Annual Review

2020

Engineering and Physical Sciences Research Council

CMAC FUTURE MANUFACTURING RESEARCH HUB

Contents

Introduction

"The 2020 Annual Review for the EPSRC Future Continuous Manufacturing and Advanced Crystallisation Research Hub (CMAC) marks the end of an unprecedented year for CMAC and all of our collaborators, partners and stakeholders. The impact of the COVID-19 pandemic on the way we work together, collaborate, plan and share our research has been significant, forcing the CMAC community to rapidly adapt and change almost every aspect of how we go about our manufacturing research, training, facilities and translation to industry programmes.

However, the response of all our staff, students, researchers, academic colleagues and industry partners has been fantastic. During the first lockdown in early 2020 our Hub research team focussed on accelerating our 'digital first' activities, developing new ways to deliver value from the information rich data and Digital Twin framework that has been a key focus of phase I of the Hub. New insights into continuous processes, improved workflows and predictive models were developed leading to an impressive body of research outputs during 2020 from our researchers across the academic teams in Bath, Cambridge, Imperial, Leeds, Loughborough, Sheffield and Strathclyde.

With laboratory work resuming in July, researchers have received superb support from our industry partners through mentoring and research meetings as well as the CMAC National Facility team, who have worked tirelessly to modify ways of working and facilities to allow ongoing and safe access to the research facilities. The team have welcomed a new cohort of PhD students and new staff to the Team. We held our first entirely virtual Open Day and planned and delivered international conferences and industry engagement events whilst many of the team continue to work from home. Moreover, in addition to the Hub research progress and new Phase II plans being finalised, our exciting portfolio of aligned manufacturing research has continued to develop. Highlights from this impressive array of projects are presented in the review. They range from low TRL research such as EPSRC ARTICULAR, our EPSRC strategic equipment awards and EPSRC Prosperity Partnership, through industrial research and translation via CMAC Tier 1 precompetitive Core projects, National Facility translational projects, MMIC Continuous Direct Compression Grand Challenge and the ISCF Digital Design Accelerator Platform (DDAP) through to SME engagement and networking with the ERDF Scout award.

This pandemic has brought the importance of medicines manufacturing research and innovation into sharp focus like never before, highlighting our needs to produce new therapeutics at scale, quickly, cost effectively and sustainably, and to have resilient and flexible supply chains to provide secure access to essential, generic medicines in times of emergency. Advanced manufacturing technology, digital transformation and a skilled pipeline of talented future leaders are crucial elements of addressing these needs and contributing to economic recovery. Through our world class collaborative programme, CMAC is committed to supporting these goals and to redouble our efforts to transform medicines manufacturing through advanced predictive development workflows, innovative digital technologies and Digital Twins and through MicroFactory based future supply chains.

As we look ahead to 2021 I, with all of my CMAC colleagues, look forward to having the opportunity to welcome you to one of our events, share more details on our work and to understand your interests and needs and work together in partnership to realise our shared goals."

Partners

ACADEMIC HUB AND SPOKES:

UKRI Engineering and Physical Sciences Research Council

University of Strathclyde Glasgow · University of Bath · University of Cambridge · Imperial College London · University of Leeds · Loughborough University · The University Of Sheffield.

TIER 1 INDUSTRY PARTNERS:

AstraZeneca · Bayer · Lilly · gsk · Novartis · Pfizer · Roche · Takeda

TIER 2 PARTNERS:

analytik · anatune Collaborate • Innovate • Automate · AWL Inspiring Innovation · blacktrace · Britest

CCDC advancing structural science · Clairet Scientific Limited · EDEM™ · Huxley Bertram

NiTech Solutions · M-STAR Simulations · Perceptive Engineering Ltd · PSE · pwc

CherryCircle · QbDVision · Snapdragon Chemistry · Technobis crystallization systems · ThermoFisher Scientific

INNOVATION SPOKES:

cpi · ICECUBES · Cancer Research UK · NPL National Physical Laboratory · diamond

MMIP · connected everything. · MHRA Regulating Medicines and Medical Devices · Scottish Enterprise

CMAC Overview

TRANSFORMING MEDICINES DEVELOPMENT AND MANUFACTURE

CMAC is an international hub of excellence for medicines manufacturing research. Our world-class facilities enable us to realise our ambitious research and exemplar technical translation activities and provide a nurturing environment for training the workforce of the future. CMAC's vision is to lead the world in advanced pharmaceutical manufacturing development underpinned by our MicroFactory and digitalisation strategies. Working in partnership with industry, its purpose is to transform current manufacturing processes into the medicine supply chain of the future.

Established in 2011, CMAC's vision has been developed through close collaboration with industry and the support of its Tier 1 partners: AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Roche and Takeda. A wide range of technology companies and innovation spokes form part of the CMAC community. CMAC is comprised of more than 100 staff and researchers, including academics, 20 post docs, 35 PhD students, 16 MSc students and an experienced support team. To date, we have saved companies in excess of £20M per annum and leveraged a £150M funding portfolio.

In 2017, the EPSRC CMAC Future Manufacturing Research Hub was launched. This seven year programme, led from the University of Strathclyde, involves academic investigators and research staff across 7 leading universities: Universities of Bath, Cambridge, Leeds, Loughborough, Sheffield, and Imperial College London. This programme is delivering predictive design tools and novel integrated continuous processing platforms for the supply of next generation high performance personalised products.

CMAC

- Delivers innovative solutions to address company-specific problems
- Creates commercial opportunities for start-ups and major global companies
- Produces a talent pipeline of highly skilled multi-disciplinary staff
- Influences policy, government, and regulators
- Collaborates with world class business and academia on an international basis.
- Drives novel approaches and options from supply chain improvement

SAVED COMPANIES ›£20M p.a.

7 LEADING UK ACADEMIC PARTNERS

MORE THAN 100 STAFF AND RESEARCHERS

9 CMAC ALUMNI WORKING AT TIER 1 COMPANIES

£25M CRITICAL MASS FUNDING FROM EPSRC

OUR VISION:

Transforming Medicines Development & Manufacture

OUR MISSION:

Transforming medicines manufacture, development time and cost to market through the use of Digital Twins and MicroFactories.

1 Develop continuous processes with 10g within a month enabling a tiered drug product approach.

Exploit production tools to accelerate product and process development.

2 Produce Digital Twins based on multiscale models.

Extract value from data and link multiscale models.

3 Demonstrate case studies and advocate business cases in development and manufacturing.

Demonstrate technical and operational benefits of digital tools and continuous processes.

4 Strengthen understanding of material attributes.

Pharmaceutical materials science underpinning stability, manufacturability and performance.

5 Paths to translation through Tier 1s, spin outs, ecosystem and MMIC.

Demonstrate impact of research through best in class translation and exemplary talent pipeline.

6 Strengthen position as Global Manufacturing Research Centre.

Attract global talent and grow funding base with cutting edge facilities.

FOCUS ON CORE PILLARS:

Research Excellence & Intensity

Outstanding Skills Development

World Class Facilities

Exemplary Translation to Industry

Productive partnerships driven by a collaborative, international outlook and regulator engagement.

External Environment

- Aging population
- Increasing cost of healthcare
- Outcomes based pricing
- Clinical advances
- Growth in emerging markets
- Cautious regulators
- Patient centricity
- Pressure on process development times and materials costs

SOURCES; KPMG, PHARMA OUTLOOK 2030; PWC PHARMA 2020

WHAT DOES THIS MEAN FOR MEDICINES MANUFACTURING?

Precision medicines driving smaller volume manufacturing and new distribution models

Adaptive and different trial design accelerating clinical and launch phases

Advance drug delivery and increasing molecular and process complexity

Continuous, miniaturised and flexible manufacturing platforms with real time process measurement and control

Advanced analytics and artificial intelligence supporting human decision-making

Digitalisation – embrace emerging technologies towards integrated design manufacturing & supply

Delivering sustainable processes

CONTINUOUS MANUFACTURING IS A CORNERSTONE

General summary of companies outlook towards continuous manufacturing.

90%

... see CM as important for the supply of their products in the next 5 to 10 years.

›80%

... consider their C-level to be well-aware about the importance of CM.

59%

... have an ambitious adoption strategy driving agenda with regulatory bodies, equipment providers, ecosystem partners etc.

17%

... consider their CM strategy as mature whereas CM strategy still at exploratory stage for all others; approximately 1/2 consider themselves early adopters.

2020 Highlights

PEOPLE

100 People in CMAC

18 CMAC Academics

20 PDRAs

35 PhDs

13 Technical Research Staff

DISSEMINATION

145 Papers since 2017

Business Insights published in 2020

20 Cover articles since 2017

>600 Engaged with Research Webinars

PUBLIC OUTREACH

13k Users

800 Followers

Outreach networks of thousands

11 Press Releases since 2017

16 Schools visited since 2017

2 Images of research winners

INFLUENCING POLICY

£30m Funding leveraged from Hub

18 Research grants leveraged from Hub

7 Policy documents

"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."

JON-PAUL SHERLOCK
CHAIR OF CMAC INDUSTRY BOARD AND AZ

"It's been a tough year, but the Hub has risen to the challenges impressively. Online events have been set up quickly and run smoothly, safe working has allowed some continuity in experimental activities and everybody has adapted to the new ways of working in very short order. I should also commend CMAC on its efforts to look after all of its researchers through stressful times."

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

Research Excellence & Intensity

“As we move into 2021, we look to complete phase I and transition to the next phase of the ambitious Hub project that will run until the end of 2023 (page 14). The Phase II plan builds on the core themes of Phase I, learning from our progress to date and further developing the role of predictive design and digital twins through an integrated Quality by Digital Design approach. We have also introduced a new theme alongside our focus on workflows, Digital Twins and MicroFactories in the form of smart development platforms or DataFactories. Our initial DataFactory focus in phase II is to establish an autonomous Crystallisation DataFactory combining robotics, automated experimentation and analysis with AI driven experimental planning to create a data-driven crystallisation development platform. The DataFactory will efficiently generate rich data describing key crystallisation parameters. These will be used to build a novel Crystallisation Parameter Database to inform a powerful predictive Crystallisation Classification System connecting molecular properties to crystallisation outcomes. MicroFactory based processes designed by rapid, model assisted process development for drug substance and drug product will address key manufacturing challenges. Our advanced characterisation and modelling activities will provide detailed insights into the fundamental transformations in systems of interest.

