Annual Review

2021

Contents

Introduction

Welcome to the 2021 Annual Review for the EPSRC Future Continuous Manufacturing and Advanced Crystallisation (CMAC) Research Hub. The report provides updates on progress across the academic team during another unprecedented year for the CMAC community. Whilst we have continued to see impacts from the pandemic across our manufacturing research, training, facilities and translation to industry programmes, I am immensely proud of the way that colleagues have continued to come together to find ways to achieve our goals and move our important work forward, despite these constraints.

With Phase II of the Hub programme underway we have been focussing on developing our Quality by Digital Design workflows, Digital Twin framework, model driven DataFactory approach and continuous MicroFactory platforms. In particular it has been important to see research collaborations resume in person with site visits restarting and new collaborations flourish as we have introduced new technologies such as robotics into our approach. 2021 has seen another year of strong research outputs from our researchers across the academic teams in Bath, Cambridge, Imperial, Leeds, Loughborough, Sheffield and Strathclyde and these are highlighted in the report. We also highlight our progress in translation programmes progressing through our strategic collaboration with the Medicines Manufacturing Innovation Centre, MMIC.

CMAC also marked 10 years of operation and growth as a leading collaborative manufacturing research centre in 2021. During the year we have worked in close partnership with our Tier 1 members to refresh our research strategy and formally launched our new 2021-2026 strategy at a dedicated event last November, also welcoming two new Tier 1 partners, UCB and Chiesi, to CMAC. Our strategy responds not just to the industry inspired research challenges in medicines manufacturing but also the wider societal needs including skills, resilient secure medicines supplies and Net Zero. Our strategy reinforces our commitment to delivering impact for all our partners and the wider society that we serve.

As travel and the ability to meet in person safely look to become increasingly possible in the coming year, we are starting to plan for more interactions between the Hub partners. We are especially pleased that the Hub Open Day is planned to run as an in person event for the first time in two years in May 2022. This year the meeting will run alongside the EPSRC ARTICULAR Showcase event and with three days of presentations, exhibitions, networking, posters and interactive demonstrations providing a timely opportunity for us to catch up with colleagues, share our recent accomplishments and build our forward plans.

Cocreation and collaboration are at the heart of what we do and is exemplified in the EPSRC Hub as a flagship programme that provides a foundation platform for CMAC to grow our partnership, research and impact. Throughout 2021, the academic team across CMAC has delivered considerable progress in developing our portfolio. These new initiatives are also highlighted in this report and show the ongoing pipeline of new ideas and the successful extension of our academic and industrial partnerships both across the UK and Internationally to establish new, complementary areas of demand-led research.

I therefore hope you find the report informative and are excited by what has already been achieved as well as the ambitious next steps. Please do not hesitate to get in touch if you would like to find out more about our programme or ways in which you can engage with us.

2021 Highlights

PEOPLE

145 People in CMAC

42 PhDs Students

13 Management and Support

32 CMAC Academics

45 Researchers

13 Technical Staff

DISSEMINATION

173 Papers across portfolio since 2017

20 Cover articles since 2017

CMAC Strategy 2021-2026 published in 2021

>200 Engaged with Research Webinars in 2021

PUBLIC OUTREACH

13.8k Website Users

900 Followers

Outreach networks of thousands

15 Press Releases since 2017

16 Schools visited since 2017

2 Images of Research winners

INFLUENCING POLICY

£30m Industrial Funding leveraged from Hub

36 Funding awards leveraged from Hub

7 Policy documents

66 The pandemic reminds us of the importance of CMAC's work. Accelerating the development of new medicines and ensuring their robust supply has never been as high profile as it is now. The outstanding ability of the Hub to respond and adapt to restrictions and support its researchers has ensured CMAC progressed a challenging research agenda, ensured a successful Mid-Term Review and delivered for Industry. Challenge drives innovation and the success of the online events are an engagement highlight I believe will become part of our new normal. I congratulate everyone associated with the Hub for and for their passion, capability and flexibility in the most difficult of years. 99

JON-PAUL SHERLOCK
CHAIR OF CMAC INDUSTRY BOARD AND AZ

66 I'm impressed with CMAC's continuing ability to evolve and seize opportunities. New funding in digital design and digital manufacture are a clear demonstration that CMAC remains committed to move forward and lead industrial change. 99

PAUL SHARRATT
CHAIR OF CMAC ADVISORY BOARD
AND SINGAPORE INSTITUTE OF TECHNOLOGY

Vision, Mission & Strategic Goals

VISION

To be a globally leading research centre to transform medicines development, manufacture, and supply.

MISSION

To deliver value to our stakeholders by creating the new science, innovative technologies & future workforce that will support the adoption of advanced CMC development, digital technologies and manufacturing approaches to enable future drug substance & drug product supply.

PILLARS AND STRATEGIC GOALS

CMAC will focus on delivering our strategic priorities for Research and for the Centre. We will achieve this by (i) continuing to focus on strengthening collaborative partnerships across the research and innovation ecosystem and (ii) growing a diverse, sustainable programme portfolio across our four pillars:

Research Excellence & Intensity

Outstanding Skills Development

World Class Facilities

Exemplary Translation to Industry

STRATEGIC RESEARCH PRIORITIES

1 Accelerate Development
- Design sustainable continuous processes for API & DP with minimal material
- Useful predictive tools for product and process development
- DataFactories: Smart, autonomous, AI-driven development platforms

2 CMC Digitalisation
- Digital Twins of materials, products & process
- Multiscale, multiphysics and hybrid modelling for CCS, MCS+, BPCS and QbDD
- Accessible CMAC toolbox of IDTs (ML/AI, AR/VR, robotics) in development & manufacture

3 Advanced Manufacture & Supply
- Innovative continuous processing
- Integrated solutions across API and DP: flexible, modular MicroFactories
- Real-time control and release
- Sustainability as value

4 Materials & Products
- Pharmaceutical materials science underpinning stability, manufacturability and performance
- Structure property relationships from molecule ⟶ crystal/particle ⟶ bulk ⟶ formulated product

STRATEGIC CENTRE PRIORITIES

1 Lab of The Future
- Cutting edge facilities
- Support portfolio of basic and applied research, talent pipeline, Digital Twins, DataFactories, MicroFactories, intelligent Workflows & materials science
- Facilitate collaboration, innovation & translation

2 Future Workforce
- Delivering the highly skilled, augmented workforce of the future
- Future research leaders for industry & academia
- Sector leading CMAC talent pipeline of 'industry ready' recruits

3 Translation & Impact
- Demonstrate case studies & advocate business case for continuous & advanced manufacturing
- Network & engage with global stakeholders including regulators
- International presence

4 World Leading Centre
- Grow position as global manufacturing research centre
- Case studies and business case for Continuous Manufacturing (CM)
- Grow and manage sustainable portfolio of funded research and translation activities
- Attract global talent

VALUES

We are guided in executing our strategy by the values that make the Centre a great place to work; an excellent, responsive partner in all our collaborations and a trusted and valued organisation in the UK and international medicines research and innovation ecosystem. We will embolden our staff and students to take on risky challenges; we will learn together from our failures and celebrate the successes we achieve together.

COLLABORATIVE: Inter-disciplinary science driven by research excellence and integrity through co-creation and co-delivery of our portfolio

INCLUSIVE: Realising our potential through equality diversity and inclusion (ED&I) active engagement and collaboration with stakeholders, embedding the principles of public life, sustainable development goals (SDGs) and Responsible Research & Innovation in how we deliver our portfolio

AMBITIOUS: Impact Focussed Research and Innovation drive us as we strive to maintain and develop both research excellence in our training and research and operational excellence as a leading manufacturing research centre

PEOPLE ORIENTED: Open and inspirational culture & environment, supporting staff and students to reach their full potential across our research, skills, facilities and translation pillars

The Need for Medicines Manufacturing Research

MEETING THE GLOBAL CHALLENGE

The need to transform how we develop and manufacture medicines has never been more important if we are to address pandemic preparedness, supply chain resilience, the ageing population, the urgency for Net Zero and to realise the economic and social benefits from a robust, sustainable medicines manufacturing sector, able to rapidly translate breakthroughs in medical science to patient benefit.

To achieve this goal we must:

- develop new science and engineering knowledge and translate it effectively to generate value
- deliver digital transformation of Chemistry, Manufacturing and Control (CMC) through industrial digital technologies
- enable the deployment of advanced process technologies to support medicines development and manufacturing
- create the skilled future workforce able to lead change

By working together to accelerate progress we can:

- grow the vital medicines manufacturing sector
- improve manufacturing productivity
- reduce environmental impact
- create wealth and jobs through new business models
- support improved patient healthcare

Medicines manufacturing (MM) is a key sector for the UK, generating exports of over £25Bn with the highest GVA of any sector (£8.5Bn), investing over £4Bn p.a. on R&D in the UK. Globally, the medicine market is projected to grow at 3–6% CAGR over the next 4 years, with the total market reaching £1.2 trillion by 2025.

The Medicines Manufacturing Industry Partnership (MMIP) in the UK along with the US FDA have identified advanced manufacturing technologies including continuous manufacturing and industrial digital technologies (IDTs) as important solutions to these issues and assure cost effective, sustainable and secure access to quality medicines. The COVID-19 pandemic has also highlighted the need to invest in resilient, productive and flexible medicines manufacturing and supply chains. Climate crisis also presents a global challenge that is driving the international community to find ways to achieve Net Zero emissions and medicines manufacturing has to adapt to meet these goals head on.

DRIVERS & DELIVERABLES

Drivers for medicines manufacturing research

Accelerate pace of manufacturing innovation through understanding the needs of:

PATIENTS: rapid translation of medical science to benefit

INDUSTRY: provide access to medicines via secure supply chains

REGULATORS: guarantee patient safety

Targeting activities that will deliver the following benefits:

- **SPEED** — Time from discovery to patient — Innovators
- **COST** — Of development to the provider/patient — Innovators, generics, SMEs
- **FLEXIBILITY** — Meet the changing demands — Life cycle, smaller volumes
- **QUALITY** — Patient safety — Efficacy
- **SUPPLY SECURITY** — Patient/Provider access — Emergencies
- **SUSTAINABILITY** — Reduce carbon footprint — Reduce waste

Collaboration is Key to Success

CMAC - CONNECTING ACADEMIC EXPERTISE WITH INDUSTRY NEED

CMAC aims to transform the current manufacturing process into the medicine supply chain of the future. Our collaborative approach brings together academic institutes, technology providers, global pharmaceutical companies and other key stakeholders to co-create and co-deliver transformative solutions.

INDUSTRY PARTNERS AND SUPPORTING ORGANISATIONS

CMAC IS A WORLD LEADING CENTRE FOR MEDICINES MANUFACTURING RESEARCH, TECHNOLOGY, TRAINING AND TRANSLATION

The Hub Vision is to revolutionise the development and supply of functional, high-value chemical and pharmaceutical products by delivering a rapid, digitally-enabled pipeline to integrate continuous manufacturing processes. The Hub research underpins the CMAC research portfolio and acts as a National Centre for the medicines manufacturing research community with focus on TRL 2-5 research.

The University of Strathclyde leads the CMAC Hub, with delivery achieved by a multidisciplinary and collaborative academic team at the UK universities of Bath, Cambridge, Imperial, Leeds, Loughborough and Sheffield.

The Hub funding period runs from January 2017 to December 2023. Hub research is now in Phase II of the project where the goal is to address the Grand Challenge "Digitally Enabled MicroFactory Based Medicines Manufacture and Supply".

SAVED COMPANIES
›£20M p.a.

11 LEADING
UK ACADEMIC PARTNERS

39 ACADEMICS AND RESEARCHERS DELIVERING EPSRC HUB

10 CMAC ALUMNI WORKING AT TIER 1 COMPANIES

£25M CRITICAL MASS FUNDING FROM EPSRC

EPSRC CMAC Future Manufacturing Research Hub Programme

The Hub is a flagship programme as part of EPSRC critical mass investments in future manufacturing research.

HUB VISION

Revolutionise the development and supply of functional, high-value chemical and pharmaceutical products by delivering a rapid, digitally-enabled pipeline to integrated continuous manufacturing processes.

PROGRAMME VISION

Key goals:

- Minimal material and experiments via predictive modelling

- Crystal attributes for enhanced manufacturability, stability and performance

- Integrated, flexible continuous process streams

Example process:
crystallise ▸ isolate ▸ compress ▸ test

Digital

Physical

Visualisation
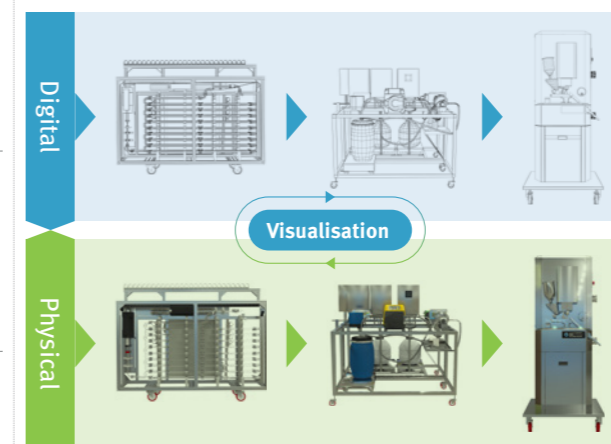
Establish digital design and digital manufacturing concepts for modular, integrated continuous processes.

1: Small Scale Experiments & Predictive Tools
Measured and predictive parameters

2: Dynamic Process Models
Predicted process performance and product attributes

3: Operate Using Flexible, Integrated Platforms
Reduced materials, cost & time plus enhanced quality

QbDD Workflow – library of workflows to set objectives and drive team from digital design to manufacture

DataFactories – access to experimental data to drive model building, development, testing and validation

Digital Twin – Model and Data libraries across materials, equipment, processes and products

MicroFactory – Modular, flexible continuous processing test beds of API and DP – validate models, control of material attributes

HUB GOALS

- Develop products and processes using minimal material and experiments exploiting predictive modelling and data

- Understand and control crystal and material attributes for enhanced manufacturability, stability and tailored performance

- Demonstrate modular, integrated, flexible multi-product and/or tailored product specification MicroFactories to enable future supply chains

EPSRC Hub Phase II Grand Challenge:

DIGITALLY ENABLED MICROFACTORY-BASED MEDICINES MANUFACTURE AND SUPPLY

The next stage of the EPSRC Hub research programme and our Phase II Grand Challenge: 'Digitally Enabled MicroFactory-Based Medicines Manufacture and Supply', commenced in 2021 for the remaining three years of the award. It is driven by a 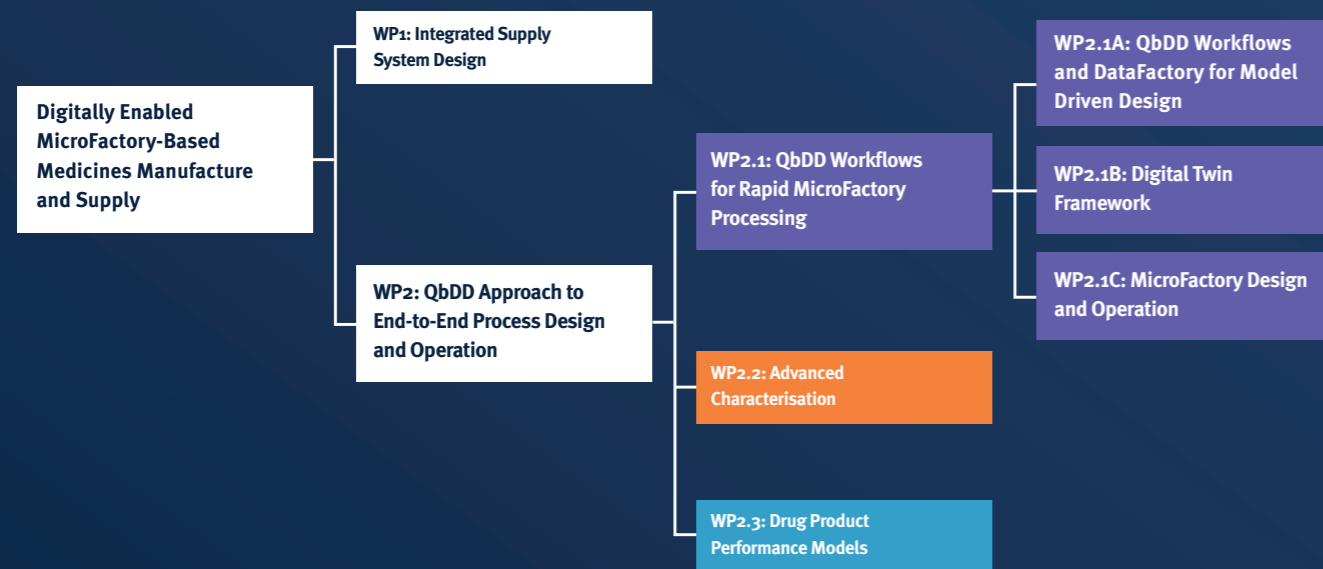pressing need to exploit new technologies to address the cost of medicines as well as achieve agility (reduced development time), sustainability (reduced material consumption) and security of supply (ability to reconfigure and/or deploy new capacity).

Our three main goals of Phase II Grand Challenge are to develop (i) QbDD Workflows for Rapid MicroFactory Processing, (ii) Advanced Characterisation and (iii) Drug Product Performance Models. These goals will enable the application of a QbDD Approach to End-to-End Process Design and Operation and are highly relevant to our industry partners needs and frame the Hub's research plan.

Phase II Work-packages for the Hub (2021-2023)

- **Digitally Enabled MicroFactory-Based Medicines Manufacture and Supply**
  - **WP1: Integrated Supply System Design**
  - **WP2: QbDD Approach to End-to-End Process Design and Operation**
    - **WP2.1: QbDD Workflows for Rapid MicroFactory Processing**
      - **WP2.1A: QbDD Workflows and DataFactory for Model Driven Design**
      - **WP2.1B: Digital Twin Framework**
      - **WP2.1C: MicroFactory Design and Operation**
    - **WP2.2: Advanced Characterisation**
    - **WP2.3: Drug Product Performance Models**

The outputs from WP1 will inform medicines supply chain needs and provide a business case for a Quality by Digital Design (QbDD) approach for end to end design, development and operation for medicines manufacturing processes. WP2 aims to formalise the exploitation of integrated data through modelling and simulation for predictive design, whilst aligning with regulatory requirements. In Phase II this approach demands a greater focus on understanding variability and uncertainty in processes and their accompanying data to establish digitally-enabled routes to define robust design spaces and effective control strategies.

This grand challenge presents significant research questions, which will deliver significant impact:

- ✪ Accelerating the development of product and optimised manufacturing processes
- ✪ Closer integration of API and Drug Product (DP) manufacture
- ✪ Use of Digital Twins to drive MicroFactory (MF) design, operation and control
- ✪ Advanced characterisation capability advances across length scales from the molecule to the particle
- ✪ Enhancement of Drug Product Performance models

Integrated Supply System Design (WP1)

The evaluation of single molecule selection and product-process supply system workflows to help examine future API selection will be extended from methodologies developed in Phase I. This is part of the integrated supply-system design analysis for multi-Active Pharmaceutical ingredient processes across the crystallisation, isolation and Drug Product objectives in the Quality by Digital Design approach to end-to-end process design and operation workpackage.

This work will include design and evaluation of MicroFactory supply networks that integrate technology-scale with manufacturing footprint considerations. The proposed design rules are applied to the assessment of alternative centralised/distributed network configuration options (see e.g., Srai, Settanni & Aulakh, 2020; Aulakh, Settanni & Srai, 2021). The analysis will support investment decisions for continuous manufacturing that jointly consider cost and supply resilience, particularly relevant in times of supply disruption. The research undertaken within WP1 has led to related Made Smarter projects, including (1) EPSRC Digital Medicines Manufacturing (DM²) Data Centre (page 40); and (2) Innovate UK Smart Pharma Supply Chains.

# QbDD Approach to E2E Process Design and Operation (WP2)

The CMAC Hub aims to digitalise Quality by Design (QbD), exploiting the extensive modelling and data driven decision support tools within an overarching Quality by Digital Design (QbDD) framework. WP2 will target the development of QbDD workflows, Digital Twins for design and operation of continuous processes, and the use of models to identify robust design spaces and inform control strategies that will be used to implement integrated continuous processes using CMAC Hub MicroFactory platforms. The technical focus driven by our partners needs, spans API particle formation (i.e. crystallisation, filtration, washing, drying) and DP secondary processing (i.e. polymer extrusion/ printing and powder compaction).

Building on the development of workflows carried out to date, we are establishing the activities required to model and predict process outcomes. Optimised experiments and measurements are driven by the model requirements. The work will include the development of models for solubility and solvent selection, optimal design of experiments for parameter estimation and validation with model-based global sensitivity and uncertainty analysis to inform selection of suitable process models.

