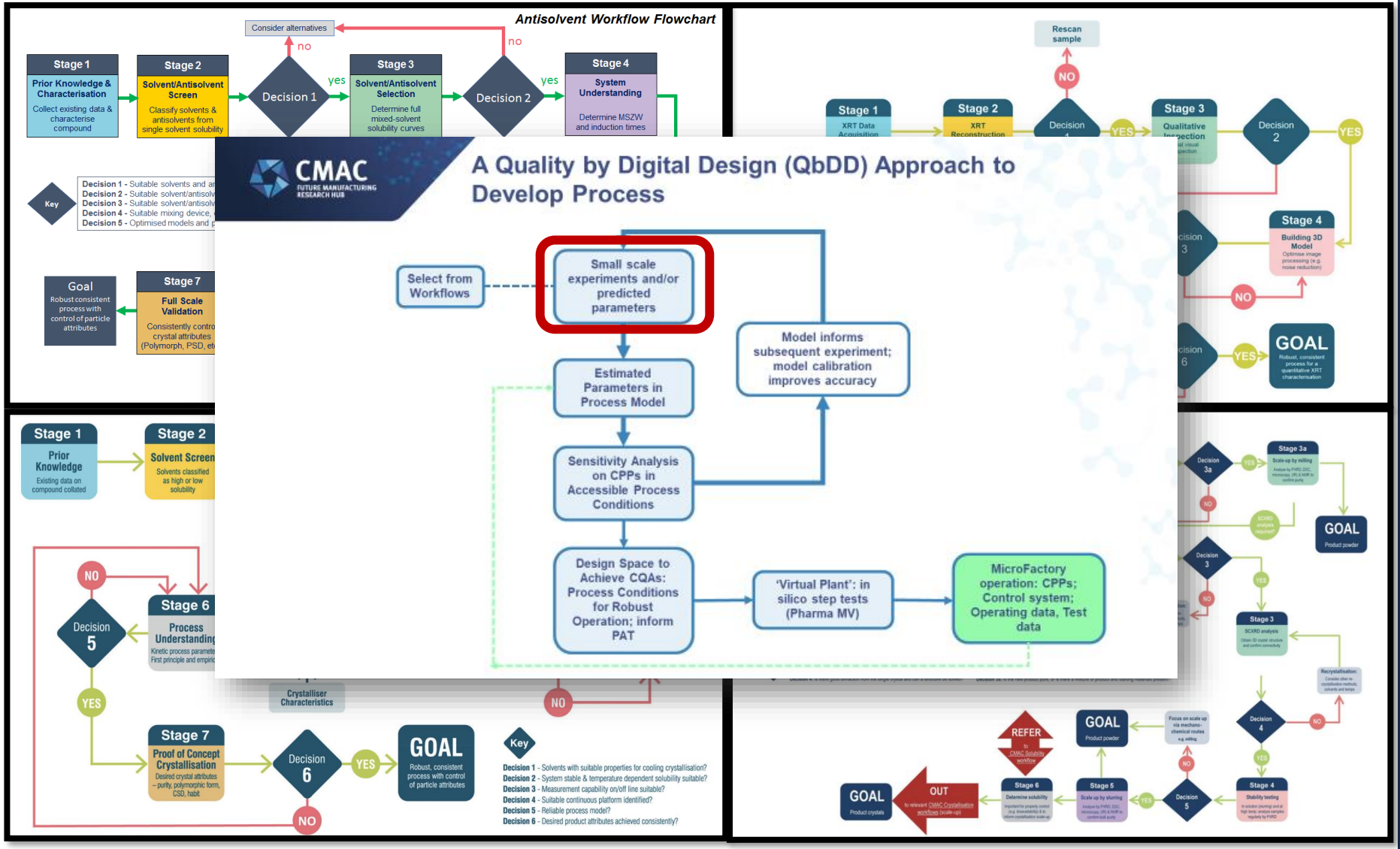

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Systematic Experimental Workflow: Process Understanding and Model Parameterisation

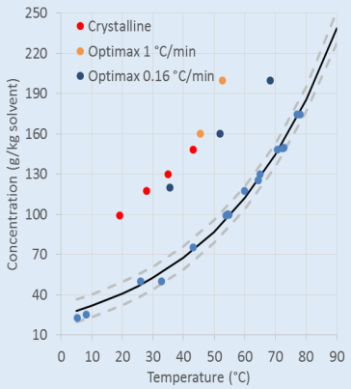
Description

- ID process conditions for desired performance.
- ID limits
- Inform platform selection, mixing, etc.

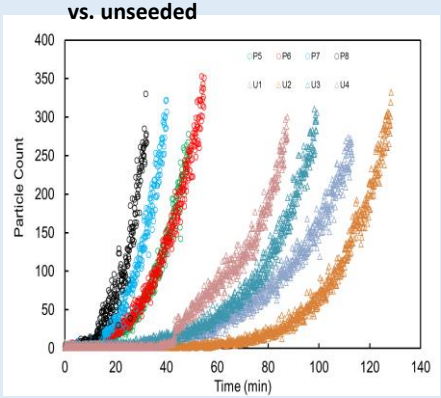
Methodology

- Range of tests developed to assess:
  - Metastable zone
  - Secondary nucleation
  - Growth rate
  - Fouling
  - Agglomeration

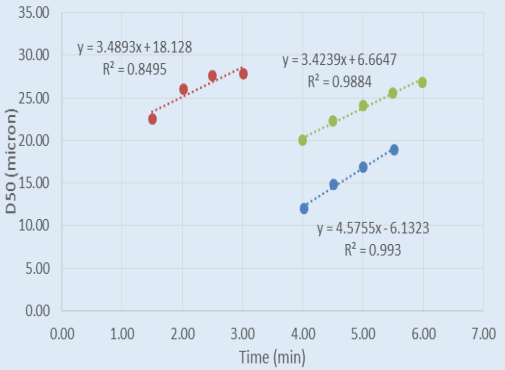
Metastable zone widths



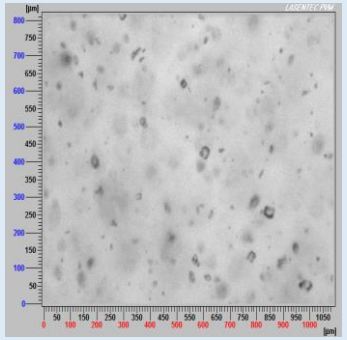
Secondary nucleation: Seeded vs. unseeded