Academic colleagues and project partners have also established a portfolio of projects aligned with and informed by the Hub programme that deepen and extend the progress being made across priority areas in our industry co-created scope. Highlights from across the suite of projects across our research, equipment, translation and Facility projects are provided here including an update on the kick-off of the new ISCF funded Digital Design Accelerator Platform (DDAP) project (see page 12 for portfolio map).”

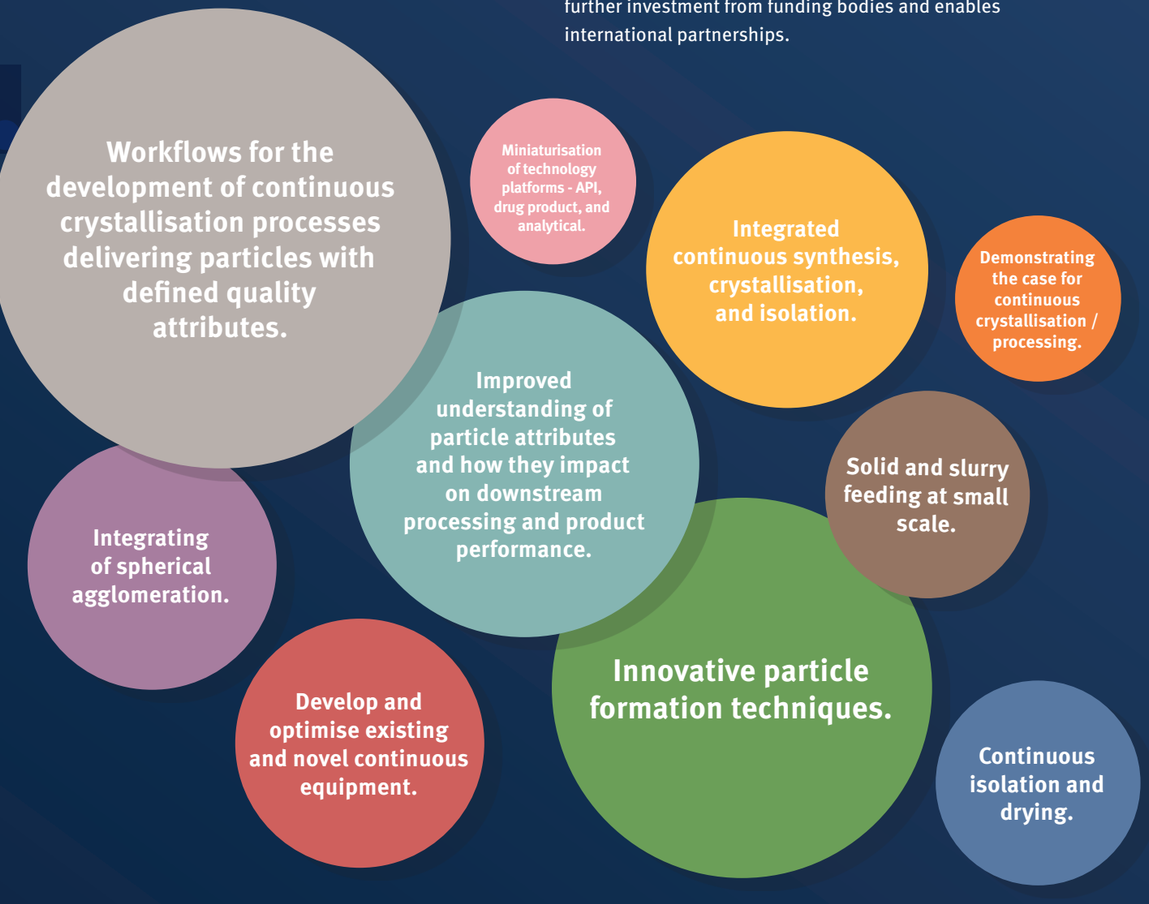
Professor Alastair Florence, CMAC Hub Director

Research Excellence & Intensity

CMAC’s leading advanced pharmaceutical manufacturing research programme is funded by the UK EPSRC’s Manufacturing Research Hubs flagship investment.

The Future CMAC Hub follows a Hub (Strathclyde) and spoke model (academic partners). This suite of partners has complementary expertise to deliver research with impact. The main thrust is to deliver manufacturing technologies that will enable industry to deliver better products, quickly, economically and sustainably.

This meets the industry demand for reduced time and costs for pharmaceutical development. The Hub platform leverages further investment from funding bodies and enables international partnerships.



RESEARCH ACROSS THE CMAC COMMUNITY IS DRIVEN BY INDUSTRY PROBLEM STATEMENTS

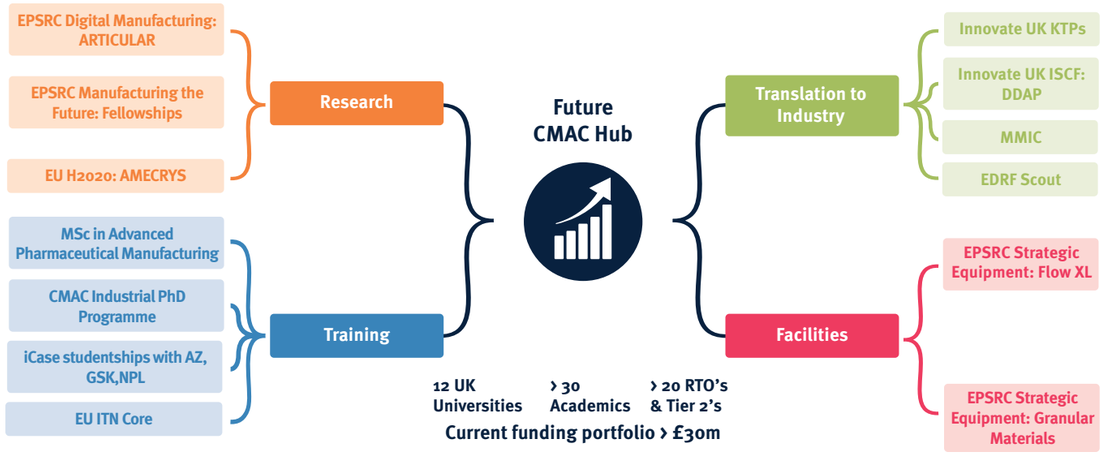
The diagram, above, shows the relative activity against the predominant problem statements, arising from CMAC Industry Roadmapping, 2017.

In 2021 The Hub moved to Phase II of the award (see page 14 for more information). Following on from this, the process of updating the Industry problems statements is now taking place as part of a CMAC Strategy Refresh that will be launched during the second half of 2021.

Research Portfolio

HUB ALIGNED PROJECTS

Collaborative Funding



The CMAC research portfolio comprises of around 75 projects that cover the CMAC research themes, including:

- Quality by Digital Design
- Digital Twins
- Workflow and model development
- Advanced measurement techniques
- Crystallisation classification system
- Manufacturability classification system
- Biorelevance performance classification system
- Primary and secondary MicroFactory processing, and
- Supply chain mapping

The individual projects are supported through the various initiatives shown in the portfolio diagram, and are underpinned by the Future CMAC Hub collaboration. The projects across CMAC are aligned and integrated where possible to allow us to exploit the rich value in the data being collected across our projects. This is a key aspect of our strategy to deliver new tools to support process development and control through rigorous understanding.

EPSRC CMAC Future Manufacturing Research Hub Programme

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.

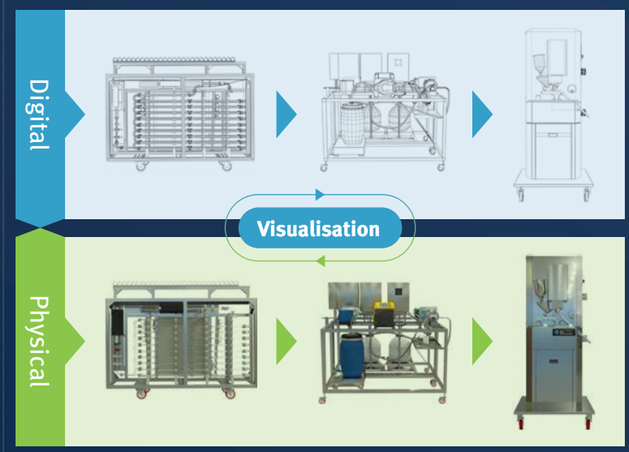
PROGRAMME VISION

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



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

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

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

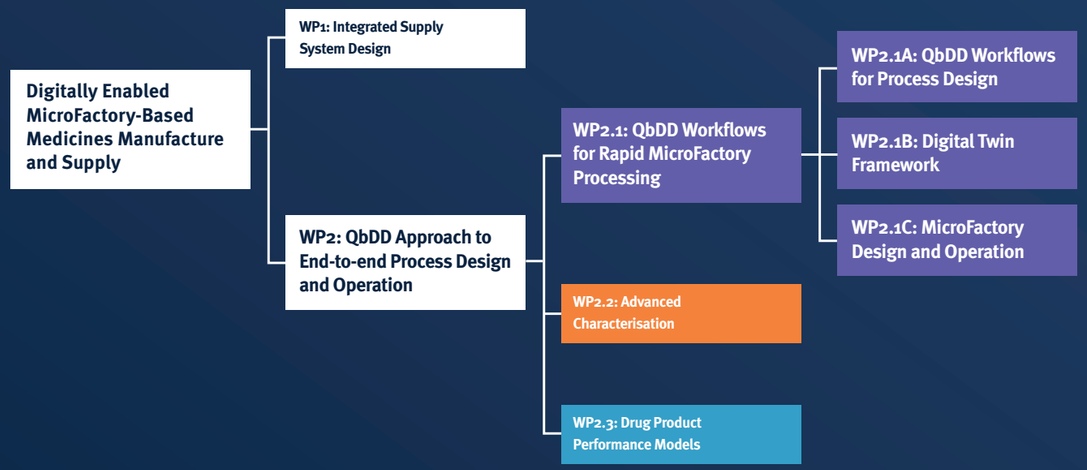
Phase II Grand Challenge:

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 remain highly relevant manufacturing research aims well-aligned with industry interests and needs and continue to frame the development of the Hub's Phase II research plan.