The QbDD Workflow will drive experimental efforts, augmented through the development of an autonomous crystallisation DataFactory (WP2.1A), populate the QbDD Digital Twin (WP2.1B), ultimately enabling transfer of process design and control strategy into operation in the MicroFactory (WP2.1C).

Overview of Grand Challenge
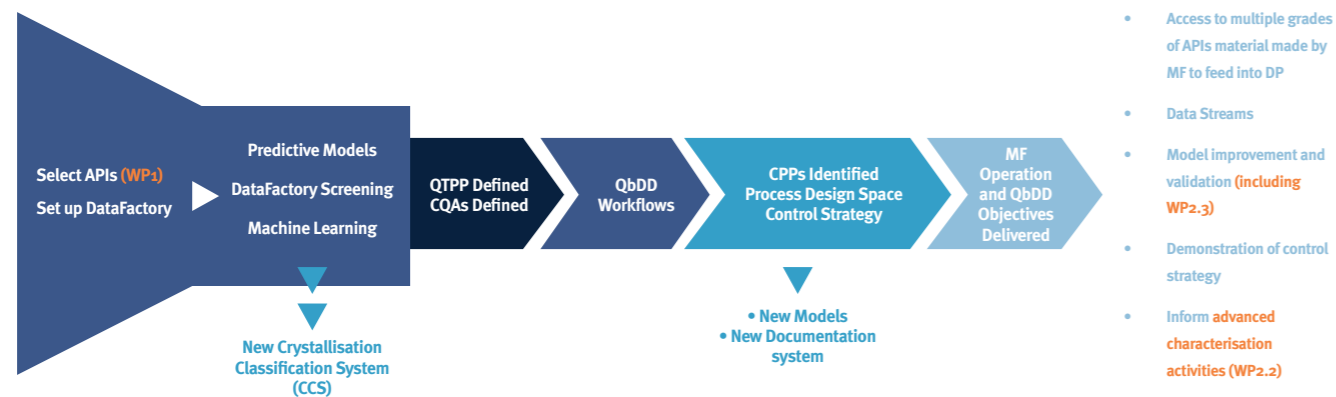
QbDD Workflows (WP2.1A)

QbDD Workflows for Rapid MicroFactory Processing.

We are developing an integrated, digitally-enabled QbDD approach that will address uncertainty and risk associated with the development of robust, capable continuous processes and extend to develop and implement strategies for advanced process control. To link this explicitly to materials characteristics, an Autonomous Crystallisation Classification DataFactory will be developed to develop a predictive Crystallisation Classification System (CCS) to enable prediction of key material and process attributes from molecular descriptors.
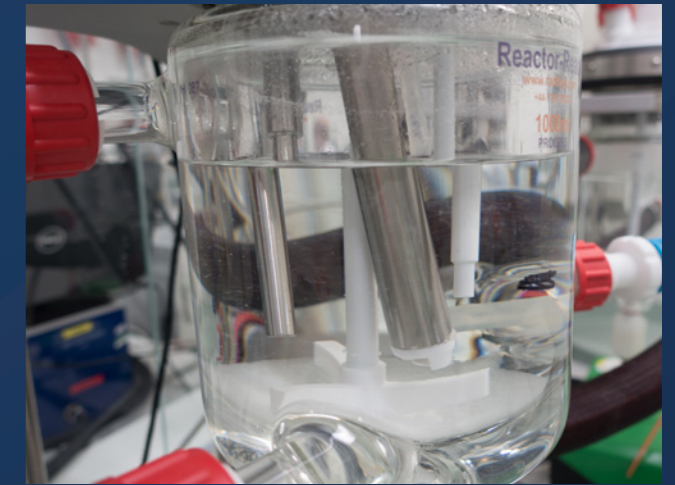
CMAC Framework for Quality by Digital Design (QbDD)
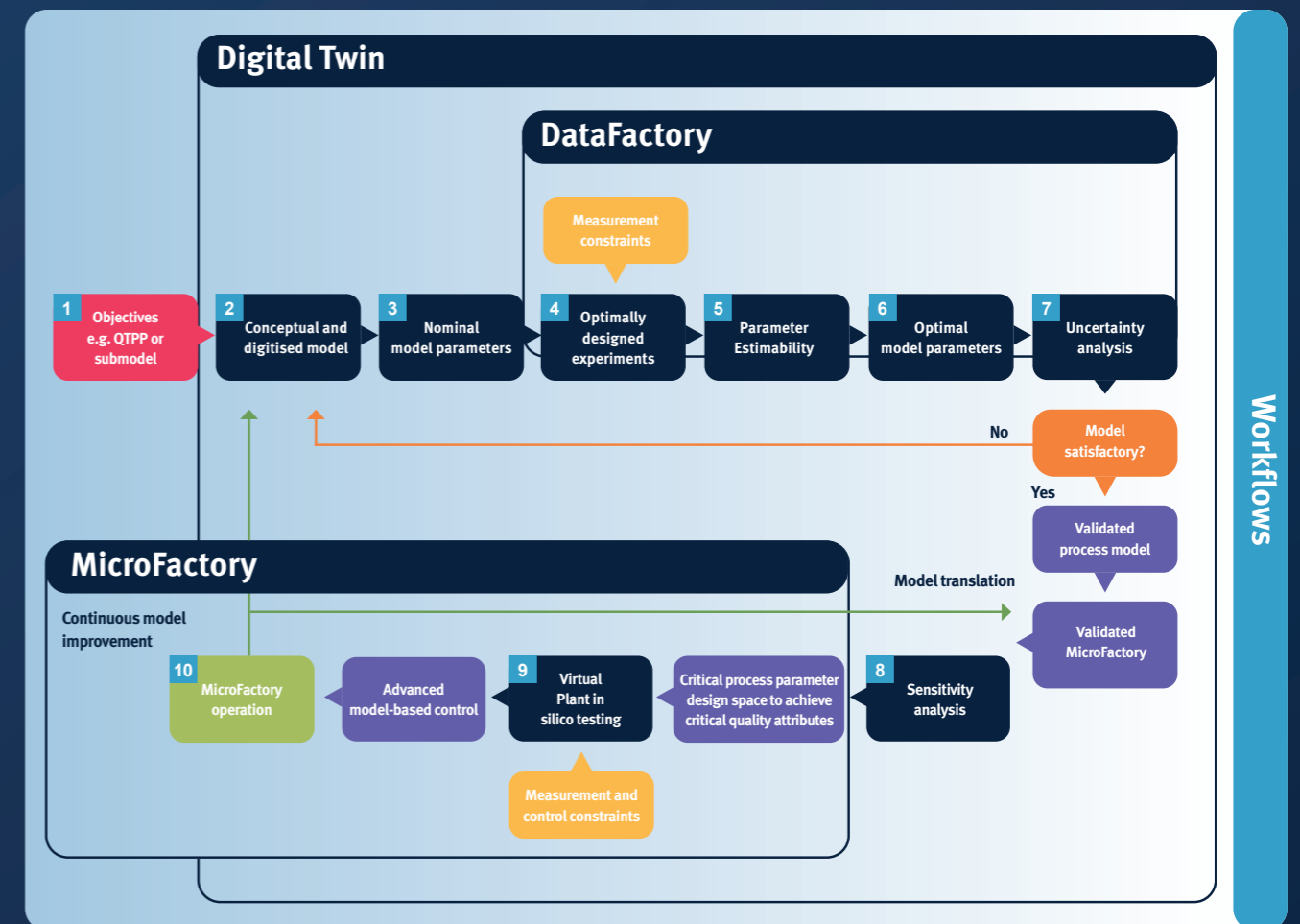
The above diagram shows CMAC Framework for Quality by Digital Design (QbDD). CMAC is developing an integrated workflow to ensure product QbDD and continuous manufacturing.

DataFactory

A new strand for Phase II is the set up and operation of a DataFactory that will inform a crystallisation classification system

DEVELOPING A CCS: AUTONOMOUS CRYSTALLISATION CLASSIFICATION DATAFACTORY

Autonomous Crystallisation Classification DataFactory
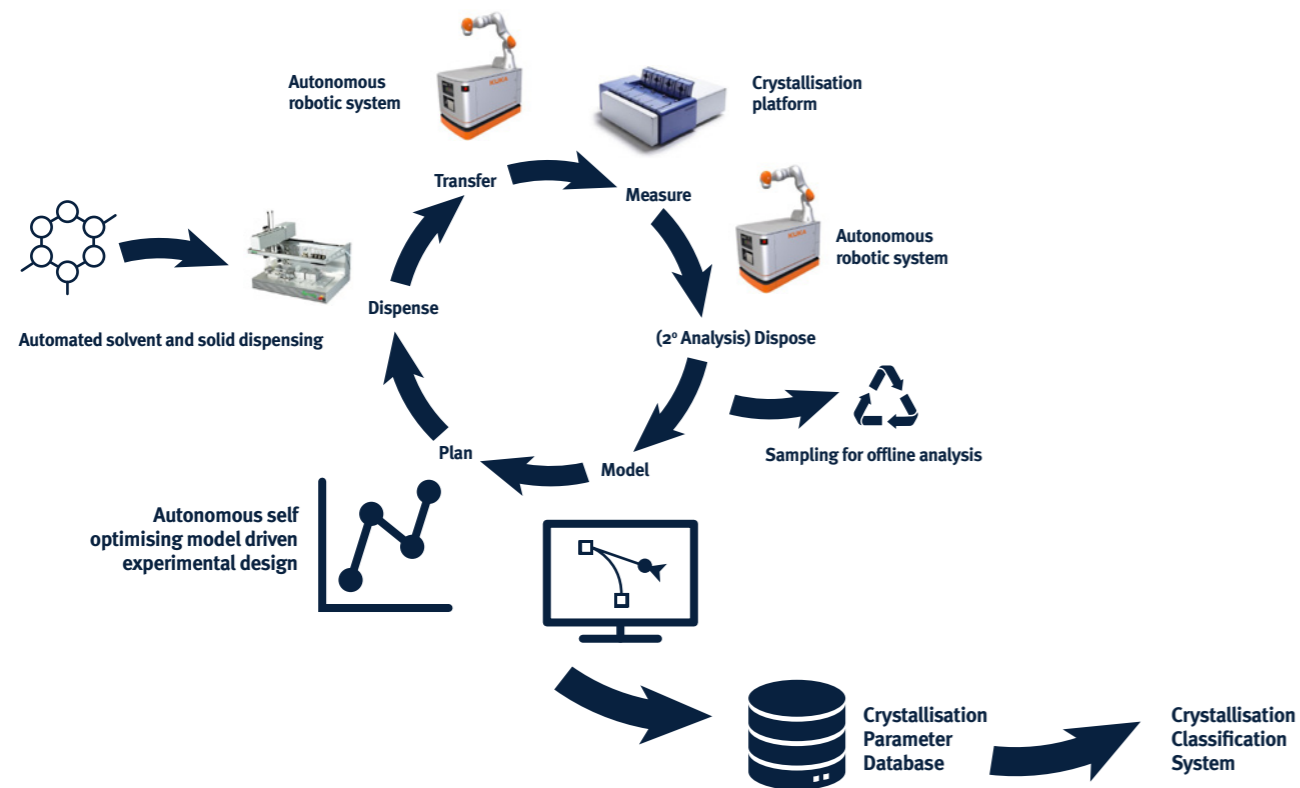
The Autonomous Crystallisation Classification DataFactory will automate experiments done on the Technobis Crystalline platform to deliver large structured data sets for interrogation by image analysis and machine learning.

It will use the Zinsser platform for dispensing solids and solvents and an autonomous robot to move samples around the lab in a "cobot" system. The crystallisation experiments will sweep through physicochemical phase space from molecule to solubility, kinetics, growth, agglomeration and fouling. The data collected will inform and optimise models of crystallisation via smart experiments. Connecting standard equipment and automating the routine, currently manual steps will give around 7000 data-rich experiments per month. The data collected will be used for research on image analysis, model development and machine learning. This will feed into work to establish a Crystallisation Parameter Database.

The Parameters derived from the measurements made from APIs screened by the DataFactory will be used to populate models that feed into the Digital Twins work (WP2.1B), and thus also into the MicroFactory process development work (WP2.1C). This work will be the basis of developing a Crystallisation Classification System (CCS).

The Hub are using mobile collaborative robotic systems to automate experimental tasks under AI control. The integrated system will accelerate the data driven development of pharmaceutical processes.

Digital Twins (WP2.1B)

The Digital Twin (DT) work in CMAC includes designing the integrated digital framework to collate, analyse, visualise and apply data, models and knowledge of the rapid design, control, operation and testing of continuous processes for API crystallisation and DP production in our MicroFactory platforms. The Digital Twin framework is supported by our broader digital platform enabling us to take a structured and systematic approach to embedding data and model driven methods across our programme.

CMAC DIGITAL PLATFORM

models · data · workflows · environments · twins

people · AI · standards · ontologies · assets

For Phase II of the Hub the DTs will combine the overarching digital definition of both the processes and products.

For example, we use the QbDD workflows (see page 15) to gather data and inform model development, optimisation and implementation. These data, models and knowledge are then captured, stored and interrogated in the DT framework. The QbDD workflow develops a specific DT for a particular API process and product.

A Digital Twin of a Mefenamic Acid MicroFactory will be demostrated at the 2022 ARTICULAR Showcase and CMAC Open days event taking place on 16-18th May in Glasgow.

Examples of DTs from phase I of the Hub include:

✿ Modelling wash performance and cake properties to facilitate continuous isolation development, aiming for smart, green pharmaceutical manufacturing with integrated modelling tools for efficient active pharmaceutical ingredient unit operations.

✿ DiPP flowsheet with integrated models including model validation for Twin Screw Granulation (TSG), FBD, VB, and Tablet. Research on the breakage kernel for TSG was published and the a training module was developed.

✿ Digital Twin for Lovastatin that was created by connecting CMAC models. Six separate processes were modelled and integrated to allow design space exploration in real time.

Digital Twin Framework

Equipment	Digital Twin		
	Visualisation Interface		
	Data Layer	Model Layer	Knowledge Layer
	Equipment	Model	Measurement	Data
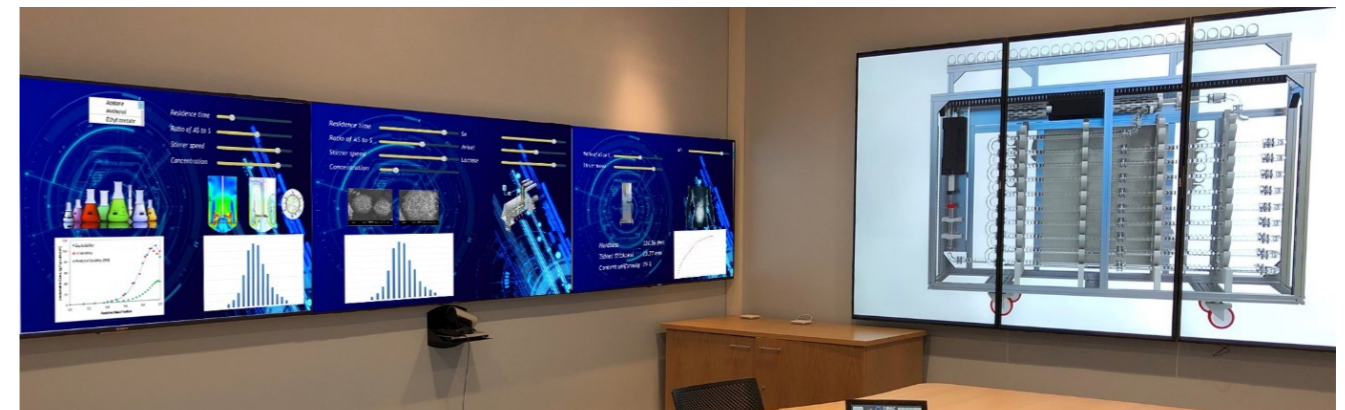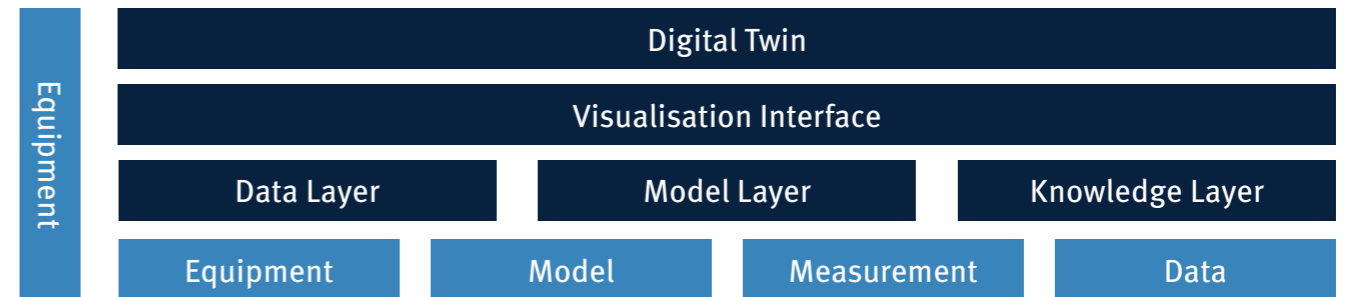
There is also ongoing work to provide user-friendly interfaces for the DTs to enable users to interact with models and data and explore design space virtually and inform decisions. There are examples of 2D interfaces for DTs of the Easymax crystalliser and a twin-screw extruder (see images below) that have been demonstrated at our Open Day and Showcase events in collaboration with the ARTICULAR project (see page 42 for more on ARTICULAR).
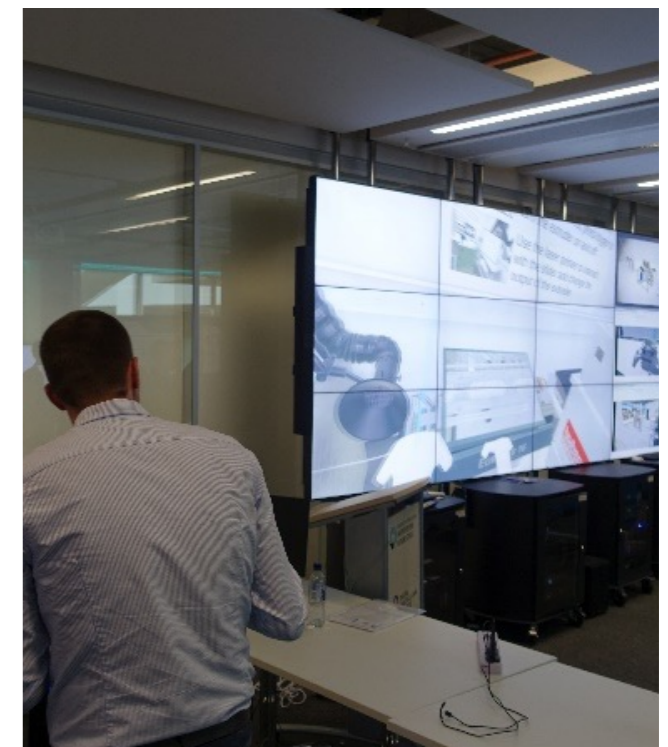
MicroFactories (WP2.1C)

Process designs will be established from data collected in the QbDD Workflows (WP2.1A), and then modelled, analysed and optimised to establish a Digital Twin (WP2.1B), for an API or drug product, that will inform MicroFactory optimal operating ranges and control strategy (WP2.1C).

For API MicroFactories the default test bed will comprise feed and seed units with a MSMPR and filtration and washing. PAT-enabled closed loop control will allow control of CQAs in real time. The Drug Product MicroFactory manufacture will be done via polymer processing using extrusion-printing technologies to exploit existing infrastructure across the Hub partners. We will also use filled capsules to develop a fully integrated digital twin spanning drug substance, drug product and performance testing.

By operating within the design space identified by the DT, we will use the MF Platforms to deliver:

- Materials of different grades to illustrate predictive control or confirm failure modes/edge of process operating ranges

- Integrated API particle formation MF (seeding, growth, particle engineering) reconfigured for needs of different systems informed by model

- Integrated sensor/PAT and control through to continuous filter wash and batch drying

- Multiple grades of multiple APIs for API validation and DP model building/testing

- Novel DP integrated polymer process platform has been developed and tested

- Material and time saving demonstrated

- CQA direct control validated

Advanced Characterisation (WP2.2)

The objectives for Advanced Characterisation in Phase II are two-fold: to integrate the deeper multi-scale understanding from the multi-technique characterisation paradigm into the QbDD MicroFactory programme, and to strategically develop joint activities started in Phase I with national (Royce, Diamond, Harwell, NPL) and international (ESRF, Argonne, Brookhaven) central research facilities with a view to establishing a Centre of Excellence in Advanced Analytical Science for Medicine Manufacturing, acting as a hub and relay for seamless knowledge transfer between fundamental and industrial research.