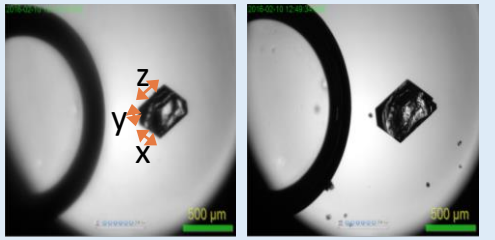


Growth rates. Bulk and single crystal

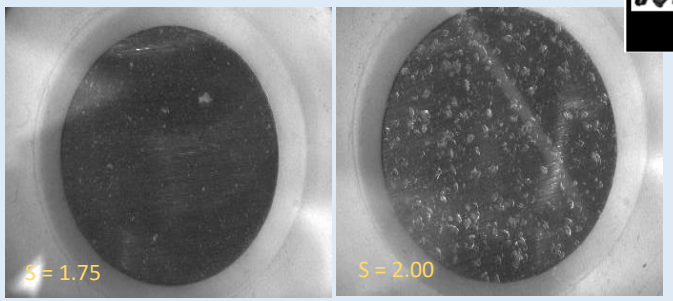


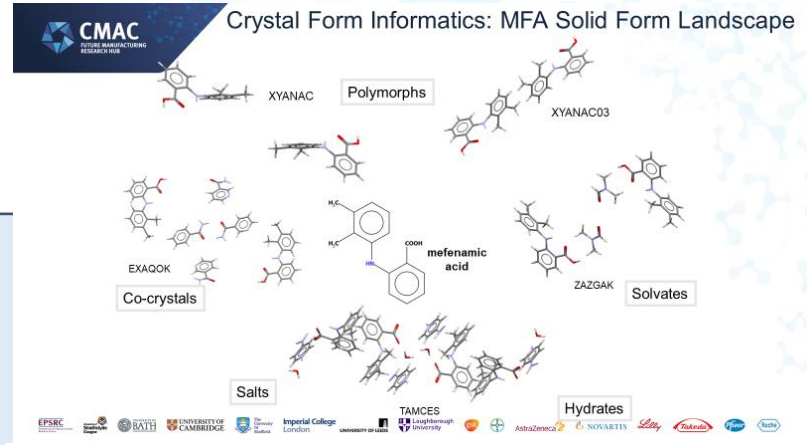
Agglomeration



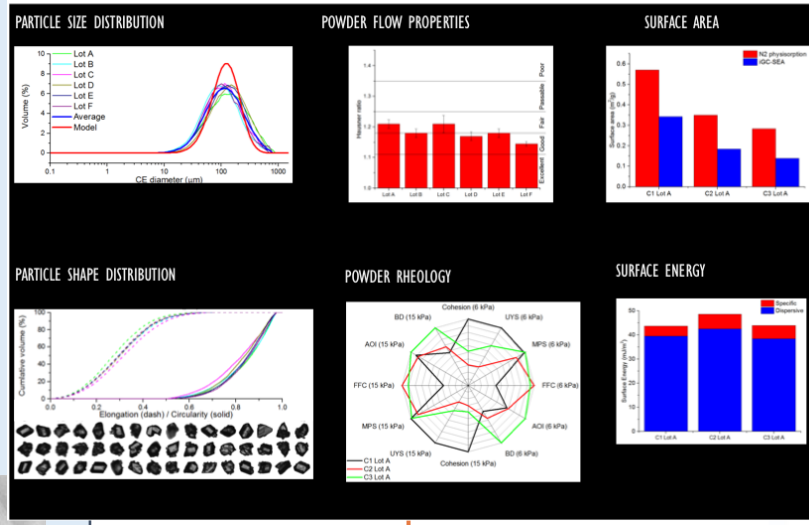


Fouling induction times





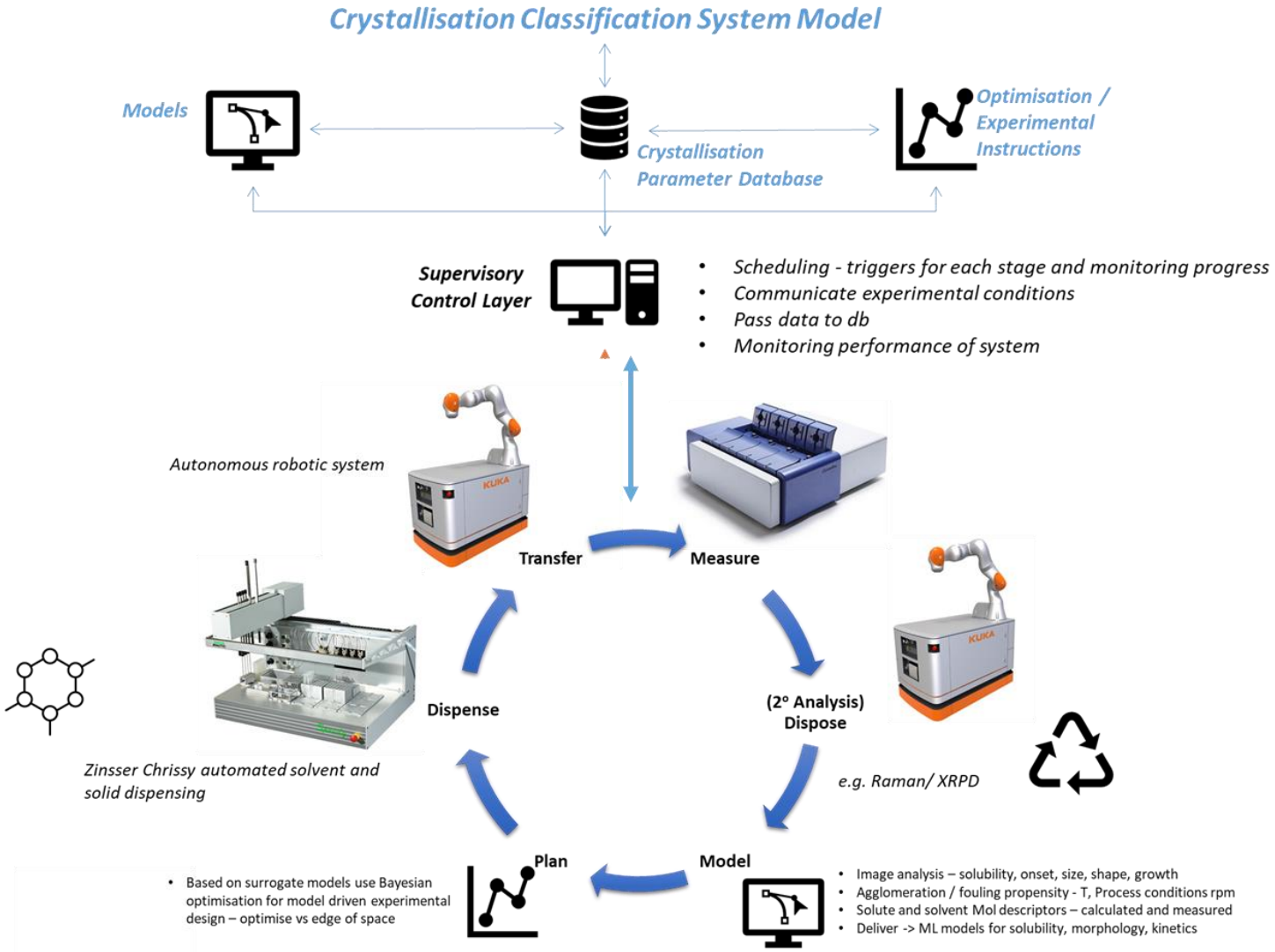
Measure Particle Outcomes



Correlation of particle structure and properties with process history

Can we accelerate? – DataFactories

Smart development platforms for data generation- utilising AI/ML, automation & collaborative robotics



- **Material sparing approaches**
- **Data rich experiments**
- **Drive model development & testing**
- **API** – ***Crystallisation Parameter Database:*** for crystallisation digital design & a ***Crystallisation Classification System (CCS)***: inform rapid development
- **DP** - ***Automated mini-batch DC & capsule filling demonstrator*** & ***Autonomous digital manufacturing demonstrator*** to predictively formulate new OSDs for phase 1 clinical supply
- Fouling, Crystallisation Scale Up & Solid Form DataFactories Under Development