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



We maintain an emphasis on supply chain network design and identifying supply demands in Work-package 1 and incorporate Quality by Digital Design (QbDD) approach to end-to-end (E2E) Process design and operation as the overarching theme for Work-package 2 (WP2). 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 new grand challenge presents significant research questions with considerable potential to deliver impact from:

- 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 DP 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-NCE/API processes across the crystallisation, isolation and DP objectives in the QbDD Approach to E2E Process Design and Operation work-package.

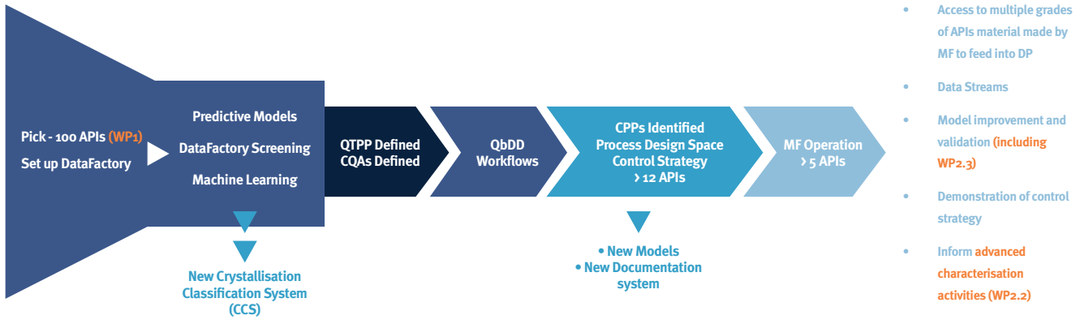
QbDD Approach to E2E Process Design and Operation (WP2)

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

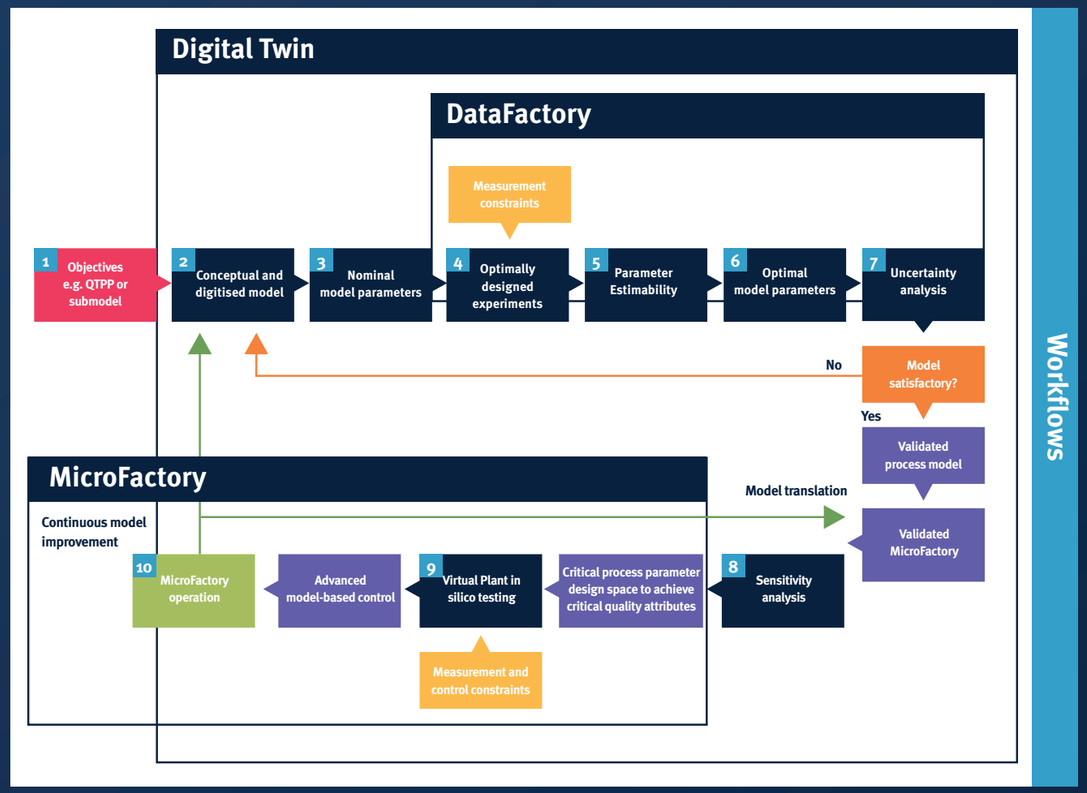


QbDD Workflows (WP2.1A)

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)



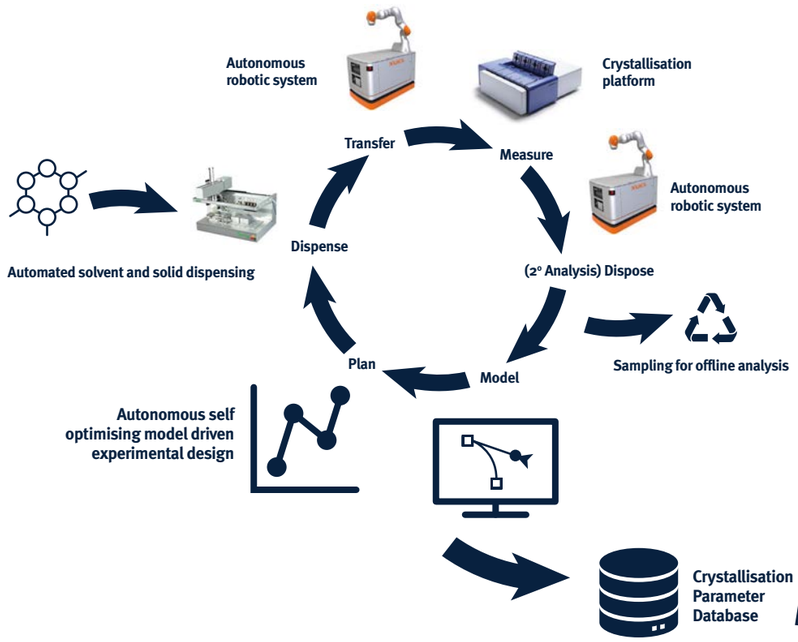
The above diagram shows CMAC Framework for Quality by Digital Design (QbDD). CMAC is developing an integrated workflow to ensure product QbDD and continuous manufacturing.

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



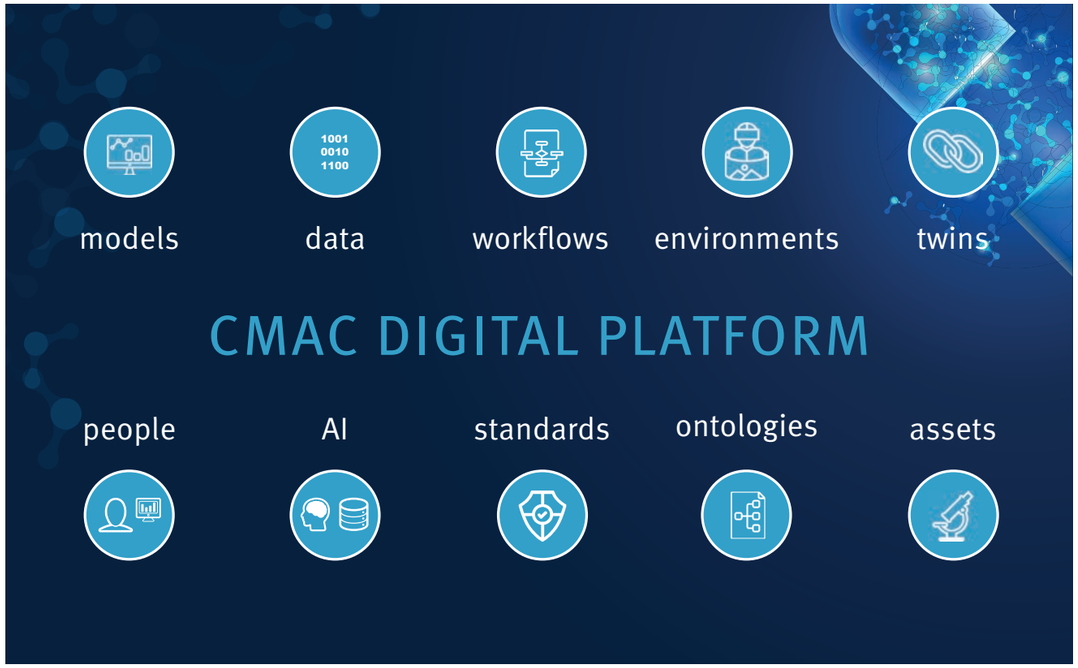
The Autonomous Crystallisation Classification DataFactory will automate experiments done on the Technobis Crystalline platform to deliver large structured data sets for interrogation by image analysis and machine learning.

It will use the Zinsser platform for dispensing solids and solvents and an autonomous robot to move samples round 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).

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. The Digital Platform supports the Digital Twins.



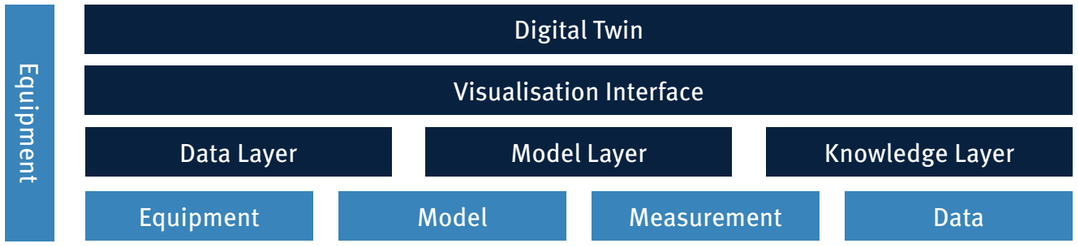
For Phase II of the Hub the DTs will combine the overarching digital definition of both the processes and products.

For example, we use the QbDD workflows (see page 16) 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.

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 (see page 41) 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 retrospectively by connecting CMAC models. 6 separate processes were modelled and integrated to allow design space exploration in real-time.