The approach for integration of deeper multi-scale understanding is to apply advanced characterisation techniques where lab based analytical tools may not provide sufficient temporal or spatial resolution. Areas of particular interest include supporting QbDD and modelling, identification of mechanistic pathways in API formation, explore the molecular basis for solvent selection. This will allow us to overcome inefficiencies and

manufacturability bottlenecks that arise from incomplete understanding of the molecular and mesoscopic structure and their impact on CQAs, such as flowability, compressibility, cohesion and particle morphology.

Drug Product (DP) Performance Models (WP2.3)

The aims of developing DP Performance models are to a) close the vast knowledge

gap for predictive performance of Oral Solid Dosage forms (OSDs), by developing mechanistic models to describe and predict tablet dissolution and disintegration, b) validate these models using cutting edge techniques, and c) integrate these models with existing and in-development model platforms for OSD manufacture, including traditional tableting and novel polymer process methods developed in the QbDD Workflows approach.

Research Outputs 2021

SAFT-γ MIE SOLUBILITY PREDICTION

The solubility of mefenamic acid and related compounds has been predicted by SAFT-γ Mie in pure and mixed solvents. Excellent agreement between the SAFT-γ Mie calculations and new experimental data in a range of solvents was obtained. This demonstrates that the theoretical approach is well-suited for the description of the thermodynamic properties.

To achieve this, the table of SAFT-γ Mie group interactions was extended by 50 and 3 new SAFT-γ Mie functional groups (aCCOOH, aCNHaC and CH3CO) were defined. The new groups identified are transferable to other molecules, in particular to other non-steroidal anti-inflammatory drugs.
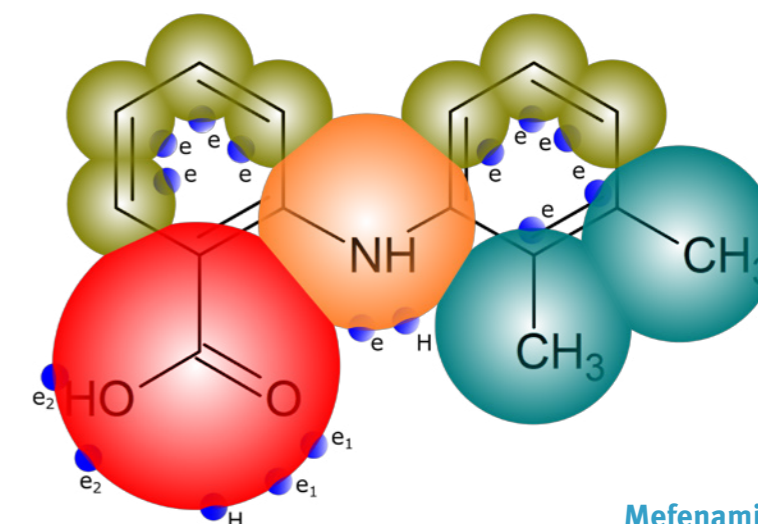
Mefenamic Acid

Febra, S. A.; Bernet, T.; Mack, C.; McGinty, J.; Onyemelukwe, I. I.; Urwin, S. J.; Sefcik, J.; ter Horst, J. H.; Adjiman, C. S.; Jackson, G.; Galindo, A., Extending the SAFT-γ Mie approach to model benzoic acid, diphenylamine, and mefenamic acid: solubility prediction and experimental measurement. Fluid Phase Equilibria 2021, 113002. https://doi.org/10.1016/j.fluid.2021.113002

SAFT-γ MIE DESIGN OF SOLVENT BLENDS FOR HYBRID COOLING AND ANTISOLVENT CRYSTALLISATION

A computer aided mixture/blend design (CAMbD) formulation has been developed for the design of optimal crystallisation solvent mixtures. The applied methodology enables the simultaneous identification of the optimal process temperature, solvent, antisolvent, and composition of solvent mixture. This has been applied to the cooling and antisolvent crystallisation of lovastatin and ibuprofen:

- For lovastatin, the combined cooling and antisolvent crystallisation leads to an increase in crystal yield compared to antisolvent or cooling crystallisation alone. Less volatile but powerful crystallisation solvents at lower temperatures can lead to better performance.

- For ibuprofen, the combined cooling and antisolvent and antisolvent alone crystallisation techniques provide similar performance, but the use of solvent mixtures throughout the crystallisation is critical to maximise crystal yields and minimise solvent consumption.

SAFT-γ Mie group-contribution has been used in the design of crystallisation solvents; based on an equilibrium model, both the crystal yield and solvent consumption are considered. Rational design of solvent blends brings significant benefits for the design of crystallisation processes, including reducing time and costs.
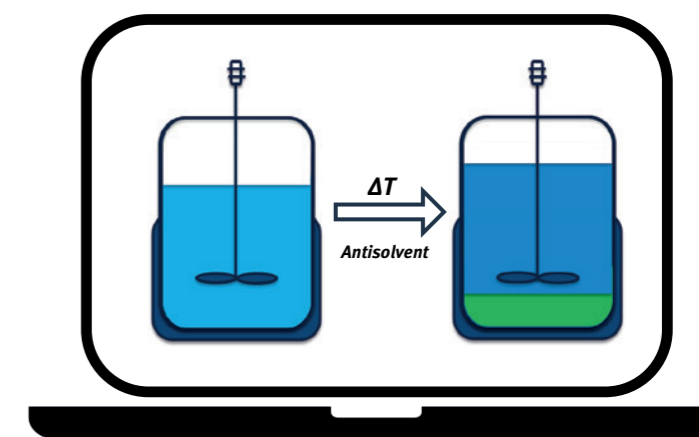
Watson, O. L; Jonuzaj, S.; McGinty, J.; Sefcik, J.; Galindo, A.; Jackson, G.; Adjiman, C. S., Computer Aided Design of Solvent Blends for Hybrid Cooling and Antisolvent Crystallization of Active Pharmaceutical Ingredients. Organic Process Research & Development 2021, 25 (5), 1123-1142. https://doi.org/10.1021/acs.oprd.0c00516

NOVEL INTEGRATED WORKFLOW FOR ISOLATION SOLVENT SELECTION

A novel integrated workflow has been developed to aid process design and rationally select optimal solvents for isolation of APIs.

The workflow is based on logical solvent ranking supported by solubility predictions, coupled with digital tools to predict the optimal purification strategy. The goal of the developed methodology is to preserve the desirable particle attributes generated during crystallisation by taking account of the risk of precipitation and particle dissolution during washing. The workflow prioritises solvents that are favourable for drying, improving process efficiency, and minimises the risk of changes to particle properties during isolation while maximizing the purity of the final isolated product using benign solvents.

Six of the nine stages in the workflow address crystallisation and wash solvent selection using predicted solubility and other relevant solvent properties (including safety, density, viscosity and thermodynamic properties). The other stages are related to the isolation performance prediction. The workflow has been tested using COSMOtherm as the solvent prediction tool and validated using experimental data.

A key element is the digital tool used to rank the isolation solvents into a list of good candidates to evaluate experimentally. This increases productivity and reduces the amount of waste generated during process development. Two different models were evaluated for estimating the isolation performance by simulating the isolation (filtration and washing) mass balance:

⚙ Model A considered washing driven by pure displacement

⚙ Model B considered washing as a combination of diffusion and axial dispersion washing

Model A predicted complete removal of impurities from the filter cake well before the required experimentally measured wash volume. The assumptions used in model A were found to be too simplistic. Model B showed good agreement with experimental data, successfully predicting the extent of impurity removal achieved during each washing step.

The proposed solvent selection workflow is a versatile prediction tool for solvent selection supporting digital process design. It is capable of transferring material property information generated using a combination of published material properties and predictions between simulated unit operations with the goal of selecting the ideal purification strategy based on testing then selecting via simulation the likely performance of the isolation process.

Ottoboni, S.; Wareham, B.; Vassileiou, A.; Robertson, M.; Brown, C. J.; Johnston, B.; Price, C. J., A Novel Integrated Workflow for Isolation Solvent Selection Using Prediction and Modeling. Organic Process Research & Development 2021. https://doi.org/10.1021/acs.oprd.0c00532
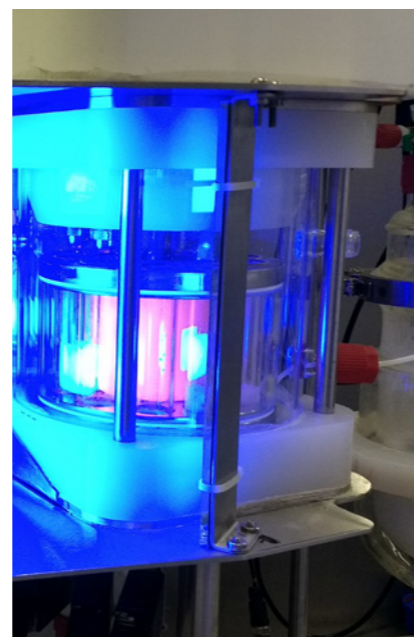
BULK AND SURFACE CONFORMATIONS IN SOLID-STATE LOVASTATIN

Combining gas-phase and solid-state modelling and spectroscopy has provided valuable insight into the conformational flexibility of the lovastatin molecule in bulk and at the particle surfaces, in a powder.

Gas-phase and periodic quantum-chemical calculations were used to study the potential energy surface associated with rotatable bonds to examine the disorder in bulk. These calculations were combined with vibrational and X-ray photoelectron spectroscopy measurements to obtain insight into the conformations in bulk and at the surface.

Molecular dynamics simulations show that the bulk disorder is driven by cooperative motion of the butyl group on the S-butanoate moiety along one crystallographic direction beyond a unit cell. The calculations show that the O-H group can rotate relatively freely between two low-energy conformers in the gas phase but is locked in position by intermolecular H-bonding interactions in the bulk crystal, and there is tentative spectroscopic evidence for the second conformer being present at the surface.

This combined approach could be applied to a wide range of molecular solids, it is therefore hoped this work will serve as a first step towards a robust protocol for the routine analysis of particle surfaces.

Pallipurath, A. R.; Skelton, J. M.; Britton, A.; Willneff, E. A.; Schroeder, S. L. M., Bulk and Surface Conformations in Solid-State Lovastatin: Spectroscopic and Molecular Dynamics Studies. Crystals 2021, 11 (5), 509. https://doi.org/10.3390/cryst11050509
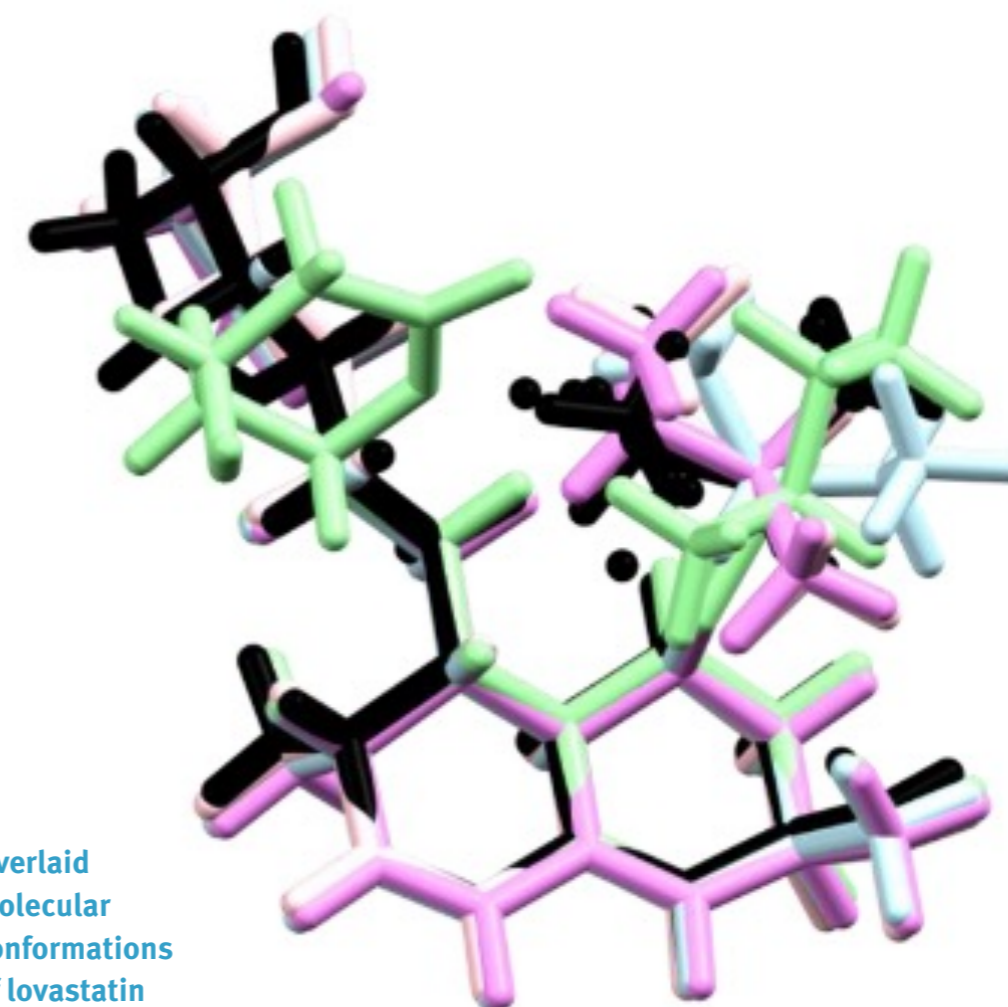
Overlaid molecular conformations of lovastatin

IMPACT OF MEFENAMIC ACID FORMULATION COMPOSITION ON PROCESSING PARAMETERS, PRODUCT PROPERTIES AND PERFORMANCE

A Hot Melt Extruder (HME) process to produce a range of Mefenamic Acid-Soluplus®-Sorbitol polymer matrix crystalline solid dispersion (CSD) formulations has been developed based on rheological screening.

The impact of drug loading on process parameters and physicochemical properties of formulations have been compared. Application of rheology screening to HME process development resulting the in the detection of suitable processing conditions (process temperature, screw speed) requiring less reduced material consumption.

Based on process and product data, three groupings of API drug loading were identified: sub-saturated, saturated, and supersaturated systems. The targeted CSD formulation containing the stable polymorphic form I was successfully obtained for formulations containing 20 – 50 % w/w drug. CSD formulations predominantly improved the consistency of

the product performance. An Amorphous Solid Dispersion (ASD) was obtained for 10% (w/w) drug loading, exhibiting faster drug release even at physiologically relevant pH. Despite superior product performance of an ASD formulation, achieving a therapeutic dose with such low drug loading would not be feasible. Additional studies into the critical concentration for amorphous material and product stability need to be carried out.

This study illustrates the impact of drug loading on process and product characteristics and how a better understanding of maximum API solubility in a given polymer system can improve targeted formulation development

Prasad, E.; Robertson, J.; Halbert, G. W., Mefenamic acid solid dispersions: Impact of formulation composition on processing parameters, product properties and performance. International Journal of Pharmaceutics 2022, 121505. https://doi.org/10.1016/j.ijpharm.2022.121505
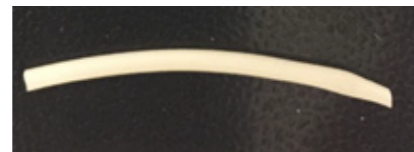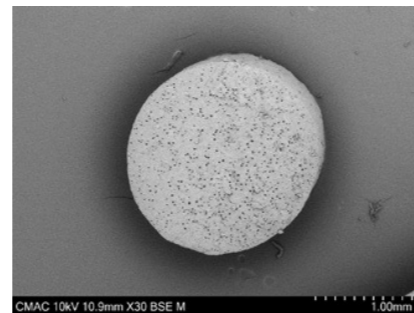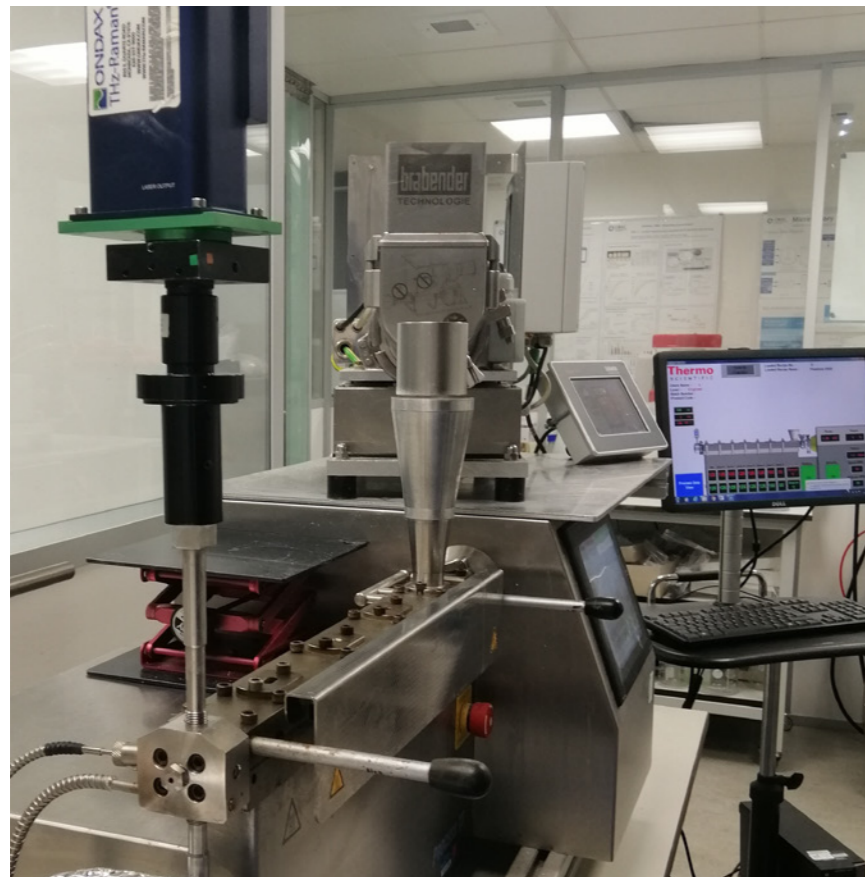
50% MFA + Soluplus + 15% Sorbitol, SEM image of extrudate face (above, top) and photograph of filament extrudate (above, bottom)

Summary of Hub 2021 Achievements

Phase II Ongoing Activities

Management

Integrated Supply System Design WP1

Advanced Characterisation WP2.2bb

Drug Product Performance Models WP2.3

QbDD Framework WP2.1

Hub Project Management

- Research teams and activity for Phase II established
- Impact Officer and Digital developer in post to support impact and translation

Supply Chain

- Integration of supply chain and QbDD Workflows kicked off
- List of APIs of interest identifed

Quality by Digital Design (QbDD) Workflow

- Workflow being developed in more detail
- Refining operational details

DataFactory Platform

- Equipment procured
- Initial coding underway
- System integration
- Tasks in QbDD Workflow being mapped
- APIs for potential MicroFactory campaigns being tested
- Ready to identify next API with goal to model an API MicroFactory process

Digital Twin

- Detailed process mapping
- Models / Digital Assets
- Data flows & structures
- ELN templates and data structure for QbDD
- Android App demo being developed for May 2022
- Development of solubility prediction tools ongoing
- Simple Digital Twin of capsule dissolution being developed in Drug Product Space

API MicroFactory Platform

- Equipment procurement complete
- Equipment upgrades ongoing
- Recent campaign ran for 40 hours
- Learning from recent campaign › URS under review
- Beamtime at Diamond to study filtration

Drug Product MicroFactory Platform

- HME-3DP platform patent application
- Publication on improved formulation of Mefenamic Acid using the HME-3DP platform

Acting as a National Hub

As an EPSRC Future Manufacturing Research Hub we have a role to work with, and on behalf of, the wider community and to act as a focus for TRL 2-5 research in the medicines manufacturing landscape. We engage and advocate on behalf of the community to influence policy, facilitate and support workshops, meetings, and events on topics within our scope. The CMAC Hub holds an important position in the collaborative research and innovation landscape in the UK.

CMAC is building on 10 years of experience as a pre-competitive collaborative R&D centre to continue to deliver on our Manufacturing the Future research portfolio and UKRI funded Doctoral Training initiatives in award winning facilities in medicines development and manufacturing.

CMAC Hub kicked of 2021 with a highly successful mid-term review from an independent panel. The Hub was commended on its collaborative achievements and in particular for research progress in development and of application of digital tools to manufacturing research. Some of these achievements were

highlighted in UKRI news across social platforms. The Hub was also recognised for demonstrating best practice across a range of operations and industry engagement was commented on as exemplar.