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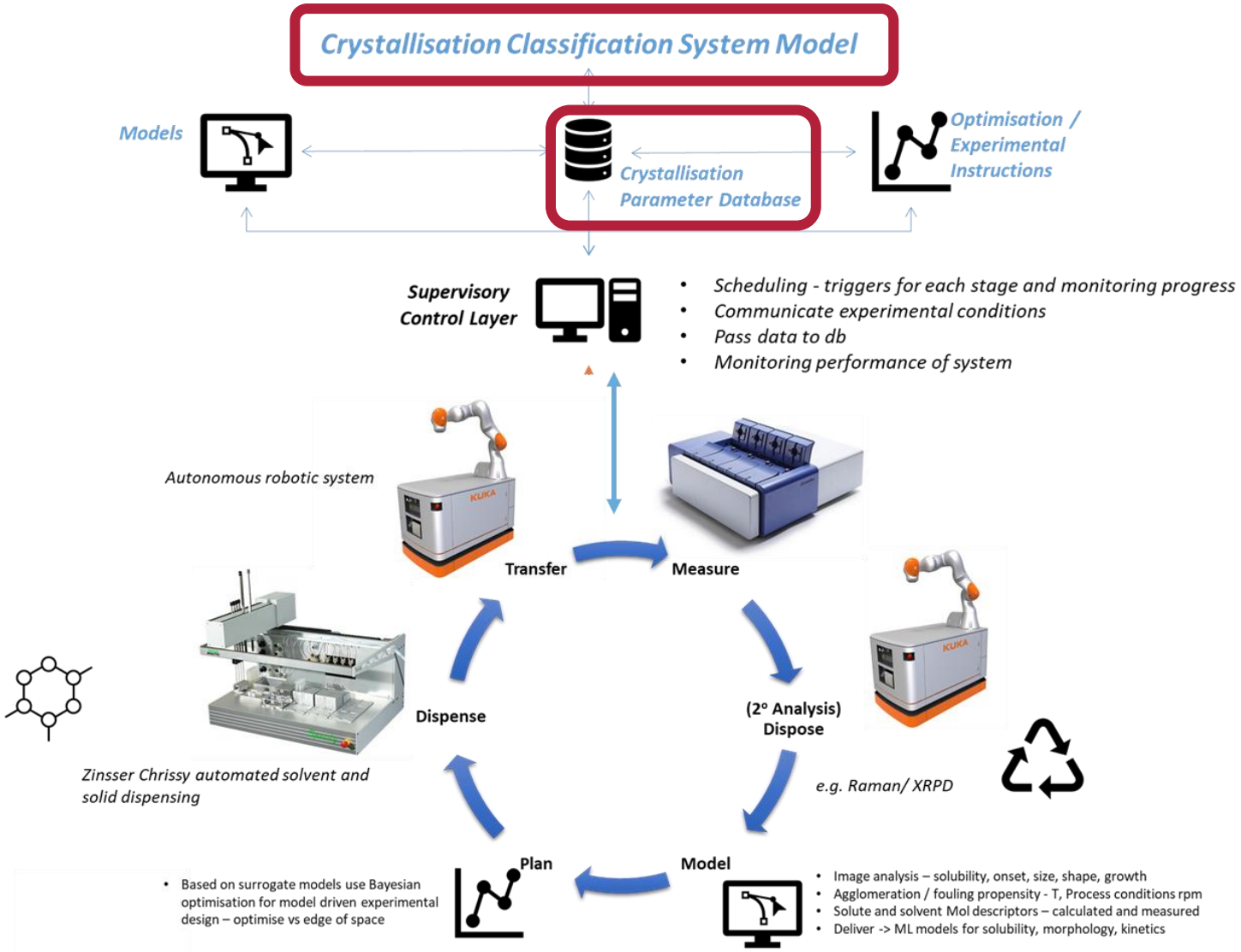

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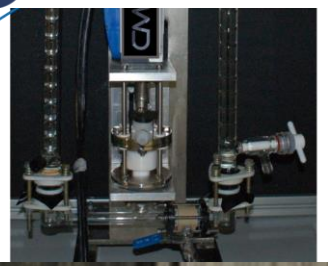
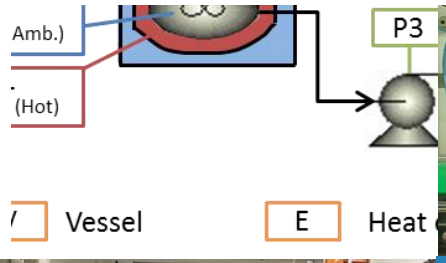
Research Excellence & Intensity

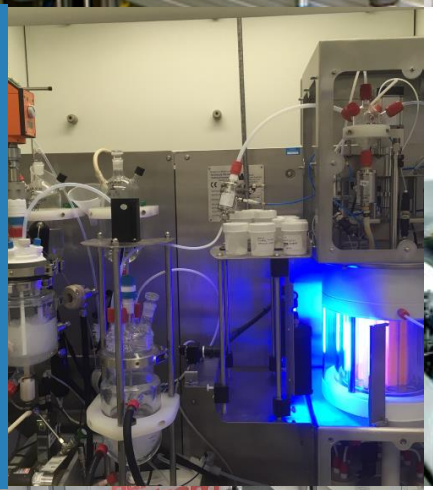
Advanced Manufacturing Technologies

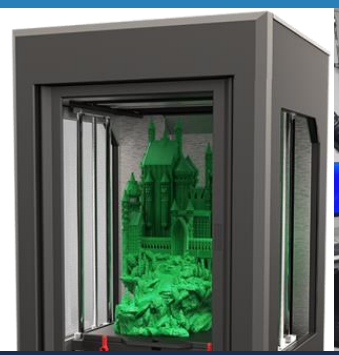




Enable design, control & production of wide range of particle attributes and bulk properties

Assess & test manufacture & performance using industrially relevant secondary processes





Suite of Individual Unit Operations & MicroFactories:

Access data **from a range of scales, geometries and modes across crystallisation and DP**

Microfactory Module Development – 5 stage MSMPR

Aim: design & build flexible, modular processing module

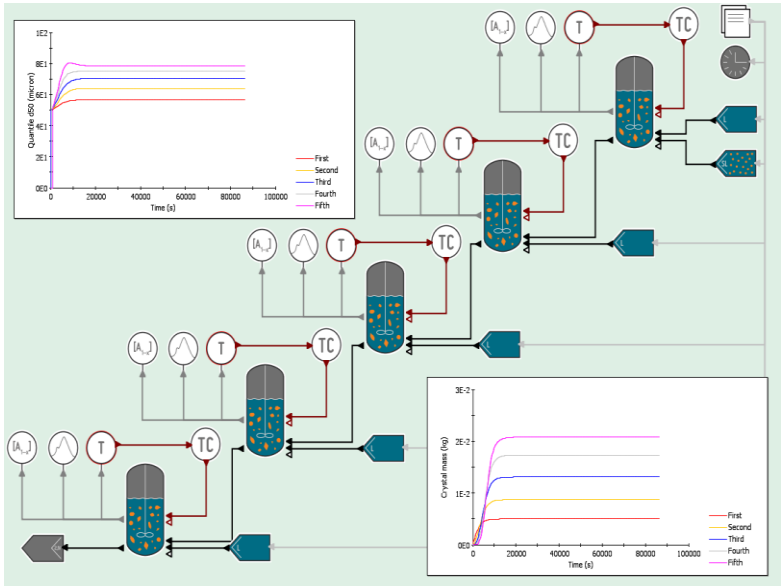
- Output includes:
  - ***Physical:*** PAT – data – automation - control
  - ***Digital:*** equipment & process models
- Make as ease as possible to deploy on new processes
- Siemens- PCS7-SiPAT + Perceptive MPC control framework
- 3DP used for rapid prototyping
- VR/AR being developed

→ Process

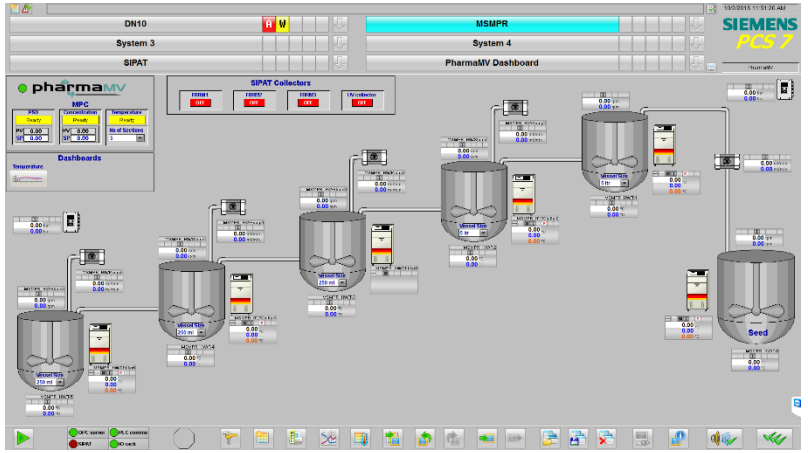
Extended with Modules for

- Seeding
- Cooling
- Antisolvent
- Sonication
- Wet milling
- Spherical Agglomeration
- Washing & Filtration