Digital Twin Framework



There is also ongoing work to provide user-friendly interfaces for the DTs. There are examples of VR (see images below) and 2D interfaces for DTs of the Easymax crystalliser and a twin-screw extruder that have been demonstrated at our Open Day and Showcase events in collaboration with the ARTICULAR project (see page 24 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). Also, data will be generated to inform the supply network analysis in WP1.

For API MicroFactories the default equipment we will use will be MSMPR, with integrated PAT-enabled closed-loop control of CQAs linked to continuous or semi-continuous filtration and washing stages with batch drying. The Drug Product MicroFactory manufacture will be done via polymer processing using extrusion-printing technologies to exploit existing infrastructure across the Hub partners.

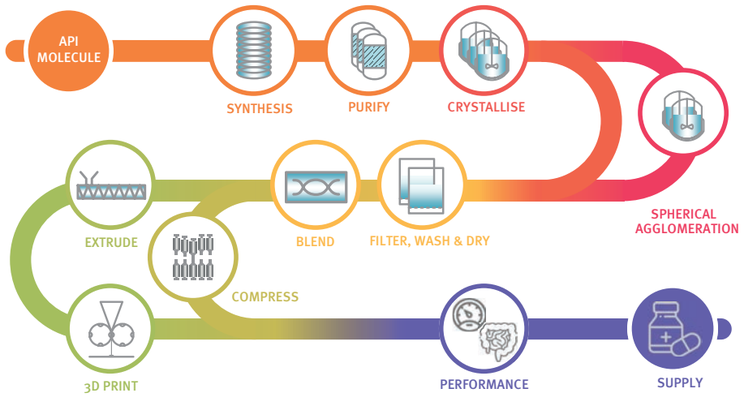
By operating within the design space identified by the DT, we will use the MF Platforms to deliver:

- Materials of different grades to illustrate predictive control or confirm failure modes/edge of process operating ranges
- Integrated API particle formation MF (purification, 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 will be 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 locally-available analytical tools provide ambiguous or no answers. The aim is to provide critical missing information required for QbDD and modelling, identification of mechanistic pathways in API formation, explore the molecular basis for solvent selection, and 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, 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.

Summary of Hub Phase I

RESEARCH OUTPUTS

Digital Design of Mefenamic Acid API Process

- End-to-end purification, particle engineering and isolation flowsheet built
- Flowsheets for individual continuous crystallisation, isolation and washing implemented in gPROMs
- Design space for process to make Mefenamic Acid API via continuous process simulated

Digital Twins

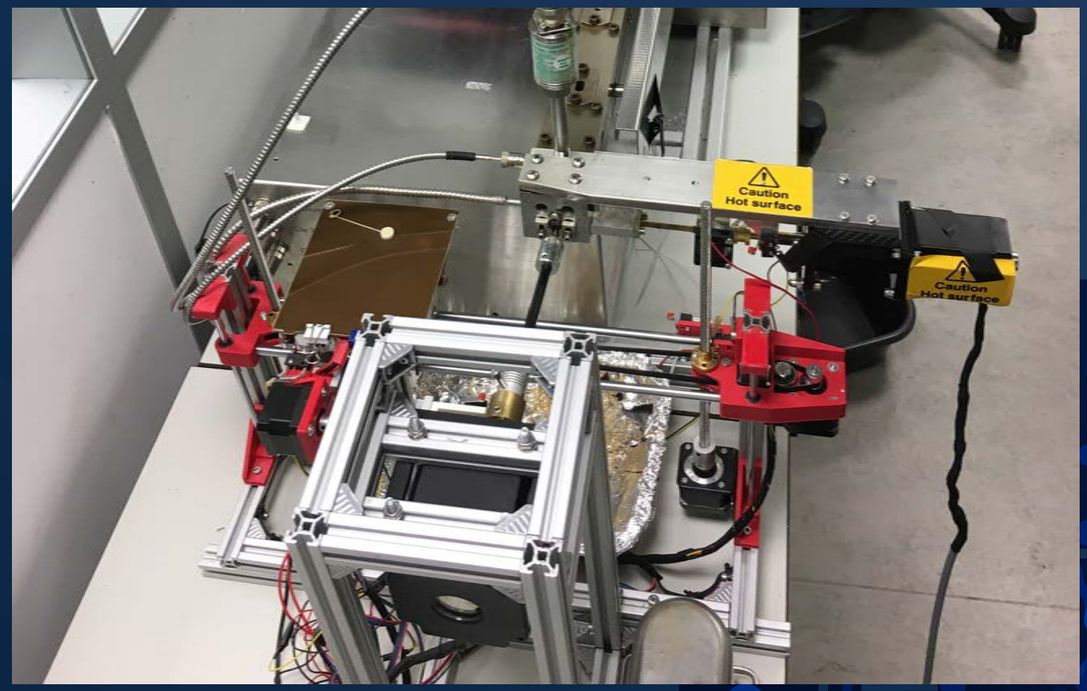
- Lovastatin primary and secondary process MicroFactory models and visualisation
- Easymax Training on VR and tablet developed
- Hot Melt Extruder VR and 2D graphics

MicroFactories

- Modular API MicroFactory assembled
- Novel combined Hot Melt Extruder and 3DPrinter unit developed and patent applied for

Platform

- Advanced Characterisation techniques used for study of particles and in situ experiments
- Digital platform established for phase II
- Expanded capability in predictive models for morphology, solubility, solvent selection
- Isolation models developed and implemented in gPROMs



Aligned Core Projects Funded by Industry

The Pre-Competitive Core Projects are funded by the 8 Tier 1 companies and are designed to develop translatable outputs to deliver impact in research areas aligned with the EPSRC Hub.

2020 PROJECTS

Spherical Agglomeration

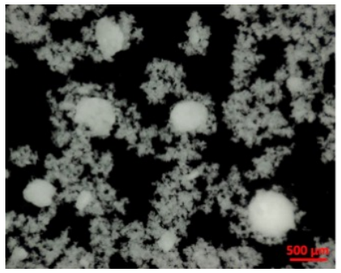
University of Sheffield and University of Strathclyde, 2-year project

- Developed a mechanistic understanding of spherical agglomeration (SA) process
- Tested scale-up robustness and impact of using agglomerates into oral solid dosage forms on dissolution rates, tabletability etc.

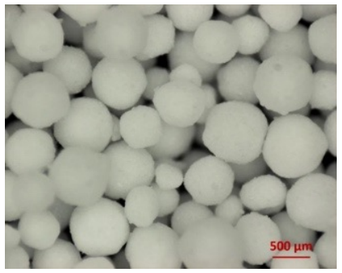
Translated Outputs: Training webinar delivered, detailed experimental report shared, workflow co-developed with the Hub research team and embedded into industry practices.

- Evaluation of the Effects of Bridging Liquid:Solid Ratios for Formation of Spherical Agglomerates

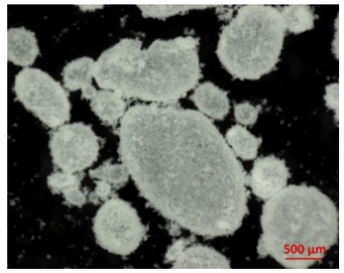
Micronised paracetamol particles suspended in heptane with water as bridging liquid



Not enough bridging liquid (‹0.7),



Optimal bridging liquid: solids ratio (0.7 to 0.8)



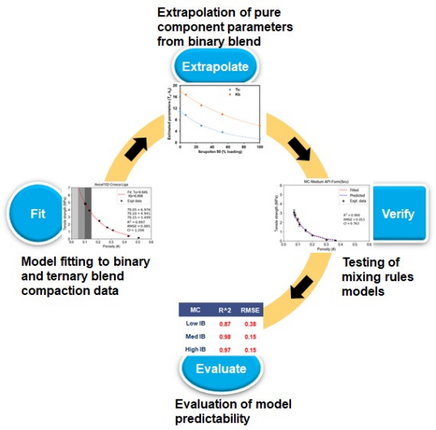
Too much bridging liquid (›0.8), paste formed

Materials Parameterisation Database Project

University of Strathclyde

- Mix of experimental and modelling work carried out to investigate whether input material properties can be used to predict compaction performance.
- Developed a predictive workflow for first-pass selection of formulation for (continuous) direct compression, based on parametarisation of models using material attributes as input.

Translated Outputs: Workflow developed, database of material properties established, predictive models built into Python and Matlab, training webinar delivered.

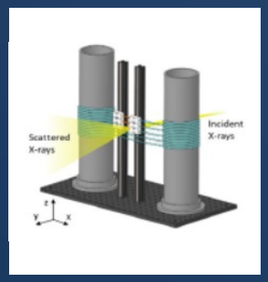


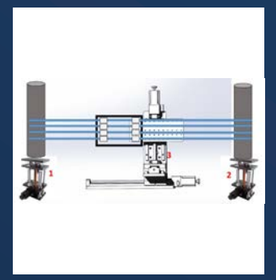
UKRI

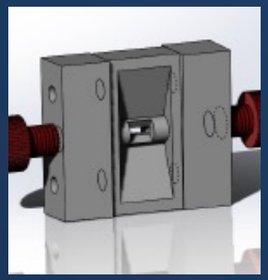
EPSRC

Flow-XI: 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-XI 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-XI 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 and it will be commissioned and available for user experiments during 2021.







Pressure-dependent In-Situ Monitoring of Granular Materials

A new Compaction Simulation Pilot Test Facility specified with instrumented dies and innovative process analytics for in-situ measurements using terahertz (THz) spectroscopy has been installed in CMAC's facilities in the last year (see also page 39). This fully integrated system is the first system in the world capable of in-situ monitoring of the physical and chemical changes of powder and granular materials under pressure using THz technology. The equipment opens up new research in 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 understanding fragmentation of pharmaceutical materials during compression and developing workflows for material-sparing experiments coupled with digital product design concepts. CMAC also launched a new partnership with Huxley-Bertram to support compaction simulation research and services.