Despite pandemic enforced restrictions, the Hub has continued to grow and strengthen stakeholder engagements across the medicines manufacturing landscape and the broader digital manufacturing community, acting on key strategic areas such as the national skills agenda, equality diversity and inclusion and sustainability. All of these are core elements of the CMAC culture.

Collaboration is a core CMAC value and the last year we have strengthened a range of national and international partnerships, engaging new partners through the recently awarded EPSRC Made Smarter Innovation Digital Medicines Manufacturing Research Centre (DM²), EPSRC International Centre to Centre DDMAP and a recent round of Hub funded Feasibility Studies.

**Dr Andrea Johnston,
CMAC Associate Director**

ACTING AS A NATIONAL HUB: ACTIVITIES

- Policy
- Events
- Engagement and Collaboration
- International Network
- Portfolio of Projects Across TRLs

External Environment

OUR AIM IS TO CONTINUE TO STRENGTHEN THE RESEARCH BASE AND ITS CONNECTION ACROSS THE MEDICINES MANUFACTURING RESEARCH AND INNOVATION ECOSYSTEM.

Building on the Hub, our 2021+ Strategic delivery plan builds on collaborations across the community to grow medicines manufacturing and accelerate the adoption of advanced manufacturing and digital technologies.

To achieve this we propose an integrated approach, harnessing the combined efforts of partners and key stakeholders to lead the transformation that will enhance quality, cost and sustainability of medicines manufacture, ultimately for the benefit of patients. Working with academic partners, Tier 1 and Tier 2 industry partners, the regulators, MMIC and other innovation partners, CMAC will support the following sector objectives:
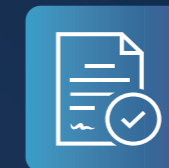
REGULATORY:

Protect and improve public health by enabling the earliest access and high-quality supply of safe, effective, and innovative products through proportionate, data-driven decisions on risk and benefits
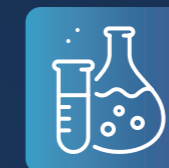
INDUSTRY:

Leveraging the combined UK innovation ecosystem to deliver a more agile, adaptable and scalable medicine manufacturing supply chain

ACADEMIA:

Benefit from strategic commitment to support the world class research and innovation base for advanced manufacturing, digitalisation and sustainabilty. Secure support to continue to deliver and grow the industry-ready, highly skilled talent pipeline and to invest in new technology

Government	Public Sector Funders
Medicines Manufacturing Industry Partnership - MMIP	
Tier 1 End Users	
Tier 2 Techs/SMEs/CMOs	
HVM Catapult CPI	Industry/Professional Bodies
National Formulation Centre	KTN / Made Smarter Innovation
Central Facilities	Innovation Centres
NPL / TUV-SUD	Regulators and Standards Agencies
Royce / Alan Turing Institute	NMIS / DPMC
MMIC	
Wider Research Community	CMAC Portfolio, National Facility & Training	International Groups and Centres
GCID and UoS Clusters	

Influencing the Advanced Manufacturing and Digital Ecosystem

ACTING AS AN INTERNATIONAL RESEARCH CENTRE, DRIVING COLLABORATION

White Papers

Business Case Insights; Regulator engagement; International (e.g. CMAC-MIT ISCMP 2014-2021)

National Digital Roadmap

Acting as a National centre

Informing strategy

Additional Recommendations

Engaging stakeholders e.g. data science, digital manufacturing standards, robotics & automation

Influencing Policy

MMIP Skills

Medicines Manufacturing Challenge Community

Manufacturing the Future utilising UK's large facilities

National Skills Agenda

113 PhD students

36 Industry Placements since 2017

41 Industrial Mentors involved

Ongoing: PDRA development; external CPD

"The demand for multi-disciplinary talent is uniquely served by CMAC"

CMAC INDUSTRY BOARD

- Creating impact from research and application of data and digital technologies
- Input and influence of policy through shaping of roadmaps for digital design, robotics & automation
- Shaping the Skills agenda for the workforce of tomorrow
- Creating infrastructure for the 'Lab of the Future'

Policy Alignment

In the UK, the Medicines Manufacturing Industry Partnership (MMIP) has a mission to support the UK to become a leading force in manufacturing innovation, to maximise Return Of Investment (ROI) from the exceptional UK R&D base, to be the leading force in manufacturing innovation, ensuring national and regional economic benefits and a secure supply of medicines for patients in the UK.

A Digital Transformation Agenda for Pharma: Digitalisation of medicines manufacturing is a key element of the MMIP strategy and is also highlighted in ABPI's Manufacturing Vision for UK Pharma and FDAs for global pharma. The Made Smarter report estimated £22.4Bn of value in the pharmaceuticals industry from adoption of IDTs to deliver digitally enabled R&D, manufacturing and supply, highlighting benefits from reduced cost, environmental impact and improved health. Given the strategic imperatives to achieve greater speed, quality, agility, security and sustainability, there is need for advanced pharmaceutical manufacturing, analytics and IDT development. The UK has supported a pipeline of industrial research programmes: ADDoPT, REMEDIES, ISCF Digital Design Accelerator Platform (DDAP) and the new Medicines Manufacturing Innovation Centre (MMIC). EPSRC has supported demand-led academic manufacturing research including the Future Continuous Manufacturing and Advanced Crystallisation (CMAC) Hub; Virtual Formulation Laboratory, ARTICULAR (AI in development) and others. DM² co-created collaborative approach will go beyond these projects and build an integrated suite of innovative digital research Platforms that will accelerate the development and adoption of IDTs in MM.

Digital Transformation and Data-Driven Research Focus: The lifeblood of data-intensive science is to enable knowledge discovery by ensuring users and machines can discover, access, integrate and analyse task-appropriate data and associated metadata or models. Strong data foundations are crucial and we will lead the sector by implementing good data management policies and FAIR principles (findable, accessible, interoperable and reusable). To maximise benefit, our approach will embed regulatory data integrity guidance and needs (e.g. FDA 21 CFR Part 11; ALCOA+).

CMAC Events

10 Year Anniversary

CMAC - THE NEXT 10 YEARS

Building on 10 years of successful operation, CMAC held a virtual event to launch its ambitious new Research Strategy. Together with our Tier 1 Industry Partners we identified a range of key challenges for our pre-competitive collaborative programme to address across our research, training and skills, translation to industry, and facilities portfolio.

The virtual event included presentations from leading academics and industrials on the evolving needs of medicines development and manufacturing, and the opportunities to transform the way we design and make medicines through world-class research.

⚙	Attendees: 171
⚙	Organisations: 64
⚙	Attendees: UK, USA, Europe, Other
⚙	No. of speakers: 11

Key 'take away' messages from the event:

- Ambitious plans for growth of CMAC
- Digitalisation will be a key part of the next 10 years of medicines manufacturing
- A strong vision for future medicines manufacturing research
- Exciting new areas identified with our industry partners that will be the focus of new co-created programmes

ideation – co-creation – co-delivery – training – translation – impact

MINI SYMPOSIA 2021

CMAC hosted an online Mini-Symposia Series (throughout June 2021) dedicated specifically to connecting PhD researchers and Tier 1 industrialists. The series included flash oral and poster presentations showcasing research excellence, 1:1 Q and A session with presenters and group networking sessions. The Series comprised of four sessions on the follow research areas:

Drug Substance (Primary Processing)

- All aspects of particle formation from fundamental mechanistic studies, through novel separation approaches, application of predictive design tools coupled with experimental work for attribute control, process and scale-up understanding. Primary processing includes crystallisation, spherical agglomeration and synthesis projects

Advanced Materials Characterisation

- Application of suitable characterisation approaches to determine which material attributes affect downstream and final product performance and how they can be measured and controlled
- Measurement techniques applicable at a range of length scales to provide fundamental process and mechanistic understanding of products and processes to enable predictive design

Digital Medicines Manufacturing

- Molecular Process Modelling
- Data Science and Application of Machine Learning / Artificial Intelligence

Drug Product (Primary to Secondary)

- All processing steps after the active ingredient has been generated in the desired solid state
- Involves filtration, washing, drying and formulation of the particles with a focus on how material attributes affect downstream processing and product performance
- Additionally, Hot Melt Extrusion, Mould and Printing, and Continuous Direct Compressions projects. Also includes particular techniques such as ToF-SIMS and Nano-CT

KEY POINTS:

89 Industrial Attendees

34 Flash oral and poster presentations

212 Networking meetings

MIT-CMAC INTERNATIONAL SYMPOSIUM ON CONTINUOUS MANUFACTURING OF PHARMACEUTICALS

An Integrated Ecosystem for Transforming Medicines Manufacturing

The jointly run symposia, between Massachusetts Institute of Technology (MIT) and CMAC Future Manufacturing Research Hub, held the 4th international symposium virtually in February 2021. The symposium brought together pharmaceutical industrialists, regulators, policy makers, academics and patient representatives, to look at how the community can grow medicines manufacturing in the UK and accelerate the adoption of advanced manufacturing and digital technologies.

The meeting was introduced by keynote speaker, Lord Bethell, UK Minister for Innovation, and included sessions from the US Food & Drug Administration (FDA) and UK Medicines and Healthcare products Regulatory Agency (MHRA). Further insights were provided from leading academic, policy, industry and patient voices.

360 Delegates

>22 Countries

>142 Organisations

~80% see continuous manufacturing as very important to the future of medicines manufacturing

70% indicated the most important factors in accelerating continuous manufacturing are skills & collaboration

Key Recommendations:

Regulatory:

- Industry needs to be more open to working with regulators in order to introduce advanced manufacturing technologies, accepting regulators as supportive partners (47 % of respondents felt regulatory was a barrier).
- Industry and regulators to work together to provide guidance and standards for the deployment of continuous platforms.

Industry:

- Investment/incentives are needed to drive adoption of new, better technologies, which improve supply chain resilience and Net Zero impact.
- Collaboration is essential (academia, industry and regulators) to keep the UK at the forefront of medicines manufacturing.
- Investment is needed in skills and innovation in industry.

Academia:

- A strategic approach to supporting the ambitious, multidisciplinary research is required to address industry needs across the full scope of medicines development and manufacture, including exposure to regulatory science within university curricula.
- Targeted and sustained investment is required in training and skills development in advanced pharmaceutical manufacturing at all levels, but in particular doctoral training to deliver the benefit of a highly trained talent pipeline.
- Ensure mechanisms are in place to support collaborations and connections across the research and innovation ecosystem to accelerate translation.
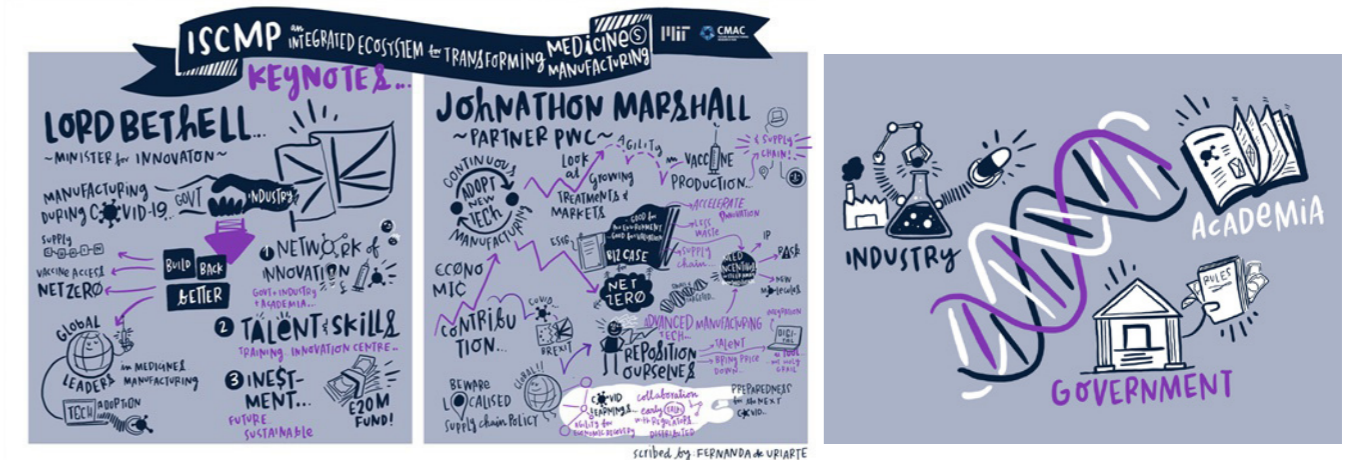
Engagement and Collaboration

VISITS AND SEMINARS

CMAC were delighted to host Professor Dame Ottoline Leyser, UKRI CEO, who visited CMAC as part of the activities surrounding COP26 Glasgow in November 2021, and Harriet Wallace, Director for International Research and Innovation, @beisgovuk visited CMAC for a tour of our facilities and to discuss research in September 2021.

Dr Andy Stewart, University of Limerick (Ireland), presented an online seminar on Applications of Transmission Electron Microscopy for Pharmaceutical research in November 2024. Following the seminar Andy engaged in a series of online discussion meetings with CMAC researchers, technicians, academics and directors.

HUB ENGAGEMENT EVENTS

The CMAC community has attended worldwide conferences and events during 2021. Many of these have been online, giving our people opportunities to engage that may not have been possible face to face. The timeline below shows some of the highlights of that activity.

BCA VIDEO

Hub PDRA Dr Anuradha Pallipurath, University of Leeds, was awarded £3K by BCA to create an educational outreach video. The video is about constructing an Ewald Sphere and also shows the derivation of the Bragg's law in both real and reciprocal space. https://www.youtube.com/watch?v=jvovCGHu9c8
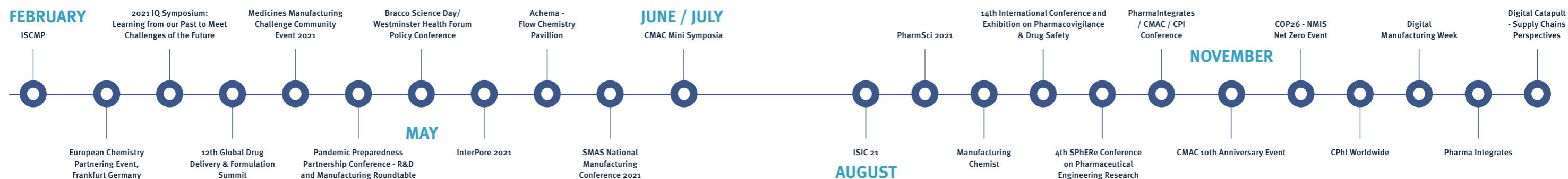
UKRI IMPACT

An impact story and film featuring CMAC was on the front page of the UKRI website in June 2021. It's still on their website: Sustainable, cost-effective medicine manufacturing – UKRI. https://www.ukri.org/our-work/investing-across-the-uk/

EXPLORATHON 2021

CMAC contributed a range of online activities for Explorathon 2021 – European Researchers Night, that took place across Scotland in September. Explorathon is delivered by a consortium of Scottish Universities and has received funding from the European Commission under the Marie Sklodowska-Curie Actions programme. The CMAC online videos and games were aligned with the four main research areas of primary processing, secondary processing, advanced characterisation and digital medicines manufacturing.

MARSHMALLOW CRYSTAL MODEL BUILDING

What is a crystal? This scientific question will be answered in an interactive demo video. How to build a crystal structure will be demonstrated using marshmallow atoms and stick bonds. https://www.explorathon.co.uk/activities/marshmallow-crystal-model-building

3D PRINTING MEDICINES

This video shows how to 3D print medicines by adding layers of material on top of each other to create a tablet. In our laboratory we use a process called Hot-Melt-Extrusion to prepare a filament, that looks like spaghetti. https://www.explorathon.co.uk/activities/3d-printing-medicines

POLYMORPHISM OF CHOCOLATE

In this video we will reveal the science behind producing the perfect chocolate bar and how we can use similar techniques to produce vitally important pharmaceutical medicines that can also be produced in a range of different polymorphs. https://www.explorathon.co.uk/activities/polymorphism-of-chocolate/

BEAT THE MACHINE AT ITS OWN GAME

Here, we have trained a computer to detect images of some of our particles. However, we also have some convincing fake images! The computer is pretty good at recognising the difference, but not perfect. We know you have never seen these images before, but can you beat the machine at detecting the fakes? Play the game at: https://explorathon.shinyapps.io/explorathon2021_btmgame

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FEBRUARY
ISCMP

2021 IQ Symposium: Learning from our Past to Meet Challenges of the Future

Medicines Manufacturing Challenge Community Event 2021

Bracco Science Day/ Westminster Health Forum Policy Conference

Achema - Flow Chemistry Pavillion

JUNE / JULY
CMAC Mini Symposia

PharmSci 2021

14th International Conference and Exhibition on Pharmacovigilance & Drug Safety

PharmaIntegrates / CMAC / CPI Conference

COP26 - NMIS Net Zero Event

Digital Manufacturing Week

Digital Catapult - Supply Chains Perspectives

NOVEMBER

European Chemistry Partnering Event, Frankfurt Germany

12th Global Drug Delivery & Formulation Summit

Pandemic Preparedness Partnership Conference - R&D and Manufacturing Roundtable

InterPore 2021

SMAS National Manufacturing Conference 2021

ISIC 21

MAY

Manufacturing Chemist

4th SPhERe Conference on Pharmaceutical Engineering Research

CMAC 10th Anniversary Event

CPhI Worldwide

Pharma Integrates

AUGUST

Feasibility Projects

As part of our engagement plans, the CMAC Hub has supported 4 feasibility projects which have been awarded and run for 6-12 months each. They have been selected to align with the Hub goals and address specific areas of interest.

Sample holder

Product   Feed

Inactive clean segment kept ready to replace a fouled segment
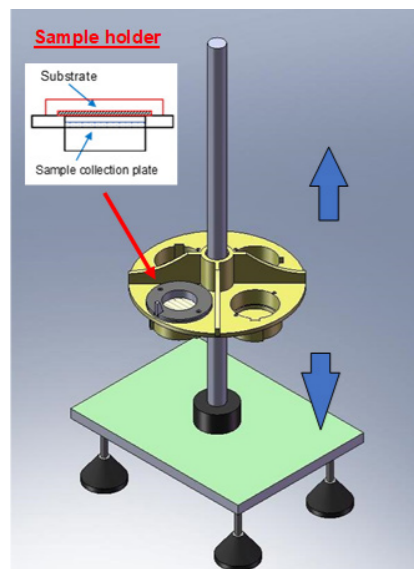
Micro to Manufacturing: Advanced Measurement and Characterisation of Inter-particle Forces with Application to the Design and Control of Flow Behaviour (6-months), University of Greenwich:

- A novel mechanical surface energy tester used to measure particle adhesion forces quickly, using only a small amount of powder.

- Predicted powder flowabilities, from particle adhesion, can be correlated with conventional measurements.

- Technique has potential to predict powder flow properties at early stage of drug formulation.

- Particle adhesion measurements used to help to develop DEM (Discrete Element Method) model simulations.

- Project Outputs: 2 papers published, joint publication in preparation, results disseminated to Tier 1 partners, detailed report complied.

A Novel Simulated Moving Plug Flow Crystalliser (SM-PFC) with Anti-Fouling Control (6-months), University of Aberdeen:

- Novel SM-PFC configuration shown to maintain product crystal specifications in the presence of heavy fouling without interrupting the process.

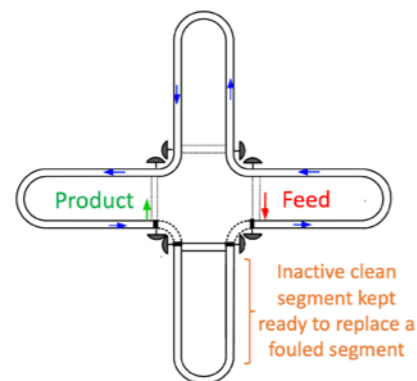- Configuration optimization performed to determine number and length of segments, temperature profile, seed rate and volumetric flowrates to maximise the time between switching events, crystal size and productivity.

- Regime map developed for 3 objectives (productivity, switching time and crystal size) for high fouling systems.

- Project Outputs: results disseminated to Tier 1 partners, detailed report complied, publication in preparation.

Voids
Crystals

100 microns
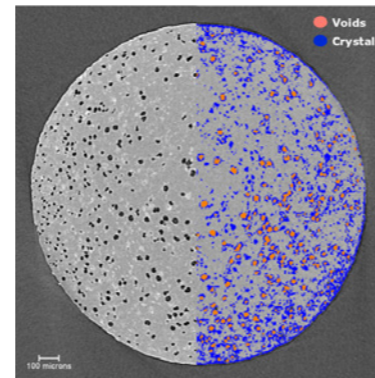
Advanced 3D Characterisation of Formulated Pharmaceutical Systems (12-months), University of Manchester:

- Changes in porosity and evidence of partial breakage in tablets investigated using x-ray computed tomography (XCT).