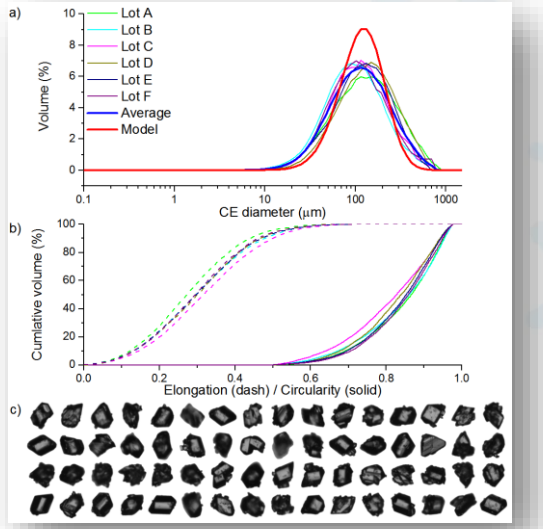
Workflow → Data/Parameters → Process Model



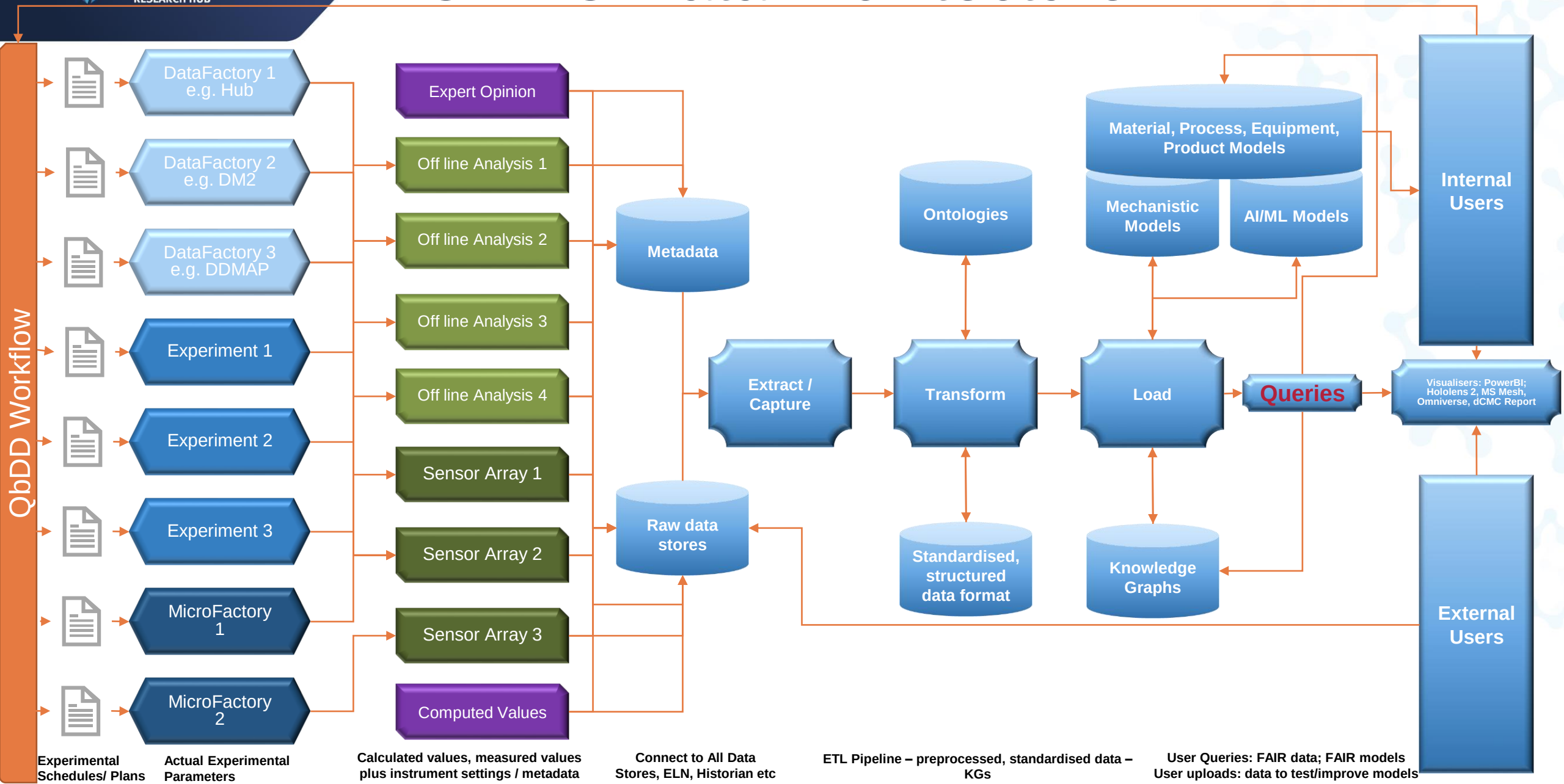
→ Automation & Control interface



→ Required Particle Attributes



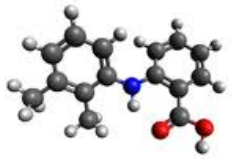
CMAC Data Architecture

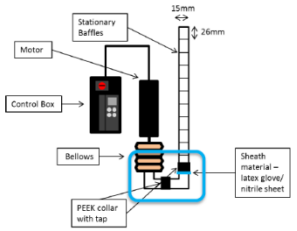


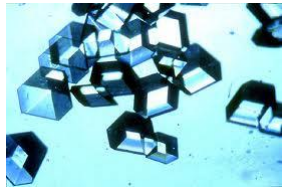
Exploiting Systematic Data to Build CCS Toolbox

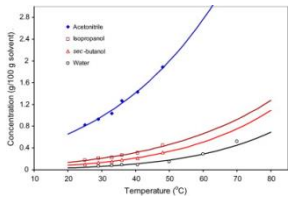
- Exploit workflows to collect systematic data, implementing FAIR principles
- Learn from experience, quickly;
- Guided by tools to right technical solution

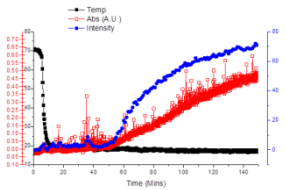
Molecule	Solubility	Kinetics	Fouling	Crystal Props	Modelling	Platform Selection & Testing	Process Optimisation
• Mol Props • Purity • Stability • Compatibility	• Solvent system • Cooling profile • Morphology	• Nucleation (1^{O} and 2^{O}) • Growth • Agglomeration • Attrition	• Supersaturation • Cooling • Fluid dynamics • MOC	• e.g. hardness • Form, BCS/DCS • Purity • Morphology • Defects • surface	• Empirical • 1st principles • Direct design/statistical models	• COBR • MSMPR • Other • STR… • PAT	• PAT enabled • Closed loop feedback control