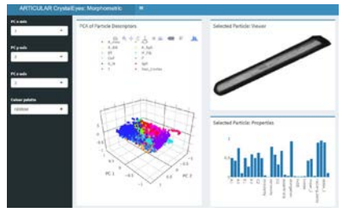
ARTICULAR
MEDICINES MADE SMARTER

EPSRC ARTICULAR 2020-21 update

ARtificial inTelligence for Integrated ICT-enabled pharmaceUticaL mAnufactuRing

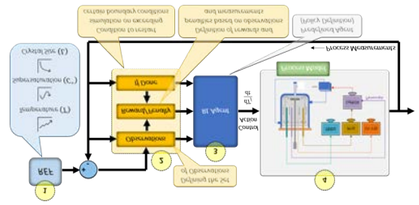
PROCESS DIGITAL TWINS

- Environment and process models for HME, tablet press and crystallisers maturing
- Integrating 24hr HME run data to complete Digital Twin demonstrator
- VR usability study to evaluate usefulness of advanced visualisation approaches coming in Summer 2021



CRYSTALEYES APP

- Unlock more information about particle shape
- Morphometrics analysis and description of particle shape complete
- Ability to spot and remove “bad” images that adversely affect downstream analysis



ARTIFICIAL INTELLIGENCE (AI)

- Novel applications of Reinforcement Learning (RL)
- Developed for trajectory tracking control of crystallisation processes
- RL vs Model Predictive Control (MPC) benchmarking underway

Engineering and Physical Sciences Research Council

THE GLASGOW SCHOOL OF ART

University of Strathclyde Glasgow

Loughborough University

The Cambridge Crystallographic Data Centre

BOOTH WELSH
Integrated Engineering Services

SIEMENS

PERCEPTIVE ENGINEERING LTD

Other Research & Translation

Medicines Manufacturing Innovation Centre - MMIC

FIGURE - AMIDS SITE, RENFREWSHIRE.

A new strategic partnership between the University of Strathclyde, CPI, AZ and GSK will create a new £56 million UK Innovation Centre. Sited in the Advanced Manufacturing Innovation District Scotland (AMIDS), the new industry-led Medicines Manufacturing Innovation Centre (MMIC) will offer pharma companies a unique service to develop and adopt novel manufacturing techniques. By transforming processes and technologies, the speed of bringing new drugs to market could improve drastically.

FIGURE – GERICKE CDC FEED MODULE

CMAC are leading one of the key grand challenges, “Development of a next generation digital test bed for continuous direct compression - CDC”. This project aims to simplify and reduce costs in drug product manufacture and development, through a reduction in processing steps and provision of digital design tools.

In the current phase, a novel modular system to enable development of CDC related materials science, process understanding and Digital Twins will be installed in the TIC building. In conjunction with pharmaceutical Industry partners, CMAC will design and operate the system. Gericke AG and Perceptive Engineering Ltd will provide the process and advanced process controls package.

Innovate UK Funded Projects

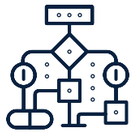
Digital Design Accelerator Platform to Connect Active Material Design to Product Performance

This Project is led by AstraZeneca. Future CMAC Hub academics Professor Alastair Florence and Professor Blair Johnston are Co-investigators.

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".

Model-based Digitalisation Framework Development for Continuous Manufacturing Processes

This Innovate UK Knowledge Transfer Partnership project is a collaboration between the University of Sheffield and Process Systems Enterprise (PSE, now a Siemens business). The aim of the 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 lead to the development of mechanistic models for continuous pharmaceutical manufacturing, successfully implemented in gPROMS Formulated Products software and validated using the continuous pharmaceutical manufacturing facilities at the University of Sheffield.



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.

Scottish Outreach (SCOUT) Project

ERDF SCOUT

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 not already have received ERDF support.

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 and the Industrial Biotechnology Innovation Centre, (IBioIC). SCOUT aims to accelerate and de-risk the growth of Scottish SMEs seeking or developing disruptive technologies.

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 for 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.

SCOUT project

Exemplary Translation to Industry

“CMAC is a world-class international hub for manufacturing research and training. Working in partnership with industry it transforms current manufacturing processes into the medicine supply chain of the future.

Our aim is an elevated level of awareness of benefits and opportunities for key stakeholders then implemented via co-creation, co-delivery, dissemination, training and finding routes to translate to higher TRL. Critical is to ensure our research strategy is consistently well informed by industry needs, prevailing government policies and emerging knowledge from the research base.

The critical mass of scientific operations, academic leadership, expertise, focus on accelerating adoption and delivering impact from our research has enabled CMAC to develop a portfolio of technologies that have now reached TRL 3-6 and continuing develop a suite of new technologies and capabilities at TRL 1-3 informed by the challenges and emerging needs of industry.

Our programme of activities offers a variety of routes to translation as well as our relationship with MMIC, and 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.”

Massimo Bresciani, CMAC Industry Director

Exemplary Translation to Industry

OVERVIEW

CMAC’s research program and translation to industry vision and plan is informed and developed through close collaboration with its industrial partners to provide answers to industry relevant questions and to drive technology transformation and implementation.

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

As such, activities are aligned across the innovation landscape, spanning multiple TRLs to address industry needs.

2020 Update

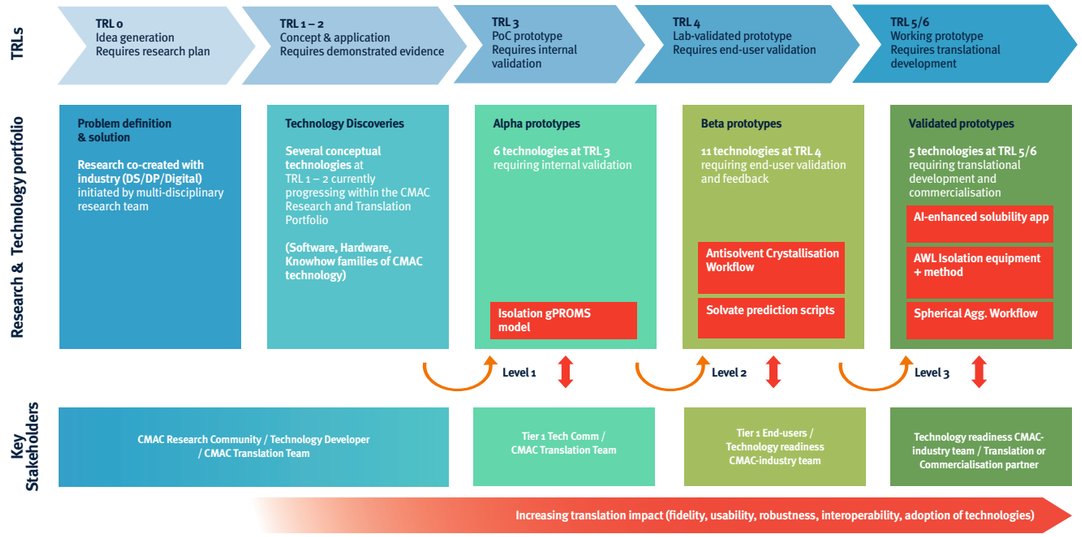
In 2020 CMAC continued to expand and develop the collaborations across large pharma (Tier 1s), large corporations and SMEs in the technology field (Tier 2s), and academia to provide an immersive ecosystem of pre-competitive research knowledge sharing and process improvement. This has been exemplified through the technical translation of a spherical agglomeration workflow, and consolidation of work on the materials parameterisation database for direct compression. This was done by way of a multi-company approach to deliver demonstrable impact through equipment set-up, process workflows, personnel training and access to research output and databases.

With the global pandemic shining a light on the importance of both collaborative working and adaptive, agile manufacturing processes, the significance of continuous manufacturing has been thrust to the forefront for change. The ‘Business Case Insights for Continuous Manufacturing’ which was carried out by CMAC and PwC exemplifies the drivers for change and the 9-lenses for consideration (refer to page 46). Building on this, CMAC have been working closely with the Tier 1 partners to define a Strategic Roadmap, affirming industry priorities and identifying areas of critical mass. This alignment will form the constructs of the future strategy and help shape the forward research programme.

CMAC has adapted to working with our global partners throughout the pandemic, hosting 2 virtual events (see pages 47-48) showcasing research on an international platform and engaging across the broader industry network. Additionally, we ran 12 webinars and focused discussion topics over the past year which has seen excellent engagement from industry to contribute to the research efforts across the breath of the programme.

Going forward, the vision is to strengthen the four pillars (see page 6) and implement a translation pipeline which will seek to expand and solidify CMAC’s reputation as a world leader in advancing pharmaceutical manufacturing research and define the forward set of strategic goals, as we enter the next phase of the hub research programme and the industry membership period.

CMAC Technology Translation Roadmap & TRL Stage Gates



Exemplary Translation to Industry

TIER 1

The continued support and engagement of Tier 1 Industry partners has been at the core of CMAC's success. Within the consortium of 8 Tier 1 partners from the global pharmaceutical industry, there is an opportunity to collaborate in a pre-competitive manner to co-develop a programme of research, and lead transformation and innovation in advanced pharmaceutical manufacturing. Industrial partners provide coordinated and sustained mentoring, direction, validation and support across the wider CMAC organisation.

CMAC, as part of the University of Strathclyde 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.

AstraZeneca · Bayer · Lilly · GSK · Novartis · Pfizer · Roche · Takeda

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 2

CMAC welcomes three Tier 2 members in 2019/20:

- Analytik - in partnership with Laminar, Korea, will provide CMAC with continuous Taylor reactors
- M-Star Simulations - collaboration activities on the development and validation of computational tools for modelling momentum, energy and mass transport within biological systems
- QbD Vision - supplied by Cherry Circle, will enable co-development of a QbD Digital Workflow.

This brings the total number of Tier 2 partners from the community of innovative technology companies to 18.

Tier 2 Membership Benefits

- Engage with leading academics and the Tier 1 community to deliver industry focused solutions
- Showcase equipment and software in award winning facilities
- Access to expertise in crystallisation, characterisation, morphology, analytical etc. fields
- Exclusive member networking events and free exhibition space
- Recruitment of CMAC trained researchers
- PhD mentorship
- Access to funding opportunities

analytik · anatune · AWL · blacktrace · Britest · CCDC · Clairet Scientific Limited · EDEM · Huxley Bertram · NiTech Solutions · M-STAR Simulations · Perceptive Engineering Ltd · PSE · pwc · CherryCircle QbDVision · Snapdragon Chemistry · Technobis Crystallization Systems · ThermoFisher Scientific

Engagement and Translation

CMAC continues to strengthen its industry engagement strategy into 2021 and beyond. 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.