- Presence of voids and possible crystallites within extrudates correlated with material composition, ongoing time-dependent crystallization studies being performed.

- Project Outputs: results disseminated to Tier 1 partners.
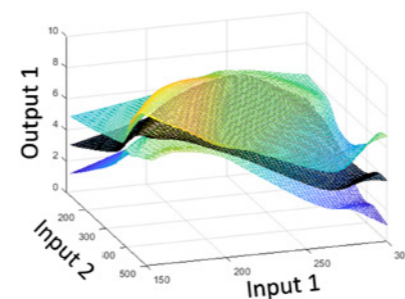
From Laboratory to Industrial Manufacture: Transforming Digital design via Robust Scaling-Up AI Platforms (6-months), University of Sheffield:

- This project will assess the optimisation performance for many-objective optimization algorithms under multiple constraints and use appropriate performance metrics and analysis tools to enhance many-objective optimization.

- Develop optimisation tools, and a demonstrator software, to be used to improve understanding of scale up processes (from lab to industrial manufacture).

Flow-Xl: A New UK Facility for Analysis of Crystallisation in Flow Systems

CMAC is a partner in the EPSRC-funded project at the University of Leeds to establish a laboratory-based facility to allow simultaneous X-ray diffraction and Raman spectroscopic monitoring of crystallisation occurring in a range of fully-integrated flow platforms that will be incorporated into the facility. Led by Professor Fiona Meldrum, Flow-Xl will support a range of projects in crystallisation science, including areas such as the formation of organic framework compounds, biomineralisation and bio-inspired crystallisation, materials discovery, production of single enantiomer crystals, polymorph selection and the development of artificial intelligence in modelling of crystallisation. Once commissioned, Flow-Xl will be open for user access, and its design allows for the incorporation of user-designed flow environments, increasing its potential range of applications. The facility is highly relevant to a number of CMAC projects.
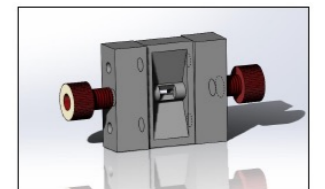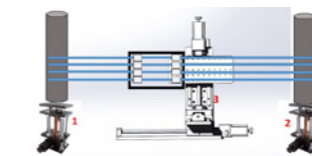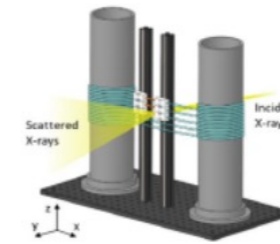
International Academic Network

CMAC Hub international academic network has gone from strength to strength over the last twelve months. Building on collaborative relations built through schemes such as EPSRC SAVI (Science Across Virtual Institutes), EPSRC Global Engagements and EU funded consortia, the Hub has been successful in two newly funded collaborative international research programmes.

EPSRC funded RiFTMaP: Right First Time Manufacture of Pharmaceuticals is led by University of Sheffield and includes Universities of Strathclyde, UCL and Purdue (USA) as academic partners. EPSRC International Centre to Centre DDMAP: Digital Design and Manufacture of Amorphous Pharmaceuticals is led by University of Strathclyde involving partner institutions Universities of Copenhagen (Denmark) and Ghent (Belgium). Both of these projects will cement collaborations of the partners and promote mobility for researchers generating industry relevant research outputs with real international impact. The Hub also secured a SUPA Saltire PhD exchange grant from the SFC (Scottish Funding Council) Saltire fund to host a PhD student from the University of Ghent and collaborate in the area of additive manufacturing of medicines.

The Hub's drive to influence regulatory policy on a global scale has continued via the collaboration with MIT and hosting its 4th International Symposium. Attended by policy makers, regulators and thought leaders from around the world the meeting outputs have been used to drive digital and skills agenda for medicines manufacturing.

Dr Andrea Johnston, CMAC Associate Director

RiFTMaP

Right First Time Manufacture of Pharmaceuticals (RiFTMaP) is a three-year £2 million EPSRC & NSF-funded collaboration project between the University of Sheffield, UCL, University of Strathclyde and Purdue University (USA). Industrial partners in the project include the following pharmaceutical, software and equipment manufacturers: Alexanderwerk, AstraZeneca, Eli Lilly, GlaxoSmithKline, Pfizer, IBM UK Lannett, Natoli Scientific and Process Systems Enterprises.

This project aims to develop right-first-time (RFT) smart manufacturing systems incorporating Industry 4.0 concepts within a systematic framework for smart continuous pharmaceutical manufacturing that will deliver key benefits to the industry including:

- Reduced time to market of new products
- Reduced waste and increased resilience
- Reduced cost of manufacture

An important and unique element of this project is the ability to validate state of the art models, control and optimization procedures on three cutting edge continuous manufacturing experimental platforms: (1) Consigma 25 wet granulation line at the University of Sheffield; (2) Dry granulation line at Purdue University; and (3) Continuous direct compression line, also at Purdue University.

The project outcomes include a framework and computational tools for optimal design of pharmaceutical processes with a real-time process management system and a flexible real-time release testing framework, all verified at pilot scale.
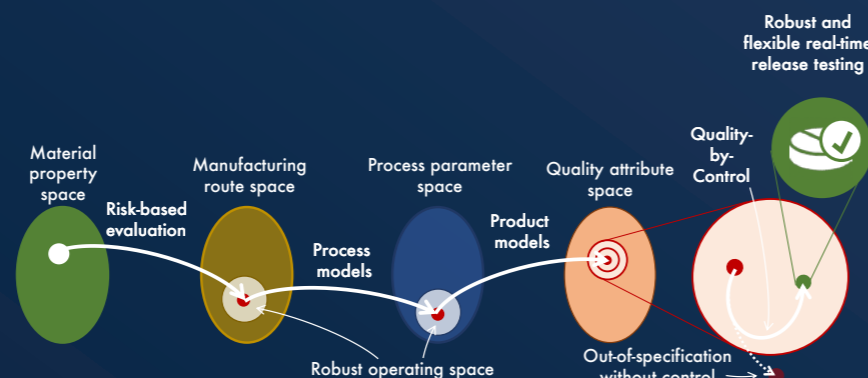
Digital Design and Manufacture of Amorphous Pharmaceuticals (DDMAP)

The Digital Design and Manufacture of Amorphous Pharmaceuticals (DDMAP) International Centre is a £1.2M EPSRC international collaboration between three world-leading research groups from the UK (CMAC, University of Strathclyde), Denmark (CPHarma, University of Copenhagen) and Belgium (CESPE, Ghent University). DDMAP is supported by the following partners: AstraZeneca, Sandoz and CCDC. The international centre will address key research questions that underpin the selection, production and application of amorphous molecular solids as well as establish a collaborative, world-leading network across Europe with expertise in medicines development and manufacture.

DDMAP has a collaborative mission to develop new science and methodologies that will de-risk the use of amorphous solid forms, reduce the cost of their development and manufacture, and accelerate the adoption of this versatile and effective solid form in the pharmaceutical industry.

Prof Alastair Florence, PI of the DDMAP international centre to centre award said: "This is a fantastic opportunity to collaborate between three leading centres across Europe and address challenges that limit the more routine exploitation of this important class of pharmaceutical materials. The multidisciplinary team will develop new understanding on the structure, transformations, processing and performance of amorphous systems through a unique international collaboration. Not only will we be building new knowledge, but also working together to create an innovative open access data resource that will allow others to benefit from the project, as well as supporting the development of the next generation of research leaders in this field."

The project will use a range of characterisation methods, modelling approaches and machine learning to understand the structure and properties of amorphous drugs and develop new methods of manufacturing involving 3D printing and other techniques. Biorelevant media that mimic conditions within the stomach and intestines will be studied to understand the mechanisms involved in the release of amorphous drugs in the body. The data and knowledge generated will be applied to determine better ways to use amorphous materials to design and make dosage forms with controlled stability and predictable, precise delivery of medicines to patients.

Image Credit: ARTICULAR: ARtificial inTelligence for Integrated ICT-enabled pharmaceUticaL mAnufactuRing (EP/R032858/1)

Map of CMAC Network

CMAC has worked with industry partners and academic collaborators globally.
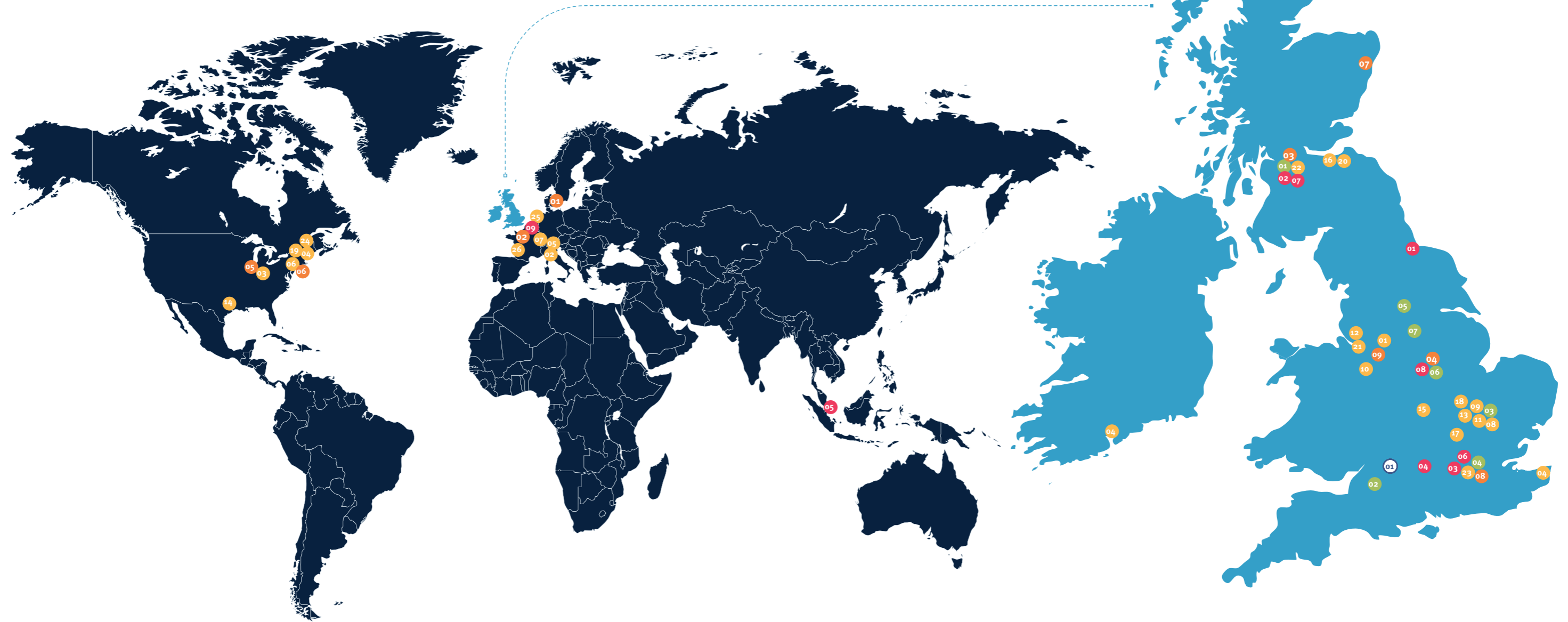
EPSRC:

01 EPSRC, Swindon, UK

ACADEMIC HUB AND SPOKES:

01 University of Strathclyde, Glasgow, UK

02 University of Bath, UK

03 University of Cambridge, UK

04 Imperial College London, UK

05 University of Leeds, UK

06 Loughborough University, UK

07 University of Sheffield, UK

ACADEMIC PARTNERS:

01 University of Copenhagen, Denmark

02 Ghent University, Belgium

03 Glasgow School of Art, UK

04 University of Nottingham, UK

05 Purdue University, Lafayette, IN, USA

06 MIT, Cambridge, MA, USA

07 University of Aberdeen, UK

08 University of Greenwich, UK

09 University of Manchester, UK

INDUSTRY PARTNERS:

01 AstraZeneca, Macclesfield, UK

02 Chiesi, Parma, Italy

03 Eli Lilly, Indianapolis, IN, USA

04 Pfizer, Sandwich, Kent, UK & Cork, Ireland & Groton, CT, USA

05 Roche, Basel, Switzerland

06 Takeda, Boston, MS, USA

07 UCB, Brussels, Belgium

08 Laminar Analytik, Cambridge (Laminar) and Korea (Analytik)

09 Anatune, Cambridge, UK

10 AWL, Stoke-on-Trent, UK

11 Blacktrace, Royston, UK

12 Britest, Daresbury, UK

13 CCDC, Cambridge, UK

14 CherryCircle Software, Inc., Austin, Texas (USA)

15 Clairet Scientific Limited, Northampton, UK

16 EDEM, Edinburgh, UK

17 GlaxoSmithKline, Stevenage, UK

18 Huxley Bertram, Cambridge UK

19 M-Star Simulations, Maryland (USA)

20 Nitech Solutions, Edinburgh, UK

21 Perceptive Engineering Ltd PerceptiveAPC, Warrington, UK

22 PWC, Glasgow, UK

23 PSE Siemens Process Systems Engineering, Hammersmith, UK

24 Snapdragon Chemistry, Waltham, MA, USA

25 Technobis Crystallization Systems – Alkmaar, The Netherlands

26 ThermoFisher Scientific, Bordeaux, France

INNOVATION SPOKES:

01 CPI, Middlesbrough UK

02 CRUK, Formulation Unit, University of Strathclyde, Glasgow

03 NPL, Teddington, UK

04 Diamond Light Source, Didcot, UK

05 NTU, Singapore

06 MHRA, London, UK

07 Scottish Enterprise, Glasgow, UK

08 Connected Everything II, Nottingham, UK

09 ICE Cubes Services, Brussels, Belgium

Research Portfolio

CMAC'S RESEARCH PORTFOLIO IS DRIVEN BY A CORE ACADEMIC TEAM WITH THE UNDERPINNING RESEARCH EXPERTISE AND CAPABILITIES TO DEVELOP NEW INTEGRATED SOLUTIONS ACROSS OUR MEDICINES MANUFACTURING SCOPE.
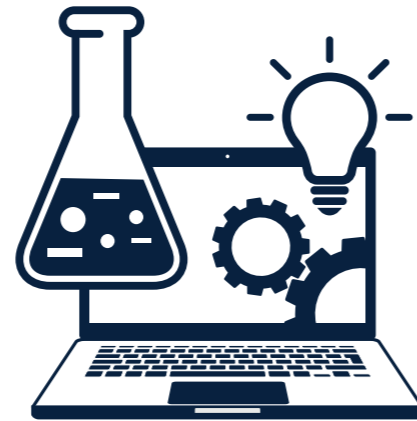
CMAC's strategy builds on the Hub project and is informed by the project portfolio of industry demand led manufacturing research. Academic strengths cover a breadth of areas including:

- Next Generation Solid State
- Smart Crystallisation, Particle Engineering and Isolation
- Smart Formulation and Drug Product Processing
- Biorelevant Release and Real Rime Release Testing
- Advanced Characterisation
- Next Generation Digital
- MicroFactories

In growing the critical mass of projects and facilities around the Hub platform, our goal is to work collaboratively to identify priority areas where we can develop further activities that target additional manufacturing research and address key industry areas of need.

Cross-Cutting Topics			TRL	Crystallisation & Isolation	Particle Engineering	Advanced Drug Product Development	Biorelevant Performance Design	
			7-9	Potential Industry Demonstrators, spin-outs, in-house company projects, SCOUT				Deploy
			4-6	CMAC Core & Proprietary Projects				
				RiFTMAP				
				ISCF Digital Design Accelerator Platform (DDAP)				Validate
					CAMS			
						MMIC GC1		
					Granular materials			
				CMAC National Facility Projects & KTPs (PSE / AZ)				
				Made Smarter Innovation – Digital Medicines Manufacturing (DM²) Research Centre				Adapt/Integrate
				EPSRC Future Continuous Manufacturing & Advanced Crystallisation Hub				Understand
			1-3	EPSRC Prosperity Partnership				
					EPSRC ARTICULAR			
				EPSRC Digital Design and Manufacture of Amorphous Pharmaceuticals (DDMAP)				
				CMAC PhD Project Portfolio				
				EPSRC Strategic Equipment (Compaction Simulator)				Discover
Embedded: Training & Skills; Advanced Technology & Facilities; Translation to Industry								

Left vertical cross-cutting topics: Data & DataFactories – smart development platforms; Digital Twins – modelling and prediction; Workflows – model driven experimental design; MicroFactories – modular, flexible processing; Net Zero – sustainable development & processes.

CMAC Portfolio Highlights

Pressure-dependent In Situ Monitoring of Granular Materials

The EPSRC funded Compaction Simulator Pilot Test Facility with instrumented dies and terahertz (THz) spectroscopy has been a key asset in the CMAC facility in the last year to support PhD projects, EPSRC funded research and industrial projects. This fully integrated system is the first system in the world capable of in situ monitoring physical and chemical changes of powder and granular materials during compaction using THz technology. This equipment supports research across three connected themes: 1) analysing phase transformations in formulated materials during compression, 2) in situ monitoring of physical bulk properties in formulated systems under pressure, and 3) enabling digital design of oral pharmaceutical drug products. The current research focus is on developing fundamental understanding of the compaction of spherical agglomerates, developing material-sparing formulation and process development workflows, as well as understanding and predicting fragmentation and agglomeration of particles during compaction and storage of solid oral dosage forms.

Community for Analytical Measurement Science (CAMS) Industry Project: Physical Stability Characterisation and Prediction

This collaborative project between the University of Strathclyde, AstraZeneca and Pfizer will develop a comprehensive understanding of the link between material attributes, the temporal nano- and microstructural evolution of pharmaceutical tablets and its effect on the in-vitro drug release performance after long-term storage. The project will make use of CMAC's cutting-edge technologies, such as X-ray computed nanotomography, terahertz time-domain spectroscopy and optical coherence tomography, to visualise and quantify structural changes of pharmaceutical tablets from a nanometre to millimetre scale.
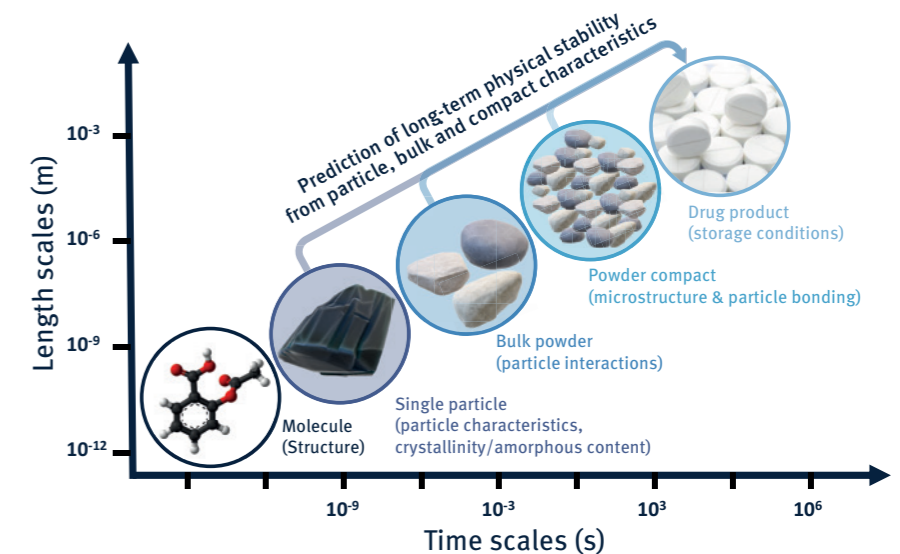
The experimental data will support the development of a coupled particle to tablet model for the prediction of structural changes of tablets during storage. The project aims to deliver workflows and innovative digital tools that are capable of predicting long-term changes of drug release kinetics. It will thus make a significant contribution towards CMAC's strategic goals in the delivery of digitally enabled R&D, manufacturing and supply, with benefits from reduced cost, environmental impact and improved health.

ARTICULAR
MEDICINES MADE SMARTER

EPSRC ARTICULAR 2021-22 UPDATE

ARtificial inTelligence for Integrated ICT-enabled pharmaceUticaL mAnufactuRing

An immersive training environment for the assembly of an EasyMax chemical stirrer

- Three training methods were developed (VR, tablet PC, and video tutorial) representing the same procedure on the EasyMax.

- A pilot study was successfully performed at the University of Strathclyde.