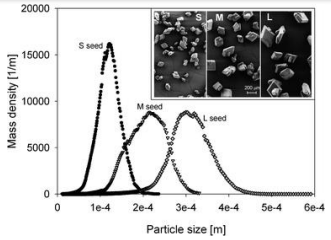


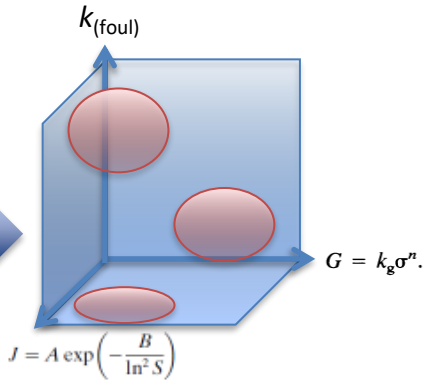








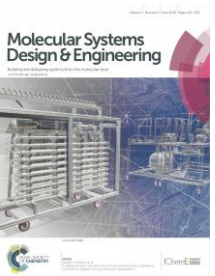




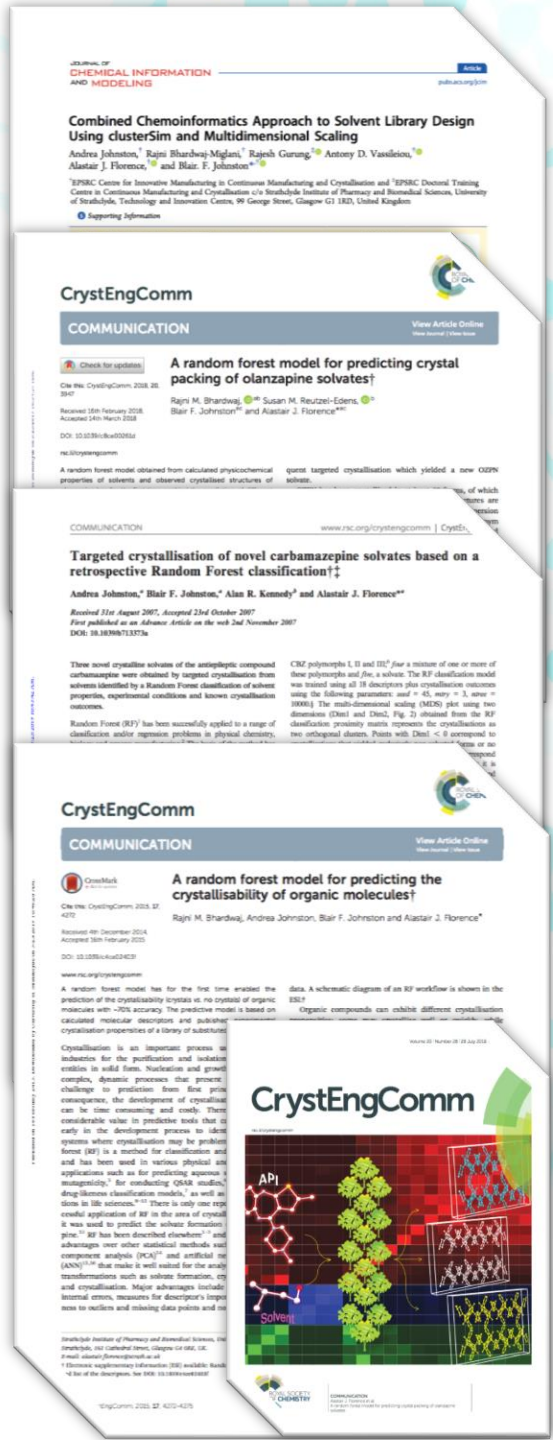
$$G = k_g \sigma^n.$$

$$J = A \exp\left(-\frac{B}{\ln^2 S}\right)$$

Crystallisation Classification



Brown et al., ***Mol. Syst. Des. Eng.***, 2018,**3**, 518-549



CCS Toolbox Development

Solubility

Crystallisability

Amorphous

Morphology

Solvate Formation

Flow Function

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e.g. Solvents & Solubility Dataset

University of Strathclyde Glasgow

Experimental Data

- Total of 714 solubility measuremen collected. Solutes were all drug-like or
  - 75 unique solutes
  - 49 unique solvents
- Melting points and enthalpies of fusion (used for COSMO-RS only)

Sources

- CMAC Tier 1 partners
- Internal CMAC experimental data
- Literature

Descriptors

- Molecular descriptor set for each solut
- COSMO-RS prediction for each system

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Couple experimental and calculated solubility values to train ML

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Solute structure | Solvent structure

Solute descriptors

COSMO-RS solubility prediction | Solute descriptors

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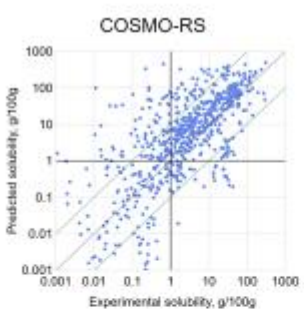
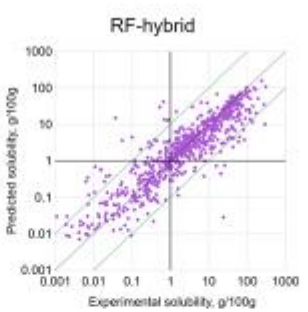
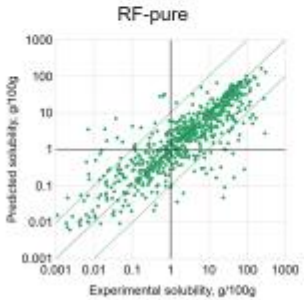
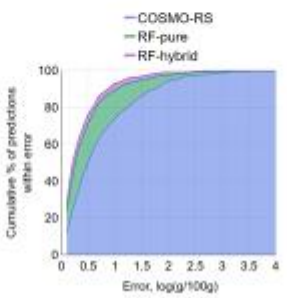




10-fold CV





Model	R^2	RMSE	MAE	FI
COSMO-RS	0.30	1.00	0.72	na
RF-pure	0.68	0.67	0.43	0.66
RF-hybrid	0.78	0.55	0.36	0.72

- **Improved overall performance by exploiting *all* data**
- **Including thermodynamic model derived data in model training**
- **Good coverage of solvent and API attributes**

- Improved solubility prediction
- Inform reliable solvent selection for crystallisation

CCS Toolbox Development

Solubility

Crystallisability

Amorphous

Morphology

Solvate Formation

Flow Function

What About Kinetics: e.g. Crystallisability?

Q. Can we estimate the likelihood of a molecule crystallising 'easily' from its molecular structure?

A. Use ML to relate molecular structure to experimental outcome.

Why Do Organic Compounds Crystallise Well or Badly or Ever so Slowly? Why Is Crystallisation Nevertheless Such a Good Purification Technique?†

A structural systematics study that monitored the crystallisation behaviour (obtain single crystals for XRD) of >400 related acylanilides…and published the results.

R/X = alkyl/alkyloxy/ halogen

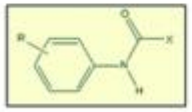
Predict Nucleation: ML Crystallisability Tool

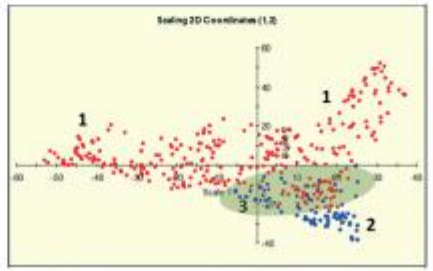
- 308 descriptors [2D (185) and 3D (123)] were calculated
- RandomForest (RF) model generated using 308 descriptors.

Selects random sample of molecules and tests prediction against outcome on that generation of RF

Best results: gives ~30% error rate in classification "crystallise" vs "not crystallise"

Actual class	Total cases	% correct	1, N=231	2, N=151	Class Error
1. crystals	303	67.7	205	98	32.34
2. no crystals	79	67.1	26	53	32.91





Extended to data from literature for estimation of nucleation and growth kinetic parameters (doi.org/10.26434/chemrxiv.11708286.v3)

CrystEngComm, 2016,17, 4272-4275

- Identify challenging nucleation properties e.g. seed / external fields
- Provide initial parameter estimates for process models