In 2020, we implemented a stage-gate process to accelerate the translation of CMAC research into industrially applicable and impactful technologies. CMAC's Research & Translation Portfolio builds upon more than 10 years of research co-created with industry in the areas of drug substance and drug product manufacturing, and digital platform.

Our translation to industry strategy is enriched and well-informed by our industrial Tier 1 and Tier 2 partners. We are leveraging our portfolio of over 22 promising technology assets across TRL 3 - 6 to deliver impact to the wider industry in a sustainable manner. Of these 22 assets, there are are 5 technologies spanning digital, workflows, and equipment that are rapidly approaching translation to industry maturity or a commercial readiness design phase.

Translating for Impact: Impurity Rejection Workflow

Our translation-first approach addresses the outcome-impact gap by ensuring industrially translatable outputs are built-in deliverables for pre-competitively funded Core Projects and are designed for direct implementation by end-users. One example of the success that can be achieved with this approach is the Impurity Rejection Workflow.

The Impurity Rejection Workflow can rapidly identify the mechanism of impurity incorporation responsible for poor impurity rejection during a crystallisation. The workflow was developed by Dr Stephanie Urwin and Professor Joop ter Horst in close collaboration with an industry steering team.

The Impurity Rejection Workflow was successfully translated via webinar to over 105 industrial attendees and tailored training workshops to over 47 company staff across 2 months. The workflow has delivered significant value to Tier 1 companies by providing a systematic approach to speed up crystallisation development. It has been applied to several commercial projects, including a soon-to-be-registered commercial compound.

Impurity Rejection Workflow Translation: Key Stats

105 Industrial webinar attendees

47 Staff trained in follow-up

1 Paper submission

7 Case studies

12 Hours of Tier 1 training

Dynamic workflow developed

3 Steering team industrialists

1 Technical Support " How To" document shared

Some stated company benefits:

- A systematic way to reduce the amount of effort and material to use
- Provides the structure and data to justify decision-making, such as changing the chemistry of the process
- Selectivity coefficient helpful in comparing the purging performance of crystallisation processes
- Improves fundamental knowledge of the impurity challenge, i.e. mechanisms of incorporation

Industry Engagement with CMAC Researcher Community

PHD PLACEMENTS WITH CMAC PARTNERS IN 2020-2021

In spite of the pandemic, 8 PhD Placements took place across 2019/20. Adapting to the global crisis, 5 were run as remote placements, ensuring that value was gained by both the companies and researchers. PhD placements remain a successful translation pathway for delivering quick-win tangible benefits to our industrial partners.

Topics included:

- Developed workflows for solid form screening and habit modification
- Advanced Characterisation of amorphous content using SAXS
- Quality optimisation through experimental design and 2D population balance modelling
- Understanding and controlling impurities in crystallisation and isolation
- Process understanding of hot melt extrusion

"Partnering with CMAC scientists to explore the in-silico design of crystal nucleation template molecules has deepened our appreciation of the challenges involved, while providing an excellent opportunity for a PhD student to develop expertise and hone skills in crystallisation and solid-state characterisation needed to tackle industrially relevant problems."

SUSAN M REUTZEL-EDENS, SR. RESEARCH ADVISOR (LILLY) ON CMAC PHD RESEARCHER HECTOR POLYZOIS' SUCCESSFUL PLACEMENT WITH ELI LILLY.

MENTOR GROUPS

CMAC Tier 1 industrial colleagues provide support, feedback and steer over 40 PhD students across various disciplines. With the large number of students across 7 universities we have developed the concept of mentor groups with a common research area. This promotes links across the CMAC researcher community and facilitates industrial input, context and translation.

The mentor sessions are intended to run along group meeting style discussions in a supportive, "critical friend" environment.

Current groups by topic:

- Advanced Materials Characterisation
- Digital Platform
- Primary Processing
- Primary to Secondary Processing

Advanced Materials Characterisation

Digital Platform

Primary Processing

Primary to Secondary Processing

Outstanding Skills Development

“CMAC has a leading training programme recognised for uniquely serving the medicines manufacturing sector talent pipeline. The training on offer covers an MSc in Advanced Pharmaceutical Manufacturing, an Industry PhD Cohort Programme, and training and development for ECRs. Continuous development and transferable skills opportunities are available to all staff and students in CMAC. This year the team did a great job at transferring modules to modes of e-learning where possible and introducing virtual team building events. An aspect which will be enhanced for the future and combined with hands-on training for blended events. The tradition of collective off-site training for entirety of CMAC at our annual summer school unfortunately had to be put on hold this year but we very much look forward to getting together in the one location for cross-team and cross-cohort building in the coming year.“

Dr Andrea Johnston, Hub Programme Manager

Outstanding Skills Development

"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

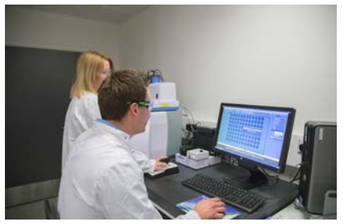
In CMAC, skills development is tailored to train interdisciplinary researchers to be ready to move to world-class academic research and industry positions as their first destination after CMAC. The bespoke training programmes are aligned to the Hub research vision and informed by the needs of our Industry partners. The CMAC researcher community benefits from a vibrant and dynamic 'ecosystem' of leading academic expertise across multiple disciplines, access to world-class facilities, and contribution from leading industrial partners. Researchers are empowered through training and support to develop technical and transferable skills, build 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. It's supported by academic staff from across the University, six academic partners and CMAC's strategic partners AstraZeneca, GlaxoSmithKline, Novartis.



CMAC INDUSTRIAL PhD PROGRAMME

CMAC's flagship PhD programme combines dynamic, interdisciplinary training with pioneering research projects that have been informed by the needs of our industrial partners. Our programme is aligned with the EPSRC Future Manufacturing Research Hub vision and benefits from access to our world-class facilities. Our bespoke PhD training programme offers a vibrant and interdisciplinary training experience that equips our students to progress onto the PhD research programme. All students undertake the formal training programme during year 1, consisting of five training weeks at the University of Strathclyde. Our training is delivered by our leading academic and industrial experts, and provides significant theoretical knowledge, hands-on experience training, and a range of transferable skills. CMAC provides a unique cohort experience, creating a community of researchers that can support each other in their future careers. Our unique PhD mentorship programme unites our researcher and industrial communities in a forum to provide insight and support to our PhD students. Our students are assigned to a mentor group depending on their research project, with each group aligned to the research scope of the CMAC Hub. Our students are mentored by leading industrialists throughout their studentships and are provided with industrial relevance, context, and advice on projects, as well and facilities opportunities for industrial placements. As part of the CMAC PhD programme, our students have the opportunity to undertake an innovative industrial placement at one of our tier 1 industrial partners. These placements provide our students with vital industrial knowledge and experience that can help shape their research projects and future careers.

- 9 new students in 2021 cohort
- 12 publications in 2020 with student named as co-author
- 4 Student Placements and 3 virtual placements in 2020
- 8 students passed their viva in 2020
- 50% of 2020 graduates went to industry first destination

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 career development opportunities. As part of core activity all ECRs receive training on Equality, Diversity & Inclusion, data management, open access publications, grant writing, routes of innovation and IP awareness. Whilst many act as champions and role models in this space. All are trained in project management and are introduced to scenario planning and multi-criteria decision analysis at early stages of joining CMAC. These concepts are reinforced throughout with, for example workshops with Tier 2 partners 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 include, but 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. CMAC are developing a formalised training and development programme, bespoke to individual early career researchers, to enhance development opportunities already in place.

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, an extensive round of hardware and software upgrades have recently been carried out, enhancing and further leveraging the initial investment. The core areas remain in solid state screening, particle engineering, drug product processing and advanced characterisation. However, significant expansion is also underway in automation, digitilisation and process modelling. 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

World Class Facilities

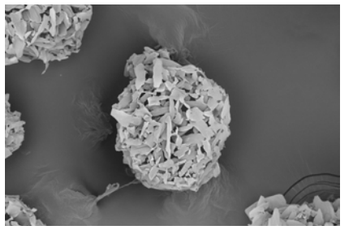
UNIVERSITY OF STRATHCLYDE

CMAC National Facility

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. This includes a comprehensive suite of high-value continuous processing equipment, novel monitoring and control systems and extensive off-line characterisation capabilities.

Huxley-Bertram Compaction Simulator

An HB50 Huxley Bertram Compaction Simulator specified with instrumented dies and innovative process analytics for in situ measurements using terahertz spectroscopy has recently been installed in CMAC's facilities. The first in world integrated compaction simulator-terahertz system was made possible by support from EPSRC. Compaction simulation research at CMAC is being led by academics and scientists expert in compaction simulation with cutting edge application and engineering support provided by Huxley Bertram's Cambridge-based staff. CMAC are pleased to offer Compaction Simulation Research Services through our National Facility Team.



Industrial Engagement

Building on our success and international recognition gained at the CPhI Excellence in Pharma Awards for outsourcing services, we have continued to work 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 an outstanding analytical capability.

Academic Excellence

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. Examples of international collaborations include a collaborative project between CMAC and CUNY on water responsive peptide crystals which made the March cover of Nature Materials.

Work with us

- To conduct confidential research and development projects, advanced analytical services, and consultancy
- Have a dedicated experienced team deliver projects
- We work with a range of companies from SMEs to large Pharma

TO FIND OUT MORE CONTACT:
national-facility@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.

Facilities at Spokes

DiPP @ Sheffield

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

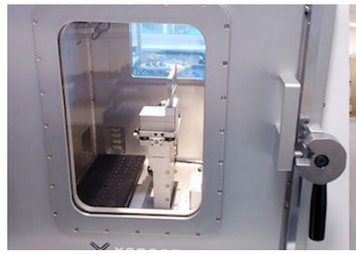
It houses a Pilot Plant which tests integrated processes with simulations and control systems in a safe, product-oriented environment, and a virtual and augmented reality lab which will be used to train researchers for the future.