- Final experiment to take place in March 2022 to determine the effectiveness of VR over the other more traditional technologies.

CRYSTALEYES APP
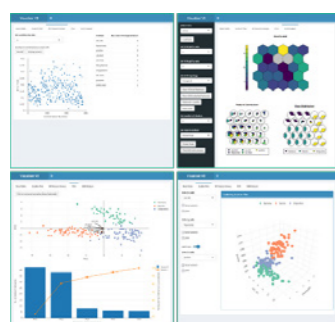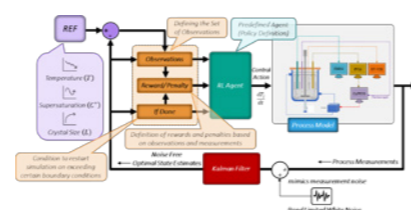
- Interface enables quick and intuitive exploration of process datasets.

- A focused set of tools are deployed in sequence to reduce data complexity.

- Users are guided through the detection of important features, as well as trends, gaps and zones of operation.

Robust Model-Based Reinforcement Learning for Controlling Crystallisation Processes

- Novel application of Reinforcement Learning (RL) and Inverse Reinforcement Learning (IRL) combined with Transfer Learning (TL) and Kalman Filtering/ state estimation techniques.

- Developed for multiple trajectory tracking control of crystallisation processes with certain uncertainties (Process & Measurement Noises, Plant-Model Mismatch, etc.).

- Establishes some initial benchmarks for RL, IRL Vs PID, MPC.

Machine learning workflow to predict mechanical properties
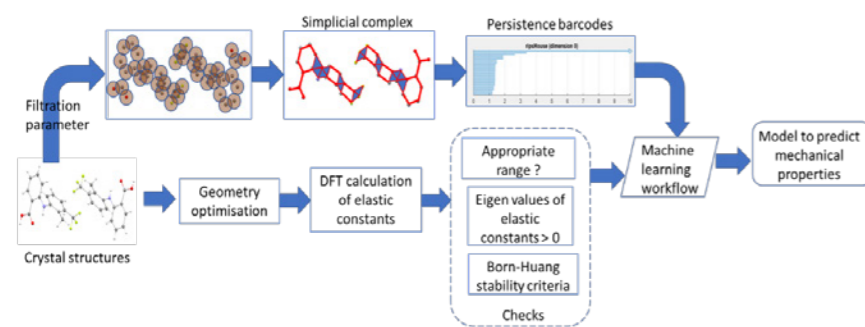
- Topological analysis based persistence homology is used to represent crystal structures.

- Computational calculation of elastic constants and mechanical properties.

- Persistence barcodes and calculated elastic constants are used to develop machine learning models to predict mechanical properties of small organic compounds.

PROSPERITY PARTNERSHIP PROJECT

Accelerated Discovery and Development of New Medicines: Prosperity Partnership for a Healthier Nation is a collaborative project with GSK as the lead industrial partner. Working with colleagues from the University of Nottingham, CMAC have been working on Theme 4: A new Digital Design toolset to enable Digital Manufacturing of novel pharmaceutical processing equipment. The collaboration in this theme brings together 3D printing capabilities (University of Nottingham) and continuous manufacturing expertise from CMAC (University of Strathclyde) to design a system for creation and study of novel continuous flow inverter (CFI) reactors..

The aim of this project is to build an adaptable platform technology based around additive manufacturing and machine learning, incorporating design optimisation, modelling, sensing and materials development that will set the basis for an agile, evolving, generative design manufacturing platform. Novel CFI

Generative design model for producing CFI geometries with identical mean residence time.
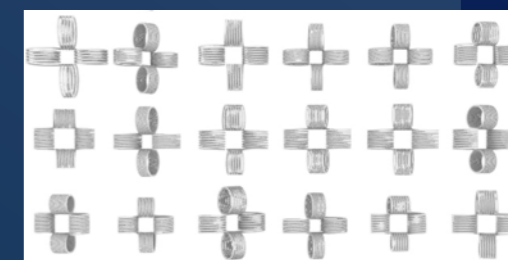
reactors (patented technology) will be used as an example for Theme 4 process development.

As a case study, this project aims to achieve continuous virus inactivation at low pH with a narrow residence time distribution and minimal pressure drop. Residence time distribution is setup as an objective for the platform and is mapped out against relevant design factors - flow, fluid density, fluid viscosity, tubing inner diameter, pitch distance and coil tube properties. Alongside CFD simulations, a bespoke test rig is used to collect the process data and assess physical geometries that will be additively manufactured at University of Nottingham.

A key aspect of the Generative design is to use process specific parameters as

optimisation input to create an array of design possibilities. Unlike traditional optimisation methods where a single initial design is studied and incrementally improved, we explore hundreds of design options simultaneously all of which fit the given input criteria. The above figure shows a series of reactor designs with the same mean residence time.

Our machine learning model, handling large input dataset, will define which geometries perform the best in respect of virus inactivation, pressure drop, size of the reactor, manufacturability and any other constraint that is set and controlled by the end-user. With such control of the process, the end-user will be fully informed to select the best CFI reactor for any continuous manufacturing process.

Digital Design Accelerator Platform to Connect Active Material Design to Product Performance (DDAP)

This 1.75 million 2-year UKRI funded project is led by AstraZeneca, with CPI, PSE, Pfizer, CCDC, Perspective Engineering and GSK all being partners. CMAC Hub academics Professor Alastair Florence and Professor Blair Johnston are Co-investigators, working with collaborators at the universities of Leeds and Sheffield.

Sophie Bailes, Associate Director in Digital Transformation at AstraZeneca said:

" We are pleased to lead this exciting collaboration between end users, technology providers and academic research in order to deliver a transformational platform with the potential to accelerate development of new medicines for patients. Through adoption of digital tools we can build in operational excellence right from the start of pharmaceutical development, improve product robustness, and drive more efficient manufacturing processes. Thereby delivering more medicines to more patients, more quickly. "

Made Smarter Innovation

DIGITAL MEDICINES MANUFACTURING (DM²) RESEARCH CENTRE

MADE SMARTER INNOVATION

DM2

DM² AIMS TO TRANSFORM MEDICINES DEVELOPMENT AND MANUFACTURING PRODUCTIVITY, AND DRIVE PATIENT-CENTRIC SUPPLY.

To achieve this, DM² will work with industrial partners to develop and accelerate the adoption of industrial digital technologies (IDTs) in the pharmaceutical sector. This will enable the required transformations in data exploitation needed to empower users across pharmaceutical supply chains.
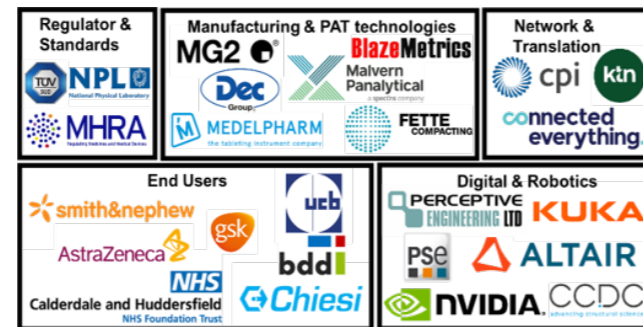
Research objectives:

- ⚙ Accelerate digitalisation in pharma sector
- ⚙ Transform medicines development and manufacturing productivity
- ⚙ Revolutionise Quality Control
- ⚙ Drive patient-centric supply
- ⚙ Enable the workforce of the future

DM² is led by the University of Strathclyde (CMAC), in partnership with Loughborough and Cambridge Universities. Established through a £5M EPSRC award, with a further £2.9M from collaborating partners, it forms part of the UKRI and Made Smarter Innovation £53M investment in smart manufacturing and connected supply chain research and innovation.

To achieve this, work will be carried out across the following five integrated platforms, designed by academic and industrial researcher teams.

DM² Partners:

Regulator & Standards
TÜV NPL
MHRA

Manufacturing & PAT technologies
MG2
Dec Group
MEDELPHARM
BlazeMetrics
Malvern Panalytical
FETTE COMPACTING

Network & Translation
cpi ktn
connected everything

End Users
smith&nephew
AstraZeneca
gsk
NHS
Calderdale and Huddersfield NHS Foundation Trust
ucb
bdd
Chiesi

Digital & Robotics
PERCEPTIVE ENGINEERING LTD
KUKA
pse
ALTAIR
NVIDIA
CCDC

	Platform 1 The Data Platform	Platform 2 Autonomous MicroScale Manufacturing	Platform 3 Digital Quality Control	Platform 4 Adaptive Digital Supply	Platform 5 DM² Network & Skills
Aims:	To address one of the sector's core digitalisation challenges - a lack of large datasets and ways to access such data.	To accelerate the development of medicine products and manufacturing processes by creating agile, small-scale production facilities and using robotic technologies.	To drive digitalisation of Quality Control (QC) aspects of medicines development - critical for ensuring a medicine's regulatory compliance and patient safety.	To generate new understanding on future supply chain needs of medicines to support adoption of adaptive digital supply chains for patient-centric supply.	To lead engagement, collaboration and skills development by establishing the DM² network & skills programme.
Objectives:	⚙ Build data systems to clean, archive and serve data across Platforms ⚙ Capture and create data models for Platforms 2 - 4 ⚙ Establish DM² Data Services with partners to maximise data value and growth ⚙ Develop novel, data driven AI tools for data handling, analysis and prediction ⚙ Develop standards to ensure accuracy and reusability, establishing "gold-standard" curated datasets	⚙ Create an automated mini-batch direct compression and capsule filling IDT manufacturing demonstrator ⚙ Demonstrate an autonomous IDT manufacturing demonstrator to predictively formulate new OSDs for phase 1 clinical supply ⚙ Develop fundamental understanding about the material – process – performance relationship for tablets and capsules	⚙ Learn to utilise prior knowledge and data against specifications to automate raw material release ⚙ Design optimal reliable operating regions (ROR) to meet CQAs and regulatory standards ⚙ Real time measured and predicted (soft sensors) CQAs to achieve predictive real time release testing (RTRT) displacing extensive off-line analysis and reducing waste by 30% ⚙ Build a self-optimising QC Digital Twin into the process to streamline regulatory compliance multiple tablet and capsule formulations alongside an advanced control and fault detection strategy	⚙ Develop three digital supply chain use-case models that capture material, information, and value flows enabling data-driven replenishment based on actual user demand ⚙ Identify relevant IDT interventions that enable actual demand-capture and automated supply & replenishment ⚙ Develop alternative digital supply chain configurations based on autonomous manufacturing driven by patient need	⚙ Act as a springboard for DM² to share developments and insights across pharma and broader digital manufacturing sectors ensuring cross-sector diffusion ⚙ Work with existing strategic networks to expand the reach of IDT dissemination and uptake ⚙ Identify skills needed for the future work-force and, with part-ners, develop and deliver training ⚙ Create case studies to inform responsible research, innovation and trust in IDTs

Knowledge Transfer Partnerships

Another area we have seen successful development in the portfolio is with establishing Knowledge Transfer Partnerships (KTP) as part of our Translation to Industry approach. We have now had 4 projects funded involving AWL Ltd and Strathclyde, PSE and Strathclyde, PSE and Sheffield as well as our latest award between AstraZeneca and Sheffield looking at the application of PDF analysis for amorphous systems. The below case studies highlight the successful completed KTP project between CMAC partners Sheffield and PSE and ongoing KTP project between Strathclyde and PSE.

Model-based Digitalisation Framework Development for Continuous Manufacturing Processes

This Innovate UK Knowledge Transfer Partnership project was a collaboration between the University of Sheffield and Process Systems Enterprise (PSE, now a Siemens business). The aim of this project was to develop a systematic methodology for the application of a mechanistic-based digitalisation framework, to enable pharmaceutical and other industries to effectively and efficiently design and implement continuous manufacturing processes.

The project has led to the development of mechanistic models for continuous pharmaceutical manufacturing, successfully implemented in gPROMS FormulatedProducts software and validated using the continuous pharmaceutical manufacturing facilities at the University of Sheffield. Overall, the project was successfully completed in March 2021 with two publication outputs and with KTP associate Dr Li Ge Wang now having assumed a new staff position at PSE.

Industrial Workflows for the Application of a User Friendly Mechanistic Modelling Toolkit

This KTP project is a joint-venture between CMAC and PSE aimed at:

- Creating industrial workflows for the application of a user-friendly mechanistic modelling toolkit for active ingredient manufacture
- Delivering step-change improvements in functionality and usability of gPROMS Formulated Products
- Developing an enhanced tool accessible to a wide range of users – from non-expert operators/users to skilled modellers/engineers

This embedded novel capability will be facilitated by an underpinning knowledge of both advanced batch and continuous pharmaceutical processes and how to integrate these to achieve robust modelling tools for end-to-end pharmaceutical manufacture.

To date, project outputs include:

- Workflows for modelling processes like crystalisation and filtration, which have subsequently been used to develop example cases for upcoming commercial releases of gPROMS FormulatedProducts
- Data requirement documents for creating robust flowsheets on gPROMS FormulatedProducts
- Conference presentations at APMF, ISIC 21 and AIChE 2021

Project SCOUT

Another project as part of our translation to industry pillar, involving CMAC, IBioIC and CPI, and funded by the ERDF scheme. SCOUT is a free service for SMEs in life sciences, biochemical and chemical supply chain sectors offering a range of services including:

- Mapping a path to commercialisation
- Support with growth challenges by providing a clear plan, new networks and knowledge from industry experts
- Making links for SMEs to parallel supply chains and increase partnerships for regulatory, process technology and digital companies
- Support to overcome barriers to R&D investment

This £882k project is part of the Advanced Manufacturing Challenge Fund, jointly funded by the European Regional Development Fund (ERDF), managed by Scottish Enterprise, along with the **Centre for Process Innovation** (CPI), **CMAC Future Manufacturing Research Hub** (CMAC) and the **Industrial Biotechnology Innovation Centre**, (IBioIC).

The SCOUT project has worked with a variety of different SMEs in Scotland throughout 2021, with the areas represented below:

- Continuous process control
- Antibacterial solutions
- Sustainable cleaning products
- Oral healthcare
- Synthetic biology
- Agritech analysis
- Insecticides
- Water treatment and cleaning

SCOUT aims to accelerate and de-risk the growth of Scottish SMEs seeking or developing disruptive technologies. Eligible chemical and biochemical supply chain companies must have an operational presence in Scotland and meet de minimis criteria for ERDF support.

MMIC GC1

Medicines Manufacturing Innovation Centre - MMIC

CMAC is working closely with MMIC to identify areas, where as part of our translation to industry framework, we can work together to accelerate translation of innovative technologies into practice.

MMIC is a strategic partnership between CPI, AZ, GSK and the University of Strathclyde to create a world class innovation centre where pharma companies can develop and adopt new manufacturing technologies. The MMIC centre is being built at the Advanced Manufacturing Innovation District in Renfrewshire and is due to come online in the first half of 2022. The MMIC operates a grand challenge (GC) model and CMAC are leading the technical development phase of one of the grand challenges, "Development of a next generation digital test bed for continuous direct compression".

Over the last year, CMAC have built clean-room facilities and constructed a modular, flexible Continuous Direct Compression system in the technology innovation centre at the University of Strathclyde. R&D activities are well underway and CMAC have been active in generating a large materials and model parameter database to enable development of a digital twin for direct compression. Specifically new tools for modelling aspects including feeder performance, residence time distributions,

micro-mixing, lubrication effects and compaction are being developed. The global aim being to predict model parameters, and hence process performance, digitally from materials properties. This approach can reduce the empirical approaches to process and product development. During the coming year, a second phase of the work will be progressed whereby the test bed will be relocated to the MMIC facility when it comes online. Multiple tablet presses will be integrated to the existing platform to expand the capability.

Industry Funded Core Projects

The Pre-Competitive Core Projects are funded by the Tier 1 companies and are designed to develop translatable outputs to deliver impact in research areas aligned with the EPSRC Hub.

Multidimensional particle characterisation from in situ sensor data

University of Strathclyde, 2-year project.

The aim of this project is to use a combination of available algorithms and recent advances in machine learning to extract the best possible representations of multidimensional particle characteristics (particle size/shape/chord length distributions and particle number densities) from in situ sensor data to enable predictive population balance modelling.

- Existing classical image analysis and chord length distribution (CLD) to particle size distribution (PSD) transformation algorithms evaluated and new machine learning (ML) image analysis and CLD to PSD transformation methods developed
- Classical image analysis algorithm applied to breakage model selection using in-line imaging dataset of silicon particle breakage
- Application of ML image analysis to (i) polystyrene spheres and ellipsoids and (ii) lactose datasets performed
- Potential methods of sensor fusion identified
- Uncertainty modelling being developed

Translated Outputs: Initial version of App with ML image analysis and CLD to PSD transformation, 2 publications in pipeline, ISIC poster presented, results disseminated to Tier 1 partners
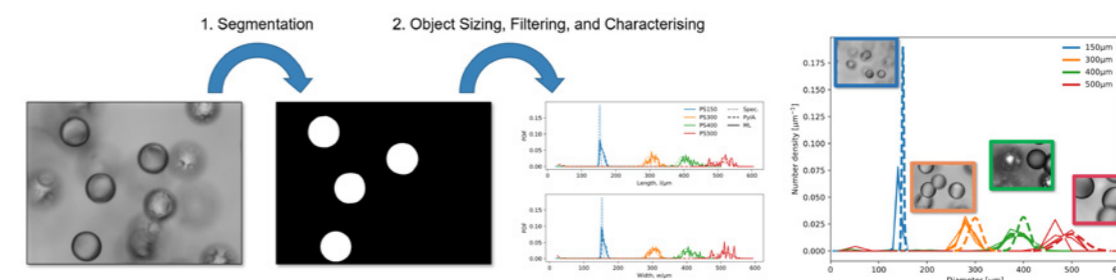
Calibration model development for in situ monitoring of solute concentration for antisolvent crystallisation

University of Strathclyde, 1-year project.

The aim of this project is to develop general rules for calibration model development, which will then form the basis of a workflow to assist with construction of the optimum calibration model for any given anti-solvent crystallisation process.

- Complete temperature and antisolvent dependant calibration data set acquired
- Evaluation of different pre-processing techniques (mean centring, baseline correction, Standard Normal Variate, Savitzky-Golay & Loading Space Standardisation) and calibration models (Partial Least Square and Multiplicative Effect Model) completed
- Application of preliminary calibration workflow to historical datasets being performed
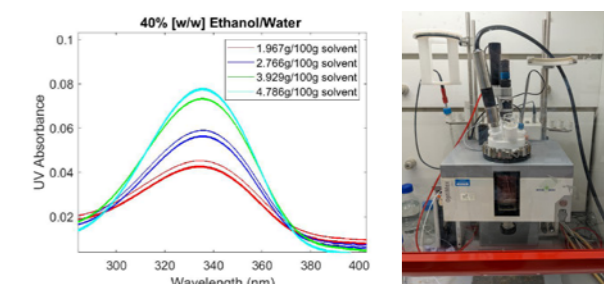
Translated Outputs: Preliminary calibration workflow, results disseminated to Tier 1 partners

Exemplary Translation to Industry

"CMAC is a world-class international Centre for Manufacturing Research and Training. We have now more than 10 years of experience and a well consolidated partnership with our Tier 1, Tier 2, industrial, academic and innovation partners, with which we built a vibrant portfolio of precompetitive programmes, multi-disciplinary and collaborative research, training and world-class facilities.

It is critical to ensure our research strategy is consistently well informed by industry needs, prevailing government policies and emerging knowledge from the research base; this has been recently reviewed and is detailed in our published CMAC 2021-2026 strategy document.

CMAC has developed leading approaches to build and deliver value from ideation, cocreation, codelivery to Translation to Industry. We work closely with industry to transform current manufacturing processes into the medicine supply chain of the future with higher sustainability profile and better quality for the patients.

The quality of our research and academic leadership has enabled CMAC to develop a rich portfolio of technologies that have now reached TRL 3-6 and continue to develop a suite of new technologies and capabilities at earlier TRL (i.e. TRL 1-3) informed by the challenges and emerging needs of industry. In addition, our unique programme includes a variety of routes to translation such as: staff exchanges, company placements, webinars, expert training workshop and e-learning modules, pre-competitive industry funded programmes and provide excellent opportunities for strategic partnership with key players active in the UK (i.e. CPI/MMIC) and internationally.

CMAC is continuing to deliver value and is intensifying its translation to industry leadership and portfolio underpinned by excellent research and innovation."

Massimo Bresciani,
CMAC Industry Director

Overview

As highlighted in the previous pages describing examples of our portfolio, our translation to industry plan is already delivering a suite of targeted interventions. However, we must do more.