CCS Toolbox Development

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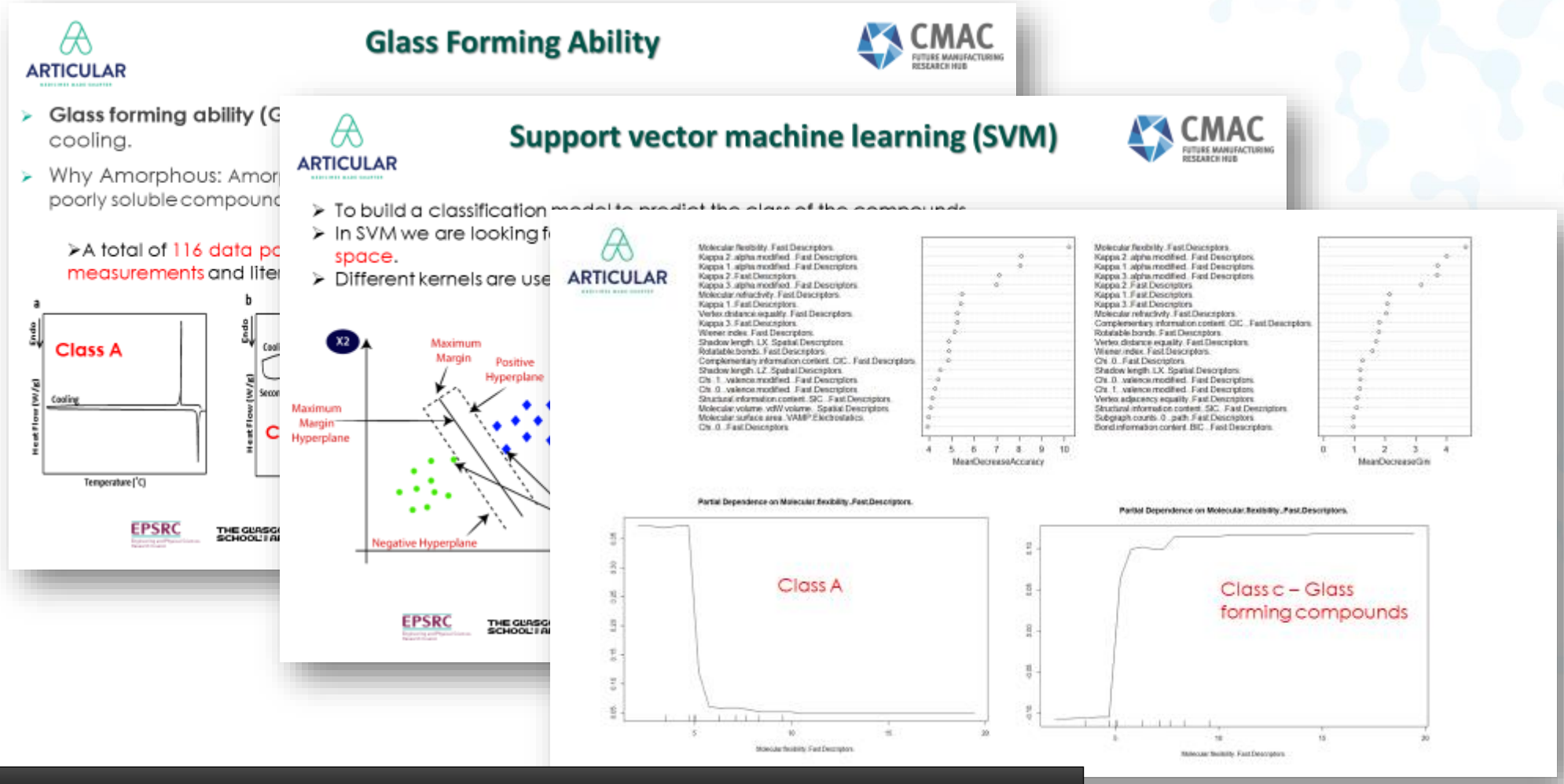


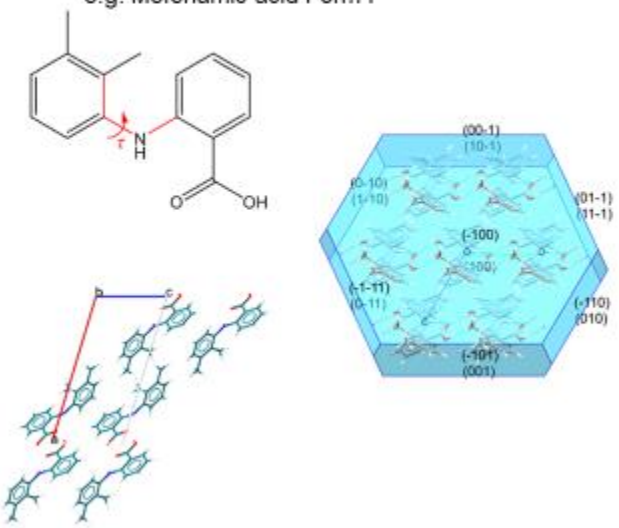
- >80% accuracy in prediction of API GFA
- Importance of interpretability in ML models e.g. ranker importance / SHAP parameters

CCS Toolbox Development

- Solubility
- Crystallisability
- Amorphous
- **Morphology**
- Solvate Formation
- Flow Function

Solvent impact on morphology

e.g. Mefenamic acid Form I



MFA form I; CCDC ref code XYANAC

Solvent impact on morphology

Polyhedral	Needle	Supersaturation dependent crystal shape
1,2 dichloroethane	1-bromobutane	1,4 dioxane
1-chlorobutane	1-methylnaphtalene	2-butanol
1-octanol	aniline	2-butanone
2-methoxyethanol	anisole	2-propanol
acetic acid	methyl acetate	butyl acetate
acetone	nitromethane	diethyl sulfide
acetonitrile	toluene	methanol
chloroform		
ethanol		
DMF		
ethyl acetate		
iodomethane		
triethylamine		
trichloroethylene		

Morphology Prediction	Accuracy
	10-fold CV
Model 2	93.5% (SD = 4.7%)

- RF Classification a useful tool to predict solvent effect on crystal morphology (93%)
- Excellent performance on solvents not in training set
- H-bonds and London Dispersion forces most important variables

Siya Nakapraves et al., submitted 2022

- >90% accuracy in prediction of shape class
- Inform solvent selection to avoid extreme morphologies

CCS Toolbox Development

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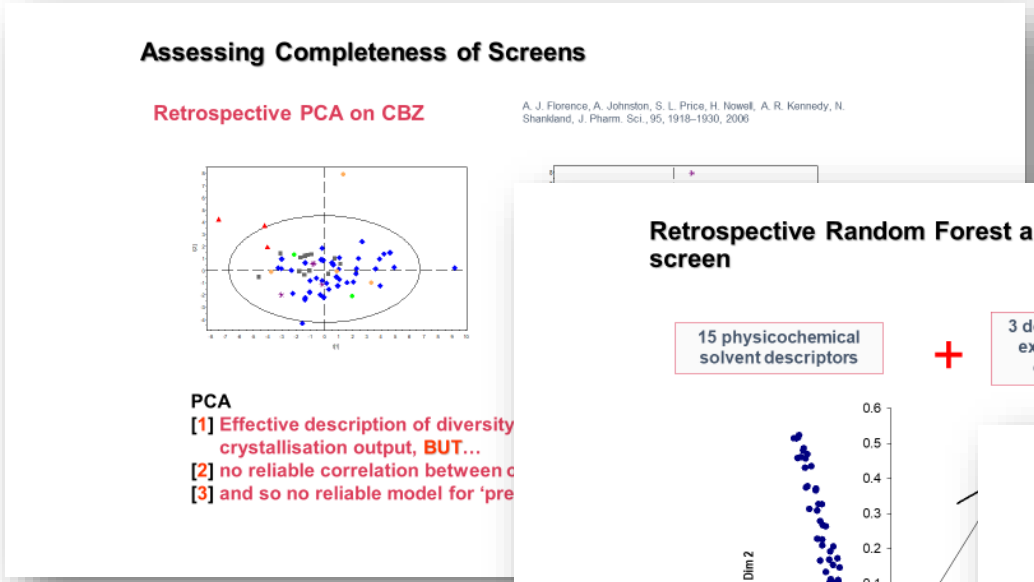