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. Commissioning of this Diamond-Leeds SAXS (DL-SAXS) facility will be completed in 2021. 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 University of Leeds. There are CMAC researchers from Universities of Leeds and Bath 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 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.

NPL

The National Physical Laboratory (NPL) is the UK's National Measurement Institute, and is a world-leading centre of excellence in developing and applying the most accurate measurement standards, science and technology available. Collaboration of strategic partners NPL and the University of Strathclyde means that CMAC-NPL researchers are co-hosted at the main NPL site at Teddington for part of their studies with access to the state of the art facilities there.

Being 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 the wider research communities in this area. We actively engage with academic, industrial, regulatory, and public communities and act on their behalf e.g. to influence policy, host events, facilitate and support workshops, support feasibility studies and develop national expertise. The Hub holds an important position in the UK research and Innovation Landscape working with other EPSRC communities, catapults, KTN’s and Medicines Manufacturing Industry partnership, engaging through a TRL journey.

Despite the challenges of 2020 associated with the pandemic, the Hub has remained engaged with all major stakeholders and hosted two well attended international virtual events: Annual Open Day in October and the fourth International Symposium of Continuous Manufacturing, co-hosted with MIT. Overall, these events brought over 600 delegates together including academics, industry thought leaders, regulators and government, to hear about the advances and overcome barriers of using continuous manufacturing for delivering medicines to patients with higher quality and productivity in a more sustainable manner.

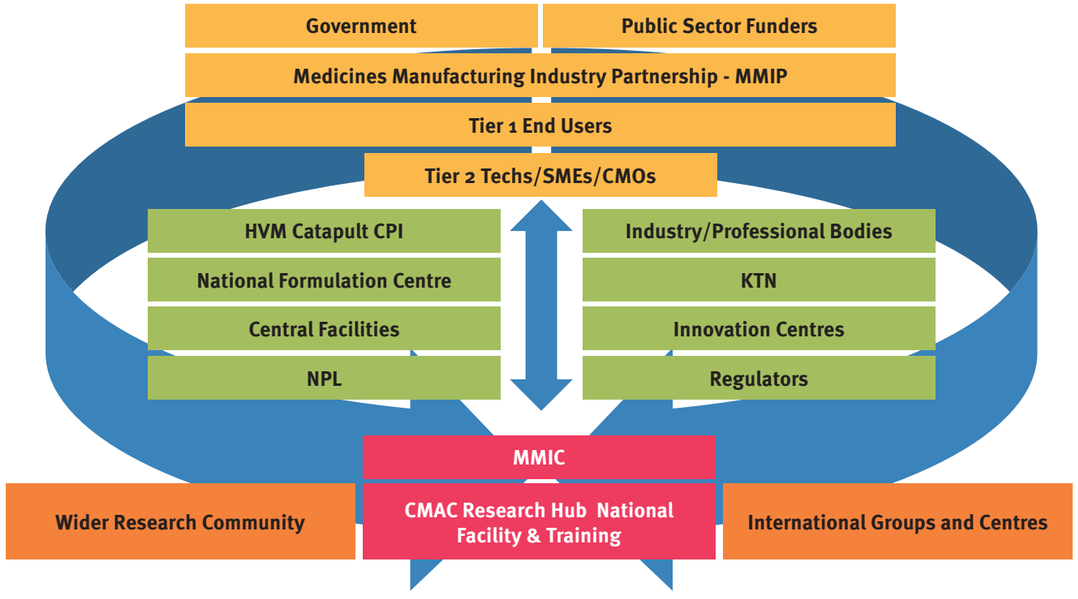
The Hub has also been pro-active in growing academic expertise and capability and recently launched a round of four funded feasibility studies covering digital manufacturing and advanced materials characterisation to develop understanding on continuous manufacturing. We look forward to working with these groups and scoping further potential future funding routes. “

Dr Andrea Johnston, Hub Programme Manager

Being 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.

LANDSCAPE MAP



KEY THEMES

1. High quality, multi-disciplinary research
2. Addressing major, long-term challenges to create outcomes for the UK Economy
3. Developing new ways of working through engagement with our Industrial partners, and seizing opportunities to deliver significant impact
4. Developing high performance, supportive and inclusive researcher teams and environments
5. Following moving strategic targets
6. Setting the agenda and leading nationally and beyond

KEY ENGAGEMENTS

CMAC are represented on exec and leadership teams of many UK and international medicines manufacturing initiatives:

- We are part of the UK’s Medicines Manufacturing Industry Partnership (MMIP) and Medicines Manufacturing Special Interest Group.
- CMAC are a strategic partner in CPI Medicines Manufacturing Innovation Centre (MMIC).
- In partnership with the National Physical Laboratory (NPL) we have a research base at central facilities, and have a MoU to enable collaboration and jointly appointed staff between our two organisations.

In addition, CMAC has strong interactions and collaborations with the wider research community including other EPSRC funded activities such as Hubs and CDTs.

UK Landscape

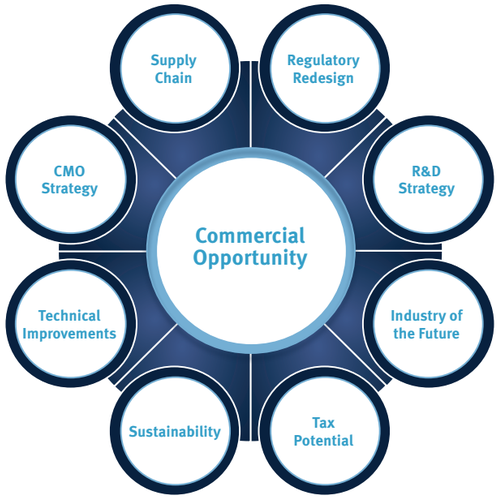
LINKING CENTRES

The CMAC Hub and National Facility are part of a wider UK landscape of Centres including Diamond Light Source, Research Complex @Harwell, The Sheffield DIPP, MMIC, The National Formulation Centre and National Physical Laboratory. Universities of Strathclyde, Sheffield and Leeds are also academic partners in the UK manufacturing Made Smarter (MMS) Fast Start project Digital Design Accelerator Platform ((see page 26)) led by AstraZeneca and involving GSK, Pfizer and CPI.

INFLUENCING POLICY

CMAC operates as a National Centre and is represented and well connected with UK wide bodies such as Medicines Manufacturing Industry Partnership (MMIP), Medicines Manufacturing Challenge Community (MMCC) and UK research network plus Connected Everything II. CMAC is a key part of the Digital Manufacturing community currently addressing the question 'how do we support the future of manufacturing in the UK?'. Through these connections we have influenced UK policy by contributing to:

- National Digital Roadmap
- Digital Roadmap for Medicines Manufacturing
- Roadmap for Standards for Digital manufacturing
- European key Enabling Technologies Roadmap
- NPL's data science and standards fore-sighting
- Manufacturing the Future Utilising UK's large Facilities



CMAC AND PWC BUSINESS CASE INSIGHTS FOR CONTINUOUS MANUFACTURING

This joint document, with input from industrial partners, seeks to review key considerations for building a successful business case for the industrial adoption of innovative Continuous Manufacturing (CM) technologies.

The report is written from the perspective of the CMAC manufacturing research programme stakeholders, hence, it targets factors directly relevant to continuous small molecule pharmaceutical manufacturing. In addition to addressing the many drivers and impacts across the entire value chain, it also puts emphasis on factors relevant to continuous drug substance manufacturing.

Nine critical considerations have been highlighted for business case development. Through each of these lenses, a holistic case for continuous manufacturing can be progressed to help drive the uptake of this currently novel technology. This document was undertaken with engagement from CMAC Tier 1 partners AstraZeneca, Eli Lilly, Pfizer, and Takeda, as well as leveraging CMAC's own extensive academic portfolio on end-to-end (E2E) processing. CMAC would like to thank all those who have contributed information and viewpoints on key technical aspects in combination with PwC's wider business case perspective, to help inform and engage senior stakeholders and drive continuous manufacturing forward.

Feasibility Projects

CMAC has supported 4 feasibility projects which have been awarded and run for 6-12 months each. The Call was managed by CMAC and EPSRC during 2020 and was open to all UK academics eligible for EPSRC funding. The 4 projects awarded were selected from over 30 EoIS and 10 full applications. They have been selected to align with the Hub goals and address specific areas of interest.

Principal investigator	Institution	Title	Duration
Dr Tong Deng	University of Greenwich	Micro to Manufacturing: Advanced Measurement and Characterisation of Inter-particle Forces with Application to the Design and Control of Flow Behaviour	6 months
Professor George Panoutsos	University of Sheffield	From Laboratory to Industrial Manufacture: Transforming Digital design via Robust Scaling-Up AI Platforms	6 months
Dr Aniruddha Majumder	University of Aberdeen	A Novel Simulated Moving Plug Flow Crystallizer (SM-PFC) with Anti-Fouling Control	6 months
Professor Philip Withers	University of Manchester	Advanced 3D Characterisation of Formulated Pharmaceutical Systems	12 months

TABLE X: FEASIBILITY PROJECTS

INTERNATIONALISATION

Internationally we have links with leading academic manufacturing research centres: MIT through co-organisation of the biannual International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP) events; The Science Foundation Ireland Research Centre for Pharmaceuticals (SSPC) in Ireland; Research Center Pharmaceutical Engineering (RCPE) Austria, Purdue University, US, Ghent University, Belgium, University of Copenhagen, Denmark and Singapore Technical university, Singapore . Through the University of Strathclyde international Strategic Partnerships Scheme we have been able to fund collaborative PhD programmes with RCPE in Austria and Singapore. We have hosted Thomas de Beer, Ghent for academic seminars and exploring opportunities with Ghent, Copenhagen and Purdue for collaborative research and training opportunities.

Early 2020 saw CMAC's first crystal growth in space experiments where Prof Joop ter Horst collaborated with European Space Agency, Ice Cubes Service to determine if protein crystal growth in micro-gravity environments would produce higher quality crystals for subsequent analysis. Further activity in Europe includes a new collaboration in a European Research Council Proof of Concept grant on printing personalised medicines on demand with the University of Stuttgart, Utrecht University, Aalto University and several European companies.