CMAC's research programme and translation to industry strategy is informed and developed through close collaboration with its industrial partners to provide answers to industry relevant needs and to drive technology transformation.

Industry partners support the Future Manufacturing Research Hub and CMAC Industrial PhD Programme, helping shape research to transform medicines development and manufacture.

CMAC's translation to industry programme of activities supports multiple routes to translation. These provide excellent opportunities for companies in the UK and internationally, both large and small, whether technology provider or large-scale pharmaceutical manufacturer to work with CMAC, join the partnership and help accelerate the adoption of advanced pharmaceutical manufacturing.

2021 Update

In 2021 CMAC continued to expand and develop collaborations across large pharma (Tier 1s), large corporations and SMEs in the technology field (Tier 2s), and academia to provide an immersive ecosystem of pre-competitive research knowledge sharing and process improvement. This has been exemplified through the technical translation of the integrated isolation model and spherical agglomeration workflow. A multi-company approach was used to deliver demonstrable impact through equipment set-up, process workflows, personnel training and access to research outputs.

The importance of collaborative working, adaptive, agile manufacturing processes and the significance of continuous manufacturing has continued to be at the forefront of CMAC activities. CMAC has continued to adapt to working with our global partners throughout the pandemic, hosting a range of virtual events including the CMAC Mini Symposia series showcasing the CMAC PhD research and Hub Academic Research Group (HARG) meetings showcasing Hub and Feasibility Studies research programmes to engage with our Tier 1 partners, and the CMAC - The Next 10 Years (see page 30) to engaging across the broader industry network. Additionally, we ran a range of webinars and focused discussion topic meetings over the past year which has seen excellent engagement from industry to contribute to the research efforts across the breath of the programme.

As CMAC enters its second decade, there is a renewed sense of urgency to accelerate translation activity to meet the demands of an ever-accelerating world of change in which its industry partners compete. Our aim is to achieve an elevated level of awareness of the benefits and opportunities for key stakeholders, and to implement via cocreation, codelivery, dissemination, training and discovery of translation routes. CMACs commitment to deliver value to its partners through exemplary translation to industry of innovative solutions towards higher TRL, commercialisation and industrial application is a core part of the recently published **CMAC 2021-26 Strategy**.

MULTIPLE ROUTES OF TRANSLATION TO INDUSTRY (T2I)

How

TRL based development and progression
- T2I via strategic partnerships (i.e. CPI/ MMIC)
- T2I in collaboration with Tier 1 and/or Tier 2
- Commercialisation via CMAC NF
- Spin offs

Staff Exchanges
- PhD placements at companies
- Company Staff at CMAC

Recruitment and Outplacement

Collaboration
- Proprietary 1:1 project collaborations
- Pre-competitive industry funded programmes

Training
- Webinars and e-learning modules
- At company sites, or at CMAC

Technology Portfolio

TRL 3 to 6: > 22 technologies in total
- 6 are at TRL 3
- 11 are at TRL 4
- 4 are TRL 5 T2I design phase
- 1 commercial readiness and 1 to commercial scale

Active in T2I phase
- Digital platforms
- Predictive models & software
- Workflows
- Databases & know-how
- Hardware & new sensors
- Skills development

KPIs: multiple conceptual technologies at TRL 1– 3 currently progressing within the CMAC research and translation portfolio; one technology progressing towards commercialisation; one upscaling to commercial GMP scale in collaboration with MMIC

Industry Engagement & Translation

CMAC continues to strengthen its industry engagement strategy. Driven by our mission to transform medicines manufacture, development time and cost to market, we are maximising our relationships with large pharma, SMEs, and academic stakeholders within our ecosystem to lead the process of solving real-world challenges while growing and enhancing our long-term sustainability.

After 10 years of operation, research activities are maturing to the stage that translation requires active management and prioritisation.

CMAC has developed a portfolio of technologies that have now reached TRL 3-6 and continues to develop a suite of new technologies and capabilities at TRL 1-3 informed by the challenges and emerging needs of industry. CMAC has instituted a stage-gate process as a means of managing technologies from low to high TRL. The purpose is to achieve a go/no-go decision on further resource investment in a technology concept.

INTERNAL DECISION GATES

CMAC Research & Translation Portfolio	Review with Research Team	Critical Decision 1: Technology value proposition (TRL 3)	Engage with Tier 1 End-users	Critical Decision 2: Technology Investment decision (TRL 5)
IP strategy • If no IP/patent, then publish and expand work as relevant reputationally **Monetisable?** • If yes, seek out commercialisation partners • If no, seek to maximise translation to industry **Academic community incentive** • IP, support to commercialise, funding, reputation, open innovation **End-user incentive** • Enhance technology capability/ competitiveness, cost saving, risk reduction/sharing, financial gain	Determine disruptive/ innovative capabilities Identify industry-specific customer jobs addressed Determine fidelity, usability, technology barriers/risks	• **Determine IP & strategy** • **Monetisation strategy/ total addressable market** • **Customer segments/ likely partners** • **Resources needed to progress technology development** • **Go/no-go decision**	Determine technology risk & readiness Determine technology future state URS/ development trajectory Determine barriers to adoption/ market entry	• IP protection • Identify translation-to-industry partners/ strategy • Value capture/business model/market research • Financial plan/resource requirements to deliver • Go/no-go decision

Objective: Achieve a go/no-go decision for further resource investments in a technology

DIGITAL TRANSLATION: CMAC ASSETSTORE

Making our toolbox of digital assets available to internal users to test and apply.

To support the growth of the CMAC digital technologies (including workflows, models, databases, datasets and training material) a CMAC AssetStore has been created. The CMAC AssetStore will act as a content management system with version control and will accelerate their development of collaborative digital technologies and prepare the digital technologies for translation.
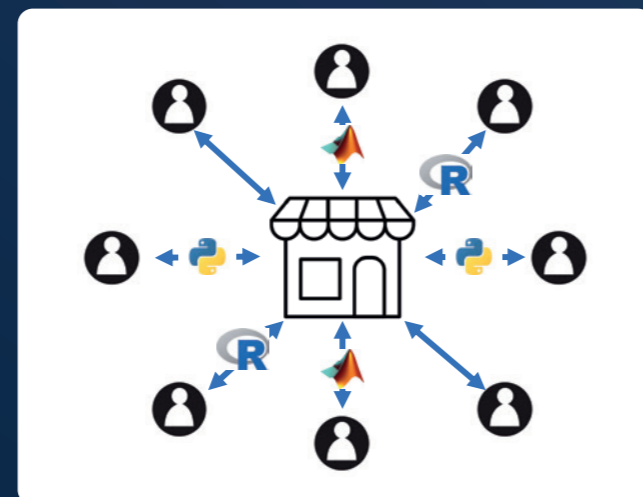
TRANSLATING FOR IMPACT: SPHERICAL AGGLOMERATION WORKFLOWS

Our industry aligned projects address the outcome-impact gap by ensuring industrially translatable outputs have built-in deliverables and are designed for direct implementation by end-users. An example of the success that can be achieved with this approach are the spherical agglomeration CMAC projects performed at the Universities of Sheffield and Strathclyde. Spherical agglomeration is a particle engineering technique that when applied significantly alters the bulk powder properties through controlled agglomeration to avoid problems associated with elongated particles or small particles such as long filtration times and poor flow properties.

CMAC spherical agglomeration Hub, Core and National Facility projects have resulted in translation of workflows and models, as well as expertise in process understanding. Two workflows have been developed, one based on fundamental mechanistic understanding of miscibility, liquid/liquid and particle/liquid interactions and rate processes incorporating detailed modelling and the other an experimental driven workflow for solvents and bridging liquid selection, CPPs and CQA control. Studies of spherical agglomeration scale-up, characterisation, tabletting and dissolution have also been performed.

KEY OUTPUTS:

122 Webinar attendees, across 2 webinars

1 Technical support report shared, 1 in draft

2 Paper submissions, 5 papers in draft form

2 Workflows: mechanistic modelling and experimental driven

Industrial application and scale-up across 12 projects, 8 APIs up to 5L reactor volume / 450g product scale

INTEGRATED FILTRATION AND WASHING MODELLING

To facilitate integrated end to end pharmaceutical manufacturing using digital design, a digital tool capable of transferring material property information between operations to predict the product attributes in integrated purification processes has been developed. In-house validation using different washing scenarios for mefenamic acid and paracetamol as representative isolation processes has been performed. The gPROMS model has been translated to a Tier1 partner for validation using industrial experimental data, with the aim of identifying the minimum criteria a filtration and washing model needs to simulate experimentally verified isolation outcomes.

KEY OUTPUTS:

20 Expert training attendees, across 2 workshops

1 Technical support report shared

3 Conference contributions and 1 paper in draft form

1 Integrated filtration and washing gPROMS model with 6 different modes

CMAC Tier 1 Partners

By the end of 2021 we had 7 Tier 1 partners following our membership renewal. This includes 2 new partners Chiesi and UCB who we are delighted to welcome to the CMAC community. Working in close partnership with our partners we have established a vibrant portfolio of pre-competitive multi-disciplinary collaborative research, training and translation projects which has been integral to the success across the past 10 years.

We have developed this further, working with our partners, to build the next phase of the Centre, geared to deliver benefits to all partners and provide value to the wider society and, ultimately, patients.

CMAC, as part of the University of Strathclyde's strategic partnership with CPI, is strategically active in some specific translation to industry priorities with MMIC. We work closely with Industrial partners in a range of collaboratively funded, high TRL activities, such as the Industrial Strategy Challenge Fund Made Smarter Digital Design of Advanced Pharmaceuticals. We are also part of the UK's Medicines Manufacturing Industry Partnership and Medicines Manufacturing Special Interest Group.

Tier 1 Membership Benefits

- Access to world class facilities
- Peer-to-peer knowledge sharing through the Technical Committee
- Engage with Tier 2 network PhD placements within industry
- Industry CPD / Placement at CMAC
- Collaborative Core Project outputs translated to industry
- Shape the forward Hub Research Programme
- Access to expertise in crystallisation, characterisation, morphology, analytical etc. fields
- Exclusive member networking events
- Proprietary Confidential Projects or Collaboration Models
- Recruitment of CMAC trained researchers PhD mentorship
- Access to funding opportunities

Tier 1 Members

AstraZeneca

Chiesi

Lilly

ucb

Pfizer

Roche

Takeda

CMAC Tier 2 Partners

CMAC's vibrant Tier 2 community consists of 17 members spanning digital solution/data analytics, advanced manufacturing platform providers, consulting firms and specialised contract research organisations. The formal partnership between CMAC and each respective Tier 2 aligns with mutual and strategic objectives. Members continue to benefit from:

Tier 2 Membership Benefits

- Engagement with leading academics and the Tier 1 community to deliver industry focused solutions
- Exclusive member networking events
- Showcasing equipment and software in our facilities
- Access to expertise across crystallisation, drug product, and advanced analytical solutions
- Opportunities for collaborative funding
- Recruitment of CMAC trained researchers

2020/2021 Highlights:

Huxley Bertram: In 2020, CMAC and Huxley Bertram activated an integrated service offering for the compaction simulator featuring a bespoke link with in situ terahertz measurements. A number of external projects have been completed and are currently in progress as a result of this partnership.

Clairet Scientific: Clairet Scientific has joined the industrial steering team on a Tier 1 pre-competitive Core Project. Clairet will contribute their expertise in complex calibration approaches for spectroscopic measurements to the project team.

Laminar and Analytik: The Laminar LCTR platform, commissioned in our facilities this year, features a unique mixing environment well-suited for crystallisation processes. CMAC will be exploring the LCTR platform across our research programme and external projects.

Please get in touch to find out more about Tier 2 benefits and becoming a Tier 2 partner: info@cmac.ac.uk
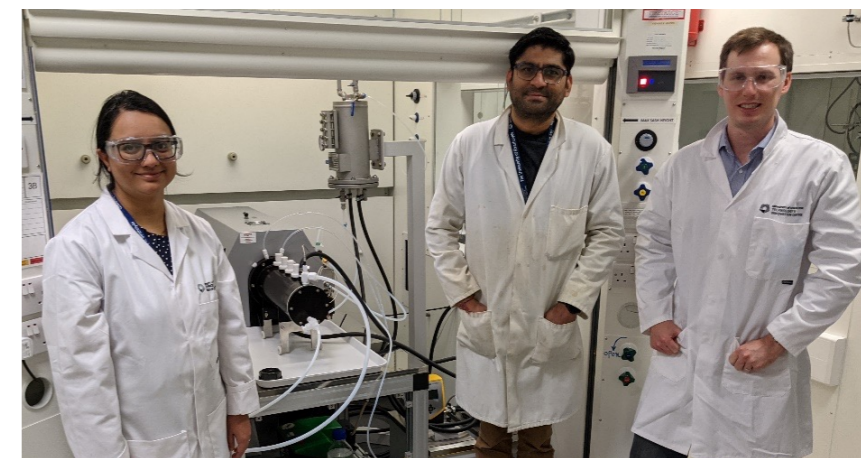
Commissioning of the Laminar LCTR platform

analytik / Laminar

anatune — Collaborate · Innovate · Automate

AWL inspiring innovation

Britest

CCDC advancing structural science

CherryCircle / QbDVision

CLAIRET SCIENTIFIC LIMITED

EDEM / ALTAIR

Huxley Bertram

M-STAR SIMULATIONS

NuTech SOLUTIONS

PERCEPTIVE ENGINEERING an Applied Materials company

pwc

SIEMENS

SNAPDRAGON CHEMISTRY

Technobis crystallization systems

ThermoFisher SCIENTIFIC

Industry Engagement with CMAC Researcher Community

PHD PLACEMENTS WITH CMAC PARTNERS IN 2020-2021

Across 2020/21, CMAC continued to deliver valuable tangible benefits to our industrial partners through PhD Placements. A total of 6 PhD Placements took place, 5 were virtual and 1 was on-site. These involved experimental and modelling focused projects cutting across smart formulation, particle engineering & isolation, smart crystallisation, and advanced characterisation research themes.

Topics included:

⚙ Washing process workflow development and implementation

⚙ Fused deposition modelling 3D printing

⚙ 2D population balance modelling for process optimisation

⚙ Statistical analysis of PXRD

⚙ CFD modelling

Highlight – Muhid Shahid's placement with AstraZeneca

CMAC PhD Researcher Muhid Shahid completed a placement with AstraZeneca in 2021. Muhid's placement project extended the application of the constant rate filtration/washing approach developed in his PhD to optimise the washing of a complex and challenging pharmaceutical product. A washing workflow was developed as part of the placement project. The workflow can be applied to process

development, helping to improve the control of impurities, enabling right-first-time manufacture and the potential to improve the sustainability of processes. This has the potential to prevent out-of-spec material on manufacture, hence preventing any rework or firefighting during development. This is estimated to save up to $100k to $1M per project.

"This placement was a great experience, allowing me to transfer and assess the skills and knowledge I have gained during the course of my PhD and translate it on an industrial compound. Even though it was a remote placement, the team at AstraZeneca made sure to make me feel included in the "company experience". I was able to experience at first-hand the collaborative and science led nature of the work carried out in the company, making it a very pleasurable experience."

MUHID BIN SHAHID, PHD RESEARCHER (CMAC)

"Muhid has pushed forward the boundaries of our understanding of washing of pharmaceutical compounds providing us with a new method to assess and optimise washing development, applying it to a relevant commercial compound. Muhid actively contributed to the team and provided valuable insight from his academic research and collaborated closely with AZ specialists in order to build his skills and deliver his project. Muhid also overcame the challenge of working remotely through clear communication and a structured approach to his project work. It was great having Muhid on the team and his success is reflected in our offering him a permanent role within the organisation."

COLM COTTER, PROCESS ENGINEERING TEAM MANAGER, ASTRAZENECA

Mentor Groups

CMAC Tier 1 industrial colleagues provide support, feedback and steer over 40 PhD students across various disciplines.

With a large number of students across 7 universities, mentor groups seek to promote links across the researcher community, facilitating industrial input, context and translation pathways. The mentor sessions run as open discussions, inviting comments and developing relationships throughout researchers' PhD projects.

Current groups by topic:

Advanced Materials Characterisation	Digital Platform
Primary Processing	Primary to Secondary Processing

Mini Symposia 2021

Building on the mentor groups, CMAC successfully hosted a Mini-Symposia Series dedicated specifically to PhD researchers and Tier 1 industrialists (June 2021). This included flash poster presentations and 1:1 networking, developing connections and showcasing research excellence, in spite of the global pandemic.

89 INDUSTRIAL ATTENDEES
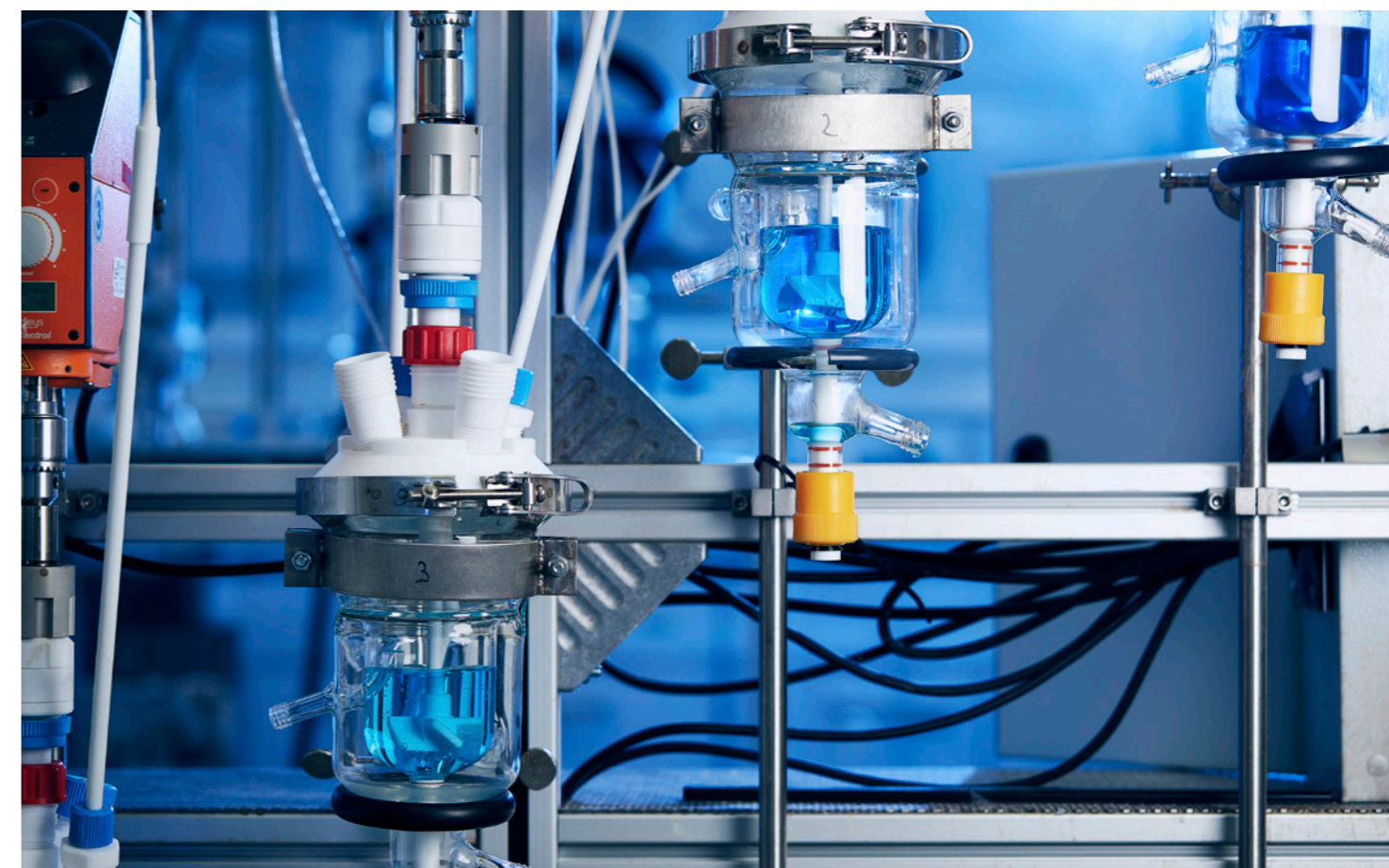
Outstanding Skills Development

"CMAC has a leading training programme, recognised for uniquely serving the talent pipeline for the medicines manufacturing sector. Training and development offerings include an MSc in Advanced Pharmaceutical Manufacturing, an Industrial PhD Cohort Programme and development of Early Career Researchers (ECRs). Continuous professional development and a wide range of transferrable skills opportunities are available to all career stages of staff regardless of career path or stage.