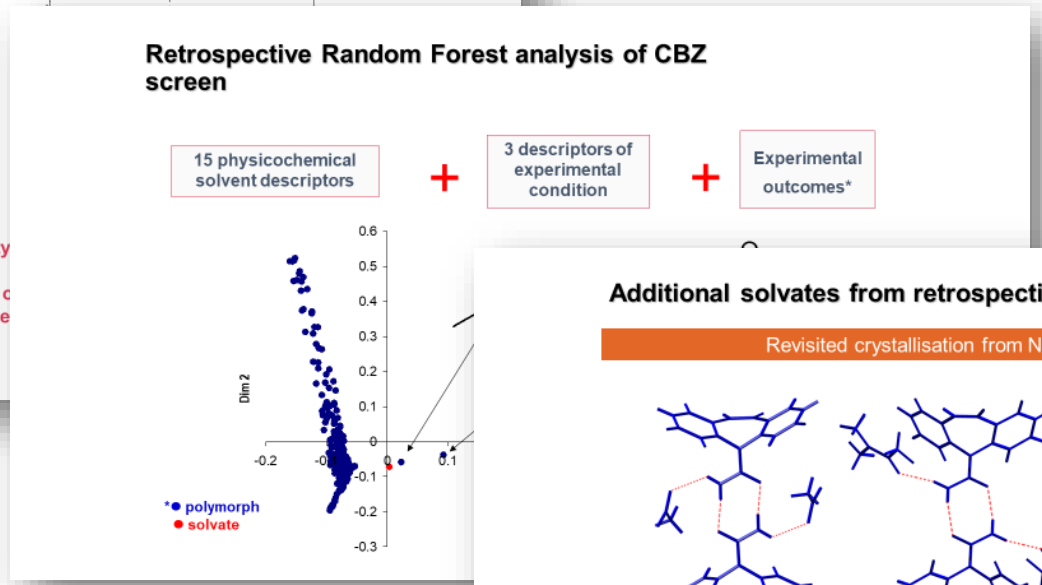

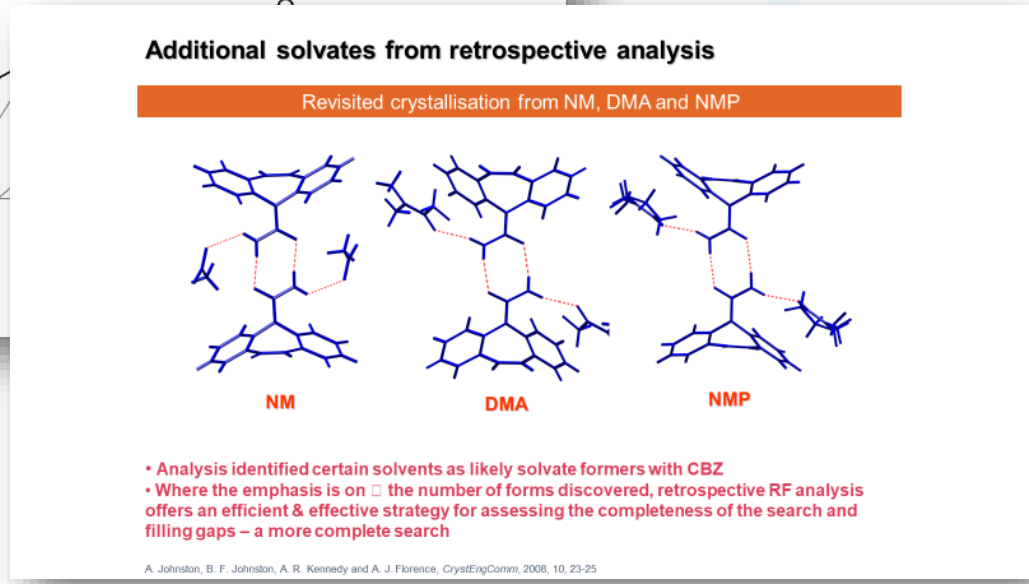

- Identify solvents/conditions to avoid during process development
- Target development where failures less likely

CCS Toolbox Development

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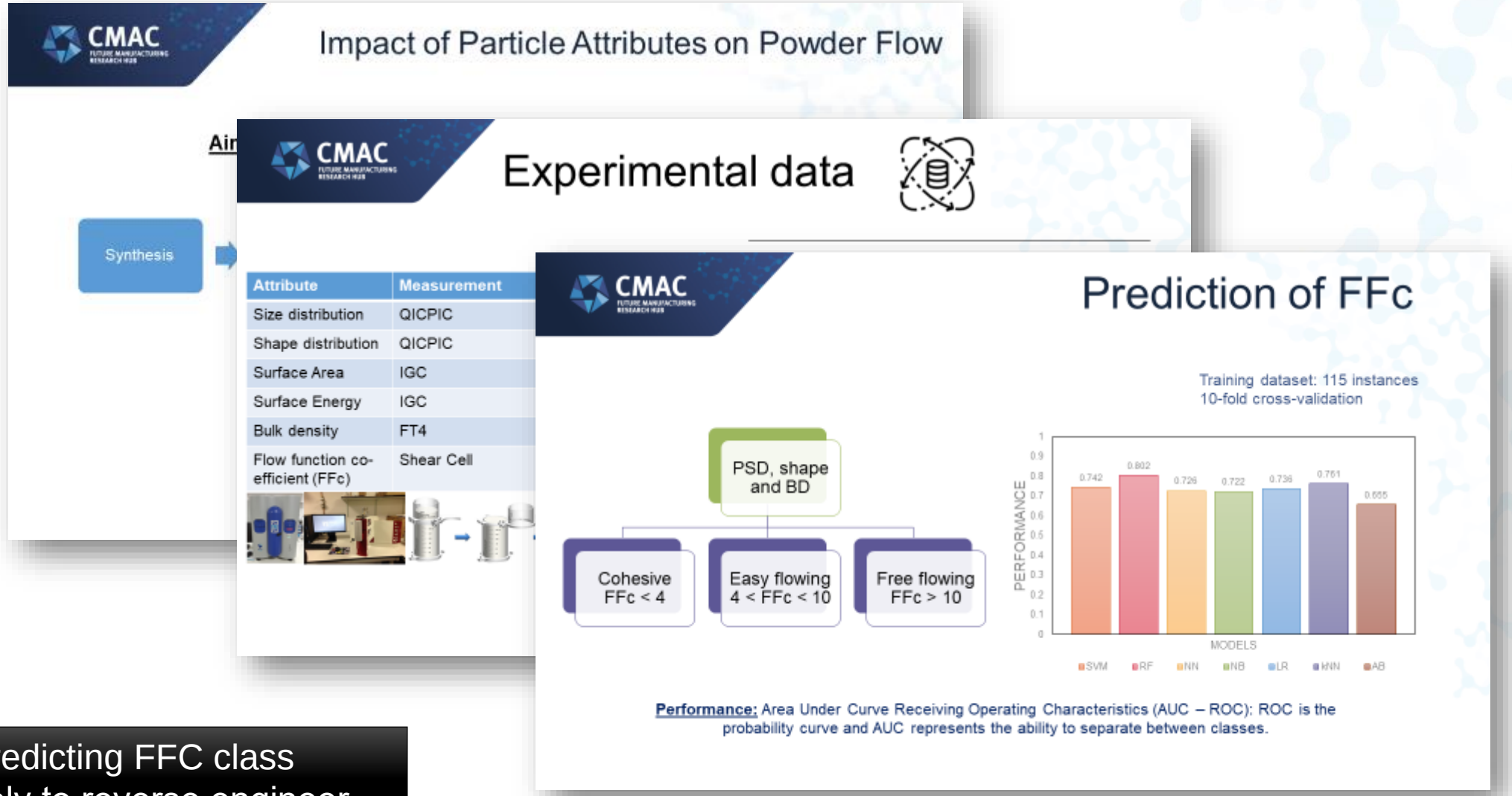
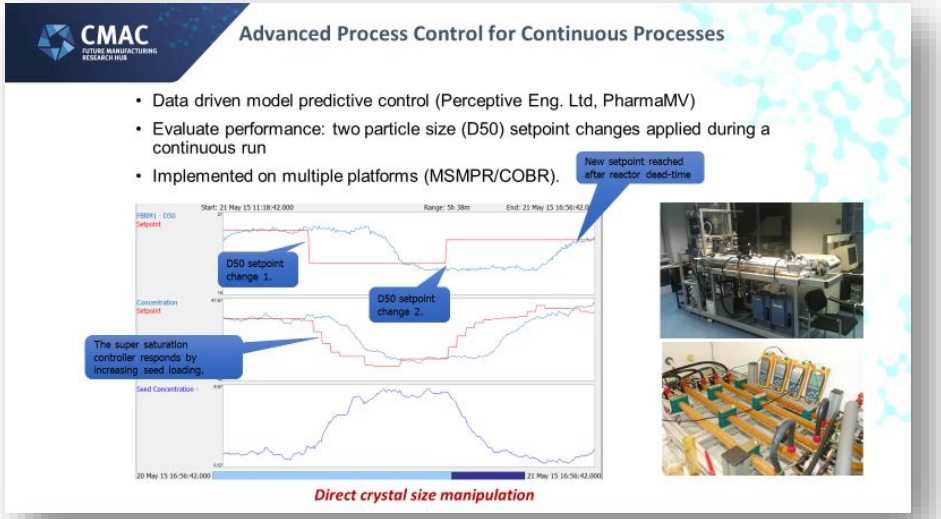