CMAC International Events

MIT-CMAC INTERNATIONAL SYMPOSIUM ON CONTINUOUS MANUFACTURING OF PHARMACEUTICALS

An Integrated Ecosystem for Transforming Medicines Manufacturing

The International Symposium on Continuous Manufacturing of Pharmaceuticals (ISCMP) was established in 2014, by request of Janet Woodcock, Head of CDER at the FDA, to align on continuous 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

70%
from poll responses indicated that 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.

CMAC VIRTUAL OPEN DAY 2020

The Future CMAC Hub award includes support for hosting CMAC Open Days which are an opportunity for both the CMAC network and new persons or groups to interact with the CMAC community and find out about the UK landscape of Continuous Pharmaceutical manufacturing. It also gives the opportunity to find out more about CMAC research via direct interactions with the researchers. In 2020 CMAC hosted our Open Day event virtually for the first time. The event was held over two afternoons and tried to recreate interactive sessions that we normally have at our face-to-face events, including poster (called "Expo" in the online platform) and breakout sessions.

Feedback on hosting our first virtual event:

> Great first day!! Very well organized, looking forward to Day 2!

> Great experience, the event was good and fantastic to be able to connect with people in the Expo.

> The overall format and execution was really excellent and should serve as a benchmark for other virtual events – congratulations to the team!

> Excellent platform, thank you so much for making this happen.

297
Attendees

70
Organisations

11
Tier 2 Booths

ATTENDEES
UK • USA
EUROPE • ASIA

>20%
ATTENDEES NEVER BEEN AT A CMAC EVENT BEFORE

66
Research Posters

PANEL SESSION

12
Speakers

5
Hub ResearchTalks

20
Digital Assets Showcased

9
CMAC workflows developed

7
Advanced Measurement Techniques showcased

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

TIER 1 INDUSTRY PARTNERS:

- 01 AstraZeneca, Macclesfield, UK
- 02 Bayer, Leverkusen, Germany
- 03 Eli Lilly, Indianapolis, IN, USA
- 04 GlaxoSmithKline, Stevenage, UK
- 05 Novartis, Basel, Switzerland
- 06 Pfizer, Sandwich, Kent, UK & Cork, Ireland & Groton, CT, USA
- 07 Roche, Basel, Switzerland
- 08 Takeda, Boston, MS, USA

TIER 2 PARTNERS:

- 01 Laminar Analytik, Cambridge (Laminar) and Korea (Analytik)
- 02 Anatune, Cambridge, UK
- 03 AWL, Stoke-on-Trent, UK
- 04 Blacktrace, Royston, UK
- 05 Britest, Daresbury, UK
- 06 CCDC, Cambridge, UK
- 07 Clairet Scientific Limited, Northampton, UK
- 08 EDEM, Edinburgh, UK
- 09 Huxley Bertram, Cambridge UK
- 10 Nitech Solutions, Edinburgh, UK

TIER 2 PARTNERS CONT:

- 11 M-Star Simulations, Maryland (USA)
- 12 Perceptive Engineering Ltd, Warrington, UK
- 13 PSE, Hammersmith, UK
- 14 PWC, Glasgow, UK
- 15 CherryCircle Software, Inc., Austin, Texas (USA)
- 16 Snapdragon Chemistry, Waltham, MA, USA
- 17 Technobis Crystallization Systems – Alkmaar, The Netherlands
- 18 Thermofisher Scientific, Bordeaux, France

INNOVATION SPOKES:

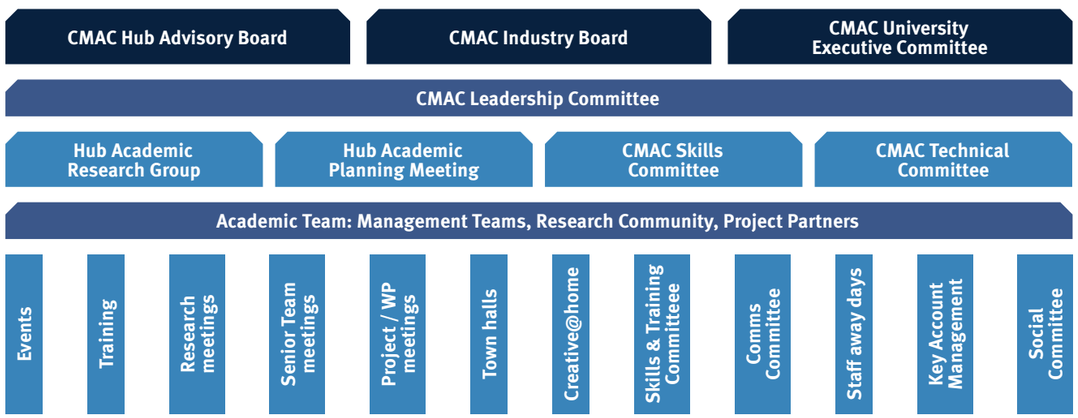
- 01 CPI, Middlesbrough UK
- 02 CRUK, Formulation Unit, University of Strathclyde, Glasgow
- 03 NPL, Teddington, UK
- 04 Diamond Light Source, Didcot, UK
- 05 RCPE, Graz, Austria
- 06 NTU, Singapore
- 07 MHRA, London, UK
- 08 Scottish Enterprise, Glasgow, UK

OTHER COLLABORATORS:

- 01 SSPC, Castleroy, Co. Limerick, Ireland
- 02 Purdue University, Lafayette, IN, USA
- 03 MIT, Cambridge, MA, USA
- 04 Connected Everything II, Nottingham, UK
- 05 ICE Cubes Services, Brussels, Belgium

CMAC Governance Structures

CMAC HUB GOVERNANCE STRUCTURES



HUB ADVISORY BOARD

Name	Organisation
Amy Robertson	AZ
Alastair Florence	CMAC
Massimo Bresciani	CMAC
Andrea Johnston	CMAC
Lorna Gray	CMAC
Dave Tudor	CPI
Sophie Walton	CPI
Nigel Westwood	CRUK
Walkiria Schlindwein	De Montfort University
Richard Bailey	EPSRC
Nilay Shah	Imperial College London
Andy Jones	Innovate UK (ISCF)
Sarah Goulding	Innovate UK (ISCF)
Adam Fine	Merck Sharp and Dohme
Ian Gilmore	NPL
Ross MacRae	Pfizer
Sean Bermingham	PSE
Johnathon Marshall	PwC
Paul Sharratt	Singapore Institute of Technology
Richard Hague	University of Nottingham
Clive Badman	University of Strathclyde

CMAC INDUSTRY BOARD

Name	Organisation
Jon-Paul Sherlock (CHAIR)	AZ
Alastair Florence	CMAC
Claire MacDonald	CMAC
Massimo Bresciani	CMAC
Jan-Olav Henck	Bayer
Olaf Queckenberg	Bayer
Chris Burcham	Eli Lilly
Sarah O'Keefe	Eli Lilly
Markus Krumme	Novartis
David Lovett	Perceptive Engineering
Geoff Gibson	Pfizer
Ivan Marziano	Pfizer
Olivier Drap	Pfizer
Pirmin Hidber	Roche
Charles Papageorgiou	Takeda
Graham Wren	University of Strathclyde

HUB ACADEMIC RESEARCH GROUP

Professor Alastair Florence, Director, University of Strathclyde (Chair)

Dr Andrea Johnston, CMAC Hub Programme Manager

Massimo Bresciani, Industry Director

Dr Ian Houson, CMAC National Facility Manager

Dr Rebecca Halliwell, Hub Funding Manager

Dr Stewart Mitchell, Project Manager

Dr Iyke Onyemelukwe, CMAC Technical Translation Manager

Miss Helen Feilden, CMAC Hub Outreach Manager

Professor Chick C. Wilson, University of Bath

Dr Laur en Hatcher, University of Bath (to end March 2020)

Dr Particia Marce Villa, University of Bath (April 2020 – Feb 2021)

Dr Ettore Settanni, University of Cambridge

Dr Jag S. Srai, University of Cambridge

Professor Amparo Galindo, Imperial College London

Professor Claire Adjiman, Imperial College London

Professor George Jackson, Imperial College London

Dr Suela Jonuzaj, Imperial College London (to Nov 2020)

Dr Thomas Bernet, Imperial College London

Dr Brahim Benyahia, Loughborough University

Professor Chris D. Rielly, Loughborough University

Dr Wei Li, Loughborough University

Dr Anuradha Pallipurath, University of Leeds

Professor Kevin Roberts, University of Leeds (to Dec 2020)

Professor Sven Schroeder, University of Leeds

Dr Thokozile Kathyola, University of Leeds

Dr Bilal Ahmed, University of Sheffield

Professor Jim Litster, University of Sheffield

Dr Rachel Smith, University of Sheffield

Dr Alison Nordon, University of Strathclyde

Dr Blair Johnston, University of Strathclyde

Dr Cameron Brown, University of Strathclyde

Dr Chris Price, University of Strathclyde

Dr Daniel Markl, University of Strathclyde

Dr Elke Prasad, University of Strathclyde

Frederik Doerr, University of Strathclyde (to Sept 2020)

Professor Gavin Halbert, University of Strathclyde

Professor Jan Sefcik, University of Strathclyde

Dr John McGinty, University of Strathclyde

Dr John Robertson, University of Strathclyde

Professor Joop ter Horst, University of Strathclyde (to March 2021)

Dr Magdalene Chong, University of Strathclyde

Dr Monika Warzecha, University of Strathclyde

Dr Murray Robertson, University of Strathclyde

Dr Sara Ottoboni, University of Strathclyde

TECHNICAL COMMITTEE

Company	Members
AZ	Amy Robertson Liz Meehan Helen Wheatcroft
Bayer	Britta Olenik Guido Wegener
Eli Lilly	Chris Burcham Joel Calvin Johnathan Wade James Wyatt Roth
GSK	Cheryl Doherty Mei Lee Richard Elkes
Novartis	Berthold Schenkel Ruairi O'Meahdra
Pfizer	Kevin Girard Paul McDaid Paul Meenan
Roche	Marcello Bosco Pirmin Hidber
Takeda	Charles Papageorgiou Justin Quon Neda Nazemifard

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CMAC
FUTURE MANUFACTURING RESEARCH HUB

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