A highlight of 2021 was the Mini Symposia Event. PhD researchers presented 31 posters and oral presentations, combined with 1:1 networking appointments in break out rooms, to Tier 1 industry partners. This provided opportunities for industry mentors and students alike to strengthen relations and gain enhanced understanding of research topics. The symposia was extremely well received by industrial members, academics and students and will be a regular event in the CMAC calendar going forth. The online training component introduced last year for PhD students has been further enhanced this year. Blended hybrid approaches have been adopted and will be made more widely available across research staff in the Centre.

Additionally, a major achievement for the Centre was the award of the DM² programme. Part of this project will focus on developing digital skills necessary for medicines manufacturing and you can read more in the DM² section (pages 44-45).

Overall it has been another amazingly successful year for the Skills Team and students. We have had 17 students complete their doctoral studies in 20/21, moving on to a range of outstanding international academic and industrial destinations. I would also extend a warm welcome to a fresh cohort of 14 students that joined join in 2021. I wish all every success with their future careers."

Dr Andrea Johnston,
CMAC Associate Director

"The demand for multidisciplinary talent is uniquely served by CMAC"

CMAC INDUSTRY PARTNERS

- World-class training programme uniquely placed to address the interdisciplinary challenges in pharmaceutical manufacturing

- Delivering the next generation of highly skilled researchers and future workforce that will drive the transformation of advanced pharmaceutical manufacturing

In CMAC, skills development is tailored to train cross-disciplinary researchers ready to move into world-class academic research and industrial positions, as their first destination after CMAC. The bespoke training programmes are aligned to the Hub research vision and informed by the needs of industry partners. The CMAC researcher community benefits from a vibrant and dynamic 'ecosystem' of leading academic expertise across multiple disciplines, with access to world-class facilities, and contributions from leading industrial partners. Researchers are empowered through training and support to develop technical and transferrable skills, build networks and collaborations, and find innovative solutions within their research themes.

CMAC has a distinctive training programme on offer across all levels:

- MSc in Advanced Pharmaceutical Manufacturing

- CMAC Industrial PhD Programme

- Early Career Researcher Development

- Transferable skills training for staff and students

MSc TRAINING

The MSc in Advanced Pharmaceutical Manufacturing has been delivered at The University of Strathclyde since 2013. The course is aligned with CMAC. The curriculum has been devised in consultation with our industry partners and is delivered by CMAC academics and industry guest lecturers. This course is designed to produce highly-skilled graduates in continuous manufacturing science and technology to meet the growing demands for expertise in this area, with graduates trained to take up jobs in food, chemical, pharmaceutical industries or continue in academia. It's supported by academic staff from across the University, six academic partners and CMACs strategic industrial partners AstraZeneca, Pfizer, Eli Lilly, Takeda, UCB and Chiesi.

CMAC Industrial PhD Programme

CMAC's flagship PhD programme combines dynamic, cross-disciplinary training, with pioneering research projects informed by the needs of our strategic industrial partners. Our programme is aligned with the EPSRC Future Manufacturing Research Hub visions and benefits from access to our world-class laboratory and training facilities. Our bespoke PhD programme offers a vibrant, multi-disciplinary experience with equal emphasis on researcher development and academic research projects, which run in parallel throughout the entirety of the PhD research studentship. All students undertake a more formal training programme during Year 1, consisting of five weeks at the University of Strathclyde, including a week-long residential Summer School. This is delivered by our leading academic and industrial experts, and provides significant theoretical knowledge, hands-on laboratory skills and, a range of vital transferrable skills; equipping each student with the fundamentals to succeed and progress to the research orientated stages of their PhD research programme. CMAC provides a unique cohort experience, creating a lasting network and community of researchers that can support each other throughout their time with CMAC and into their future careers. Our unique PhD Mentorship programme brings together our research and industrial communities in an informal forum designed to provide support and insight to our PhD students. Our students are mentored by leading industrialists throughout their studentships providing them with industrial relevance, context, project advice and opportunities for network building. These professional relationships are further enhanced towards the final stages of the PhD programme, when students have the opportunity to undertake an innovative industrial placement at one of our Tier 1 strategic pharmaceutical partners. These placements provide our students with vital industrial knowledge and experience working within a Global Pharmaceutical company, thereby helping to shape the research projects and future career aspirations of each student.

- 14 new students in 2021 Cohort
- 6 student placements in 2021 (5 virtual and 1 on-site)

RECRUITED	IN STUDY	GRADUATED

RECRUITED
- 133 students
- 10 universities
- 30 countries
- 25 academic supervisors

IN STUDY
- 42 students
- 5 universities
- 41 industry mentors

GRADUATED
- 91 students
- 400 research years
- 50% gender ratio

- 100% recruitment rate
- 50% Industry
- 45% academia
- 3 continents
- >50 organisations

Demonstrating relevance of training through talent pipeline high transition to industry roles and prestigious academic positions

CMAC FUTURE MANUFACTURING RESEARCH HUB
Developing Talent for Future Medicines Manufacturing Leaders

Air Products	Communications	Jansen
Almac Group	Roche	Pharmaceuticals
Cambrex	UoSheffield	CMAC Hub
AstraZeneca	GSK	
Chameleon	PSE	

EARLY CAREER RESEARCHER DEVELOPMENT

Early Career Researchers, (ECRs), spanning the CMAC portfolio of UKRI, industry or facility funded research activity have access to a wide range of a career development opportunities. As part of their core activities, ECRs receive training on equality, diversity and inclusion, data management, open access publications, grant writing, routes of innovation and IP awareness. Whilst many already have existing skills in this space and represent champions in their fields and role models, our Early Career Researchers are offered formal training in various key areas, particularly project management, scenario planning and multi-criteria decision analysis. These concepts are reinforced throughout with for example, workshops with Tier 2 companies such as Britest and PWC. Tier 2 partners generally form a strong platform for contributing to ECR training and deliver hands-on, 2-3 day workshops. These workshops include, but are not limited to, solid-state prediction tools from CCDC and particle imaging analysis from Huxley Bertram, basic and advanced process modeling from PSE and process control methods by PEL. ECRs also engage with industry colleagues through a variety of mechanisms including mentor groups, events and Impact Acceleration Account work and are strongly encouraged to submit applications to CMAC Skunkworks programme to develop their ideas for innovation, thereby supporting their individual career development opportunities. CMAC is developing a formalised training and development programme, bespoke to individual early career researchers, to build upon the development opportunities already in place.
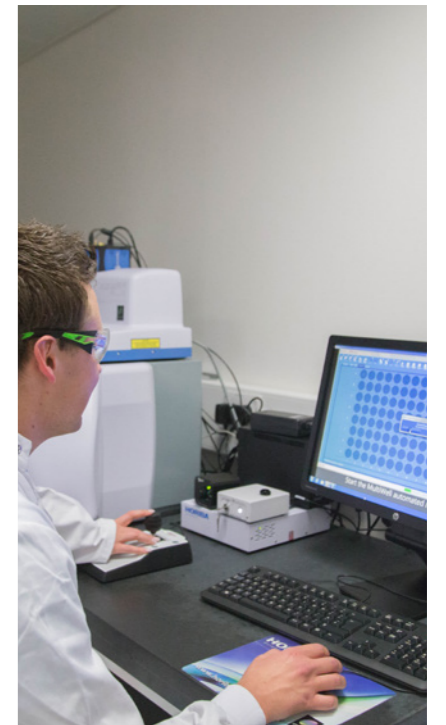
TRANSFERRABLE SKILLS TRAINING FOR STAFF AND STUDENTS

All of CMACs partner universities are signatories of the Researcher Development Concordat (2019) which is supported by the UKRI.

As such, CMAC is committed to ensuring we promote a positive research culture that supports and enables individual researchers to realise their full potential. Transferrable skills are widely recognised as an essential part of fulfilling and successful careers. Such skills are integral to CMAC staff and students, given the cross-disciplinary and translational nature of CMAC and the requirement to be agile and flexible whilst working within this environment. Emphasis is placed upon enhancing the key transferrable skillsets appropriate to all career stages within CMAC, including: **Problem solving, Analytical Reasoning, Critical Thinking, Leadership, Adaptability, Teamwork, Communication, Organisation.** Transferrable skills are not only achieved through daily research activities but are delivered through workshops, formal training events, and seminars e.g. a Responsible Research and Innovation seminar will be delivered by the Strathclyde Business School to all of CMAC's 2021 PhD cohort.

In CMAC, we ensure that our PhD students have their informal training rewarded and recognised. One example is the PGCert programme at the University of Strathclyde, which generally can be broken down into the following areas: Researcher Knowledge and Intellectual Abilities; Personal Effectiveness; Researcher Engagement, Influence and Impact; Governance and Organisation. Evidence is uploaded by students throughout their PhD programme and assessed at intervals, resulting in a formal qualification in Post Graduate Certificate in Researcher Development awarded alongside their Doctorate.

World Class Facilities

The CMAC facilities at the University of Strathclyde remain at the forefront of all our activities and offer unparalleled research capabilities. Thanks to a government uplift award of £0.5 M, allocated as a result of UKRPIF capital funding in 2014, there have been significant investments this year in X-ray, crystallisation and isolation equipment in addition to new initiatives in the automation and digital space.

Through our Tier 2 partnership with Laminar, a new processing unit based on Taylor Couette technology is now operational. And through the EPSRC Digitial Medicines Manufacturing Research Centre (DM²), there are initial developments in the drug product space.

A dedicated National Facility team, including a number of highly skilled specialists are on-hand to provide services and training, in addition to supporting and maintaining our world-leading instrumentation

Dr Thomas McGlone, Technical Operations Manager

NATIONAL FACILITY 2021 OUTPUTS:

12 process development / particle engineering projects

10's of Kgs produced & delivered for clients to demonstrate PoC

4 CMAC workflows applied to client assets

5 SMEs supported through analytical & consultancy projects

>25 research staff/ programs supported

CMAC National Facility

UNIVERSITY OF STRATHCLYDE

The award winning CMAC National Facility at the University of Strathclyde has unparalleled research capabilities to identify, understand, monitor and control critical aspects of advanced manufacturing research. The facility is in the fortunate position of being closely aligned with the latest research in innovation, which provides an efficient means of translation to industry. These translational services are provided by a dedicated team from the CMAC National Facility. These services include a comprehensive suite of high-value continuous processing equipment, novel monitoring and control systems and extensive off-line characterisation capabilities.

Academic Support

CMAC is built upon a collaborative ethos whether working with multidisciplinary local academic teams or international researchers. The National Facility team play a critical role in supporting this value whether by working to support individual researchers to access and use the facilities or in the provision of research services. The team continues to support key ongoing CMAC portfolio projects, providing key operational and technical support , including for example the CMAC Hub mefenamic acid MicroFactory project.

Robotics

We are in the process of implementing a Kuka KMR iiwa with mobile platform into a Crystallisation Data Factory where new and existing instrumentation will be integrated via automated solutions and intelligent process design. Standard 'work-horse' equipment will be connected and automated, removing routine, manual steps and allowing ca. 1000 data rich experiments to be carried out per month. These experiments will sweep through the physicochemical operative space from molecular to solubility and kinetics, to particle growth, agglomeration and fouling.

ToF-SIMS Workshop and Feasibility Call

The CMAC National Facility held an online Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) workshop and put out a call for feasibility studies using the technique. Speakers from CMAC and the National Centre of Excellence in Mass Spectrometry Imaging (NiCE-MSI) at NPL presented a general overview of the technique, examples from previous CMAC projects, case studies and a discussion around current areas of research using ToF-SIMS. The workshop had 14 attendees and 5 feasibility projects were selected.

Industry Access

We have continued to optimise the translation of the core research outputs into our industrial partners and clients. Over the last year the team has worked on a broad range of projects such as: in-silico assisted solid state screening & crystallisation process design, particle engineering via spherical agglomeration, amorphous precipitation & characterisation underpinned by outstanding analytical capabilities. A successful case study was completed with ENOUGH and IBioIC into analytical techniques for determining fungal morphology and nutrient feed composition in a food application. See: https://www.ibioic.com/case-study-database/analytical-techniques-for-fungal-morphology-and-nutrient-feed-composition-in-a-food-application

Work with us

- To conduct applied research in process development, particle engineering and advanced analytical services
- To engage with a dedicated team of highly skilled development & characterisation scientists
- To gain access to world class manufacturing research facility and the extensive equipment capability

Bawuah, P.; Markl, D.; Turner, A.; Evans, M.; Portieri, A.; Farrell, D.; Lucas, R.; Anderson, A.; Goodwin, D. J.; Zeitler, J. A., A Fast and Non-destructive Terahertz Dissolution Assay for Immediate Release Tablets. Journal of Pharmaceutical Sciences 2021, 110 (5), 2083-2092. https://doi.org/10.1016/j.xphs.2020.11.041

Laskar, P.; Somani, S.; Mullin, M.; Rothwelle, J. Tate, R.J.; Warzech, M.; Bowering, D; Keating P.; Irving, C.; Leunge H. Y.; Dufès C., Octadecyl chain-bearing PEGylated poly(propyleneimine)-based dendrimersomes: physicochemical studies, redox-responsiveness, DNA condensation, cytotoxicity and gene delivery to cancer cells. Biomater. Sci., 2021, 9, 1431-1448. https://doi.org/10.1039/D0BM01441A

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Warzecha, M.; Florence, A. J.; Vekilov, P. G., The ambiguous functions of the precursors that enable nonclassical modes of olanzapine nucleation and growth. Crystals, 2021, 11 (7). 738. https://doi.org/10.3390/cryst11070738

TO FIND OUT MORE CONTACT:
info@cmac.ac.uk

Facilities at Spokes

CAMBRIDGE - IFM

The Centre for International Manufacturing team at Cambridge develops general purpose supply network design frameworks and tools with the view of bridging disciplinary silos.

These tools are embodied in a physical "Interactive Supply Network Design Lab" facility. Within the facility, a facilitator engages with small groups of experienced practitioners through a Supply Network reconfiguration decision process underpinned by real-world data, with the aid of multi-user interactive touch screen tables, showing multiple layers of data visualisation and analysis enabled by industry-grade software tools. Future state network designs are explored through a Visual-Interactive approach from a tactical decision-making perspective, with participants experimenting 'live' with underlying assumptions.

The interactive and engaging nature of the network design process, from unit operations to global manufacturing networks, challenges the normative approach where specialist modelling is independently carried out and then 'thrown-over-the-wall' to management. Rather, the facility helps industry explore future value network configurations which, when aligned with a series of advanced manufacturing technology interventions, enable alternative routes to production and delivery to end-users.

The facility has been used on a number of occasions across different industry audiences including FMCG, Consumer electronics/3DP and Pharmaceutical compounds. For CMAC the facility underpinned the exploration of viable combinations of MicroFactory modular units to assist with location decision, scale of operations, implications on responsiveness and inventory/service level.
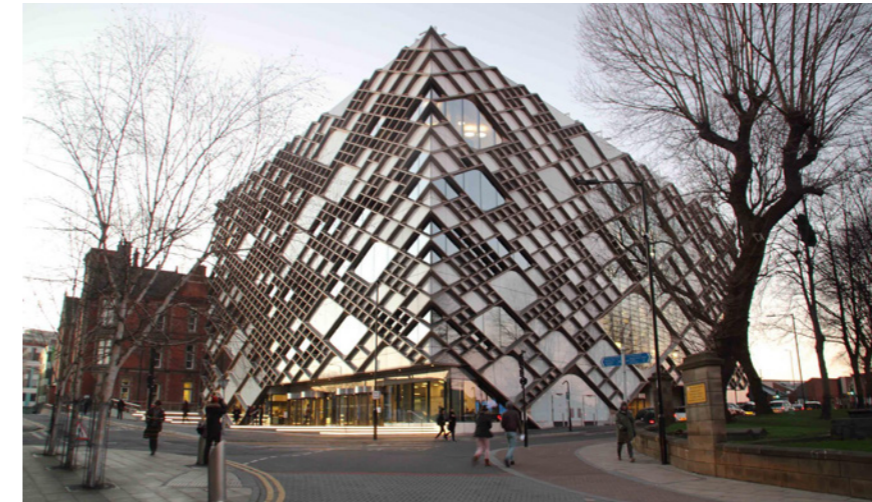
DiPP @ Sheffield

The Diamond Pilot Plant (DiPP) at The University of Sheffield has a state-of-the-art facility, The Diamond, which is a multi-disciplinary teaching space.

It houses a Pilot Plant which tests integrated processes with simulations and control systems in a safe, product-oriented environment, and a virtual and augmented reality lab which will be used to train researchers for the future.

Diamond-Leeds SAXS (DL-SAXS) Facility

Through EPSRC Strategic Equipment funding, the CMAC spoke University of Leeds and Diamond Light Source have jointly installed a new state-of-the-art small angle X-ray scattering (SAXS) facility at the UK Harwell Science and Innovation Campus. The facility provides the UK user community year-round access to nano- and mesoscale process and product characterisation, for a broad range of systems, including soft matter, polymers, biomaterials and formulations. DL-SAXS is a multi-user and multidisciplinary, providing more than 160 days of experimental beamtime per year. The facility encourages and supports the development of inline process research applications and provides training for the next generation of SAXS users. It serves both fundamental and applied research communities, including use for industrial users. It will act as a hub for strengthening and connecting activities to other SAXS facilities in the UK, and support users in the design,

application and preparation of SAXS/WAXS experiments with cutting-edge X-ray scattering techniques at Diamond Light Source, most importantly those available at the I22 SAXS beamline.

The facility is based on a Xenocs Xeuss 3.0 Small- and Wide Angle X-ray Scattering (SAXS/WAXS) instrument, which provides a platform for advanced materials characterisation as well as in situ and operando experiments under process and synthesis conditions. Strategic emphasis is placed on the development of new sample

environments and on feasibility testing prior to synchrotron SAXS experiments. Novel optics combined with scatterless-slit collimation facilitate nanoscale structure analysis from 0.1 to 500 nm. The metal-jet (Gallium alloy) X-ray source provides very high photon flux at 9.2 keV and is complemented with an X-ray micro-focus source at 17.5 keV (molybdenum). This not only allows the investigation of a wide range of processes and products, but also facilitates the integration of sample cells equipped with highly absorbing window materials, such as high-pressure sample environments.

Contact: **diamond-leeds-saxs-facility**

Innovation Spoke Facilities

Diamond Light Source

CMAC has access to the Research Complex at Harwell and Diamond Light Source on the Harwell Science and Innovation Campus, through academic spoke partners at the University of Leeds. There are CMAC researchers from the University of Leeds who are based at Harwell for some or all of their time. The facilities give capability to undertake advanced measurements at all length scales, for both surface and interface analysis, can use contrast agents and can undertake process studies: in situ / operando / in-line.

MMIC

The University of Strathclyde is a strategic partner in a new £56 million UK Medicines Manufacturing Innovation Centre (MMIC), which will revolutionise the way medicines are manufactured. The world-first, industry-led MMIC will offer pharma companies, from start-ups through to multinational organisations, a service to develop and adopt novel manufacturing techniques to adapt into their own manufacturing processes. The centre is to be located in Renfrewshire and will be operational in 2022. The project is led by the Centre for Process Innovation (CPI), in partnership with the University of Strathclyde, the Medicines Manufacturing Industry Partnership (MMIP), and founding industry partners, AstraZeneca and GSK. The university is leading the work package of the development phase of a next generation continuous direct compression digital test bed and demonstrator.

Supported by Scottish Enterprise (£15 million), UK Research and Innovation through Innovate UK (£13 million), GSK and AstraZeneca (£7 million each), the MMIC is one of the first projects across the UK to receive funding from the UK's Industrial Strategy Challenge Fund.

CMAC Publications in 2021

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CMAC Governance Structures

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| CMAC Hub Management Committee |

| Hub Academic Research Group | Hub Academic Planning Meeting | CMAC Skills Committee | CMAC Technical Committee |

| Academic Team: Management Teams, Research Community, Project Partners |

Events | Training | Research meetings | Senior Team meetings | Project / WP meetings | Town halls | Creative@home | Skills & Training Committee | Comms Committee | Staff away days | Key Account Management | Social Committee

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Pressure-dependent In situ Monitoring of Granular Materials

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Community for Analytical Measurement Science (CAMS) funded Understanding long- term stability of solid pharmaceutical dosage forms

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Multidimensional particle characterisation from in situ sensor data Core Project

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Innovate UK Knowledge Transfer Partnership: Model-based Digitalisation Framework Development for Continuous Manufacturing Processes

University / Company	Name
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Partner	Siemens PSE

Innovate UK Knowledge Transfer Partnership: Industrial Workflows for the Application of a User friendly Mechanistic Modelling Toolkit

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Partner	Siemens PSE

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Calibration model development for in situ monitoring of solute concentration for anti-solvent crystallisation Core Project

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