- >80% accuracy in predicting FFC class
- Ongoing work to apply to reverse engineer…

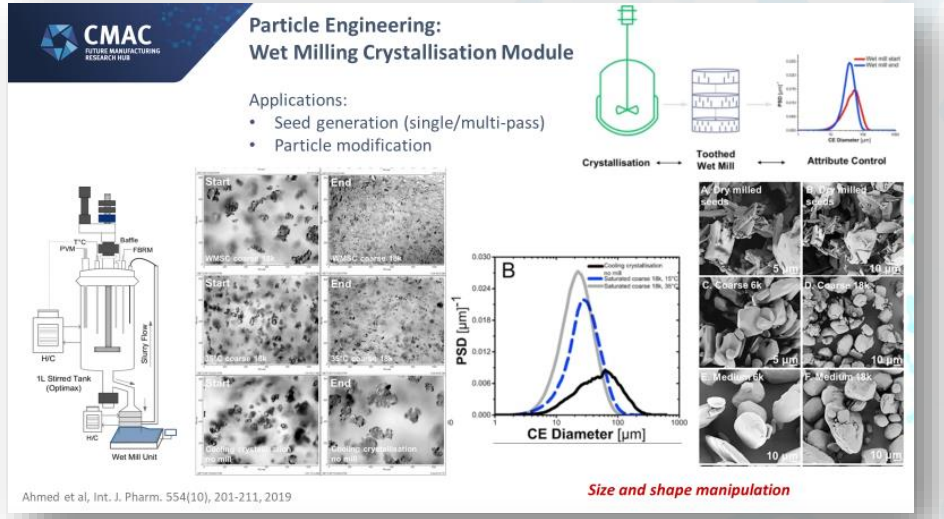
e.g. Make Particles with Desirable Properties

e.g. Use as design objectives for crystallisation and particle engineering approaches

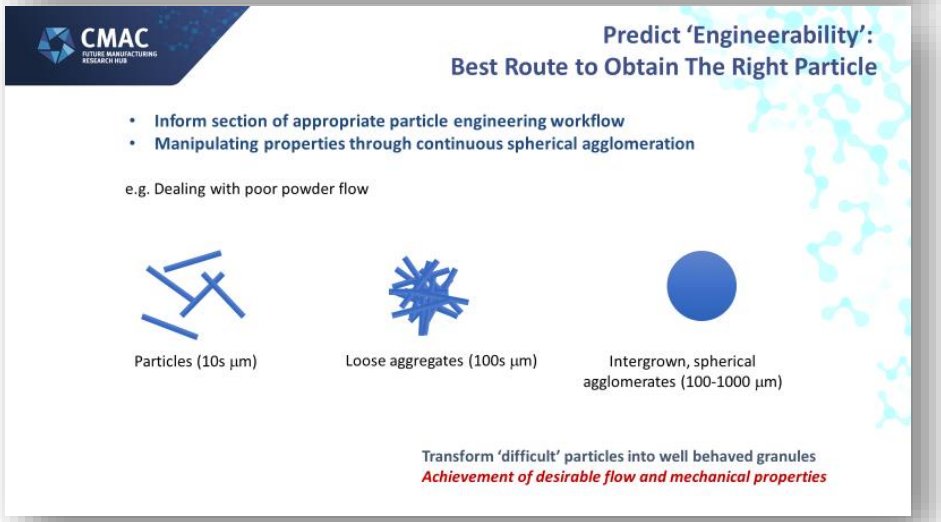
APC



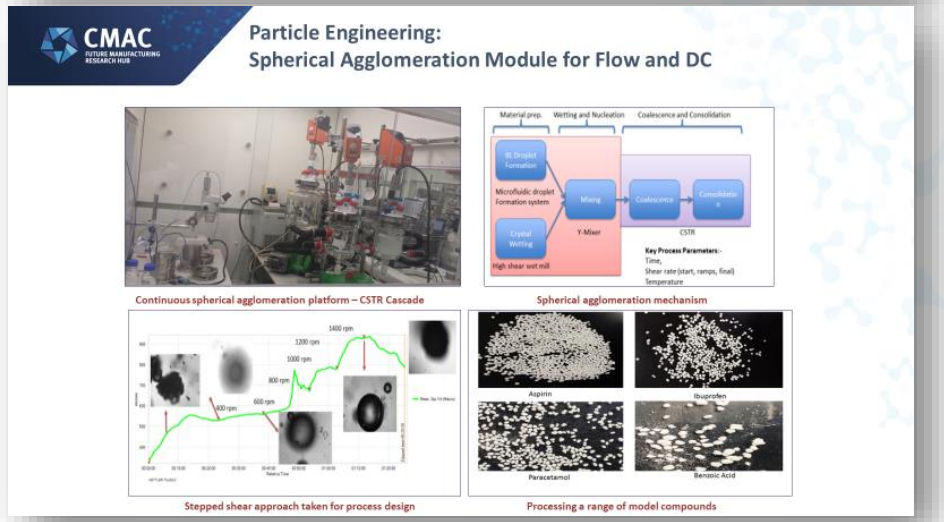
Wet Milling



Spherical Agglomeration



Spherical Co-Agglomeration



A Research Agenda for Impact

CMAC FUTURE MANUFACTURING RESEARCH HUB

Strategic Statement of Intent: *Create value to partners* from a co-created, high quality research portfolio across advanced manufacturing, digital technologies, materials science to enable QbDD and digitalised CMC processes

	2022	2023	2024	2025	2026
Timeline:					
Objectives:	Target Areas	Co-deliver solutions	Assess research tools	Drive acceptance & adoption	Tools in practice
Activities:	Implement strategic roadmap priorities	Collaborative research delivery	Disseminate outputs + integrated toolbox informing new projects	Target remaining gaps in roadmap	Sustain work & community
Deliverables:	Co-created research proposals in priority areas + Formulate Hub-follow on plan	DataFactory; Microfactory; Digital Twin ex Hub & DM^2 + EPSRC critical mass post 2023 + 1st versions of CCS; MCS+	Demonstration of research tools from portfolio in Tier 1 development pipelines + BPCS development	Integrated toolbox of CCS; MCS+, BPCS enabling QbDD	Digitalised CMC process implemented in NDA
Impacts:	Managed portfolio of collaborative research	CMAC Tier 1/2s actively engaged in research + new tools developed	Research impacting Tier 1 internal development pipeline	Speed, material sparing, sustainability and quality objectives validated	IDTs and Advanced Technologies implemented across Tier 1s

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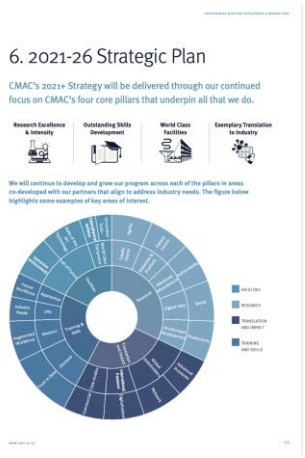
The Future: agile, flexible, sustainable development, manufacture & supply

CMAC Lab of the Future: QbDD embedded via integrated manufacturing science + data driven development tools + advanced process technology + useful Digital Technologies + talented researchers

CMAC
FUTURE MANUFACTURING RESEARCH HUB

Research Excellence & Intensity

Thanks



Academic Partners

Supporters / End Users

Please get in touch if interested to find out more & to

- Engage
- Co-create
- Co-deliver
- Train
- Disseminate
- Translate

To drive forward medicines development, manufacturing & supply

Acknowledgements

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